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(54) Benævnelse: **KOMBINATION AF DIREKTE VIRKENDE ANTIVIRALE MIDLER OG RIBAVIRIN TIL BEHANDLING AF HCV-PATIENTER**

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DESCRIPTION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/783,437, filed March 14, 2013.

FIELD OF THE INVENTION

[0002] The present invention relates to interferon-free treatment for hepatitis C virus (HCV).

BACKGROUND OF THE INVENTION

[0003] The HCV is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

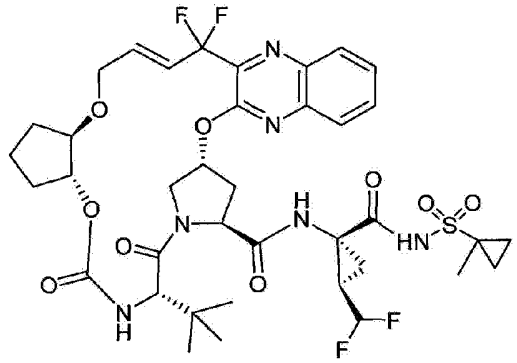
[0004] Chronic HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often incomplete. Therefore, there is a need for new therapies to treat HCV infection.

[0005] US 2012/070416 discloses compounds or pharmaceutically acceptable salts, esters, or prodrugs thereof which inhibit serine protease activity, particularly the activity of hepatitis C virus (HCV) NS3-NS4A protease. Consequently, these compounds interfere with the life cycle of the hepatitis C virus and are useful as antiviral agents. US 2012/004196 concerns compounds effective in inhibiting replication of Hepatitis C virus ("HCV"). This publication also relates to processes of making such compounds, compositions comprising such compounds, and methods of using such compounds to treat HCV infection.

BRIEF SUMMARY OF THE INVENTION

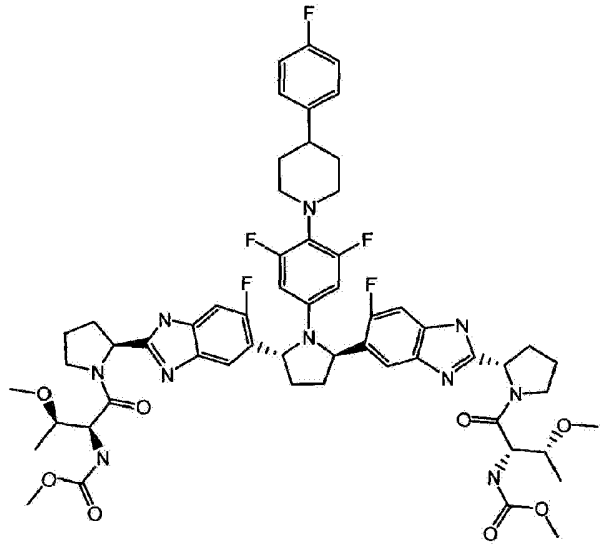
[0006] The present invention is directed to a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to

said patient, and said treatment lasts for 8, 9, 10, 11, 12 or 16 weeks, and wherein said at least two DAAs comprise:



Compound 1

or a pharmaceutically acceptable salt thereof, and



Compound 2

or a pharmaceutically acceptable salt thereof.

[0007] Thus, one aspect of the present invention relates to a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient, and said treatment is given to a subject in need of such treatment. The methods comprise administering at least two direct acting antiviral agents (DAAs) and ribavirin to the subject for a duration of no more than 12 weeks, or for another duration as set forth herein. The at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). Preferably, the duration of the treatment is 12 weeks. The duration of the treatment can also be, for example, no more than 8 weeks. Preferably, the two or more DAAs are administered in amounts effective to provide a sustained virological response (SVR) or achieve another desired measure of effectiveness in the subject. The subject is not administered interferon during the treatment regimen. Put another way, the methods exclude the administration of interferon to the subject, thereby avoiding the side effects associated with

interferon.

[0008] Another aspect of the present invention relates to a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient population, wherein said treatment does not include administration of interferon to said patient population, and said treatment is given for treating the population of subjects having HCV infection. The methods comprise administering at least two DAAs and ribavirin to the subjects for a duration of no more than 12 weeks. The at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). Preferably, the at least two DAAs are administered to the subjects in amounts effective to result in SVR or another measure of effectiveness in at least about 70% of the population, preferably at least about 80% of the population, or more preferably at least about 90% of the population.

[0009] In any method described herein, the at least two DAAs comprise (a) Compound 1 or a pharmaceutically acceptable salt thereof, and (b) Compound 2 or a pharmaceutically acceptable salt thereof. The at least two DAAs can also optionally comprise another anti-HCV agent. The other optional anti-HCV agent can be selected from protease inhibitors, nucleoside or nucleotide polymerase inhibitors, non-nucleoside polymerase inhibitors, NS3B inhibitors, NS4A inhibitors, NS5A inhibitors, NS5B inhibitors, cyclophilin inhibitors, or combinations thereof. For example, in some embodiments, the DAAs used in the present invention comprise or consist of (a) Compound 1 or a pharmaceutically acceptable salt thereof, and (b) Compound 2 or a pharmaceutically acceptable salt thereof. For another example, the DAAs used in the present invention comprise or consist of (a) Compound 1 or a pharmaceutically acceptable salt thereof, (b) Compound 2 or a pharmaceutically acceptable salt thereof, and (c) a HCV polymerase inhibitor, wherein said HCV polymerase inhibitor can be a nucleotide or nucleoside polymerase inhibitor or a non-nucleoside or non-nucleotide polymerase inhibitor.

[0010] Examples of the other optional antic-HCV agent include PSI-7977 (sofosbuvir), PSI-938, BMS-790052 (daclatasvir), BMS-650032 (asunaprevir), BMS-791325, GS-5885 (ledipasvir), GS-9451 (tegobuvir), GS-9190, GS-9256, BI-201335, BI-27127, telaprevir, VX-222, TMC-435 (simepravir), MK-5172, MK-7009 (vaniprevir), danoprevir, R7128 (mericitabine), and any combination thereof.

[0011] In any method described herein, the DAAs can be administered in any effective dosing schemes and/or frequencies; for example, they can each be administered daily. Each DAA can be administered either separately or in combination, and each DAA can be administered once a day, twice a day, or three times a day. Preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof) are administered once daily.

[0012] Preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 100 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically

acceptable salt thereof) is administered from 50 to 500 mg once daily. More preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 200 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. Highly preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 400 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. For instance, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered 120 mg once daily. For another instance, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) can be administered 240 mg once daily.

[0013] According to an aspect of the instant invention, Compound 1 (or the salt thereof) and Compound 2 (or the salt thereof) can be administered concurrently or sequentially. Preferably, Compound 1 (or the salt thereof) and Compound 2 (or the salt thereof) can be administered once daily. As an example, the patient being treated is infected with HCV genotype 1, such as genotype 1a or 1b. As another example, the patient is infected with HCV genotype 2. As another example, the patient is infected with HCV genotype 3. As another example, the patient is infected with HCV genotype 4. As another example, the patient is infected with HCV genotype 5. As another example, the patient is infected with HCV genotype 6. As yet another example, the patient is a HCV-treatment naive patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. As used in this application, the interferon non-responder patients include partial interferon responders and interferon rebound patients. *See* GUIDANCE FOR INDUSTRY - CHRONIC HEPATITIS C VIRUS INFECTION: DEVELOPING DIRECT-ACTING ANTIVIRAL AGENTS FOR TREATMENT (FDA, September 2010, draft guidance) for the definitions of naive, partial responder, responder relapser (i.e., rebound), and null responder patients. The interferon non-responder patients also include null responder patients. In one example of this aspect of the invention, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naive patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naive patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naive patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naive patient infected with HCV genotype 3. In yet another example, the treatment

lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3.

[0014] A treatment regimen as encompassed in the present invention generally constitutes a complete treatment regimen, i.e., no subsequent interferon-containing regimen is intended. Thus, a treatment or use described herein generally does not include any subsequent interferon-containing treatment. The present invention is defined in the appended claims. Subject matters which are not encompassed by the scope of the claims do not form part of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015]

Figure 1 shows the predicted median SVR percentages and 90% SVR confidence intervals for interferon-free, 2-DAA regimens comprising the use of Compound 1 (400 mg once daily) and Compound 2 (120 mg once daily) for use to treat genotype 1 naïve subjects.

