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(71) Applicant (for all designated States except US):

(72) Inventors:

JANETKA, James, W. [US/US]; 3612 Stearns Hill Road, Waltham, MA 02451 (US); LEDFORD, Brian, E. [US/US]; 36 School Street, Hopkinton, MA 01748 (US); MULLICAN, Michael, D. [US/US]; 110 Parker Road, Needham, MA 02194 (US).

(74) Agents:
HALEY, James, F., Jr.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US) et al.


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PENTACYCLIC COMPOUNDS USEFUL AS INHIBITORS OF HEPATITIS C VIRUS NS3 HELICASE

(57) Abstract

The present invention relates to compounds which are useful in inhibiting the hepatitis C virus NS3 helicase. These compounds are useful in pharmaceutical compositions and method for treating and preventing HCV infection.
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PENTACYCLIC COMPOUNDS USEFUL AS INHIBITORS OF HEPATITIS C VIRUS NS3 HELICASE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to compounds which are useful in inhibiting the hepatitis C virus NS3 helicase. These compounds are useful in pharmaceutical compositions and method for treating and preventing HCV infection.

BACKGROUND OF THE INVENTION


Upon first exposure to HCV only about 20% of infected individuals develop acute clinical hepatitis while others appear to resolve the infection spontaneously. In most instances, however, the virus establishes a chronic infection that persists for decades
[Iwarson, S. "The Natural Course of Chronic Hepatitis" FEMS Microbiology Reviews 14, pp. 201-204 (1994)]. This usually results in recurrent and progressively worsening liver inflammation, which often leads to more severe disease states such as cirrhosis and hepatocellular carcinoma [Kew, M.C., "Hepatitis C and Hepatocellular Carcinoma", FEMS Microbiology Reviews, 14, pp. 211-220 (1994); Saito, I., et al. "Hepatitis C Virus Infection is Associated with the Development of Hepatocellular Carcinoma" Proc. Natl. Acad. Sci. USA 87, pp. 6547-6549 (1990)]. Unfortunately, there are no broadly effective treatments for the debilitating progression of chronic HCV.


Proteolytic processing of the HCV polyprotein by virally-encoded proteases generates several nonstructural (NS) proteins with enzymatic activities essential for the replicative cycle of the virus [P. Neddermann et al., *Biol. Chem.*, 378, pp. 469-476 (1997)]. NS2 encodes a presumed metalloprotease, NS5B is a RNA-dependent RNA polymerase, and NS3 is a bifunctional enzyme with a serine protease localized to the N-terminal 181 residues of the protein and a RNA helicase in the C-terminal 465 amino acids. The NS3 protease performs an intramolecular cleavage at the NS3/NS4A junction to form a tight noncovalent NS3-NS4A complex necessary for efficient processing of the remaining polyprotein [C. Failla et al., *J. Virol.*, 69, pp. 1769-1777 (1995); R. Bartenschlager et al., *J. Virol.*, 69, pp. 7519-7528 (1995); Y. Tanji et al., *J. Virol.*, 69, pp. 1575-1581 (1995)]. To date, no evidence exists to suggest that the serine protease and helicase domains are separated by proteolytic processing of NS3 in vivo. This may reflect economical packaging of these enzymatic components, or could imply a functional interdependence between the two domains.

Numerous studies have demonstrated that the serine protease [J. L. Kim et al., *Cell*, 87, pp. 343-355]

In addition to HCV, all flavi- and pestiviruses sequenced to date contain conserved helicase sequence motifs in their homologous NS3 proteins, suggesting that this enzyme plays an important role in the HCV replicative cycle [R. H. Miller et al., Proc. Natl. Acad. Sci. USA, 87, pp. 2057-2061 (1990)]. Consistent with this possibility, helicase encoding sequences have been identified in other viruses and helicases are suggested to catalyze the separation of double-stranded nucleic acid structures during transcription and genome replication [G. Kadare et al., J. Virol., 71, pp. 2583-2590 (1997)]. Previous studies with poliovirus, a positive-stranded RNA virus of the Picornaviridae family, show that mutation of conserved sequence motifs in the 2C helicase inhibits virus replication and proliferation [C. Mirzayan et al., Virology, 189, pp. 547-555 (1992)].

Similar mutational studies on the helicases encoded by herpes simplex virus type 1 and bovine papilloma virus also show that these enzymes are critical for virus replication [P. MacPherson et al., Virology, 204, pp. 403-408 (1994); R. Martinez et al., J. Virol., 66, pp. 6735-6746 (1992)]. Thus, the ability to inhibit helicase activity in HCV may provide an avenue for the therapeutic treatment of HCV infection.
SUMMARY OF THE INVENTION

The present invention provides compounds which inhibit HCV NS3 helicase. These compounds are mono-, di- and tri-substituted pentacycles, wherein the pentacyclic ring may contain up to 3 heteroatoms and may be saturated, partially unsaturated or fully unsaturated.

The compounds of this invention may be formulated into pharmaceutically acceptable compositions useful for the treatment and the prevention of HCV infection. Such compositions and the methods of using them to treat or prevent HCV infection are also part of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound by

formula 1:

\[ \text{structure diagram} \]

1, wherein:

the ring containing X\(^1\), X\(^2\) and X\(^3\) is saturated, partially unsaturated or fully unsaturated;

each of L\(^1\) and L\(^2\) is independently selected from a single or double bond, \((C_1-C_{10})\)-straight or branched alkyl, \((C_2-C_{10})\)-straight or branched alkenyl or \((C_2-C_{12})\)-straight or branched alkynyl, wherein, in said alkyl, alkenyl or alkynyl chain, any -CH\(_2\)- group is optionally replaced with -O-, -S-, -NH-, -C(O)-, -C(S)-, -C(N=O)-, -S(O)- or -S(O)\(_2\)-; any =CH- or -CH= group is optionally replaced with =N- or =N=; and any hydrogen atom is optionally replaced by R\(^1\), R\(^2\), or R\(^3\);
each of $W^1$ and $W^2$ is independently selected from H, a monocyclic or bicyclic ring system, wherein in said ring system:

i. each ring comprises 5 to 6 ring atoms

ii. no more than 4 ring atoms are selected from N, O or S;

iii. any CH$_2$ is optionally replaced with C(O);

iv. any S is optionally replaced with S(O) or S(O$_2$);

v. up to 3 hydrogen atom bound to said ring atoms are optionally and independently replaced with R$^1$, R$^2$, or R$^3$; and

vi. said bicyclic ring system is optionally benzofused;

each of X$^1$, X$^2$, and X$^3$ are independently selected from C, CH, CH$_2$, N, NH, O, S, S(O) or S(O$_2$), wherein any hydrogen atom present in X$^2$ or X$^3$ is optionally and independently replaced with R$^1$, R$^2$, or R$^3$;

