Compounds of Formula (I): wherein $R^1$, $R^2$, $R^A$, $R^B$, $Z^1$, $Z^2$, $Z^3$, $Z^4$, $Z^5$ and $Z^6$ are defined herein. The compounds are useful as inhibitors of the function of NS5A protein encoded by HCV for the treatment of hepatitis C viral infection.
HEPATITIS C INHIBITOR COMPOUNDS

RELATED APPLICATIONS
This application claims benefit of U.S. Serial No. 61/299186, filed January 28, 2010, and U.S. Serial No. 61/327900 filed April 26, 2010, both of which are herein incorporated by reference.

FIELD OF THE INVENTION
The present invention relates to compounds, and their use as inhibitors of the function of N5A protein encoded by HCV, pharmaceutical compositions containing such compounds and methods for using these compounds in the treatment of HCV infection.

BACKGROUND OF THE INVENTION
It is estimated that at least 170 million persons worldwide are infected with the hepatitis C virus (HCV). Acute HCV infection progresses to chronic infection in a high number of cases, and, in some infected individuals, chronic infection leads to serious liver diseases such as cirrhosis and hepatocellular carcinoma. The development of new and specific anti-HCV treatments is a high priority and virus-specific functions essential for replication are the most attractive targets for drug development.


SUMMARY OF THE INVENTION
The present invention provides a novel series of compounds having inhibitory activity against HCV replication. The compounds of the invention may be used to inhibit the function of the NS5A protein encoded by HCV and may be used to reduce HCV replication.

Further objects of this invention arise for one skilled in the art from the following
description and the examples.

The invention provides a compound of Formula (I) and a racemate, diastereoisomer, optical isomer or salt thereof:

![Chemical Structure of Formula (I)](image)

wherein:
- \( Z^1, Z^2, Z^3, Z^4, Z^5 \) and \( Z^6 \) are each independently selected from \( \text{CH} \) or \( \text{N} \);
- \( R^A \) and \( R^B \) are each 1 or 2 substituents independently selected from hydrogen, \((\text{C}_{1-6})\text{alkyl}\), \((\text{C}_{1-6})\text{haloalkyl}\), \(-0-(\text{C}_{1-6})\text{alkyl}\), \(\text{NH}_2\), \(-\text{NH}((\text{C}_{1-6})\text{alkyl})\); \(-\text{NH}((\text{C}_{1-6})\text{alkyl})_2\); and \(\text{CN}\);
- \( R^1 \) and \( R^2 \) are each independently selected from \((\text{C}_{1-6})\text{alkyl}\), \((\text{C}_{3-7})\text{cycloalkyl}\) and \(-(\text{C}_{1-6})\text{alkyl}-\text{aryl}\);
- wherein each said alkyl, cycloalkyl and alkyl-aryl is optionally substituted 1 to 3 times with aryl, \(-0-(\text{C}_{1-6})\text{alkyl}\), \(-0-(\text{C}_{1-6})\text{alkyl}\); \(-\text{N}(\text{R}^1)\text{R}^2\);
- \( R^1 \) and \( R^9 \) are independently selected from \(\text{H}\), \((\text{C}_{1-6})\text{alkyl}\) and \(-\text{C}(=\text{O})0-(\text{C}_{1-6})\text{alkyl}\).

Furthermore, the invention provides a compound of Formula (II) and a racemate, diastereoisomer, optical isomer or salt thereof:

![Chemical Structure of Formula (II)](image)

wherein:
- \( R^1 \) and \( R^2 \) are each independently selected from \(\text{H}\), \((\text{C}_{1-6})\text{alkyl}\) and \(-\text{C}(=\text{O})0-(\text{C}_{1-6})\text{alkyl}\).
R\(^1\) and R\(^2\) are each independently selected from (C\(_6\))alkyl, (C\(_3\)–7)cycloalkyl and -(C\(_6\))alkyl-aryl;

wherein each said alkyl, cycloalkyl and alkyl-aryl is optionally substituted 1 to 3 times with aryl, -O-(C\(_1\)–6)alkyl and -N(R\(^f\))R\(^g\);

R\(^f\) and R\(^g\) are independently selected from H, (C\(-2\))alkyl and -C(=0)0 -(C\(_1\)–6)alkyl.

Another aspect of this invention provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as a medicament.

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

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

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of a hepatitis C viral infection in a human being having or at risk of having the infection.

Another important aspect of the invention involves a method of treating or preventing a hepatitis C viral infection in a human being by administering to the human being an anti-hepatitis C virally effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof, or a composition as described above, alone or in combination with at least one other antiviral agent, administered together or separately.

Also within the scope of this invention is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as described herein, for the manufacture of a medicament for the treatment or prevention of hepatitis C viral infection in a human being.
An additional aspect of this invention refers to an article of manufacture comprising a composition effective to treat a hepatitis C viral infection; and packaging material comprising a label which indicates that the composition can be used to treat infection by the hepatitis C virus; wherein the composition comprises a compound of Formula (I) according to this invention or a pharmaceutically acceptable salt thereof.

Still another aspect of this invention relates to a method of inhibiting the replication of hepatitis C virus comprising exposing the virus to an effective amount of the compound of Formula (I), or a salt thereof, under conditions where replication of hepatitis C virus is inhibited.

Further included in the scope of the invention is the use of a compound of Formula (I), or a salt thereof, to inhibit the replication of hepatitis C virus.

In another aspect the invention provides novel intermediates useful in the production of compounds of Formula (I) or Formula (II). In particular, the novel intermediates comprise one or more of the intermediates selected from the group consisting of intermediates designated 15a1, 15b1, 15c1, 15d1, 16a1, 16b1, 17a1, 17a1, 18a1, 26a3, 27a1, 27a2, 28a1, 29a1 and 30a1, as disclosed in the Examples.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_{1-6}-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the first named subgroup is the radical attachment point, for example, the substituent "-C_{1-3}-alkyl-aryl" means an aryl group which is bound to a -C_{1-3}-alkyl group, wherein the -C_{1-3}-alkyl-group is bound to the core. In the previous example of "-C_{1-3}-alkyl-aryl", substituents may be attached to either the C_{1-3}-alkyl or aryl portion.
thereof or both, unless specified otherwise.

In case a compound of the present invention or an intermediate used in the synthesis of a compound of the present invention is depicted in the form of a chemical name and as a formula, the formula shall prevail in case of any discrepancy between the name and formula.

The term “C_{1,1}-alkyl”, wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C_{1,5}-alkyl embraces the radicals H_{3}, H_{3}-CH_{2}, H_{3}-CH_{2}-CH_{2}, H_{3}-CH(\text{CH}_{3}), H_{3}-\text{CH}_{2}-\text{CH}_{2}-\text{CH}_{2},
H_{3}-\text{CH}_{2}-\text{CH(\text{CH}_{3})}, H_{3}-\text{CH(\text{CH}_{3})}-\text{CH}_{2}, H_{3}-\text{C(\text{CH}_{3})}_{2}, H_{3}-\text{CH}_{2}-\text{CH}_{2}-\text{CH}_{2}-\text{CH}_{2},
H_{3}-\text{CH}_{2}-\text{CH}_{2}-\text{CH(\text{CH}_{3})}, H_{3}-\text{CH}_{2}-\text{CH(\text{CH}_{3})}-\text{CH}_{2}, H_{3}-\text{CH(\text{CH}_{3})}_{2}-\text{CH}_{2}, H_{3}-\text{C(\text{CH}_{3})}_{2}-\text{CH}_{2},
H_{3}-\text{CH(\text{CH}_{3})}-\text{CH(\text{CH}_{3})}, and H_{3}-\text{CH}_{2}-\text{CH(\text{CH}_{3})}_{2}.