Figure 2 illustrates the predicted median SVR percentages and 90% SVR confidence intervals for interferon-free, 2-DAA regimens comprising the use of Compound 1 (400 mg once daily) and Compound 2 (60 mg once daily) for use to treat genotype 1 naïve subjects.

Figure 3 depicts the predicted median SVR percentages and 90% SVR confidence intervals for interferon-free, 2-DAA regimens comprising the use of Compound 1 (600 mg once daily) and Compound 2 (480 mg once daily) for use to treat genotype 1 naïve subjects.

Figure 4 shows the predicted median SVR percentages and 90% SVR confidence intervals for interferon-free, 2-DAA regimens comprising the use of Compound 1 (400 mg once daily) and Compound 2 (120 mg once daily) for use to treat genotype 3 naive subjects.

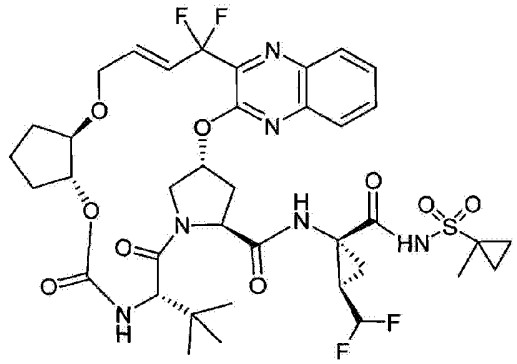
Figure 5 illustrates the predicted median SVR percentages and 90% SVR confidence intervals for interferon-free, 2-DAA regimens comprising the use of Compound 1 (400 mg once daily) and Compound 2 (60 mg once daily) for use to treat genotype 3 naive subjects.

Figure 6 shows the predicted median SVR percentages and 90% SVR confidence intervals for interferon-free, 2-DAA regimens comprising the use of Compound 1 (600 mg once daily) and Compound 2 (480 mg once daily) for use to treat genotype 3 naïve subjects.

Figure 7 depicts the synergistic effect of the combination of Compound 1 and Compound 2 on HCV inhibition *in vitro*.

DETAILED DESCRIPTION OF THE INVENTION

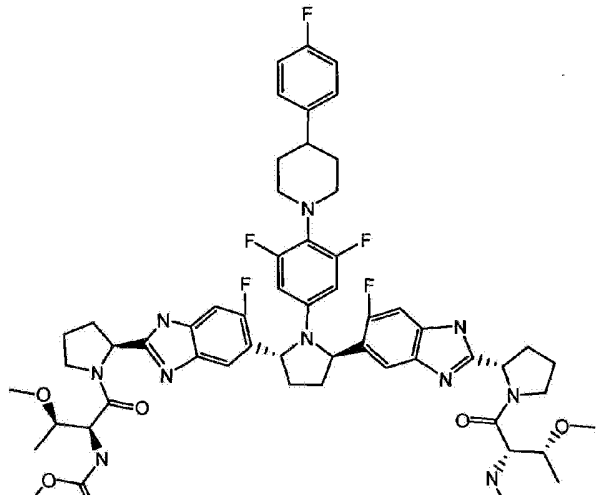
[0016] The aspects of the present invention include administering Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof) and ribavirin to a subject in need thereof. Compound 1 has the following structure:



Compound 1

Compound 1 is a potent HCV protease inhibitor and is described in U.S. Patent Application Publication No. 2012/0070416.

[0017] Compound 2 has the following structure:



Compound 2

Compound 2 is a potent NS5A inhibitor and is described in U.S. Patent Application Publication No. 2012/0220562.

[0018] The current standard of care (SOC) for the treatment of HCV includes a course of treatment of interferon, e.g. pegylated interferon (e.g., pegylated interferon-alpha-2a or pegylated interferon-alpha-2b, such as PEGASYS by Roche, or PEG-INTRON by Schering-Plough) and the antiviral drug ribavirin (e.g., COPEGUS by Roche, REBETOL by Schering-Plough, or RIBASPHERE by Three Rivers Pharmaceuticals). The treatment often lasts for 24-48 weeks, depending on hepatitis C virus genotype. Other interferons include interferon-alpha-2a (e.g., Roferon-A by Roche), interferon-alpha-2b (e.g., Intron-A by Schering-Plough), and interferon alfacon-1 (consensus interferon) (e.g., Infergen by Valeant).

[0019] The interferon-based treatment may be physically demanding, and can lead to temporary disability in some cases. A substantial proportion of patients will experience a panoply of side effects ranging from a "flu-like" syndrome (the most common, experienced for a few days after the weekly injection of interferon) to severe adverse events including anemia, cardiovascular events and psychiatric problems such as suicide or suicidal ideation. The latter are exacerbated by the general physiological stress experienced by the patients.

[0020] The present invention is directed to a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient, in order to provide effective treatment of HCV infection without the use of interferon and for a shorter period of time, for example and without limitation, a treatment duration of no more than 16 weeks, alternatively no more than twelve weeks, alternatively no more than eleven weeks, alternatively no more than ten weeks, alternatively no more than nine weeks, or alternatively no more than eight weeks.

[0021] In one aspect, the present invention encompasses methods for treating HCV infection in a subject comprising administering at least two DAAs and ribavirin, in the absence of interferon, to the subject for a duration of no more than twelve weeks, alternatively no more than eight weeks. Put another way, the methods exclude interferon. The at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof), which can be co-administered, or administered separately or independently, with the same or different dosing frequencies. Preferably, the at least two DAAs are administered once a day. They can also be administered, for example, twice a day or three times a day.

[0022] Various measures may be used to express the effectiveness of a method encompassed by the present invention. One such measure is SVR, which, as used herein,

means that the virus is undetectable at the end of therapy and for at least 8 weeks after the end of therapy (SVR8); preferably, the virus is undetectable at the end of therapy and for at least 12 weeks after the end of therapy (SVR12); more preferably, the virus is undetectable at the end of therapy and for at least 16 weeks after the end of therapy (SVR16); and highly preferably, the virus is undetectable at the end of therapy and for at least 24 weeks after the end of therapy (SVR24). SVR24 is often considered as a functional definition of cure; and a high rate of SVR at less than 24 week post-treatment (e.g., SVR8 or SVR12) can be predictive of a high rate of SVR24.

[0023] In some embodiments, a treatment regimen encompassed by the invention comprises treating a population of subjects having HCV infection (e.g. treatment naïve subjects), and the regimen comprises administering at least two DAAs and ribavirin to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein the at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof), and are administered to the subjects in amounts effective to provide an SVR (e.g., SVR12 or SVR24) in at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, alternatively about 100% of the population. In some embodiments, a treatment regimen encompassed by the invention comprises treating a population of IFN experienced subjects (e.g., interferon non-responders) having HCV infection, and the method comprises administering at least two DAAs and ribavirin to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein the at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof), and are administered to the subjects in amounts effective to provide an SVR (e.g., SVR12 or SVR24) in at least about 50% of the population, alternatively at least about 55% of the population, alternatively at least about 60% of the population, alternatively at least about 65% of the population, alternatively at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, or alternatively about 100% of the population.

[0024] It was unexpected that an interferon-free treatment using a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof) and ribavirin, and for a duration of no more than 12 weeks, can achieve significant SVR.

[0025] Accordingly, in one aspect, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient, said treatment comprising administering to a patient in need thereof ribavirin and an effective amount of the combination of the at least two

DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 8 weeks and does not include administration of any interferon. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0026] In yet another aspect, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient, said treatment comprising administering to a patient in need thereof ribavirin and an effective amount of the combination of the at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 16 weeks) and does not include administration of any interferon. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0027] In yet another aspect, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include

administration of interferon to said patient, said treatment comprising administering to a patient in need thereof ribavirin and an effective amount of the combination of the at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 12 weeks and does not include administration of any interferon. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir. As used in this application, a HCV polymerase inhibitor can be a nucleoside polymerase inhibitor, a nucleotide polymerase inhibitor, a non-nucleoside polymerase inhibitor, or a non-nucleotide polymerase inhibitor.