Y is selected from -OH, -N(R$^4$)$_2$, -SH, -S(O$_2$)R$^4$, -S(O)R$^4$, -N(R$^4$)$_2$C(=NR$^4$)N(R$^4$)$_2$, -C(=NR$^4$)N(R$^4$)$_2$, -C(O)OR$^4$, -C(O)N(R$^4$)$_2$, -C(H)R$^4$OR$^4$, -C(R$^1$)$_2$N(R$^4$)$_2$, -C(R$^1$)$_2$-OR$^3$, -C(R$^1$)$_2$N(R$^3$)R$^4$, -N(R$^3$)R$^4$, -OR$^3$;

each R$^1$ is independently selected from H, (C$_1$-C$_6$)-straight or branched alkyl, or (C$_2$-C$_6$)-straight or branched alkenyl, wherein up to 2 hydrogen atoms in said alkyl or alkenyl are optionally and independently replaced with R$^2$ or R$^3$;

each R$^2$ is a monocyclic or bicyclic ring system wherein in said ring system:

i. each ring comprises 5 to 6 ring atoms independently selected from C, N, O or S;
ii. no more than 4 ring atoms are selected from N, O or S;

iii. any CH₂ is optionally replaced with C(O);

iv. any S is optionally replaced with S(O) or S(O)₂; and

v. up to 3 hydrogen atoms bound to said ring atoms are optionally and independently replaced with R³ or (CH₃)ₙR³; wherein n is 1, 2 or 3;

each R³ is independently selected from -F, -Cl, -Br,

- I, -CN, -NO₂, -CF₃, -OCF₃, -OR⁴, -OC(O)R⁴, -OC(O)OR⁴,
- C(O)R⁴, -C(C)OR⁴, -C(O)N(R⁴)₂, -C(O)C(O)R⁴, -C(O)C(O)OR⁴,
- C(O)C(O)N(R⁴)₂, -C(=NR⁴)N(R⁴)₂, -SR⁴, -S(O)R⁴, -S(O)₂R⁴,
- N(R⁴)₂, -N(R⁴)C(O)R⁴, -N(R⁴)C(O)OR⁴, -N(R⁴)C(O)N(R⁴)₂,
- N(R⁴)C(O)C(O)R³, -N(R⁴)C(O)C(O)OR⁴, -N(R⁴)C(O)C(O)N(R⁴)₂,
- N(R⁴)C(=NR⁴)N(R⁴)₂, -N(R⁴)C(=NR⁴)N(R⁴)₂, -N(R⁴)S(O)₂R⁴,
- N(R⁴)S(O)₂N(R⁴)₂, -P(O)(OR)N(R⁴)₂, -P(O)(OR)₄,
- OR⁴, -OC(O)R⁴, -OC(O)OR⁴, -C(O)R⁴, -C(O)OR⁴,
- C(O)N(R⁴)₂, -C(O)C(O)R⁴, -C(O)C(O)OR⁴,
- C(O)C(O)N(R⁴)₂, -C(=NR⁴)N(R⁴)₂, -SR⁴, -S(O)R⁴,
- S(O)₂R⁴, -N(R⁴)C(O)R², -N(R⁴)C(O)OR²,
- N(R⁴)C(O)N(R⁴)₂, -N(R⁴)C(O)C(O)R², -N(R⁴)C(O)C(O)OR²,
- N(R⁴)C(O)C(O)N(R⁴)₂, -N(R⁴)C(O)C(O)N(R⁴)₂,
- N(R⁴)C(=NR⁴)N(R⁴)₂, -N(R⁴)S(O)₂R², -N(R⁴)S(O)₂N(R⁴)₂, -P(O)(OR)N(R⁴)₂, -P(O)(OR)₄,
- OR⁴, or -P(O)(OR)₂;

25 each R⁴ is independently selected from H, (C₁₋₆)-straight or branched alkyl, or (C₂₋₆)-straight or branched alkenyl, wherein up to 3 hydrogen atoms in said alkyl or alkenyl are optionally and independently replaced with R²; or, when two R⁴ groups are bound to the same atom, said two R⁴ groups are taken together with the atom to which they are bound to form a monocylic ring system wherein in said ring system:
1. each ring comprises 5 to 6 ring atoms independently selected from C, N, O or S;
   ii. no more than 4 ring atoms are selected from N, O or S;
   iii. any CH2 is optionally replaced with C(O);  
   iv. any S is optionally replaced with S(O) or S(O)2; and 
   v. up to 3 hydrogen atoms bound to said ring atoms are optionally and independently replaced with C1–C6 straight or branched alkyl.

   It should be understood that when L1 (or L2) is a single bond, the portion of the compound designated as W1–L1–X1– has the structure W1–X1– (or W2–C–). When L1 (or L2) is a double bond, the portion of the compound designated as W1–L1–X1– has the structure W1=X1– (or W2–C=).

   It should also be understood that the terms “alkyl”, “alkenyl” and “alkynyl”, when used to define L1 or L2 denote straight or branched chains which are bound to the rest of the molecules at two ends (i.e., one end is bound to W1 (or W2) and the other is bound to X1 (or C)). This means, with respect to the definitions of L1 and L2, the terms “alkyl”, “alkenyl” and “alkynyl” have a slightly different meaning than that which is known in the art. This minor difference, however, would be well understood by those in the art. For example, if L1 is a C3 straight alkyl chain, then the portion of the molecule containing L1 would be represented by W1–CH2–CH2–CH2–X1. In this example L1 is –CH2–CH2–CH2–, rather than the accepted definition of a C3 straight alkyl chain -- –CH2–CH2–CH3 -- which is chemically incompatible with the depicted structure of the molecule.
It should also be noted that formula I is intended to encompass structures wherein \( L^1 \) and/or \( L^2 \) may be bound to the rest of the molecule at either end by a single or a double bond. Therefore, in the above example, when \( L^1 \) is a C₃ straight alkyl chain, then the portion of the molecule containing \( L^1 \) could also be represented by \( W^1=\text{CH}-\text{CH}_2-\text{CH}-X^1- \), \( W^1=\text{CH}-\text{CH}_2-\text{CH}=X^1- \), or \( W^1=\text{CH}_2-\text{CH}_2-\text{CH}=X^1- \).

The above definitions include certain polymers and multimers which are not part of the present invention. Thus, whenever \( R^3 \) replaces a hydrogen atom in \( W^1 \), \( W^2 \), \( R^1 \) or \( R^2 \), any \( R^4 \) present in said hydrogen atom-replacing \( R^3 \) group is not substituted with \( R^2 \). This restriction eliminates those undesired polymers.

The invention includes all stereoisomers and racemic forms of the above compounds. The invention also includes pharmaceutically acceptable salts of the compounds. And the invention includes tautomers of the above compounds.

The term "monocyclic ring system", as used herein, includes saturated, partially unsaturated and fully unsaturated ring structures. The term "bicyclic ring system", as used herein, includes systems wherein each ring is independently saturated, partially unsaturated and fully unsaturated. Examples of monocyclic and bicyclic ring systems useful in \( W^1 \), \( W^2 \) and \( R^2 \) include, but are not limited to, cyclopentane, cyclopentene, indane, indene, cyclohexane, cyclohexene, cyclohexadiene, benzene, tetrahydronaphthalene, decahydronaphthalene, naphthalene, pyridine, piperidine, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3,4-tetrazine, 1,2,4,5-
tetrazine, 1,2,3,4-tetrahydroquinoline, quinoline,
1,2,3,4-tetrahydroisoquinoline, isoquinoline, cinnoline,
phthalazine, quinazoline, quinoxaline, 1,5-naphthyridine,
1,6-naphthyridine, 1,7-naphthyridine, 1,8-naphthyridine,
2,6-naphthyridine, 2,7-naphthyridine, pteridine,
acridine, phenazine, 1,10-phenanthroline, dibenzopyrans, 1-
benzopyrans, phenothiazine, phenoxazine, thianthrene,
dibenzo-p-dioxin, phenoxathiin, phenothionine,
morpholine, thiomorpholine, tetrahydropyran, pyran,
benzopyran, 1,4-dioxane, 1,3-dioxane, dihyropyridine,
dihydropyran, 1-pyridine, quinuclidine,
triazolopyridine, β-carboline, indolizine, quinolizidine,
tetrahydroanaphtheridine, diazaphenanthrenes, thiopyran,
tetrahydrothiopyran, benzodioxane, furan, benzofuran,
tetrahydrofuran, pyrrole, indole, thiophene,
benzothiopene, carbazole, pyrrolidine, pyrazole,
isoazole, isothiazole, imidazole, oxazole, thiazole,
1,2,3-triazole, 1,2,4-triazole, 1,2,3-oxadiazole, 1,2,4-
oxadiazole, 1,3,4 oxadiazole, 1,2,5-oxadiazole, 1,2,3-
thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,5
thiadiazole, tetrazole, benzothiazole, benzoxazole,
benzotriazole, benzimidazole, benzopyrazole,
benzisothiazole, benzisoxazole and purine.

