



**DIRECCIÓN DE NU
PRESENTACIÓN DE OPOSICION**

1. Oposición a solicitud de:

- ☒ Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: 12-154-969

Solicitante: ABBOTT LABORATORIES.

Apoderado: MARGARITA CASTELLANOS ABONDADO.

Título de la Nueva Creación: COMPOSICIONES SOLIDAS

Gaceta: 664 de 22 de marzo de 2013, No. de publicación 208

2. Datos del Opositor

☐ Persona Natural

☒ Persona Jurídica

TECNOQUIMICAS S.A.

Nombre o denominación /Razón social completa

Documento de identificación: C.C. ☐ C.E. ☐ NIT ☒ Otro ☐ Cuál
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Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

REYES VILLAMIZAR JOSE LUIS

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En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación

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Copias para traslado

A hand-drawn sketch of a roof structure. It features two gables on the left and right sides, connected by a central horizontal line. The drawing is simple, using black ink on a white background.

Nombre y apellidos

79.152.473

44655

C.C.

T.P.

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 12-154-969

TÍTULO SOLICITADO: COMPOSICIONES SÓLIDAS.

PUBLICACIÓN: Gaceta 664 de 22/03/2013, N° de publicación 208.

PRIORIDAD: US 61/339.964 de 10/03/2010

SOLICITANTE: ABBOTT LABORATORIES.

APODERADO: MARGARITA CASTELLANOS ABONDANO

TRÁMITE: PRESENTACION DE OPOSICION

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **12-154-959**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16, 18 y 20 d) de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUIMICAS S.A.**, legítimo interés para remitir esta Información, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTOS DE LA OPOSICION

La solicitud colombiana en trámite **12-154-959** referida a composiciones sólidas que comprenden un compuesto (I) amorfo, una dispersión sólida que contiene un polímero hidrofílico farmacéuticamente aceptable y un agente tensoactivo, no reúne los requisitos necesarios para otorgársele el privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

- En primer lugar, es necesario resaltar que el capítulo reivindicatorio de la solicitud colombiana en curso presenta graves fallas en cuanto a claridad y concisión, dado que:
 - si lo que se pretende proteger es una composición como tal y no un nuevo compuesto o polimorfo, siendo tal compuesto un componente más de la supuesta nueva composición debería caracterizarse mediante nomenclatura farmacéutica y no mediante su nombre químico que no permite de manera directa una fácil comparación entre estructuras con respecto al arte previo más próximo, tratando así de enmascarar materia ya conocida o carente totalmente de nivel inventivo,
 - tampoco debería identificarse mediante un nombre tipo pseudónimo, tal como: "compuesto I" cuando en efecto se tiene su nombre químico lo que hace que se enmascare su real identidad, debería denominarse con su nombre común y adicionalmente, revelar su estructura molecular con el fin de poder realizar comparaciones inequívocas entre las composiciones reivindicadas en la solicitud en trámite frente a las composiciones pertenecientes a la misma área del estado de la técnica.

- De forma similar el polimorfo que se pretende incorporar en la composición tampoco se identifica sino que simplemente se denomina como una "forma amorfa" lo cual no tiene validez, toda vez que una persona medianamente conocedora de la materia sabe que un polimorfo tiene la misma fórmula pero su conformación estructural y espacial es diferente y debe ser identificado plenamente mediante parámetros como punto de fusión, métodos de difracción y su nombre específico, de tal forma que se permita una diferenciación con lo previamente existente que permita evidenciar un salto técnico contundente.
- De otro lado, debe notar ese Despacho que el mismo título de la solicitud "COMPOSICIONES SOLIDAS" es ambiguo y no describe de manera directa lo que realmente se pretende proteger, de tal forma que pareciera pretender exclusividad sobre cualquier tipo de composición cuya forma farmacéutica será en estado sólido.
- En un tercer aspecto, es importante señalar que no tienen naturaleza inventiva reivindicaciones tales como la 3, 4 y 5 referidas a parámetros propios de los componentes seleccionados tales como el "Tg" de los polímeros o el "HLB" de los tensoactivos, ya que una persona medianamente versada en la formulación farmacéutica, debe reconocer que dichos parámetros se encuentran relacionados a ensayos rutinarios de laboratorio de control de calidad y no a actividades industriales.
- Adicionalmente, ante la pretensión de realizar una combinación entre un inhibidor del HCV tal como el compuesto (I) y otro inhibidor de la proteasa tal como el Ritonavir, debemos recordar a ese Despacho, **todo efecto sinérgico o terapéutico** entre fármacos no podría tomarse propiamente como *una invención*, sino que corresponde a *un descubrimiento*, dado que dicho efecto sinérgico o terapéutico ocurre dentro del organismo y se hace evidente a través de los respectivos ensayos preclínicos y/o clínicos mediante los cuales todo fármaco o combinación de fármacos deben ser evaluados. Se enfatiza además, en que la combinación de fármacos para tratar ciertas patologías, hace parte de las actividades de la profesión médica más no de las actividades industriales.

- Es así como se puede concluir que la sola combinación de fármacos para tratar ciertas patologías, en ausencia de un problema técnico relativo a la formulación conjunta o a la inclusión de los compuestos activos en una misma formulación farmacéutica determinada, hace parte de las actividades de la profesión médica (específicamente al campo farmacológico), no de las actividades industriales, y por lo tanto dicha combinación no tiene efectos evidentes a nivel técnico, sino exclusivamente a nivel fisiológico, o si se prefiere, a nivel clínico o terapéutico, con lo que dicha combinación se enmarca dentro de la improcedencia de patentabilidad implícita en el Artículo 20 de la norma Andina.
- Como si fuera poco, se presenta una composición en la reivindicación independiente que dicen contener polímeros “aceptables” y tensoactivos “aceptables”, realizando una selección de tales excipientes en las posteriores reivindicaciones independientes que no implican mérito inventivo sino que hacen referencia a simples técnicas de formulación mediante las cuales se desarrollan productos farmacéuticos que sean viables en cualquiera de sus formas y que constituyen elementos claramente conocidos para una persona medianamente versada en la formulación de productos farmacéuticos, así que de ninguna manera puede ser inventivo **escoger uno u otro excipiente** para conseguir las características deseadas en un producto comercialmente aceptable a nivel farmacéutico y terapéutico.
- En cuanto al **proceso de elaboración** reivindicado (19) que consiste en **secar el solvente** o el proceso de elaboración reivindicado (20) que consiste en **solidificar una mezcla**, y a la vista de lo conocido y de las técnicas complejas referidas por cualquiera de las anterioridades expuestas en el presente trámite, no se considera que requiera ningún esfuerzo inventivo para un experto en la materia practicar las operaciones mencionadas y con menor razón llevadas a cabo de forma independiente, toda vez que esa simple práctica de “secar” en un caso o de “solidificar” en el otro caso, hace parte de cualquier proceso convencional que es conocimiento de conjunto que una persona versada en materia farmacéutica recibe cuando estudia los principios básicos de farmacotécnica, por ende, su contenido es obvio y no puede ser catalogado como inventivo ni sujeto a examen o estudio de patentabilidad.

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- Sin perjuicio de lo anterior, y ahora refiriéndonos al nivel inventivo de la solicitud colombiana en trámite, procederemos a demostrar que existen documentos en los que se revela con anterioridad la obviedad de las composiciones reivindicadas y de las combinaciones entre inhibidores de la proteasa tales como los reivindicados, en el tratamiento de pacientes con el virus de la hepatitis C, Veamos:

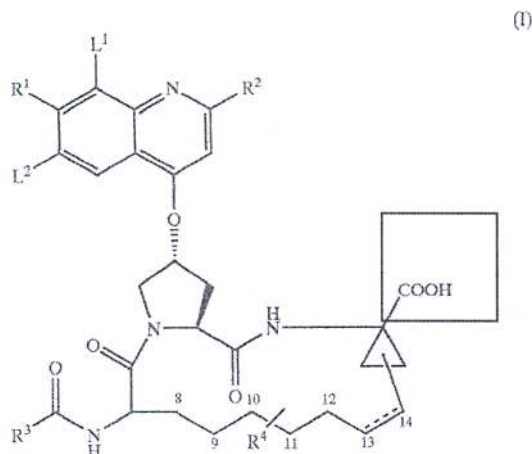
La reivindicación 1 de la solicitud colombiana en trámite pretende proteger lo siguiente:

- 1) Una composición sólida caracterizada porque comprende:
 - a) (2R,6S,13aS,14aR,16aS,Z)-N-(ciclopropilsulfonil)-6-(5-metilpirazin-2-carboxamido)-5,16-dioxo-2-(fenantridin-6-iloxi)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadeca hidrociclopropa[e]pirrolo[1,2-a][1,4]diazaciclopentadecin-14a-carboxamida o una sal farmacéuticamente aceptable de ésta, en una forma amorfa
 - b) Un polímero hidrofílico farmacéuticamente aceptable
 - c) un agente tensoactivo farmacéuticamente aceptable

Dicha composición se encuentra afectada por los siguientes documentos del Estado de la Técnica:

- La publicación americana US 2004/0229776 "**Pharmaceutical compositions for hepatitis C viral protease inhibitors**" del 18/11/2004 divulga composiciones farmacéuticas en general con inhibidores de la proteasa del virus de la hepatitis C, con estructura macrocíclica tal y como los que se pretenden proteger por la presente solicitud colombiana en trámite (a pesar de no haberse proporcionado la estructura por parte del solicitante comprenden el núcleo pirrolo diazaciclo pentadecin-carboxamida):

[0003] 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:



La única diferencia entre este tipo de compuesto y el pirrolodiazaciclopentadecin-carboxamida reivindicado por la solicitud en trámite, consiste en dos de los sustituyentes que presenta la molécula objeto de estudio, a saber el **fenantridin-O** en la posición 2 y el **pirazin-carboxamido** de la posición 7, sin embargo tales diferencias no parecen conceder una ventaja excepcional ya que la anterioridad en mención explícitamente enseña [0015] que **es la carboxamida terminal** la responsable no sólo de la potencia y reversibilidad observada en este tipo de inhibidores, sino de la excelente especificidad para la proteasa del HCV comparado con otras proteasas y que está presente tanto en el compuesto de la solicitud como en el de la anterioridad.

(pág 1):

[0015] 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 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.

(...)

Como si fuera poco, la misma anterioridad sugiere los mismos excipientes para incrementar la solubilidad y mejorar las características de dispersión sólida, tal

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como se pretende proteger en la reivindicación 2 de la presente solicitud colombiana en trámite:

(pág 6):

[0111] In certain circumstances, e.g. for the purpose of increasing solubility, improving dispersability, pharmaceutically acceptable hydrophilic solvents can optionally be used in the composition, which include, for example, pro-

pylene 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. 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. (...)

Como se puede evidenciar, la presente publicación revela precisamente los mismos tensoactivos y específicamente el mismo polímero seleccionado por la solicitud en trámite:

[0112] 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.

[0113] 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. (...)

b

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Adicional a lo considerado hasta ahora, en el siguiente párrafo de la anterioridad en mención, ya había sido considerada la idea de combinar el inhibidor de proteasa con principios activos adicionales al igual que sucede en la solicitud colombiana en trámite:

(pág 2):

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. (...)

(pág 21):

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. (...)

- **La publicación americana US 2009/0269305 “*Novel macrocyclic inhibitors of hepatitis C virus replication*”** del 29 de octubre 2009 enseña diversos tipos de compuestos inhibidores de la proteasa para el virus de la hepatitis C que, al igual que los descritos en la anterior publicación, contiene el mismo tipo de compuestos de estructura principal macrocíclica, en donde cada uno de los revelados solamente consiste en una variante del enseñado por la solicitud, con algún sustituyente que difiere del compuesto reivindicado para la composición que se pretende proteger en la presente solicitud en trámite:

(57)

ABSTRACT

The embodiments provide compounds of the general Formulae I, II, III, IV, V, VI, VII, and X, as well as compositions, including pharmaceutical compositions, comprising a subject compound. The embodiments further provide treatment methods, including methods of treating a hepatitis C virus infection and methods of treating liver fibrosis, the methods generally involving administering to an individual in need thereof an effective amount of a subject compound or composition. (...)

