



Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

05-110321

54. TITULO

COMPOSICIONES FARMACEUTICAS PARA INHIBIDORES DE LA PROTEASA DEL
VIRUS DE LA HEPATITIS C

51. CLASIFICACION INTERNACIONAL

**A61K47/00; A61K38/06;
A61P31/12**

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. BOGOTA, D.C.,

28/10/2005.

SS


Industria y Comercio

SUPERINTENDENCIA

PETITORIO

SUPERINDUSTRIA Y COMERCIO

 Radicación : 16110-02 16110-02
 Fecha (MM/AA): 2005-10-18 16:56:07
 Trámite : 011 PCT-PRIENT 3/9 FASE NACI 411 PREP-NAC
 Dependencias: 2000 DIVISION DE MARCAS COMERCIALES

SUPERINDUSTRIA Y COMERCIO

**FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL**
SOLICITUD DE:

1

☒ 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 la Republica Federal de Alemania.

 Dirección: Binger strasse 173, 55218
 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@camyp.com.
 Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

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

4

**INVENTOR (ES)
(72)**

 1. Shirllynn CHEN
 Boehringer Ingelheim Pharmaceuticals,
 Inc., 900 ridgebury Road, P.O. Box 368,
 Ridgefield, CT 06877-0368
 Estados Unidos de América

 3. Zeren WANG
 Boehringer Ingelheim Pharmaceuticals,
 Inc., 900 ridgebury Road, P.O. Box 368,
 Ridgefield, CT 06877-0368
 Estados Unidos de América

 2. Xiaohui MEI
 Boehringer Ingelheim Pharmaceuticals,
 Inc., 900 ridgebury Road, P.O. Box 368,
 Ridgefield, CT 06877-0368
 Estados Unidos de América

5

PCT (86)

 Solicitud Internacional No. PCT/US2004/008837

 Fecha: 23 de marzo de 2004

 Publicación Internacional No. WO 2004/093915 A1

 Fecha: 4 de noviembre de 2004

6

Título (54)
**COMPOSICIONES FARMACEUTICAS PARA INHIBIDORES DE LA PROTEASA DEL
VIRUS DE LA HEPATITIS C**

7

Clasificación Internacional (51) A61K 47/00
A61K3806. A61P31/12

8

Prioridad

 SI ☒ NO ☐
(33) País de Origen
US
(32) Fecha
2 de abril de 2003
(31) Número de Solicitud
60/459.765

9

Comprobante de pago No.: 05-81.676
Fecha: octubre 24 de 2005

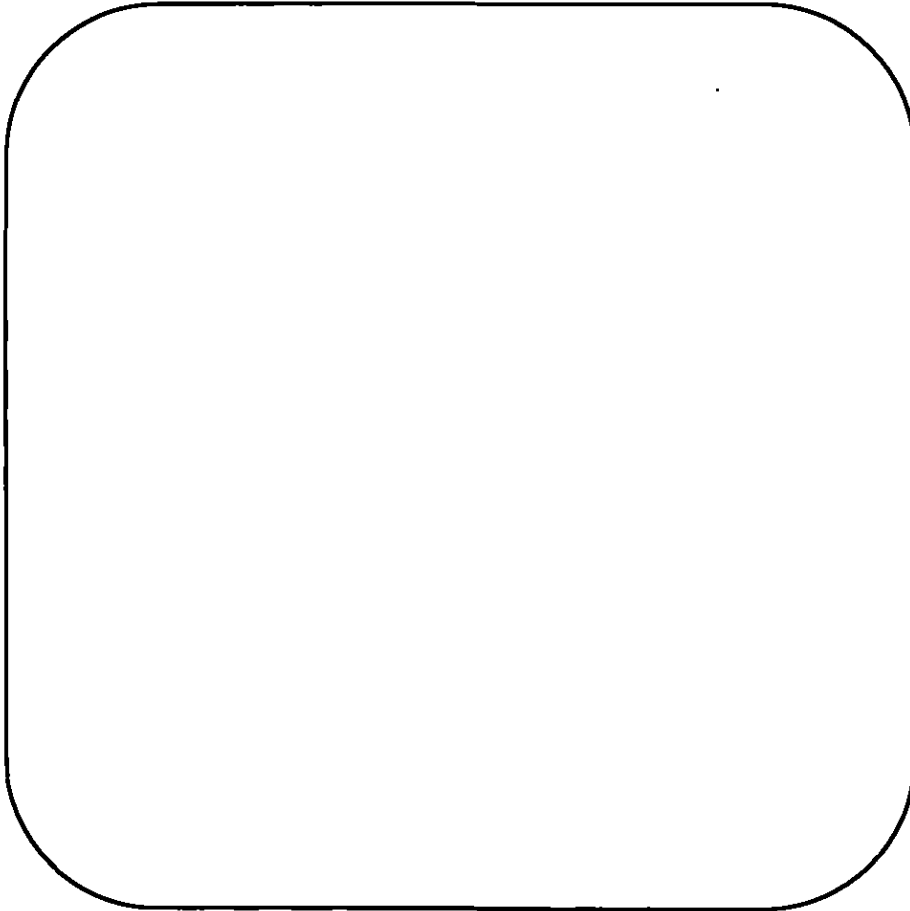
10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ 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



12

Solicito la concesión de la patente,

NOMBRE:

EMILIO FERRERO

FIRMA:

C.C. 438.019 de Usaquén T.P. 31.929

JDF

DOCUMENTOS ANEXOS

1. ☒ **Publicación Internacional WO 2004/093915 A1**

Descripción:

Páginas 41 en el idioma original

Páginas 38 en español

Reivindicaciones: Número (s) 28

Figuras: Número (s) 0

2. ☒ **Forma PCT/RO/101. PCT Request**
3. ☐ **Forma PCT/RO/106. Invitation to Correct Defects.**
4. ☒ **Forma PCT/ISA/210. Informe de Búsqueda Internacional.**
5. ☐ **Forma PCT/ISA/220. Notificación De La Transmisión Del Informe De Búsqueda Internacional Y De La Opinión Escrita De La Administración Encargada De La Búsqueda Internacional, O De La Declaración.**
6. ☐ **Forma PCT/ISA/237. Opinión Escrita De La Administración Encargada De La Búsqueda Internacional.**
7. ☒ **Forma PCT/IB/304. Notification Concerning Submission Or Transmittal Of Priority Document.**
8. ☐ **Forma PCT/IB/306. Notification Of The Recoding Of A Change.**
Descripción De Modificación:

9. ☒ **Forma PCT/IB/308. Notice Informing The Applicant Of The Communication Of The International Application To The Designated Offices.**
10. ☒ **Forma PCT/IB/332. Information Concerning Elected Offices Notified Of Their Election.**
11. ☐ **FORMA PCT/IB/345. Communication in cases for which no other form is applicable.**

12. ☒ **Forma PCT/IPEA/401. PCT Demand**
13. ☒ **Forma PCT/IPEA/402. Notification Of Receipt Of Demand By Competent International Preliminary Examining Authority.**
14. ☐ **Forma PCT/IPEA/408. Written Opinion.**
15. ☒ **Forma PCT/IPEA/416. Notification Of Transmittal Of The International Preliminary Examination Report.**
16. ☒ **Forma PCT/IPEA/409. Informe Del Examen Preliminar Internacional.**
17. ☐ **Traducción Al Español Del Informe Del Examen Preliminar Internacional.**
18. ☐ **Traducción Al Español De Los Anexos Presentados Junto Con El Informe Del Examen Preliminar Internacional.**
19. ☒ **Extracto de publicación.**

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 constituida y ejerce su objeto social de conformidad con las leyes de la República Federal de Alemania.

Que los señores Dr. DIETER LAUDIN Y Dr. GERHARD HUBER

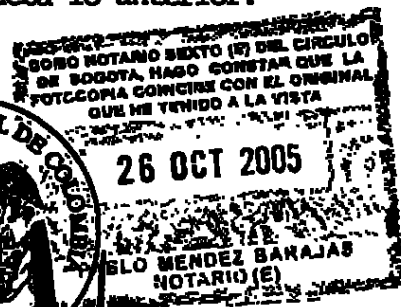
quien(es) firman el presente documento tiene (n) facultad legal suficiente para representar a la mencionada firma y otorgar poderes en su nombre.

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

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



PAGADO

BOE II 210 67.1



MINISTERIO DE RELACIONES
EXTERIORES

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

ENE - 11 A 11:44

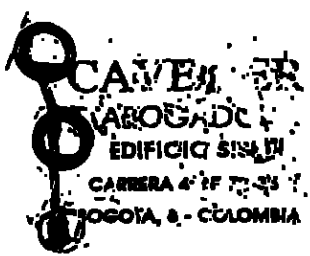
REGISTRACIONES
ANALIT DE BOGOTA D C

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

26 OCT 2005

PAULO MENDEL LARAJAS
NOTARIO (R)

1-245133-027



CAVELIER ABOGADOS
EDIFICIO SISA III
CARRERA 4ª # 72-35
BOGOTÁ, D. C. COLOMBIA

REPRESENTACION Y PODER

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.

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 N° 72-35, Bogotá, Colombia, en obediencia 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 N° 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 or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time as the principal representative shall be present.

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, for which purpose we authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, especially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in 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

INTERNATIONAL GMBH

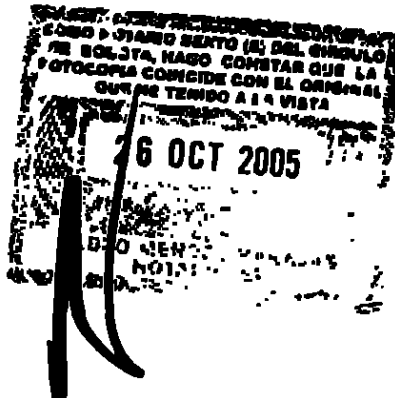
in/en ppa. ppa.
Dr. Dieter Laudien Dr. Gerhard Huber
Signature Firma

LEGALIZATION

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 dárselo. 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 Power-of-Attorney, (2) that it is in actual exercise of company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).



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.

Vorseitige, vor mir gefertigte Namensunterschriften der Herren:

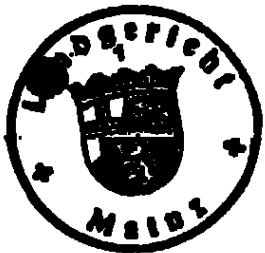
1. Dr. Dieter L a u d i e n, Dipl.-Chemiker, wohnhaft in 55127 Mainz,.
2. Dr. Gerhard H u b e r, Rechtsanwalt, wohnhaft in 55411 Bingen,

- mir bekannt -

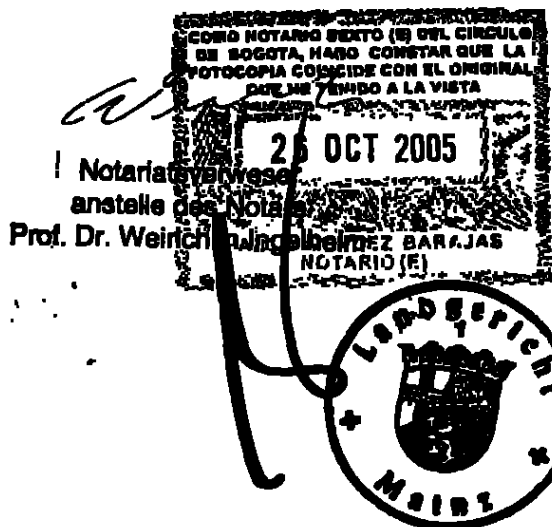
beglaubige ich hiermit.

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.

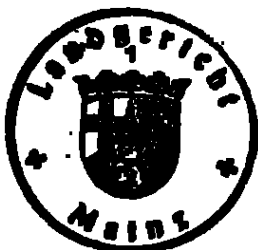
Ingelheim am Rhein, den 12. Dezember 1995/hün



- 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 beigedruckten Dienst - ~~scheins~~ - 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

Hans Paul Tüllenber
(Dr. Hans Paul Tüllenber)

Kostenberechnung:
Gebühr für Legalisation
(Wert: DM 5.00.-)
JV KostO. v. 28.7.1987
BGBl. I S. 881
DM 120.-

7

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:)

Legalización

Protocolo notarial No. 2659/95 V

Certifico la autenticidad de las firmas antecedentes a las que me presentas 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.

8

Igualmente certifico, por haber examinado en la fecha el Registro de Comercio del Juzgado Municipal de Bingen, HR B 1063, que la firma Boehringer 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.

Ingelheim am Rhein, 12 de diciembre de 1995/hün

Fdo.: firma ilegible

(Hilo y oblea roja en relieve:)

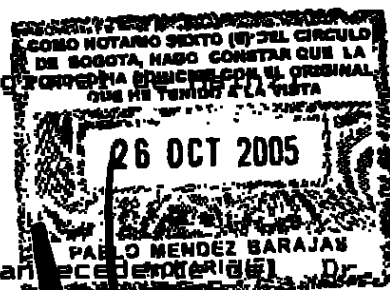
El notario suplente

El notario suplente - Ingelheim

del notario de Ingelheim

Prof. Dr. Weirich

(dos sellos redondos en tinta del Tribunal Registral)



910 E 1

Se certifica la autenticidad de la firma anterior de 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

LUZ ARY...
ADUC...
Resolución No. 54, 11/11/95

9

El Presidente del Tribunal Regional

(E) Fdo.: firma ilegible

(Dr. Hanns Paul Tüttenberg)

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. 189 del 18 de diciembre de 1995, y por el Ministerio de Relaciones Exteriores de Colombia bajo el No. 051606 del 4 de enero de 1996. Pagados derechos y Fondo Rotatorio US\$ 106,--

ES TRADUCCION FIEL Y COMPLETA, de la cual se archiva en los archivos de estas oficinas para su confrontación

Santafé de Bogotá, 6 de enero de 1996.

LUZ ARRIETA DE HERRERA
TRADUCTORA INTERPRETE DE LA
LENGUA

Notario (S)
Pablo Méndez Barajas

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

C. C. Juan Carlos Forero
COINCIDE CON LA REGISTRADA POR EL (ELLA)
EN ESTA NOTARIA
09 ENE 1996
SANTAFE DE BOGOTA C.C.



NO SE ASUME
RESPONSABILIDAD DEL TEXTO
1496 ENE 10 A 11:33
JEFE DE ASISTENCIAS
SANTAFE DE BOGOTA D.C.

COMO NOTARIO SEXTO (N) DEL CIRCULO
DE NOTARIA HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
26 OCT 2005
PABLO MENDEZ BARAJAS
NOTARIO (E)

MINISTERIO DE RELACIONES
EXTERIORES

1496911
CUVA FURIA
PROHIBIDO
LAS FUNCIONES

El Presidente del Tribunal Regional

(E) Fdo.: firma ilegible

(Dr. Hanns Paul Tüttenberg)

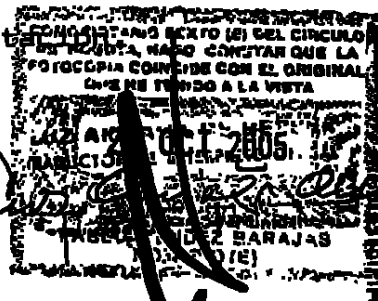
Costas

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. 129 del 10 de
diciembre de 1995, y por el Ministerio de Relaciones Exteriores
de Colombia bajo el No. 051606 del 4 de enero de 1996.
Pagados derechos y Fondo Rotatorio US\$ 106,--

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los
archivos de estas oficinas para su confrontación.

Santafé de Bogotá, 6 de enero de 1996.



NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

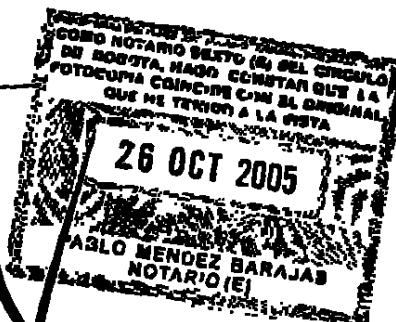
Bogotá,,D. C. 11 ENE 1996
Ante M, PABLO MENDEZ BARAJAS S.
NOTARIO SEXTO ENCARGADO DEL CIRCULO DE BOGOTA
Compareció(eron) [Signature]

quien(es) exhibió(aron) la(s) 2877-9124
438014

y la(s) Libreta(s) Milibares [Signature]

domiciliada(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.

[Signature]
[Signature]



TELEFAX (57) (1) 3527850
TELEX 43479 CAVE CO
12317407375 CAVE OC

CAVELIER

ABOGADOS

EDIFICIO SISKI
CARRERA 49, No. 72-33
BOGOTA 8, COLOMBIA

CORREO ELECTRONICO MUNDIAL: CAVE

TELEFONO (57) (1) 3120100

CABLES: CAVELEYES

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

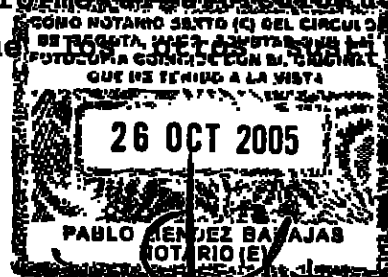
Poderdante: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

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 los autos faltan en este momento.

Señor Jefe,



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

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

C. C. _____
COINCIDE CON LA REGISTRADA POR EL (ELLA)
EN ESTA NOTARIA
09 ENE 1996
SANTAFE DE BOGOTA D.C.



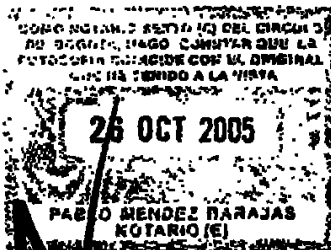
NO SE ASUME
RESPONSABILIDAD DEL TEXTO

09 ENE 10 A 11:33

JEFE DE ASISTENCIAS
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES
EXTERNALES

801911
C. C. FERNANDEZ
BOGOTA D.C.
C. C. FERNANDEZ
BOGOTA D.C.
C. C. FERNANDEZ
BOGOTA D.C.



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

374

CESION

Yo, (nosotros) abajo firmado (s)

1. Shirlynn CHEN
2. Xiaohui MEI
3. Zeren WANG

Domiciliado(s)
en

1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA
2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA
3. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA

Declaro(amos) bajo juramento ser único(s) y verdadero(s)
inventor(es) de la invención:
**COMPOSICIONES FARMACEUTICAS PARA INHIBIDORES
DE LA PROTEASA DEL VIRUS DE LA HEPATITIS C**

declaro(amos) así mismo que cedo(amos) y transfiero(amos), 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. Shirlynn CHEN
2. Xiaohui MEI
3. Zeren WANG

of

1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA
2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA
3. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA

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

**"Pharmaceutical compositions for hepatitis C viral
protease inhibitors"**

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 14th Day of July, 2005
en/in Ridgefield, Connecticut USA

Firma/Signature


Shirlynn CHEN


Xiaohui MEI

Zeren WANG

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 14th day of July
2005 ____ before me, a Notary Public of _____

The State of Connecticut
personally appeared Shirlynn CHEN
Xiaohui MEI

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



Jeanne E. ROGERS
Notary Public
My Comisión Expires: 11/30/2006

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
-
-

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

THIS PUBLIC DOCUMENT

2. has been signed by **JEANNE E. ROGERS**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **November 26, 2001 to November 30, 2006**

CERTIFIED

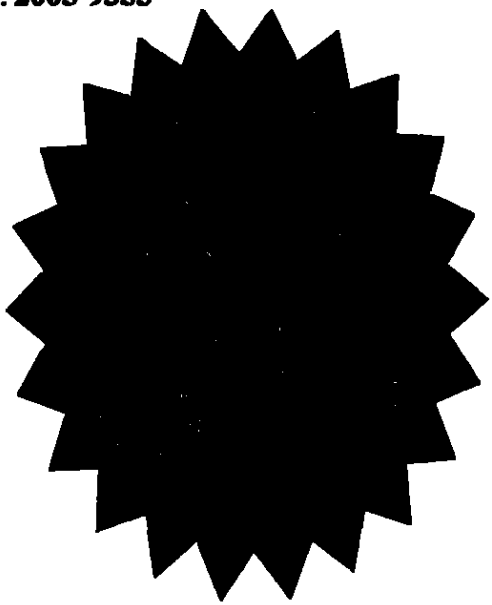
5. at Hartford, Connecticut

6. on **July 28, 2005**

7. by **SUSAN BYSIEWICZ** Secretary of the State of Connecticut

8. Number : **2005-9355**

9. Seal :



10. Signature

Secretary of the State

TRADUCCIÓN OFICIAL No 10.14/05a realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y 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. Shirlynn CHEN, 2. Xiaohui MEI y 3. Zeren WANG, domiciliados en 1. Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877, Estados Unidos de América, 2. Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Box 368, Ridgefield, Connecticut 06877, Estados Unidos de América y 3. Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Box 368, Ridgefield, Connecticut 06877, Estados Unidos de América, respectivamente, declaran bajo juramento ser únicos y verdaderos inventores de: "COMPOSICIONES FARMACÉUTICAS PARA INHIBIDORES DE LA PROTEASA DEL VIRUS DE LA HEPATITIS C" y declaran así mismo que ceden y transfieren sin limitación a favor de Boehringer Ingelheim International GmbH, 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 las citadas compañías quedan facultadas para solicitar en su nombre la patente correspondiente en Colombia.

Dado y firmado el 14 de julio de 2005 en Ridgefield, Connecticut, Estados Unidos de América.

<u>Firma Ilegible</u>	<u>Firma Ilegible</u>
Shirlynn CHEN	Xiaohui MEI

(Anexo) CERTIFICACIÓN NOTARIAL del 14 de julio de 2005 en donde se certifica las firmas de Shirlynn CHEN y Xiaohui MEI en el anterior documento y su capacidad legal para otorgarlo.

Firma ilegible

Jeanne E. Rogers
NOTARIO PÚBLICO
Mí Comisión Vence: 11/30/2006

CAVELIER

ABOGADOS

EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTÁ, 8 - COLOMBIA

374

Case 9-279

CESION

Yo, (nosotros) abajo firmado (s)

1. Shirlynn CHEN
2. Xiaohui MEI
3. Zeren WANG

Domiciliado(s)

en

1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA
2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA
3. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA

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

COMPOSICIONES FARMACEUTICAS PARA INHIBIDORES
DE LA PROTEASA DEL VIRUS DE LA HEPATITIS C

declaro(amos) así mismo que cedo(amos) y transfiero(emos), 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.

Dado y firmado hoy/Given and signed this 2 Day of July, 2005

en/in Farmingdale, New York USA

Firma/Signature

Shirlynn CHEN

Xiaohui MEI

© CAVELIER ABOGADOS
WFFODE01- 374

ASSIGNMENT

I (we), the undersigned

1. Shirlynn CHEN
2. Xiaohui MEI
3. Zeren WANG

of

1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA
2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA
3. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368, Ridgefield,
Connecticut 06877, USA

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

"Pharmaceutical compositions for hepatitis C viral
protease inhibitors"

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

August, 30.

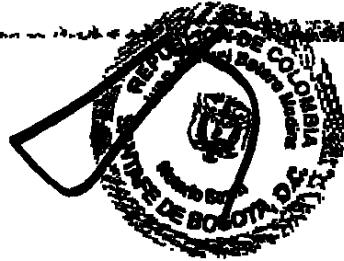

Zeren WANG

MINISTERIO DE RELACIONES
EXTERNOES

170539
Diego Vargas
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPLEA
LAS FUENTES INDICADAS

NOTA ASUME
RESPONSABILIDAD DEL TEXTO
2005 OCT 19 P 2:47
JEFE DE LOCALIZACIONES
SANTAFE DE BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE
Diego Felipe
Diego Vargas
CÓNCIDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTE REGISTRO
SANTAFE DE BOGOTA. 19 OCT 2005



I, EDWARD P. ROMAINÉ, Clerk of the County of Suffolk, and also Clerk of the Supreme Court for said County, the same being a Court of Record, DO HEREBY CERTIFY that

GLENN CORBETT

whose name is subscribed to the deposition or certificate of the proof or acknowledgment of the annexed instrument and thereon written was at the time of taking such deposition or proof or acknowledgment a NOTARY PUBLIC in and for such County, duly commissioned and sworn, and authorized by the laws of said State to take depositions and to administer oaths to be used in any Court of said State and for general purposes; and also to take acknowledgments and proofs of deeds of conveyances for land, tenements or hereditaments in said State of New York. And further that I am well acquainted with the handwriting of such NOTARY PUBLIC and verily believe that the signature of said deposition or certificate of proof or acknowledgment is genuine.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the Seal

of the said Court and County the 19th day of September, 2005.

Edward P. Romaine

Clerk

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 2 day of July August
2005 ____ before me, a Notary Public of _____

The State of New York
personally appeared Zeren WANG

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

GLENN BERBETT
Notary Public, State of New York
No. 01CO4842646
Qualified in Suffolk County
Commission Expires 7/1/06

Notary Public

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

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America

This public document

2. has been signed by Edward P. Romaine

3. acting in the capacity of County Clerk

4. bears the seal/stamp of the county of Suffolk

Certified

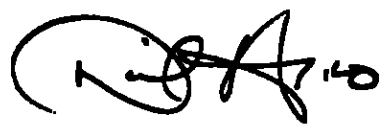
5. At Albany, New York 6. the 28th day of September 2005

7. by Special Deputy Secretary of State, State of New York

8. No. A-72786C

9. Seal/Stamp

10. Signature



Daniel E Shapiro
Special Deputy Secretary of State

TRADUCCIÓN OFICIAL No 10.14/05b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y 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. Shirlynn CHEN, 2. Xiaohui MEI y 3. Zeren WANG, domiciliados en 1. Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Box 368, Ridgefield, Connecticut 06877, Estados Unidos de América, 2. Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Box 368, Ridgefield, Connecticut 06877, Estados Unidos de América y 3. Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Box 368, Ridgefield, Connecticut 06877, Estados Unidos de América, respectivamente, declaran bajo juramento ser únicos y verdaderos inventores de: "COMPOSICIONES FARMACÉUTICAS PARA INHIBIDORES DE LA PROTEASA DEL VIRUS DE LA HEPATITIS C" y declaran así mismo que ceden y transfieren sin limitación a favor de Boehringer Ingelheim International GmbH, 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 las citadas compañías quedan facultadas para solicitar en su nombre la patente correspondiente en Colombia.

Dado y firmado el 2 de agosto de 2005 en Farmingdale, Nueva York, Estados Unidos de América.

Firma Ilegible
Zeren WANG

(Anexo) CERTIFICACIÓN NOTARIAL del 2 de agosto de 2005 en donde se certifica la firma de Zeren WANG en el anterior documento y su capacidad legal para otorgarlo.

Notario Público Firma ilegible
GLENN CORDETT
Notario Público, Estado de Nueva York
No. 01CO4842646
Calificado en el Condado de Suffolk
Comisión Vence 4/11/06

Estado de Nueva York

118868

Declaración Juramentada

Condado de Suffolk

Yo, EDWARD P. ROMAINÉ, Secretario del Condado de Suffolk y así mismo Secretario de la Corte Suprema de dicho Condado, el cual es un tribunal de registro, POR EL PRESENTE CERTIFICO que

Glenn Corbett

cuyo nombre ha sido suscrito en la declaración o certificado de la prueba o reconocimiento del instrumento anexo y en él escrito, era al momento de tomar dicha declaración o reconocimiento un NOTARIO PÚBLICO en y para dicho Condado, debidamente comisionado, juramentado y autorizado por las leyes de dicho Estado para tomar declaraciones y para administrar juramentos a ser usados en cualquier Tribunal del mencionado Estado y para fines generales; así como para tomar reconocimientos y pruebas de escrituras de tierras, inmuebles y herencias en el mencionado Estado de Nueva York. Y adicionalmente que estoy bien familiarizado con la escritura de dicho NOTARIO PÚBLICO y verdaderamente considero que la firma en dicha declaración o certificado de prueba o reconocimiento es auténtica.

EN TESTIMONIO DE LO CUAL, he firmado y colocado mi sello oficial al presente hoy 19 de Septiembre de 2005.