Additional monocyclic and bicyclic structures
falling within the above description may be found in A.R.
Katritzky, and C.W. Rees, eds. "Comprehensive
Heterocyclic Chemistry: Structure, Reactions, Synthesis
and Use of Heterocyclic Compounds, Vol. 1-8," Pergamon
Press, NY (1984), the disclosure of which is herein
incorporated by reference.

It should be understood that heterocycles
referred may be attached to the rest of the compound by
any atom of the heterocycle which results in the creation of a stable structure.

The term "ring atom", as used herein, refers to a backbone atom that makes up the ring. Such ring atoms are selected from C, N, O or S and are bound to 2 or 3 other such ring atoms (3 in the case of certain ring atoms in a bicyclic ring system). The term "ring atom" does not include hydrogen.

According to one preferred embodiment, X¹ is N, X² is S, X³ is N and the pentacyclic ring which comprises X¹, X² and X³ has the structure:

According to another preferred embodiment, one of L¹ or L² is a single bond and the other is a single bond or methylene.

According to another preferred embodiment, Y is -OH or N(R⁴)₂. Even more preferred is when Y is -NH(R⁴). Most preferred is when Y is NH₂.

According to yet another preferred embodiment, neither W¹ nor W² is hydrogen. Even more preferred is when at least one of W¹ or W² is phenyl, methylphenyl or chlorophenyl and the other is selected from phenyl, methylphenyl, chlorophenyl, ethylphenyl, isopropylphenyl, t-butylphenyl, methoxyphenyl, cyclohexylphenyl, bisphenyl, furyl, thiophenyl, benzothiophenyl, naphthyl, phenylmethylyphenyl, 3-chloro-4-methylphenyl, 3-fluoro-4-methylphenyl, methoxycarboxyphenyl, fluorenyl, oxofluorenyl, oxobenzochromenyl, phenoxyphenyl, benzoxyphenyl, indanyl, benzoylphenyl, 3,4-methylenedioxyphenyl, hydroxyphenyl, thiadiazolylphenyl.
Some of the more preferred inhibitors are depicted in Table 1, below.

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<td><img src="image2" alt="Structure 49" /> F&lt;sub&gt;4&lt;/sub&gt;CO&lt;sup&gt;-&lt;/sup&gt;</td>
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<td>50</td>
<td><img src="image4" alt="Structure 50" /> OH F&lt;sub&gt;4&lt;/sub&gt;CO&lt;sup&gt;-&lt;/sup&gt;</td>
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<td><img src="image6" alt="Structure 51" /> F&lt;sub&gt;4&lt;/sub&gt;CO&lt;sup&gt;-&lt;/sup&gt;</td>
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<td><img src="image8" alt="Structure 52" /> Br&lt;sup&gt;-&lt;/sup&gt; N&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
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The compounds of this invention may be synthesized by methods well-known in the art. For example, compounds containing the preferred thiadiaolyl core and wherein Y is NH₂ or NH(R¹) may be synthesized by the scheme depicted below.

Scheme 1

Other compounds of this invention may be prepared by analogous routes of synthesis. Examples of synthesis step used in preparing compounds of this invention may be found, for example, in K. Hagiwara et al., *J. Pesticide Sci.*, 17, pp. 251-259 (1992).

The HCV NS3 helicase contains a binding site for ATP (which is cleaved by the ATPase activity of the helicase) and a separate binding site for double-stranded polynucleotides (which are unwound by the unwinding activity of the helicase). The energy generated by cleavage of ATP is required for the unwinding activity.

The compounds of this invention are designed to bind Hepatitis C helicase and therefore are expected to inhibit, either directly or indirectly, the unwinding activity of the helicase. Therefore, the compounds of this invention can be assayed for their ability to inhibit ATP cleavage or to inhibit unwinding activity. Assays for each of the activities are known in the art ([M. E. Pullman et al., "Partial Resolution of the Enzymes Catalyzing Oxidative Phosphorylation", *J. Biol. Chem.*, 235, pp. 3322-28 (1980); C. H. Gross et al., "Mutational Analysis of Vaccinia Virus Nucleoside Triphosphate Phosphohydrolase II, a DExH Box RNA Helicase", *J. Virol.*, 69, pp. 4727-36 (1995)]) and are described in detail in the Example section.

According to another embodiment, the invention
provides a composition comprising a compound of this invention or a pharmaceutically acceptable salt thereof, as described above, and a pharmaceutically acceptable carrier.

If pharmaceutically acceptable salts of the compounds of this invention are utilized in these compositions, those salts are preferably derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydriodicide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides,
bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

The compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

Pharmaceutically acceptable carriers that may be used in these compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

According to a preferred embodiment, the compositions of this invention are formulated for pharmaceutical administration to a mammal, preferably a human being.
Such pharmaceutical compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term “parenteral” as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as those described in Pharmacopeia Helvetica (Ph. Helv.) or similar alcohol.
The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.
For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or
dispersing agents.

The amount of compound present in the above-described composition should be sufficient to cause a detectable decrease in ATPase activity and/or unwinding activity of the HCV NS3 helicase, as measured by any of the assays described in the examples.

According to another embodiment, the compositions of this invention may further comprise an anti-viral agent effective against hepatitis C virus infection. Such agents include, but are not limited to, inhibitors of HCV NS3 protease, such as those described in WO 98/17679; inhibitors of HCV polymerase; IMPDH inhibitors, such as mycophenolic acid, mycophenolate mofetil, and those described in any of United States Patents 5,380,879; 5,441,953; 5,493,030; 5,633,279; 5,444,072; 5,536,747; 5,538,969; 5,554,612; and 5,807,876 or in PCT publications WO 95/22535; WO 95/22538; WO 95/22536; WO 95/22537; WO 95/22534; and WO 97/40028 (the disclosures of each of the above-cited patents and publications are herein incorporated by reference); interferons, such as alpha-interferon; ribavirin; and ZSK (California Institute of Molecular Medicine, Inc.).

The amount of the anti-viral agent present in the compositions of this invention should be between 10-100% of the amount of that agent normally used in a monotherapy for anti-viral activity. Such amounts are known in the art and/or described in the patent applications referred to above.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body
weight, general health, sex, diet, time of
administration, rate of excretion, drug combination, and
the judgment of the treating physician and the severity
of the particular disease being treated. The amount of
active ingredients will also depend upon the particular
compound and anti-viral agent, if present, in the
composition.