Adicionalmente y de la misma manera que pretende protegerse en la solicitud en trámite, todas las variantes reivindicadas incluyen sus sales y polimorfos.

(pág 20):

[0423] Various forms are included in the embodiments, including polymorphs, solvates, hydrates, conformers, salts, and prodrug derivatives. A polymorph is a composition having the same chemical formula, but a different structure. A

La presente publicación americana sugiere la forma de realizar sus composiciones y los excipientes comúnmente utilizados en ellas en diversos tipos de formas farmacéuticas posibles, veamos:

(pág 41):

[0863] A subject pharmaceutical composition comprises a subject compound; and a pharmaceutically acceptable excipient. A wide variety of pharmaceutically acceptable excipients is known in the art and need not be discussed in detail herein. Pharmaceutically acceptable excipients have been amply described in a variety of publications, including, for example, A. Gennaro (2000) "Remington: The Science and Practice of Pharmacy," 20th edition, Lippincott, Williams, & Wilkins; Pharmaceutical Dosage Forms and Drug Delivery Systems (1999) H. C. Ansel et al., eds., 7th ed., Lippincott, Williams, & Wilkins; and Handbook of Pharmaceutical Excipients (2000) A. H. Kibbe et al., eds., 3rd ed. Amer. Pharmaceutical Assoc.

[0864] The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily available to the public.

(...)

(pág 45):

[0916] The agents can be formulated into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

(...)

(pág 45):

[0911] As such, administration of the agents can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, subcutaneous, intramuscular, transdermal, intratracheal, etc., administration. In many embodiments, administration is by bolus injection, e.g., subcutaneous bolus injection, intramuscular bolus injection, and the like.

Así mismo, la anterioridad en mención, había considerado las combinaciones entre este tipo de compuestos macrocíclicos con otros inhibidores de la proteasa y

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menciona específicamente combinaciones con **RITONAVIR** tal y como pretende protegerse en las reivindicaciones 15 a 18 de la presente solicitud:

(pág 45):

[0914] In pharmaceutical dosage forms, the agents may be administered in the form of their pharmaceutically acceptable salts, or they may also be used alone or in appropriate association, as well as in combination, with other pharmaceutically active compounds. The following methods and excipients are merely exemplary and are in no way limiting.

(pág 46):

[0926] In some embodiments, the method further includes administration of ritonavir. Ritonavir, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazamidecan-13-oic acid, 5-thiazolylmethyl ester[5S-(5R*,8R*,10R*,11R*)], available from Abbott Laboratories, is an inhibitor of the protease of the human immunodeficiency virus and also of the cytochrome P450 3A and P450 2D6 liver enzymes frequently involved in hepatic metabolism of therapeutic molecules in man. Because of its strong inhibitory effect on cytochrome P450 3A and the inhibitory effect on cytochrome P450 2D6, ritonavir at doses below the normal therapeutic dosage may be combined with other protease inhibitors to achieve therapeutic levels of the second protease inhibitor while reducing the number of dosage units required, the dosing frequency, or both.

Por último, la anterioridad menciona procedimientos complejos de elaboración que también incluyen el secado del solvente tal como se revela en la presente solicitud:

(pág 67):

General Procedure A

[1148] Compound 1 (10 g, 15.9 mmol.) was dissolved in methanol (100 mL), 5 M NaOH solution (95 mL) was added, the resulting mixture was heated to 50° C. and stirred overnight, after completion of the reaction. The mixture was cooled by ice water, 2 M HCl was added to acidify the mixture to pH=3-4, then the mixture was extracted by EtOAc, the organic layers were combined, washed by brine, dried, the solvent was removed under reduced pressure, the crude compound 2 (7.5 g) was used directly in the next step.

De acuerdo a los dos documentos mas cercanos encontrados en el estado del arte, el problema técnico objetivo a resolver por la presente invención podría definirse "*cómo lograr una composición alternativa en forma sólida para el tratamiento del virus de la hepatitis C*", por lo tanto, la solicitud tal como se reivindica es obvia porque el experto medianamente versado en la materia

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enfrentado al problema técnico y conociendo las estructuras que conllevan inequívocamente a la actividad como inhibidor de la proteasa sobre el virus de hepatitis C enseñadas por el estado de la técnica y su sustituyente clave, tal y como lo es la carboxamida terminal, simplemente emplearía los conocimientos facilitados por ambas anterioridades para lograr una formulación alternativa, y sugeriría pequeñas modificaciones estructurales que no afecten la actividad farmacológica para hallar así otra alternativa que no supera en ningún aspecto técnico ni terapéutico lo previamente existente.

- Adicional a lo anterior, encontramos que la patente europea **EP 2468286** ***“Macrocyclic hepatitis C serine protease inhibitors”*** del 10 de septiembre del 2009 si bien no enseña cómo elaborar la composición sólida de la solicitud colombiana en trámite ni los excipientes reivindicados para llegar a tal fin, el compuesto (I) contenido en la composición sólida y que se pretende proteger en la solicitud en trámite, **no es nuevo** si se tiene en cuenta que dicha anterioridad revela diversos compuestos macrocíclicos útiles para el virus de la hepatitis C, específicamente revela en el ejemplo 49 (pág 41) el compuesto (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy) 1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadeca hydrocyclopropa[e]pyrrolo [1,2-a] [1,4] diazacyclopentadecine-14a-carboxamide idéntico indudablemente al revelado en la reivindicación 1 del expediente colombiano:

SUMMARY OF THE INVENTION

[0005] The present invention relates to novel macrocyclic compounds and methods of treating a hepatitis C infection in a subject in need of such therapy with said macrocyclic compounds. The compounds of the present invention interfere with the life cycle of the hepatitis C virus and are useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the compounds of the present invention, or pharmaceutically acceptable salts, esters or prodrugs thereof, in combination with a pharmaceutically acceptable carrier or excipient.

Para terminar, es importante resaltar que la patente europea en mención contempla la posibilidad de combinar el compuesto (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy) 1,2,3,5,6,7,8,9,10,11,13a,14, 14a,15,16,16a-hexadeca hydrocyclopropa[e]pyrrolo [1,2-a] [1,4] diazacyclopentadecine-14a-carboxamide con Ritonavir [0053] tal y como pretende protegerse en las reivindicaciones 15 a 18 de la presente solicitud, veamos:

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[0053] In another embodiment, the compounds or pharmaceutical compositions of the invention are administered with ritonavir, either simultaneously or sequentially. In certain embodiments, a compound or a pharmaceutical composition of the invention is administered in the same composition as ritonavir. In another embodiment, a compound or a pharmaceutical composition thereof of the invention is administered in a different composition than ritonavir.

En consecuencia, queda irrefutablemente demostrado que **cualquier modalidad particular generada** por la solicitud colombiana en trámite, era absolutamente conocida y obvia al momento de la presente solicitud, el problema técnico ya había sido solucionado y eran conocidos los posibles tensoactivos y el polímero más adecuado para conformar la composición que permitiera lograr efectos relacionados con una buena estabilidad, dispersabilidad y solubilidad, por tanto, la presente solicitud colombiana se hace totalmente obvia y no merece reconocimiento de nivel inventivo.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente solicito que su despacho se abstenga de conceder el privilegio de patente solicitado para la presente combinación farmacéutica de principios activos, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16, 18 y 20 literal d de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

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VI. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La publicación Americana US 2004/0229776 "*Pharmaceutical compositions for hepatitis C viral protease inhibitors*". 18-11-2004. págs 1, 2, 6, 21.
- La publicación Americana US 2009/0269305 "*Novel macrocyclic inhibitors of hepatitis C virus replication*". 29-10-2009. págs abstract, 1, 6, 20, 21, 41, 45, 46, 67.
- La patente europea EP 2468286 "*Macrocyclic hepatitis C serine protease inhibitors*" del 10-09-2009. págs. abstract, 41.

VII. ANEXOS

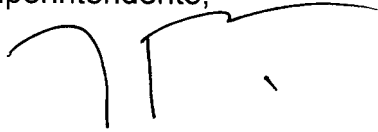
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de TECNOQUIMICAS S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A., las recibirá en sus oficinas localizadas en la Calle 23 N° 7-39 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.

~~16~~ 16



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3286

NOTARIA TERCERA
ENCUENTRO

ESCRITURA NUMERO CUATRO MIL QUINIENTOS -
TREINTA Y NUEVE (No. 4.539) -----

En la ciudad de Cali, Capital del Departamento del Valle del Cauca, República de Colombia, a los VEINTITRES (23) días -
del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario

T E R C E R O (3o.) del Círculo de Cali, - - - - -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali, identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: ----.

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de junio de 1957, reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali -----

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de Bogotá, identificado con C.C. # 79.152.473 de Isaquén, abogado en ejercicio, portador de la T.P 44655 del C.S. de la J., domiciliado en Bogotá, D.C., República de Colombia con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos u otros de diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

Como Notario Ventres de este Círculo
hago constar que esta fotocopia coincide
con su fotocopia auténtica que he tenido
a la vista.
13 AGO 2007
WILLY VALENZUELA
NOTARIO VENTRES
Bogotá D.C. - Colombia

4539
OCT 23

LUZ MERY CORREA
ELABORACION DE ESCRITURAS
Notaría 3 de Cali

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.-----

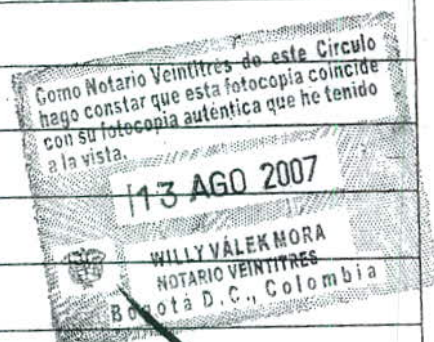
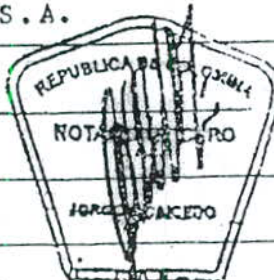
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.-----

Se agregan comprobantes. Derechos \$30.000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

91 *Juan m. Barberi*

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO



US 20040229776A1

18

(19) **United States**
(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0229776 A1**
Chen et al. (43) **Pub. Date: Nov. 18, 2004**

(54) **PHARMACEUTICAL COMPOSITIONS FOR
HEPATITIS C VIRAL PROTEASE
INHIBITORS**

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(21) **Appl. No.: 10/807,023**

(22) **Filed: Mar. 23, 2004**

Related U.S. Application Data

(60) **Provisional application No. 60/459,765, filed on Apr.
2, 2003.**

Publication Classification

(51) **Int. Cl.⁷ A61K 38/12; A61K 31/4709**
(52) **U.S. Cl. 514/9; 514/10; 514/312**

(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.