The term “carbocyde” means a mono- or multi-ring structure consisting only of carbon containing between one and four rings wherein such rings may be attached together in a pendent manner or may be fused. The term “carbocyde” refers to fully saturated and aromatic ring systems and partially saturated ring systems. The term “carbocyde” additionally encompasses spiro systems, and bridged systems.

The term “C_{3,4}-cycloalkyl”, wherein n is an integer 4 to n, either alone or in combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to n C atoms. For example the term C_{3,4}-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term “aryl” as used herein, either alone or in combination with another radical, denotes a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, napthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and dihydronaphthyl.
The term "halo" as used herein is intended to mean a halogen substituent selected from fluoro, chloro, bromo or iodo.

Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

An asterisk or the designation ' is used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers, atropisomers) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

One skilled in the art would know how to separate, enrich, or selectively prepare the enantiomers of the compounds of the present invention. Preparation of pure stereoisomers, e.g. enantiomers and diastereomers, or mixtures of desired enantiomeric excess (ee) or enantiomeric purity, are accomplished by one or more of the many methods of (a) separation or resolution of enantiomers, or (b) enantioselective synthesis known to those of skill in the art, or a combination thereof. These resolution methods generally rely on chiral recognition and include but not limited to chromatography using chiral stationary phases, enantioselective host-guest complexation, resolution or synthesis using chiral auxiliaries, enantioselective synthesis, enzymatic and nonenzymatic kinetic resolution, or spontaneous enantioselective crystallization. Such methods are disclosed generally in Chiral Separation Techniques: A Practical Approach (2nd Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T.E. Beesley and R.P.W. Scott, Chiral Chromatography,
John Wiley & Sons, 1999; and Satinder Ahuja, Chiral Separations by Chromatography, Am. Chem. Soc., 2000. Furthermore, there are equally well-known methods for the quantitation of enantiomeric excess or purity, including but not limited to GC, HPLC, CE, or NMR, and assignment of absolute configuration and conformation, including but not limited to CD, ORD, X-ray crystallography, or NMR.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include acetates, ascorbates, benzenesulfonates, benzoates, besylates, bicarbonates, bitartrates, bromides/hydrobromides, Ca-edetates/edetates, camsylates, carbonates, chlorides/hydrochlorides, citrates, edisylates, ethane disulfonates, estolates esylates, fumarates, gluceptates, gluconates, glutamates, glycolates, glycollylrnsilates, hexylresorcinates, hydabamines, hydroxymaleates, hydroxynapthoates, iodides, isothionates, lactates, lactobionates, malates, maleates, mandelates, methanesulfonates, mesylates, methylbromides, methylnitrates, methylsulfates, mucates, napsylates, nitrates, oxalates, pamoates, pantothencates, phenylacetates, phosphates/diphosphates, polygalacturonates, propionates, salicylates, stearates, subacetates, succinates, sulfamides, sulfates, tannates, tartrates, teoclates, toluenesulfonates, triiodiiodides, ammonium, benzathines, chloroprocaines, cholines, diethanolamines, ethylenediamines, meglumines and procaines. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like, (also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19; and...

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate salts) also comprise a part of the invention.

The term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of the hepatitis C disease and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood.

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

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 for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or
The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

**PREFERRED EMBODIMENTS**

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

Any and each of the following definitions may be combined with each other.

Examples of preferred embodiments for the group shown below:

include:

C-A:
R-A: R is selected from (C-6)alkyl, (C3-7)cycloalkyl and -(C-6)alkyl-aryl;
wherein each said alkyl, cycloalkyl and alkyl-aryl is optionally substituted 1 to 3 times with aryl, -0-(C1-6)alkyl, -0-C(=0)-N((C-6...e)alkyl)2 and -N(Rf)Rg;
Rf and Rg are independently selected from H, (C-6)alkyl and -C(=0)(C-6)alkyl.

R-B: R1 is selected from (C1-5)alkyl, (C3-7)cycloalkyl and -(C1-5)alkyl-phenyl;
wherein each said alkyl, cycloalkyl and alkyl-phenyl is optionally substituted 1 to 3 times with phenyl, -0-(C1-5)alkyl, -0-C(=0)-N((C-6...g)alkyl)2 and -N(Rf)Rg;
Rf and Rg are independently selected from H, (C1-3)alkyl and -C(=0)(C1-3)alkyl.

R-C: R1 is selected from (C1-5)alkyl, (C2)cycloalkyl and -(C1-2)alkyl-phenyl;
wherein each said alkyl, cycloalkyl and alkyl-phenyl is optionally substituted 1 to 2 times with phenyl, -0-(C1-2)alkyl and -N(Rf)Rg;
Rf and Rg are independently selected from H, (C1-2)alkyl and -C(=0)(C1-2)alkyl.

R-D: R1 is selected from (C1-5)alkyl;
wherein each said alkyl is optionally substituted 1 to 2 times with -0-(d)alkyl and -N(Rf)Rg;
Rf and Rg are independently selected from H and \(-\text{C} (=\text{O})\text{O} -(\text{C}-i)\text{alkyl}\).

**Rf-E:** Rf is selected from

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

and

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

**Rf-F:** Rf is selected from

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

and

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

**R2:**

**R2-A:** R2 is selected from \((\text{C}_1)\text{alkyl}, (\text{C}_3)\text{cycloalkyl and -(C-}_{\text{i}}\text{alkyl-aryl})\);

wherein each said alkyl, cycloalkyl and alkyl-aryl is optionally substituted 1 to 3 times with aryl, \(-\text{C} (=\text{O})(\text{C}-_{\text{i}}\text{alkyl})_2\) and \(-\text{N}(\text{R}_f)\text{R}_g\);

Rf and Rg are independently selected from H, \((\text{C}_1)\text{alkyl and -(C}=\text{O})\text{O} -(\text{C}_1)\text{alkyl}\).

**R2-B:** R2 is selected from \((\text{C}_1)\text{alkyl}, (\text{C}_3)\text{cycloalkyl and -(C-}_{\text{i}}\text{alkyl-phenyl})\);

wherein each said alkyl, cycloalkyl and alkyl-phenyl is optionally substituted 1 to 3 times with phenyl, \(-\text{C} (=\text{O})(\text{C}-_{\text{i}}\text{alkyl})_2\) and \(-\text{N}(\text{R}_f)\text{R}_g\);

Rf and Rg are independently selected from H, \((\text{C}_1)\text{alkyl and -(C}=\text{O})\text{O} -(\text{C}_1)\text{alkyl}\).

- 11 -
R²-C: R² is selected from (C₁₋₅)alkyl, (C₃)cycloalkyl and -(C₁₋₂)alkyl-phenyl;
wherein each said alkyl, cycloalkyl and alkyl-phenyl is optionally substituted 1 to 2 times with phenyl, -0-(d)alkyl and -N(R¹)R⁸;
R¹ and R⁸ are independently selected from H, (C₁₋₂)alkyl and -C(=O)0 - (C₁₋₂)alkyl.

R²-D: R² is selected from (C₁₋₅)alkyl;
wherein each said alkyl is optionally substituted 1 to 2 times with -0-(d)alkyl and -N(R¹)R⁸;
R¹ and R⁸ are independently selected from H and -C(=O)0 - (C₃)alkyl.

R²-E: R² is selected from

The following table represents further embodiments E-1 to E-14 of the compounds of Formula (I):
Examples of most preferred compounds according to this invention are each single compound listed in Tables 1 and 2.

### PHARMACEUTICAL COMPOSITION

Suitable preparations for administering the compounds of Formula I will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatitives and powders etc. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.-%, preferably 0.1 to 50 wt.-% of the composition as a whole.

Suitable tablets may be obtained, for example, by mixing one or more compounds according to formula I with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also consist of several layers.