Firma ilegible Secretario

Apostilla

(Convention de La Haye du 5 Octobre 1961)

- 1. País: **Estados Unidos de América**
Este documento público
- 2. ha sido firmado por **Edward P. Romaine**
- 3. actuando en calidad de **Secretario de Condado**
- 4. lleva el sello/estampilla del condado de **Suffolk**

Certificado:

5. en Nueva York, Nueva York 6. el 28 de Septiembre de 2005
7. por el Suplente Especial del Secretario de Estado, Estado de Nueva York
8. No. A-72786C
9. Sello/estampilla: 10. Firma:



Firma ilegible

Daniel E Shapiro

Suplente Especial del Secretario de Estado

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

DVZ/ID-7170/WPCL002G/COLO 09255-841-026-9

Diego F. Vargas
DIEGO F. VARGAS
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLÉS - INGLÉS - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1995
MINISTERIO DE JUSTICIA

MINISTERIO DE RELACIONES
EXTERIORES

170530
Diego Vargas
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NU DE AGUME
RESPONSABILIDAD DEL TEXTO
2005 OCT 19 P 12:47
JEFE DE LOCALIZACIONES
SANTAFE DE BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE SANTA
BOGOTA, HAGO CONSTAR QUE LA FIRMA
Diego Vargas
COINCIDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA. 19 OCT 2005


(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
4 November 2004 (04.11.2004)

PCT

(10) International Publication Number
WO 2004/093915 A1

- (51) International Patent Classification⁷: **A61K 47/00, 38/06**

(21) International Application Number: **PCT/US2004/008837**

(22) International Filing Date: **23 March 2004 (23.03.2004)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
60459,765 2 April 2003 (02.04.2003) US

(71) Applicant (for all designated States except US): **BOEHRINGER INGELHEIM INTERNATIONAL, GMBH (DE/DE); Binger Str. 173, 55216 Ingelheim (DE).**

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CHEN, Shih-lynn [US/US]; Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US). MEI, Xiaohui [CN/US]; Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US). WANG, Zeren [US/US]; Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US).**

(74) Agents: **RAYMOND, Robert, P. et al.; Boehringer Ingelheim Corporation, 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US).**
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): **AH, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GH, GI, GM, GR, GU, HK, HN, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.**

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

Published:

 - with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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: **PHARMACEUTICAL COMPOSITIONS FOR HEPATITIS C VIRAL PROTEASE INHIBITORS**

(57) Abstract: Disclosed are pharmaceutical compositions of hepatitis C viral protease inhibitors, and methods of using these compositions for inhibiting the replication of the hepatitis C virus (HCV) and for the treatment of an HCV infection. These compositions are lipid based systems and comprise the hepatitis C viral protease inhibitor together with at least one pharmaceutically acceptable amine, at least one pharmaceutically acceptable base, at least one pharmaceutically acceptable oil and optionally one or more additional ingredients.

WO 2004/093915 A1

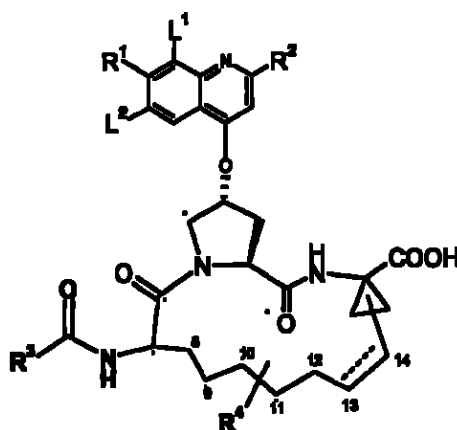
Pharmaceutical Compositions for Hepatitis C Viral Protease Inhibitors

FIELD OF THE INVENTION

- 5 The present invention relates in general to pharmaceutical compositions of hepatitis C viral protease inhibitors, methods of using these compositions for inhibiting the replication of the hepatitis C virus (HCV) and for the treatment of an HCV infection.

BACKGROUND OF THE INVENTION

- 10 It has recently been discovered that certain macrocyclic compounds are potent and specific inhibitors of hepatitis C virus (HCV) protease. In particular, compounds of the following formula I have been found to be an especially potent class of inhibitors against the NS3 serine protease of HCV:



(I)

15

wherein:

— designates an optional bond forming a double bond between positions 13 and 14;

- 20 R^1 is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, hydroxy, or $N(R^5)_2$, wherein each R^5 is independently H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

L^1 , L^2 are each independently H, halogen, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, or $-S-C_{1-4}$ alkyl (the sulfur being in any oxidized state);

R^2 is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{2-7} alkoxyalkyl, C_6 or 10 aryl or Het, wherein Het is a five-, six-, or seven-membered saturated or unsaturated heterocycle containing from one to four ring heteroatoms selected from nitrogen, oxygen and sulfur;

- 5 said cycloalkyl, aryl or Het being optionally substituted with R^6 ,
 wherein R^6 is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, NO_2 , $N(R^7)_2$, $NH-C(O)-R^7$; or $NH-C(O)-NH-R^7$, wherein each R^7 is independently: H, C_{1-6} alkyl or C_{3-6} cycloalkyl;
 or R^6 is $NH-C(O)-OR^8$ wherein R^8 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

10

R^3 is R^9O- or R^9NH- , wherein R^9 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

- R^4 is H or from one to three substituents on any available carbon atom at positions 8,
 15 9, 10, 11, 12, 13 or 14, said substituent independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy, halo, amino, oxo, thio or C_{1-6} thioalkyl;

- See Tsantizos et al., U.S. Application Serial No. 09/760,946, filed on January 16,
 20 2001, now U.S. Patent No. 6,608,027 B1 (Boehringer Ingelheim (Canada), Ltd.), which is herein incorporated by reference in its entirety and is hereinafter referred to as "Tsantizos et al". See also the corresponding WO 00/59929. In addition, see Llinas-Brunet, U.S. Provisional Application No. 60/504,839, filed on September 22, 2003, which is herein incorporated by reference in its entirety and is hereinafter
 25 referred to as "Llinas-Brunet".

- A structural feature of the compounds of formula I is the presence of the C-terminal carboxylic acid functionality, which was shown to be responsible not only for the potency and reversibility observed for this inhibitor series, but also for the excellent
 30 specificity for HCV protease compared to other serine/cysteine proteases. An HCV serine protease inhibitor such as the compounds of formula I would be expected to be an antiviral agent acting via a novel mechanism, i.e. blockage of a virus-encoded essential function for HCV replication. A drug acting through this mechanism should

suppress viral replication of all HCV genotypes and therefore provide tangible benefits to patients with chronic hepatitis C.

5 A common problem among protease inhibitors is that these compounds are lipophilic and have low aqueous solubility. Because of the poor aqueous solubility, conventional solid and liquid pharmaceutical preparations containing these inhibitors may not be absorbed by the patient in a satisfactory manner. Of the various factors that can affect the bioavailability of a drug when administered orally, (which include aqueous solubility, drug absorption through the gastrointestinal tract, dosage strength
10 and first pass effect), aqueous solubility is often found to be among the most important factors. Poorly water soluble compounds often exhibit either erratic or incomplete absorption in the digestive tract, and thus produce a less than desirable response.

15 The compounds of formula I are zwitterionic and are capable of forming salts with strong acids and bases. Attempts to identify salts of such compounds in solid forms, which would substantially improve aqueous solubility, have not been successful. Various salts of these compounds have been found to be very hygroscopic, reducing the stability of the compounds. In addition, formulations of salts of these compounds
20 generally are prone to precipitation of the parent free-acid in the gastrointestinal tract. Representative compounds of formula I have shown poor bioavailability when administered to animals as an aqueous suspension, suggesting that conventional formulations containing these inhibitors may not be absorbed in a satisfactory manner. Thus, there is a need in the art for pharmaceutical compositions of the formula I
25 compounds having improved bioavailability.

Methods of formulating certain lipophilic macrocyclic compounds into pharmaceutical formulations have been previously reported. For example, Cavanak, U.S. Pat. No. 4,388,307, discloses the preparation of emulsified formulations of
30 commercially available cyclosporins, and Hauer et al, U.S. Pat. Nos. 5,342,625, and Meizner et al. WO 93/20833 disclose the preparation of cyclosporin microemulsions and microemulsion pre-concentrates. Komiya et. al, U.S. Pat. Nos. 5,504,068, further discloses the preparation of an enhanced topical formulations of cyclosporin.

Examples of "self-emulsifying" formulations of lipophilic compounds include Lipari et al, WO 96/36316, which discloses a self-emulsifying pre-concentrate comprising a lipophilic compound, d-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS) and a lipophilic phase. Gao et al., U.S. Pat. Nos. 6,121,313 discloses a self-emulsifying formulation of a pyranone protease inhibitor comprising the pyranone compound, a mixture of mono- and di-glycerides, one or more solvents and one or more surfactants; and Gao et al, U.S. Pat. No. 6,231,887 B1 discloses a self-emulsifying formulation of a pyranone protease inhibitor comprising the pyranone compound, an amine, one or more solvents and one or more surfactants.

Yu et al U.S. Pat. Nos. 5,360,615 and 5,071,643 disclose the preparation of a solvent system for enhancing the solubility of acidic, basic or amphoteric compounds by partial ionization comprising a mixture of polyethylene glycol, hydroxide or hydrogen ion, and water. Morton et al U.S. Pat. No. 5,376,688 discloses solutions of acidic, basic or amphoteric pharmaceutical agents comprising the pharmaceutical agent, an ionic species and a solvent system. Bhagwat et. al U.S. Pat. Nos. 6,056,977 teaches the use of polysaccharide based matrix for sustained release of a sulfonylurea.

A self-emulsifying drug delivery system (SEDDS) having improved bioavailability has recently been developed for the compounds of formula (I), as described in U.S. Application No. 10/357,919 (S. Chen et al.), filed February 4, 2003, and in PCT/US03/03380 (Boehringer Ingelheim Pharmaceuticals, Inc.), filed February 5, 2003, published as WO 03/066103 A1. This formulation comprises a compound of formula (I), about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a mixture of pharmaceutically acceptable amines, one or more pharmaceutically acceptable oils, optionally one or more pharmaceutically acceptable hydrophilic solvents, optionally one or more pharmaceutically acceptable polymers, and optionally one or more pharmaceutically acceptable surfactants. However, it has been found that this formulation may not be fully optimized with respect to its chemical stability and therefore may require storage under refrigerated conditions.

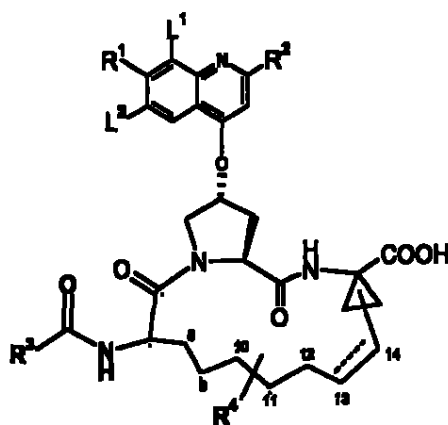
BRIEF SUMMARY OF THE INVENTION

The present invention overcomes the aforementioned problems by providing pharmaceutical compositions of the formula I compounds having acceptable bioavailability and also improved chemical stability as compared to the previous SEDDS formulation.

The pharmaceutical compositions of the present invention all comprise a compound of formula I together with one or more pharmaceutically acceptable amines, bases and oils. The compositions of the present invention may optionally include one or more additional ingredients, e.g., pharmaceutically acceptable solvents, surfactants, polymers, etc., as will be discussed in more detail below. The present invention is also directed to the methods of manufacturing these compositions, as described hereinafter.

In a general embodiment, the pharmaceutical composition of the present invention comprises:

(a) a compound of formula (I):



(I)

20

wherein:

— designates an optional bond forming a double bond between positions 13 and 14;

R¹ is H, halo, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆

cycloalkoxy, hydroxy, or $N(R^5)_2$, wherein each R^5 is independently H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

L^1, L^2 are each independently H, halogen, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, or $-S-C_{1-4}$ alkyl (the
5 sulfur being in any oxidized state);

R^2 is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{2-7} alkoxyalkyl, C_6 or 10 aryl or Het, wherein Het is a five-, six-, or seven-membered saturated or unsaturated heterocycle containing from one to four
10 ring heteroatoms selected from nitrogen, oxygen and sulfur;
said cycloalkyl, aryl or Het being optionally substituted with R^6 ,
wherein R^6 is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, NO_2 , $N(R^7)_2$, $NH-C(O)-R^7$; or $NH-C(O)-NH-R^7$, wherein each R^7 is independently: H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

15 or R^6 is $NH-C(O)-OR^8$ wherein R^8 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^3 is R^9O- or R^9NH- , wherein R^9 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^4 is H or from one to three substituents on any available carbon atom at positions 8,
20 9, 10, 11, 12, 13 or 14, said substituent independently selected from the group
consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy, halo, amino, oxo, thio
or C_{1-6} thioalkyl;
or a tautomer thereof;

- (b) about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a
25 mixture of pharmaceutically acceptable amines;
 - (c) about 0.1 to 10% by weight of a pharmaceutically acceptable base or a mixture
of pharmaceutically acceptable bases;
 - (d) one or more pharmaceutically acceptable oils;
 - 30 (e) optionally one or more pharmaceutically acceptable hydrophilic solvents;
 - (f) optionally one or more pharmaceutically acceptable polymers;
- and

(g) optionally one or more pharmaceutically acceptable surfactants;

Another important aspect of the present invention involves a method of inhibiting the
5 replication of hepatitis C virus by exposing the virus to a hepatitis C viral NS3
protease-inhibiting amount of a pharmaceutical composition of the present invention.

Another important aspect of the present invention involves a method of treating a
hepatitis C viral infection in a mammal by administering to the mammal in need
10 thereof a therapeutically effective amount of a pharmaceutical composition of the
present invention.

The present invention is also directed to the use of a composition as described above
for the preparation of a medicament for the treatment of hepatitis C viral infection.
15

BRIEF DESCRIPTION OF THE DRAWINGS

20 Figure 1 shows the impurity profile of a formulation according to the present
invention containing tromethamine and sodium hydroxide and a comparative
formulation without sodium hydroxide.

Figure 2 shows the impurity profile of a second formulation according to the present
25 invention containing tromethamine and sodium hydroxide and a comparative
formulation without sodium hydroxide.

30 **DETAILED DESCRIPTION OF THE INVENTION**

Definition of Terms and Conventions Used

Terms not specifically defined herein should be given the meanings that would be
given to them by one of skill in the art in light of the disclosure and the context. As

used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

A. Chemical and Pharmaceutical Nomenclature, Terms, and Conventions

5 In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C₁₋₆ alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named group is the radical attachment point, for example, "thioalkyl" means a monovalent radical of the formula HS-Alk-. Unless otherwise
10 specified below, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups.

The term "C₁₋₆ alkyl" as used herein, either alone or in combination with another substituent, means acyclic, straight or branched chain alkyl substituents containing
15 from 1 to six carbon atoms and includes, for example, methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, and 1,1-dimethylethyl.

The term "C₃₋₆ cycloalkyl" as used herein, either alone or in combination with another substituent, means a cycloalkyl substituent containing from three to six carbon atoms
20 and includes cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "C₁₋₆ alkoxy" as used herein, either alone or in combination with another substituent, means the substituent C₁₋₆ alkyl-O- wherein alkyl is as defined above containing up to six carbon atoms. Alkoxy includes methoxy, ethoxy, propoxy, 1-
25 methylethoxy, butoxy and 1,1-dimethylethoxy. The latter substituent is known commonly as *tert*-butoxy.

The term "C₃₋₆ cycloalkoxy" as used herein, either alone or in combination with another substituent, means the substituent C₃₋₆ cycloalkyl-O- containing from 3 to 6
30 carbon atoms.

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

The term "haloalkyl" as used herein means as used herein, either alone or in combination with another substituent, means acyclic, straight or branched chain alkyl substituents having one or more hydrogens substituted for a halogen selected from
5 bromo, chloro, fluoro or iodo.

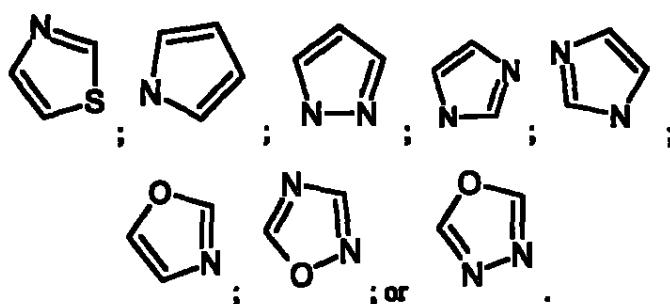
The term "thioalkyl" as used herein means as used herein, either alone or in combination with another substituent, means acyclic, straight or branched chain alkyl substituents containing a thiol (HS) group as a substituent. An example of a thioalkyl
10 group is a thiopropyl, e.g., HS-CH₂CH₂CH₂- is one example of a thiopropyl group.

The term "C₆ or C₁₀ aryl" as used herein, either alone or in combination with another substituent, means either an aromatic monocyclic system containing 6 carbon atoms or an aromatic bicyclic system containing 10 carbon atoms. For example, aryl
15 includes a phenyl or a naphthyl - ring system.

The term "Het" as used herein, either alone or in combination with another substituent, means a monovalent substituent derived by removal of a hydrogen from a five-, six-, or seven-membered saturated or unsaturated (including aromatic)
20 heterocycle containing carbon atoms and from one to four ring heteroatoms selected from nitrogen, oxygen and sulfur. Examples of suitable heterocycles include: tetrahydrofuran, thiophene, diazepine, isoxazole, piperidine, dioxane, morpholine, pyrimidine or



The term "Het" also includes a heterocycle as defined above fused to one or more other cycle be it a heterocycle or any other cycle. One such examples includes triazolo[4,5-b]-pyridine. Although generally covered under the term "Het", the term
25 "heteroaryl" as used herein precisely defines an unsaturated heterocycle for which the double bonds form an aromatic system. Suitable examples of heteroaromatic system
30 include: quinoline, indole, pyridine,



5 The term "oxo" means the double-bonded group (=O) attached as a substituent.

The term "thio" means the double-bonded group (=S) attached as a substituent.

The term "compounds of the invention", and equivalent expressions, are meant to
 10 embrace compounds of Formula (I) as herein described, including the tautomers and
 isomers thereof, where the context so permits. In general, the compounds of the
 invention and the formulas designating the compounds of the invention are
 understood to only include the stable compounds thereof and exclude unstable
 compounds, even if an unstable compound might be considered to be literally
 15 embraced by the compound formula.

The term "stable compound" means a compound that is sufficiently robust to survive
 isolation to a useful degree of purity from a reaction mixture and formulation into an
 efficacious pharmaceutical composition. For example, a compound which would
 20 have a "dangling valency" or is a "carbanion" is not a compound contemplated by the
 invention.

The term "pharmaceutical composition of the invention" and equivalent expressions is
 meant to embrace all the various types of pharmaceutical compositions as described
 25 hereinafter, unless it is clear from the context that reference is being made to a
 particular type of pharmaceutical composition within the scope of the present
 invention.

The term "pharmaceutically acceptable" with respect to a substance as used herein means that substance 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, and effective for the intended use when the substance is used in a pharmaceutical composition.

10 The term "semi-solid" means a material that is neither solid (elastic behavior) nor liquid (viscous behavior) and possesses the characteristics of both viscosity and elasticity. Examples of semi-solid materials include gels, ointments, creams, and highly viscous liquids.

15 The term "about" means within 20%, preferably within 10%, and more preferably within 5% of a given value or range. For example, "about 10%" means from 8% to 12%, preferably from 9% to 11%, and more preferably from 9.5% to 10.5%. When the term "about" is associated with a range of values, e.g., "about X to Y %", the term "about" is intended to modify both the lower (X) and upper (Y) values of the recited range. For example, "about 0.1 to 10%" is equivalent to "about 0.1% to about 10%".

All percentages recited for amounts of ingredients in the compositions are percentages by weight with respect to the whole composition.

25 **B. Isomer Terms and Conventions**

The terms "isomers" or "stereoisomers" mean compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the arrangement or configuration of the atoms in space. The term includes optical isomers and geometric isomers.

The term "optical isomer" means a stable isomer that has at least one chiral atom or restricted rotation giving rise to perpendicular dissymmetric planes (e.g., certain biphenyls, allenes, and spiro compounds) and can rotate plane-polarized light.

Because asymmetric centers and other chemical structure exist in the compounds of formula I which may give rise to optical isomerism, the invention contemplates optical isomers and mixtures thereof. The compounds of formula I include asymmetric carbon atoms and may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. Typically, such compounds will be prepared as a racemic mixture. If desired, however, such compounds can be prepared or isolated as pure optical isomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. Individual stereoisomers of compounds are prepared by synthesis from optically active starting materials containing the desired chiral centers or by preparation of mixtures of enantiomeric products followed by separation, such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, use of chiral resolving agents, or direct separation of the enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or are made by the methods described below and resolved by techniques well-known in the art.

The term "enantiomers" means a pair of optical isomers that are non-superimposable mirror images of each other.

The term "diastereoisomers" means optical isomers which are not mirror images of each other.

The term "racemic mixture" means a mixture containing equal parts of individual enantiomers.

The term "non-racemic mixture" means a mixture containing unequal parts of individual enantiomers or stereoisomers.

The term "geometrical isomer" means a stable isomer which results from restricted freedom of rotation about double bonds (e.g., *cis*-2-butene and *trans*-2-butene) or in a cyclic structure (e.g., *cis*-1,3-dichlorocyclobutane and *trans*-1,3-dichlorocyclobutane). Because carbon-carbon double (olefinic) bonds, cyclic structures, and the like may be

present in the compounds of formula I, the invention contemplates each of the various stable geometric isomers and mixtures thereof resulting from the arrangement of substituents around these double bonds and in these cyclic structures. The substituents and the isomers are designated using the *cis/trans* convention.

5

Some of the compounds of formula I can exist in more than one tautomeric form. As mentioned above, the compounds of formula I include all such tautomers.

In general, all tautomeric forms and isomeric forms and mixtures thereof, for example, individual geometric isomers, stereoisomers, optical isomers or racemic or non-racemic mixtures of isomers, of a chemical structure or compound is intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure.

15 C. Pharmaceutical Administration and Treatment Terms and Conventions

The term "patient" includes both human and non-human mammals.

The term "therapeutically effective amount" means an amount of a compound according to the invention which, when administered to a patient in need thereof, is sufficient to effect treatment of a hepatitis C viral infection. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the prior art, and this disclosure.

The terms "treating" or "treatment" mean the treatment of a hepatitis C viral infection in a patient, and include:

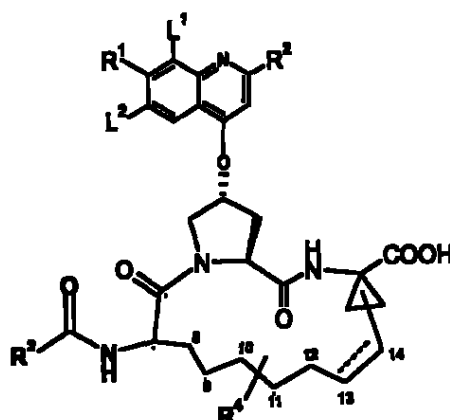
- (i) preventing the hepatitis C viral infection from occurring in a patient, in particular, when such patient is predisposed to such disease-state but has not yet been diagnosed as having it;
- (ii) inhibiting or ameliorating the hepatitis C viral infection, i.e., arresting or slowing its development; or
- (iii) relieving the hepatitis C viral infection, i.e., causing regression or cure of the disease-state.

Preferred Embodiments of the Invention

The preferred embodiment which we refer to herein as the "Lipid-Based System" is directed to a pharmaceutical composition comprising:

5

(a) a compound of formula (I):



(I)

10 wherein:

— designates an optional bond forming a double bond between positions 13 and 14;

R¹ is H, halo, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, hydroxy, or N(R⁵)₂, wherein each R⁵ is independently H, C₁₋₆ alkyl or

15 C₃₋₆ cycloalkyl;

L¹, L² are each independently H, halogen, C₁₋₄ alkyl, -O-C₁₋₄ alkyl, or -S-C₁₋₄ alkyl (the sulfur being in any oxidized state);

20

R² is H, halo, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ thioalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, C₂₋₇ alkoxyalkyl, C₆ or ₁₀ aryl or Het, wherein Het is a five-, six-, or seven-membered saturated or unsaturated heterocycle containing from one to four ring heteroatoms selected from nitrogen, oxygen and sulfur;

25 said cycloalkyl, aryl or Het being optionally substituted with R⁶,

wherein R^6 is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, NO_2 , $N(R^7)_2$, $NH-C(O)-R^7$, or $NH-C(O)-NH-R^7$, wherein each R^7 is independently: H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

or R^6 is $NH-C(O)-OR^8$ wherein R^8 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

5

R^3 is R^9O- or R^9NH- , wherein R^9 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^4 is H or from one to three substituents on any available carbon atom at positions 8,
10 9, 10, 11, 12, 13 or 14, said substituent independently selected from the group
consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy, halo, amino, oxo, thio
or C_{1-6} thioalkyl;

or a tautomer thereof;

15

(b) about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a
mixture of pharmaceutically acceptable amines;

(c) about 0.1 to 10% by weight of a pharmaceutically acceptable base or a mixture
20 of pharmaceutically acceptable bases;

(d) one or more pharmaceutically acceptable oils;

(e) optionally one or more pharmaceutically acceptable hydrophilic solvents;

25

(f) optionally one or more pharmaceutically acceptable polymers;

and

(g) optionally one or more pharmaceutically acceptable surfactants.

30

The amount of the active ingredient (formula (I) compound) that may be present in
the lipid-based system composition may vary widely or be adjusted widely depending
on the intended route of administration, the potency of the particular active ingredient

being used, the severity of the hepatitis C viral infection and the required concentration. In a particular embodiment, the compound of formula (I) is present in the lipid-based system in an amount of from about 1% to 50% by weight, preferably from about 5% to 30% by weight, more preferably from about 10% to 20% by weight.

5

Pharmaceutically acceptable amines useful in the composition include, for example, C₁₋₆ alkylamine, di-(C₁₋₆ alkyl)-amine or tri-(C₁₋₆ alkyl)-amine, wherein one or more alkyl groups thereof may be optionally substituted by one or more hydroxy groups, or C₁₋₆ alkylenediamine, a basic amino acid or choline hydroxide, or mixtures thereof.

10 Specific amines include ethanolamine, diethanolamine, triethanolamine, tris(hydroxymethyl)aminomethane, ethylenediamine, dimethylaminoethanol, or meglumine, or mixtures thereof. A preferred amine is tris(hydroxymethyl)aminomethane (also called "Tris" or "Tromethamine"). The amine is present in an amount of about 0.1 to 10% by weight, more preferably in an amount of from about 0.5% to 7% by weight; even more preferably from about 0.5%
15 to 5% by weight.

Pharmaceutically acceptable bases useful in the composition include, for example, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum
20 hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum hydroxide. Also suitable are bases which are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginate, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty
25 acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and
30 sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Preferred cations include sodium, potassium, lithium, magnesium, calcium and ammonium. Some preferred bases

include sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, magnesium hydroxide, magnesium aluminum hydroxide. The pharmaceutically acceptable base is present in the composition in an amount of from about 0.1 to 10% by weight, for example about 0.1 to 5% by weight, for example
5 about 0.1 to 3% by weight.

Pharmaceutically acceptable oils useful in the composition includes a broad spectrum of water-immiscible materials such as, for example, medium or long chain mono-, di- or triglycerides, vegetable oils such as soybean oil, avocado oil, squalene oil, sesame
10 oil, olive oil, canola oil, corn oil, rapeseed oil, safflower oil, and sunflower oil, fish oils, flavored oils, water insoluble vitamins, fatty acids, and mixtures thereof. More preferred oils include mono-, di- or triglycerides of caprylic fatty acids; mono-, di- or triglycerides of capric fatty acids; oleic acid, and mixtures thereof. Some preferred oils include those commercially available under the trade names: Capmul MCM,
15 Capmul MCM C-8, Capmul MCM C-10, Capmul PG-8, Miglyol 810, Captex 355, Miglyol 812, Captex 200, Myvacet, Myverol 18-92, Maisine, and Ariacel 186. The amount of oil(s) in the composition may vary over a wide range and the optimum amount for a particular composition will depend on the type and amount of other the other ingredients in the composition as can be determined by the skilled
20 pharmaceutical technician. In general, however, the pharmaceutically acceptable oil is present in an amount of from about 1% to 99% by weight, more preferably in an amount of from about 20% to 70% by weight.