According to another embodiment, the invention
provides a method of detecting HCV helicase activity in a
biological sample suspected of containing a polypeptide
having HCV NS3 helicase activity comprising the step of
contacting said biological sample with a compound of this
invention. The term "biological sample", as used herein
includes cell cultures or extracts thereof; biopsied
material obtained from a mammal or extracts thereof; and
blood, saliva, urine, feces, semen, tears, or other body
fluids or extracts thereof. The term "biological sample"
also includes living organisms, in which case "contacting
a compound of this invention with a biological sample
suspected of containing HCV NS3 helicase" is synonymous
with the term "administering said compound to the living
organism."

The term "polypeptide having HCV helicase
activity", as used herein, means any polypeptide which
demonstrates activity in at least, but not limited to,
the unwinding assay described in Example 57. Preferably,
that term means a polypeptide encoded by a naturally
occurring or an experimentally produced strain of
hepatitis C virus or a polypeptide having a consensus
amino acid sequence derived from polypeptides having the
aforementioned activities encoded by two or more strains
of hepatitis C virus.
The term "detecting HCV helicase activity", as used herein includes inhibiting the helicase activity, if present, in said sample; determining the presence or absence of HCV helicase activity in said sample; quantitating the HCV helicase activity in said sample; and, in the case of a living organism, treating and/or reducing the severity of an HCV viral infection. Each of these is clearly useful in diagnostic and therapeutic applications relating to HCV.

In a preferred embodiment, the invention provides a method of treating an HCV viral infection in a mammal comprising the step of administering to said mammal a pharmaceutically acceptable composition described above. In this embodiment, if the patient is also administered an anti-viral agent, it may be delivered together with the compound of this invention in a single dosage form, or, as a separate dosage form. When administered as a separate dosage form, the anti-viral agent may be administered prior to, at the same time as, or following administration of a pharmaceutically acceptable composition comprising a compound of this invention.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.
Example 1

Synthesis of Compound 1

5-Amino-3-phenyl-2-p-tolyl-[1,2,4]thiadiazol-2-ium chloride

Step 1

To a solution of 1.51 g (14.2 mmol) of p-toluidine in 20 mL of CH2Cl2 was added dropwise 1.60 mL (2.0 g, 14.2 mmol) of benzoyl chloride. The white suspension was treated with 20 mL of saturated aqueous NaHCO3. The resulting biphasic mixture was stirred for 3 hours at room temperature. The layers were separated and the organic layer was washed with 20 mL of 0.5 N aqueous HCl and 20 mL of saturated aqueous NaCl and dried over Na2SO4. The clear solution was concentrated to give 2.50 g (83.1 % yield) N-p-tolyl-benzamide as a white solid which was used without further purification in Step 2.

Step 2

A 25 mL round bottom flask equipped with a stir bar and reflux condenser was charged with 1.15 g (5.45 mmol) of N-p-tolyl-benzamide and treated with 2.0 mL (3.26 g, 27.4 mmol) of thionyl chloride. The reaction mixture was heated to reflux for 1 hr and the excess thionyl chloride was removed by concentration in vacuo to give N-p-tolyl-benzimidoyl chloride which was used without further purification in Step 3.
Step 3

The crude imino chloride was dissolved in 10 mL of acetonitrile and treated with 600 mg (5.88 mmol) of 1-amino-2-thio-3,4,5-triazole at room temperature. The resulting suspension was allowed to stir for 12 hr and filtered. The crude product was recrystallized from methanol to yield 1.00 g (60.3 % yield) of the title compound as a white crystalline solid: $^1$H NMR (500 MHz, DMSO-d$_6$) δ 10.4 (1 H, s, NH$_2$), 10.2 (1 H, s, NH$_2$), 7.7-7.3 (9 H, m, Ar), 2.5 (3 H, s, Me) ppm; MS 268.1 (M+H).

Example 2

Synthesis of Compound 2

\[
\text{Br} \quad \begin{array}{c}
\text{N} \quad \text{S} \\
\text{N} \quad \text{NH} \\
\text{CH}_3
\end{array}
\]

5-Methylamino-3-phenyl-2-phenyl-[1,2,4]thiadiazol-2-ium bromide

Steps 1 and 2 were carried out as described above.

Step 3

The crude imino chloride (prepared from 2.0 of benzanilide by similar method described in Example 1, Step 3) was dissolved in 10 mL of acetone and treated with 2.0 g (24.7 mmol) of sodium thiocyanate. The resulting orange suspension was stirred at room temperature for 8 hrs and filtered. The filtrate, containing the crude isothiocyanate, was concentrated to an orange crystalline solid and dissolved in 10 mL of
acetonitrile. The reaction mixture was then treated with 3.0 mL (38.7 mmol) of 40% solution of aqueous methylamine. The resulting yellow solution was allowed to stir at room temperature for 8 hrs and then decanted to remove a small amount of black precipitate. The yellow solution was then concentrated to a solid, which was azeotroped from acetonitrile (2x 10 mL) and methanol (1x 10 mL) and then dissolved in 20 mL of carbon tetrachloride. To the stirring solution was then added 1 mL (3.10 g, 19.4 mmol) of bromine. The resulting red suspension was allowed to stir for 8 h and then concentrated to a thick red oil. The crude product was triturated with methanol followed by recrystallization from methanol, to yield 570 mg (1.64 mmol, 16.2 %) of a light yellow solid: 1H NMR (500 MHz, CDCl₃) 10.3 (1 H, s, NHCH₃), 7.6 - 7.2 (10 H, m, Ar), 3.4 (3 H, d, j = 5.0 Hz, NHCH₃) ppm; LC/MS: 268 (M+H).

Compounds 3 through 55 were prepared as described in Example 1 and 2.

Example 3

MS (M+1) = 254
1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.1 (1 H, s, NH₂), 7.7-7.5 (10 H, m, Ar) ppm.

Example 4

MS (M+1) = 284
1H NMR (500 MHz; DMSO-d6) δ = 10.3 (1 H, s, NH₂), 10.0 (1 H, s, NH₂), 7.7-7.6 (5 H, m, Ar), 7.5 (2 H, d, j = 8 Hz,
MeO-Ar), 7.0 (2 H, d, j = 8 Hz, MeO-Ar) 3.9 (3 H, s, MeO) ppm

Example 5
Compound 5

5 MS (M+1) = 288
1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 7.7-7.5 (9 H, m, Ar) ppm

Example 6
Compound 6

10 MS (M+1) = 284
1H NMR (500 MHz; DMSO-d6) δ = 10.4 (1 H, s, NH₂), 10.1 (1 H, s, NH₂), 7.7-7.1 (9 H, m, Ar), 3.9 (3 H, s, MeO) ppm

Example 7
Compound 7

15 MS (M+1) = 268
1H NMR (500 MHz; DMSO-d6) δ = 10.2 (1 H, s, NH₂), 10.1 (1 H, s, NH₂), 7.8 (2 H, d, Ar), 7.7 (1 H, dd, Ar), 7.6 (2 H, dd, Ar), 7.4 (3 H, m, Ar), 7.3 (2 H, d, Ar), 5.3 (2 H, s, ArCH₂) ppm

Example 8
Compound 8

20 MS (M+1) = 284
1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 7.7-7.1 (9 H, m, Ar), 3.7 (3 H, s, MeO) ppm
Example 9

Compound 9

MS (M+1) = 284

1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 7.7-7.1 (9 H, m, Ar), 4.0 (3 H, s, MeO) ppm