According to an alternate embodiment, the pharmaceutical composition of this
invention may additionally comprise at least one other anti-HCV agent.

The term "other anti-HCV agent" as used herein means those agents that are effective for diminishing or preventing the progression of hepatitis C related symptoms of disease. Such agents can be selected from: immunomodulatory agents, inhibitors of HCV NS3 protease, inhibitors of the function of NS5A protein encoded by HCV, inhibitors of HCV polymerase or inhibitors of another target in the HCV life cycle. Examples of anti-HCV agents include, α- (alpha), β- (beta), δ- (delta), γ- (gamma), ω- (omega) or τ- (tau) interferon, pegylated α-interferon, ribavirin, amantadine, taribavirin (Viramidine), Nitazoxannide and BMS-791325.

The term "immunomodulatory agent" as used herein includes those agents (compounds or biologicals) that are effective to enhance or potentiate the immune system response in a human being. Immunomodulatory agents include, but are not limited to, inosine monophosphate dehydrogenase inhibitors, class I interferons, class II interferons, consensus interferons, asialo-interferons, pegylated interferons and conjugated interferons, including but not limited to interferons conjugated with other proteins including but not limited to human albumin. Class I interferons are a group of interferons that all bind to receptor type I, including both naturally and synthetically produced class I interferons, while class II interferons all bind to receptor type II. Examples of class I interferons include, but are not limited to, α- , β-, δ-, ω-, and τ-interferons, while examples of class II interferons include, but are not limited to, γ-interferons.

The term "inhibitor of HCV NS5A" as used herein means an agent (compound or biological) that is effective to inhibit the function of HCV NS5A in a human being. Inhibitors of HCV NS5A include, for example, BMS-790052, AZD7295 and PPI-461 .

The term "inhibitor of HCV NS3 protease" as used herein means an agent (compound or biological) that is effective to inhibit the function of HCV NS3 protease in a human being. Inhibitors of HCV NS3 protease include, for example, those compounds described in WO 99/07733, WO 99/07734, WO 00/09558, WO 00/09543, WO 00/59929, WO 03/064416, WO 03/064455, WO 03/064456, WO
The term "inhibitor of HCV polymerase" as used herein means an agent (compound or biological) that is effective to inhibit the function of an HCV polymerase in a human being. This includes, for example, inhibitors of HCV NS3B polymerase.


The term "inhibitor of another target in the HCV life cycle" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of HCV in a human being other than by inhibiting the function of the HCV NS3 protease. This includes agents that interfere with either host or HCV viral targets necessary for the HCV life cycle or agents which specifically inhibit in HCV cell culture assays through an undefined or incompletely defined mechanism.

Inhibitors of another target in the HCV life cycle include, for example, agents that inhibit viral targets such as Core, E1, E2, p7, NS2/3 protease, NS3 helicase, NS4A, NS5B polymerase, NS5A and internal ribosome entry site (IRES), or host targets such as cyclophilin B, phosphatidylinositol 4-kinase Ilia, CD81, SR-B1, Claudin 1, VAP-A, VAP-B. Specific examples of inhibitors of another target in the HCV life
The term "HIV inhibitor" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of HIV in a human being. This includes agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HIV in a human being. HIV inhibitors include, for example, nucleoside inhibitors, non-nucleoside inhibitors, protease inhibitors, fusion inhibitors and integrase inhibitors.

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

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

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

The dose range of the compounds of the invention applicable per day is usually from 0.01 to 100 mg/kg of body weight, preferably from 0.1 to 50 mg/kg of body weight. Each dosage unit may conveniently contain from 5% to 95% active compound (w/w). Preferably such preparations contain from 20% to 80% active compound.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the combination will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

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

EXAMPLES
Other features and advantages of the present invention will become apparent from
the following more detailed Examples which illustrate, by way of example, the principles of the invention. As is well known to a person skilled in the art, reactions are performed in an inert atmosphere (including but not limited to nitrogen or argon) where necessary to protect reaction components from air or moisture. Temperatures are given in degrees Celsius (°C). Solution percentages and ratios express a volume to volume relationship, unless stated otherwise. Flash chromatography is carried out on silica gel (SiO₂) according to the procedure of W.C. Still et al., J. Org. Chem., (1978), 43, 2923.

Preparative RP-HPLC is performed under standard conditions using one of the following specific measuring conditions:

Compounds are purified by preparative RP-HPLC under standard conditions using a Waters SunFire Prep OBD™ C18 column (5µm, 19 x 50 mm) eluting with a linear acetonitrile gradient containing 10 mM Ammonium Bicarbonate (pH 10) over 10 minutes at 30 ml/min. Fractions containing the desired product are pooled and lyophilized.

Compounds are purified by preparative RP-HPLC under standard conditions using a Waters XBridge Prep OBD™ C18 (5µm, 19 x 50 mm) eluting with a linear acetonitrile gradient containing 10 mM Ammonium Formate (pH 3.8) over 10 minutes at 30 ml/min. Fractions containing the desired product are pooled and lyophilized.

Compounds are purified by preparative RP-HPLC under standard conditions using a Waters SunFire Prep OBD™ C18 column (5µm, 19 x 50 mm) eluting with a linear acetonitrile gradient containing 10 mM Ammonium Bicarbonate (pH 10) or a Waters XBridge Prep OBD™ C18 (5µm, 19 x 50 mm) eluting with a linear acetonitrile gradient containing 10 mM Ammonium Formate (pH 3.8) over 10 minutes at 30 ml/min. Fractions containing the desired product are pooled and lyophilized.

Analytical UPLC is performed under standard conditions using one of the following specific measuring conditions:
Analytical UPLC is carried out under standard conditions using a Waters ACQUITY UPLC® HSS T3 column (1.8 µm, 2.1 x 50 mm) eluting with a segmented linear acetonitrile gradient containing 0.06% TFA (v/v) over 2.6 minutes at 0.9 ml/min.

Analytical UPLC is also carried out under standard conditions using a Waters ACQUITY UPLC® BEH C18 column (1.8 µm, 2.1 x 30 mm) eluting with a linear methanol gradient containing 10 mM Ammonium Bicarbonate (pH 10) over 2.2 min at 0.75 ml/min or a Waters ACQUITY UPLC® HSS C18 column (1.8 µm, 2.1 x 30 mm) eluting with a linear methanol gradient containing 10 mM Ammonium Formate (pH 3.8) over 2.3 minutes at 0.8 ml/min.

Mass spectral analyses are recorded using electrospray mass spectrometry.

Abbreviations or symbols used herein include:
- Ac: acetyl; AcOH: acetic acid; BEH: ethylene bridged hybrid; Bn: benzyl (phenylmethyl); BOC or Boc: tert-butyloxycarbonyl; Bu: butyl; DCM: dichloromethane; DIPEA: diisopropylethylamine; DMAc: dimethylacetamide; DME: dimethoxyethane; DMF: N,N-dimethylformamide; EC₅₀: 50% effective concentration; EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; Et: ethyl; Et₃N: triethylamine; Et₂O: diethyl ether; EtOAc: ethyl acetate; EtOH: ethanol; Hex: hexane; HATU: N,N,N',N'-tetramethyl-0-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate; HPLC: high performance liquid chromatography; HOBt: 1-hydroxybenzotriazole; HSS: high strength silica; IC₅₀: 50% inhibitory concentration; 'Pr or i-Pr: 1-methylethyl (iso-propyl); LC-MS: liquid chromatography-mass spectrometry; m/z: mass-to-charge ratio; [M+H]⁺: protonated molecular ion; Me: methyl; MeCN: acetonitrile; MeOH: methanol; MS: mass spectrometry; NaHMDS: sodium-1,1,1,3,3,3-hexamethyldisilazane; NBS: N-bromosuccinimide; NMP: N-Methyl-2-pyrrolidone; NMR: nuclear magnetic resonance spectroscopy; OBD: optimum bed density; Pd(dppf)Cl₂: 1,1'-bis(diphenylphosphino)-ferrocenedichloropalladium(II); Ph: phenyl; Pr: propyl; Prep LCMS: preparative liquid chromatography-mass spectrometry; RP-HPLC: reversed-phase high pressure liquid chromatography; RT: room temperature (approximately 18°C to 25°C); tert-butyl or t-butyl: 1,1-dimethylethyl; TBTU: 0-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyllumonium tetrafluoroborate; TFA: trifluoroacetic acid; THF: tetrahydrofuran; TLC: thin layer chromatography.
Example 1
Preparation of intermediate 1a4