PHARMACEUTICAL COMPOSITIONS FOR HEPATITIS C VIRAL PROTEASE INHIBITORS

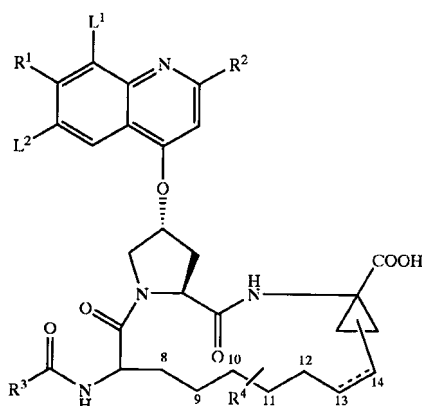
[0001] This application claims benefit to U.S. Provisional Application No. 60/459,765, filed Apr. 2, 2003, which application is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] 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

[0003] 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:



[0004] wherein:

[0005] - - - designates an optional bond forming a double bond between positions 13 and 14;

[0006] 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;

[0007] 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);

[0008] 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;

[0009] said cycloalkyl, aryl or Het being optionally substituted with R^6 ,

[0010] 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;

[0011] or R^6 is $NH-C(O)-OR^8$ wherein R^8 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

[0012] R^3 is R^9O- or R^9NH- , wherein R^9 is C_{1-6} alkyl or C_{3-6} cycloalkyl;

[0013] 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;

[0014] See Tsantrizos et al., U.S. application Ser. No. 09/760,946, filed on Jan. 16, 2001, now U.S. Pat. No. 6,608,027 B1 (Boehringer Ingelheim (Canada), Ltd.), which is herein incorporated by reference in its entirety and is hereinafter referred to as "Tsantrizos et al". See also the corresponding WO 00/59929. In addition, see Llinas-Brunet, U.S. Provisional Application No. 60/504,839, filed on Sep. 22, 2003, which is herein incorporated by reference in its entirety and is hereinafter referred to as "Llinas-Brunet".

[0015] 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 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.

[0016] 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 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.

[0017] 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 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 compounds having improved bioavailability.

[0018] 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 commercially available cyclosporins, and Hauer et al, U.S. Pat. No. 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. No. 5,504,068, further discloses the preparation of an enhanced topical formulations of cyclosporin.

[0019] 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. No. 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.

[0020] 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. No. 6,056,977 teaches the use of polysaccharide based matrix for sustained release of a sulfonyleurea.

[0021] 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 Ser. No. 10/357,919 (S. Chen et al.), filed Feb. 4, 2003, and in PCT/US03/03380 (Boehringer Ingelheim Pharmaceuticals, Inc.), filed Feb. 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

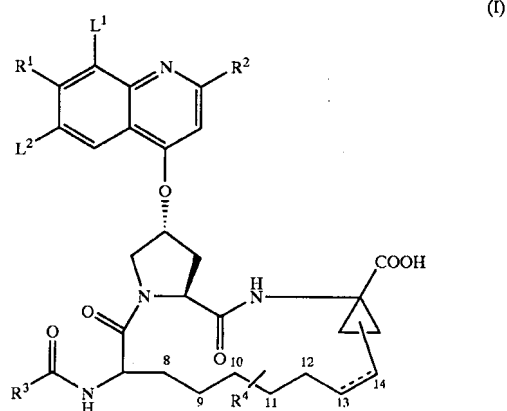
[0022] The present invention overcomes the aforementioned problems by providing pharmaceutical compositions of the formula I compounds having acceptable bioavailability and also improved chemical stability as compared to the previous SEDDS formulation.

[0023] 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.

[0024] In a general embodiment, the pharmaceutical composition of the present invention comprises:

[0025] (a) a compound of formula (I):



[0026] wherein:

[0027] - - - designates an optional bond forming a double bond between positions 13 and 14;

[0028] 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 C₃₋₆ cycloalkyl;

[0029] L¹, L² are each independently H, halogen, C₁₋₄ alkyl, —O—C₁₋₄alkyl, or —S—C₁₋₄alkyl (the sulfur being in any oxidized state);

[0030] R² is H, halo, C₁₋₆ alkyl, C₃₋₄ cycloalkyl, C₁₋₄ 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;

[0031] said cycloalkyl, aryl or Het being optionally substituted with R⁶,

[0032] wherein R⁶ is H, halo, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, NO₂, N(R⁷)₂, NH—C(O)—R⁷; or NH—C(O)—NH—R⁷, wherein each R⁷ is independently: H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

[0033] or R⁶ is NH—C(O)—OR⁸ wherein R⁸ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

[0034] R³ is R⁹O— or R⁹NH—, wherein R⁹ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

[0035] R⁴ is H or from one to three substituents on any available carbon atom at positions 8, 9, 10, 11, 12, 13

compound is intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure.

[0081] C. Pharmaceutical Administration and Treatment Terms and Conventions

[0082] The term "patient" includes both human and non-human mammals.

[0083] 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.

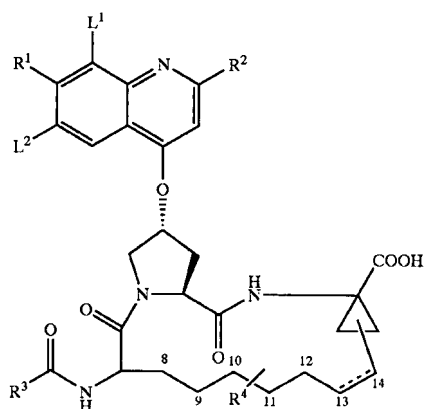
[0084] The terms "treating" or "treatment" mean the treatment of a hepatitis C viral infection in a patient, and include:

- [0085] (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;
- [0086] (ii) inhibiting or ameliorating the hepatitis C viral infection, i.e., arresting or slowing its development; or
- [0087] (iii) relieving the hepatitis C viral infection, i.e., causing regression or cure of the disease-state.

PREFERRED EMBODIMENTS OF THE INVENTION

[0088] The preferred embodiment which we refer to herein as the "Lipid-Based System" is directed to a pharmaceutical composition comprising:

[0089] (a) a compound of formula (I):



[0090] wherein:

[0091] - - - designates an optional bond forming a double bond between positions 13 and 14;

[0092] R¹ is H, halo, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkoxy, hydroxy, or N(R⁵)₂, wherein each R⁵ is independently H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

[0093] 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);

[0094] 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;

[0095] said cycloalkyl, aryl or Het being optionally substituted with R⁶,

[0096] wherein R⁶ is H, halo, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, NO₂, N(R⁷)₂, NH—C(O)—R⁷; or NH—C(O)—NH—R⁷, wherein each R⁷ is independently: H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

[0097] or R⁶ is NH—C(O)—OR⁸ wherein R⁸ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

[0098] R³ is R⁹O— or R⁹NH—, wherein R⁹ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

[0099] 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 or C₁₋₆ thioalkyl;

[0100] or a tautomer thereof;

[0101] (b) about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a mixture of pharmaceutically acceptable amines;

[0102] (c) about 0.1 to 10% by weight of a pharmaceutically acceptable base or a mixture of pharmaceutically acceptable bases;

[0103] (d) one or more pharmaceutically acceptable oils;

[0104] (e) optionally one or more pharmaceutically acceptable hydrophilic solvents;

[0105] (f) optionally one or more pharmaceutically acceptable polymers; and

[0106] (g) optionally one or more pharmaceutically acceptable surfactants.

[0107] 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.

[0108] 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. Specific amines include ethanolamine, diethanolamine, triethanolamine, tris(hydroxymethyl)aminomethane, ethylenediamine, dimethylaminoethanol, or meglumine, or mixtures

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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% to 5% by weight.

[0109] Pharmaceutically acceptable bases useful in the composition include, for example, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum 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, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinonesulfonic 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 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 about 0.1 to 3% by weight.

[0110] 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 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, 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 Arlacel 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 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.

[0111] In certain circumstances, e.g. for the purpose of increasing solubility, improving dispersability, pharmaceutically acceptable hydrophilic solvents can optionally be used in the composition, which include, for example, pro-

pylene glycol, polypropylene glycol, polyethylene glycol (e.g., PEG 400), glycerol, ethanol, dimethyl isosorbide, glycofurool, propylene carbonate, dimethyl acetamide, water, or mixtures thereof; preferably, propylene glycol, polyethylene glycol, ethanol, water, or mixtures thereof. 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.

[0112] 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.

[0113] 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.

[0114] 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".

[0115] A particular embodiment of the SEDDS composition according to the present invention is directed to a pharmaceutical composition, comprising:

- [0116] (a) about 5% to 30% by weight of a compound of formula (I);
- [0117] (b) about 0.1% to 7% by weight of a pharmaceutically acceptable amine;
- [0118] (c) about 0.1% to 5% by weight of a pharmaceutically acceptable base;
- [0119] (d) about 1% to 99% by weight of a pharmaceutically acceptable oil;
- [0120] (e) up to about 70% by weight of a pharmaceutically acceptable hydrophilic solvent;
- [0121] (f) optionally up to about 50% by weight of a pharmaceutically acceptable polymer; and

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.

[0213] 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.

EXAMPLES

[0214] 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

[0215] 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

[0216] 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

[0217] Preparation of Formulations 1-3:

[0218] 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 continued at 40° C. until the drug was completely solubilized. These formulations can be filled into hard shell or soft gelatin capsules.

[0219] Chemical Stability Studies

[0220] 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 different temperatures: 50, 60 and 70° C. Samples were pulled and analyzed by HPLC for assay and impurity.

[0221] FIGS. 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 days at 70° C. As can be seen in FIGS. 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).

[0222] A more comprehensive follow-up study was conducted on Formulations #1 and #3 (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 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 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	6.5		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



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ABSTRACT

The embodiments provide compounds of the general Formu-
lae I, II, III, IV, V, VI, VII, and X, as well as compositions,
including pharmaceutical compositions, comprising a subject
compound. The embodiments further provide treatment
methods, including methods of treating a hepatitis C virus
infection and methods of treating liver fibrosis, the methods
generally involving administering to an individual in need
thereof an effective amount of a subject compound or com-
position.

alkyl group attached thereto and dialkylamino refers to nitrogen radical with two alkyl groups attached thereto.

[0410] The term "cyanoamino" used herein refers to nitrogen radical with nitrile group attached thereto.

[0411] The term "carbamyl" used herein refers to RNHC(O)O—.

[0412] The term "keto" and "carbonyl" used herein refers to C=O.

[0413] The term "carboxy" used herein refers to —COOH.

[0414] The term "sulfamyl" used herein refers to —SO₂NH₂.

[0415] The term "sulfonyl" used herein refers to —SO₂—.

[0416] The term "sulfinyl" used herein refers to —SO—.

[0417] The term "thiocarbonyl" used herein refers to C=S.

[0418] The term "thiocarboxy" used herein refers to CSOH.

[0419] As used herein, a radical indicates species with a single, unpaired electron such that the species containing the radical can be covalently bonded to another species. Hence, in this context, a radical is not necessarily a free radical. Rather, a radical indicates a specific portion of a larger molecule. The term "radical" can be used interchangeably with the terms "group" and "moiety."

[0420] As used herein, a substituted group is derived from the unsubstituted parent structure in which there has been an exchange of one or more hydrogen atoms for another atom or group. Unless otherwise indicated, when substituted, the substituent group(s) is (are) one or more group(s) individually and independently selected from C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, C₃-C₇ cycloalkyl (optionally substituted with halo, alkyl, alkoxy, carboxyl, CN, —SO₂-alkyl, —CF₃, and —OCF₃), C₃-C₆ heterocycloalkyl (e.g., tetrahydrofuryl) (optionally substituted with halo, alkyl, alkoxy, carboxyl, CN, —SO₂-alkyl, —CF₃, and —OCF₃), aryl (optionally substituted with halo, alkyl, alkoxy, carboxyl, CN, —SO₂-alkyl, —CF₃, and —OCF₃), heteroaryl (optionally substituted with halo, alkyl, alkoxy, carboxyl, CN, —SO₂-alkyl, —CF₃, and —OCF₃), halo (e.g., chloro, bromo, iodo and fluoro), cyano, hydroxy, C₁-C₆ alkoxy, aryloxy, sulfhydryl (mercapto), C₁-C₆ alkylthio, arylthio, mono- and di-(C₁-C₆)alkylamino, quaternary ammonium salts, amino(C₁-C₆)alkoxy, hydroxy (C₁-C₆)alkylamino, amino(C₁-C₆)alkylthio, cyanoamino, nitro, carbamyl, keto (oxo), carbonyl, carboxy, glycolyl, glycol, hydrazino, guanyl, sulfamyl, sulfonyl, sulfinyl, thiocarbonyl, thiocarboxy, and combinations thereof. The protecting groups that can form the protective derivatives of the above substituents are known to those of skill in the art and can be found in references such as Greene and Wuts *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1999. Wherever a substituent is described as "optionally substituted" that substituent can be substituted with the above substituents unless the context clearly dictates otherwise.