Example 10

Compound 10

MS (M+1) = 288

1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.1 (1 H, s, NH₂), 7.9-7.5 (9 H, m, Ar) ppm

Example 11

Compound 11

MS (M+1) = 268

1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 7.8-7.0 (9 H, m, Ar), 2.6 (3 H, s, Me) ppm

Example 12

Compound 12

MS (M+1) = 304

1H NMR (500 MHz; DMSO-d6) δ = 10.6 (1 H, s, NH₂), 10.0 (1 H, s, NH₂), 8.2 (1 H, d, Ar), 8.1 (1 H, dd, Ar), 7.9 (2 H, dd, Ar), 7.7 (2 H, dd, Ar), 7.6 (1 H, t, Ar), 7.45 (3 H, dd, Ar), 7.3 (2 H, t, Ar) ppm

Example 13

Compound 13

MS (M+1) = 304

1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.0 (1 H, s, NH₂), 8.3 (1 H, s, Ar), 8.1 (1 H, d, Ar), 8.0 (2 H,
dd, Ar), 7.7 (2 H, m, Ar), 7.55 (4 H, m, Ar), 7.4 (2 H, dd, Ar) ppm

Example 14
Compound 14

5 MS (M+1) = 302
1H NMR (500 MHz; DMSO-d6) δ = 10.6 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 7.7-7.3 (8 H, m, Ar), 2.3 (3 H, s, Me) ppm

Example 15
Compound 15

10 MS (M+1) = 302
1H NMR (500 MHz; DMSO-d6) δ = 10.7 (1 H, s, NH₂), 10.3 (1 H, s, NH₂), 7.9-7.3 (8 H, m, Ar), 2.4 (3 H, s, Me) ppm

Example 16
Compound 16

15 MS (M+1) = 268
1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.0 (1 H, s, NH₂), 7.7-7.4 (9 H, m, Ar), 2.4 (3 H, s, Me) ppm

Example 17
Compound 17

20 MS (M+1) = 282
1H NMR (500 MHz; DMSO-d6) δ = 10.4 (1 H, s, NH₂), 10.1 (1 H, s, NH₂), 7.55 (1 H, dd, Ar), 7.5 (2 H, d, Ar), 7.45 (2 H, d, Ar), 7.4 (2 H, dd, Ar), 7.35 (2 H, d, Ar), 2.7 (2 H, q, ArCH₂CH₃), 1.2 (3 H, t, CH₂CH₃) ppm
Example 18

Compound 18

MS (M+1) = 296
1H NMR (500 MHz; DMSO-d6) δ = 10.4 (1 H, s, NH₂), 10.1 (1 H, s, NH₂), 7.55 (1 H, dd, Ar), 7.5 (2 H, d, Ar), 7.45 (2 H, d, Ar), 7.4 (2 H, dd, Ar), 7.35 (2 H, d, Ar), 3.0 (1 H, q, ArCH(CH₃)₂), 1.2 (6 H, d, CH₂(CH₃)₂) ppm

Example 19

Compound 19

MS (M+1) = 310
1H NMR (500 MHz; DMSO-d6) δ = 10.4 (1 H, s, NH₂), 10.1 (1 H, s, NH₂), 7.55 (5 H, m, Ar), 7.45 (2 H, d, Ar), 7.4 (2 H, m, Ar), 1.3 (9 H, d, C(CH₃)₃) ppm

Example 20

Compound 20

MS (M+1) = 268
1H NMR (500 MHz; DMSO-d6) δ = 10.6 (1 H, s, NH₂), 10.3 (1 H, s, NH₂), 7.8-7.4 (9 H, m, Ar), 2.5 (3 H, s, Me) ppm

Example 21

Compound 21

MS (M+1) = 318
1H NMR (500 MHz; DMSO-d6) δ = 10.2 (1 H, s, NH₂), 10.1 (1 H, s, NH₂), 8.0 (2 H, m, Ar), 7.9 (2 H, d, Ar), 7.75 (1 H, d, Ar), 7.7 (1 H, dd, Ar), 7.65 (2 H, d, Ar), 7.6 (1 H, d, Ar), 7.55 (3 H, m, Ar), 5.85 (2H, s, ArCH₂N) ppm
Example 22

Compound 22

MS (M+1) = 260

1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 8.1 (1 H, s, Ar), 7.9-7.7 (5 H, m, Ar), 6.9-6.8 (2 H, m, Ar) ppm

Example 23

Compound 23

MS (M+1) = 244

1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.0 (1 H, s, NH₂), 8.2-8.1 (1 H, m, Ar), 8.0-7.8 (5 H, m, Ar), 7.3-7.2 (1 H, m, Ar), 7.2-7.1 (1 H, m, Ar) ppm

Example 24

Compound 24

MS (M+1) = 310

1H NMR (500 MHz; DMSO-d6) δ = 10.6 (1 H, s, NH₂), 10.0 (1 H, s, NH₂), 8.2-7.6 (10 H, m, Ar) ppm

Example 25

Compound 25

MS (M+1) = 268

1H NMR (500 MHz; DMSO-d6) δ = 10.6 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 7.8-7.4 (9 H, m, Ar) 2.4 (3 H, s, Me) ppm

Example 26

Compound 26

MS (M+1) = 284

1H NMR (500 MHz; DMSO-d6) δ = 10.6 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 7.7-7.1 (9 H, m, Ar) 3.8 (3 H, s, MeO) ppm

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Example 27

**Compound 27**

MS (M+1) = 304

1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 8.1 (2 H, m, Ar), 8.0 (1 H, d, Ar), 7.7 (1 H, d, Ar), 7.6 (2 H, m, Ar), 7.5 (1 H, t, Ar), 7.45 (2 H, m, Ar), 7.3 (3 H, m, Ar) ppm

Example 28

**Compound 28**

MS (M+1) = 304

1H NMR (500 MHz; DMSO-d6) δ = 10.5 (1 H, s, NH₂), 10.1 (1 H, s, NH₂), 7.95 (3 H, m, Ar), 8.0 (2 H, dd, Ar), 7.7 (1 H, t, Ar), 7.6 (3 H, m, Ar), 7.5 (3 H, m, Ar), 7.4 (1 H, dd, Ar) ppm

Example 29

**Compound 29**

MS (M+1) = 330

1H NMR (500 MHz; DMSO-d6) δ = 10.7 (1 H, s, NH₂), 10.3 (1 H, s, NH₂), 8.1-7.5 (14 H, m, Ar) ppm

Example 30

**Compound 30**

MS (M+1) = 342

1H NMR (500 MHz; DMSO-d6) δ = 10.6 (1 H, s, NH₂), 10.2 (1 H, s, NH₂), 8.3-7.5 (12 H, m, Ar), 4.2 (2 H, s, CH₂) ppm
Example 31
Compound 31

MS (M+1) = 336

This compound was produced by combinatorial chemistry techniques, and therefore, no NMR data is available. The same is true for all subsequent compounds for which NMR data is not reported.