In certain circumstances, e.g. for the purpose of increasing solubility, improving
25 dispersability, pharmaceutically acceptable hydrophilic solvents can optionally be used in the composition, which include, for example, propylene glycol, polypropylene glycol, polyethylene glycol (e.g., PEG 400), glycerol, ethanol, dimethyl isosorbide, glycofurol, propylene carbonate, dimethyl acetamide, water, or mixtures thereof; preferably, propylene glycol, polyethylene glycol, ethanol, water, or mixtures thereof.
30 A preferred solvent is a mixture of propylene glycol, ethanol and water. The amount of solvent in the composition may vary over a wide range and the optimum amount for a particular composition will depend on the type and amount of other the other ingredients in the composition as can be easily determined by the skilled worker. In

general, however, the solvent(s) are present in an amount of up to about 70% by weight, preferably from about 10% to 30% by weight.

To adjust the viscosity of the formulations or to improve stability, pharmaceutically acceptable polymers can optionally be used in the composition, which include, for example, polyethylene glycols (e.g., PEG 1000, PEG 1500, PEG 3350, PEG 6000 and PEG 8000), polyvinylpyrrolidones (e.g., Kollidon 12 PF, Kollidon 17 PF, Kollidon 25 PF, Kollidon 30 PF, Kollidon 90 PF etc.), polyvinylalcohols, cellulose derivatives (e.g., hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC)), polyacrylates, polymethacrylates, sugars (e.g., lactose), polyols, and mixtures thereof. When used in the composition, the pharmaceutically acceptable polymer is preferably be present in an amount up to about 50% by weight, preferably about 1 to 20% by weight.

To facilitate self-emulsification, pharmaceutically acceptable surfactants can optionally be used in the composition, which include, for example, vitamin derivatives such as Vitamin E TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate), polyoxyl castor oils (e.g., Cremophor EL), polyoxyl hydrogenated castor oils, polysorbates (e.g., Tween 80), peglicol 6-oleate, polyoxyethylene stearates, polyglycolized glycerides (e.g., Gelucire 44/14) or poloxamers (e.g., Pluronic F68), sodium lauryl sulfate and mixtures thereof. Preferred surfactants include Vitamin E TPGS, polyoxyl 40 hydrogenated castor oil or polyoxyl 35 castor oil, and mixtures thereof.

When used in the composition, the surfactant is preferably present in an amount of up to about 70% by weight, preferably from about 20% to 50% by weight. This type of lipid-based system of the present invention further incorporating a surfactant is generally referred to herein as "self-emulsifying drug delivery system" or "SEDDS".

A particular embodiment of the SEDDS composition according to the present invention is directed to a pharmaceutical composition, comprising:

- (a) about 5% to 30% by weight of a compound of formula (I);
- (b) about 0.1% to 7% by weight of a pharmaceutically acceptable amine;

- (c) about 0.1% to 5% by weight of a pharmaceutically acceptable base;
- (d) about 1% to 99% by weight of a pharmaceutically acceptable oil;
- (e) up to about 70% by weight of a pharmaceutically acceptable hydrophilic solvent;
- 5 (f) optionally up to about 50% by weight of a pharmaceutically acceptable polymer; and
- (g) up to about 70% by weight of a pharmaceutically acceptable surfactant.

A further particular embodiment of the SEDDS composition according to the present invention is directed to a pharmaceutical composition, comprising:

- (a) about 10% to 20% by weight of a compound of formula (I);
- (b) about 0.1% to 5% by weight of a pharmaceutically acceptable amine;
- (c) about 0.1% to 3% by weight of a pharmaceutically acceptable base;
- (d) about 20% to 70% by weight of a pharmaceutically acceptable oil;
- 15 (e) about 10% to 30% by weight of a pharmaceutically acceptable hydrophilic solvent;
- (f) optionally about 1% to 20% by weight of a pharmaceutically acceptable polymer; and
- (g) about 20% to 50% by weight of a pharmaceutically acceptable surfactant.
- 20

A further particular embodiment of the SEDDS composition according to the present invention is directed to a pharmaceutical composition, comprising:

- 25 (a) about 10% to 20% by weight of a compound of formula (I);
- (b) about 0.1% to 5% by weight of tris(hydroxymethyl)aminomethane;
- (c) about 0.1% to 3% by weight of sodium hydroxide;
- (d) about 20% to 70% by weight of a triglyceride of caprylic fatty acid or a triglyceride of capric fatty acid, or mixtures thereof;
- 30 (e) about 10% to 30% by weight of a mixture of propylene glycol, ethanol and optionally water;
- (f) optionally about 1% to 20% by weight of polyethylene glycol or polyvinylpyrrolidone; and

- (g) about 20% to 50% by weight of d-alpha tocopheryl polyethylene glycol 1000 succinate or polyoxyl 35 castor oil (Cremophor EL).

A further particular embodiment of the SEDDS composition according to the present invention is directed to a pharmaceutical composition, comprising:

- (a) about 10% to 15% by weight of a compound of formula (I);
- (b) about 0.1% to 2% by weight of tris(hydroxymethyl)aminomethane;
- (c) about 0.1% to 1% by weight of sodium hydroxide;
- (d) about 20% to 30% by weight of Capmul MCM or Captex 355;
- (e) about 15% to 25% by weight of a mixture of propylene glycol, ethanol and water, and
- (f) about 40% to 50% by weight of d-alpha tocopheryl polyethylene glycol 1000 succinate; and
- (g) about 0.01% to 1% of dl-alpha-tocopherol.

The Lipid-Based System composition may be prepared in a conventional manner, for example, by a method comprising: mixing together the liquid components, e.g., the pharmaceutically acceptable oil(s), and any surfactant(s) and solvent(s); dissolving the pharmaceutically acceptable amine(s), base(s) and polymer(s) in the resulting mixture; optionally heating the mixture obtained if necessary to sufficiently melt one or more of the components of the mixture; adding the compound of formula (I) to the resulting mixture and further mixing until all or substantially all of the compound of formula I is solubilized. This method of preparing the composition constitutes another aspect of the present invention. The resulting solution is then optionally formulated into the desired dosage form, for example, capsules, including hard shell or softgel capsules (e.g., hard or soft gelatin capsules), by known manufacturing technology. The composition may also be in the form of a liquid solution or semi-solid for oral, parenteral, rectal or topical administration. Examples of soft gelatin capsules that can be used include those disclosed in EP 649651 B1 and US Patent 5,985,321.

Optional Additional Ingredients

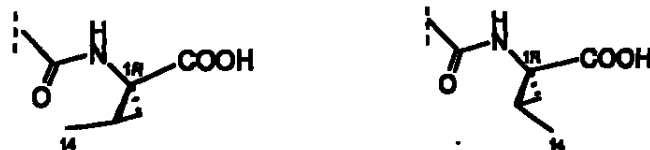
If desired, the compositions according to the present invention may further include conventional pharmaceutical additives as is necessary or desirable to obtain a suitable formulation, such as antioxidants, lubricants, disintegrants, preservatives, buffers, stabilizers, thickening agents, coloring agents, flavoring agents, fragrances, etc. Additional additives that may be useful in the compositions of the invention are disclosed in Tsantrizos et al.

In one preferred embodiment, the compositions according to the present invention further contain one or more antioxidants. Preferred antioxidants include, for example, ascorbic acid, sulfatide salts, citric acid, propyl gallate, dl- α -tocopherol, ascorbyl palmitate, BHT or BHA. If present, the antioxidant is generally present in an amount of from about 0.01% to 1% by weight.

Compounds of Formula (I)

Preferred embodiments for the compounds of formula (I) in the compositions are as set forth below.

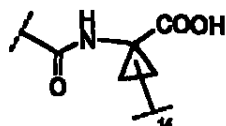
Preferred embodiments include compounds of formula I as described above, wherein the cyclopropyl moiety is selected from the 2 different diastereoisomers where the 1-carbon center of the cyclopropyl has the *R* configuration as represented by structures (i) and (ii):



14 syn to the amide (i), or 14 syn to the COOH (ii).

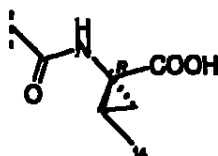
More preferably, position 14 is linked to cyclopropyl group in the configuration *syn* to the COOH group as represented by structure (ii).

Thus, in one embodiment, in the compound of formula (I) the following moiety:



has the configuration represented by the following diastereoisomer:

5



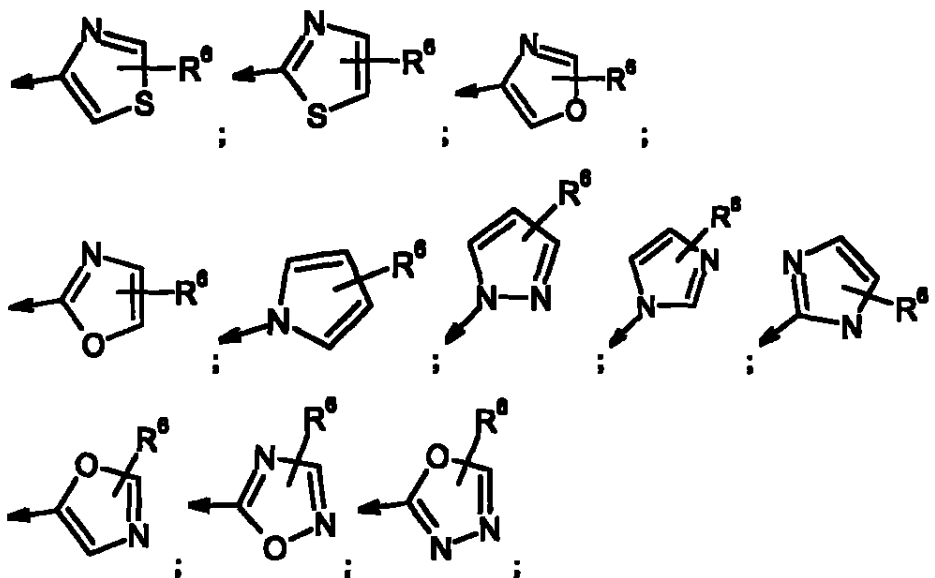
in which configuration position 14 is linked *syn* to the COOH group.

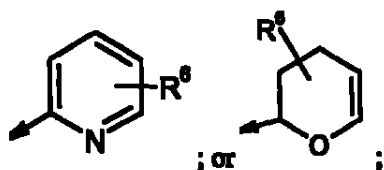
In another embodiment, in the compound of formula (I):

- 10 R^1 is H, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, chloro, or $N(R^5)_2$, wherein R^5 is H or C_{1-6} alkyl;

L^1 and L^2 are each H; and

- 15 R^2 is H, C_{1-6} thioalkyl, C_{1-6} alkoxy, phenyl or Het selected from the following:





wherein R^6 is H, C_{1-6} alkyl, $NH-R^7$, $NH-C(O)-R^7$, $NH-C(O)-NH-R^7$,
 wherein each R^7 is independently: H, C_{1-6} alkyl, or C_{3-6} cycloalkyl;
 or $NH-C(O)-OR^8$, wherein R^8 is C_{1-6} alkyl.

5

In another embodiment, in the compounds of formula (I):

L^1 and L^2 are each H.

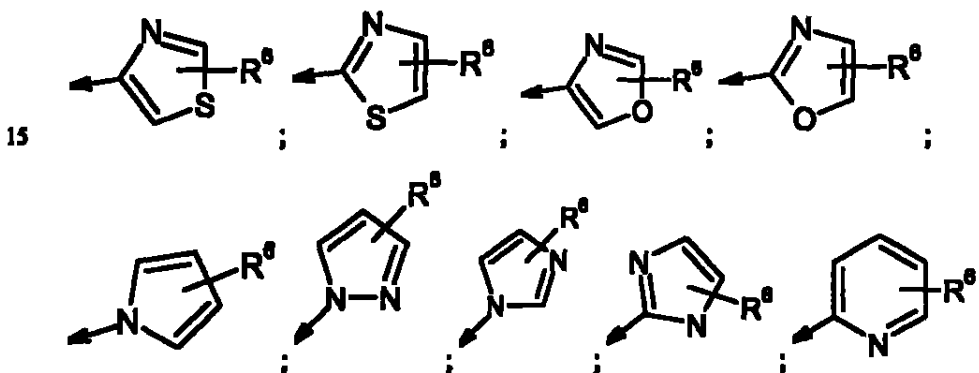
In another embodiment, in the compound of formula (I):

10

R^1 is H or C_{1-6} alkoxy.

In another embodiment, in the compound of formula (I):

R^2 is C_{1-4} alkoxy, phenyl or Het selected from the following groups:



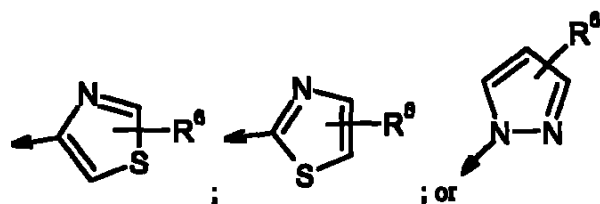
15

wherein R^6 is H, C_{1-6} alkyl, $NH-R^7$, or $NH-C(O)-R^7$;
 wherein each R^7 is H, C_{1-6} alkyl or C_{3-6} cycloalkyl,
 or $NH-C(O)-OR^8$, wherein R^8 is C_{1-6} alkyl.

20

In another embodiment, in the compound of formula (I):

R^2 is ethoxy, or Het selected from the following groups:

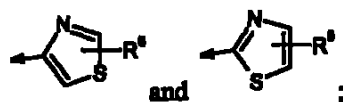
48
48

wherein R^6 is NHR^7 or $NH-C(O)-R^7$, wherein R^7 is H, C_{1-6} alkyl or C_{3-6} cycloalkyl;
or R^6 is $NH-C(O)-OR^8$, wherein R^8 is C_{1-6} alkyl.

5

In another embodiment, in the compound of formula (I):

R^2 is selected from the following groups:



10 R^6 is NHR^7 , wherein each R^7 is independently: H, C_{1-6} alkyl, or C_{3-6} cycloalkyl.

In another embodiment, in the compound of formula (I):

R^3 is R^9O- , wherein R^9 is butyl, cyclobutyl or cyclopentyl.

15

In another embodiment, in the compound of formula (I):

the bond at position 13-14 is a single bond.

20 In another embodiment, in the compound of formula (I):

the bond at position 13-14 is a double bond and said double bond is *cis*.

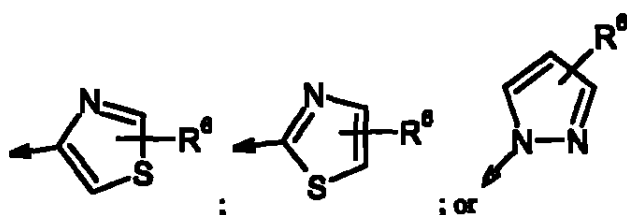
In another embodiment, in the compound of formula (I):

R^4 is H or C_{1-6} alkyl.

25

In another embodiment, in the compound of formula (I):

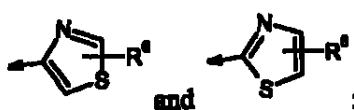
R^1 is methoxy;

48
40

wherein R^6 is NHR^7 or $NH-C(O)-R^7$, wherein R^7 is H, C_{1-6} alkyl or C_{3-6} cycloalkyl;
or R^6 is $NH-C(O)-OR^8$, wherein R^8 is C_{1-6} alkyl.

5

In another embodiment, in the compound of formula (I):
 R^2 is selected from the following groups:



10 R^6 is NHR^7 , wherein each R^7 is independently: H, C_{1-6} alkyl, or C_{3-6} cycloalkyl.

In another embodiment, in the compound of formula (I):
 R^3 is R^9O- , wherein R^9 is butyl, cyclobutyl or cyclopentyl.

15

In another embodiment, in the compound of formula (I):
the bond at position 13-14 is a single bond.

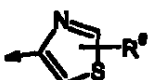
20 In another embodiment, in the compound of formula (I):
the bond at position 13-14 is a double bond and said double bond is *cis*.

In another embodiment, in the compound of formula (I):
 R^4 is H or C_{1-6} alkyl.

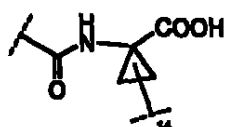
25

In another embodiment, in the compound of formula (I):
 R^1 is methoxy;

L^1 and L^2 are each H;

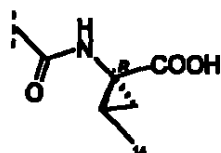
R^2 is  wherein R^6 is $NH-(C_{1-4}alkyl)$ or $NH-(C_{3-6}cycloalkyl)$;

- 5 R^3 is R^9O- , wherein R^9 is butyl, cyclobutyl or cyclopentyl;
 R^4 is H or $C_{1-6}alkyl$;
 and following moiety:



10

has the configuration represented by the following diastereoisomer:



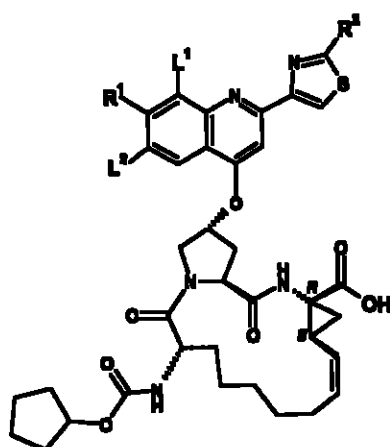
in which configuration position 14 is linked *syn* to the $COOH$ group.

15

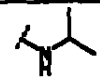
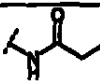
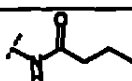
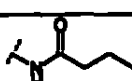
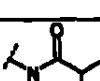
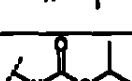
Tables of Compounds

The following tables list compounds representative of the compounds of formula (I).

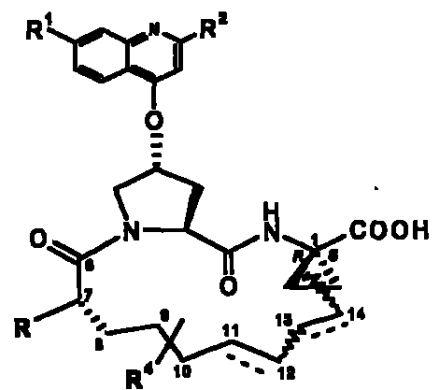
20 Table 1:



Cpd #	L ¹	R ¹	L ¹	R ¹	MS (M+H) ⁺
101	H	-OMe	Me		789.4
102	H	-OMe	Me		789.3
103	H	-OMe	Me		817.4
104	H	-OMe	Me		803.4
105	H	-OMe	Br		867.3 869.3
106	H	-OMe	Br		853.3 855.3
107	H	-OMe	Cl		809.3 811.3
108	H	-OMe	Cl		823.3 825.3
109	Me	-OMe	Me		803.4
110	Me	-OMe	Me		817.4

Cpd #	L ¹	R ¹	L ¹	R ¹	MS (M+H) ⁺
111	H	-OMe	F		793.4
112	H	-OMe	F		807.3
113	H	-OMe	Cl		837.3 839.2
114	H	-OMe	Br		881.2 883.2
115	H	-OMe	Br		881.2 883.2
116	H	-OMe	Br		897.2 899.2

5 **Table 2:**



directed to a single stereoisomer at the cyclopropyl moiety, wherein R, R⁴, said
double bond position, cyclopropyl group to 14-position bond stereochemistry, and R¹
10 and R² are defined as follows:

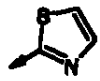
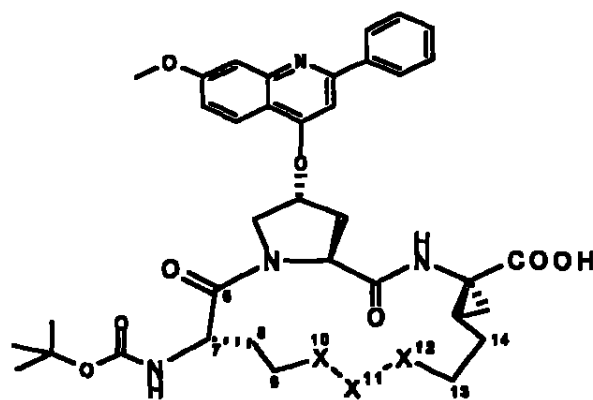
Cpd #	R:	R':	double bond:	cyclopropyl to 14-position bond stereochemistry:	R ¹ :	R ² :
205	NH-Boc	11-OH 12-OH cis	none	1R or 1S, 14 is syn to acid	H	H;
206	NH-Boc	H	13,14- cis	1R, 14 is syn to acid	H	H;
207	NH-Boc	H	13,14- cis	1R, 14 is syn to acid	OMe	H;
208	NH-Boc	H	13,14- cis	1R, 14 is syn to acid	OMe	phenyl;
209	NH-C(O)- NH-tBu	H	13,14- cis	1R, 14 is syn to acid	OMe	phenyl;
210	NH-Boc	H	13,14- cis	1S, 14 is syn to acid	OMe	phenyl;
214	NH-Boc	10-oxo	13,14- cis	1R, 14 is syn to acid	OMe	phenyl;
215	NH-Boc	H	none	1R, 14 is syn to acid	OMe	phenyl;
217	NH-Boc	10-OH (mixt dia stereo)	13,14- cis	1R, 14 is syn to acid	OMe	phenyl;
218	NH-Boc	10-oxo	13,14- cis	1R, 14 is syn to amide	OMe	phenyl;
And 220	NH-Boc	H	13,14- cis	1R, 14 is syn to amide	OMe	

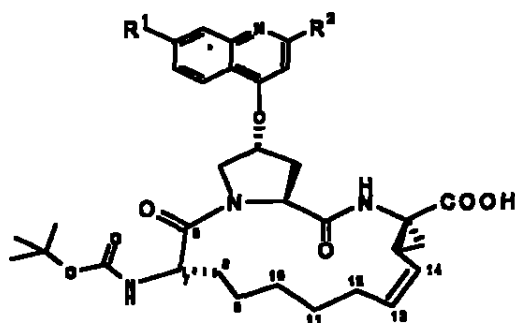
Table 3:



wherein the bond from position 14 to the cyclopropyl group is *syn* to the COOH, X₁₀, X₁₁, and X₁₂ are defined as follows:

Cpd #	X ₁₀ :	X ₁₁ :	X ₁₂ :
502	CH ₂	CH ₂	CH ₂

5 **Table 4:**



wherein the bond from position 14 to the cyclopropyl group is *syn* to the COOH, and

10 R¹ and R² are defined as follows:

Cpd #	R ¹ :	R ² :
601	N(Me) ₂	

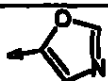
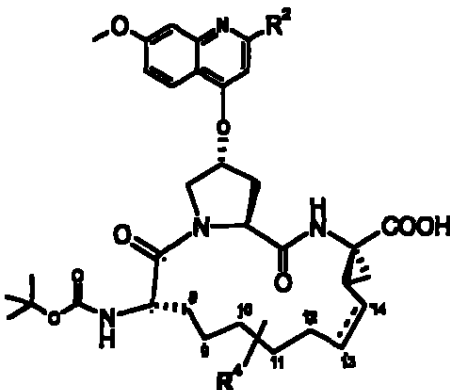
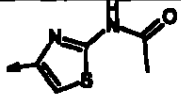
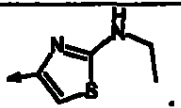
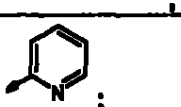
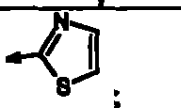
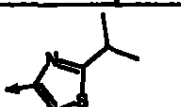
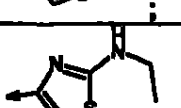
Cpd #	R ¹ :	R ² :
602	OH	(CF ₃) ₂
and 603	OMe	

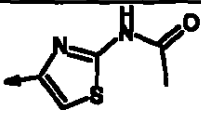
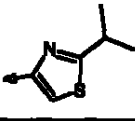
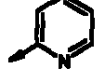
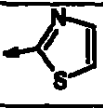
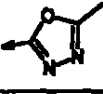
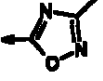
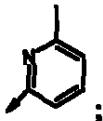
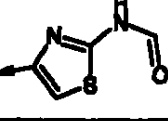
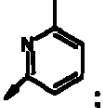
Table 5:

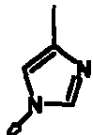
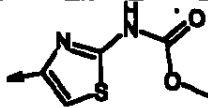
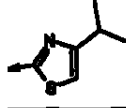
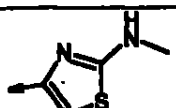
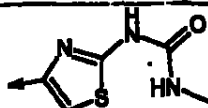
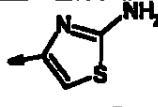
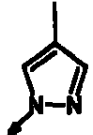


5

wherein the bond from position 14 to the cyclopropyl group is *syn* to the COOH, and R⁴, the 13,14 double bond and R² are defined as follows:

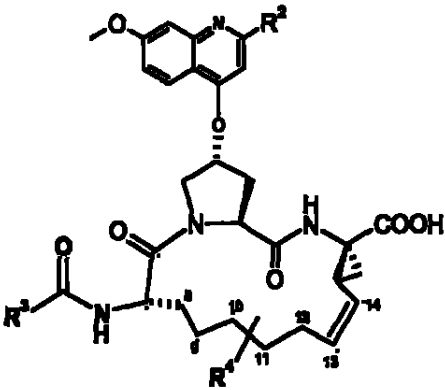
Cpd #	R ⁴ :	13,14 double bond:	R ² :
702	H	Cis	
703	H	None	
704	H	Cis	
705	H	Cis	
707	H	Cis	
708	H	Cis	

Cpd #	R ¹ :	13,14 double bond:	R ² :
709	H	None	
710	H	None	
711	H	None	
712	H	Cis	-OEt;
713	H	None	
714	H	None	-OEt;
715	H	Cis	
716	H	Cis	
717	H	Cis	
718	H	Cis	
719	H	Cis	
720	H	None	
721	H	None	

Cpd #	R ¹ :	13,14 double bond:	R ² :
722	H	Cis	
723	H	None	
724	H	None	
725	H	Cis	
726	H	Cis	
727	H	Cis	-CH ₂ -OMe;
728	H	Cis	Me;
729	H	Cis	
730	H	None	
731	H	Cis	
732	H	Cis	
733	H	Cis	
734	H	Cis	

Cpd #	R ¹ :	13,14 double bond:	R ² :
735	H	Cis	
736	H	Cis	
737	H	Cis	
738	H	Cis	
739	10-(R) Me	none	Ph;
740	10-(S) Me	none	Ph;
and 741	H	Cis	

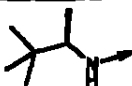
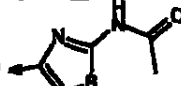
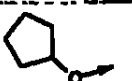
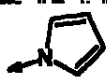
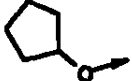
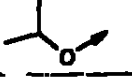
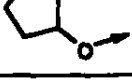
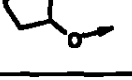
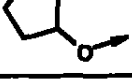
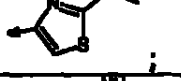
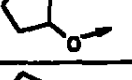
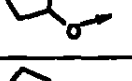
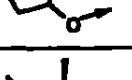
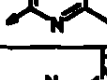
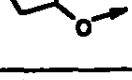
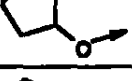
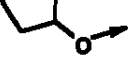
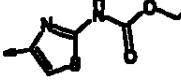
Table 6



5

wherein the bond from position 14 to the cyclopropyl group is *syn* to the COOH, said 13,14 double bond is *cis*, R³, R⁴ and R² are defined as follows:

Cpd #	R ³ :	R ⁴ :	R ² :
801		H	

Cpd #	R ³ :	R ⁴ :	R ² :
804		H	
805		H	
807		H	OBt;
808		H	OBt;
809		H	
810		H	
811		H	
812		H	
814		H	
815		H	
816		H	
817		H	
818		H	
819		H	

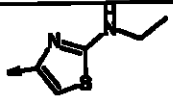
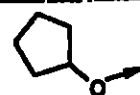
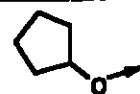
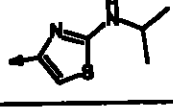
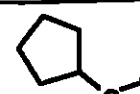
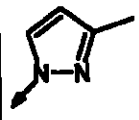
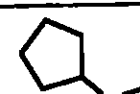
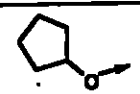
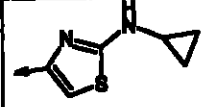
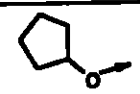
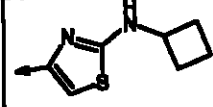
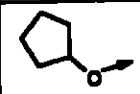
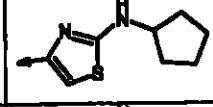
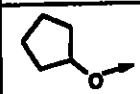
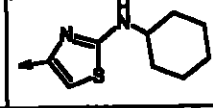
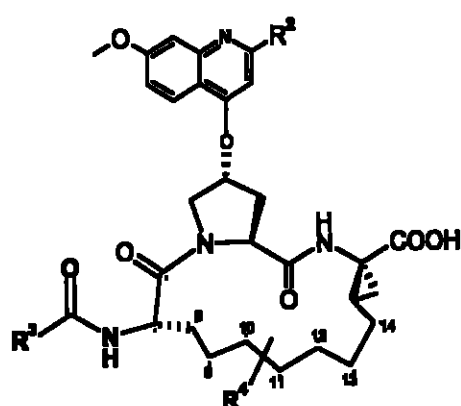
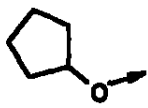
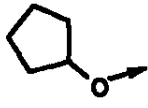
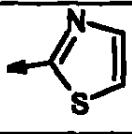
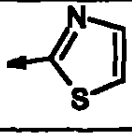
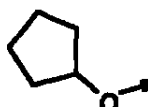
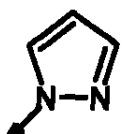
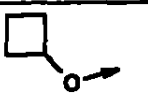
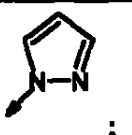
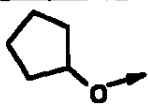
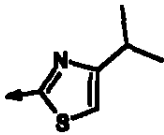
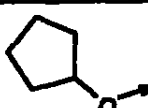
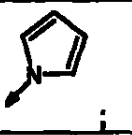
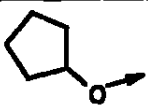
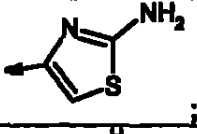
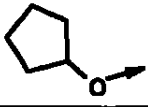
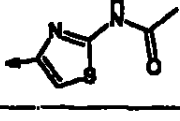
Cpd #	R ³ :	R ⁴ :	R ⁵ :
820		H	 ;
821		H	 ;
822		H	 ;
823		H	 ;
824		10- (R) Mo	OE _t ;
825		H	 ;
826		H	 ;
827		H	 ;
and 828		H	 .