Step 1:
To a solution of 4-bromo-3-methylbenzoic acid 1a1 (Aldrich) (3 g, 14 mmoles), N,N-dimethylhydroxylamine hydrochloride (1.36 g, 14 mmoles), EDCI (4 g, 21 mmoles) and HOBt (1.94 g, 14 mmoles) in DMF (20 mL) is added DIPEA (7.3 mL, 42 mmoles). After stirring at RT for 24 hours, the reaction mixture is concentrated and the product is purified by flash chromatography using DCM to afford 1a2.

Step 2:
To a solution of 1a2 (1.53 g, 5.9 mmoles) in THF (50 mL) at -70°C is added a methyllithium solution in Et2O (1.6M, 38.7 mL, 62 mmoles). The reaction is allowed to reach RT and is then stirred for 16 hours. The reaction mixture is concentrated and the residue is partitioned between DCM and a saturated aqueous solution of NH4Cl. The organic layer is dried with MgSO4, filtered and concentrated. The product is purified by flash chromatography using 25% DCM in hexanes to afford 1a3.

Step 3:
1a3 (7.5 g, 17 mmoles), bis(pinacolato)diboron (8.7 g, 34 mmoles), potassium acetate (4.2 g, 43 mmoles) and Pd(P(Ph)3)4 (1 g, 0.9 mmol) are placed in DMAc (70 mL). The mixture is degassed with argon for 15 minutes and heated at 85°C for 20 hours. The reaction mixture is cooled to RT and partitioned between EtOAc and water. The layers are separated and the aqueous phase is extracted with EtOAc. The combined organic layers are washed with water and brine, dried over Na2SO4.
and concentrated. The product is purified by flash chromatography using 20%-30% EtOAc in petroleum ether to afford 1a4.

**Example 2**

**Preparation of intermediate 2a2**

\[
\begin{array}{c}
\text{Br} \quad \text{N} \quad \text{Br} \\
\text{2a1} \\
\end{array} 
\rightarrow 
\begin{array}{c}
\text{O} \quad \text{N} \quad \text{Br} \\
\text{2a2} \\
\end{array}
\]

To a solution of 2,5-dibromo-3-picoline 2a1 (Aldrich) (25 g, 99.6 mmole) in anhydrous Et₂O (800 mL) at -78°C under a nitrogen atmosphere is added a N-butyllithium solution in hexanes (2.4 M, 42.4 mL, 99.6 mmole). The reaction mixture is stirred for 30 minutes then DMAc (13.9 mL, 149.5 mmole) is added and stirred for 1 hour at 0°C. The reaction mixture is neutralized with a saturated aqueous solution of NH₄Cl at 0°C and extracted with EtOAc. The organic layer is washed with brine, dried over Na₂SO₄ and concentrated. The product is recrystallized from Et₂O to afford 2a2.

**Example 3**

**Preparation of intermediate 3a1**

\[
\begin{array}{c}
\text{O} \quad \text{N} \quad \text{Br} \\
\text{2a2} \\
\end{array} 
\rightarrow 
\begin{array}{c}
\text{O} \quad \text{B} \quad \text{O} \\
\text{1a4} \\
\end{array} 
\rightarrow 
\begin{array}{c}
\text{O} \quad \text{N} \quad \\
\text{3a1} \\
\end{array}
\]

To a solution of 2a2 (7 g, 32.7 mmole) in a mixture of DME (60 mL) / EtOH (15 mL) / water (15 mL), 1a4 (9.4 g, 36.0 mmole) and Na₂CO₃ (7.6 g, 71.9 mmole) are added at RT and the reaction mixture is degassed with argon for 15 minutes. Pd(P(Ph)₃)₄ (1.9 g, 1.6 mmole) is added and the solution is degassed for 10 minutes. The reaction mixture is heated at 115°C for 5 hours, cooled to RT, diluted with water and extracted with EtOAc. The combined organic layers are washed with brine, dried over Na₂SO₄, filtered and concentrated. The product is purified by flash chromatography using 15%-25% EtOAc in petroleum ether to afford 3a1.

**Example 4**

**Preparation of intermediate 4a2**

- 21 -
A mixture of 5-chloro-2-bromopyrimidine \(4a1\) (Matrix Scientific) (11 g, 57 mmoles) and tributyl(1-ethoxyvinyl)tin (22.6 g, 63 mmoles) in DMF (100 mL) is degassed with argon for 30 minutes and \(\text{PdCl}_2(\text{PPh}_3)_2\) (0.8 g, 1.1 mmol) is added. The reaction is heated to 70°C for 2.5 hours and cooled to RT. An aqueous solution of KF is added. The mixture is poured in water and extracted with EtOAc. The combined organic layers are concentrated and purified by flash chromatography using 2% EtOAc in hexanes to afford \(4a2\).

**Example 5**

**Preparation of intermediate 5a2**

\[
\begin{align*}
\text{\(4a2\)} & \quad \text{\(5a2\)} \\
\end{align*}
\]

To a solution of \(4a2\) (5.8 g, 31 mmoles) in a mixture of DME (60 mL) / EtOH (16 mL) / water (16 mL), \(5a1\) (Aldrich) (5.7 g, 35 mmoles) and \(\text{Na}_2\text{C}O_3\) (7.3 g, 69 mmoles) are added. The reaction mixture is degassed with argon for 15 minutes. \(\text{Pd}(\text{Ph}_3)_4\) (3.6 g, 3.1 mmoles) is added and the reaction mixture is degassed for 10 minutes. The solution is heated at 115°C for 5 hours and then is cooled to RT. The reaction mixture is diluted with water and extracted with EtOAc. The combined organic layers are washed with brine, dried over \(\text{Na}_2\text{SO}_4\), filtered and concentrated. The product is purified by flash chromatography using 15%-25% EtOAc in petroleum ether to afford \(5a2\).

**Example 6**

**Preparation of intermediate 6a2**

\[
\begin{align*}
\text{\(6a1\)} & \quad \text{\(5a1\)} & \quad \text{\(6a2\)} \\
\end{align*}
\]
1-(6-bromopyridin-3-yl)ethanone 6a1 (Aldrich) (5 g, 25.0 mmoles) and 4-acetylphenylboronic acid 5a1 (Aldrich) (4.5 g, 27.5 mmoles) are dissolved in DMF (200 mL) and water (50 mL). The suspension is heated to 60°C and degassed with argon for 15 minutes. Pd(dppf)Cl2 (0.91 g, 1.3 mmol) and Na2CO3 (10.6 g, 100 mmoles) are added and the mixture is heated at 130 °C for 1 hour. The reaction mixture is cooled to RT and poured into water (400 mL). The precipitate is collected by filtration and dissolved in DCM (500 mL). The organic layer is washed with water, dried over Na2SO4, filtered and concentrated. The residue is dissolved in 2% MeOH in DCM and filtered over a silica gel column to afford 6a2.