[0421] Asymmetric carbon atoms may be present in the compounds described. All such isomers, including diastereomers and enantiomers, as well as the mixtures thereof are intended to be included in the scope of the recited compound. In certain cases, compounds can exist in tautomeric forms. All tautomeric forms are intended to be included in the scope. Likewise, when compounds contain an alkenyl or alkenylene group, there exists the possibility of cis- and trans-isomeric forms of the compounds. Both cis- and trans-isomers, as well as the mixtures of cis- and trans-isomers, are contemplated.

Thus, reference herein to a compound includes all of the aforementioned isomeric forms unless the context clearly dictates otherwise.

[0422] Isotopes may be present in the compounds described. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0423] Various forms are included in the embodiments, including polymorphs, solvates, hydrates, conformers, salts, and prodrug derivatives. A polymorph is a composition having the same chemical formula, but a different structure. A solvate is a composition formed by solvation (the combination of solvent molecules with molecules or ions of the solute). A hydrate is a compound formed by an incorporation of water. A conformer is a structure that is a conformational isomer. Conformational isomerism is the phenomenon of molecules with the same structural formula but different conformations (conformers) of atoms about a rotating bond. Salts of compounds can be prepared by methods known to those skilled in the art. For example, salts of compounds can be prepared by reacting the appropriate base or acid with a stoichiometric equivalent of the compound. A prodrug is a compound that undergoes biotransformation (chemical conversion) before exhibiting its pharmacological effects. For example, a prodrug can thus be viewed as a drug containing specialized protective groups used in a transient manner to alter or to eliminate undesirable properties in the parent molecule. Thus, reference herein to a compound includes all of the aforementioned forms unless the context clearly dictates otherwise.

[0424] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the embodiments. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the embodiments.

[0425] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the embodiments belong. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the embodiments, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

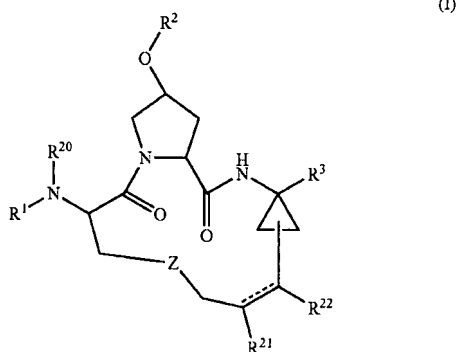
[0426] It must be noted that as used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a method" includes a plurality of such methods and reference to "a dose"

includes reference to one or more doses and equivalents thereof known to those skilled in the art, and so forth.

[0427] The present embodiments provide compounds of Formulae I, II, III, IV, V, VI, VII, and X, as well as pharmaceutical compositions and formulations comprising any compound of Formulae I, II, III, IV, V, VI, VII, and X. A subject compound is useful for treating HCV infection and other disorders, as discussed below.

Formula I

[0428] The embodiments provide a compound having the structure of Formula I:



[0429] or a pharmaceutically acceptable salt or prodrug thereof wherein:

[0430] R^1 is $-(CR^5R^6)_nR^4$;

[0431] n is 0, 1 or 2;

[0432] R^2 is selected from the group consisting of aryl, heteroaryl and polycyclic moiety, each optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, nitro, hydroxy, cyanoamino, $-SH$, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_qC_{3-7}$ cycloalkyl, C_{3-6} heterocycloalkyl, aryl, heteroaryl, aryloxy, arylthio, C_{1-6} alkylthio, $-N[(CH_2)_pOH][(CH_2)_pOH]$, $-S(O)_2NR^{1a}R^{1b}$, $-NHC(O)NR^{1a}R^{1b}$, $-NHC(S)NR^{1a}R^{1b}$, $-C(O)NR^{1a}R^{1b}$, $-NR^{1a}R^{1b}$, $-C(O)R^{2a}$, $-C(O)OR^{2a}$, $-NHC(O)R^{2a}$, $-SO_mR^{2a}$, $-NHC(O)R^{2a}$, $-NHS(O)_2R^{2a}$, $-NR^{2a}[(CH_2)_pOH]$, $-O[(CH_2)_pNR^{3a}R^{3b}]$, $-S[(CH_2)_pNR^{3a}R^{3b}]$, $-(CH_2)_pNR^{3a}R^{3b}$, $-(CH_2)_pR^{4a}$, $-O(CH_2)_pR^{4a}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; said aryl and heteroaryl as an optional substituent are each further optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, heteroaryl, $-NR^{1a}R^{1b}$, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

[0433] R^4 is selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, nitro, hydroxy, cyanoamino, $-SH$, C_{1-6} alkyl optionally substituted with up to 5 fluoro, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_qC_{3-7}$ cycloalkyl, C_{3-6} heterocycloalkyl, aryl, heteroaryl,

aryloxy, arylthio, C_{1-6} alkylthio, $-N[(CH_2)_pOH][(CH_2)_pOH]$, $-S(O)_2NR^{1a}R^{1b}$, $-NHC(O)NR^{1a}R^{1b}$, $-NHC(S)NR^{1a}R^{1b}$, $-C(O)NR^{1a}R^{1b}$, $-NR^{1a}R^{1b}$, $-C(O)R^{2a}$, $-C(O)OR^{2a}$, $-NHC(O)R^{2a}$, $-NHC(O)OR^{2a}$, $-SO_mR^{2a}$, $-NHS(O)_2R^{2a}$, $-NR^{2a}[(CH_2)_pOH]$, $-O[(CH_2)_pNR^{3a}R^{3b}]$, $-S[(CH_2)_pNR^{3a}R^{3b}]$, $-(CH_2)_pNR^{3a}R^{3b}$, $-(CH_2)_pR^{4a}$ and $-O(CH_2)_pR^{4a}$;

[0434] R^{1a} and R^{1b} are each separately a hydrogen atom, or separately selected from the group consisting of C_{1-6} alkyl, C_{3-7} cycloalkyl, and phenyl, each optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, $-(CH_2)_qC_{3-7}$ cycloalkyl, C_{2-6} alkenyl, hydroxy- C_{1-6} alkyl, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or R^{1a} and R^{1b} are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

[0435] each R^{2a} is separately selected from the group consisting of C_{1-6} alkyl, C_{3-7} cycloalkyl, and $C_{6 \text{ or } 10}$ aryl, each optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, $-(CH_2)_qC_{3-7}$ cycloalkyl, C_{1-6} alkoxy, phenyl, and hydroxy- C_{1-6} alkyl; or R^{2a} is a tetrahydrofuran ring linked through the C_3 or C_4 position of the tetrahydrofuran ring; or R^{2a} is a tetrahydropyran ring linked through the C_4 position of the tetrahydropyran ring;

[0436] R^{3a} and R^{3b} are each separately selected from the group consisting of hydrogen and C_{1-6} alkyl; or R^{3a} and R^{3b} are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

[0437] each R^{4a} is separately imidazolyl or pyrazolyl;

[0438] each m is separately 0, 1 or 2;

[0439] each p is separately an integer selected from 1-6;

[0440] each q is separately 0, 1 or 2;

[0441] each r is separately an integer selected from 1-6;

[0442] R^3 is $-C(O)NHS(O)_2R^9$, where R^9 is selected from the group consisting of C_{1-6} alkyl, $-(CH_2)_qC_{3-7}$ cycloalkyl, $-(CH_2)_qC_{6 \text{ or } 10}$ aryl, and a heteroaromatic ring, each optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, nitro, hydroxy, $-COOH$, C_{1-6} alkyl, $-(CH_2)_qC_{3-7}$ cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, hydroxy- C_{1-6} alkyl, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro, or R^9 is $-NR^{9a}R^{9b}$; or R^3 is a $-CONHO(CH_2)_mR^{10}$ where R^{10} is selected from the group consisting of C_{1-6} alkyl, $-(CH_2)_qC_{3-7}$ cycloalkyl, optionally substituted aryl and optionally substituted heteroaryl; or R^3 is a carboxylic acid;

[0443] wherein R^{9a} and R^{9b} are each separately a hydrogen atom, or separately selected from the group consisting of C_{1-6} alkyl, $-(CH_2)_qC_{3-7}$ cycloalkyl, and $C_{6 \text{ or } 10}$ aryl, each optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, $-(CH_2)_qC_{3-7}$ cycloalkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, hydroxy- C_{1-6} alkyl, phenyl, C_{1-6} alkyl substituted with up to 5 fluoro, and C_{1-6} alkoxy substituted with up to 5 fluoro,

tease, including, but not limited to amino acid residues that form the NS3 protease S2 pocket. For example the P₂ moiety may form a hydrogen bond with at least one amino acid selected from His57, Arg155, Val78, Asp79, Gln80 and Asp81. In some instances, P₂ may form both a non-polar interaction and a hydrogen bond with peptide backbone or side chain moieties or atoms located in the substrate binding pocket of NS3 protease, such amino acids selected from His57, Arg155, Val78, Asp79, Gln80 and Asp81. Such hydrogen bond and non-polar interactions may occur with the same amino acid residue or with different amino acid residues in the NS3 protease S2 pocket. In an embodiment of the compound of the general formulae (X) and (Xa), P₂ is positioned by L to provide this configuration, where L is a moiety as described above. In some embodiments, P₂ may be selected from the group consisting of unsubstituted aryl, substituted aryl, unsubstituted heteroaryl, substituted heteroaryl, unsubstituted heterocyclic and substituted heterocyclic.

[0861] In another embodiment of the compound of the general formulae (X) and (Xa), the R⁵⁰ and R⁶⁰ moieties have a size, configuration and/or positioning such that, upon binding of the compound to NS3 protease, at least one atom of R⁵⁰ or R⁶⁰ is within 5 Å or less of any backbone or side chain atom of at least one NS3 protease residue selected from the group consisting of Arg123, Ala156, Ala157, Val158, Cys159, and Asp168. In an embodiment, R⁵⁰ is H and R⁶⁰ is selected from the group consisting of unsubstituted aryl, substituted aryl, unsubstituted heteroaryl, substituted heteroaryl, unsubstituted heterocyclic and substituted heterocyclic; or R⁵⁰ and R⁶⁰ taken together with the nitrogen to which they are attached form a moiety selected from the group consisting of unsubstituted heteroaryl, substituted heteroaryl, unsubstituted heterocyclic and substituted heterocyclic.

Compositions

[0862] The present embodiments further provide compositions, including pharmaceutical compositions, comprising compounds of the general Formulae I, II, III, IV, V, VI, VII, or X.

[0863] A subject pharmaceutical composition comprises a subject compound; and a pharmaceutically acceptable excipient. A wide variety of pharmaceutically acceptable excipients is known in the art and need not be discussed in detail herein. Pharmaceutically acceptable excipients have been amply described in a variety of publications, including, for example, A. Gennaro (2000) "Remington: The Science and Practice of Pharmacy," 20th edition, Lippincott, Williams, & Wilkins; Pharmaceutical Dosage Forms and Drug Delivery Systems (1999) H. C. Ansel et al., eds., 7th ed., Lippincott, Williams, & Wilkins; and Handbook of Pharmaceutical Excipients (2000) A. H. Kibbe et al., eds., 3rd ed. Amer. Pharmaceutical Assoc.

[0864] The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily available to the public.

[0865] The present embodiments provide for a method of inhibiting NS3/NS4 protease activity comprising contacting a NS3/NS4 protease with a compound disclosed herein.