[0028] In yet another aspect, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient, said treatment comprising administering to a patient in need thereof ribavirin and an effective amount of the combination of the at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 11 weeks and does not include administration of any interferon. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0029] In yet another aspect, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient, said treatment comprising administering to a patient in need thereof ribavirin and an effective amount of the combination of the at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 10 weeks and does not include administration of any interferon. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0030] In yet another aspect, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient, said treatment comprising administering to a patient in need thereof ribavirin and an effective amount of the combination of the at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 9 weeks and does not include administration of any interferon. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0031] In each aspect, embodiment, example or method described herein, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered, for example and without limitation, from 100 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) can be administered, for example and without limitation, from 50 to 500 mg once daily. More preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 200 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. Highly preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 400 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. Preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered 120 mg once daily. Also preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) can be administered 240 mg once daily.

[0032] In each aspect, embodiment, example or method described herein, ribavirin can be any suitable form or formulation of ribavirin including its well-known pro-drugs. Exemplary formulations of ribavirin include COPEGUS®, REBETOL® and RIBASPHERE®. An exemplary pro-drug of ribavirin is taribavirin having the chemical name of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamidine. Ribavirin and taribavirin may be administered in accordance with ribavirin and taribavirin administration well known in the art. In some embodiments, COPEGUS® or REBETOL® is administered in a daily dosage amount of from about 500 mg to about 1500 mg in one dose or in divided doses. In some embodiments, COPEGUS® or REBETOL® is administered in a daily dosage amount of about 800 mg. In some embodiments, REBETOL® is administered in a daily dosage amount of about 1000 mg. In some embodiments, COPEGUS® or REBETOL® is administered in a daily dosage amount of about 1200 mg. In some embodiments, REBETOL® is administered in a daily dosage amount of about 1400 mg. Suitable dosages of ribavirin are often dependent on the weight of the subject, for example about 1000-1200 mg. Suitable total daily dosages of ribavirin include, but are not limited to about 400 mg to about 1400 mg a day, alternatively about 800 mg to about 1400 mg per day, alternatively about 400 mg to about 1200 mg, alternatively about 800 mg to about 1200 mg.

[0033] A method encompassed by the present invention can be used to treat a naïve patient or a treatment experienced patient. Treatment experienced patients include interferon non-responders (e.g., null responders), partial responders, and relapsers. A method encompassed by the present invention can also be used to treat patients who are not candidates for interferon treatment. Patients who are not candidates for interferon treatment include one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking

interferon.

[0034] In any method described herein, one or more additional DAAs can be optionally used in the treatment regimen in addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). These additional DAAs can be HCV protease inhibitors, HCV nucleoside or nucleotide polymerase inhibitors, HCV non-nucleoside polymerase inhibitors, HCV NS3B inhibitors, HCV NS4A inhibitors, HCV NS5A inhibitors, HCV NS5B inhibitors, HCV entry inhibitors, cyclophilin inhibitors, or combinations thereof.

[0035] Preferred HCV protease inhibitors for this purpose include telaprevir (Vertex), boceprevir (Merck), BI-201335 (Boehringer Ingelheim), GS-9451 (Gilead), and BMS-650032 (BMS). Other suitable protease inhibitors include ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BMS-650032 (BMS), danoprevir (RG7227/ITMN-191, Roche), GS-9132 (Gilead), GS-9256 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir (Schering-Plough Corp), PHX-1766 (Phenomix), TMC-435 (Tibotec), vaniprevir (MK-7009, Merck), VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof.

[0036] Preferred non-nucleoside HCV polymerase inhibitors for use in the present invention include GS-9190 (Gilead), BI-207127 (Boehringer Ingelheim), and VX-222 (VCH-222) (Vertex & ViraChem). Preferred nucleotide HCV polymerase inhibitors include PSI-7977 (Gilead), and PSI-938 (Gilead). Other suitable examples of suitable HCV polymerase inhibitors include ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination thereof. A polymerase inhibitor may be a nucleoside or nucleotide polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Gilead), PSI-938 (Gilead), RG7128 (Roche), TMC64912 (Medivir), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination therefore. A polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as PF-00868554 (Pfizer), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir (Gilead)" TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof.

[0037] Preferred NS5A inhibitors include BMS-790052 (BMS) and GS-5885 (Gilead). Non-limiting examples of suitable NS5A inhibitors include GSK62336805 (GlaxoSmithKline), ACH-2928 (Achillion), AZD2836 (Astra-Zeneca), AZD7295 (Astra-Zeneca), BMS-790052 (BMS), BMS-824393 (BMS), GS-5885 (Gilead), PPI-1301 (Presidio), PPI-461 (Presidio) A-831 (Arrow

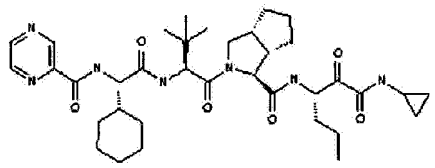
Therapeutics), A-689 (Arrow Therapeutics) or a combination thereof.

[0038] Non-limiting examples of suitable cyclophilin inhibitors include alisporovir (Novartis & Debiopharm), NM-811 (Novartis), SCY-635 (Scynexis), or a combination thereof.

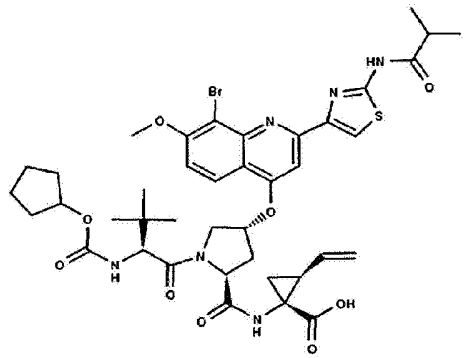
[0039] Non-limiting examples of suitable HCV entry inhibitors include ITX-4520 (iTherx), ITX-5061 (iTherx), or a combination thereof.

[0040] Specific examples of other DAA agents that are suitable for inclusion in a method encompassed by the present invention include AP-H005, A-831 (Arrow Therapeutics) (NS5A inhibitor), A-689 (Arrow Therapeutics) (NS5A inhibitor), INX08189 (Inhibitex) (polymerase inhibitor), ITMN-191 (Intermune/Roche) (NS3/4A Protease inhibitor), VBY-376 (Protease Inhibitor) (Virobay), ACH-1625 (Achillion, Protease inhibitor), IDX136 (Idenix, Protease Inhibitor), IDX316 (Idenix, Protease inhibitor), VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191 (Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), R7128 (Roche), PF-868554 (Pfizer) (non-nucleoside polymerase inhibitor), PF-4878691 (Pfizer), IDX-184 (Idenix), IDX-375 (Idenix, NS5B polymerase inhibitor), PPI-461 (Presidio), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), CTS-1027 (Conatus), GS-9620 (Gilead), PF-4878691 (Pfizer), RO5303253 (Roche), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), GSK62336805 (GlaxoSmithKline), or any combinations thereof.