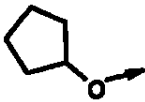
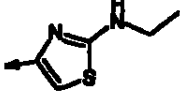
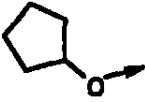
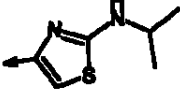
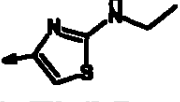
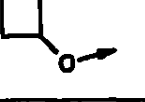
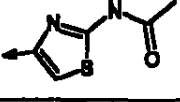
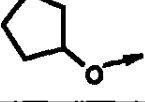
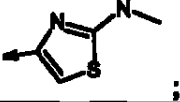
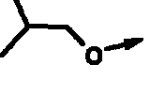
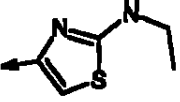
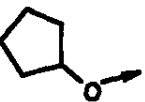
Table 7



wherein the bond from position 14 to the cyclopropyl group is *syn* to the COOH, and
 R^3 , R^4 and R^5 are defined as follows:

5

Cpd #	R^3 :	R^4 :	R^5 :
901		H	OBt;
902		H	
903		H	
904		H	
905		H	
906		H	
907		H	
908		H	
909		H	

Cpd #	R ³ :	R ⁴ :	R ⁵ :
910		H	
911		H	
912		H	
913		H	
914		H	
915		H	
and 916		10 (R) Me	OEt.

A preferred compound of formula (I) for the compositions of the invention described
5 herein is Compound #822. Additional specific compounds that are representative of
the compounds of formula (I) may be found in Tsantrizos et al. and WO 00/59929.

The compounds of formula I may be synthesized by the procedures fully set forth in
Tsantrizos et al.; WO 00/59929; and Llinas-Brunet.

10

Methods of Therapeutic Use

The compounds of formula I are effective as HCV protease inhibitors, and these
15 compounds and pharmaceutical compositions comprising these compounds are

therefore useful in inhibiting the replication of HCV and in the treatment of HCV infections, as set forth in Tsantrizos et al.; WO 00/59929 and Llinas-Brunet.

As discussed above, the pharmaceutical compositions of the present invention may be formulated into a variety of dosage forms depending upon the particular composition contemplated. Likewise, a variety of modes of administration are possible depending upon the particular composition and dosage form, although oral administration by tablet, capsule or suspension are the preferred modes of administration.

Dosage levels of the compounds of formula (I) and various treatment regimens in the monotherapy for the prevention and treatment of HCV infection are as set forth in Tsantrizos et al.; WO 00/59929 and Llinas-Brunet. As the skilled artisan will appreciate, however, lower dosages may be possible with the compositions of the present invention depending on the level of improvement in bioavailability.

Combination therapy is also possible with one or more additional therapeutic or prophylactic agents as fully described by Tsantrizos et al.; WO 00/59929 and Llinas-Brunet. The additional agent(s) may be combined with the compounds of this invention to create a single dosage form or, alternatively, these additional agent(s) may be separately administered to a mammal as part of a multiple dosage form.

20

In order that this invention be more fully understood, the following examples of are set forth. These examples are for the purpose of illustrating embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

25

Examples

Formulation #1 (comparative)

Ingredient	Weight (mg/g)	%(w/w)
Compound #822	100	10
Tromethamine	10	1
Water	20	2
Ethanol	100	10
Propylene glycol	50	5

Alpha-Tocopherol	4	0.4
Capmul MCM	220	22
V _E TPGS	516	49.6

Formulation #2

Ingredient	Weight (mg/g)	%(w/w)
Compound #822	100	10
Tromethamine	10	1
Sodium hydroxide	3	0.3
Water	17	1.7
Ethanol	100	10
Propylene glycol	50	5
Alpha-Tocopherol	4	0.4
Capmul MCM	220	22
V _E TPGS	516	49.6

5

Formulation #3

Ingredient	Weight (mg/g)	%(w/w)
Compound #822	100	10
Tromethamine	10	1
Sodium hydroxide	3	0.3
Water	30	3
Ethanol	100	10
Propylene glycol	50	5
Alpha-Tocopherol	4	0.4
Captex 355	220	22
V _E TPGS	483	48.3

10

Preparation of Formulations 1-3:

First, the liquid components such as Capmul MCM, Captex 355, propylene glycol, alpha-tocopherol, water and ethanol were mixed together in a tightly closed container. V_E TPGS was melted at 40°C and then transferred into the container. And then tromethamine and/or sodium hydroxide solution was added to the above mixture. Finally, Compound #822 was added to the container and stirring was

15

continued at 40°C until the drug was completely solubilized. These formulations can be filled into hard shell or soft gelatin capsules.

5 **Chemical Stability Studies**

The major degradation products of compound #822 in the formulation were identified and characterized by LC/MS. To compare different formulations, accelerated stability study was conducted: formulations were sealed into amber ampules and stored at
10 different temperatures: 50, 60 and 70°C. Samples were pulled and analyzed by HPLC for assay and impurity.

Figure 1 and 2 are impurity profiles of formulations containing compound #822, based on data obtained during an initial study. All formulations were analyzed after 5
15 days at 70°C. As can be seen in Figures 1 and 2, the level of the major degradation product 1 is lower in Formulations #2 and #3 of the invention than in comparative Formulation #1 (without base).

A more comprehensive follow-up study was conducted on Formulations #1 and #3
20 (the formulations used in this follow-up study were from a different lot and therefore exhibit slightly different levels of impurities vs. the formulations used in the initial study). Both total impurity and the level of major degradation product 1 have been significantly decreased with Formulation #3 compared to Formulation #1. Tables 1a and 1b summarize the amounts of total impurity and major degradation product 1 in
25 Formulation #3 versus comparative Formulation #1 upon storage at different temperatures. It is clear that Formulation #3 is more stable than Formulation #1, having a lower level of both total impurity and major degradation product 1 upon storage. According to Arrhenius equation, $t_{0.1, 25}$ (time for degradation product 1 to reach 0.1% at 25°C) of Formulation #3 is 232 days as compared to 99 days for
30 Formulation #1.

Table 1a. Summary of Total Impurity in Formulations #1 and #3.

Time (day)	Formulation #1 (%)			Formulation #3 (%)		
	70°C	60°C	50°C	70°C	60°C	50°C
1	1.51			1.05		
3	2.12	1.82		1.56	1.28	
5	2.91			2.12		
7	4.07	3.34	1.19	2.94	2.49	1.02
15	7.37	6.6		5.25	4.78	1.44
22	10.39	7.92		7.51	6.37	
28	12.02	10.04	2.95	9.96	7.44	2.25
42			4.48			3.61
56			5.7			4.15

Table 1b. Summary of Major Degradation Product 1 in Formulations #1 and #3.

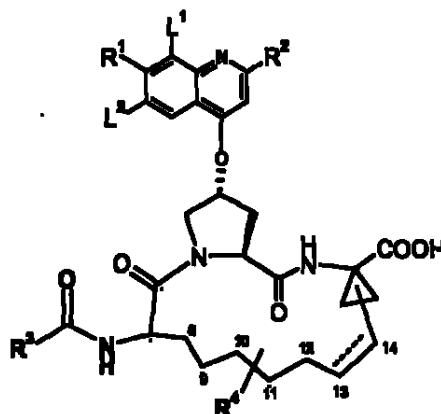
Time (day)	Formulation #1 (%)			Formulation #3 (%)		
	70°C	60°C	50°C	70°C	60°C	50°C
1	0.37			0.15		
3	0.66	0.48		0.29	0.23	
5	1.01			0.47		
7	1.43	1.15	0.26	0.68	0.55	0.13
15	2.9	2.48		1.44	1.21	0.25
22	4.21	3.15		2.23	1.68	
28	5.32	3.9	0.96	3.08	2.1	0.5
42			1.55			0.81
56			2.09			1.07

5

CLAIMS

1. A pharmaceutical composition comprising:

(a) a compound of formula (I):



(I)

wherein:

— designates an optional bond forming a double bond between positions 13 and

10 14;

R^1 is H, halo, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, hydroxy, or $N(R^5)_2$, wherein each R^5 is independently H, C_{1-4} alkyl or C_{3-6} cycloalkyl;

15

L^1 , L^2 are each independently H, halogen, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, or $-S-C_{1-4}$ alkyl (the sulfur being in any oxidized state);

20 R^2 is H, halo, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{2-7} alkoxyalkyl, C_6 or 10 aryl or Het, wherein Het is a five-, six-, or seven-membered saturated or unsaturated heterocycle containing from one to four ring heteroatoms selected from nitrogen, oxygen and sulfur, said cycloalkyl, aryl or Het being optionally substituted with R^6 ,

25 wherein R^6 is H, halo, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, NO_2 , $N(R^7)_2$, $NH-C(O)-R^7$, or $NH-C(O)-NH-R^7$, wherein each R^7 is independently: H, C_{1-6}

alkyl or C₃₋₆ cycloalkyl;

or R⁶ is NH-C(O)-OR⁸ wherein R⁸ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

5 R³ is R⁹O- or R⁹NH-, wherein R⁹ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R⁴ is H or from one to three substituents on any available carbon atom at positions 8, 9, 10, 11, 12, 13 or 14, said substituent independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, hydroxy, halo, amino, oxo, thio
10 or C₁₋₆ thioalkyl;

or a tautomer thereof;

(b) about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a
15 mixture of pharmaceutically acceptable amines;

(c) about 0.1 to 10% by weight of a pharmaceutically acceptable base or a mixture of pharmaceutically acceptable bases;

20 (d) one or more pharmaceutically acceptable oils;

(e) optionally one or more pharmaceutically acceptable hydrophilic solvents;

(f) optionally one or more pharmaceutically acceptable polymers;
25 and

(g) optionally one or more pharmaceutically acceptable surfactants.

2. A pharmaceutical composition according to claim 1, wherein the compound of
30 formula (I) is present in an amount of from about 1% to 50% by weight.

3. A pharmaceutical composition according to claim 1 or 2, wherein the amine is present in an amount of from about 0.5% to 7% by weight.

4. A pharmaceutical composition according to any of the preceding claims,
wherein the amine is a C₁₋₆ alkylamine, di-(C₁₋₆ alkyl)-amine or tri-(C₁₋₆ alkyl)-
amine, wherein one or more alkyl groups thereof may be optionally substituted by one
5 or more hydroxy groups, or the amine is C₁₋₆ alkylenediamine, a basic amino acid or
choline hydroxide, or mixtures thereof.
5. A pharmaceutical composition according to any of the preceding claims,
wherein the amine is selected from ethanolamine, diethanolamine, triethanolamine,
10 tris(hydroxymethyl)aminomethane, ethylenediamine, dimethylaminoethanol, or
meglumine, or mixtures thereof.
6. A pharmaceutical composition according to any of the preceding claims,
wherein the base is present in an amount of from about 0.1% to 5% by weight.
15
7. A pharmaceutical composition according to any of the preceding claims,
wherein the base is selected from sodium hydroxide, potassium hydroxide, sodium
hydrogen carbonate, aluminum hydroxide, magnesium hydroxide, magnesium
aluminum hydroxide.
20
8. A pharmaceutical composition according to any of the preceding claims,
wherein the pharmaceutically acceptable oil is present in an amount of from about
20% to 70% by weight.
- 25 9. A pharmaceutical composition according to any of the preceding claims,
wherein the pharmaceutically acceptable oil is selected from: medium or long chain
mono-, di- or triglycerides, water insoluble vitamins, fatty acids and mixtures thereof.
10. A pharmaceutical composition according to any of the preceding claims,
30 wherein the pharmaceutically acceptable oil is selected from: triglycerides of caprylic
fatty acids; triglycerides of capric fatty acids; and mixtures thereof.
11. A pharmaceutical composition according to any of the preceding claims,

wherein the pharmaceutically acceptable hydrophilic solvent is selected from propylene glycol, polypropylene glycol, polyethylene glycol, glycerol, ethanol, dimethyl isosorbide, glycofurol, propylene carbonate, dimethyl acetamide, water, or mixtures thereof.

5

12. A pharmaceutical composition according to any of the preceding claims, wherein the pharmaceutically acceptable hydrophilic solvent is selected from propylene glycol, polyethylene glycol, ethanol, water, and mixtures thereof.

10

13. A pharmaceutical composition according to any of the preceding claims, wherein the pharmaceutically acceptable polymer is present in an amount of up to about 50% by weight.

15

14. A pharmaceutical composition according to any of the preceding claims, wherein the pharmaceutically acceptable polymer is selected from polyethylene glycols, polyvinylpyrrolidones, polyvinylalcohols, cellulose derivatives, polyacrylates, polymethacrylates, sugars, polyols, and mixtures thereof.

20

15. A pharmaceutical composition according to any of the preceding claims, wherein the pharmaceutically acceptable surfactant is present in an amount of up to about 70% by weight.

25 16. A pharmaceutical composition according to any of the preceding claims, wherein the pharmaceutically acceptable surfactant is selected from d-alpha tocopheryl polyethylene glycol 1000 succinate, polyoxyl castor oils, polysorbates, peglicol 6-oleate, polyoxyethylene stearates, polyglycolized glycerides or poloxamers, or sodium lauryl sulfate and mixtures thereof.

30

17. A pharmaceutical composition according to any of the preceding claims, wherein the pharmaceutically acceptable surfactant is selected from d-alpha tocopheryl polyethylene glycol 1000 succinate, polyoxyl 40 hydrogenated castor oil,

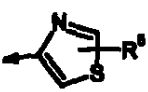
polyoxyl 35 castor oil, polyoxypropylene-polyoxyethylene block copolymer, or sodium lauryl sulfate, and mixtures thereof.

18. A pharmaceutical composition according to any of the preceding claims, wherein in the compound of formula (I):

R^1 is methoxy;

L^1 and L^2 are both H;

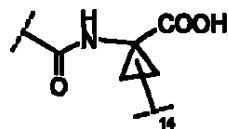
10

R^2 is  wherein R^5 is $NH-(C_{1-4}alkyl)$ or $NH-(C_{3-6}cycloalkyl)$;

R^3 is R^9O- , wherein R^9 is butyl, cyclobutyl or cyclopentyl;

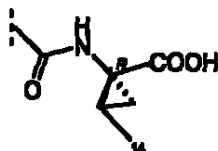
R^4 is H or $C_{1-6}alkyl$;

and following moiety:



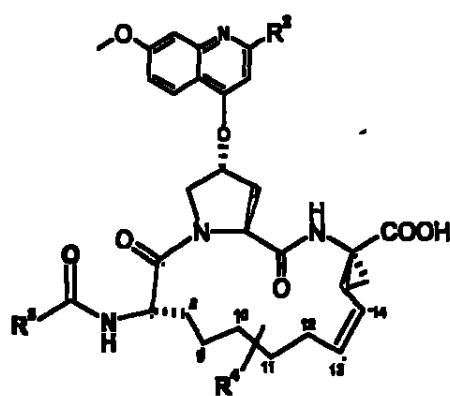
15

has the configuration represented by the following diastereoisomer:



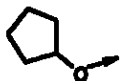
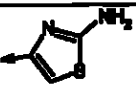
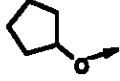
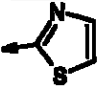
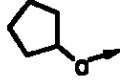
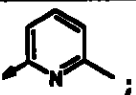
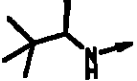
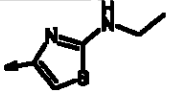
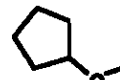
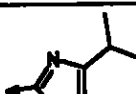
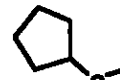
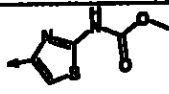
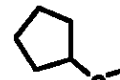
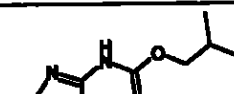
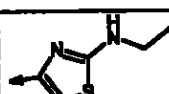
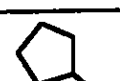
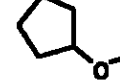
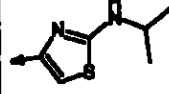
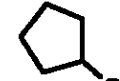
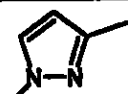
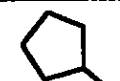
in which configuration position 14 is linked *syn* to the COOH group.

19. A pharmaceutical composition according to any of the preceding claims, wherein the compound of formula (I) is selected from the compounds listed in the following table:



wherein the bond from position 14 to the cyclopropyl group is *syn* to the COOH, said 13,14 double bond is *cis*, R^3 , R^4 and R^2 are defined as follows:

Cpd #	R^3	R^4	R^2
801		H	;
804		H	;
805		H	;
807		H	OR _t
808		H	OR _t
809		H	;
810		H	;
811		H	;

Cpd #	R ³ :	R ⁴ :	R ² :
812		H	 ;
814		H	 ;
815		H	 ;
816		H	 ;
817		H	 ;
818		H	 ;
819		H	 ;
820		H	 ;
821		H	 ;
822		H	 ;
823		H	 ;
824		10- (R) Me	OBt;

Cpd #	R ³ :	R ⁴ :	R ² :
825		H	
826		H	
827		H	
and 828		H	

20. A pharmaceutical composition according to claim 19, wherein the compound of formula (I) is compound 822.

5 21. A pharmaceutical composition according to any of the preceding claims, comprising:

(A)

- (a) about 5% to 30% by weight of a compound of formula (I);
- 10 (b) about 0.1% to 7% by weight of a pharmaceutically acceptable amine;
- (c) about 0.1% to 5% by weight of a pharmaceutically acceptable base;
- (d) about 1% to 99% by weight of a pharmaceutically acceptable oil;
- (e) up to about 70% by weight of a pharmaceutically acceptable hydrophilic solvent;
- 15 (f) optionally up to about 50% by weight of a pharmaceutically acceptable polymer; and
- (g) up to about 70% by weight of a pharmaceutically acceptable surfactant;

or

20 (B)

- 5 (a) about 10% to 20% by weight of a compound of formula (I);
(b) about 0.1% to 5% by weight of a pharmaceutically acceptable amine;
(c) about 0.1% to 3% by weight of a pharmaceutically acceptable base;
(d) about 20% to 70% by weight of a pharmaceutically acceptable oil;
(e) about 10% to 30% by weight of a pharmaceutically acceptable
hydrophilic solvent;
(f) optionally about 1% to 20% by weight of a pharmaceutically
acceptable polymer; and
(g) about 20% to 50% by weight of a pharmaceutically acceptable
10 surfactant;

or

(C)

- 15 (a) about 10% to 20% by weight of a compound of formula (I);
(b) about 0.1% to 5% by weight of tris(hydroxymethyl)aminomethane;
(c) about 0.1% to 3% by weight of sodium hydroxide;
(d) about 20% to 70% by weight of a triglyceride of caprylic fatty acid or a
20 triglyceride of capric fatty acid, or mixtures thereof;
(e) about 10% to 30% by weight of a mixture of propylene glycol, ethanol
and optionally water;
(f) optionally about 1% to 20% by weight of polyethylene glycol or
polyvinylpyrrolidone; and
25 (g) about 20% to 50% by weight of d-alpha tocopheryl polyethylene
glycol 1000 succinate or polyoxyl 35 castor oil (Cremophor EL);
or

(D)

- 30 (a) about 10% to 15% by weight of a compound of formula (I);
(b) about 0.1% to 2% by weight of tris(hydroxymethyl)aminomethane;
(c) about 0.1% to 1% by weight of sodium hydroxide;

- (d) about 20% to 30% by weight of Capmul MCM or Captex 355;
- (e) about 15% to 25% by weight of a mixture of propylene glycol, ethanol and water;
- (f) about 40% to 50% by weight of d-alpha tocopheryl polyethylene glycol 1000 succinate; and
- (g) about 0.01% to 1% of dl- α -tocopherol.

22. A pharmaceutical composition according to any of the preceding claims, in the form of a fluid dosage form selected from a hard shell or softgel capsule or in the form of a solid dosage form selected from a powder, a tablet or a capsule.

23. A pharmaceutical composition according to any of the preceding claims, further comprising one or more antioxidants.

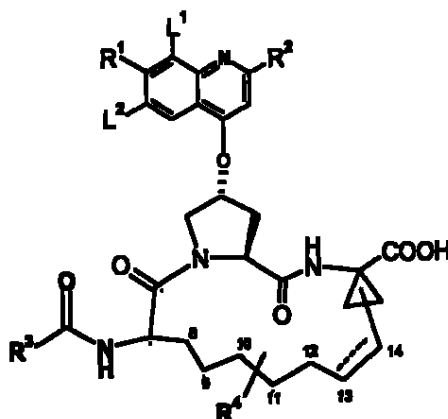
24. A method of manufacturing a pharmaceutical composition according to any of the preceding claims, said method comprising:

(a) mixing together the pharmaceutically acceptable oil(s), surfactant(s) and solvent(s); (b) dissolving the pharmaceutically acceptable amine(s), base(s) and polymer(s) in the mixture obtained in step (a); (c) optionally heating the mixture obtained in step (b) if necessary to sufficiently melt one or more of the components of the mixture; (d) adding the compound of formula (I) to the mixture obtained in steps (b) or (c) and mixing.

25. 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 composition according to any of claims 1 to 23.

26. A method of treating a hepatitis C viral infection in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of the composition according to any of claims 1 to 23.

27. Use of a compound of the following formula (I):



(I)

wherein:

— designates an optional bond forming a double bond between positions 13 and 14;

R^1 is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, hydroxy, or $N(R^5)_2$, wherein each R^5 is independently H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

L^1 , L^2 are each independently H, halogen, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, or $-S-C_{1-4}$ alkyl (the sulfur being in any oxidized state);

R^2 is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{2-7} alkoxyalkyl, C_{6-10} aryl or Het, wherein Het is a five-, six-, or seven-membered saturated or unsaturated heterocycle containing from one to four ring heteroatoms selected from nitrogen, oxygen and sulfur; said cycloalkyl, aryl or Het being optionally substituted with R^6 ,

wherein R^6 is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, NO_2 , $N(R^7)_2$, $NH-C(O)-R^7$; or $NH-C(O)-NH-R^7$, wherein each R^7 is independently: H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

or R^6 is $NH-C(O)-OR^8$ wherein R^8 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

77.

R^3 is R^9O- or R^9NH- , wherein R^9 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

5 R^4 is H or from one to three substituents on any available carbon atom at positions 8, 9, 10, 11, 12, 13 or 14, said substituent independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy, halo, amino, oxo, thio or C_{1-6} thioalkyl;

10 or a tautomer thereof;

for the preparation of a pharmaceutical composition for the treatment of hepatitis C viral infection, wherein said pharmaceutical composition comprises:

15

(a) a compound of formula (I) as described above;

20 (b) about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a mixture of pharmaceutically acceptable amines;

(c) about 0.1 to 10% by weight of a pharmaceutically acceptable base or a mixture of pharmaceutically acceptable bases;

25 (d) one or more pharmaceutically acceptable oils;

(e) optionally one or more pharmaceutically acceptable hydrophilic solvents;

30 (f) optionally one or more pharmaceutically acceptable polymers;
and

(g) optionally one or more pharmaceutically acceptable surfactants.

35 28. Use of a composition according to any of claims 1 to 23 for the preparation of a medicament for the treatment of hepatitis C viral infection.

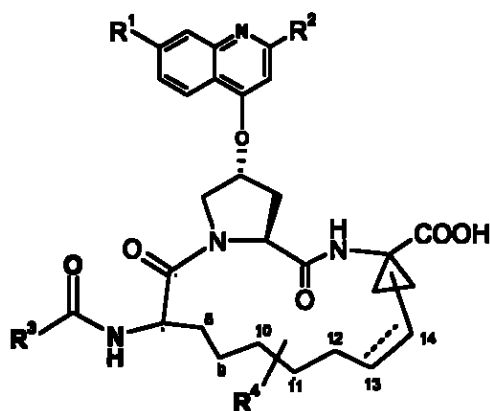
Composiciones farmacéuticas para inhibidores de la proteasa del virus de la hepatitis C

CAMPO DE LA INVENCION

La presente invención se refiere en general a composiciones farmacéuticas de inhibidores de la proteasa del virus de la hepatitis C, a métodos para usar estas composiciones para inhibir la replicación del virus de la hepatitis C (VHC) y para el tratamiento de una infección por el VHC.