Example 7
Preparation of intermediate 7a2

To a stirred solution of 4,4′-diacetylbiphenyl 7a1 (Alfa) (20 g, 83.9 mmoles) in DCM (200 mL), bromine (8.7 mL, 167.9 mmoles) is added slowly under a nitrogen atmosphere. The mixture is stirred under nitrogen for 20 hours at RT. The resulting slurry is charged with DCM (200 mL) and concentrated to ~160 mL. The slurry is diluted with THF and solvent is exchanged to a target volume of ~50 mL via vacuum distillation. The slurry is cooled to RT over 1 hour and stirred for an additional hour. The solid is filtered and washed with DCM to afford 7a2.

Example 7b
Preparation of intermediate 7b1

To a solution of 3a1 (6g, 22 mmoles) in DCM (80 mL), 2 drops of HBr solution in AcOH is added. Bromine (2.3 mL, 45 mmoles) is added at RT. The resulting reaction mixture is stirred at 35 °C overnight. The obtained solid is filtered, washed with DCM and dried to afford 7b1.

Example 8
Preparation of intermediate 8a1

To 6a2 (4.0 g, 16.7 mmoles) in DCM (200 mL) is added DIPEA (7.0 mL, 40.1 mmoles) and the mixture is cooled to 0°C. TMSOTf (7.0 mL, 38.5 mmoles) is added and the mixture is stirred at 0°C for 15 minutes. A solution of NBS (6.0 g, 33.4 mmoles) in DCM (200 mL) is added and the mixture is stirred for 15 minutes. The reaction mixture is poured into water. The organic layer is separated, dried over Na₂SO₄, filtered and concentrated. The product is purified by flash chromatography using 1% MeOH in DCM to afford 8a1.

Example 9

Preparation of intermediate 9a2

Step 1:
5a2 (7.0 g, 26 mmoles) is dissolved in THF (110 mL) and water (55 mL). NBS (4.6 g, 26 mmoles) is added, the mixture is stirred at RT for 30 minutes and filtered to afford 9a1.

Step 2:
To a solution of 9a1 (7 g, 22 mmoles) in AcOH (1000 mL) is added dropwise a solution of bromine in AcOH (1.6 mL, 31 mmoles). The reaction mixture is stirred at RT overnight. Bromine (0.3 mL, 7 mmoles) is added and the resulting solid is filtered and washed with DCM to afford 9a2.

Example 10

Preparation of intermediate 10a2
To a solution of L-alanine 10a1 (Aldrich) (15 g, 168 mmoles) in 1N NaOH (168 mL) is added Na₂CO₃ (8.9 g, 84 mmoles). The solution is cooled to 0°C and methyl chloroformate (13.5 mL, 172 mmoles) is added dropwise. The reaction mixture is stirred at RT for 3.5 hours. The solution is washed with Et₂O and acidified (pH=1) with 1N HCl. The aqueous layer is extracted with DCM. The organic layer is washed with brine, dried over Na₂SO₄ and concentrated to afford 10a2.

The following intermediates are prepared analogously to the procedure described in Example 10 using the appropriate amino acid derivative.
Example 11
Preparation of intermediate 11a2

To Boc-O-methyl-L-serine dicyclohexylammonium salt 11a1 (Chem-Impex) (4.5 g, 11.2 mmoles) in 1,4-dioxane at 0°C is added an 8M HCl solution in 1,4-dioxane and the mixture is stirred for 2 hours at RT. The reaction mixture is concentrated and codistilled with 1,4-dioxane until dryness. The salt is dissolved in 1N NaOH (22.5 ml, 22.5 mmoles) and Na₂CO₃ (0.6 g, 5.6 mmoles) is added at 0°C followed by dropwise addition of methyl chloroformate (0.87 ml, 11.2 mmoles). The reaction mixture is stirred at RT for 3 hours. The solution is washed with ether and acidified (pH=1) with 1N HCl. The aqueous layer is extracted with DCM and the organic layer is washed with brine, dried over Na₂SO₄ and concentrated to afford 11a2.
Example 12

Preparation of intermediate 12a4

\[
\begin{align*}
\text{HO-} & \quad \text{Step 1} \quad \text{NO} \quad \text{Step 2} \quad \text{Na}^- \quad \text{Step 3} \\
\text{12a1} & \quad \rightarrow \quad \text{12a2} & \quad \rightarrow \quad \text{12a3} \\
\text{12a4} & \\
\end{align*}
\]

Step 1:
To a solution of methyl (R)-mandelate 12a1 (Aldrich) (200 mg, 1.2 mmol) in THF (4.5 mL) at 0°C is added NaHMDS in THF (1M, 1.8 mL, 1.8 mmol). The mixture is stirred for 15 minutes and then a solution of dimethylcarbamy1 chloride (0.2 mL, 2.4 mmoles) in THF (1.5 mL) is added. The reaction mixture is stirred overnight at RT and neutralized with a saturated aqueous solution of NH_4Cl. Water is added and the aqueous layer is extracted with EtOAc. The combined organic layers are dried with MgSO_4, filtered and concentrated. The product is purified by flash chromatography using EtOAc in hexanes to afford 12a2.

Step 2:
12a2 is dissolved in a mixture of THF (1.7 mL) / MeOH (0.6 mL). 1N NaOH (0.5 mL, 0.5 mmol) is added and the mixture is stirred at RT for 2 hours. The reaction is concentrated, co-evaporated successively with MeOH, MeCN and Et_2O and dried under high vacuum to afford 12a3.

Step 3:
To a solution of 12a3 (44.1 mg, 180 µmol) in DCM (1 mL) at 0°C is added DMF (5 µL) and oxalyl chloride (0.1 mL, 270 µmol). The solution is stirred overnight at RT. The reaction mixture is concentrated to afford 12a4.
Example 13
Preparation of intermediate 13a2

To a suspension of D-2-phenylglycine hydrochloride 13a1 (Aldrich) (1 g, 6.6 mmol) in MeOH (17 mL) at 0°C is slowly added sodium cyanoborohydride (0.96 g, 15.2 mmol). Acetaldehyde is added dropwise over 10 minutes. The reaction mixture is stirred at 0°C for 45 minutes and is then stirred for 4 hours at RT. The reaction mixture is filtered. Concentrated HCl is added to adjust the pH to ~2 and the solution is concentrated. The product is recrystallized from EtOH to afford 13a2.

Example 14
Preparation of intermediate 14a9

Step 1:
(R)-l-phenylethanamine (Aldrich) 14a2 (250 mL, 1960 mmol) is dissolved in toluene (2 L). To this solution, Na₂S₂O₄ (696 g, 4900 mmol) is added followed by dropwise addition of ethyl 2-oxoacetate (Aldrich) 14a1 (389 mL, 1960 mmol). The reaction is stirred at RT for 60 minutes. The solids are filtered and the filtrate is evaporated to obtain 14a3.

Step 2:
**14a3** (415 g, 2022 mmol) is dissolved in DMF (1250 mL) at RT. TFA (156 mL, 2022 mmol) is added, followed after 2 minutes by freshly distilled cyclopentadiene (Aldrich) **14a4** (267 g, 4044 mmol) and water (1.1 mL, 60.7 mmol). The mixture is stirred at RT overnight. The reaction is concentrated and the residue is poured into a 10% aqueous solution of NaHCO₃. To this mixture is added Et₂O, water and solid Na₂CO₃ until the pH is ~8. The organic layer is separated and the aqueous layer is extracted with Et₂O. The combined organic layers are washed with water, brine and dried over Na₂SO₄. The solvent is evaporated and the product is purified by flash chromatography using 15% EtOAc in heptanes to afford **14a5**.