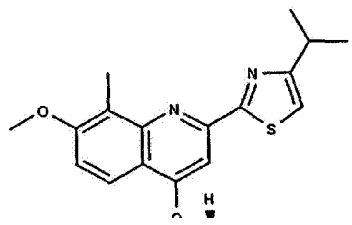
[0041] The chemical structures of some of these optional HCV inhibitors are provided below:

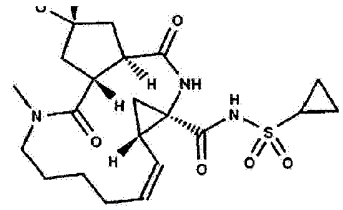


Telaprevir

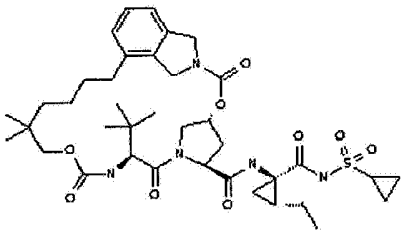


BI-201335

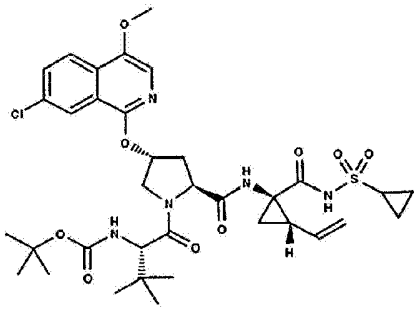




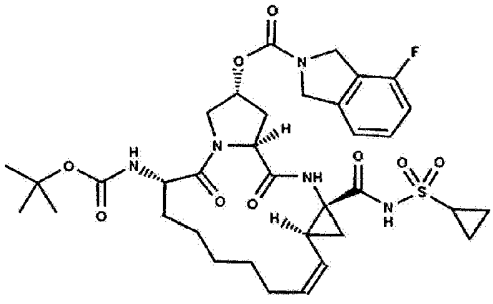
TMC-435 (TMC-435350)



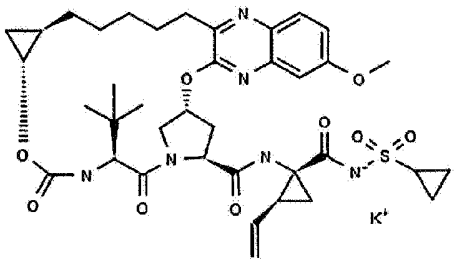
Vaniprevir, MK-7009



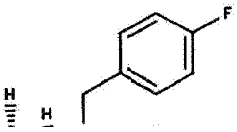
BMS-650032 (Asunaprevir)

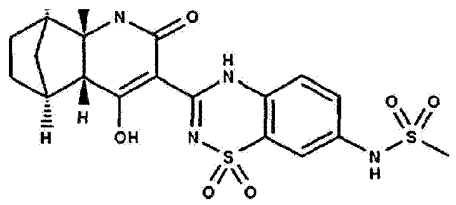


danoprevir

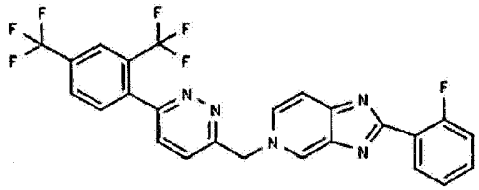


MK-5172

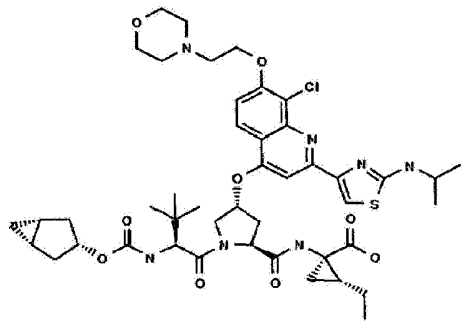




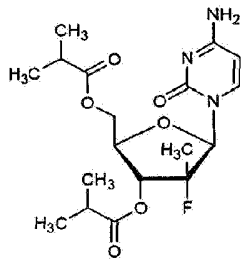
ANA-598 (Setrobuvir)



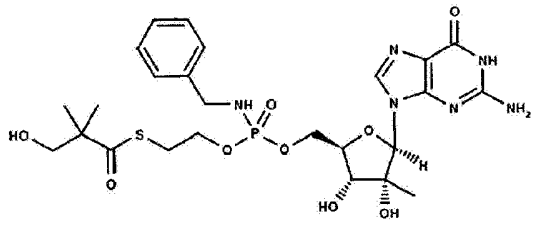
GS-333126 (GS-9190 or tegobuvir)



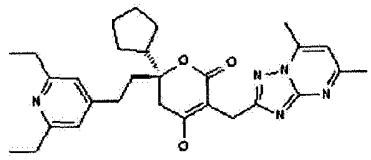
GS-9451



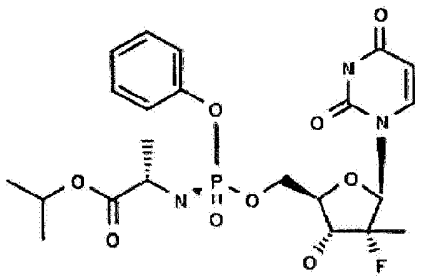
Mericitabine (R-4048 or RG7128)



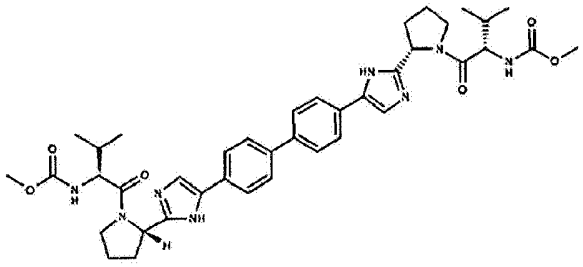
IDX-184



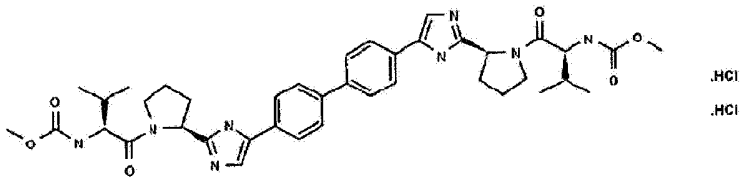
filibuvir (PF-00868554)



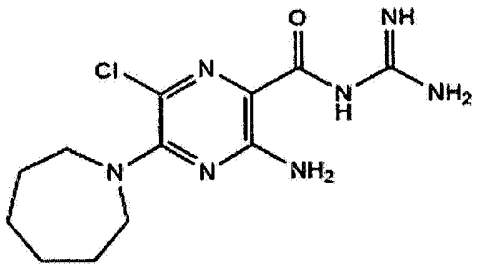
PSI-7977



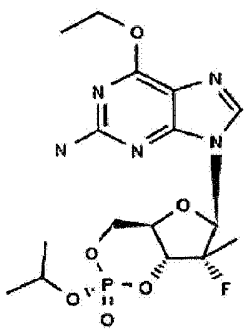
BMS-790052 (daclatasvir)



Daclatasvir dihydrochloride



BIT-225



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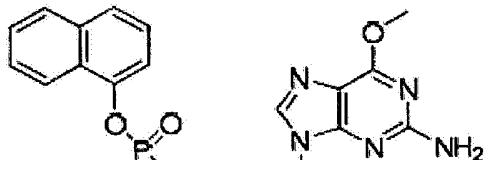
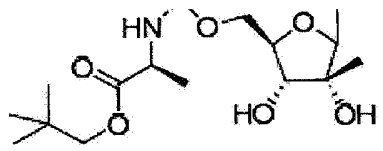
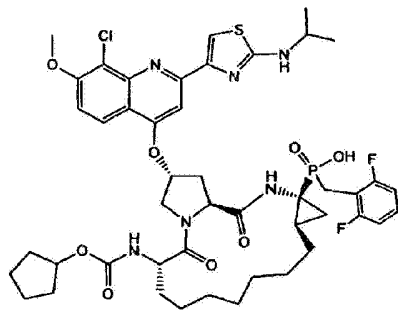
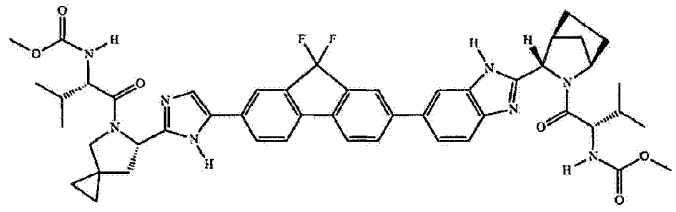




INX-189



GS-9256



GS-5885

[0042] Any HCV inhibitor or DAA described herein encompasses its suitable salt forms when it is used in therapeutic treatments or pharmaceutical formulations.