ANTECEDENTES DE LA INVENCION

Recientemente se ha descubierto que ciertos compuestos macrocíclicos son inhibidores potentes y específicos de la proteasa del virus de la hepatitis C (VHC). En particular, se ha encontrado que compuestos de la siguiente fórmula I son una clase de inhibidores especialmente potentes contra la serina-proteasa NS3 del VHC:



(I)

en la que:

— indica un enlace opcional que forma un doble enlace entre las posiciones 13 y 14;

R^1 es H, halógeno, alquilo C_{1-6} , cicloalquilo C_{3-6} , halógenoalquilo C_{1-6} , alcoxi C_{1-6} , cicloalcoxi C_{3-6} , hidroxil, o $N(R^5)_2$, en el que cada R^5 es independientemente H, alquilo C_{1-6} o cicloalquilo C_{3-6} ;

R^2 es H, halógeno, alquilo C_{1-6} , cicloalquilo C_{3-6} , halógenoalquilo C_{1-6} , tioalquilo C_{1-6} , alcoxi C_{1-6} , cicloalcoxi C_{3-6} , alcoxi alquilo C_{2-7} , arilo o Het C_6 a 10 , en el que Het es un heterociclo saturado o insaturado, de cinco, seis o siete miembros que contiene de uno a cuatro heteroátomos en el anillo seleccionados de nitrógeno, oxígeno y azufre;

estando dicho cicloalquilo, arilo o Het opcionalmente sustituido con R^6 ,

en el que R^6 es H, halógeno, alquilo C_{1-6} , cicloalquilo C_{3-6} , alcoxi C_{1-6} , cicloalcoxi

C_{3-6} , NO_2 , $N(R^7)_2$, $NH-C(O)-R^7$; o $NH-C(O)-NH-R^7$, en los que cada R^7 es independientemente: H, alquilo C_{1-6} o cicloalquilo C_{3-6} ;

o R^6 es $NH-C(O)-OR^8$, en el que R^8 es alquilo C_{1-6} o cicloalquilo C_{3-6} ;

R^5 es R^9O- o R^9NH- , en los que R^9 es alquilo C_{1-6} o cicloalquilo C_{3-6} ;

5 R^4 es H o de uno a tres sustituyentes en cualquier átomo de carbono disponible en las posiciones 8, 9, 10, 11, 12, 13 ó 14, seleccionado dicho sustituyente independientemente del grupo que consta de: alquilo C_{1-6} , halógenoalquilo C_{1-6} , alcoxi C_{1-6} , hldroxi, halógeno, amino, oxo, tio o tioalquilo C_{1-6} .

Véase, Tsantrizos et al., Solicitud de EE.UU. No. de serie 09/760.946, 10 presentada el 16 de Enero, 2001, ahora patente de EE.UU. No. 6.808.027 B1 (Boehringer Ingelheim (Canada), Ltd.), que se incorpora en la presente memoria como referencia en su totalidad, y se denomina en lo sucesivo "Tsantrizos et al." Véase también el correspondiente documento WO 00/59929 (Boehringer Ingelheim (Canada) Ltd.).

15 Una característica estructural de los compuestos de fórmula I es la presencia de la función ácido carboxílico C-terminal, que ha mostrado ser responsable no sólo de la potencia y reversibilidad observadas para esta serie de Inhibidores, si no también de la excelente especificidad por la proteasa del VHC comparado con otras serina/cisteína-proteasas. Se esperaba que un Inhibidor de serina-proteasa del VHC tal 20 como los compuestos de fórmula I fuera un agente antivírico que actuara por un nuevo mecanismo, es decir, el bloqueo de una función esencial para la replicación del VHC codificada por el virus. Un fármaco que actuara por este mecanismo suprimiría la replicación vírica de todos los genotipos del VHC, y por lo tanto proporcionaría beneficios tangibles a pacientes con hepatitis C crónica.

25 Un problema común entre los inhibidores de proteasas es que estos compuestos son lipófilos y tienen baja solubilidad acuosa. Debido a la poca solubilidad acuosa, las preparaciones farmacéuticas sólidas y líquidas convencionales que contienen estos Inhibidores, no pueden ser absorbidas por el paciente de forma satisfactoria. De los diferentes factores que pueden afectar a la biodisponibilidad de un 30 fármaco cuando se administra por vía oral (que incluyen solubilidad acuosa, absorción del fármaco por el tracto gastrointestinal, concentración de la dosificación y efecto de primero paso), con frecuencia la solubilidad acuosa está entre los factores más importantes. Los compuestos poco solubles en agua con frecuencia presentan absorción errática o incompleta en el tracto digestivo, y por lo tanto producen una 35 respuesta menos que deseable.

Los compuestos de fórmula I son lones híbridos, y pueden formar sales con ácidos y bases fuertes. Los intentos de identificar sales de dichos compuestos en formas sólidas que mejorarían sustancialmente la solubilidad acuosa, no han tenido éxito. Se ha encontrado que diferentes sales de estos compuestos son muy higroscópicas, reduciendo la estabilidad de los compuestos. Además, las formulaciones de las sales de estos compuestos en general son propensas a la precipitación del ácido libre padre en el tracto gastrointestinal. Compuestos de fórmula I representativos han mostrado poca biodisponibilidad cuando se administran a animales en forma de una suspensión acuosa, sugiriendo que las formulaciones convencionales que contienen estos inhibidores no pueden ser absorbidas de un modo satisfactorio. Por lo tanto, se necesitan en la técnica composiciones farmacéuticas de los compuestos de fórmula I que tengan mejor biodisponibilidad.

Se han descrito previamente métodos para formular ciertos compuestos macrocíclicos lipófilos en formulaciones farmacéuticas. Por ejemplo, Cavanak, patente de EE.UU. nº 4.388.307, describe la preparación de formulaciones emulsionadas de ciclosporinas disponibles en el comercio, y Hauer et al., patente de EE.UU. nº 5.342.625, y Melzner et al., documento WO 93/20833, describen la preparación de microemulsiones y preconcentrados de microemulsiones de ciclosporina. Komlya et al., patente de EE.UU. nº 5.504.068, describen además la preparación de formulaciones tópicas de ciclosporina potenciadas.

Entre los ejemplos de formulaciones "autoemulsionantes" de compuestos lipófilos se incluyen Lipari et al., documento WO 96/36316, que describe un preconcentrado autoemulsionante que comprende un compuesto lipófilo, succinato de *d*-alfa-tocoferil-polietilenglicol 1000 (TPGS, por sus siglas en inglés *d-alpha-tocopheryl polyethylene glycol 1000 succinate*) y una fase lipófila. Gao et al., patente de EE.UU. nº 6.121.313, describe una formulación autoemulsionante de un inhibidor de proteasa de piranona que comprende el compuesto de piranona, una mezcla de mono y diglicéridos, uno o más disolventes y uno o más tensioactivos; y Gao et al., patente de EE.UU. nº 6.231.887 B1 describe una formulación autoemulsionante de un inhibidor de proteasa de piranona que comprende el compuesto de piranona, una amina, uno o más disolventes y uno o más tensioactivos.

Yu et al., patentes de EE.UU. nº 5.360.615 y 5.071.643, describen la preparación de un sistema disolvente para potenciar la solubilidad de los compuestos ácidos, básicos o anfóteros por ionización parcial, que comprende una mezcla de polietilenglicol, hidróxido o ion hidrógeno y agua. Morton et al., patente de EE.UU., nº

5.376.688, describen soluciones de agentes farmacéuticos ácidos, básicos o anfóteros que comprenden el agente farmacéutico, una especie iónica y un sistema disolvente. Bhagwat et al., patente de EE.UU. n° 6.056.977, enseñan el uso de una matriz basada en polisacárido para la liberación sostenida de una sulfonilurea.

5 Recientemente se ha desarrollado un sistema de liberación de fármaco autoemulsionante (SEDDS, por sus siglas en inglés *self-emulsifying drug delivery system*) que tiene mejor biodisponibilidad para los compuestos de fórmula (I), como se describe en la solicitud de EE.UU. n° 10/357.919 (S. Chen et al.), presentada el 4 de Febrero, 2003, y en el documento PCT/US03/03380 (Boehringer Ingelheim
10 Pharmaceuticals, Inc.), presentado el 5 de Febrero, 2003, publicado como WO 03/066103 A1. Esta formulación comprende un compuesto de fórmula (I), aproximadamente 0,1 a 10% en peso de una amina farmacéuticamente aceptable o una mezcla de aminas farmacéuticamente aceptables, uno o más aceites farmacéuticamente aceptables, uno o más disolventes hidrófilos farmacéuticamente
15 aceptables, opcionalmente uno o más polímeros farmacéuticamente aceptables, y opcionalmente uno o más tensioactivos farmacéuticamente aceptables. Sin embargo, se ha encontrado que esta formulación no se puede optimizar completamente con respecto a su estabilidad química y por lo tanto puede requerir almacenamiento en condiciones refrigeradas.

20 BREVE SUMARIO DE LA INVENCION

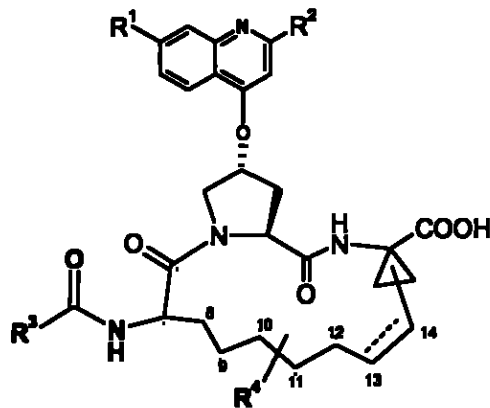
La presente invención supera los problemas mencionados proporcionando composiciones farmacéuticas de los compuestos de fórmula I que tienen biodisponibilidad aceptable y también mejor estabilidad química comparadas con la formulación de SEDDS previa.

25 Las composiciones farmacéuticas de la presente invención comprenden todas un compuesto de fórmula I junto con una o más aminas, bases y aceites farmacéuticamente aceptables. Las composiciones de la presente invención pueden incluir opcionalmente uno o más ingredientes adicionales, por ejemplo, disolventes, tensioactivos, polímeros farmacéuticamente aceptables, etc., como se discutirá con
30 más detalle a continuación. La presente invención también se dirige a los métodos para fabricar estas composiciones, como se describe en lo sucesivo.

En una realización general, la composición farmacéutica de la presente invención comprende:

(a) un compuesto de fórmula (I):

- 5 -



(I)

en la que:

— indica un enlace opcional que forma un doble enlace entre las posiciones 13 y 14;

- 5 R¹ es H, halógeno, alquilo C₁₋₆, cicloalquilo C₃₋₆, halógenoalquilo C₁₋₆, alcoxi C₁₋₆, cicloalcoxi C₃₋₆, hidroxil, o N(R⁵)₂, en el que cada R⁵ es independientemente H, alquilo C₁₋₆ o cicloalquilo C₃₋₆;
- R² es H, halógeno, alquilo C₁₋₆, cicloalquilo C₃₋₆, halógenoalquilo C₁₋₆, tioalquilo C₁₋₆, alcoxi C₁₋₆, cicloalcoxi C₃₋₆, alcoxialquilo C₂₋₇, arilo o Het C₆ ó 10, en el que Het es un
- 10 heterociclo saturado o insaturado, de cinco, seis o siete miembros que contiene de uno a cuatro heteroátomos en el anillo seleccionados de nitrógeno, oxígeno y azufre;
- estando dicho cicloalquilo, arilo o Het opcionalmente sustituido con R⁶,
 en el que R⁶ es H, halógeno, alquilo C₁₋₆, cicloalquilo C₃₋₆, alcoxi C₁₋₆, cicloalcoxi C₃₋₆, NO₂, N(R⁷)₂, NH-C(O)-R⁷; o NH-C(O)-NH-R⁷, en los que cada R⁷ es
- 15 independientemente: H, alquilo C₁₋₆ o cicloalquilo C₃₋₆;
 o R⁶ es NH-C(O)-OR⁸, en el que R⁸ es alquilo C₁₋₆ o cicloalquilo C₃₋₆;
- R³ es R⁶O- o R⁶NH-, en los que R⁶ es alquilo C₁₋₆ o cicloalquilo C₃₋₆;
- R⁴ es H o de uno a tres sustituyentes en cualquier átomo de carbono disponible en las posiciones 8, 9, 10, 11, 12, 13 ó 14, seleccionado dicho sustituyente
- 20 independientemente del grupo que consta de: alquilo C₁₋₆, halógenoalquilo C₁₋₆, alcoxi C₁₋₆, hidroxil, halógeno, amino, oxo, tio o tioalquilo C₁₋₆;
- o uno de sus tautómeros;
- (b) aproximadamente 0,1 a 10% en peso de una amina farmacéuticamente aceptable o una mezcla de aminas farmacéuticamente aceptables;
- 25 (c) aproximadamente 0,1 a 10% en peso de una base farmacéuticamente

aceptable o una mezcla de bases farmacéuticamente aceptables;

(d) uno o más aceites farmacéuticamente aceptables;

(e) opcionalmente uno o más disolventes hidrófilos farmacéuticamente aceptables;

5 (f) opcionalmente uno o más polímeros farmacéuticamente aceptables; y

(g) opcionalmente uno o más tensioactivos farmacéuticamente aceptables.

Otro aspecto importante de la presente invención implica 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, de una composición farmacéutica de la
10 invención.

Otro aspecto importante de la presente invención implica un método para tratar una infección por el virus de la hepatitis C en un mamífero administrando al mamífero que lo necesita, una cantidad terapéuticamente eficaz de una composición farmacéutica de la presente invención. Con respecto a esto, la presente invención
15 también se dirige al uso de los compuestos de fórmula (I) descritos antes para preparar una composición farmacéutica para tratar la infección por el virus de la hepatitis C, en el que la composición farmacéutica comprende:

(a) un compuesto de fórmula (I) como se ha descrito antes;

20 (b) aproximadamente 0,1 a 10% en peso de una amina farmacéuticamente aceptable o una mezcla de aminas farmacéuticamente aceptables;

(c) aproximadamente 0,1 a 10% en peso de una base farmacéuticamente aceptable o una mezcla de bases farmacéuticamente aceptables;

(d) uno o más aceites farmacéuticamente aceptables;

25 (e) opcionalmente uno o más disolventes hidrófilos farmacéuticamente aceptables;

(f) opcionalmente uno o más polímeros farmacéuticamente aceptables; y

(g) opcionalmente uno o más tensioactivos farmacéuticamente aceptables.

La presente invención también se dirige al uso de una composición como se ha descrito antes para preparar un medicamento para tratar la infección por el virus de la
30 hepatitis C.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La Figura 1 muestra el perfil de impurezas de una formulación de acuerdo con la presente invención que contiene trometamina e hidróxido sódico y una formulación comparativa sin hidróxido sódico.

35 La Figura 2 muestra el perfil de impurezas de una segunda formulación de

acuerdo con la presente invención, que contiene trometamina e hidróxido sódico y una formulación comparativa sin hidróxido sódico.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Definición de los términos y convenios usados

5 Las expresiones que no se definen específicamente en la presente memoria vendrán dadas por los significados que normalmente les daría un experto en la técnica a la luz de la descripción y del contexto. Sin embargo, como se usa en la memoria descriptiva, salvo que se especifique lo contrario, las siguientes expresiones tienen el significado indicado y se observan los siguientes convenios.

10 A. Nomenclatura, términos y convenios químicos y farmacéuticos

En los grupos, radicales o restos definidos a continuación, el número de átomos de carbono con frecuencia se especifica después del grupo, por ejemplo, alquilo C₁₋₆ significa un grupo o radical alquilo que tiene de 1 a 6 átomos de carbono. En general, para grupos que comprenden dos o más subgrupos, el último grupo nombrado es el punto de unión del radical, por ejemplo "tioalquilo" significa un radical monovalente de fórmula HS-Alq-. Salvo que se especifique lo contrario a continuación, las definiciones convencionales regulan las expresiones, y se suponen y alcanzan las valencias de los átomos estables convencionales en todas las fórmulas y grupos.

20 La expresión "alquilo C₁₋₆" tal como se usa en la presente memoria, sola o combinada con otro sustituyente, significa sustituyentes alquilo de cadena acíclica, lineal o ramificada que contienen de 1 a seis átomos de carbono, e incluye, por ejemplo, metilo, etilo, propilo, butilo, hexilo, 1-metiletilo, 1-metilpropilo, 2-metilpropilo, y 1,1-dimetiletilo.

25 La expresión "cicloalquilo C₃₋₆" tal como se usa en la presente memoria, sola o combinada con otro sustituyente, significa un sustituyente cicloalquilo que contiene de tres a seis átomos de carbono, e incluye ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

30 La expresión "alcoxi C₁₋₆" tal como se usa en la presente memoria, sola o combinada con otro sustituyente, significa el sustituyente alquil(C₁₋₆)-O-, en el que alquilo es como se ha definido antes y contiene hasta seis átomos de carbono. Alcoxi incluye metoxi, etoxi, propoxi, 1-metiletoxi, butoxi, y 1,1-dimetiletoxi. El último sustituyente se conoce normalmente como terc-butoxi.

35 La expresión "cicloalquilo C₃₋₆" tal como se usa en la presente memoria, sola o combinada con otro sustituyente, significa el sustituyente cicloalquil(C₃₋₆)-O- que contiene de 3 a 6 átomos de carbono.

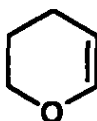
El término "halógeno" tal como se usa en la presente memoria, significa un sustituyente halógeno seleccionado de bromo, cloro, flúor, o yodo.

El término "halógenoalquilo" tal como se usa en la presente memoria, solo o combinado con otro sustituyente, significa sustituyentes alquilo de cadena acíclica, lineal o ramificada que tienen uno o más hidrógenos sustituidos por un halógeno seleccionado de bromo, cloro, flúor o yodo.

El término "tioalquilo" tal como se usa en la presente memoria, solo o combinado con otro sustituyente, significa sustituyentes alquilo de cadena acíclica, lineal o ramificada que contienen un grupo tiol (HS) como sustituyente. Un ejemplo de un grupo tioalquilo es un tiopropilo, por ejemplo, $\text{HS-CH}_2\text{CH}_2\text{CH}_2$ es un ejemplo de un grupo tiopropilo.

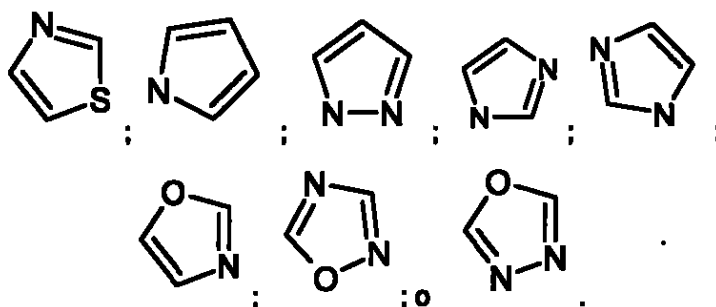
La expresión "arilo C_6 o C_{10} " tal como se usa en la presente memoria, sola o combinada con otro sustituyente, significa un sistema monocíclico aromático que contiene 6 átomos de carbono o un sistema bicíclico aromático que contiene 10 átomos de carbono. Por ejemplo, arilo incluye un sistema de anillo de un fenilo o un naftilo.

El término "Het" tal como se usa en la presente memoria, solo o combinado con otro sustituyente, significa un sustituyente monovalentes obtenido por eliminación de un hidrógeno de un heterociclo saturado o insaturado (Incluyendo aromático) de cinco, seis o siete miembros, que contiene átomos de carbono y de uno a cuatro heteroátomos en el anillo, seleccionados de nitrógeno, oxígeno y azufre. Entre los ejemplos de heterociclos adecuados se incluyen: tetrahidrofurano, tiofeno, diazepina, isoxazol, piperidina, dioxano, morfollina, pirimidina o



El término "Het" también incluye un heterociclo como se ha definido antes, condensado con uno o más ciclos distintos sean un heterociclo o cualquier otro ciclo. Entre uno de dichos ejemplos se incluye tiazolo[4,5-b]piridina. Aunque en general está cubierto por el término "Het", el término "heteroarilo" tal como se usa en la presente memoria exactamente define un heterociclo insaturado para el cual los dobles enlaces forman un sistema aromático. Entre los ejemplos de sistema heteroaromático se incluyen: quinolina, indol, piridina,

- 9 -



El término "oxo" significa el grupo con doble enlace (=O) unido como sustituyente.

5 El término "tio" significa el grupo con doble enlace (=S) unido como sustituyente.

La expresión "compuestos de la invención", y expresiones equivalentes, quiere decir que abarcan compuestos de Fórmula (I) como se describen en la presente memoria, incluyendo sus tautómeros e isómeros, donde el contexto lo permita. En general, los compuestos de la invención y las fórmulas que designan los compuestos de la invención, se entiende que sólo incluyen sus compuestos estables y excluyen compuestos inestables, incluso si se puede considerar que un compuesto inestable es abarcado literalmente por la fórmula del compuesto.

15 La expresión "compuesto estable" significa un compuesto que es suficientemente robusto para sobrevivir al aislamiento de una mezcla de reacción en un grado de pureza útil, y a la formulación en una composición farmacéutica eficaz. Por ejemplo, un compuesto que tuviera una "valencia vacante" o fuera un "carbanión" no es un compuesto contemplado por la invención.

20 La expresión "composición farmacéutica de la invención" y expresiones equivalentes se entiende que abarcan todos los diferentes tipos de composiciones farmacéuticas como se describen en lo sucesivo, salvo que esté claro en el contexto que se hace referencia a un tipo particular de composición farmacéutica dentro del alcance de la presente invención.

25 La expresión "farmacéuticamente aceptable" con respecto a una sustancia tal como se usa en la presente memoria, significa que la sustancia, dentro del alcance del razonable criterio médico, que es adecuada para usar en contacto con los tejidos de seres humanos y animales inferiores sin excesiva toxicidad, irritación, respuesta alérgica, y similares, se corresponde con una relación beneficio/riesgo razonable, y es eficaz para el uso pretendido cuando la sustancia se usa en una composición farmacéutica.

30

El término "semisólido" significa un material que no es ni sólido (comportamiento elástico) ni líquido (comportamiento viscoso) y tiene las características tanto de viscosidad como de elasticidad. Entre los ejemplos de materiales semisólidos se incluyen geles, pomadas, cremas, y líquidos altamente viscosos.

El término "aproximadamente" significa dentro de 20%, preferiblemente dentro de 10%, y más preferiblemente dentro de 5% de un valor o intervalo dado. Por ejemplo, "aproximadamente 10%" significa de 8% a 12%, preferiblemente de 9% a 11%, y más preferiblemente de 9,5% a 10,5%. Cuando el término "aproximadamente" está asociado con un intervalo de valores, por ejemplo, "aproximadamente X a Y%", el término "aproximadamente" se pretende que modifique tanto el valor inferior (X) como el superior (Y) del intervalo citado. Por ejemplo, "aproximadamente 0,1 a 10%" es equivalente a "aproximadamente 0,1% a aproximadamente 10%".

Todos los porcentajes citados para cantidades de ingredientes en las composiciones, son porcentajes en peso con respecto a la composición completa.

B. Términos y convenios de isómeros

Los términos "isómeros" y "estereoisómeros" significan compuestos que tienen el mismo número y tipo de átomos, y por lo tanto el mismo peso molecular, pero difieren con respecto a la disposición o configuración de los átomos en el espacio. El término incluye isómeros ópticos y geométricos.

La expresión "isómero óptico" significa un isómero estable que tiene al menos un átomo quiral, o rotación restringida que da lugar a planos disimétricos perpendiculares (por ejemplo, ciertos bifenilos, alenos y compuestos espiral) y pueden rotar la luz polarizada plana. Puesto que existen centros asimétricos y otras estructuras químicas en los compuestos de fórmula I que pueden dar lugar a isomería óptica, la invención contempla sus isómeros ópticos y mezclas. Los compuestos de fórmula I incluyen átomos de carbono asimétricos y por lo tanto pueden existir como estereoisómeros individuales, racematos y mezclas de enantiómeros y diastereoisómeros. Típicamente, dichos compuestos se prepararán como una mezcla racémica. Sin embargo, si se desea, dichos compuestos se pueden preparar o aislar como isómeros ópticos puros, es decir, como enantiómeros o diastereoisómeros individuales, o como mezclas enriquecidas en un estereoisómero. Los estereoisómeros individuales de los compuestos se preparan por síntesis a partir de materias primas ópticamente activas que contienen los centros quirales deseados o por preparación de mezclas de productos enantiómeros seguido de separación, tal como por conversión

en una mezcla de diastereoisómeros seguido de separación o recristalización, técnicas cromatográficas, uso de agentes de resolución quirales, o separación directa de los enantiómeros en columnas cromatográficas quirales. Los compuestos de partida de estereoquímica particular están disponibles en el comercio o se preparan por métodos descritos a continuación y se resuelven por técnicas conocidas en la técnica.

El término "enantiómeros" significa una pareja de isómeros ópticos que son imágenes especulares no superponibles entre sí.

El término "diastereoisómeros" significa isómeros ópticos que no son imágenes especulares entre sí.

10 La expresión "mezcla racémica" significa una mezcla que contiene partes iguales de enantiómeros individuales.

La expresión "mezcla no racémica" significa una mezcla que contiene partes desiguales de los enantiómeros o estereoisómeros individuales.

15 La expresión "isómero geométrico" significa un isómero estable que resulta de la libertad de rotación restringida alrededor de dobles enlaces (por ejemplo, *cis*-2-buteno y *trans*-2-buteno) o en una estructura cíclica (por ejemplo, *cis*-1,3-diclorociclobutano y *trans*-1,3-diclorociclobutano). Puesto que puede haber dobles enlaces carbono-carbono (olefínicos), estructuras cíclicas, y similares, en los compuestos de fórmula I, la invención contempla cada uno de los diferentes isómeros geométricos estables y sus mezclas, que resultan de la disposición de los sustituyentes alrededor de estos dobles enlaces y en estas estructuras cíclicas. Los sustituyentes e isómeros se designan usando el convenio *cis/trans*.

20 Algunos de los compuestos de fórmula (I) pueden existir en más de una forma tautómera. Como se ha mencionado antes, los compuestos de fórmula (I) incluyen todos dichos tautómeros.

25 En general, se incluyen todas las formas tautómeros y formas isómeras y sus mezclas, por ejemplo, isómeros geométricos individuales, estereoisómeros, isómeros ópticos, o mezclas racémicas o no racémicas de los isómeros, de una estructura química o compuestos, salvo que se indique la estereoquímica específica o forma isómera en el nombre o estructura del compuesto.

C. Términos y convenios de administración farmacéutica y tratamiento

El término "paciente" incluye tanto mamíferos humanos como no humanos.

35 La expresión "cantidad terapéuticamente eficaz" significa una cantidad de un compuesto de acuerdo con la invención, que cuando se administra a un paciente que lo necesita, es suficiente para realizar el tratamiento de la infección por el virus de la

hepatitis C. Dicha cantidad terapéuticamente eficaz puede ser determinada rutinariamente por un experto en la técnica teniendo en cuenta su propio conocimiento, la técnica anterior, y esta descripción.

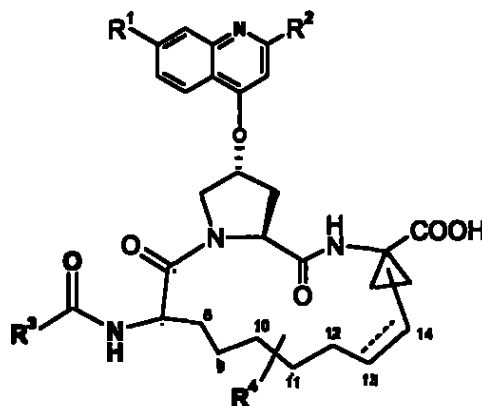
Los términos "tratar" o "tratamiento" significan el tratamiento de una infección por el virus de la hepatitis C en un paciente, e incluyen:

- (i) prevenir que se produzca la infección por el virus de la hepatitis C en un paciente, en particular, cuando dicho paciente está predispuesto a dicho estado patológico, pero todavía no se le ha diagnosticado que lo tenga;
- (ii) inhibir o mejorar la infección por el virus de la hepatitis C, es decir, parar o ralentizar su desarrollo; o
- (iii) aliviar la infección por el virus de la hepatitis C, es decir, producir retroceso o cura del estado patológico.

