METHODS FOR TREATING HCV

FIELD

[0001] The present invention relates to pan-genotypic HCV inhibitors and methods of using the same to treat HCV infection.

BACKGROUND

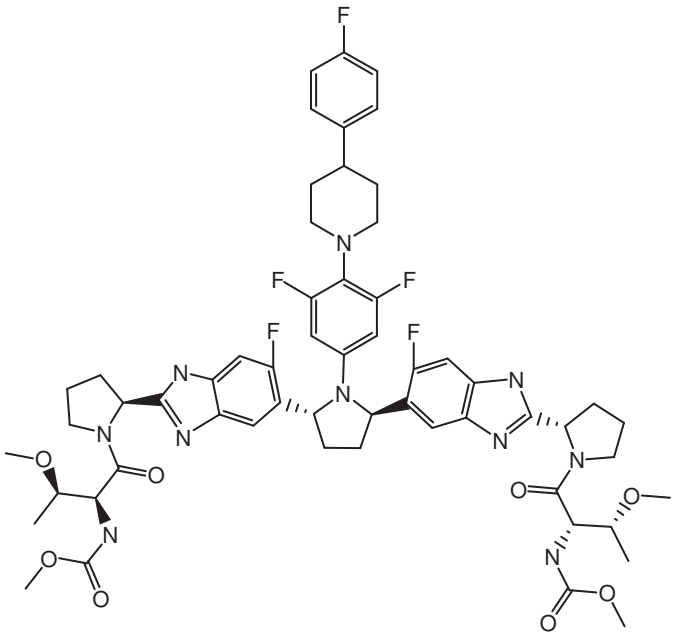
[0002] Hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 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.

[0003] 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 inadequate. Therefore, there is a need for new drugs to treat HCV infection.

SUMMARY

[0004] It was surprisingly discovered that methyl {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate (hereinafter "Compound 1") and its pharmaceutically acceptable salts are pan-genotypic HCV inhibitors. These compounds are effective in inhibiting a wide array of HCV genotypes and variants, such as HCV genotype 1, 2, 3, 4, 5, and 6.

[0004a] In a first aspect, there is provided a use of Compound 1 having the formula



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment for HCV in an HCV patient,

wherein said compound is to be used in combination with a HCV protease inhibitor or an HCV polymerase inhibitor,

wherein said patient is not genotyped for said treatment, further wherein said patient is infected with HCV genotype 1, 2, 3, 4, 5, or 6,

wherein said treatment lasts for less than 8, 12 or 16 weeks and does not include administration of interferon to said patient.

[0005] Accordingly, a first example of the disclosure features methods for treating HCV. The methods comprise administering an effective amount of Compound 1 or a pharmaceutically acceptable salt thereof to an HCV patient, regardless of the specific HCV genotype(s) that the patient has. Therefore, the patient preferably is not genotyped before the treatment, and the treatment can be initiated without pre-screening the patient for specific HCV genotypes.

[0006] In one embodiment of this example of the disclosure, the patient is infected with genotype 2, such as genotype 2a or 2b. In another embodiment of this example of the disclosure, the patient is infected with genotype 3, such as genotype 3a. In another embodiment of this example of the disclosure, the patient is infected with genotype 4, such as genotype 4a. In yet another embodiment of this example of the disclosure, the patient is infected with genotype 5, such as genotype 5a. In still yet embodiment of this example of the disclosure, the patient is infected with genotype 6, such as genotype 6a.

[0007] In another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with another anti-HCV agent. Non-limiting examples of said another anti-HCV agent include HCV polymerase inhibitors, HCV protease inhibitors, other HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0008] In yet another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor or an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0009] In another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0010] In another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0011] In another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor and an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is

infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0012] In this example of the disclosure, as well as each and every embodiment and example described hereunder, the treatment preferably lasts for less than 24 weeks and does not include administration of interferon to said patient. Such a treatment can, for example, comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor or an HCV polymerase inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient. For example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor, to said patient. For another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV polymerase inhibitor, to said patient. For yet another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient.