[0866] The present embodiments provide for a method of treating hepatitis by modulating NS3/NS4 protease comprising contacting a NS3/NS4 protease with a compound disclosed herein.

[0867] Example compounds of Formulae I, II, III, IV, V, VI, and VII include Compound Numbers 101-492, 701, 1001-1075, and 1077-1147 as set forth herein.

[0868] Preferred embodiments provide a method of treating a hepatitis C virus infection in an individual, the method comprising administering to the individual an effective amount of a composition comprising a preferred compound.

[0869] Preferred embodiments provide a method of treating liver fibrosis in an individual, the method comprising administering to the individual an effective amount of a composition comprising a preferred compound.

[0870] Preferred embodiments provide a method of increasing liver function in an individual having a hepatitis C virus infection, the method comprising administering to the individual an effective amount of a composition comprising a preferred compound.

[0871] In many embodiments, a subject compound inhibits the enzymatic activity of a hepatitis virus C (HCV) NS3 protease. Whether a subject compound inhibits HCV NS3 protease can be readily determined using any known method. Typical methods involve a determination of whether an HCV polyprotein or other polypeptide comprising an NS3 recognition site is cleaved by NS3 in the presence of the agent. In many embodiments, a subject compound inhibits NS3 enzymatic activity by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%, or more, compared to the enzymatic activity of NS3 in the absence of the compound.

[0872] In many embodiments, a subject compound inhibits enzymatic activity of an HCV NS3 protease with an IC₅₀ of less than about 50 μM, e.g., a subject compound inhibits an HCV NS3 protease with an IC₅₀ of less than about 40 μM, less than about 25 μM, less than about 10 μM, less than about 1 μM, less than about 100 nM, less than about 80 nM, less than about 60 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM, or less.

[0873] In many embodiments, a subject compound inhibits the enzymatic activity of a hepatitis virus C (HCV) NS3 helicase. Whether a subject compound inhibits HCV NS3 helicase can be readily determined using any known method. In many embodiments, a subject compound inhibits NS3 enzymatic activity by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%, or more, compared to the enzymatic activity of NS3 in the absence of the compound.

[0874] In many embodiments, a subject compound inhibits HCV viral replication. For example, a subject compound inhibits HCV viral replication by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%, or more, compared to HCV viral replication in the absence of the compound. Whether a subject compound inhibits HCV viral replication can be determined using methods known in the art, including an in vitro viral replication assay.

Treating a Hepatitis Virus Infection

[0875] The methods and compositions described herein are generally useful in treatment of an of HCV infection.

such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols.

Formulations

[0908] The above-discussed active agent(s) can be formulated using well-known reagents and methods. Compositions are provided in formulation with a pharmaceutically acceptable excipient(s). A wide variety of pharmaceutically acceptable excipients is known in the art and need not be discussed in detail herein. Pharmaceutically acceptable excipients have been amply described in a variety of publications, including, for example, A. Gennaro (2000) "Remington: The Science and Practice of Pharmacy," 20th edition, Lippincott, Williams, & Wilkins; Pharmaceutical Dosage Forms and Drug Delivery Systems (1999) H. C. Ansel et al., eds., 7th ed., Lippincott, Williams, & Wilkins; and Handbook of Pharmaceutical Excipients (2000) A. H. Kibbe et al., eds., 3 ed. Amer. Pharmaceutical Assoc.

[0909] The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily available to the public.

[0910] In some embodiments, an agent is formulated in an aqueous buffer. Suitable aqueous buffers include, but are not limited to, acetate, succinate, citrate, and phosphate buffers varying in strengths from about 5 mM to about 100 mM. In some embodiments, the aqueous buffer includes reagents that provide for an isotonic solution. Such reagents include, but are not limited to, sodium chloride; and sugars e.g., mannitol, dextrose, sucrose, and the like. In some embodiments, the aqueous buffer further includes a non-ionic surfactant such as polysorbate 20 or 80. Optionally the formulations may further include a preservative. Suitable preservatives include, but are not limited to, a benzyl alcohol, phenol, chlorobutanol, benzalkonium chloride, and the like. In many cases, the formulation is stored at about 4° C. Formulations may also be lyophilized, in which case they generally include cryoprotectants such as sucrose, trehalose, lactose, maltose, mannitol, and the like. Lyophilized formulations can be stored over extended periods of time, even at ambient temperatures.

[0911] As such, administration of the agents can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, subcutaneous, intramuscular, transdermal, intratracheal, etc., administration. In many embodiments, administration is by bolus injection, e.g., subcutaneous bolus injection, intramuscular bolus injection, and the like.

[0912] The pharmaceutical compositions of the embodiments can be administered orally, parenterally or via an implanted reservoir. Oral administration or administration by injection is preferred.

[0913] Subcutaneous administration of a pharmaceutical composition of the embodiments is accomplished using standard methods and devices, e.g., needle and syringe, a subcutaneous injection port delivery system, and the like. See, e.g., U.S. Pat. Nos. 3,547,119; 4,755,173; 4,531,937; 4,311,137; and 6,017,328. A combination of a subcutaneous injection port and a device for administration of a pharmaceutical composition of the embodiments to a patient through the port is referred to herein as "a subcutaneous injection port delivery system." In many embodiments, subcutaneous administration is achieved by bolus delivery by needle and syringe.

[0914] In pharmaceutical dosage forms, the agents may be administered in the form of their pharmaceutically acceptable salts, or they may also be used alone or in appropriate association, as well as in combination, with other pharmaceutically active compounds. The following methods and excipients are merely exemplary and are in no way limiting.

[0915] For oral preparations, the agents can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators, such as corn starch, potato starch or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives and flavoring agents.

[0916] The agents can be formulated into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

[0917] Furthermore, the agents can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. The compounds of the embodiments can be administered rectally via a suppository. The suppository can include vehicles such as cocoa butter, carbowaxes and polyethylene glycols, which melt at body temperature, yet are solidified at room temperature.

[0918] Unit dosage forms for oral or rectal administration such as syrups, elixirs, and suspensions may be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet or suppository, contains a predetermined amount of the composition containing one or more inhibitors. Similarly, unit dosage forms for injection or intravenous administration may comprise the inhibitor(s) in a composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

[0919] The term "unit dosage form," as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of compounds of the embodiments calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. The specifications for the novel unit dosage forms of the embodiments depend on the particular compound employed and the effect to be achieved, and the pharmacodynamics associated with each compound in the host.

[0920] The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily available to the public.

Other Antiviral or Antifibrotic Agents

[0921] As discussed above, a subject method will in some embodiments be carried out by administering an NS3 inhibitor that is a compound of Formulae I, II, III, IV, V, VI, VII, or X, and optionally one or more additional antiviral agent(s).

[0922] In some embodiments, the method further includes administration of one or more interferon receptor agonist(s). Interferon receptor agonists are described herein.

[0923] In other embodiments, the method further includes administration of pirfenidone or a pirfenidone analog. Pirfenidone and pirfenidone analogs are described herein.

[0924] Additional antiviral agents that are suitable for use in combination therapy include, but are not limited to, nucleotide and nucleoside analogs. Non-limiting examples include azidothymidine (AZT) (zidovudine), and analogs and derivatives thereof; 2',3'-dideoxyinosine (DDI) (didanosine), and analogs and derivatives thereof; 2',3'-dideoxycytidine (DDC) (dideoxycytidine), and analogs and derivatives thereof; 2',3'-didehydro-2',3'-dideoxythymidine (D4T) (stavudine), and analogs and derivatives thereof; combivir; abacavir; adefovir dipoxil; cidofovir; ribavirin; ribavirin analogs; and the like.

[0925] In some embodiments, the method further includes administration of ribavirin. Ribavirin, 1- β -D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, Calif., is described in the Merck Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Pat. No. 4,211,771. Some embodiments also involve use of derivatives of ribavirin (see, e.g., U.S. Pat. No. 6,277,830). The ribavirin may be administered orally in capsule or tablet form, or in the same or different administration form and in the same or different route as the NS-3 inhibitor compound. Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, intravenously, by suppository, by sustained release dosage form, etc. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

[0926] In some embodiments, the method further includes administration of ritonavir. Ritonavir, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazamidecan-13-oic acid, 5-thiazolylmethyl ester[5S-(5R*,8R*,10R*,11R*)], available from Abbott Laboratories, is an inhibitor of the protease of the human immunodeficiency virus and also of the cytochrome P450 3A and P450 2D6 liver enzymes frequently involved in hepatic metabolism of therapeutic molecules in man. Because of its strong inhibitory effect on cytochrome P450 3A and the inhibitory effect on cytochrome P450 2D6, ritonavir at doses below the normal therapeutic dosage may be combined with other protease inhibitors to achieve therapeutic levels of the second protease inhibitor while reducing the number of dosage units required, the dosing frequency, or both.

[0927] Coadministration of low-dose ritonavir may also be used to compensate for drug interactions that tend to decrease levels of a protease inhibitor metabolized by CYP3A. Its structure, synthesis, manufacture and formulation are described in U.S. Pat. No. 5,541,206 U.S. Pat. No. 5,635,523 U.S. Pat. No. 5,648,497 U.S. Pat. No. 5,846,987 and U.S. Pat. No. 6,232,333. The ritonavir may be administered orally in capsule or tablet or oral solution form, or in the same or different administration form and in the same or different route as the NS-3 inhibitor compound. Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, intravenously, by suppository, by sustained release dosage

form, etc. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

[0928] In some embodiments, an additional antiviral agent is administered during the entire course of NS3 inhibitor compound treatment. In other embodiments, an additional antiviral agent is administered for a period of time that is overlapping with that of the NS3 inhibitor compound treatment, e.g., the additional antiviral agent treatment can begin before the NS3 inhibitor compound treatment begins and end before the NS3 inhibitor compound treatment ends; the additional antiviral agent treatment can begin after the NS3 inhibitor compound treatment begins and end after the NS3 inhibitor compound treatment ends; the additional antiviral agent treatment can begin after the NS3 inhibitor compound treatment begins and end before the NS3 inhibitor compound treatment ends; or the additional antiviral agent treatment can begin before the NS3 inhibitor compound treatment begins and end after the NS3 inhibitor compound treatment ends.

Methods of Treatment

Monotherapies

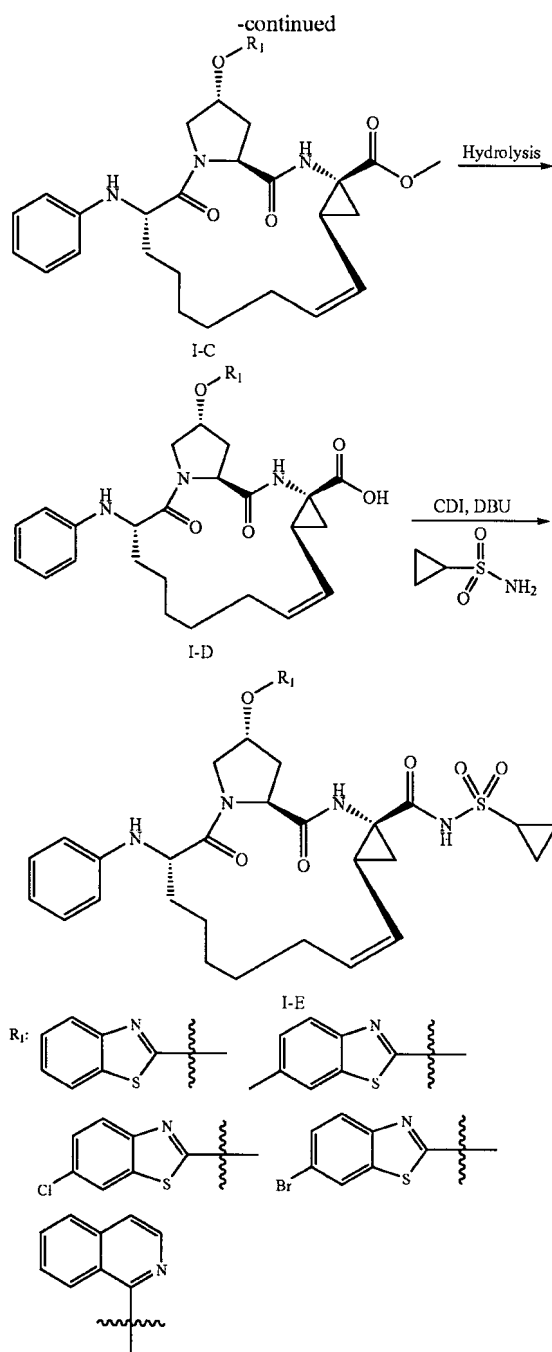
[0929] The NS3 inhibitor compounds described herein may be used in acute or chronic therapy for HCV disease. In many embodiments, the NS3 inhibitor compound is administered for a period of about 1 day to about 7 days, or about 1 week to about 2 weeks, or about 2 weeks to about 3 weeks, or about 3 weeks to about 4 weeks, or about 1 month to about 2 months, or about 3 months to about 4 months, or about 4 months to about 6 months, or about 6 months to about 8 months, or about 8 months to about 12 months, or at least one year, and may be administered over longer periods of time. The NS3 inhibitor compound can be administered 5 times per day, 4 times per day, tid, bid, qd, qod, biw, tiw, qw, qow, three times per month, or once monthly. In other embodiments, the NS3 inhibitor compound is administered as a continuous infusion.