Realizaciones preferidas de la invención

La realización preferida a la que se denominará en la presente memoria "sistema basado en lípidos", se dirige a una composición farmacéutica que comprende:

- (a) un compuesto de fórmula (I):



(I)

en la que:

— indica un enlace opcional que forma un doble enlace entre las posiciones 13 y 14;

R^1 es H, halógeno, alquilo C_{1-6} , cicloalquilo C_{3-6} , halógenoalquilo C_{1-6} , alcoxi C_{1-6} , cicloalcoxi C_{3-6} , hidroxil, o $N(R^5)_2$, en el que cada R^5 es independientemente H, alquilo C_{1-6} o cicloalquilo C_{3-6} ;

R^2 es H, halógeno, alquilo C_{1-6} , cicloalquilo C_{3-6} , halógenoalquilo C_{1-6} , tioalquilo C_{1-6} , alcoxi C_{1-6} , cicloalcoxi C_{3-6} , alcoxi alquilo C_{2-7} , arilo o Het C_6 a 10 , en el que Het es un

heterociclo saturado o insaturado, de cinco, seis o siete miembros que contiene de uno a cuatro heteroátomos en el anillo seleccionados de nitrógeno, oxígeno y azufre;

estando dicho cicloalquilo, arilo o Het opcionalmente sustituido con R^6 ,

en el que R^6 es H, halógeno, alquilo C_{1-6} , cicloalquilo C_{3-6} , alcoxi C_{1-6} , cicloalcoxi

5 C_{3-6} , NO_2 , $N(R^7)_2$, $NH-C(O)-R^7$; o $NH-C(O)-NH-R^7$, en los que cada R^7 es independientemente: H, alquilo C_{1-6} o cicloalquilo C_{3-6} ;

o R^6 es $NH-C(O)-OR^8$ en el que R^8 es alquilo C_{1-6} o cicloalquilo C_{3-6} ;

R^6 es R^9O- o R^9NH- , en los que R^9 es alquilo C_{1-6} o cicloalquilo C_{3-6} ;

10 R^4 es H o de uno a tres sustituyentes en cualquier átomo de carbono disponible en las posiciones 8, 9, 10, 11, 12, 13 ó 14, seleccionado dicho sustituyente independientemente del grupo que consta de: alquilo C_{1-6} , halógenoalquilo C_{1-6} , alcoxi C_{1-6} , hidroxil, halógeno, amino, oxo, tio o tioalquilo C_{1-6} ;

o uno de sus tautómeros;

15 (b) aproximadamente 0,1 a 10% en peso de una amina farmacéuticamente aceptable o una mezcla de aminas farmacéuticamente aceptables;

(c) aproximadamente 0,1 a 10% en peso de una base farmacéuticamente aceptable o una mezcla de bases farmacéuticamente aceptables;

(d) uno o más aceites farmacéuticamente aceptables;

20 (e) opcionalmente uno o más disolventes hidrófilos farmacéuticamente aceptables;

(f) opcionalmente uno o más polímeros farmacéuticamente aceptables; y

(g) opcionalmente uno o más tensioactivos farmacéuticamente aceptables.

La cantidad del ingrediente activo (compuesto de fórmula (I)) que puede estar presente en la composición del sistema basado en lípidos, puede variar ampliamente o se puede ajustar dependiendo mucho de la vía de administración pretendida, la potencia del ingrediente activo particular que se va a usar, la gravedad de la infección por el virus de la hepatitis C y la concentración deseada. En una realización particular, el compuesto de fórmula (I) está presente en el sistema basado en lípidos en una cantidad de aproximadamente 1% a 50% en peso, preferiblemente de 25 aproximadamente 5% a 30% en peso, más preferiblemente de aproximadamente 10% a 20% en peso.

Entre las aminas farmacéuticamente aceptables útiles en la composición se incluyen, por ejemplo, alquilamina C_{1-6} , di-(alquil C_{1-6})-amina o tri-(alquil C_{1-6})-amina, en las que uno o más de sus grupos alquilo pueden estar opcionalmente sustituidos con 35 uno o más grupos hidroxil, o alquilen(C_{1-6})-diamina, un aminoácido básico o hidróxido

de colina, o sus mezclas. Entre las aminas específicas se incluyen etanolamina, dietanolamina, trietanolamina, tris(hidroximetil)aminometano, etilendiamina, dimetilaminoetanol, o meglumina, o sus mezclas. Una amina preferida es tris(hidroximetil)aminometano (también denominada "Tris" o "Trometamina"). La amina
5 está presente en una cantidad de aproximadamente 0,1 a 10% en peso, más preferiblemente en una cantidad de aproximadamente 0,5% a 7% en peso; incluso más preferiblemente de aproximadamente 0,5% a 5% en peso.

Entre las bases farmacéuticamente aceptables útiles en la composición se incluyen, por ejemplo, hidróxido potásico, hidróxido sódico, hidrógeno-carbonato
10 sódico, hidróxido de aluminio, carbonato cálcico, hidróxido magnésico, silicato de aluminio-magnesio, silicato de aluminio sintético, hidrotalcita sintética, hidróxido de aluminio-magnesio. También son adecuadas bases que son sales de un ácido farmacéuticamente aceptable, tales como ácido acético, ácido acrílico, ácido adípico, ácido algínico, ácido alcanosulfónico, aminoácidos, ácido ascórbico, ácido benzoico,
15 ácido bórico, ácido butírico, ácido carbónico, ácido cítrico, ácidos grasos, ácido fórmico, ácido fumárico, ácido glucónico, ácido hidroquinosulfónico, ácido isoascórbico, ácido láctico, ácido maleico, ácido oxálico, ácido para-bromofenilsulfónico, ácido propiónico, ácido p-toluenosulfónico, ácido salicílico, ácido esteárico, ácido succínico, ácido tánico, ácido tartárico, ácido tioglicólico, ácido toluenosulfónico, ácido úrico, y
20 similares. También se pueden usar sales de ácidos polipróticos, tales como fosfato sódico, hidrógeno-fosfato disódico, y dihidrógeno-fosfato sódico. Cuando la base es una sal, el catión puede ser cualquier catión conveniente y farmacéuticamente aceptable, tal como amonio, metales alcalinos, metales alcalinotérreos, y similares. Entre los cationes preferidos se incluyen sodio, potasio, litio, magnesio, calcio y
25 amonio. Algunas bases preferidas incluyen hidróxido sódico, hidróxido potásico, hidrógeno-carbonato sódico, hidróxido de aluminio, hidróxido magnésico, hidróxido de aluminio-magnesio. La base farmacéuticamente aceptable está presente en la composición en una cantidad de aproximadamente 0,1 a 10% en peso, por ejemplo aproximadamente 0,1 a 5% en peso, por ejemplo, aproximadamente 0,1 a 3% en peso.

30 Entre los aceites farmacéuticamente aceptables útiles en la composición se incluyen un amplio espectro de materiales inmiscibles con el agua, tales como por ejemplo, mono, di o triglicéridos de cadena media o larga, aceites vegetales tales como aceite de soja, aceite de aguacate, aceite de escualeno, aceite de sésamo, aceite de oliva, aceite de cáñola, aceite de maíz, aceite de colza, aceite de cartamo, y aceite de
35 grasol, aceites de pescado, aceites aromáticos, vitaminas insolubles en agua, ácidos

grasos y sus mezclas. Entre los aceites más preferidos se incluyen mono, di o triglicéridos de ácido graso caprílico; mono, di o triglicéridos de ácido graso cáprico; ácido oleico y sus mezclas. Entre algunos aceites preferidos se incluyen los disponibles en el comercio con las marcas comerciales: Capmul MCM, Capmul MCM C-8, Capmul MCM C-10, Capmul PG-8, Miglyol 810, Captex 355, Miglyol 812, Captex 200, Myvacet, Miverol 18-92, Malsine, y Arlacel 188. La cantidad del(los) aceite(s) en la composición puede variar en un amplio intervalo, y la cantidad óptima para una composición particular dependerá del tipo y cantidad de los otros ingredientes en la composición como puede determinar el experto en la técnica farmacéutica. Sin embargo, en general, el aceite farmacéuticamente aceptable está presente en una cantidad de aproximadamente 1% a 99% en peso, más preferiblemente en una cantidad de aproximadamente 20% a 70% en peso.

En algunas circunstancias, por ejemplo, con el propósito de aumentar la solubilidad, mejorar la dispersabilidad, se pueden usar opcionalmente disolventes hidrófilos farmacéuticamente aceptables en la composición, los cuales incluyen, por ejemplo, propilenglicol, polipropilenglicol, polietilenglicol (por ejemplo, PEG 400), glicerol, etanol, dimetil-isosorbida, glicofuro, carbonato de propileno, dimetil-acetamida, agua, o sus mezclas; preferiblemente, polietilenglicol, etanol, agua o sus mezclas.

Un disolvente preferido es una mezcla de propilenglicol, etanol y agua. La cantidad de disolvente en la composición puede variar en un amplio intervalo y la cantidad óptima para una composición particular dependerá del tipo y cantidad de los otros ingredientes en la composición, como puede determinar fácilmente un experto en la técnica. Sin embargo, en general, el(los) disolvente(s) están presentes en una cantidad de hasta aproximadamente 70% en peso, preferiblemente de aproximadamente 10% a 30% en peso.

Para ajustar la viscosidad de la formulación o mejorar la estabilidad, se pueden usar polímeros farmacéuticamente aceptables en la composición, los cuales incluyen, por ejemplo, polietilenglicoles (por ejemplo, PEG 1000, PEG 1500, PEG 3350, PEG 6000 y PEG 8000), polivinilpirrolidonas (por ejemplo, Kollidon 12 PF, Kollidon 17 PF, Kollidon 25 PF, Kollidon 30 PF, Kollidon 90 PF etc.), poli(alcoholes vinílicos), derivados de celulosa (por ejemplo, hidroxipropilmetil-celulosa (HPMC), hidroxipropil-celulosa (HPC)), poliacrilatos, polimetacrilatos, azúcares (por ejemplo, lactosa), polioles, y sus mezclas. Cuando se usa en la composición, el polímero farmacéuticamente aceptable está presente en una cantidad de hasta aproximadamente 50% en peso, preferiblemente aproximadamente 1 a 20% en peso.

Para facilitar la autoemulsión, se pueden usar opcionalmente en la composición tensioactivos farmacéuticamente aceptables, los cuales incluyen, por ejemplo, derivados de vitaminas tales como Vitamina E TPGS (succinato de d-alfa-tocoferil-polietilenglicol 1000), aceites de ricino polietoxilados (por ejemplo, Cremophor EL),
5 aceites de ricino hidrogenados polietoxilados, polysorbatos (por ejemplo, Tween 80), oleato de peglicol-6, estearatos de polioxetileno, glicéridos poliglicolizados (por ejemplo, Gelucire 44/14) o poloxámeros (por ejemplo, Pluronic F68), lauril-sulfato sódico y sus mezclas. Entre los tensioactivos preferidos se incluyen Vitamina E TPGS, aceite de ricino hidrogenado polietoxilado-40 o aceite de ricino polietoxilado-35, y sus
10 mezclas.

Cuando se usa en la composición, el tensioactivo está presente preferiblemente en una cantidad de hasta aproximadamente 70% en peso, preferiblemente de aproximadamente 20% a 50% en peso. Este tipo de sistema basado en lípidos de la presente invención que además incorpora un tensioactivo se denomina en general en
15 la presente memoria "sistema de liberación de fármaco autoemulsionante" o "SEDDS".

Una realización particular de la composición de SEDDS de acuerdo con la presente invención se dirige a una composición farmacéutica, que comprende:

- (a) aproximadamente 5% a 30% en peso de un compuesto de fórmula (I);
- (b) aproximadamente 0,1% a 7% en peso de una amina farmacéuticamente
20 aceptable;
- (c) aproximadamente 0,1% a 5% en peso de una base farmacéuticamente aceptable;
- (d) aproximadamente 1% a 99% en peso de un aceite farmacéuticamente aceptable;
- 25 (e) hasta aproximadamente 70% en peso de un disolvente hidrófilo farmacéuticamente aceptable;
- (f) opcionalmente hasta aproximadamente 50% en peso de un polímero farmacéuticamente aceptable; y
- (g) hasta aproximadamente 70% en peso de un tensioactivo farmacéuticamente
30 aceptable.

Una realización particular adicional de la composición de SEDDS de acuerdo con la presente invención se dirige a una composición farmacéutica, que comprende:

- (a) aproximadamente 10% a 20% en peso de un compuesto de fórmula (I);
- (b) aproximadamente 0,1% a 5% en peso de una amina farmacéuticamente
35 aceptable;

(c) aproximadamente 0,1% a 3% en peso de una base farmacéuticamente aceptable;

(d) aproximadamente 20% a 70% en peso de un aceite farmacéuticamente aceptable;

5 (e) aproximadamente 10% a 30% en peso de un disolvente hidrófilo farmacéuticamente aceptable;

(f) opcionalmente aproximadamente 1% a 20% en peso de un polímero farmacéuticamente aceptable; y

10 (g) aproximadamente 20% a 50% en peso de un tensioactivo farmacéuticamente aceptable.

Una realización particular adicional de la composición de SEDDS de acuerdo con la presente invención se dirige a una composición farmacéutica, que comprende:

(a) aproximadamente 10% a 20% en peso de un compuesto de fórmula (I);

(b) aproximadamente 0,1% a 5% en peso de tris(hidroximetil)aminometano;

15 (c) aproximadamente 0,1% a 3% en peso de hidróxido sódico;

(d) aproximadamente 20% a 70% en peso de un triglicérido de ácido graso caprílico o un triglicérido de ácido graso cáprico, o sus mezclas;

(e) aproximadamente 10% a 30% en peso de una mezcla de propilenglicol, etanol y opcionalmente agua;

20 (f) opcionalmente aproximadamente 1% a 20% en peso de polietilenglicol o polivinilpirrolidona; y

(g) aproximadamente 20% a 50% en peso de succinato de d-alfa-tocoferil-polietilenglicol 1000 o aceite de ricino polietoxilado-35 (Cremophor EL).

25 Una realización particular adicional de la composición de SEDDS de acuerdo con la presente invención se dirige a una composición farmacéutica, que comprende:

(a) aproximadamente 10% a 15% en peso de un compuesto de fórmula (I);

(b) aproximadamente 0,1% a 2% en peso de tris(hidroximetil)aminometano;

(c) aproximadamente 0,1% a 1% en peso de hidróxido sódico;

(d) aproximadamente 20% a 30% en peso de Capmul MCM o Captex 355;

30 (e) aproximadamente 15% a 25% en peso de una mezcla de propilenglicol, etanol y agua;

(f) aproximadamente 40% a 50% en peso de succinato de d-alfa-tocoferil-polietilenglicol 1000; y

(g) aproximadamente 0,01% a 1% en peso de dl- α -tocoferol.

35 La composición de sistema basado en lípidos se puede preparar de una forma

convencional, por ejemplo, por un método que comprende: mezclar entre sí los componentes líquidos, por ejemplo, el(los) aceite(s) farmacéuticamente aceptable(s), y cualesquiera tensioactivo(s) y disolvente(s); disolver la(s) amina(s), base(s) y polímero(s) en la mezcla resultante; opcionalmente calentar la mezcla obtenida si es necesario para fundir suficientemente uno o más componentes de la mezcla; añadir el compuesto de fórmula (I) a la mezcla resultante y mezclar más hasta que todo o sustancialmente todo el compuesto de fórmula I se haya solubilizado. Este método de preparar las composiciones constituye otro aspecto de la presente invención. Después, la solución resultante se formula opcionalmente en la forma de dosificación deseada, por ejemplo, cápsulas, incluyendo cápsulas de cubierta dura o de gel blando (por ejemplo, cápsulas de gelatina dura o blanda), por tecnología de fabricación conocida. La composición también puede estar en forma de una solución líquida o semisólida para administración por vía oral, parenteral, rectal o tópica. Entre los ejemplos de cápsulas de gelatina blanda que se pueden usar se incluyen las descritas en los documentos EP 649651 B1 y patente de EE.UU. 5.985.321.

Ingredientes adicionales opcionales

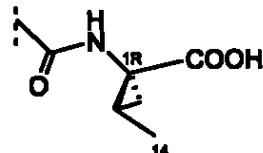
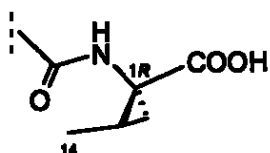
Si se desea, las composiciones de acuerdo con la presente invención pueden incluir además aditivos farmacéuticos convencionales cuando sea necesario o conveniente obtener una formulación adecuada, tal como antioxidantes, lubricantes, disgregantes, conservantes, tampones, estabilizantes, agentes espesantes, agentes colorantes, agentes de sabor, fragancias, etc. Tsantizos et al., describen aditivos adicionales que pueden ser útiles en las composiciones de la invención.

En una realización preferida, las composiciones de acuerdo con la invención contienen además uno o más antioxidantes. Entre los antioxidantes preferidos se incluyen, por ejemplo, ácido ascórbico, sales de sulfátido, ácido cítrico, galato de propilo, dl- α -tocoferol, palmitato de ascorbilo, BHT o BHA. Si está presente, el antioxidante generalmente está presente en una cantidad de aproximadamente 0,01% a 1% en peso.

Compuestos de fórmula (I)

Las realizaciones preferidas para los compuestos de fórmula (I) en las composiciones son las expuestas a continuación.

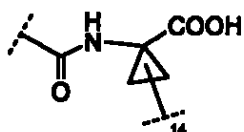
Las realizaciones preferidas incluyen compuestos de fórmula I como se ha descrito antes, en la que el resto ciclopropilo se selecciona de 2 diastereoisómeros diferentes, donde el centro del carbono 1 del ciclopropilo tiene la configuración R representado por las estructuras (i) y (ii):



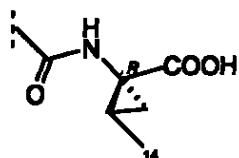
14 *sin* respecto a la amida (i), o 14 *sin* respecto al COOH (ii).

Más preferiblemente, la posición 14 está unida al grupo ciclopilo en la configuración *sin* respecto al grupo COOH, como se representa en la estructura (ii).

- 5 Por lo tanto, en una realización, en el compuesto de fórmula (I) el siguiente resto:



tiene la configuración representada por el siguiente diastereoisómero:

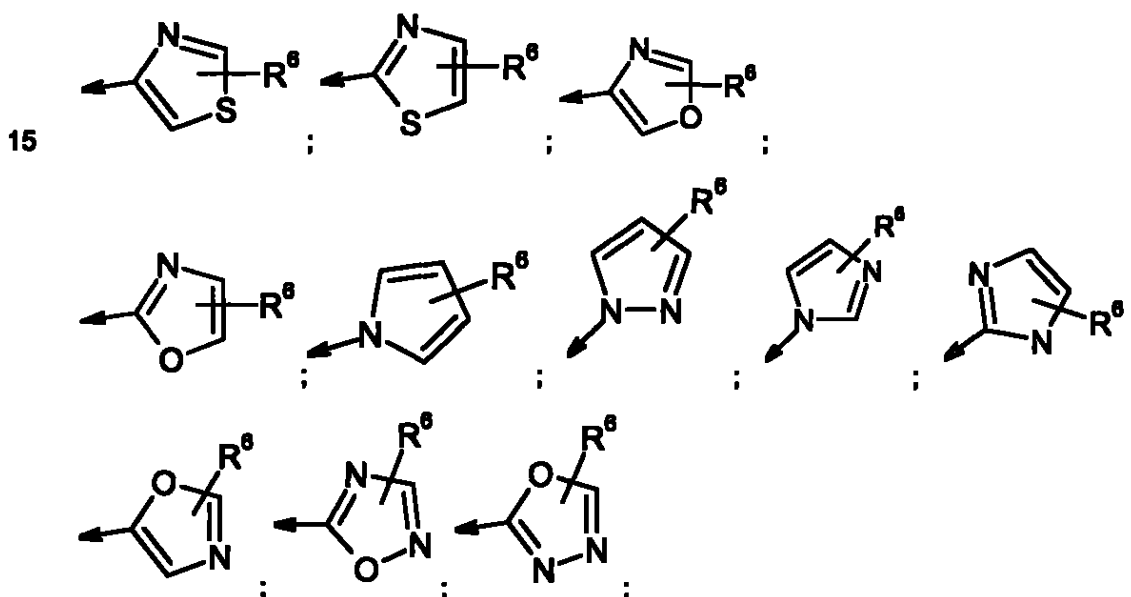


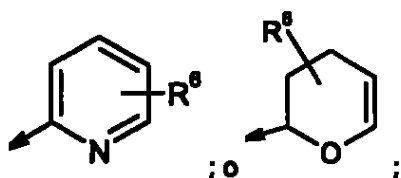
- 10 en cuya configuración la posición 14 está unida *sin* respecto al grupo COOH.

En otra realización, en el compuesto de fórmula (I):

R^1 es H, alquilo C_{1-6} , alcoxi C_{1-6} , hidroxil, cloro, o $N(R^5)_2$, en el que R^5 es H o alquilo C_{1-6} ; y

R^2 es H, tioalquilo C_{1-6} , alcoxi C_{1-6} , fenilo o Het seleccionado de los siguientes:





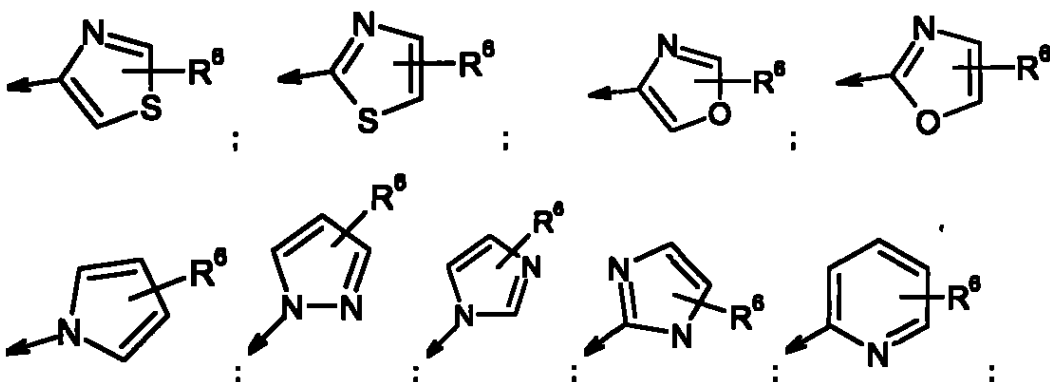
en los que R^6 es H, alquilo C_{1-6} , $NH-R^7$, $NH-C(O)-R^7$, $NH-C(O)-NH-R^7$,
 en los que cada R^7 es Independientemente: H, alquilo C_{1-6} , o cicloalquilo C_{3-6} ;
 o $NH-C(O)-OR^8$, en el que R^8 es alquilo C_{1-6} .

5 En otra realización, en el compuesto de fórmula (I):

R^1 es H o alcoxi C_{1-6} .

En otra realización, en el compuesto de fórmula (I):

R^2 es alcoxi C_{1-4} , fenilo o Het seleccionado de los siguientes grupos:



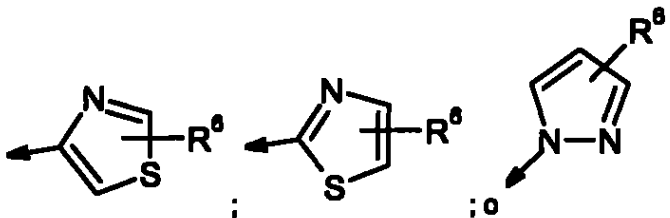
10

en los que R^6 es H, alquilo C_{1-6} , $NH-R^7$, o $NH-C(O)-R^7$;
 en los que cada R^7 es H, alquilo C_{1-6} o cicloalquilo C_{3-6} , o
 $NH-C(O)-OR^8$, en el que R^8 es alquilo C_{1-6} .

En otra realización, en el compuesto de fórmula (I):

15

R^2 es etoxi, o Het seleccionado de los siguientes grupos:



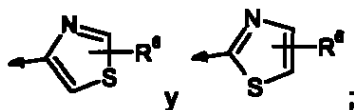
en los que R^6 es NHR^7 o $NH-C(O)-R^7$, en los que R^7 es H, alquilo C_{1-6} o
 cicloalquilo C_{3-6} ;

o R^6 es $NH-C(O)-OR^8$, en el que R^8 es alquilo C_{1-6} .

20

En otra realización, en el compuesto de fórmula (I):

R^2 se selecciona de los siguientes grupos:



R^6 es NHR^7 , en el que cada R^7 es independientemente: H, alquilo C_{1-6} , o cicloalquilo C_{3-6} .

En otra realización, en el compuesto de fórmula (I):

5 R^3 es R^6O- , en el que R^6 es butilo, ciclobutilo o ciclopentilo.

En otra realización, en el compuesto de fórmula (I):

el enlace en la posición 13-14 es un enlace sencillo.

En otra realización, en el compuesto de fórmula (I):

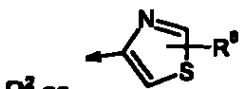
el enlace en la posición 13-14 es un doble enlace y dicho doble enlace es *cis*.

10 En otra realización, en el compuesto de fórmula (I):

R^4 es H o alquilo C_{1-6} .

En otra realización, en el compuesto de fórmula (I):

R^1 es metoxi;

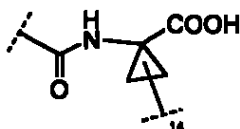


15 R^2 es en el que R^6 es NH-(alquilo C_{1-4}) o NH-(cicloalquilo C_{3-6});

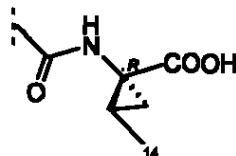
R^3 es R^6O- , en el que R^6 es butilo, ciclobutilo o ciclopentilo;

R^4 es H o alquilo C_{1-6} ;

y el siguiente resto:



tiene la configuración representada por el siguiente diastereoisómero:



20

en cuya configuración la posición 14 está unida *sin* respecto al grupo COOH.

Tablas de compuestos

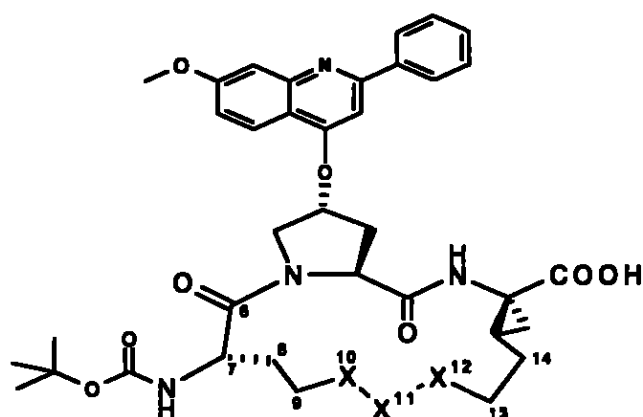
Las siguientes tablas listan compuestos representativos de los compuestos de fórmula (I).