Example 32
Compound 32

10
MS (M+1) = 344

Example 33
Compound 33

MS (M+1) = 302

Example 34
Compound 34

15
MS (M+1) = 330

Example 35
Compound 35

MS (M+1) = 312

Example 36
Compound 36

20
MS (M+1) = 286
Example 37

Compound 37

MS (M+1) = 346

Example 38

Compound 38

MS (M+1) = 312

Example 39

Compound 39

MS (M+1) = 298

Example 40

Compound 40

MS (M+1) = 318

1H NMR (500 MHz; DMSO-d6) δ = 10.25 (s, 1 H), 10.0 (s, 1 H), 8.0–7.9 (m, 4 H), 7.8 (d, 2 H), 7.7 (dd, 1 H), 7.65 (dd, 2 H), 7.55 (dd, 2 H), 7.4 (d, 1 H), 5.5 (s, 2 H) ppm

Example 41

Compound 41

MS (M+1) = 360

Example 42

Compound 42

MS (M+1) = 294

Example 43

Compound 43

MS (M+1) = 344
1H NMR (500 MHz; DMSO-d6) δ = 10.7 (1H, s, NH), 7.6-7.2 (15H, m, Ar), 5.0 (2H, d, J = 5 Hz, CH₂Ph) ppm

Example 44

Compound 44

MS (M+1) = 358

1H NMR (500 MHz; DMSO-d6) δ = 10.0 (1H, s, NH), 7.6-7.2 (15H, m, Ar), 4.0 (2H, m, CH₂CH₂Ph), 3.1 (2H, m, CH₂CH₂Ph) ppm

Example 45

Compound 45

MS (M+1) = 330

Example 46

Compound 46

MS (M+1) = 330

Example 47

Compound 47

MS (M+1) = 358

Example 48

Compound 48

MS (M+1) = 372

Example 49

Compound 49

MS (M+1) = 356
Example 50

Compound 50

MS (M+1) = 270

Example 51

Compound 51

MS (M+1) = 338

Example 52

Compound 52

MS (M+1) = 303

10 1H NMR (500 MHz; DMSO-d6) δ = 10.2 (1 H, s, NH), 7.6-7.1 (9 H, m, Ar), 2.4 (3H, d, J = 5 Hz, CH3) ppm

Example 53

Compound 53

MS (M+1) = 317

15 1H NMR (500 MHz; DMSO-d6) δ = 10.3 (1 H, s, NH), 7.6-7.1 (9 H, m, Ar), 3.8 (2H, m, CH2CH3), 2.4 (3H, d, J = 5 Hz, CH3CH3) ppm

Example 54

Compound 54

MS (M+1) = 379

20 1H NMR (500 MHz; DMSO-d6) δ = 10.7 (1 H, s, NH), 7.6-7.1 (14 H, m, Ar), 5.0 (2H, d, J = 5 Hz, CH2Ph) ppm

Example 55

Compound 55

MS (M+1) = 400
1H NMR (500 MHz; DMSO-d6) δ = 10.7 (1 H, s, NH), 7.8-7.2 (15 H, m, Ar), 5.0 (2H, d, J = 5 Hz, CH₂Ph) ppm

Example 56

Synthesis of Compound 56

Compound 56 was synthesized by the scheme depicted below.


MS (M+1) = 237

1H NMR (500 MHz; DMSO-d6) δ = 7.4-7.2 (m, 10 H), 4.7 (m, 1 H), 3.35 (dd, 2 H), 2.95 (d, 2 H) ppm
Example 57

Assays

A. Unwinding assay

The standard 3'-tailed double-stranded RNA/DNA hybrid was prepared as described as follows. The long 98-nucleotide ("nt") RNA template was transcribed from a BsrBI-digested plasmid pSP65 (Promega, Madison, WI) in the presence of [α-32P-GTP] (New England Nuclear, Boston, MA). The short 34-nt DNA release strand corresponds to a SP6 RNA transcript from a BamHI-digested pSP64 (Promega).

Standard helicase reactions (20 μl) were carried out as follows. HCV NS3 helicase (0.3 or 1 nM) was added to a mixture of 25 mM morpholinepropanesulfonic acid (MOPS)-NaOH (pH 6.5), 1 mM ATP, 0.5 mM MnCl2, 2 mM dithiothreitol (DTT), 0.1 mg of bovine serum albumin (BSA) per ml, 4 units of Rnasin (Promega), and 5 nM of 3'-tailed double-stranded RNA/DNA hybrid substrate. Mixtures were incubated for 20 min at 37°C and stopped by the addition of 5 liters of 5X loading buffer (100 mM Tris-Cl (pH7.5), 20 mM EDTA, 50 % glycerol, 0.5 % SDS, 0.1 % NP-40, 0.1 % bromophenol blue, and 0.1 % xylene cyanole). The reactions were then electrophoresed on 10% PAGE with 0.5x TBE and 0.1 % SDS. Gels were dried and exposed using Fuji 1500 phosphorimager (Fuji, Stamford, CT). Helicase activity was determined by radioactivity of the double-stranded substrate and single-stranded template.

B. Spectrophotometric Assay of ATPase Activity

ATPase activity of HCV NS3 helicase in the presence or absence of inhibitor was monitored by
following the rate of ADP production using a coupled enzyme assay. In this assay, an amount of NADH equal to ADP is oxidized to NAD$^+$ resulting in a decrease in absorbance at 340 nm. A reaction mix consisting of buffer, pH 7.0, coupling enzyme components, poly(rU), and HCV NS3 helicase was prepared and aliquoted into wells. Various concentrations of inhibitor in DMSO were added to the wells and incubated for 15 minutes at 30°C. Reactions were initiated with ATP. The final concentrations of assay components in 200 μl reaction are as follows: 44 mM MOPS, pH 7.0, 8.8 mM NaCl, 2.2 mM MgCl$_2$, 17.6% v/v glycerol, 2.5 mM PEP, 0.2 mM NADH, 12.5 μg/mL pyruvate kinase, 12.5 μg/mL lactate dehydrogenase, 1 μM poly(rU), 2 nM HCV NS3 helicase, 2% DMSO with varying concentrations of inhibitor, and 100 μM ATP.

Absorbance at 650 nm was used as a check for insolubility of inhibitors. The rate data was fitted to equation (1) to calculate the IC$_{50}$ for the inhibitors. Y, B, and X are the observed rate, inverse of maximum rate in the absence of inhibitor, and inhibitor concentration, respectively.

$$Y = IC_{50} / (B \times (X + IC_{50}))$$

(1)

C. **HPLC Assay of ATPase Activity**

ATPase activity of HCV helicase in the presence or absence of inhibitor was also measured by quantifying the ADP produced from ATP using an HPLC method. A reaction mix consisting of buffer, pH 7.0, poly(rU), and HCV NS3 helicase was prepared and aliquoted into wells. Various concentrations of inhibitor in DMSO were added to the wells and incubated for 15 minutes at 30°C. Reactions were initiated with ATP. The final
concentrations of assay components in 200 µl reaction are as follows: 44 mM MOPS, pH 7.0, 8.8 mM NaCl, 2.2 mM MgCl₂, 17.6% v/v glycerol, 1 µM poly(rU), 2 nM trHCV NS3 Helicase, 2% DMSO with varying concentrations of inhibitor, and 100 µM ATP.

After 15 minutes the reaction was quenched with 50 µl of 0.5 M EDTA. A Gilson UniPoint System Software (Gilson, Inc., Middletown, WI) controlled the autosampling of 20 µLs from each reaction well on a 96-well plate using Gilson components. The mobile phase was an isocratic solution of 0.15 M triethylamine, 6% methanol, and phosphoric acid to pH 5.5. ADP and ATP peaks were separated using the Phenomenex Columbus (Torrence, CA)

5 µ, C18, 100 Å, 100 X 4.60 mm reverse phase HPLC.