[0930] In many embodiments, an NS3 inhibitor compound of the embodiments is administered orally.

[0931] In connection with the above-described methods for the treatment of HCV disease in a patient, an NS3 inhibitor compound as described herein may be administered to the patient at a dosage from about 0.01 mg to about 100 mg/kg patient bodyweight per day, in 1 to 5 divided doses per day. In some embodiments, the NS3 inhibitor compound is administered at a dosage of about 0.5 mg to about 75 mg/kg patient bodyweight per day, in 1 to 5 divided doses per day.

[0932] The amount of active ingredient that may be combined with carrier materials to produce a dosage form can vary depending on the host to be treated and the particular mode of administration. A typical pharmaceutical preparation can contain from about 5% to about 95% active ingredient (w/w). In other embodiments, the pharmaceutical preparation can contain from about 20% to about 80% active ingredient.

[0933] Those of skill will readily appreciate that dose levels can vary as a function of the specific NS3 inhibitor compound, the severity of the symptoms and the susceptibility of the subject to side effects. Preferred dosages for a given NS3 inhibitor compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given interferon receptor agonist.



[1147] Macrocyclics of general structures I-D and I-E can be synthesized as shown in Scheme I. The isoindoline carbamate 1 can be treated under basic conditions to hydrolyse the isoindoline carbamate thereby providing alcohol 2. The alcohol 2 can be treated with a heteroaryl chloride, such as 2-chlorobenzothiazole, 2-chloro-6-methylbenzothiazole, 2,6-dichlorobenzothiazole, 6-bromo-2-chlorobenzothiazole, 1-chloroisoquinoline and the like, under basic conditions to afford a compound of general structure I-A. The compound of general structure I-A can be treated with acid in methanol to

remove the Boc protecting group and form a methyl ester thereby providing a compound of general structure I-B. The compound of general structure I-B can be treated with optionally substituted aryl boronic acids under Cu²⁺-catalyzed conditions thereby providing N-aryl compounds of general structure I-C. The compounds of general structure I-C can be treated under basic conditions to hydrolyse the methyl ester thereby providing carboxylic acids of general structure I-D. Finally, acids of general structure I-D can be coupled with sulfonamides (or sulfamides, not shown) thereby providing compounds of general structure I-E.

Example 1-1

General Procedure A

[1148] Compound 1 (10 g, 15.9 mmol.) was dissolved in methanol (100 mL), 5 M NaOH solution (95 mL) was added, the resulting mixture was heated to 50° C. and stirred overnight, after completion of the reaction. The mixture was cooled by ice water, 2 M HCl was added to acidify the mixture to pH=3-4, then the mixture was extracted by EtOAc, the organic layers were combined, washed by brine, dried, the solvent was removed under reduced pressure, the crude compound 2 (7.5 g) was used directly in the next step.

Example 1-2

General Procedure B

[1149] A solution of Compound 2 (5 g, 1 mL/100 mg) in DMF was added slowly to a mixture of NaH was dissolved in DMF (1.5 mL/100 mg NaH), cooled to 0-5° C. The mixture was stirred for 2 h at 0-5° C., then heteroaryl halide (2c) was added, the resulting mixture was warmed to room temperature and stirred for 12 h. The mixture was cooled to 0° C. (ice water bath), then 2 M HCl was carefully added to lower the pH (pH=3-4). The acidic mixture was extracted by EtOAc. The combined organic layers were washed by brine and dried. The solvent was removed under reduced pressure and the crude product was purified by column chromatography to afford general compound I-A (3.0 g, 60-70% yield).

Example 1-3

General Procedure C

[1150] General compound I-A (3.0 g) was dissolved in HCl in MeOH (25 mL/g, compound I-A), the resulting mixture was stirred at room temperature for 12 h. The solvent was removed then aqueous NaHCO₃ was added to neutralize any remaining acid. The basic mixture was extracted by EtOAc. The EtOAc layer was dried and then the solvent was removed to afford a crude residue. Crude general compound I-B (2.8 g) was used without further purification in the next step.

Example 1-4

General Procedure D

[1151] A mixture of general compound I-B (400 mg, 0.80 mmol.), phenylboronic acid (146.8 mg, 1.2 mmol.), Cu(OAc)₂ (188 mg, 1.0 mmol.), pyridine (316 mg, 4 mmol.), pyridine N-Oxide (76 mg, 0.8 mmol.) and molecular sieves 4



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(54) Macrocytic hepatitis C serine protease inhibitors

(57) The present invention relates to novel macrocyclic compounds and methods of use thereof. The present invention further relates to pharmaceutical compositions comprising the compounds of the present invention, or pharmaceutically acceptable salts, esters, or prodrugs thereof, in combination with a pharmaceutically acceptable carrier or excipient.

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Description

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional patent application Ser. No. 61/191,725, filed September 11, 2008, and U.S. provisional patent application Ser. No. 61/209,689, filed March 10, 2009. The disclosures of the aforementioned patent applications are incorporated herein in their entirety by this reference.

TECHNICAL FIELD

[0002] The present invention relates to novel macrocycles having activity against the hepatitis C virus (HCV) and useful in the treatment of HCV infections. More particularly, the invention relates to macrocyclic compounds, compositions containing such compounds and methods for using the same, as well as processes for making such compounds.

BACKGROUND OF THE INVENTION

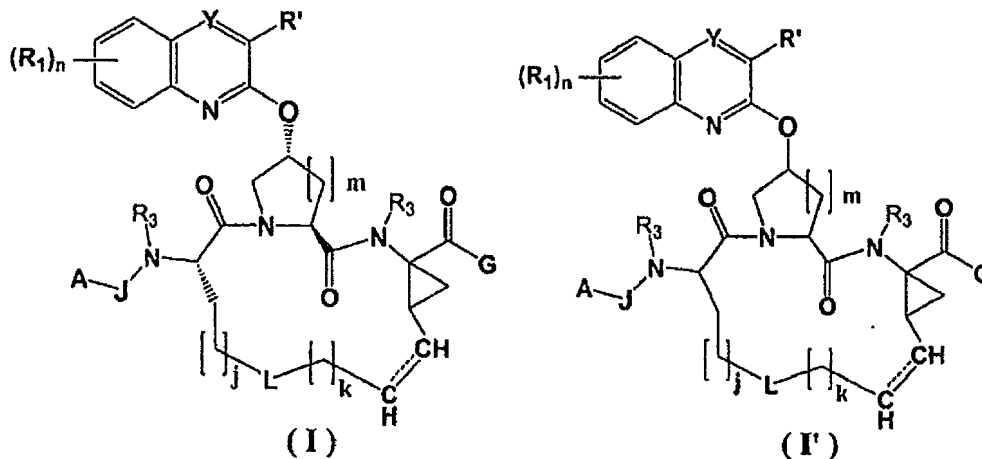
[0003] HCV is the principal cause of non-A, non-B hepatitis and is an increasingly severe public health problem both in the developed and developing world. It is estimated that the virus infects over 200 million people worldwide, surpassing the number of individuals infected with the human immunodeficiency virus (HIV) by nearly five fold. HCV infected patients, due to the high percentage of individuals inflicted with chronic infections, are at an elevated risk of developing cirrhosis of the liver, subsequent hepatocellular carcinoma and terminal liver disease. HCV is the most prevalent cause of hepatocellular cancer and cause of patients requiring liver transplantations in the western world.

[0004] There are considerable barriers to the development of anti-HGV therapeutics, which include, but are not limited to, the persistence of the virus, the genetic diversity of the virus during replication in the host, the high incident rate of the virus developing drug-resistant mutants, and the lack of reproducible infectious culture systems and small-animal models for HCV replication and pathogenesis. In a majority of cases, given the mild course of the infection and the complex biology of the liver, careful consideration must be given to antiviral drugs, which are likely to have significant side effects.

SUMMARY OF THE INVENTION

[0005] The present invention relates to novel macrocyclic compounds and methods of treating a hepatitis C infection in a subject in need of such therapy with said macrocyclic compounds. The compounds of the present invention interfere with the life cycle of the hepatitis C virus and are useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the compounds of the present invention, or pharmaceutically acceptable salts, esters or prodrugs thereof, in combination with a pharmaceutically acceptable carrier or excipient.

[0006] In one aspect, the invention provides a compound of formula I or formulae I':



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

J is absent, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, -C

(O)-, -O-C(O)-, -N(R₃)-C(O)-, -C(S)-, -C(=NR₄)-, -S(O)-, -S(O₂)-, or -N(R₃)-;

A is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted arylalkyl, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted carbocyclic;

Each R₁ is independently selected from

(i) halogen, hydroxy, amino, -CN, -CF₃, -N₃, -NO₂, -OR₄, -SR₄, -SOR₄, -SO₂R₄, -N(R₃)S(O₂)-R₄, -N(R₃)S(O₂)NR₃R₄, -NR₃R₄, -C(O)OR₄, -C(O)R₄, -C(O)NR₃R₄, or -N(R₃)C(O)R₄;

(ii) optionally substituted aryl;

(iii) optionally substituted heteroaryl;

(iv) optionally substituted heterocyclic;

(v) optionally substituted carbocyclic; or

(vi) optionally substituted alkyl, optionally substituted alkenyl; or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

G is -E-R₅;

wherein E is absent; optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; or -O-, -S-, -N(R₃)-, -N(R₃)S(O_p)-, -N(R₃)C(O)-, -N(R₃)C(O)S(O_p)-, -OS(O_p)-, -C(O)S(O_p)-, or -C(O)N(R₃)S(O_p)-;

p is 0, 1, or 2;

R₅ is H; optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;

R₃ and R₄ are each independently selected at each occurrence from the following; optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclic; optionally substituted carbocyclic; or hydrogen;

L is absent or is selected from optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

Y is N or -C(R'')-;

wherein A, R₁, R', and/or R'' can be taken together to form a ring;

j = 0, 1, 2, 3, or 4;

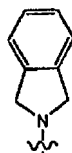
k = 0, 1, 2, or 3;

m = 0, 1, or 2;

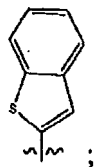
n is 0, 1, 2, 3, or 4; and

— denotes a carbon-carbon single or double bond,

wherein if Y is N, then R' is optionally substituted heterocyclic, optionally substituted heteroaryl, optionally substituted aryl or optionally substituted carbocyclic, and comprises two or more fused rings, and wherein R' is not



or



wherein if Y is -C(R'')-, then R' and R'' taken together with the carbon atoms to which they are attached form an aryl

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to produce Example 47.