25

Tabla 1:

Comp. #	R:	R ^A :	doble enlace:	Estereoquímica del ciclopropilo respecto al enlace de la posición 14:	R ¹ :	R ² :
205	NH-Boc	11-OH 12-OH cis	no	1R o 1S, 14 es <i>sin</i> respecto al ácido	H	H;
206	NH-Boc	H	13,14- <i>cis</i>	1R, 14 es <i>sin</i> respecto al ácido	H	H;
207	NH-Boc	H	13,14- <i>cis</i>	1R, 14 es <i>sin</i> respecto al ácido	OMe	H;
208	NH-Boc	H	13,14- <i>cis</i>	1R, 14 es <i>sin</i> respecto al ácido	OMe	fenilo;
209	NH- C(O)- NH-tBu	H	13,14- <i>cis</i>	1R, 14 es <i>sin</i> respecto al ácido	OMe	fenilo;
210	NH-Boc	H	13,14- <i>cis</i>	1S, 14 es <i>sin</i> respecto al ácido	OMe	fenilo;
214	NH-Boc	10-oxo	13,14- <i>cis</i>	1R, 14 es <i>sin</i> respecto al ácido	OMe	fenilo;
215	NH-Boc	H	no	1R, 14 es <i>sin</i> respecto al ácido	OMe	fenilo;
217	NH-Boc	10-OH (mezcla diastereo.)	13,14- <i>cis</i>	1R, 14 es <i>sin</i> respecto al ácido	OMe	fenilo;
218	NH-Boc	10-oxo	13,14- <i>cis</i>	1R, 14 es <i>sin</i> respecto al amida	OMe	fenilo;
y 220	NH-Boc	H	13,14- <i>cis</i>	1R, 14 es <i>sin</i> respecto al amida	OMe	

Tabla 2:

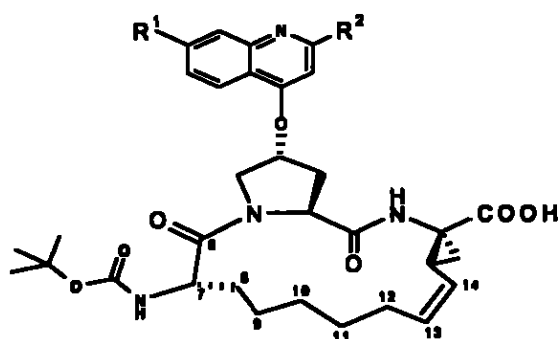


en el que el enlace de la posición 14 respecto al grupo ciclopropilo es *sin* respecto al COOH, X_{10} , X_{11} , y X_{12} se definen como sigue:

Comp.#	X ₁₀ :	X ₁₁ :	X ₁₂ :
502	CH ₂	CH ₂	CH ₂ .

5

Tabla 3:



en el que el enlace de la posición 14 respecto al grupo ciclopropilo es *sin* respecto al COOH, y R¹ y R² se definen como sigue:

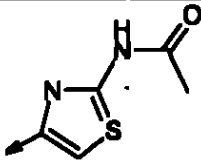
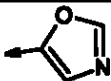
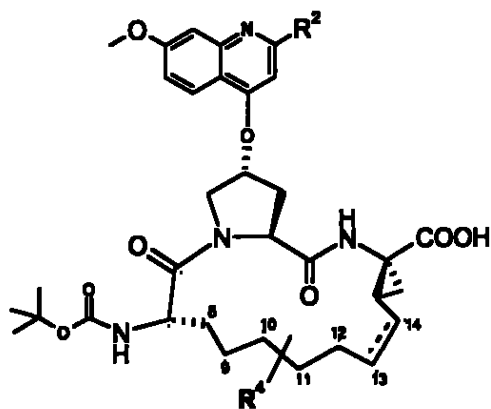
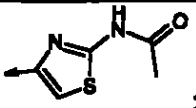
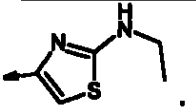
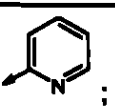
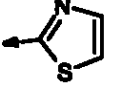
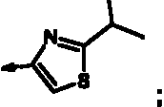
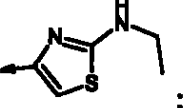
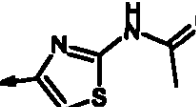
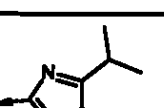
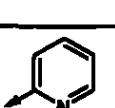
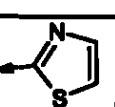
Comp. #	R ¹ :	R ² :
601	N(Me) ₂	
602	OH	(CF ₃);
y 603	OMe	

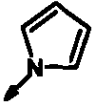
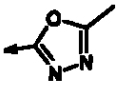
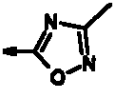
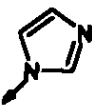
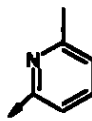
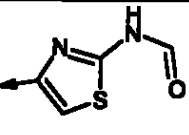
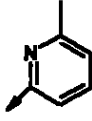
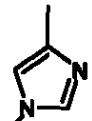
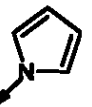
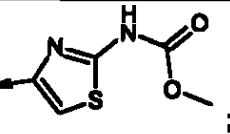
Tabla 4:

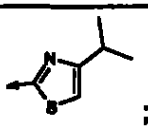
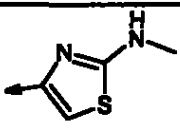
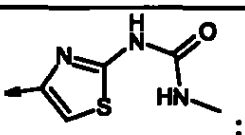
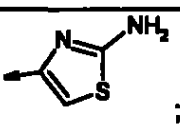
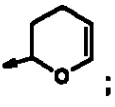
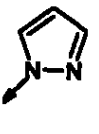
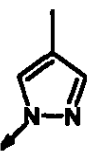
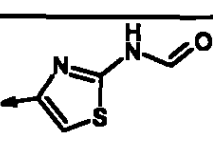


5

en el que el enlace de la posición 14 respecto al grupo ciclopropilo es *sin* respecto al COOH, y R⁴, el doble enlace de 13,14 y R² se definen como sigue:

Comp. #	R ¹ :	doble enlace 13,14	R ² :
702	H	Cis	 ;
703	H	No	 ;
704	H	Cis	 ;
705	H	Cis	 ;
707	H	Cis	 ;
708	H	Cis	 ;
709	H	No	 ;
710	H	No	 ;
711	H	No	 ;
712	H	Cis	-OEt;
713	H	No	 ;
714	H	No	-OEt;

Comp. #	R ⁴ :	doble enlace 13,14	R ² :
715	H	Cis	 ;
716	H	Cis	 ;
717	H	Cis	 ;
718	H	Cis	 ;
719	H	Cis	 ;
720	H	No	 ;
721	H	No	 ;
722	H	Cis	 ;
723	H	No	 ;
724	H	No	 ;

Comp. #	R ⁴ :	doble enlace 13,14	R ² :
725	H	Cis	 ;
726	H	Cis	 ;
727	H	Cis	-CH ₂ -OMe;
728	H	Cis	Me;
729	H	Cis	 ;
730	H	No	 ;
731	H	Cis	 ;
732	H	Cis	 ;
733	H	Cis	 ;
734	H	Cis	 ;
735	H	Cis	 ;

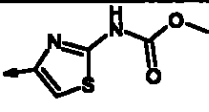
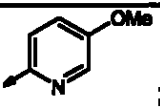
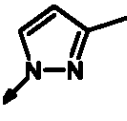
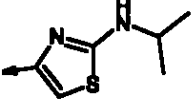
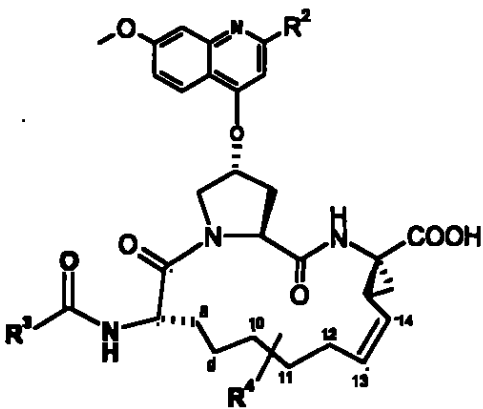
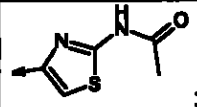
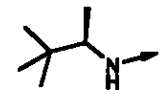
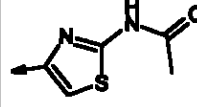
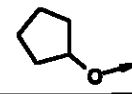
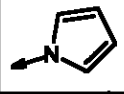
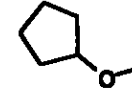
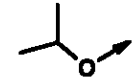
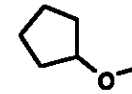
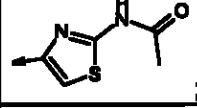
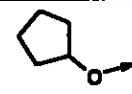
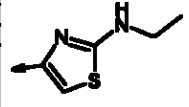
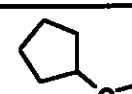
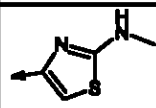
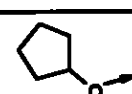
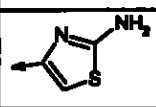
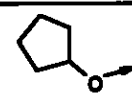
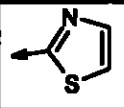
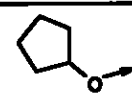
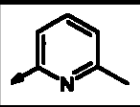
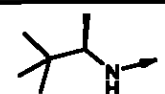
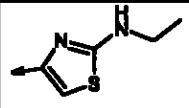
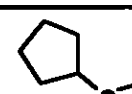
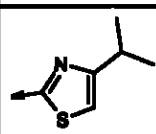
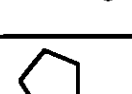
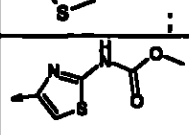
Comp. #	R ⁴ :	doble enlace 13,14	R ² :
736	H	Cis	 ;
737	H	Cis	 ;
738	H	Cis	 ;
739	10-(R) Me	no	F;
740	10-(S) Me	no	F;
y 741	H	Cis	

Tabla 5



en el que el enlace de la posición 14 respecto al grupo ciclopropilo es *sin* respecto al
5 COOH, dicho doble enlace 13,14 es *cis*, R³, R⁴ y R² se definen como sigue:

Comp. #	R ¹ :	R ⁴ :	R ² :
801		H	
804		H	
805		H	
807		H	OEt;
808		H	OEt;
809		H	
810		H	
811		H	
812		H	
814		H	
815		H	
816		H	
817		H	
818		H	

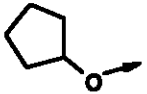
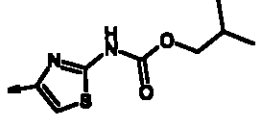
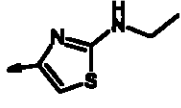
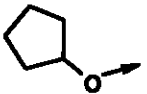
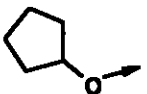
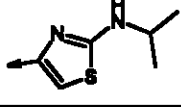
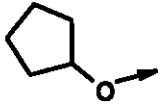
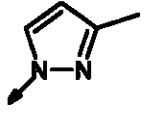
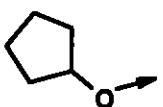
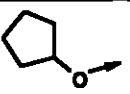
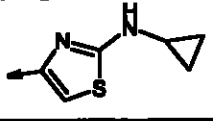
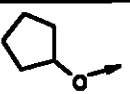
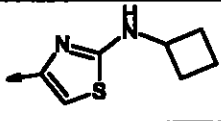
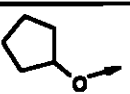
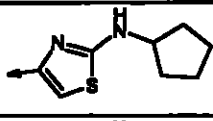
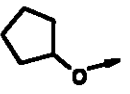
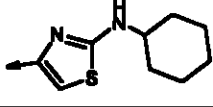
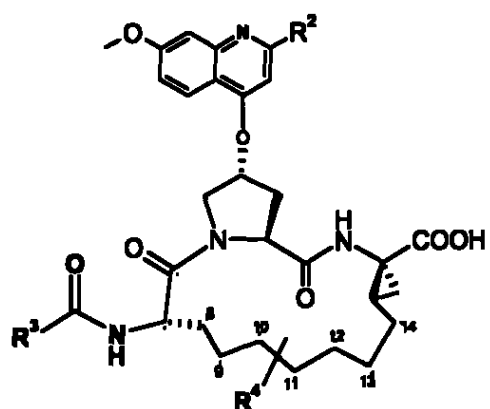
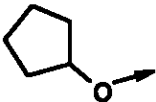
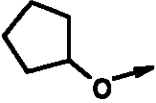
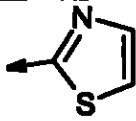
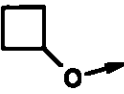
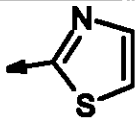
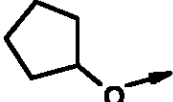
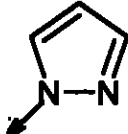
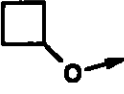
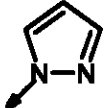
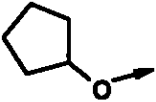
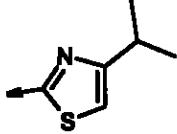
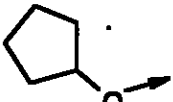
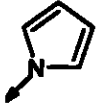
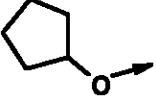
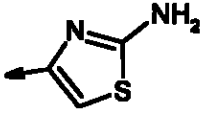
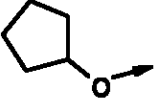
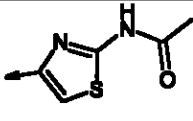
Comp. #	R ³ :	R ⁴ :	R ¹ :
819		H	
820		H	
821		H	
822		H	
823		H	
824		10- (R) Me	OEt;
825		H	
826		H	
827		H	
y 828		H	

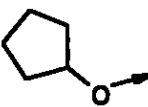
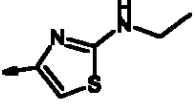
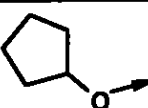
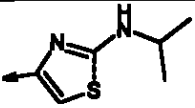
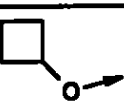
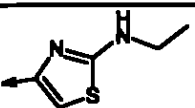
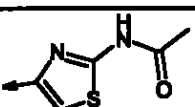
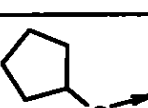
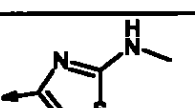
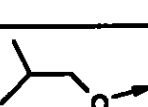
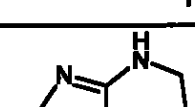
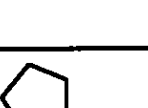
Table 6

en el que el enlace de la posición 14 respecto al grupo ciclopropilo es *sin* respecto al COOH, y R^3 , R^4 y R^5 se definen como sigue:

109
110

Comp. #	R ³ :	R ⁴ :	R ² :
901		H	OEt;
902		H	 ;
903		H	 ;
904		H	 ;
905		H	 ;
906		H	 ;
907		H	 ;
908		H	 ;
909		H	 ;

110
111

Comp. #	R ³ :	R ⁴ :	R ² :
910		H	 ;
911		H	 ;
912		H	 ;
913		H	 ;
914		H	 ;
915		H	 ;
y 916		10 (R) Me	OEt.

Un compuesto preferido de fórmula (I) para cualquiera de las composiciones de la invención descritas en la presente memoria, es el compuesto #822. Se pueden encontrar compuestos específicos adicionales que son representativos de los compuestos de fórmula (I), en Tsantrizos et al. y documento WO 00/59929.

Los compuestos de fórmula I se pueden sintetizar por procedimientos expuestos con detalle por Tsantrizos et al. y en el documento WO 00/59929.

Métodos de uso terapéutico

Los compuestos de fórmula I son eficaces como inhibidores de la proteasa del VHC, y por lo tanto estos compuestos y composiciones farmacéuticas que comprenden estos compuestos son útiles para inhibir la replicación del VHC en el tratamiento de infecciones por el VHC, como exponen con detalle Tsantrizos et al. y en el documento WO 00/59929.

112

5 Como se ha discutido antes, las composiciones farmacéuticas de la presente invención se pueden formular en una variedad de formas de dosificación dependiendo de la composición particular contemplada. Igualmente, son posibles una variedad de modos de administración dependiendo de la composición particular y forma de dosificación, aunque los modos de administración preferidos son la administración por vía oral mediante comprimido, cápsula o suspensión.

10 Los niveles de dosificación de los compuestos de fórmula (I) y diferentes regímenes de tratamiento en la monoterapia para prevenir y tratar la infección por el VHC son expuestos por Tsantrizos et al. y en el documento WO 00/59929. Sin embargo, como apreciarán los expertos en la técnica, son posibles dosificaciones menores con las composiciones de la presente invención dependiendo del nivel de mejora de la biodisponibilidad. También es posible la terapia de combinación con uno o más agentes terapéuticos o profilácticos adicionales como describen con detalle Tsantrizos et al. y en el documento WO 00/59929. El(los) agente(s) adicional(es) se puede(n) combinar con los compuestos de esta invención para crear una sola forma de dosificación, o alternativamente, este(estos) agente(s) adicional(es) se puede(n) administrar por separado a un mamífero como parte de una forma de dosificación múltiple.

20 Con el fin de que se entienda más completamente esta invención, se exponen los siguientes ejemplos. Estos ejemplos tienen el propósito de ilustrar realizaciones de esta invención, y no se pretende que limiten el alcance de la invención de ninguna forma.

Ejemplos

Formulación # 1 (comparativa)

Ingrediente	Peso (mg/g)	% (peso/peso)
Compuesto #822	100	10
Trometamina	10	1
Agua	20	2
Etanol	100	10
Propilenglicol	50	5
Alfa-Tocoferol	4	0,4
Capmul MCM	220	22
V _E TPGS	516	49,6

25

Formulación # 2

112
113

Ingrediente	Peso (mg/g)	% (peso/peso)
Compuesto #822	100	10
Trometamina	10	1
Hidróxido sódico	3	0,3
Agua	17	1,7
Etanol	100	10
Propilenglicol	50	5
Alfa-Tocoferol	4	0,4
Capmul MCM	220	22
V _E TPGS	516	49,6

Formulación # 3

Ingrediente	Peso (mg/g)	% (peso/peso)
Compuesto #822	100	10
Trometamina	10	1
Hidróxido sódico	3	0,3
Agua	30	3
Etanol	100	10
Propilenglicol	50	5
Alfa-Tocoferol	4	0,4
Captex 355	220	22
V _E TPGS	483	48,3

Preparación de las formulaciones 1-3:

- 5 Primero se mezclaron entre sí los componentes líquidos tales como Capmul MCM, Captex 355, propilenglicol, alfa-tocoferol, agua y etanol, en un recipiente firmemente cerrado. Se fundió la V_E TPGS a 40°C y después se transfirió al recipiente. Y después se añadieron trometamina y/o solución de hidróxido sódico a la mezcla anterior. Finalmente, se añadió el compuesto #822 al recipiente y se continuó agitando
- 10 a 40°C hasta que el fármaco se solubilizó completamente. Estas formulaciones se pueden cargar en cápsulas de cubierta dura o gelatina blanda.

Estudios de estabilidad química

- Los productos de degradación principales del compuesto #822 en la formulación se identificaron y caracterizaron por LC/MS. Para comparar diferentes
- 15 formulaciones, se llevaron a cabo estudios de estabilidad acelerada: las formulaciones

se sellaron en ampollas de color ámbar y se almacenaron a diferentes temperaturas: 50, 60 y 70°C. Se sacaron muestras y se analizaron por HPLC para ensayo e impurezas.

Las Figuras 1 y 2 son perfiles de impurezas de las formulaciones que contienen el compuesto #822, basados en los datos obtenidos durante un estudio inicial. Todas las formulaciones se analizaron después de 5 días a 70°C. Como puede verse en las Figuras 1 y 2, el nivel del producto 1 de degradación principal es menor en las Formulaciones #2 y #3 de la invención que en la Formulación #1 comparativa (sin base).

Se llevó a cabo un estudio de seguimiento más completo en las Formulaciones #1 y #3 (las formulaciones usadas en este estudio de seguimiento eran de un lote diferente y por lo tanto presentaban niveles ligeramente diferentes de impurezas frente a las formulaciones usadas en el estudio inicial). Tanto las impurezas totales como el nivel del producto 1 de degradación principal han disminuido significativamente con la Formulación #3 comparada con la Formulación #1. Las Tablas 1a y 1b resumen las cantidades de impurezas totales y producto 1 de degradación principal en la Formulación #3 frente a la Formulación #1 comparativa, después de almacenamiento a diferentes temperaturas. Es evidente que la Formulación #3 es más estable que la Formulación #1, y tiene un nivel inferior tanto de impurezas totales como del producto 1 de degradación principal después de almacenamiento. De acuerdo con la ecuación de Arrhenius, $t_{0.1, 25}$ (tiempo para que el producto 1 de degradación alcance 0,1% a 25°C) de la Formulación #3 es 232 días comparado con 99 días para la Formulación #1.

114
115

Tabla 1a. Resumen de las impurezas totales en las Formulaciones #1 y #3.

Tiempo (días)	Formulación #1 (%)			Formulación #3 (%)		
	70°C	60°C	50°C	70°C	60°C	50°C
1	1,51			1,05		
3	2,12	1,82		1,56	1,28	
5	2,91			2,12		
7	4,07	3,34	1,19	2,94	2,49	1,02
15	7,37	6,5		5,25	4,78	1,44
22	10,39	7,92		7,51	6,37	
28	12,02	10,04	2,95	9,96	7,44	2,25
42			4,48			3,61
56			5,7			4,15

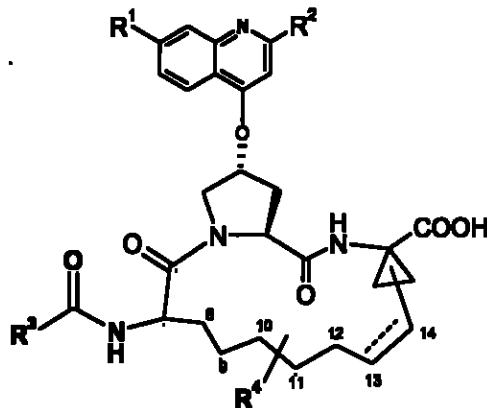
Tabla 1b. Resumen del producto 1 de degradación principal en las Formulaciones #1 y #3.

Tiempo (días)	Formulación #1 (%)			Formulación #3 (%)		
	70°C	60°C	50°C	70°C	60°C	50°C
1	0,37			0,15		
3	0,66	0,48		0,29	0,23	
5	1,01			0,47		
7	1,43	1,15	0,26	0,68	0,55	0,13
15	2,9	2,46		1,44	1,21	0,25
22	4,21	3,15		2,23	1,68	
28	5,32	3,9	0,96	3,08	2,1	0,5
42			1,55			0,81
56			2,09			1,07

REIVINDICACIONES

1. Una composición farmacéutica que comprende:

(a) un compuesto de fórmula (I):



(I)

en la que:

— indica un enlace opcional que forma un doble enlace entre las posiciones 13 y 14;

R¹ es H, halógeno, alquilo C₁₋₆, cicloalquilo C₃₋₆, halógenoalquilo C₁₋₆, alcoxi C₁₋₆, cicloalcoxi C₃₋₆, hidroxil, o N(R⁵)₂, en el que cada R⁵ es independientemente H, alquilo C₁₋₆ o cicloalquilo C₃₋₆;

R² es H, halógeno, alquilo C₁₋₆, cicloalquilo C₃₋₆, halógenoalquilo C₁₋₆, tioalquilo C₁₋₆, alcoxi C₁₋₆, cicloalcoxi C₃₋₆, alcoxialquilo C₂₋₇, arilo o Het C₆ a 10, en el que Het es un heterociclo saturado o insaturado, de cinco, seis o siete miembros que contiene de uno a cuatro heteroátomos en el anillo seleccionados de nitrógeno, oxígeno y azufre;

estando dicho cicloalquilo, arilo o Het opcionalmente sustituido con R⁶,

en el que R⁶ es H, halógeno, alquilo C₁₋₆, cicloalquilo C₃₋₆, alcoxi C₁₋₆, cicloalcoxi C₃₋₆, NO₂, N(R⁷)₂, NH-C(O)-R⁷; o NH-C(O)-NH-R⁷, en los que cada R⁷ es independientemente: H, alquilo C₁₋₆ o cicloalquilo C₃₋₆;

o R⁸ es NH-C(O)-OR⁸, en el que R⁸ es alquilo C₁₋₆ o cicloalquilo C₃₋₆;

R³ es R⁹O- o R⁹NH-, en los que R⁹ es alquilo C₁₋₆ o cicloalquilo C₃₋₆;

R⁴ es H o de uno a tres sustituyentes en cualquier átomo de carbono disponible en las posiciones 8, 9, 10, 11, 12, 13 ó 14, seleccionado dicho sustituyente independientemente del grupo que consta de: alquilo C₁₋₆, halógenoalquilo C₁₋₆, alcoxi C₁₋₆, hidroxil, halógeno, amino, oxo, tio o tioalquilo C₁₋₆.

218
117

- 40 -

o uno de sus tautómeros;

(b) aproximadamente 0,1 a 10% en peso de una amina farmacéuticamente aceptable o una mezcla de aminas farmacéuticamente aceptables;

5 (c) aproximadamente 0,1 a 10% en peso de una base farmacéuticamente aceptable o una mezcla de bases farmacéuticamente aceptables;

(d) uno o más aceites farmacéuticamente aceptables;

(e) opcionalmente uno o más disolventes hidrófilos farmacéuticamente aceptables;

(f) opcionalmente uno o más polímeros farmacéuticamente aceptables; y

10 (g) opcionalmente uno o más tensioactivos farmacéuticamente aceptables.

2. Una composición farmacéutica de acuerdo con la reivindicación 1, en la que el compuesto de fórmula (I) está presente en una cantidad de aproximadamente 1% a 50% en peso.

15

3. Una composición farmacéutica de acuerdo con la reivindicación 1 ó 2, en la que la amina está presente en una cantidad de aproximadamente 0,5% a 7% en peso.

20 4. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que la amina es una alquilamina C₁₋₆, di-(alquil C₁₋₆)-amina o tri-(alquil C₁₋₆)-amina, en la que uno o más de sus grupos alquilo pueden estar opcionalmente sustituidos con uno o más grupos hidroxilo, o la amina es alquilen(C₁₋₆)-diamina, o un aminoácido básico, o hidróxido de colina o sus mezclas.

25 5. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que la amina se selecciona de etanolamina, dietanolamina, trietanolamina, tris(hidroxi metil)aminometano, etilendiamina, dimetilaminoetanol, o meglumina, o sus mezclas.

30 6. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que la base está presente en una cantidad de aproximadamente 0,1% a 5% en peso.

35 7. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que la base se selecciona de hidróxido sódico,

hidróxido potásico, hidrógeno-carbonato sódico, hidróxido de aluminio, hidróxido magnésico, hidróxido de aluminio-magnesio.

5 8. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el aceite farmacéuticamente aceptable está presente en una cantidad de aproximadamente 20% a 70% en peso.

10 9. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el aceite farmacéuticamente aceptable se selecciona de: mono, di o triglicéridos de cadena media o larga, vitaminas insolubles en agua, ácidos grasos y sus mezclas.

15 10. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el aceite farmacéuticamente aceptable se selecciona de: triglicéridos de ácidos grasos caprílicos; triglicéridos de ácidos grasos cápricos; y sus mezclas.

20 11. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el disolvente hidrófilo farmacéuticamente aceptable se selecciona de propilenglicol, polipropilenglicol, polietilenglicol, glicerol, etanol, dimetil-isosorbida, glicofurol, carbonato de propileno, dimetilacetamida, agua, o sus mezclas.

25 12. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el disolvente hidrófilo farmacéuticamente aceptable se selecciona de propilenglicol, polietilenglicol, etanol, agua, y sus mezclas.

30 13. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el polímero farmacéuticamente aceptable está presente en una cantidad de hasta aproximadamente 50% en peso.

35 14. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el polímero farmacéuticamente aceptable se selecciona de polietilenglicoles, polivinilpirrolidonas, poli(alcoholes vinílicos), derivados de celulosa, poliacrilatos, polimetacrilatos, azúcares, polioles y sus mezclas.

15. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el tensioactivo farmacéuticamente aceptable está presente en una cantidad de hasta aproximadamente 70% en peso.

5

16. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el tensioactivo farmacéuticamente aceptable se selecciona de succinato de d-alfa-tocoferil-polietilenglicol 1000, aceites de ricino polietoxilados, polisorbatos, oleato de peglicol-6, estearatos polioxietilénicos, glicéridos poliglicolizados o poloxámeros, o lauril-sulfato sódico, o sus mezclas.

10

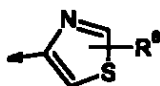
17. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el tensioactivo farmacéuticamente aceptable se selecciona de succinato de d-alfa-tocoferil-polietilenglicol 1000, aceite de ricino hidrogenado polietoxilado-40, aceite de ricino polietoxilado-35, copolímero de bloques de polioxipropileno-polioxietileno, o lauril-sulfato sódico, y sus mezclas.