The results of these assays for compounds 1 - 53 are depicted in Table 2, below:

**TABLE 2. Assays of HCV NS3 helicase inhibitors.**

<table>
<thead>
<tr>
<th>Cmpd#</th>
<th>Coupled NS3 ATPase (%inhibition@ 30 µM)</th>
<th>HPLC ATPase IC50 (µM)</th>
<th>Helicase Unwinding IC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
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<td>G</td>
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<td>3</td>
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<td>F</td>
<td></td>
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<td></td>
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<td>G</td>
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<tr>
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<td>H</td>
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<td>18</td>
<td>A</td>
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</table>

**SUBSTITUTE SHEET (RULE 26)**
<table>
<thead>
<tr>
<th>Cmpd#</th>
<th>Coupled NS3 ATPase (% inhibition @ 30 μM)</th>
<th>HPLC ATPase IC50 (μM)</th>
<th>Helicase Unwinding IC50 (μM)</th>
</tr>
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<tbody>
<tr>
<td>19</td>
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<td>E</td>
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<td>56</td>
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</tbody>
</table>

In the above table, values designated "A" represent >75% inhibition; "B" represents between 50 and 75% inhibition; "C" represents between 25 and 50% inhibition; and "D" represents less than 25% inhibition. Values designated "E" represent an IC50 of less than 25 μM; "F" represents an IC50 of between 25 and 50 μM; "G"
represents an IC₅₀ of between 50 and 75 µM; and "H" represents an IC₅₀ of greater than 75 µM. Blank values reflect that a particular assay was not performed for that inhibitor.

While we have hereinbefore presented a number of embodiments of this invention, it is apparent that our basic construction can be altered to provide other embodiments which utilize the methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the claims appended hereto rather than the specific embodiments which have been presented hereinbefore by way of example.
We claim:

1. A compound of the formula 1:

   \[ \text{1, wherein:} \]
   
   the ring containing \( X^1 \), \( X^2 \) and \( X^3 \) is saturated, partially unsaturated or fully unsaturated;

   each of \( L^1 \) and \( L^2 \) is independently selected from a single or double bond, \((C_1-C_{10})\)-straight or branched alkyl, \((C_2-C_{10})\)-straight or branched alkenyl or \((C_2-C_{10})\)-straight or branched alkynyl, wherein, in said alkyl, alkenyl or alkynyl chain, any \(-\text{CH}_2-\) group is optionally replaced with \(-\text{O}-, -\text{S}-, -\text{NH}-, -\text{C(O)}-, -\text{C(S)}-, -\text{C(=NOH)}-, -\text{S(O)}-\) or \(-\text{S(O)}_2-\); any \(-\text{CH}=\) or \(-\text{CH}_2=\) group is optionally replaced with \(-\text{N}=\) or \(-\text{N}2=\); and any hydrogen atom is optionally replaced by \( R^1 \), \( R^2 \), or \( R^3 \); and wherein the bond between any of \( L^1 \) and \( W^1 \); \( L^1 \) and \( X^1 \); \( L^2 \) and \( W^2 \); or \( L^2 \) and the ring carbon located between \( X^1 \) and \( X^3 \) is a single or a double bond;

   each of \( W^1 \) and \( W^2 \) is independently selected from \( H \), a monocyclic or bicyclic ring system, wherein in said ring system:

   i. each ring comprises 5 to 6 ring atoms independently selected from \( C, N, O \) or \( S \);

   ii. no more than 4 ring atoms are selected from \( N, O \) or \( S \);

   iii. any \( \text{CH}_2 \) is optionally replaced with \( \text{C(O)} \);
iv. any S is optionally replaced with S(O) or S(O$_2$);

v. up to 3 hydrogen atom bound to said ring atoms are optionally and independently replaced with R$^1$, R$^2$, or R$^3$; and

vi. said bicyclic ring system is optionally benzofused;

each of X$^1$, X$^2$, and X$^3$ are independently selected from C, CH, CH$_2$, N, NH, O, S, S(O) or S(O$_2$), wherein any hydrogen atom present in X$^2$ or X$^3$ is optionally and independently replaced with R$^1$, R$^2$, or R$^3$;

Y is selected from -OH, -N(R$^4$)$_2$, -SH, -S(O$_2$)R$^4$, -S(O)R$^4$, -N(R$^4$)C(=NR$^4$)N(R$^4$)$_2$, -C(=NR$^4$)N(R$^4$)$_2$, -C(O)OR$^4$, -C(O)N(R$^4$)$_2$, -C(O)R$^4$, -C(H)R$^4$OR$^4$, -C(R$^1$)$_2$-N(R$^4$)$_2$, -C(R$^1$)$_2$-OR$^3$, -C(R$^1$)$_2$-N(R$^3$)R$^4$, -N(R$^3$)R$^4$, -OR$^3$;

each R$^1$ is independently selected from H, (C$_1$-C$_6$)-straight or branched alkyl, or (C$_2$-C$_6$)-straight or branched alkenyl, wherein up to 2 hydrogen atoms in said alkyl or alkenyl are optionally and independently replaced with R$^2$ or R$^3$;

each R$^2$ is a monocyclic or bicyclic ring system wherein in said ring system:

i. each ring comprises 5 to 6 ring atoms independently selected from C, N, O or S;

ii. no more than 4 ring atoms are selected from N, O or S;

iii. any CH$_2$ is optionally replaced with C(O);

iv. any S is optionally replaced with S(O) or S(O)$_2$; and

v. up to 3 hydrogen atoms bound to said ring atoms are optionally and independently replaced with R$^3$ or (CH$_2$)$_n$R$^3$; wherein n is 1, 2 or 3;
each R₃ is independently selected from -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -OCF₃, -OR, -OC(O)R', -OC(O)OR', -C(O)R', -C(O)OR', -C(O)N(R')₂, -C(O)C(O)R', -C(O)C(O)OR', -C(O)C(O)N(R')₂, -C(=NR')₂N(R')₂, -SR', -S(O)R', -S(O)₂R', -N(R')₂, -N(R')C(O)R', -N(R')C(O)OR', -N(R')C(O)N(R')₂, -N(R')C(O)C(O)R', -N(R')C(O)C(O)OR', -N(R')C(O)N(R')₂, -N(R')C(=NR')₂N(R')₂, -N(R')C(=NR')₂N(R')₂, -N(R')S(O)₂R', -N(R')S(O)₂N(R')₂, -P(O)(OR)N(R')₂, -P(O)(OR)₂, -OR', -OC(O)R', -OC(O)OR', -C(O)R', -C(O)OR', -C(O)N(R')₂(R'), -C(O)C(O)R', -C(O)C(O)OR', -C(O)C(O)N(R')₂(R'), -C(O)C(O)N(R')₂(R'), -SR', -S(O)R', -S(O)₂R', -N(R')₂, -N(R')C(O)R', -N(R')C(O)R', -N(R')C(O)C(O)R', -N(R')C(O)OR', -N(R')C(O)N(R')₂, -N(R')C(=NR')₂N(R')₂, -N(R')C(=NR')₂N(R')₂, -N(R')S(O)₂R', -N(R')S(O)₂N(R')₂, -P(O)(OR)N(R')₂, -P(O)(OR)₂, or -P(O)(OR')₂; and each R₄ is independently selected from H, (C₁-C₆)-straight or branched alkyl, or (C₂-C₆)-straight or branched alkenyl, wherein up to 3 hydrogen atoms in said alkyl or alkenyl are optionally and independently replaced with R₂; or, when two R₄ groups are bound to the same atom, said two R₄ groups are taken together with the atom to which they are bound to form a monocyclic ring system wherein in said ring system:

i. each ring comprises 5 to 6 ring atoms independently selected from C, N, O or S;

ii. no more than 4 ring atoms are selected from N, O or S;

iii. any CH₂ is optionally replaced with C(O);

iv. any S is optionally replaced with S(O) or S(O)₂; and

v. up to 3 hydrogen atoms bound to said ring
atoms are optionally and independently replaced with C₁–C₆ straight or branched alkyl.