**Step 3:**
**14a5** (238.3 g, 878 mmol) is dissolved in EtOH (2 L) and K₂C₂O₄ (121 g, 878 mmol) is added under a nitrogen atmosphere. To the reaction mixture Pd/C (23.4 g, 21.95 mmol) is added and the mixture is stirred under a hydrogen atmosphere at RT overnight. The reaction mixture is degassed with nitrogen and filtered. The solids are washed with EtOH and, to the filtrate, is added concentrated HCl (80 mL). The mixture is concentrated and the residue is co-evaporated with EtOH until a solid is formed. The suspension is stirred in a mixture of Et₂O and /PrOH. The resulting product is filtered, washed with a mixture of Et₂O and /PrOH and dried under vacuum to afford **14a6**.

**Step 4:**
In an autoclave, **14a6** (102 g, 329 mmol) is dissolved in EtOH (400 mL). K₂C₂O₄ (45.5 g, 329 mmol) is added and the mixture is degassed with nitrogen. Pd/C (7.0 g, 65.8 mmol) is added and H₂-pressure (8 bar) is applied. The reaction is stirred at RT for 20 hours. The reaction mixture is degassed with nitrogen and filtered. The filtrate is concentrated and the residue is suspended in Et₂O. 4N HCl in 1,4-dioxane (82 mL, 329 mmol) is then added. The resulting solid is filtered, washed with Et₂O and dried to afford **14a7**.

**Step 5:**
**14a7** (61 g, 297 mmol) is dissolved in 6N HCl (494 mL, 2966 mmol) and the mixture is heated to reflux overnight. The mixture is cooled to RT and the solvent is evaporated. The residue is dissolved in /PrOH and Et₂O is added. The product is
filtered, washed with \( \text{Et}_2\text{O} \) and dried to afford 14a8.

**Step 6:**

14a8 (46.6 g, 262 mmol) is dissolved in a mixture of water (300 mL) / MeOH (600 mL) and 2N NaOH (288 mL, 577 mmol) is added. The reaction is cooled to 0°C and a solution of di-f-Butyl dicarbonate (63.0 g, 288 mmol) in MeOH (100 mL) is added. The mixture is stirred at RT for 48 hours. The reaction mixture is concentrated and the residue is partitioned between EtOAc and a saturated aqueous solution of NaHCO\(_3\). The aqueous layer is extracted with EtOAc and the combined organic layers are washed with a saturated aqueous solution of NaHCO\(_3\). The combined aqueous layers are acidified to pH~3 with citric acid. The acidified aqueous layer is extracted with EtOAc. The combined organic layers are washed with water and brine, dried over Na\(_2\)SO\(_4\) and concentrated to afford 14a9.

**Example 15**

**Preparation of intermediate 15a1**

14a9 (3.1 g, 12.9 mmol) is dissolved in MeCN (33 mL). 7a2 (2.5 g, 6.3 mmol) and DIPEA (2.3 mL, 13.3 mmol) are added and the reaction is stirred at RT for 6 hours. The MeCN is evaporated and the residue is dissolved in toluene (60 mL). The remaining solid is filtered. NH\(_4\)OAc (9.7 g, 126 mmol) is added and the solution is heated to 100°C overnight. The mixture is diluted with water and filtered. The solid is washed with EtOAc and dried under high vacuum to afford 15a1 (\( t_R \) (min) 1.7; (M+H)\(^+\) 677.6).

The following intermediates are prepared analogously to the procedure described in Example 15 starting from the appropriate dibromoketone derivative.
Example 16

Preparation of intermediate 16a1

15a1 (4.3 g, 6.4 mmol) is dissolved in MeOH (50 mL). Concentrated HCl (7.6 mL) is added and the mixture is stirred at 50°C for 4 hours. The solvent is evaporated. The product is co-evaporated with toluene, triturated with Et20 and filtered. The resulting solid is dried under high vacuum to afford 16a1 (tR (min) 1.0; (M+H)+ 477.4).

The following intermediate is prepared analogously to the procedure described in Example 16 starting from the appropriate BOC protected amine derivative.
Example 17
Preparation of intermediate 17a1

15c1 (1.6 g, 2.4 mmol) is dissolved in 4 M HCl in 1,4-dioxane (1.8 mL) and DCM (10 mL). The reaction mixture is stirred at RT overnight. The reaction is concentrated and placed under high vacuum to afford 17a1 (tR (min) 1.2; (M+H)+ 478.3).

Example 18
Preparation of intermediate 18a1

15d1 (1.6 g, 2.4 mmol) is dissolved in 4 M HCl in 1,4-dioxane (1.8 mL). The reaction mixture is stirred at RT overnight. The reaction is concentrated and placed under high vacuum to afford 18a1 (tR (min) 1.8; (M+H)+ 479.3).

Example 19
Preparation of compound 1002

Step 1:
16a1 (1 g, 1.6 mmol), 10b2 (0.7 g, 3.9 mmol) and HATU (1.4 g, 3.7 mmol) are
loaded in a 100 mL round bottom flask. DMF (30 mL) is added followed by DIPEA (2.8 mL, 16.1 mmol) and the mixture is stirred at RT for 1 hour. The solution is diluted with EtOAc and washed with water, a 5% solution of aqueous Na₂CO₃ and brine. The organic layer is dried with Na₂SO₄, filtered and concentrated. The residue is co-evaporated with Et₂O and dried under high vacuum. The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford 1002.

Step 2:
1002 (400 mg, 0.5 mmol) is dissolved in MeOH (40 mL). A 1M solution of HCl in Et₂O (4 mL, 4 mmol) is added and the reaction mixture is concentrated. The residue is dissolved in water and MeCN is added. The mixture is frozen and lyophilized to afford the dihydrochloride salt of 1002.

Example 20
Preparation of compound 1016

10h2 (19.1 mg, 100 μmol) is loaded in an 8 mL vial. Solutions of 16a1 (25 mg, 40 μmol) in DMF (0.5 mL) and HATU (36.1 mg, 95 μmol) in DMF (0.5 mL) are added followed by DIPEA (75 μL, 429 μmol). The mixture is stirred at RT for 1 hour and neutralized with AcOH (100 μL). The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford 1016.

The following compounds are prepared analogously to the procedure described in Example 20 starting from the appropriate amino acid derivative: 1006, 1007, 1015, 1017, 1018, 1019 and 1021.
Example 21
Preparation of compound 1004

10d2 (28.0 mg, 133 µmol), 16a1 (27 mg, 43 µmol) and HATU (50 mg, 132 µmol) are loaded in an 8 mL vial. DMF (1 mL) is added followed by DIPEA (40 µL, 230 µmol) and the mixture is stirred at RT for 1 hour. The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford 1004.

The following compound is prepared analogously to the procedure described in Example 21 starting from the appropriate amino acid derivative: 1005.

Example 22
Preparation of compound 1001

10a2 (20.0 mg, 136 µmol), 16a1 (35 mg, 56 µmol) and HATU (50 mg, 132 µmol) are loaded in an 8 mL vial. DMF (1 mL) is added followed by DIPEA (100 µL, 574 µmol) and the mixture is stirred at RT for 1 hour. The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford 1001.

The following compound is prepared analogously to the procedure described in Example 22 starting from the appropriate amino acid derivative: 1003.
Example 23
Preparation of compound 2011

10b2 (20 mg, 115 \mu\text{mol}) is loaded in an 8 mL vial. Solutions of 16b1 (25 mg, 38 \mu\text{mol}) in DMF (0.5 mL) and HATU (34.3 mg, 90 \mu\text{mol}) in DMF (0.5 mL) are added followed by DIPEA (90 \mu\text{L}, 515 \mu\text{mol}). The mixture is stirred at RT for 1 hour and neutralized with AcOH (100 \mu\text{L}). The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford 2011.

The following compound is prepared analogously to the procedure described in Example 23 starting from the appropriate amino acid derivative: 2001.