Example 48. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

[0232] Example 48 can be prepared according to the procedure described for the preparation of Example 42, replacing 2-methylpyrimidine-5-carboxylic acid from Example 42a with 5-methylpyrazine-2-carboxylic acid in Example 48a to produce (S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 42 to produce Example 48.

Example 49. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 49a.

(S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoic acid.

[0233] Boc-2(S)-amino-non-8-eoic acid dicyclohexylamine salt can be suspended in isopropyl acetate, washed several times with an aqueous citric acid solution and then once with water. The washed product, concentrated and then rediluted in isopropyl acetate, can be reacted with HCl to produce 2(S)-amino-non-8-eoic acid HCl salt. 5-Methyl-2-pyrazinecarboxylic acid, N,N'-disuccinimidyl carbonate, and N,N-dimethylaminopyridine can be dissolved in N-methyl-2-pyrrolidone (NMP) and stirred. 2(S)-Amino-non-8-eoic acid HCl salt is subsequently added, followed by triethylamine, and stirred to produce the title compound of Example 49a, which can be crystallized out by adding HCl followed by water.

Example 49b.

[0234] (1R,2S)-ethyl-1-((2S,4R)-N-(tert-butoxycarbonyl)-1-((S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoyl)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate (2S,4R)-N-Boc-4-hydroxyproline can be reacted with 6-chlorophenanthridine in NMP, in the presence of sodium t-butoxide, to produce (2S,4R)-1-(tert-butoxycarbonyl)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxylic acid, Methyl tertiary butyl ether (MTBE) and water can then be added. The aqueous layer is separated, washed, and then HCl is added, followed by extraction with MTBE. The extracted product can be mixed with diisopropylethylamine (DIPEA) and HATU (CAS # 48893-10-1), and then reacted with (1R,2S)-ethyl-1-amino-2-vinylcyclopropanecarboxylate tosylate salt in dimethylformide (DMF) and toluene. The reaction produces (2S,4R)-tert-butyl 2-((1R,2S)-1-(ethoxycarbonyl)-2-vinylcyclopropylcarbamoyl)-4-(phenanthridin-6-yloxy)pyrrolidine-1-carboxylate, which can be extracted with MTBE and washed with HCl, further extracted, washed, dried, and dissolved in 2-propanol.

[0235] HCl can be added to the 2-propanol solution to produce (1R,2S)-ethyl 1-((2S,4R)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, which can be crystallized out by neutralizing with NaOH.

[0236] (1R,2S)-ethyl 1-((2S,4R)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, the title compound of Example 49a, N-hydroxy-5-norbomene-2,3-dicarboximide, and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride can be mixed and stirred in DMF, followed by addition of N,N-dimethylethylene diamine. The reaction produces (1R,2S)-ethyl 1-((2S,4R)-1-((S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoyl)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, which can be dissolved in isopropyl acetate and extracted with aqueous H₃PO₄, and then extracted with aqueous K₂HPO₄. The product can be reacted with di-tert-butylidicarbonate in the presence of dimethylaminopyridine, followed by extraction with a mixture of a citric acid solution and a sodium chloride solution, to produce the title compound of Example 49b.

Example 49c.

[0237] (2R,6S,13aS,14aR,16aS,Z)-ethyl-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate hydrochloride

[0238] The product of Example 49b can be subject to ring-closing metathesis in the presence of Zhan-B catalyst in toluene to produce (2R,6S,13aS,14aR,16aS,Z)-15-tert-butyl 14a-ethyl 6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-2,3,5,6,7,8,9,10,11,13a,14,14a,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a,15(1H)-dicarboxylate. The catalyst can be quenched with imidazole after the reaction.

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[0239] The ring-closed product in toluene can be solvent switched to acetonitrile, followed by addition of hydrogen chloride in dioxane and heated to produce the title compound of Example 49c.

Example 49d.

[0240] (2R, 6S, 13aS, 14aR, 16aS, Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

[0241] The isolated product of Example 49c can be mixed with tetrahydrofuran, water and LiOH·H₂O, and then heated and stirred. The reaction mixture can be later cooled, added with aqueous H₃PO₄, aqueous NaCl and 2-methyl tetrahydrofuran, and the organic layer is separated, washed and filtered. MeCN is added to the concentrated organic layer, heated and cooled, and then diethylamine is added. The slurry is heated and cooled to form (2R,6S,13aS,14aR,16aS, Z)-6-(5-Methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate diethylamine salt, which can be further washed and dried.

[0242] The diethylamine salt can be mixed with tetrahydrofuran, 2-methyl tetrahydrofuran and aqueous H₃PO₄. The organic layer is separated, washed with aqueous NaCl, and then concentrated and/or purified. The product can be subsequently mixed with NMP, followed by addition of carbonyldiimidazole (CDI) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Cyclopropylsulfonamide can be subsequently added. The reaction mixture is stirred for hours. Isopropyl acetate can then be added, followed by aqueous KH₂PO₄ and then aqueous H₃PO₄. The organic layer can be isolated, washed, and purified to produce the title compound of Example 49d. The isolated product can be further dissolved in isopropyl acetate and then the solution is diluted with ethanol. Water can be added to the resulting solution in portion-wise manner with adequate hold-times after each addition to ensure de-supersaturation. Water addition is terminated just as the ternary solvent system becomes bi-phasic due to the partial immiscibility of isopropyl acetate, ethanol, water solvent system. The slurry can be stirred for hours and then the solid is isolated via filtration and drying to produce the crystalline hydrate of the title compound.

Example 50. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

[0243] Example 50 can be prepared according to the procedure described for the preparation of Example 49, replacing 5-methylpyrazine-2-carboxylic acid from Example 49a with -(1,5-dimethyl-1H-pyrazole-3-carboxylic acid in Example 50a to produce (S)-2-(1,5-dimethyl-1H-pyrazole-3-carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 49 to produce Example 50.

Example 51. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

[0244] Example 51 can be prepared according to the procedure described for the preparation of Example 49, replacing 5-methylpyrazine-2-carboxylic acid from Example 49a with 5-methyl-1H-pyrazole-3-carboxylic acid in Example 51 a to produce (S)-2-(5-methyl-1H-pyrazole-3-carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 49 to produce Example 51.

Example 52. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-fluorobenzamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

[0245] Example 52 can be prepared according to the procedure described for the preparation of Example 49, replacing 5-methylpyrazine-2-carboxylic acid from Example 49a with 2-fluorobenzoic acid in Example 52a to produce (S)-2-(2-fluorobenzamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 49 to produce Example 52.

with a Victor II luminometer (Perkin-Elmer). To determine HCV RNA levels, RNA extractions can be performed using the CellsDirect kit (Invitrogen), and the HCV RNA copy number can be measured using the Superscript III Platinum One-Step qRT-PCR system (Invitrogen) and primers specific to the HCV 5' nontranslated region. Cytotoxicity can be determined by the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay as follows. Replicon cells is plated in 96-well plates (4000 cells per well), the next day compound dilutions are added as in the activity assay, and the cells are grown in the presence of the inhibitors for 4 days. The MTT solution is diluted in DMEM containing 5% FBS and 60 μ l of the solution is added to the cells. After 4 hrs, the cells are solubilized by the addition of 3Q μ l SDS (20% in 0.02 N HCl). The plates are incubated overnight and the optical density can be measured at 570nm. To determine compounds' EC₅₀ and TD₅₀, luciferase, RNA inhibition and MTT data can be analyzed using the GraphPad Prism 4 software (equation: sigmoidal dose-response - variable slope).

Mutants in transient replicons

[0259] Mutations detected in resistance selection studies can be introduced into wild type transient replicon constructs based on genotypes 1a-H77 and 1b-N. Both replicons are bicistronic sub-genomic constructs containing a firefly luciferase reporter similar to those described above, but they do not contain a Neo selectable marker and are therefore only suitable for transient replication assays. The 1a-H77 replicon for transient assays further differs from the replicon in the stable cell line in that it contains NS2 through NS5B in the second cistron. The 1b-N strain replicon contains NS3 through NS5B in the second cistron, with adaptive mutations E1202G in NS3 and S2204I in NS5A. Mutagenesis can be performed using the Stratagene QuikChange XL II site-directed mutagenesis kit. Mutants' sequences can be confirmed, plasmids can be linearized with *Xba* I restriction enzyme and used as template for in vitro transcription reactions to make mutant replicon RNA for transient transfections. In vitro transcription can be performed with the T7 Megascript kit (Ambion).

[0260] Transient replicon transfections can be performed essentially as described by Mo et al. (Antimicrob Agents Chemother (2005) 49(10):4305-4314) with slight modifications. Fifteen micrograms of template RNA can be used to electroporate 3×10^6 cells in a 200 μ l volume in a 0.2 cm cuvette. The cells used for transient transfections can be Huh7 cells obtained by curing replicon-containing cells with IFN (Mo et al., *supra*). Electroporation can be done with a Gene Pulser II (Bio-Rad, CA) at 480V and 25 μ F, using two manual pulses. Transfected cells can be diluted to 7.5×10^4 cells/ml and plated in 96 well plates at 7.5×10^3 cells per well in DMEM with 5% FBS and 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen). Four hours post-transfection, one plate is harvested for luciferase measurement; this plate may provide a measure of the amount of input RNA that can be translated, and thus of transfection efficiency. To the remaining plates, test compound serial dilutions in DMSO can be added (0.5% DMSO final concentration), and plates are incubated for 4 days.

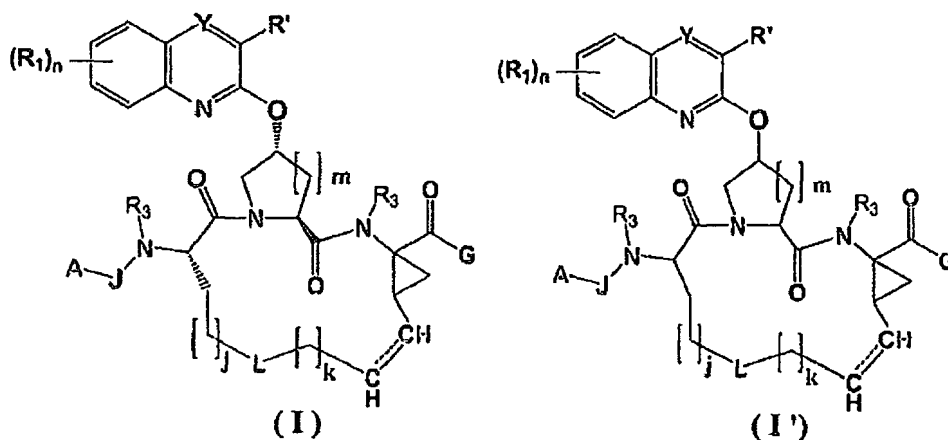
[0261] Exemplary compounds of the present invention were tested for their anti-HCV activities. Many of the compounds tested showed unexpected anti-HCV activities, including excellent activities in biochemical assays against HCV proteases representing various HCV genotypes, superior activities in standard HCV replicon assays including activity against 1a-H77 and 1b-con1 HCV strains in the absence or presence of 40% human plasma, and/or excellent activities in transient replicon assays against drug-resistant mutants in a number of different HCV genetic backgrounds.