2. The compound according to claim 1, wherein X¹ is N, X² is S, X³ is N and the pentacyclic ring which comprises X¹, X² and X³ has the structure:

3. The compound according to claim 1, wherein one of L¹ or L² is a single bond and the other is a single bond or methylene.

4. The compound according to claim 1, wherein Y is –OH or N(R⁴)₂.

5. The compound according to claim 4, wherein Y is –NH(R⁴).

6. The compound according to claim 5, wherein Y is NH₂.

7. The compound according to claim 1, wherein neither W¹ nor W² is hydrogen.

8. The compound according to claim 7, wherein at least one of W¹ or W² is selected from phenyl, methylphenyl or chlorophenyl and the other is selected from phenyl, methylphenyl, chlorophenyl, ethylphenyl, isopropylphenyl, t-butylphenyl, methoxyphenyl, cyclohexylphenyl, bisphenyl, furyl, thiophenyl, benzothiophenyl, naphthyl, phenylmethylphenyl, 3-chloro-4-methylphenyl, 3-fluoro-4-methylphenyl,
methoxycarboxyphenyl, fluorenyl, oxofluorenyl, oxobenzochromenyl, phenoxyphenyl, benzoxoxyphenyl, indanyl, benzoylphenyl, 3,4-methylene dioxyphenyl, hydroxyphenyl, or thiadiazolylphenyl.

9. A composition comprising a compound according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

10. The composition according to claim 9, wherein said composition is formulated for administration to a mammal.

11. The composition according to claim 10, additionally comprising an additional anti-viral agent effective against hepatitis C virus infection.

12. The composition according to claim 11, wherein said additional anti-viral agent is selected from an inhibitor of HCV NS3 protease; an inhibitors of HCV polymerase; an IMPDH inhibitor, such as mycophenolic acid, mycophenolate mofetil, and derivatives thereof; interferons, such as alpha-interferon; ribavirin; or ZSX.

13. A method of detecting HCV helicase activity in a biological sample suspected of containing a polypeptide having HCV helicase activity, comprising the step of contacting said biological sample with a compound according to any one of claims 1 to 8 or a composition according to any one of claims 9 to 12.

14. A method of treating or reducing the severity of a hepatitis C virus infection in a mammal
comprising the step of administering to said mammal a composition according to any one of claims 10 to 12.

15. The method according to claim 14 insofar as that claim depends from claim 10, additionally comprising the step of administering to said mammal an additional anti-viral agent effective against hepatitis C virus infection, wherein said additional anti-viral agent is administered to said patient prior to, simultaneously with or following administration of a composition according to claim 10.

16. The method according to claim 15, wherein said additional anti-viral agent is selected from an inhibitor of HCV NS3 protease; an inhibitors of HCV polymerase; an IMPDH inhibitor, such as mycophenolic acid, mycophenolate mofetil, and derivatives thereof; interferons, such as alpha-interferon; ribavirin; or ZSX.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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<th>C07B417/04</th>
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According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

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<td>IPC 7 C07D C07C A61K</td>
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Documented searched other than minimum documentation to the extent that such documents are included in the fields searched

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>GOERDELER J ET AL: &quot;Ring cleaving cycloadditions, VI. Reaction of 5-imino-.DELTA.3-1,2,4-thiadiazolines with heterocumulenes (preparative aspects)&quot; CHEM. BER. (CHBEAM, 00092940); 1979; VOL. 112 (2); PP. 517-31, XP000872420 Univ. Bonn; Inst. Org. Chem. Biochem.; Bonn; Ger. see compounds 4, 14 and schemes 1 and 2</td>
<td>1-5,7,8</td>
</tr>
<tr>
<td>ZYABREV V S ET AL: &quot;Acylation of 5-amino-2-aryl-3-phenyl-1,2,4-thiadiazolium chlorides&quot; ZH. ORG. KHIM. (ZORKAE, 05147492); 1988; VOL. 24 (8); PP. 1754-62, XP000872419 USSR (SU) see scheme on page 1756</td>
<td>1-8</td>
</tr>
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**Further documents are listed in the continuation of box C.**

**Patent family members are listed in annex.**

**Date of the actual completion of the international search**

16 February 2000

**Date of mailing of the international search report**

16.03.00

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax (+31-70) 340-3018

**Authorized officer**

Scruton-Evans, I
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<tr>
<td>X</td>
<td>SCHRODER U ET AL: &quot;Substituted 1,2,4-thiadiazolium dichloroaurates(I) and tetrachloroaurates(III) as products of the reaction of N-(thiocarbamoyl)benzamidines with tetrachlorogold(III) compounds&quot; Z. NATURFORSCH., B: CHEM. SCI. (ZNBSEN,09320776);1997; VOL.52 (5); PP.620-628, XP000872440 Universität Leipzig;Inst. Anorganische Chemie; Leipzig; D-04103; Germany (DE) see compounds 1a,2a,1b,3b,</td>
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<td>X</td>
<td>ZYABREV V S ET AL: &quot;Recyclization of dehydrohalogenation products of 2,3,5-trisubstituted 1,2,4-thiadiazolium salts containing an active methylene group on N2&quot; RUSS. J. ORG. CHEM. (RJOCEQ,10704280);1997; VOL.33 (11); PP.1645-1651, XP000872422 Institute of Bioorganic and Petroleum Chemistry, Ukrainian National Academy of Sciences;Kiev; 253660; Ukraine (UA) see compounds IVa,IVb</td>
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<td>P,X</td>
<td>GUTTMANN M ET AL: &quot;Voltammetric characterization of the electrochemical redox behavior of N-thiocarbamoyl-benzamidines and 1,2,4-thiadiazolium salts&quot; MONATSH. CHEM. (MOCMB7,00269247);1999; VOL.130 (6); PP.753-768, XP000872409 Univ. Leipzig;Institut Anorganische Chemie; Leipzig; D-04103; Germany (DE) see scheme 2 and 3 and compound 1b</td>
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<td>WO 97 43310 A (SCHERING CORPORATION;USA) 20 November 1997 (1997-11-20) the whole document</td>
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<td>WO 99 50230 A (VERTEX PHARMA;FARMER LUC J (US); TUNG ROGER D (US); BHISETTI GOVI) 7 October 1999 (1999-10-07) the whole document</td>
<td>1-16</td>
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INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. X Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
   Although claims 13-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. X Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
   see FURTHER INFORMATION sheet PCT/ISA/210

3.☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest  ☐ The additional search fees were accompanied by the applicant’s protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1996)
Continuation of Box I.2

Present claims 1-16 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the examples, and closely related homologous compounds wherein the core is a 1,2,4-thiadiazole, L1 is absent or CH, W1 is phenyl, L2 is absent, W2 is phenyl, and Y is N(R4)2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
<table>
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<td>WO 9743310 A</td>
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| WO 9950230 A                           | 07-10-1999      | AU 3376699 A            | 18-10-1999      |