Example 24
Preparation of compound 2010

10a2 (28.3 mg, 192 \mu\text{mol}), 17a1 (50 mg, 80 \mu\text{mol}) are loaded in an 8 mL vial. DMF (4.0 mL) is added followed by Et3N (89 \mu\text{L}, 642 \mu\text{mol}). HATU (73.2 mg, 192 \mu\text{mol}) is added and the mixture is stirred at RT overnight. The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford 2010.

The following compounds are prepared analogously to the procedure described in Example 24 starting from the appropriate amino acid derivative: 2007, 2008 and 2009.
Example 25
Preparation of compound 2005

To a solution of 18a1 (50 mg, 76 µmol) in NMP (1.0 mL) is added DIPEA (132 µL, 757 µmol) followed by 10h2 (43.4 mg, 227 µmol). HATU (86.3 mg, 227 µmol) is added and the reaction is stirred at RT for 2 hours. The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford 2005.

The following compounds are prepared analogously to the procedure described in Example 25 starting from the appropriate amino acid derivative: 2002, 2003, 2004 and 2006.

Example 26
Preparation of intermediate 26a3

Step 1:
14a9 (15 g, 62.2 mmol) is dissolved in a mixture of MeCN (400 mL) / THF (50 mL) and to this solution is added 2,4’-dibromoacetophenone (Aldrich) 26a1 (17.3 g, 62.2
mmol) and DIPEA (11.7 mL, 68.4 mmol). The reaction mixture is stirred at RT for 48 hours. The solvent is evaporated under reduced pressure. The residue is dissolved in EtOAc, washed with a 10% aqueous solution of NH₄Cl and brine, dried over Na₂SO₄, filtered and concentrated. The product is co-evaporated with DCM to afford 26a2.

Step 2:
26a2 (27.5 g, 59.6 mmol) is dissolved in xylene (300 mL) and NH₄OAc (92 g, 1192 mmol) is added. The reaction is heated to 140°C and stirred for 18 hours. After cooling to RT, the mixture is diluted with water and extracted with EtOAc. The combined organic layers are washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue is purified by flash chromatography using 33% EtOAc in heptanes to afford 26a3 (tR (min) 1.7; (M+H)⁺ 418.2/420.2).

Example 27
Preparation of intermediates 27a1 and 27a2

26a3 (600 mg, 1.43 mmol), bis(pinacolato)diboron (900 mg, 3.54 mmol), KOAc (560 mg, 5.7 mmol) and Pd(dpdpf)Cl₂ (60 mg, 0.07 mmol) are loaded in a 20 mL microwave vial. The solids are dissolved in DMF (6 mL). The reaction mixture is degassed with argon and stirred at 80°C overnight. The reaction mixture is partitioned between EtOAc and water. The solid in suspension is filtered. The organic layer is separated, washed with water and brine, dried with NaCl / Na₂SO₄, filtered and concentrated. The product is purified by flash chromatography using 0% to 5% EtOH in DCM. The product is triturated with n-hexane and the remaining solid is dried to afford a mixture of 27a1 (tR (min) 2.0; (M+H)⁺ 466.2) and 27a2 (tR (min) 1.4; (M+H)⁺ 384.1).
Example 28

Preparation of intermediate 28a1

26a3 (5 g, 12 mmol) is suspended in MeOH (50 mL). Concentrated HCl (9.6 mL, 120 mmol) is added and the mixture is stirred at 50°C overnight. The reaction mixture is concentrated. The residue is lyophilized to afford 28a1 (t_R (min) 1.8; (M+H)^+ 318.0/320.0).

Example 29

Preparation of intermediate 29a1

28a1 (4.6 g, 11.7 mmol) and 10b2 (3.1 g, 17.5 mmol) are dissolved in DMF (75 mL). DIPEA (10.2 mL, 58.3 mmol) is added followed by TBTU (5.6 g, 17.5 mmol) and the mixture is stirred for 16 hours. The reaction is concentrated to a volume of 15 mL. The mixture is partitioned between an aqueous solution of NH₄Cl and EtOAc. The layers are separated and the organic layer is extracted with an aqueous solution of Na₂CO₃, dried over Na₂SO₄, filtered and concentrated. The product is purified by flash chromatography using 0% to 7% MeOH in DCM to afford 29a1 (t_R (min) 1.5; (M+H)^+ 475.3/477.2).
Example 30

Preparation of intermediate 30a2

Step 1:

29a1 (204 mg, 0.43 mmol), a mixture of 27a1 and 27a2 (200 mg, 0.43 mmol) and a 2 M aqueous solution of Na₂CO₃ (0.7 mL, 1.4 mmol) are loaded in a 20 mL vial. DME (2.2 mL) is added and the reaction mixture is degassed with argon for 10 minutes. Pd(P(Ph)₃)₄ is added, the mixture is degassed with argon for 5 minutes and heated to 90°C for 60 hours. The reaction mixture is partitioned between EtOAc and water and the layers are separated. The aqueous layer is extracted with DCM. The combined organic layers are dried with MgSO₄, filtered and concentrated. The product is purified by flash chromatography using 0% to 10% MeOH in DCM to afford 30a1 (t_R (min) 1.6; (M+H)+ 634.2).

Step 2:

30a1 (267 mg, 0.36 mmol) is dissolved in a 4 M solution of HCl in 1,4-dioxane (1.8 mL, 7.3 mmol) and stirred at RT overnight. The mixture is concentrated and dried under high vacuum to afford 30a2.

Example 31

Preparation of compound 1008
30a2 (40 mg, 54 μmol), 13a1 (12.3 mg, 59 μmol) are loaded in a flask. DMF (0.5 mL), Et3N (37 μL, 269 μmol), TBTU (24.6 mg, 65 μmol) are added and the reaction is stirred at RT overnight. The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford 1008.

Example 32
Preparation of compound 1013

11a2 (8.8 mg, 60 μmol) is loaded in an 8 mL vial. Solutions of 30a2 (30 mg, 40 μmol) in DMF (0.5 mL) and HATU (20 mg, 53 μmol) in DMF (0.5 mL) are added followed by DIPEA (75 μL, 429 μmol). The mixture is stirred at RT for 1 hour and neutralized with AcOH (100 μL). The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford 1013.

The following compounds are prepared analogously to the procedure described in Example 32 starting from the appropriate amino acid derivative: 1009, 1010, 1011, 1012, 1014 and 1020.

Example 33
Preparation of compound 1022
To a solution of \textbf{30a2} (60 mg, 81 µmol) in DCM (1 mL) is added Et$_3$N (0.1 mL, 404 µmol) and a solution of \textbf{12a4} (39 mg, 161 µmol) in DCM (1 mL). The reaction mixture is stirred at RT for 4 hours and concentrated. The product is purified by preparative RP-HPLC. The fractions are concentrated and lyophilized to afford \textbf{1022}.

Example 34

HCV replicon RNA replication assay

\textit{HCV replicons:}

Two subgenomic replicons designated HCVPV1a and HCVPV1b are generated based on the wildtype sequence for genotype 1a, strain H77 (GenBank accession no. AF009606) and the wildtype sequence CON-1 genotype b (GenBank accession number AJ238799), see \textit{Science 1999, 285:} 110-113. HCV genotype 1a subgenomic fragment NS2-NS3-NS4A-NS4B-NS5A-NS5B is drawn from the reference nucleic acid encoding residues 811 to 3011 of AF009606, HCV genotype 1b subgenomic fragment NS2-NS3-NS4A-NS4B-NS5A-NS5B is drawn from the reference nucleic acid encoding residues 811 to 3010 of CON-1 (GenBank accession number AJ238799). Both subgenomic replicons contain a hybrid HCV-poliovirus (PV) 5'UTR, a modified luciferase reporter gene expressed as a luciferase-FMDV2A-neomycin phosphotransferase gene fusion and a NS2-NS5B subgenomic fragment with its 3'UTR. The replication of both HCV NS2-NS5B subgenomic replicons is enhanced by cell-culture adaptive mutations in the NS3 and the NS4B coding regions for the genotype 1a replicon and in the NS3, NS4A and NS5A coding regions for the genotype 1b.