[0043] In some embodiments, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient and is carried out for treating patients infected with HCV genotype 1, such as 1a or 1b. The methods comprise administering to such a patient the combination of the at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0044] In some embodiments, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient and is carried out for treating patients with HCV genotype 2 or 3 infection. The methods comprise administering to such a patient the combination of the at least 2 DAAs and ribavirin for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0045] In some embodiments, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient and is carried out for treating patients with HCV genotype 2 infection. The methods comprise administering to such a patient the combination of the at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0046] In some embodiments, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient and is carried out for treating patients with HCV genotype 3 infection. The methods comprise administering to such a patient the combination of the at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include

administration of interferon, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0047] In some embodiments, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient and is carried out for treating patients with HCV genotype 4 infection. The methods comprise administering to such a patient the combination of the at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0048] In some embodiments, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient and is carried out for treating patients with HCV genotype 5 infection. The methods comprise administering to such a patient the combination of the at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, e.g., the

duration being 12 weeks, or the duration being 8 weeks.

[0049] In some embodiments, the present invention concerns a combination of at least two direct acting antiviral agents (DAAs) and ribavirin for use in a method for treatment of hepatitis C virus infection, said method comprising administering the said combination of at least two DAAs and ribavirin to an hepatitis C virus patient, wherein said treatment does not include administration of interferon to said patient and is carried out for treating patients with HCV genotype 6 infection. The methods comprise administering to such a patient the combination of the at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of interferon, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0050] It will be understood that the specific dose level 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, route of administration, rate of excretion, drug combination, and the severity of the disease undergoing therapy.

[0051] In any method described herein, Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) may be co-formulated in a single dosage form. Non-limiting examples of suitable dosage forms include liquid or solid dosage forms. Preferably, Compound 1 and Compound 2 are formulated in a single solid dosage form in which at least one of the DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. The other DAAs can also be in an amorphous form or molecularly dispersed in the matrix, or formulated in different form(s) (e.g., in a crystalline form). More preferably, each of the two DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant.

[0052] In any method described herein, the patient being treated can be a treatment-naïve patient.

[0053] In any method described herein, the patient being treated can be an interferon non-responder.

[0054] In any method described herein, the patient being treated can be an interferon null-

responder.

[0055] In any method described herein, the patient being treated can be without cirrhosis.

[0056] In any method described herein, the patient being treated can be a cirrhotic patient.

[0057] In any method described herein, the patient being treated can be a patient with compensated cirrhosis.

Example 1. Clinical Modeling for Interferon-free DAA Combination Therapies

[0058] Treatment regimens comprising administration of Compound 1 and Compound 2 were evaluated using clinical models described in example 6 of U.S. Patent Application Publication No. 2013/0102526, filed October 19, 2012 and entitled "Methods for Treating HCV", which example 6 is incorporated herein by reference. These treatment regimens comprised administration of Compound 1 and Compound 2, but did not include administration of either interferon or ribavirin. However, similar SVR rates are expected when ribavirin is added to these regimens.

[0059] Figure 1 shows the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimens consisting of the use of Compound 1 (400 mg once daily) and Compound 2 (120 mg once daily) to treat genotype 1 naïve subjects. Different treatment durations were assessed. The predicted SVR rate for a 12-week treatment was about 95%. As used in all of the figures of the present application, the vertical bar at the top of each SVR percentage column represents the 90% SVR confidence interval, and the x-axis ("Time (weeks)") indicates the duration of each treatment regimen.

[0060] Figure 2 illustrates the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimens consisting of the use of Compound 1 (400 mg once daily) and Compound 2 (60 mg once daily) to treat genotype 1 naïve subjects. Different treatment durations were assessed. The predicted SVR rate for a 12-week treatment was about 85-90%.

[0061] Figure 3 shows the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimens consisting of the use of Compound 1 (600 mg once daily) and Compound 2 (480 mg once daily) to treat genotype 1 naïve subjects. Different treatment durations were assessed. The predicted SVR rate for a 12-week treatment was about 100%.

[0062] Figure 4 depicts the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimen consisting of the use of Compound 1 (400 mg once daily) and Compound 2 (120 mg once daily) to treat genotype 3 naïve subjects. Different treatment durations were assessed. The predicted SVR rate for a 12-week treatment was about 95%.

[0063] Figure 5 illustrates the predicted median SVR percentages and 90% SVR confidence

intervals for 2-DAA regimen consisting of the use of Compound 1 (400 mg once daily) and Compound 2 (60 mg once daily) to treat genotype 3 naive subjects. Different treatment durations were assessed. The predicted SVR rate of a 12-week treatment was about 85-90%.

[0064] Figure 6 shows the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimens consisting of the use of Compound 1 (600 mg once daily) and Compound 2 (480 mg once daily) to treat genotype 3 naïve subjects. Different treatment durations were assessed. The predicted SVR rate of a 12-week treatment was about 100%.

Example 2. Combination of Compound 1 and Compound 2 *In Vitro*

[0065] Figure 7 shows that the combination of Compound 1 and Compound 2 exhibits significant synergistic effect on HCV inhibition as tested in HCV GT 1b Con-1 replication cells. The result was generated using Prichard and Shipman model (Prichard et al. ANTIVIRAL RESEARCH 14:181-205 (1990)).

[0066] Compound 1 inhibited replication of HCV stable subgenomic replicons containing NS3 genes from GT 1a, 1b, 2a, 3a, 4a, or 6a with EC_{50} values ranging from 0.85 to 2.8 nM. Of note, Compound 1 was potent against replicon containing GT3a protease, with an EC_{50} value of 1.6 nM. Compound 1 retained its activity against common GT1a and 1b variants at NS3 amino acid positions 155 and 168 that conferred resistance to other HCV protease inhibitors (Pis). Resistant colony selection studies in GT1a and 1b subgenomic replicon cells identified A156T in GT1a and A156V in GT1b as the most frequent variants, which conferred 1400- and 1800-fold reduced susceptibility to Compound 1, respectively. However, these variants had *in vitro* replication capacities of only 1.5% and 9.2% that of their corresponding wild-type replicons. In a replicon containing GT3a NS3 protease, Compound 1 selected very few colonies at concentrations ≥ 100-fold over its EC50 value. The colonies that survived the selection contained either A156G alone, or Q168R co-selected with Y56H, which conferred 1500- or 1100-fold loss in susceptibility to Compound 1, respectively.

Table 2. Antiviral Activity of Compound 1 in the HCV Subgenomic Stable Replicon Cell Culture Assay

HCV Replicon Subtype	N[b]	0% Human Plasma[a] Mean EC_{50}, nM, ± Std. Dev.
Genotype 1a	9	0.85 ± 0.15
Genotype 1b	8	0.94 ± 0.35
Genotype 2a	2	2.7 ± 1.1
Genotype 3a	2	1.6 ± 0.49
Genotype 4a	4	2.8 ± 0.41
Genotype 6a	4	0.86 ± 0.11

a. The 0% human plasma assay contains 5% fetal bovine serum

b. Number of independent replicates

Table 3. Antiviral Activity of Compound 1 in the HCV Subgenomic Stable Replicon Cell Culture Assay

HCV Replicon Subtype	N[b]	40% Human Plasma[a] Mean EC_{50}, nM, ± Std. Dev.
Genotype 1a	10	5.3 ± 1.0
Genotype 1b	8	10 ± 5.0

a. The 0% human plasma assay contains 5% fetal bovine serum
b. Number of independent replicates

[0067] When tested against common HCV genotype 1 NS3 resistance-associated variants, such as V36M, R155K, D168A and D168V in GT 1a (H77), or T54A, R155K, D168V and V170A in GT 1b (Con-1), Compound 1 showed inhibitory activity nearly equivalent to that against wild-type HCV replicon. Compound 1 was also shown to have potent activity against many NS5A inhibitor and NS5B inhibitor resistance-associated variants *in vitro* (e.g., M28T, M28V, Q30D, Q30R, Y93C, Y93H, Y93N, L31V+Y93H, C316Y, M414T, Y448C, Y448H, S556G and S559G in GT 1a, and L28T, Y93H, S282T, C316Y, Y448H and S556G in GT 1b).