[0013] In this example of the disclosure, as well as each and every embodiment and example described hereunder, the treatment preferably lasts for no more than 12 weeks (e.g., the treatment lasts for 8, 9, 10, 11, or 12 weeks; preferably, the treatment lasts for 12 weeks), and does not include administration of interferon to said patient. Such a treatment can, for example, comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor or an HCV polymerase inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient. For example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor, to said patient. For another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV polymerase inhibitor, to said patient. For yet another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient.

[0014] In this example of the disclosure, as well as each and every embodiment and example described hereunder, the treatment may or may not include administration of ribavirin to said patient; for example, the treatment can include administration of ribavirin to said patient.

[0015] In a second example, the present disclosure features methods of treating HCV. The methods comprising administering an effective amount of Compound 1 or a pharmaceutically acceptable salt thereof to an HCV patient, wherein said patient is infected with HCV genotype 2, 3, 4, 5, or 6.

[0016] In one embodiment of this example of the disclosure, the patient is infected with genotype 2, such as genotype 2a or 2b. In another embodiment of this example of the disclosure, the

patient is infected with genotype 3, such as genotype 3a. In another embodiment of this example of the disclosure, the patient is infected with genotype 4, such as genotype 4a. In yet another embodiment of this example of the disclosure, the patient is infected with genotype 5, such as genotype 5a. In still yet embodiment of this example of the disclosure, the patient is infected with genotype 6, such as genotype 6a.

[0017] In another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with another anti-HCV agent. Non-limiting examples of said another anti-HCV agent include HCV polymerase inhibitors, HCV protease inhibitors, other HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0018] In yet another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor or an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0019] In another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0020] In another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0021] In another embodiment of this example of the disclosure, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor and an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0022] In this example of the disclosure, as well as each and every embodiment and example described hereunder, the treatment preferably lasts for less than 24 weeks and does not include administration of interferon to said patient. Such a treatment can, for example, comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor or an HCV polymerase inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient. For example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor, to said patient. For another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV polymerase inhibitor, to said patient. For yet another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient.

[0023] In this example of the disclosure, as well as each and every embodiment and example described hereunder, the treatment preferably lasts for no more than 12 weeks (e.g., the treatment lasts for 8, 9, 10, 11, or 12 weeks; preferably, the treatment lasts for 12 weeks), and does not include administration of interferon to said patient. Such a the treatment can, for example, comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor or an HCV polymerase inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient. For example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor, to said patient. For another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV polymerase inhibitor, to said patient. For yet another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient.

[0024] In this example of the disclosure, as well as each and every embodiment and example described hereunder, the treatment may or may not include administration

of ribavirin to said patient; for example, the treatment includes administration of ribavirin to said patient.

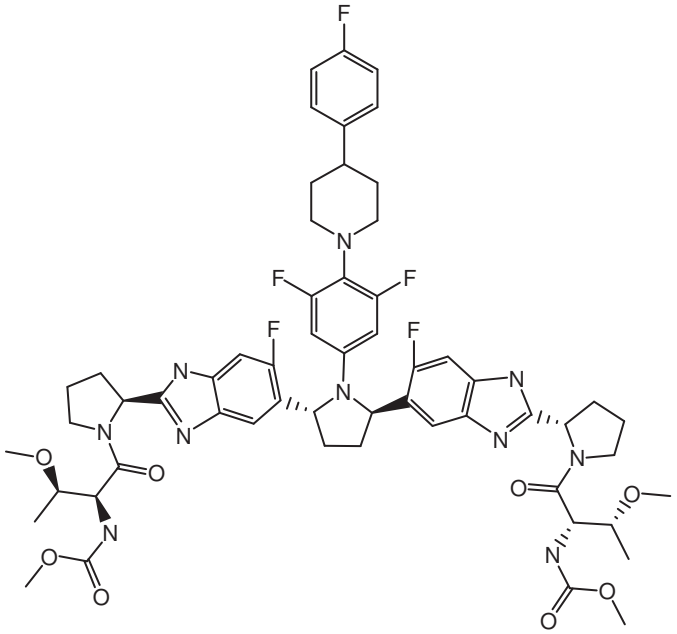
[0025] The present disclosure also features Compound 1 or a pharmaceutically acceptable salt thereof for use to treat an HCV patient regardless of the specific HCV genotype(s) that the patient has. Such uses are illustrated in the first example of the disclosure described above, including each and every embodiment and example described thereunder.