15

18. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que en el compuesto de fórmula (I):

20

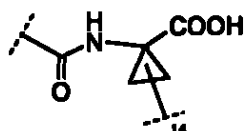
R^1 es metoxi;

R^2 es  en el que R^6 es NH-(alquilo C_{1-4}) o NH-(cicloalquilo C_{3-6});

R^3 es R^9O- , en el que R^9 es butilo, ciclobutilo o ciclopentilo;

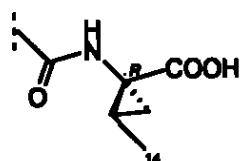
R^4 es H o alquilo C_{1-6} ;

y el siguiente resto:



25

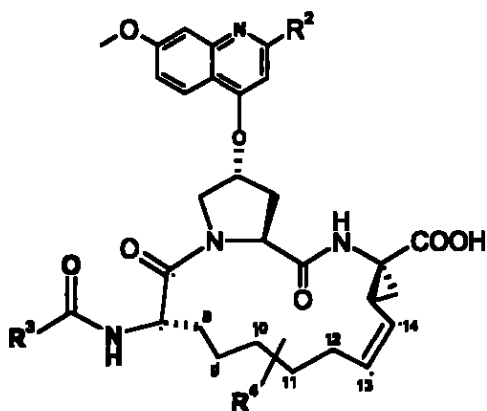
tiene la configuración representada por el siguiente diastereoisómero:



en cuya configuración la posición 14 está unida *sin* respecto al grupo COOH.

Fig
126

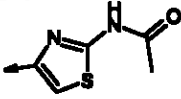
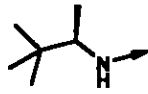
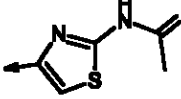
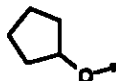
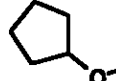
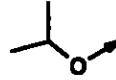
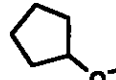
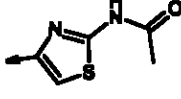
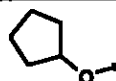
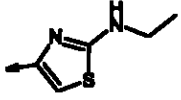
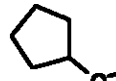
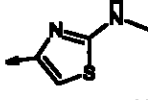
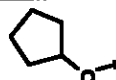
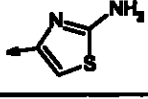
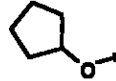
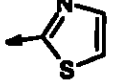
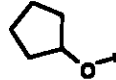
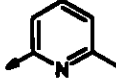
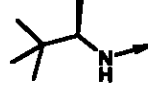
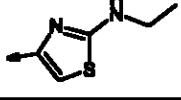
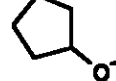
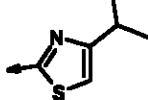
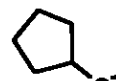
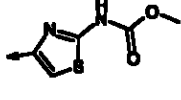
19. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en la que el compuesto de fórmula (I) se selecciona de los compuestos listados en la siguiente tabla:



5

en los que el enlace de la posición 14 al grupo ciclopropilo es *sin* respecto al COOH, dicho doble enlace 13,14 es *cis*, R³, R⁴ y R² son como se definen a continuación:

120
121

Comp. #	R ¹ :	R ² :	R ³ :
801		H	
804		H	
805		H	
807		H	OEt;
808		H	OEt;
809		H	
810		H	
811		H	
812		H	
814		H	
815		H	
816		H	
817		H	
818		H	

12x
122

Comp. #	R ³ :	R ⁴ :	R ² :
819		H	
820		H	
821		H	
822		H	
823		H	
824		10- (R) Me	OEt;
825		H	
826		H	
827		H	
y 828		H	

20. Una composición farmacéutica de acuerdo con la reivindicación 19, en la que el compuesto de fórmula (I) es el compuesto 822.

5 21. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, que comprende:

(A)

(a) aproximadamente 5% a 30% en peso de un compuesto de fórmula (I);

12
123

- (b) aproximadamente 0,1% a 7% en peso de una amina farmacéuticamente aceptable;
- (c) aproximadamente 0,1% a 5% en peso de una base farmacéuticamente aceptable;
- 5 (d) aproximadamente 1% a 99% en peso de un aceite farmacéuticamente aceptable;
- (e) hasta aproximadamente 70% en peso de un disolvente hidrófilo farmacéuticamente aceptable;
- (f) opcionalmente hasta aproximadamente 50% en peso de un polímero farmacéuticamente aceptable; y
- 10 (g) hasta aproximadamente 70% en peso de un tensioactivo farmacéuticamente aceptable;
- o
- (B)
- 15 (a) aproximadamente 10% a 20% en peso de un compuesto de fórmula (I);
- (b) aproximadamente 0,1% a 5% en peso de una amina farmacéuticamente aceptable;
- (c) aproximadamente 0,1% a 3% en peso de una base farmacéuticamente aceptable;
- 20 (d) aproximadamente 20% a 70% en peso de un aceite farmacéuticamente aceptable;
- (e) aproximadamente 10% a 30% en peso de un disolvente hidrófilo farmacéuticamente aceptable;
- (f) opcionalmente aproximadamente 1% a 20% en peso de un polímero farmacéuticamente aceptable; y
- 25 (g) aproximadamente 20% a 50% en peso de un tensioactivo farmacéuticamente aceptable;
- o
- (C)
- 30 (a) aproximadamente 10% a 20% en peso de un compuesto de fórmula (I);
- (b) aproximadamente 0,1% a 5% en peso de tris(hidroximetil)aminometano;
- (c) aproximadamente 0,1% a 3% en peso de hidróxido sódico;
- (d) aproximadamente 20% a 70% en peso de un triglicérido de ácido graso caprílico o un triglicérido de ácido graso cáprico, o sus mezclas;
- 35 (e) aproximadamente 10% a 30% en peso de una mezcla de propilenglicol,

123
124

etanol y opcionalmente agua;

(f) opcionalmente aproximadamente 1% a 20% en peso de polietilenglicol o polivinilpirrolidona; y

(g) aproximadamente 20% a 50% en peso de succinato de d-alfa-tocoferil-polietilenglicol 1000 o aceite de ricino polietoxilado-35 (Cremophor EL);

o

(D)

(a) aproximadamente 10% a 15% en peso de un compuesto de fórmula (I);

(b) aproximadamente 0,1% a 2% en peso de tris(hidroximetil)aminometano;

10 (c) aproximadamente 0,1% a 1% en peso de hidróxido sódico;

(d) aproximadamente 20% a 30% en peso de Capmul MCM o Captex 355;

(e) aproximadamente 15% a 25% en peso de una mezcla de propilenglicol, etanol y agua;

15 (f) aproximadamente 40% a 50% en peso de succinato de d-alfa-tocoferil-polietilenglicol 1000; y

(g) aproximadamente 0,01% a 1% en peso de dl- α -tocoferol.

20 22. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, en forma de una forma de dosificación fluida seleccionada de una cápsula de cubierta dura o gel blando, o en forma de una forma de dosificación sólida seleccionada de un polvo, un comprimido o una cápsula.

25 23. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, que además comprende uno o más antioxidantes.

24. Un método para fabricar una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones precedentes, comprendiendo dicho método:

30 (a) mezclar entre sí el(los) aceite(s), tensioactivo(s) y disolvente(s) farmacéuticamente aceptables; (b) disolver la(s) amina(s), base(s) y polímero(s) farmacéuticamente aceptables; (c) opcionalmente calentar la mezcla obtenida en la etapa (b) si es necesario para fundir suficientemente uno o más de los componentes de la mezcla; (d) añadir el compuesto de fórmula (I) a la mezcla obtenida en las etapas (b) o (c) y mezclar.

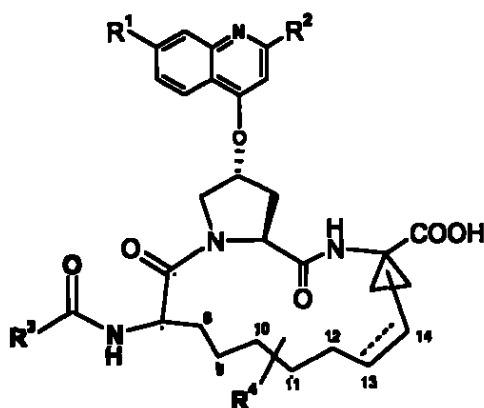
35 25. Un método de inhibición de la replicación del virus de la hepatitis C por

125

exposición del virus a una cantidad de la composición de acuerdo con cualquiera de las reivindicaciones 1 a 23, inhibidora de la proteasa NS3 del virus de la hepatitis C.

26. Un método de tratamiento de una infección por el virus de la hepatitis C en un mamífero que comprende administrar a un mamífero que lo necesite una cantidad terapéuticamente eficaz de la composición de acuerdo con cualquiera de las reivindicaciones 1 a 23.

27. Uso de un compuesto de la siguiente fórmula (I):



(I)

en la que:

— indica un enlace opcional que forma un doble enlace entre las posiciones 13 y 14;

R¹ es H, halógeno, alquilo C₁₋₆, cicloalquilo C₃₋₆, halógenoalquilo C₁₋₆, alcoxi C₁₋₆, cicloalcoxi C₃₋₆, hidroxil, o N(R⁵)₂, en el que cada R⁵ es independientemente H, alquilo C₁₋₆ o cicloalquilo C₃₋₆;

R² es H, halógeno, alquilo C₁₋₆, cicloalquilo C₃₋₆, halógenoalquilo C₁₋₆, tioalquilo C₁₋₆, alcoxi C₁₋₆, cicloalcoxi C₃₋₆, alcoxialquilo C₂₋₇, arilo o Het C₆₋₁₀, en el que Het es un heterociclo saturado o insaturado, de cinco, seis o siete miembros que contiene de uno a cuatro heteroátomos en el anillo seleccionados de nitrógeno, oxígeno y azufre;

estando dicho cicloalquilo, arilo o Het opcionalmente sustituido con R⁶,

en el que R⁶ es H, halógeno, alquilo C₁₋₆, cicloalquilo C₃₋₆, alcoxi C₁₋₆, cicloalcoxi C₃₋₆, NO₂, N(R⁷)₂, NH-C(O)-R⁷; o NH-C(O)-NH-R⁷, en los que cada R⁷ es independientemente: H, alquilo C₁₋₆ o cicloalquilo C₃₋₆;

o R⁶ es NH-C(O)-OR⁸, en el que R⁸ es alquilo C₁₋₆ o cicloalquilo C₃₋₆;

125
126

- 49 -

R^3 es R^3O- o R^3NH- , en los que R^3 es alquilo C_{1-6} o cicloalquilo C_{3-6} ;

R^4 es H o de uno a tres sustituyentes en cualquier átomo de carbono disponible en las posiciones 8, 9, 10, 11, 12, 13 ó 14, seleccionado dicho sustituyente independientemente del grupo que consta de: alquilo C_{1-6} , halógenoalquilo C_{1-6} , alcoxi C_{1-6} , hidroxí, halógeno, amino, oxo, tio o tioalquilo C_{1-6} .

o uno de sus tautómeros;

para preparar una composición farmacéutica para tratar la infección vírica de la hepatitis C, en el que dicha composición farmacéutica comprende:

(a) un compuesto de fórmula (I) como se ha descrito antes;

(b) aproximadamente 0,1 a 10% en peso de una amina farmacéuticamente aceptable o una mezcla de aminas farmacéuticamente aceptables;

(c) aproximadamente 0,1 a 10% en peso de una base farmacéuticamente aceptable o una mezcla de bases farmacéuticamente aceptables;

(d) uno o más aceites farmacéuticamente aceptables;

(e) opcionalmente uno o más disolventes hidrófilos farmacéuticamente aceptables;

(f) opcionalmente uno o más polímeros farmacéuticamente aceptables; y

(g) opcionalmente uno o más tensioactivos farmacéuticamente aceptables.

28. Uso de una composición de acuerdo con cualquiera de las reivindicaciones 1 a 23, para preparar un medicamento para tratar la infección vírica de la hepatitis C.

25

30 COLO 09255-841-026-9
PRP/WPCL9255/ID-000344

PCT REQUEST

Original (for SUBMISSION)

L27.
128

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.158)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	9_279 PCT
1	Title of Invention	PHARMACEUTICAL COMPOSITIONS FOR HEPATITIS C VIRAL PROTEASE INHIBITORS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name:	BOEHRINGER INGELHEIM INTERNATIONAL, GMBH
II-5	Address:	Binger Str. 173 55216 Ingelheim Germany
II-6	State of nationality	DE
II-7	State of residence	DE
II-8	Telephone No.	496132778536
II-9	Facsimile No.	496132774377

PCT REQUEST

Original (for SUBMISSION)

128
129

III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	CHEN, Shirlynn
III-1-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US
III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	MEI, Xiaohui
III-2-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-2-6	State of nationality	CN
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	WANG, Zeren
III-3-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US

PCT REQUEST

Original (for SUBMISSION)

129
130

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	RAYMOND, Robert, P.
IV-1-2	Address:	Boehringer Ingelheim Corporation 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
IV-1-3	Telephone No.	203-798-9988
IV-1-4	Facsimile No.	203-798-4408
IV-1-5	Agent's registration No.	25,089
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	DEVLIN, Mary-Ellen, M. (27,928); STEMPEL, Alan, R. (28,991); BOTTINO, Anthony, P. (41,629); POCCHIARI, Susan, K. (45,016); DATLOW, Philip, I. (41,482); WITKOWSKI, Timothy, X. (40,232); DOW, David, A. (46,124); SMALL, Andrea, D. (54,859)
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	02 April 2003 (02.04.2003)
VI-1-2	Number	60/459,765
VI-1-3	Country	US
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

PCT REQUEST

Original (for SUBMISSION)

130
131

VII	Declarations	Number of declarations	
VII-1	Declaration as to the identity of the inventor	-	
VII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	✓
IX-2	Description	41	-
IX-3	Claims	12	-
IX-4	Abstract	1	✓
IX-5	Drawings	2	-
IX-7	TOTAL	61	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	reference no. BII - POA	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	 DATLOW, Philip, I.	
X-1-2	Name of signatory		
X-1-3	Capacity		

BT
132

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

INTERNATIONAL SEARCH REPORT

National Application No
/US2004/008837135
133A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/00 A61K38/06

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 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, 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.
P,X	WO 03/066103 A (BOEHRINGER INGELHEIM PHARMA) 14 August 2003 (2003-08-14) cited in the application page 50, line 10 - line 18; claim 1	1-28
Y	WO 00/59929 A (BOEHRINGER INGELHEIM CA LTD ; GOUDREAU NATHALIE (CA); GHIRO ELISE (CA)) 12 October 2000 (2000-10-12) cited in the application page 16, line 10 - line 20; claim 1	1-28
Y	WO 99/06044 A (MOROZOWICH WALTER ; UPJOHN CO (US); GAO PING (US)) 11 February 1999 (1999-02-11) page 3, line 13 - line 25; examples	1-28

☐ Further documents are filed 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.
"A" document member of the same patent family

Date of the actual completion of the international search

8 September 2004

Date of mailing of the international search report

16/09/2004

Name and mailing address of the ISA

European Patent Office, P.B. 6818 Patentkan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Winger, R

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/008837

Box I 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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 25 and 26 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 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 dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II 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.

133
134

INTERNATIONAL SEARCH REPORT

International Application No

/US2004/008837

134
135

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 03066103	A	14-08-2003	WO	03066103 A1		14-08-2003
			US	2003195228 A1		16-10-2003
WO 0059929	A	12-10-2000	AU	3548000 A		23-10-2000
			BG	105970 A		31-05-2002
			BR	0009599 A		15-01-2002
			WO	0059929 A1		12-10-2000
			CA	2367127 A1		12-10-2000
			CN	1346365 T		24-04-2002
			CZ	20013467 A3		12-06-2002
			EE	200100516 A		16-12-2002
			EP	1169339 A1		09-01-2002
			EP	1437362 A1		14-07-2004
			HR	20010720 A1		31-12-2002
			HU	0300121 A2		28-06-2003
			ID	30459 A		06-12-2001
			JP	2002542160 T		10-12-2002
			NO	20014857 A		31-10-2001
			NZ	515286 A		27-02-2004
			PL	350855 A1		10-02-2003
			SK	14072001 A3		05-03-2002
			TR	200102878 T2		21-01-2002
			US	2004002448 A1		01-01-2004
			US	6608027 B1		19-08-2003
WO 9906044	A	11-02-1999	AT	225174 T		15-10-2002
			AT	265847 T		15-05-2004
			AU	728626 B2		11-01-2001
			AU	8573898 A		22-02-1999
			AU	728698 B2		18-01-2001
			AU	8573998 A		22-02-1999
			BR	9810729 A		08-08-2000
			BR	9811058 A		05-09-2000
			CA	2294031 A1		11-02-1999
			CA	2294033 A1		11-02-1999
			CN	1261790 T		02-08-2000
			CN	1112927 B		02-07-2003
			DE	69808463 D1		07-11-2002
			DE	69808463 T2		26-06-2003
			DE	69823663 D1		09-06-2004
			DK	989851 T3		27-01-2003
			DK	999826 T3		26-07-2004
			EP	0989851 A1		05-04-2000
			EP	0999826 A1		17-05-2000
			ES	2184310 T3		01-04-2003
			FI	20000170 A		28-01-2000
			FI	20000172 A		28-01-2000
			HK	1028879 A1		31-10-2003
			HU	0002440 A2		28-09-2001
			JP	2002510330 T		02-04-2002
			JP	2002511099 T		09-04-2002
			NO	20000466 A		28-03-2000
			NO	20000467 A		29-03-2000
			NZ	502566 A		28-03-2002
			NZ	502569 A		31-05-2002
			PL	338335 A1		23-10-2000
			PL	338509 A1		06-11-2000
			PT	989851 T		31-12-2002

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:
IPEA/ EPO

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 8-279PCT	
International application No. PCT/US2004/008837	International filing date (day/month/year) 23/03/2004
(Earliest) Priority date (day/month/year) 02/04/2003	
Title of invention Pharmaceutical Compositions for Hepatitis C Viral Protease Inhibitors	
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.)	
BOEHRINGER INGELHEIM INTERNATIONAL GMBH Binger Strasse 173 55216 Ingelheim Germany	
Telephone No. 4961327700	
Facsimile No. 4961327798898	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: DE	State (that is, country) of residence: 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.)	
CHEN, Shirlynn 900 Ridgebury Rd. P.O. Box 368 Ridgefield, CT 06877-0368 United States	
State (that is, country) of nationality: US	State (that is, country) of residence: US
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.)	
MEI, Xiaohui 900 Ridgebury Rd. P.O. Box 368 Ridgefield, CT 06877-0368 United States	
State (that is, country) of nationality: CN	State (that is, country) of residence: US
☒ Further applicants are indicated on a continuation sheet.	

137
130

Continuation of Box No. II APPLICANT(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the demand.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> WANG, Zeren 900 Ridgebury Rd. P.O. Box 368 Ridgefield, CT 06877-0368 United States	
State (that is, country) of nationality: US	State (that is, country) of residence: US
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	
State (that is, country) of nationality:	State (that is, country) of residence:
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	
State (that is, country) of nationality:	State (that is, country) of residence:
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	
State (that is, country) of nationality:	State (that is, country) of residence:
☐ Further applicants are indicated on another continuation sheet.	

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ 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.)

RAYMOND, Robert P.; MORRIS, Michael P.; DEVLIN, Mary-Ellen M.;
STEMPEL, Alan, R.; WITKOWSKI, Timothy, X.; BOTTINO, Anthony,
P.; DATLOW, Philip, I.; POCCHIARI, Susan, K.; DOW, David, A.;
SMALL, Andrea, D.; BLANKINSHIP, Thomas
Boehringer Ingelheim Corp.
900 Ridgebury Road, P.O. Box 388
Ridgefield, CT 06877-0388

Telephone No.

203-798-9988

Facsimile No.

203-798-4408

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 filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☒ as originally filed☐ as amended under Article 342. ☐ 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 54bis.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.

139
140

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:

- | | | |
|--|---|--------|
| 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 |

For International Preliminary
Examining Authority use only
received not received

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Near 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).


Philip I. Datlow, Agent

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 54bis.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 54bis.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 54bis.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

L40
141

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

Date of mailing (day/month/year) 02 July 2004 (02.07.2004)	
Applicant's or agent's file reference 9_279 PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2004/008837	International filing date (day/month/year) 23 March 2004 (23.03.2004)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 02 April 2003 (02.04.2003)
Applicant BOEHRINGER INGELHEIM INTERNATIONAL, GMBH et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable) An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
02 April 2003 (02.04.2003)	60/459,765	US	28 June 2004 (28.06.2004)

received
7/10/04

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.65	Authorized officer Claudine PERGOD Telephone No. (41-22) 338 8207
--	---

From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To: **GRP II**
DND FILED 10.4.04
RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 388
Ridgefield, CT 06877-0388
ETATS-UNIS D'AMERIQUE

**ENTRE U.P. - 10-2-05****IMPORTANT NOTICE**

Date of mailing (day/month/year)

11 November 2004 (11.11.2004)

Applicant's or agent's file reference

9_279 PCT

International application No.

PCT/US2004/008837

International filing date (day/month/year)

23 March 2004 (23.03.2004)

Priority date (day/month/year)

02 April 2003 (02.04.2003)

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL, GMBH et al

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does apply, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).
2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
04 November 2004 (04.11.2004)

CH

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

FI, LU, SE, TZ, UG, ZM

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS** for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 20 MONTHS from the priority date.

In practice, time limits other than the 20-month time limit will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

received
12/10/04 JR

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Nora Lindner

Facsimile No. +41 22 740 14 35

Facsimile No. +41 22 338 89 65

From the INTERNATIONAL BUREAU

PCTINFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Article 31(7) and Rule 61.3)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

ENTR U.P. - 10.2.2005

Date of mailing (day/month/year)
04 November 2004 (04.11.2004)Applicant's or agent's file reference
9_279 PCT

IMPORTANT INFORMATION

International application No.
PCT/US2004/008837International filing date (day/month/year)
23 March 2004 (23.03.2004)Priority date (day/month/year)
02 April 2003 (02.04.2003)

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL, GMBH et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR

National: BG, CA, CN, CZ, DE, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

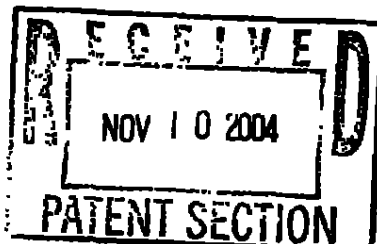
EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BW, BY, BZ, CH, CO, CR, CU, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NA, NI, NZ, OM, PG, PH, PT, SC, SD, SE, SG, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

3. Since the election(s) was (were) made before the expiration of 19 months from the priority date, the applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary report on patentability (Chapter II of the Patent Cooperation Treaty) (Article 36(3)(b) and Rule 74.1).

Some Offices have fixed time limits expiring later than the above-mentioned time limit. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters, the *PCT Newsletter* and the WIPO Internet site, updated regularly.

received
11/12/04The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Nora Lindner

Facsimile No. +41 22 740 14 35

Facsimile No. +41 22 338 89 65

Form PCT/IB/332 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

243
144
FD

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

DATE R.P. - 10.2.05

Date of mailing
(day/month/year) 13-10-2004

Applicant's or agent's file reference
9-279PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US2004/008837

International filing date (day/month/year)
23/03/2004

Priority date (day/month/year)
02/04/2003

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL, GMBH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

06/10/2004

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is after the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 20 months from the priority date (or later in some Offices). However, in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

received
10/20/04

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

FERRO VASCONCELOS M

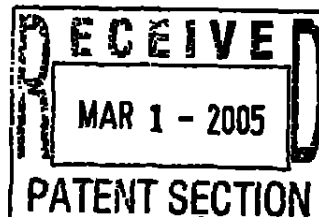
Tel. (+49-89) 2399-7905

Form PCT/IPA/402 (April 2002; reprint January 2004)

(08/10/2004)



PATENT COOPERATION TREATY



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

GRP II 15

PCT

144
145

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

Discovered - Filed - 10.4.2004

ENFS N.P. - 10.2.2005

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing
(day/month/year) 22.02.2005

Applicant's or agent's file reference
9-279PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US2004/008837

International filing date (day/month/year)
23.03.2004

Priority date (day/month/year)
02.04.2003

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL, GMBH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

received
3/2/2005

Name and mailing address of the international
preliminary examining authority:



European Patent Office
D-80286 Munich
Tel. +49 89 2399 - 0 Tlx 523856 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Ladumer, Y

Tel. +49 89 2399-7913



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

145
146

Applicant's or agent's file reference 9-279PCT		FOR FURTHER ACTION		See Form PCT/PEA/18
International application No. PCT/US2004/008837		International filing date (day/month/year) 23.03.2004	Priority date (day/month/year) 02.04.2003	
International Patent Classification (IPC) or national classification and IPC A61K47/00, A61K38/06				
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 807 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 06.10.2004		Date of completion of this report 22.02.2005		
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523856 apmu d Fax: +49 89 2399 - 4485		Authorized Officer Winger, R Telephone No. +49 89 2399-8129 		

245
147

Box No. 1 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

1-41 as originally filed

Claims, Numbers

1-28 as originally filed

Drawings, Sheets

1/2-2/2 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."

LAJ
148

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2004/008837

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. 25,26 (industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 25,26 (industrial applicability) 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

148
149

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2004/008837

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	1-28
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-28
Industrial applicability (IA)	Yes: Claims	1-24,27,28
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)

see separate sheet

149
150

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/US2004/008837

Re Section III

1. Claims 25 and 26 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 Section V

2. **Prior Art:** Reference is made to the following documents cited in the International Search Report

D1: WO 03/066103 A

D2: WO 00/59929 A

D3: WO 99/06044 A

- 2.1 Document D1 discloses a pharmaceutical composition comprising the compound of the invention and a mixture of pharmaceutical acceptable amines and oils, carriers or hydrophilic solvents. Formulations 11 and 12 comprise compound 822, tromethamine and Mg-Stearate. Assuming the priority to be valid, document D1 does not constitute prior art for the international phase.
- 2.2 Document D2 discloses pharmaceutical compositions of compound I with conventional pharmaceutically-acceptable carriers, adjuvants or vehicles. The carboxylic acid may be in the form of a salt.
- 2.3 Document D3 discloses the use of amines to increase bioavailability of protease inhibitors.

3. **Novelty (Article 33(2) PCT):**

Claim 1 relates to a composition comprising a compound of formula I, a pharmaceutically acceptable amine, a pharmaceutically active base and pharmaceutically acceptable oils, claims 24-28 relate to their manufacture and use for treating hepatitis C viral infection. Document D2, which is considered to represent the closest prior art document, differs in that no amine and no base is disclosed as part of the composition.

150
151

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/US2004/008837

4. Inventive Step (Article 33(3) PCT):

The problem to be solved can be regarded as to provide compositions with acceptable bioavailability and improved chemical stability.

The use of amines to improve bioavailability seems to be obvious in view of document D3. In addition, in view of the broad term "amine" it seems unlikely that all compounds falling under this definition solve the problem. The same is true for the broad term "base". It is also noted, that amines fall under the definition of base. Besides, as document D2 also includes pharmaceutically acceptable salts the selection of any amine (as amine or base) seems to be an obvious choice for the person skilled in the art. Thus, the subject-matter of claims 1-28 does not seem to involve an inventive step.

Re Section VI

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-03066103	14.08.2003	05.02.2003	07.02.2003

152
152

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicación : 05116321 00000000 Folios: 152
Fecha (FEB): 2005-10-28 16:56:07
Tramite : 011 PC1-PATENTE 379 FASE NUL1 411 PRESENTAC
Dependencia: 2020 DIVISION DE MARCAS COMERCIALES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 05 - 81,676
FECHA : OCTUBRE 24 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	31956195	24/10/2005	38,640,040.00

***** CONCEPTO *****

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. _____

Colo 09255-841-026-9

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA	()	()
INCOMPLETA	()	()
DISEÑO INDUSTRIAL	()	()
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA	()	()
INCOMPLETA	()	()
ESQUEMA DE TRAZADO	()	()
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA	()	()
INCOMPLETA	()	()

ble: 

Fecha:

154

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 154

2020
Bogotá D.C.,

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

REFERENCIA	Radicación No.	05 110321
	Solicitud internacional	US2004/008837
	Fecha inicio fase nacional	02/11/2005
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	173
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá D.C.,

14 MAR. 2006

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11