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

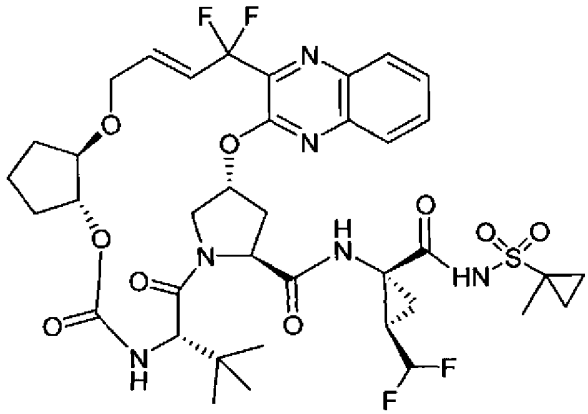
- US61783437A **[0001]**
- US2012070416A **[0005]**
- US2012004196A **[0005]**
- US20120070416A **[0016]**
- US20120220562A **[0017]**
- US20130102526A **[0058]**

Non-patent literature cited in the description

- **PRICHARD et al.**ANTIVIRAL RESEARCH, 1990, vol. 14, 181-205 [0065]

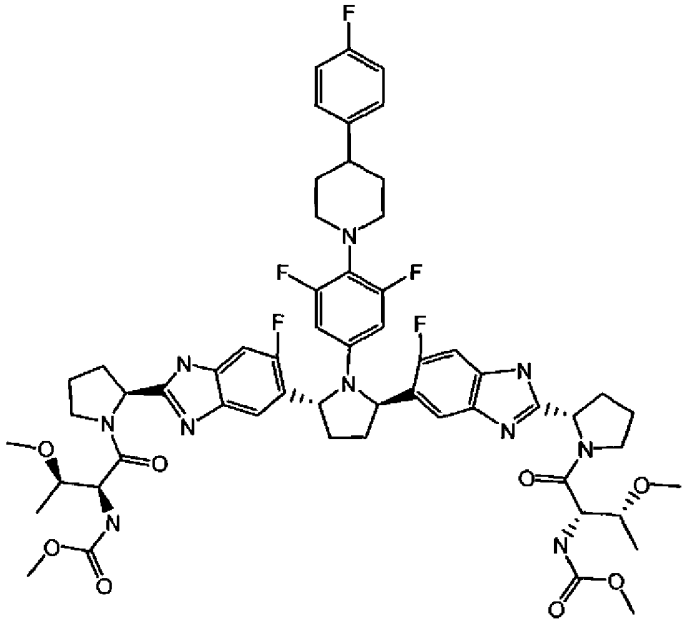
Patentkrav

1. Kombination af mindst to direkte virkende antivirale midler (DAA'er) og ribavirin til anvendelse i en fremgangsmåde til behandling af hepatitis C-virusinfektion, hvilken fremgangsmåde omfatter administrering af kombinationen af mindst to DAA'er og ribavirin til en hepatitis C-viruspatient, hvor behandlingen ikke indbefatter administration af interferon til patienten, og behandlingen varer i 8, 9, 10, 11, 12 eller 16 uger, og hvor de mindst to DAA'er omfatter:



Forbindelse 1

eller et farmaceutisk acceptabelt salt deraf og <



Forbindelse 2

2. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge krav 1, hvor behandlingen varer i 12 uger.

3. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge krav 1, hvor behandlingen varer i 8 uger.

4. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er inficeret med hepatitis C-virusgenotype 1.

5. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er inficeret med hepatitis C-virusgenotype 1a.

6. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er inficeret med hepatitis C-virusgenotype 2.

7. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er inficeret med hepatitis C-virusgenotype 3.

8. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er inficeret med hepatitis C-virusgenotype 4.

9. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er inficeret med hepatitis C-virusgenotype 5.

10. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er inficeret med hepatitis C-virusgenotype 6.

11. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten ikke har cirrose.

12. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten har kompenseret cirrose.

13. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er en behandlingsnaiv patient.

14. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er en interferon-non-responder.

15. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-3, hvor patienten er en behandlingserfaren patient.

16. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-15, hvor de mindst to DAA'er består af (1) forbindelse 1 eller et farmaceutisk acceptabelt salt deraf og (2) forbindelse 2 eller et farmaceutisk acceptabelt salt deraf.

17. Kombination af mindst to DAA'er og ribavirin til anvendelse ifølge et hvilket som helst af kravene 1-16, hvor forbindelse 1 eller et farmaceutisk acceptabelt salt deraf og forbindelse 2 eller et farmaceutisk acceptabelt salt deraf administreres en gang dagligt til patienten.