Stable replicon cell lines are established as described, for example, in \textit{Science 1999, 285:} 110-113. The amount of luciferase expressed by selected cells directly correlates with the level of HCV RNA replication, as measured by real-time PCR.

\textit{HCV replicon RNA replication assay:} To generate cell lines harboring the replicon containing the NS3 substitutions, Huh-7 cells are electroporated with 1-10 µg of purified \textit{in vitro} transcripts and stable cell lines are selected in the presence of G418 (0.25 mg /ml).
The stable HCV replicon cells are maintained in Dulbecco’s Modified Eagle Medium (DMEM) supplemented with 10% FBS and 0.25 mg/ml G418 (standard medium). During the assay, DMEM supplemented with 10% FBS, containing 0.5% DMSO and lacking neomycin are used as assay medium.

For the assay, the cell stocks are trypsinized and diluted in assay medium to distribute 70 µl (8,000 ells) in black 96-well plates. The plates are then incubated at 37°C until compound addition. The test compound in 100% DMSO is first diluted in assay medium to a final DMSO concentration of 0.5%. Serial dilutions are prepared in assay medium to generate nine-concentration dose response curves. A fixed volume from each well of the compound dilution plate is transferred to a corresponding well of the cell culture plate. The cell culture plate is incubated at 37°C with 5% CO₂ for 72 hours. Following the 72h incubation period, the medium is aspirated from the 96-well assay plate and a volume of 50 µl of 1X Glo Lysis Buffer (Promega) is added to each well. The luciferase activity is determined using Bright-Glo luciferase substrate (Promega) according to the manufacturer’s instructions and the luminescence is detected on a Packard Topcount instrument. The luminescence (CPS) in each well of the culture plate is a measure of the amount of HCV RNA replication in the presence of various concentrations of inhibitor. The % inhibition is calculated for each inhibitor concentration and used to determine the concentration that results in 50% inhibition of HCV replication (EC₅₀).

TABLES OF COMPOUNDS

Representative compounds according to this invention are listed in Tables 1 and 2. All of the compounds listed in Tables 1 and 2 below are tested in the assay of Example 34.

All of the compounds in Tables 1 and 2 are synthesized analogously to the Examples described above. Retention times (tᵣ) for each compound are measured using the standard analytical HPLC or UPLC conditions described in the Examples. As is well known to one skilled in the art, retention time values are sensitive to the specific measurement conditions. Therefore, even if identical conditions of solvent, flow rate, linear gradient, and the like are used, the retention time values may vary
when measured, for example, on different HPLC or UPLC instruments. Even when measured on the same instrument, the values may vary when measured, for example, using different individual HPLC or UPLC columns, or, when measured on the same instrument and the same individual column, the values may vary, for example, between individual measurements taken on different occasions. A person skilled in the art will recognize that obvious modifications to the synthetic methods, including the amount of time indicated to perform the various steps, may be required to generate each of the specific compounds listed in Tables 1 and 2.

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Each reference, including all patents, patent applications, and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the...
above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.
What is claimed is:

1. A compound of Formula (I) or salt thereof:

   ![Chemical Structure](image)

   wherein
   
   \(Z^1, Z^2, Z^3, Z^4, Z^5\) and \(Z^6\) are each independently selected from \(\text{CH}\) or \(\text{N}\);
   
   \(R^A\) and \(R^B\) are each 1 or 2 substituents independently selected from hydrogen, \((\text{C}_{1-6})\text{alkyl}\), \((\text{C}_{1-6})\text{haloalkyl}\), halo, \(-\text{O}(\text{C}_{1-6})\text{alkyl}\), \(-\text{NH}_2\), \(-\text{NH}(\text{C}_{1-6})\text{alkyl}\), \(-\text{CN}\);
   
   \(R^1\) and \(R^2\) are each independently selected from \((\text{C}_{1-6})\text{alkyl}\), \((\text{C}_{3-7})\text{cycloalkyl}\) and \(-\text{(C}_{1-6})\text{alkyl-aryl}\);
   
   wherein each said alkyl, cycloalkyl and alkyl-aryl is optionally substituted 1 to 3 times with aryl, \(-\text{O}(\text{C}_{1-6})\text{alkyl}\), \(-\text{O}(\text{C}(=0))\text{alkyl}\), \(-\text{NH}(\text{C}_{1-6})\text{alkyl}\), \(-\text{N}(\text{C}(=0))\text{alkyl}\), \(-\text{N}(\text{C}(=0))\text{alkyl}\) and \(-\text{R}^1\text{R}^2\);
   
   \(R^f\) and \(R^g\) are independently selected from \(\text{H}\), \((\text{C}_{1-6})\text{alkyl}\) and \(-\text{C}(=0)\text{H}_2\) - \((\text{C}_{1-6})\text{alkyl}\).

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, having the formula:

   ![Chemical Structure](image)

   wherein \(R^1\) and \(R^2\) are as defined in claim 1.
3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, having the formula:

\[
\text{Chemical Structure}
\]

wherein \( R^1 \) and \( R^2 \) are as defined in claim 1.

4. The compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein \( R^1 \) is selected from \((C_{1-5})\text{alkyl,}
\( (C_3)\text{cycloalkyl and -(C}_{1-2}\text{-alkyl-phenyl;}
\)

wherein each said alkyl, cycloalkyl and alkyl-phenyl is optionally substituted 1 to 2 times with phenyl, \(-0-(C_{1-2})\text{alkyl and } -N(R^1)R^3; \)
\( R^1 \) and \( R^9 \) are independently selected from \( H, (C_{1-2})\text{alkyl and } -C(=0)0 - (C_{1-2})\text{alkyl.}

5. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein \( R^1 \) is selected from \( -52 - \)
6. The compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is selected from

![Chemical structures](image1)

and

![Chemical structures](image2)

7. The compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein $R^2$ is selected from $(C_{1-5})$-alkyl, $(C_3)$-cycloalkyl and $(C_2)$-alkyl-phenyl;

wherein each said alkyl, cycloalkyl and alkyl-phenyl is optionally substituted 1 to 2 times with phenyl, $-0-(C_{1-2})$-alkyl and $-N(R^4)R^5$; $R^4$ and $R^5$ are independently selected from $H$, $(C_{1-2})$-alkyl and $-C(=O)0$.

8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein $R^2$ is selected from
The compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein \( R^2 \) is selected from

\[
\text{and}
\]

9. The compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein \( R^2 \) is selected from

\[
\text{and}
\]

10. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, having the formula:

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11. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, having the formula:

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12. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 11 as a medicament.
13. A pharmaceutical composition comprising an anti-hepatitis C virally effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 11 in admixture with at least one pharmaceutically acceptable carrier medium or auxiliary agent.

14. The pharmaceutical composition according to claim 13 further comprising a therapeutically effective amount of at least one other antiviral agent.

15. Use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of hepatitis C viral infection in a human being.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC: C07D 519/00 (2006.01) , A61K 31/439 (2006.01) , A61K 31/444 (2006.01) , A61K 31/506 (2006.01) , A61P 31/14 (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**
Minimum documentation searched (classification system followed by classification symbols)
IPC (2006.01) : C07D, A61K, A61P

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN (chemical structure), Esp@cenet, Canadian Patent Database : keywords: hepatitis, , Boehringer (assignee)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C.

See patent family annex.

**Date of the actual completion of the international search**
9 March 2011 (09-03-2011)

**Date of mailing of the international search report**
8 April 2011 (08-04-2011)

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### Information on Patent Family Members

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