[0262] The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

[0263] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. Such equivalents are intended with be encompassed by the following claims,

[0264] The present invention is further defined by the following embodiments:

1. A compound of formula I or I':



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

J is absent, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, -C(O)-, -O-C(O)-, -N(R₃)-C(O)-, -C(S)-, -C(=NR₄)-, -S(O)-, -S(O)₂-, or -N(R₃)-;

A is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted arylalkyl, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted carbocyclic;

Each R₁ is independently selected from

- (i) halogen, hydroxy, amino, -CN, -CF₃, -N₃, -NO₂, -OR₄, -SR₄, -SOR₄, -SO₂R₄, -N(R₃)S(O)₂-R₄, -N(R₃)(SO₂)NR₃R₄, -NR₃R₄, -C(O)-OR₄, -C(O)R₄, -C(O)NR₃R₄, or -N(R₃)C(O)R₄;
- (ii) optionally substituted aryl;
- (iii) optionally substituted heteroaryl;
- (iv) optionally substituted heterocyclic;
- (v) optionally substituted carbocyclic; or
- (vi) optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

G is -E-R₅;

wherein E is absent; optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; or -O-, -S-, -N(R₃)-, -N(R₃)S(O)_p-, -N(R₃)C(O)-, -N(R₃)C(O)S(O)_p-, -OS(O)_p-, -C(O)S(O)_p-, or -C(O)N(R₃)S(O)_p-;

p is 0, 1, or 2;

R₅ is H; optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;

R₃ and R₄ are each-independently selected at each occurrence from the following: optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclic; optionally substituted carbocyclic; or hydrogen;

L is absent or is selected from optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

Y is N or -C(R'')-;

wherein A, R₁, R' and/or R'' can be taken together to form a ring;

j = 0, 1, 2, 3, or 4;

k = 0, 1, 2, or 3;

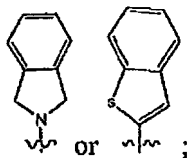
m = 0, 1, or 2;

n is 0, 1, 2, 3, or 4; and

denotes a carbon-carbon single or double bond,

wherein if Y is N, then R' is optionally substituted heterocyclic or optionally substituted carbocyclic, and comprises two or more fused rings, and wherein R' is not

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wherein if Y is -C(R'')-, then R' and R'' taken together with the carbon atoms to which they are attached form an aryl or heteroaryl ring, each said ring is optionally substituted;

provided that said compound is not tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

2. The compound of item 1, or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein R' is H, Y is N, and wherein k=3, j=1 and L is absent.

3. The compound of item 2, or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein R₁ is hydrogen or halogen, E is NHS(O)- or -NHS(O₂)-, and R₅ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyridinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, or imidazolyl, each of which is optionally substituted.

4. The compound of item 2, or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein J is -C(O)- and A is optionally substituted -C₁-C₈ alkyl, containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted -C₁-C₈ alkoxy, optionally substituted heteroaryl, optionally substituted -C₃-C₁₂ cycloalkyl, or optionally substituted -C₃-C₁₂ heterocycloalkyl.

5. The compound of item 1, or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Y is -C(R'')-, and R' and R'' taken together with the carbon atoms to which they are attached form an aryl or heteroaryl ring, each said ring is optionally substituted, and wherein k=3, j=1 and L is absent.

6. The compound of item 5, or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein R₁ is hydrogen or halogen; E is -NHS(O)- or -NHS(O₂)-, and R₅ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyridinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, or imidazolyl, each of which is optionally substituted.

7. The compound of item 5, or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein J is -C(O)- and A is optionally substituted -C₁-C₈ alkyl, containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted -C₁-C₈ alkoxy, optionally substituted heteroaryl, optionally substituted -C₃-C₁₂ cycloalkyl, or optionally substituted -C₃-C₁₂ heterocycloalkyl.

8. The compound of item 5, or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein R' and R'' together form an optionally substituted aryl.

9. The compound of item 5, or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein R' and R'', and the atoms to which each is attached, form an aryl which is substituted by (R₂)_x, wherein each R₂ is independently selected from

(i) halogen, hydroxy, amino, -CN, -CF₃, -N₃, -NO₂, -OR₄, -SR₄, -SOR₄, -SO₂R₄, -NHS(O₂)-R₄, -NHS(O₂)NR₃R₄, -NR₃R₄, -C(O)OR₄, -C(O)R₄, -C(O)NR₃R₄, or -N(R₃)C(O)R₄;

(ii) optionally substituted aryl;

(iii) optionally substituted heteroaryl;

(iv) optionally substituted heterocyclic;

(v) optionally substituted carbocyclic; or

(vi) optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

and x is 0, 1, 2, 3, or 4.

10. The compound of item 5, or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein R₁ is hydrogen or halogen; E is -NHS(O)- or -NHS(O₂)-, and R₅ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyridinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, or imidazolyl, each of which is optionally substituted.

11. A compound of item 1, or a pharmaceutically acceptable salt, ester or prodrug thereof, selected from the following:

(2) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(isonicotinamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(3) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(2-fluorobenzamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(4) N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-6-yl)-5-methylisoxazole-3-carboxamide;

(5) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(6) N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-6-yl)-isoxazole-5-carboxamide;

(7) N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-6-yl)-thiazole-4-carboxamide;

(8) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(9) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(10) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1,3-dimethyl-1H-pyrazole-4-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(11) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(3-fluorobenzamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(12) tert-butyl ((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-6-yl)carbamate;

(13) N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonyl)carbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-6-yl)-5-methylisoxazole-3-carboxamide;

(14) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(15) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(16) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; and

(17) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide.

12. A compound of item 1, or a pharmaceutically acceptable salt, ester or prodrug thereof, selected from the following:

A

(24) tert-butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyle)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(25) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyrazine-2-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(26) Cyclopentyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyle)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(27) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(28) N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyle)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide;

(29) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(30) N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyle)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)thiazole-5-carboxamide;

(31) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-fluorobenzamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(32) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyridazine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(33) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(34) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(35) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-hydroxy-2-methylpropanamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(36) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(37) Cyclopentyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyle)-2-(2-fluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(38) tert-Butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyle)-2-(2,9-difluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(39) tert-butyl (2R,6S,13aR,14aR,16aS)-14a-(cyclopropylsulfonylcarbamoyle)-5,16-dioxo-2-(phenanthridin-6-yloxy)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

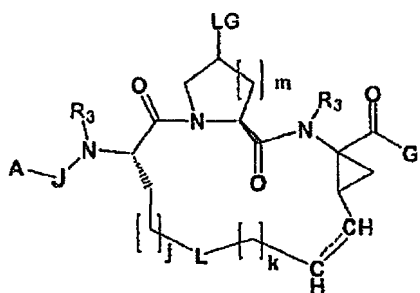
(40) Cyclopentyl (2R,6S,13aR,14aR,16aS)-14a-(cyclopropylsulfonylcarbamoyle)-5,16-dioxo-2-(phenanthridin-6-yloxy)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate; and

(41) tert-Butyl (2R,6S,13aR,14aR,16aS)-5,16-dioxo-2-(phenanthridin-6-yloxy)-14a-(thiophen-2-ylsulfonylcarbamoyle)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of item 1 or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient.

14. A method of treating a viral infection in a subject, comprising administering to the subject a therapeutically effective amount of a compound of item 1 or a pharmaceutically acceptable salt, ester or prodrug thereof.

15. A method of producing a compound of formula 1, or a pharmaceutically acceptable salt, ester or prodrug thereof, comprising the step of reacting a compound of formula II:



(II);

wherein,

J is absent, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, -C(O)-, -O-C(O)-, -N(R₃)-C(O)-, -C(S)-, -C(=NR₄)-, -S(O)-, -S(O₂)-, or -N(R₃)-;

A is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted arylalkyl, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted carbocyclic;

G is -E-R₅;

wherein E is absent; optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; or -O-, -S-, -N(R₃)-, -N(R₃)S(O_p)-, -N(R₃)C(O)-, -N(R₃)C(O)S(O_p)-, -OS(O_p)-, -C(O)S(O_p)-, or -C(O)N(R₃)S(O_p)-;

p is 0, 1, or 2;

R₅ is H; optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;

Each R₃ is independently selected at each occurrence from the following: optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclic; optionally substituted carbocyclic; or hydrogen;

L is absent or is selected from optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

j = 0, 1, 2, 3, or 4;

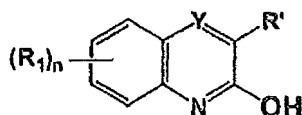
k = 0, 1, 2, or 3;

m = 0, 1, or 2; and

— denotes a carbon-carbon single or double bond; and

LG is a leaving group;

with a compound of formula III:



(III);

wherein:

Each R₁ is independently selected from

- (i) halogen, hydroxy, amino, -CN, -CF₃, -N₃, -NO₂, -OR₄, -SR₄, -SOR₄, -SO₂R₄, -N(R₃)S(O)₂-R₄, -N(R₃)S(O)₂NR₃R₄, -NR₃R₄, -C(O)OR₄, -C(O)R₄, -C(O)NR₃R₄, or -N(R₃)C(O)R₄;
 (ii) optionally substituted aryl;
 (iii) optionally substituted heteroaryl;
 (iv) optionally substituted heterocyclic;
 (v) optionally substituted carbocyclic; or
 (vi) optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

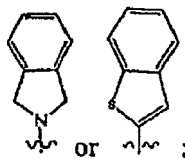
R₃ and R₄ are each independently selected at each occurrence from the following, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclic; optionally substituted carbocyclic; or hydrogen;

n is 0, 1, 2, 3, or 4;

Y is N or CRⁿ;

wherein A, R₁, R' and/or R'' can be taken together to form a ring;

wherein if Y is N, then R' is optionally substituted heterocyclic or optionally substituted carbocyclic, and comprises two or more fused rings, and wherein R' is not

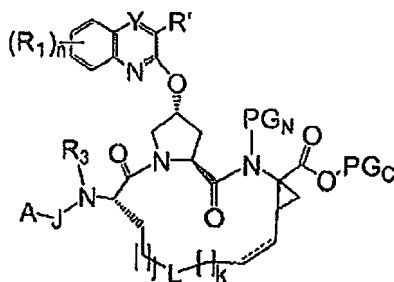


wherein if Y is -C(R'')-, then R' and R'' taken together with the carbon atoms to which they are attached form an aryl or heteroaryl ring, each said ring is optionally substituted;

provided that said compound is not tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5, 16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

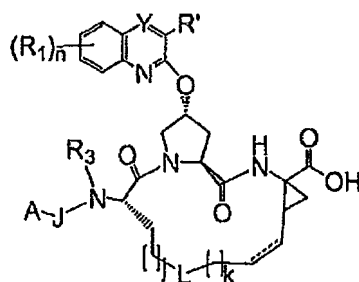
to thereby produce a compound of formula I.

16. A method of preparing a compound of formula I according to item 1, or a pharmaceutically acceptable salt, ester or prodrug thereof, comprising deprotecting



to form

CPS



which is then reacted with H-G to form said compound, wherein PG_N is an amino protecting group and PG_C is a carboxylic acid protecting group.

Claims

1. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyrazine-2-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.
2. A compound: N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonyl carbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.
3. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.
4. A compound: N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonyl carbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)thiazole-5-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.
5. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyridazine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.
6. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.
7. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
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 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 13 - 0062367
		Bogotá D.C., Junio 25 de 2013 - 16:14:38

RECIBIDO DE : REYES Y REYES ABOGADOS	NI 900.048.328
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*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	559950160	25/06/2013	750.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	559950171	25/06/2013	50.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	559950311	25/06/2013	325.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	559950322	25/06/2013	240.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	559950333	25/06/2013	200.000.00

CONSIGNACION	BANCO DE BOGOTA	062754387	559950355	25/06/2013	2.140.000.00
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*** Conceptos Pagados ***			
CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	1632 OPOSICION NUEVA CRACION / PRESENTACION	325.000.00	325.000.00
			\$325.000.00

SON: **TRESCIENTOS VEINTICINCO MIL PESOS MONEDA CORRIENTE***

Responsable: 
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 12-154969- -00005-0000

Fecha: 2013-06-25 17:01:06 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 46