DRAWINGS

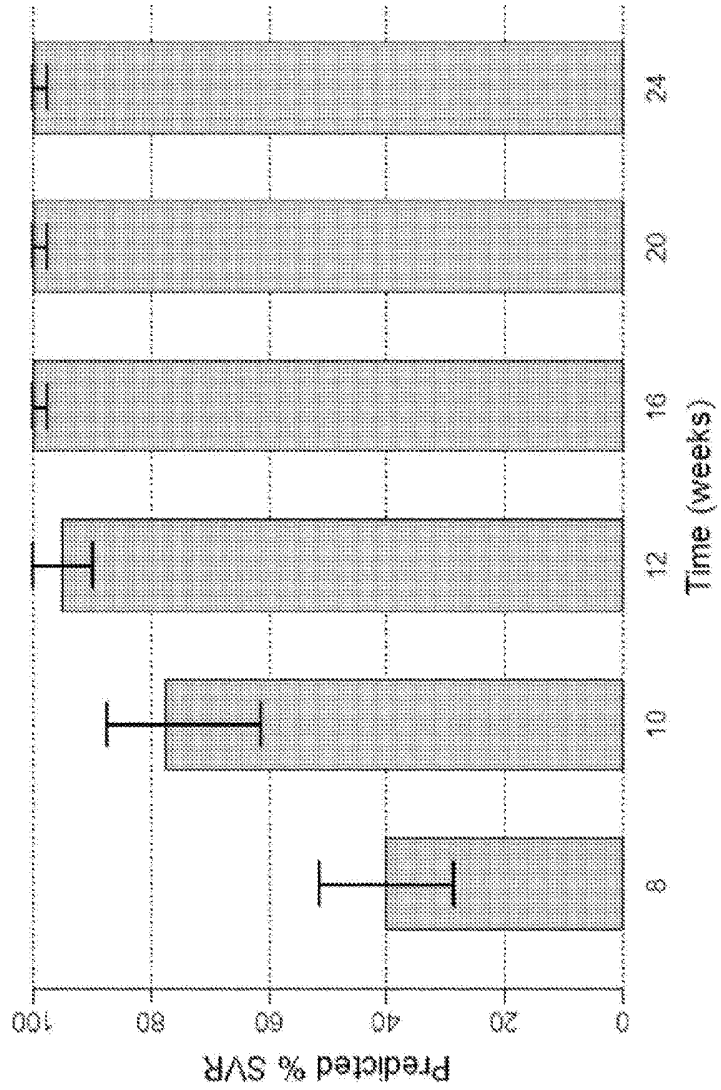


Figure 1

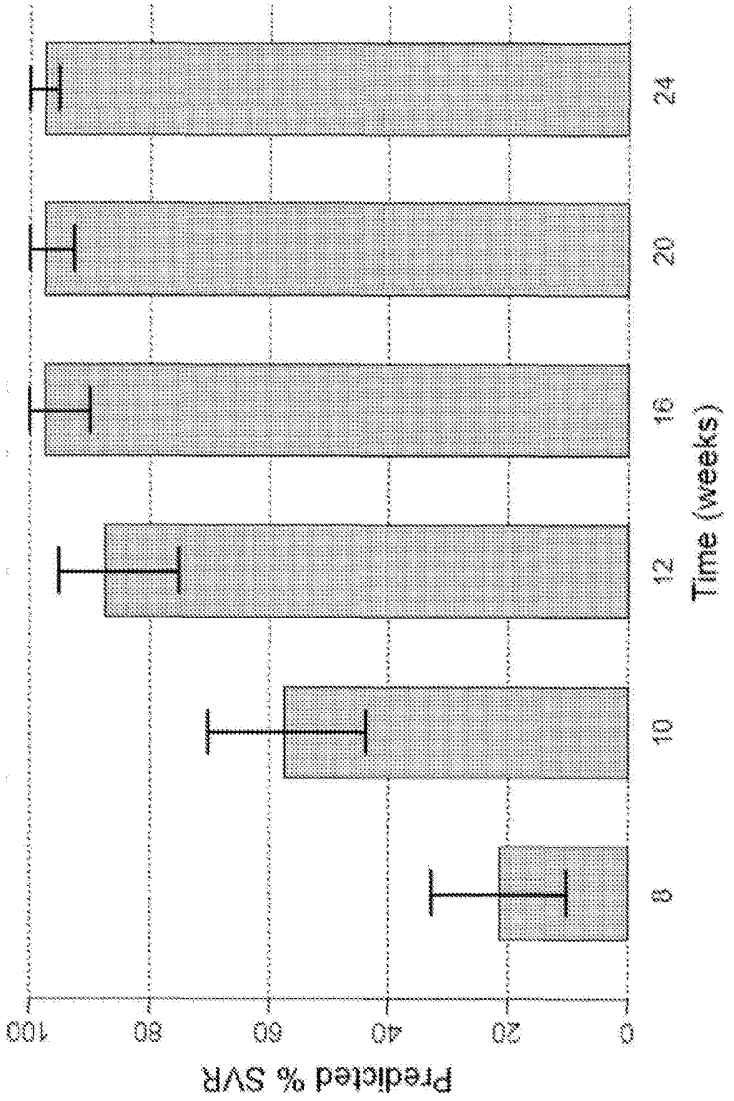


Figure 2

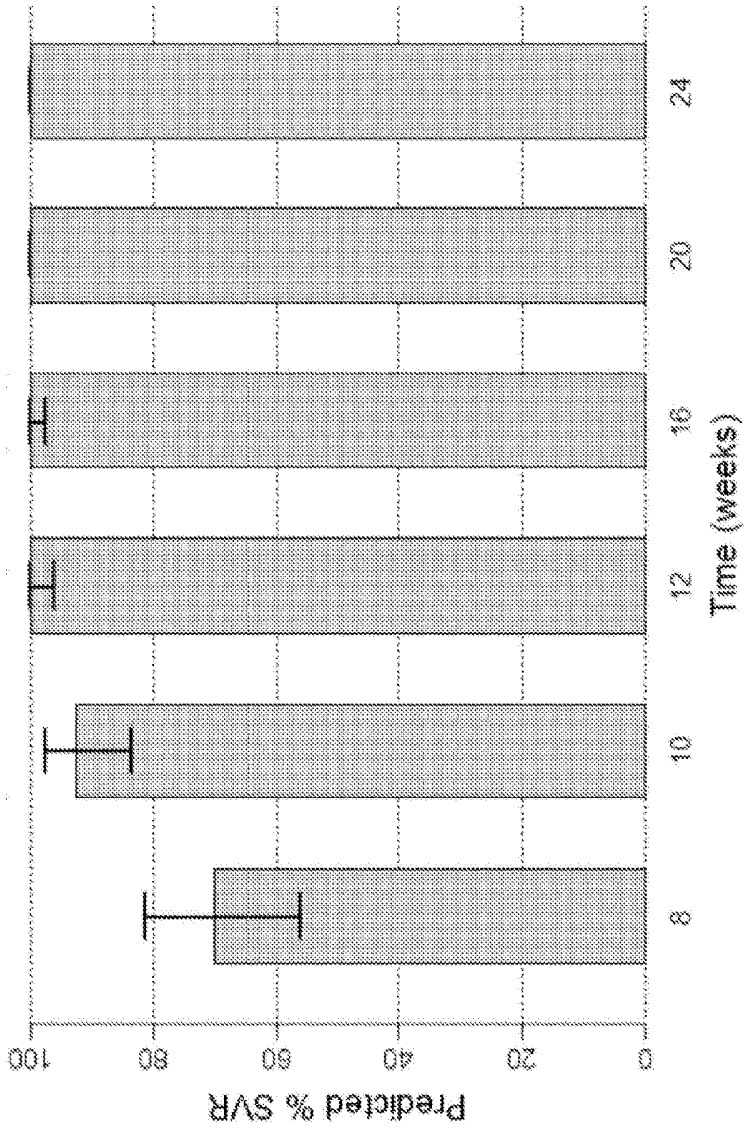


Figure 3

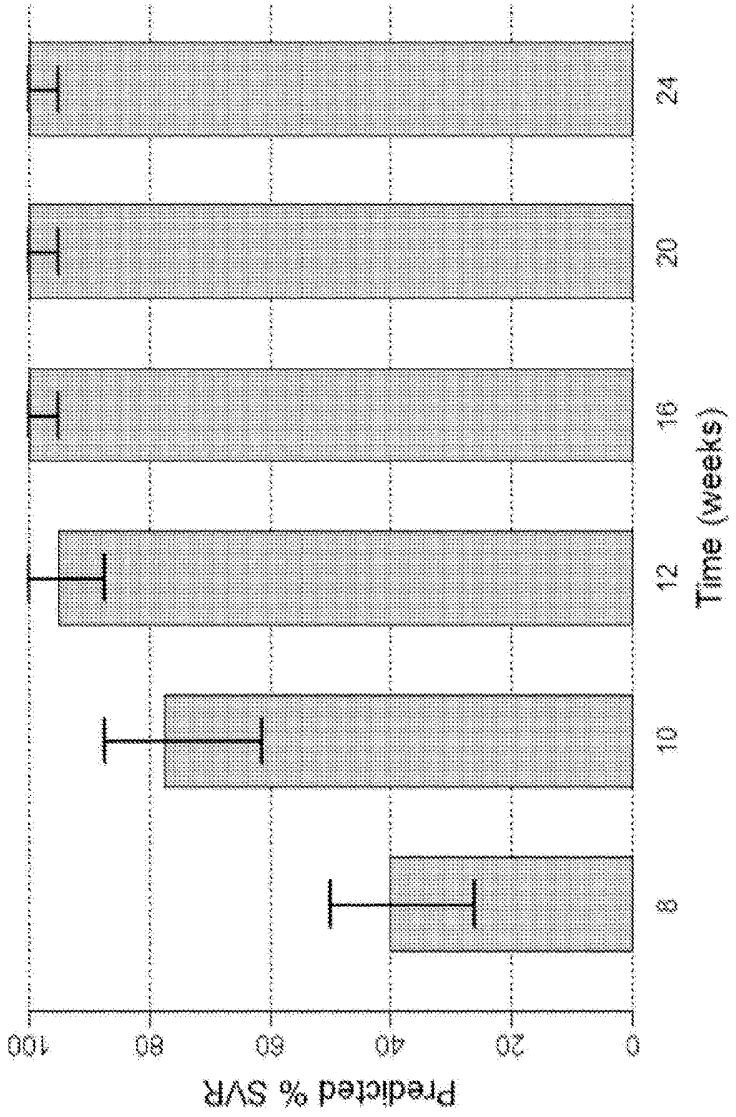


Figure 4

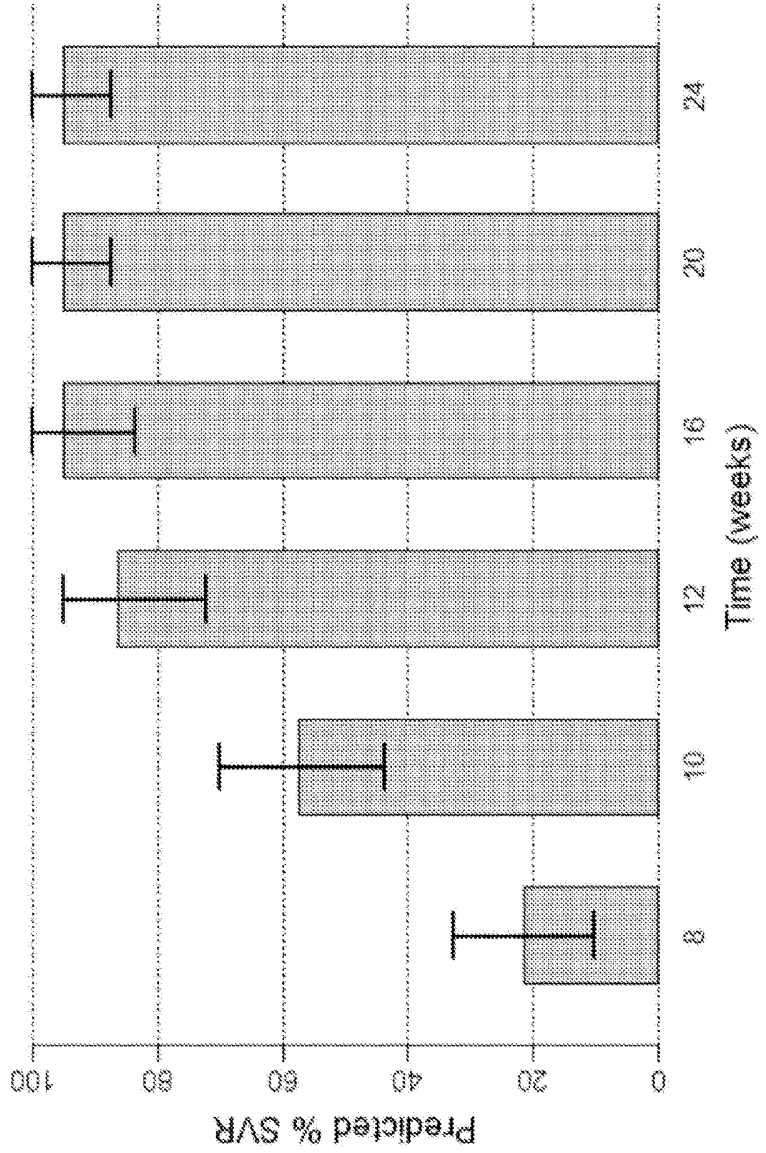