[0026] The present disclosure further features Compound 1 or a pharmaceutically acceptable salt thereof for use to treat an HCV patient infected with HCV genotype 2, 3, 4, 5, or 6. Such uses are illustrated in the second example of the disclosure described above, including each and every embodiment and example described thereunder.

[0027] Other features, objects, and advantages of the present disclosure are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred examples of the disclosure, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the disclosure will become apparent to those skilled in the art from the detailed description.

DETAILED DESCRIPTION

[0028] Compound 1, also known as methyl {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate, is described in U.S. Patent Application Publication No. 2012/0004196, the entire content of which is incorporated herein by reference.

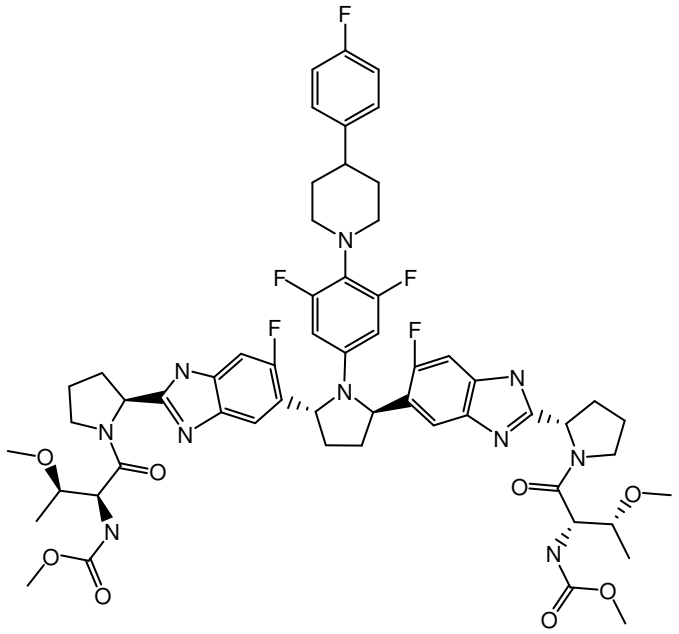


Compound 1

[0029] Compound 1 was found to have EC_{50} values of less than 10 pM against stable subgenomic replicons with NS5A from a broad range of clinically relevant HCV genotypes, such as

What is claimed is:

1. Use of Compound 1 having the formula



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment for HCV in an HCV patient,

wherein said compound is to be used in combination with a HCV protease inhibitor or an HCV polymerase inhibitor,

wherein said patient is not genotyped for said treatment, further wherein said patient is infected with HCV genotype 1, 2, 3, 4, 5, or 6,

wherein said treatment lasts for less than 8, 12 or 16 weeks and does not include administration of interferon to said patient.

2. The use of claim 1, wherein said patient is infected with HCV genotype 1.

3. The use of claim 1, wherein said patient is infected with HCV genotype 2.

4. The use of claim 1, wherein said patient is infected with HCV genotype 3.

5. The use of claim 1, wherein said patient is infected with HCV genotype 4.

6. The use of claim 1, wherein said patient is infected with HCV genotype 5.

7. The use of claim 1, wherein said patient is infected with HCV genotype 6.

8. The use according to one of claims 1-7, where said Compound 1 or the salt thereof is for use in combination with another anti-HCV agent, wherein said another anti-HCV agent is selected from the group consisting of HCV polymerase inhibitors, HCV protease inhibitors, other HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, and internal ribosome entry site (IRES) inhibitors.

9. The use according to one of claims 1-8, wherein said Compound 1 is for use in combination with an HCV protease inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor.

10. The use according to one of claims 1-9, wherein said Compound 1 is for use in combination with an HCV protease inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, and wherein said treatment lasts for no more than 8 weeks.

11. The use according to one of claims 1 -9, wherein said Compound 1 is for use in combination with an HCV protease inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, and wherein said treatment lasts for no more than 12 weeks.

12. The use according to one of claims 1-9, wherein said Compound 1 is for use in combination with an HCV protease inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, and wherein said treatment lasts for no more than 16 weeks.