Figure 5

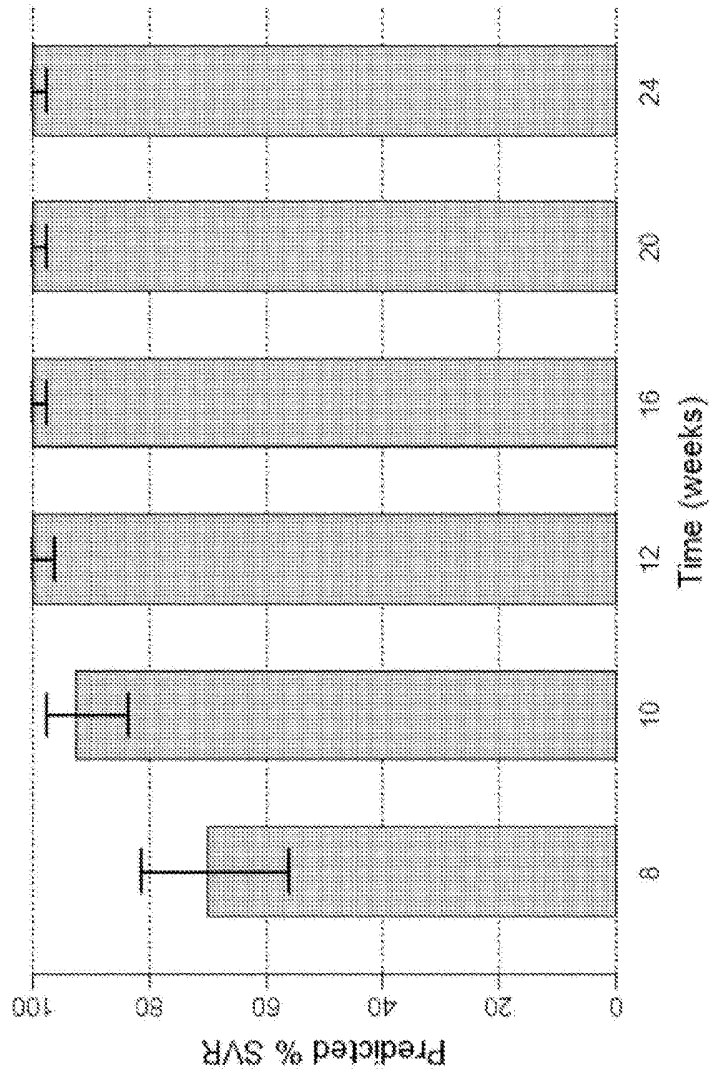


Figure 6

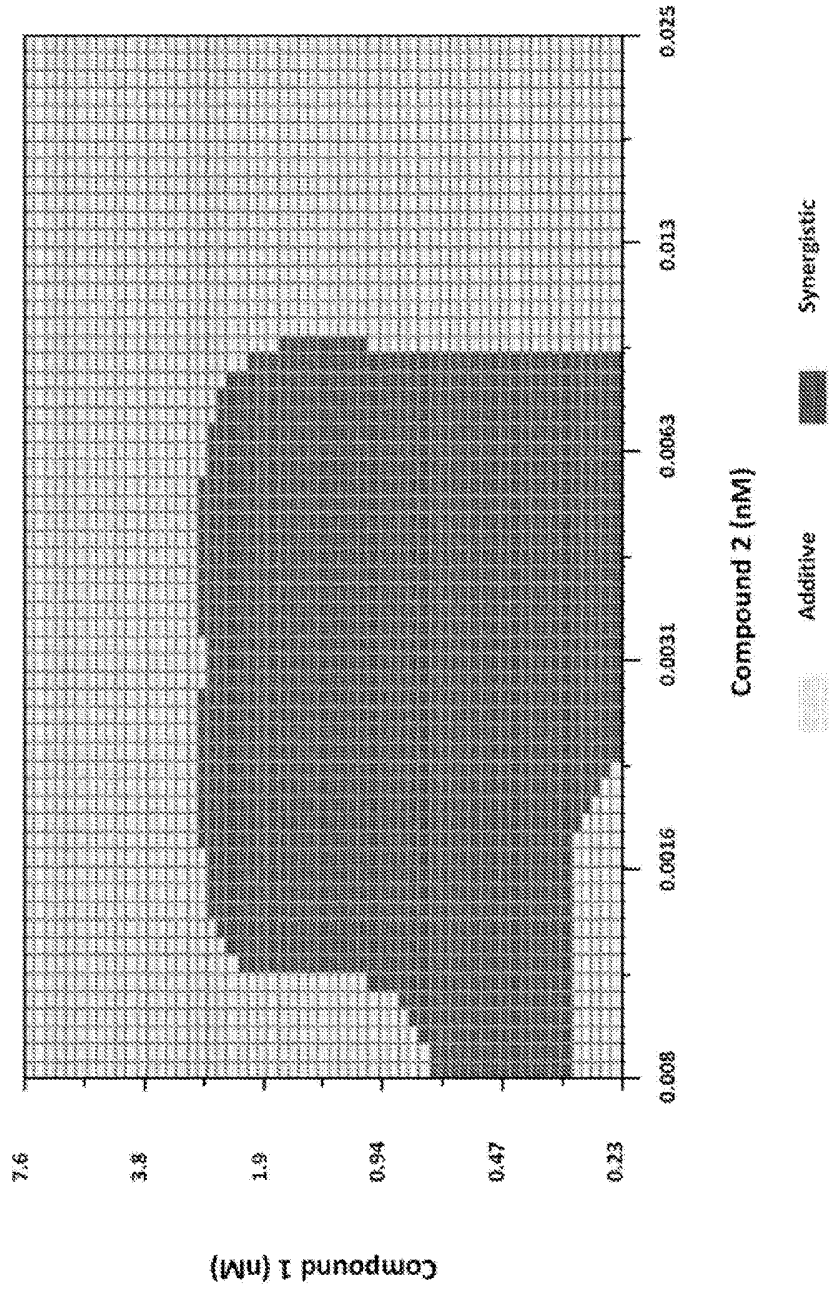

Compound 1 (nM)
7.6
3.8
1.9
0.94
0.47
0.23
0.008
0.0016
0.0031
0.0063
0.013
0.025
Compound 2 (nM)
Additive
Synergistic

Figure 7