HETEROCYCLE-SUBSTITUED TETRACYCLIC COMPOUNDS AND METHODS OF USE THEREOF FOR THE TREATMENT OF VIRAL DISEASES

FIELD OF THE INVENTION

The present invention relates to novel Heterocycle-Substituted Tetracyclic Compounds, compositions comprising at least one Heterocycle-Substituted Tetracyclic Compound, and methods of using the Heterocycle-Substituted Tetracyclic Compounds for treating or preventing HCV infection in a patient.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is a major human pathogen. A substantial fraction of these HCV-infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma, which are often fatal.

Recent attention has been focused toward the identification of inhibitors of HCV NS5A. HCV NS5A is a 447 amino acid phosphoprotein which lacks a defined enzymatic function. It runs as 56kd and 58kd bands on gels depending on phosphorylation state (Tanji, *et al. J. Virol.* 69:3980-3986 (1995)). HCV NS5A resides in replication complex and may be responsible for the switch from replication of RNA to production of infectious virus (Huang, Y, *et al., Virology* 364:1-9 (2007)).

Multicyclic HCV NS5A inhibitors have been reported. See U.S. Patent Publication Nos. US20080311075, US20080044379, US20080050336, US20080044380, US20090202483 and US2009020478. HCV NS5A inhibitors having fused tricyclic moieties are disclosed in International Patent Publication Nos. WO 10/065681, WO 10/065668, and WO 10/065674.

Other HCV NS5A inhibitors and their use for reducing viral load in HCV infected humans have been described in U.S. Patent Publication No. US20060276511.

SUMMARY

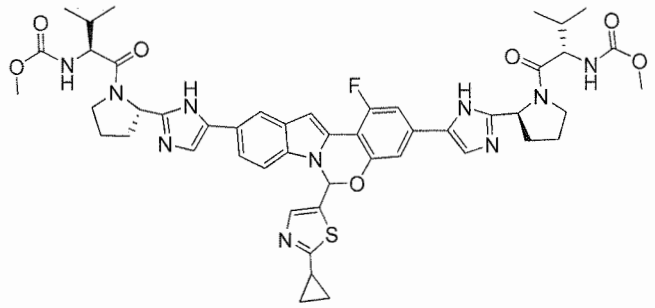
~~In one aspect, t~~The present disclosure provides ~~a~~ compounds of Formula (I):

with up to 5 groups, each independently selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, -O-C_1-C_6 alkyl, $-N(R^6)_2$ and -O-(C_1-C_6 haloalkyl), and wherein said C_3-C_7 cycloalkyl group can be optionally fused to a 4 to 6-membered monocyclic heterocycloalkyl group, and wherein said 4 to 8-membered monocyclic heterocycloalkyl group and said C_3-C_7 cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic C_3-C_6 cycloalkyl group; and wherein said C_3-C_7 cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic 3 to 6-membered monocyclic heterocycloalkyl group, and wherein two R^7 groups, that are attached to a common carbon atom, together with the common carbon atom to which they are attached, join to form a C_3-C_7 cycloalkyl group;

each occurrence of R^8 is independently C_1-C_6 alkyl, C_3-C_7 cycloalkyl and C_6-C_{10} aryl; and

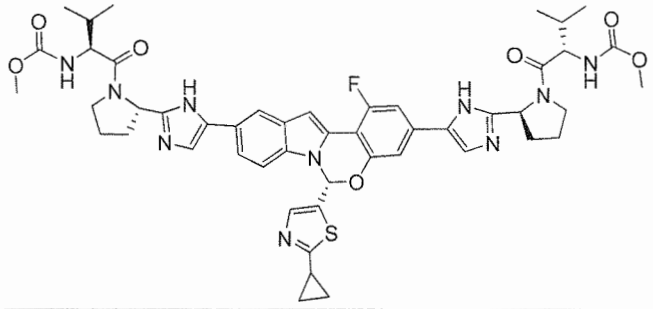
each occurrence of m is independently 0 or 1.

In one aspect, there is provided a compound having the structure:



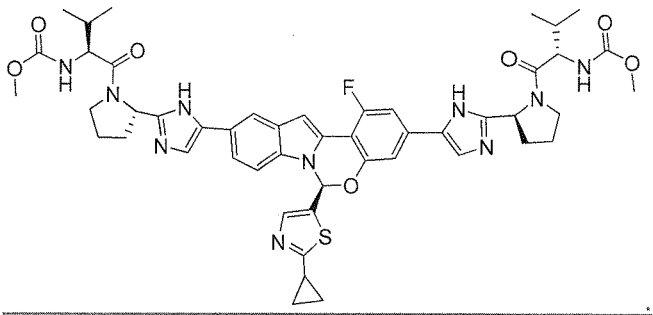
or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the structure:

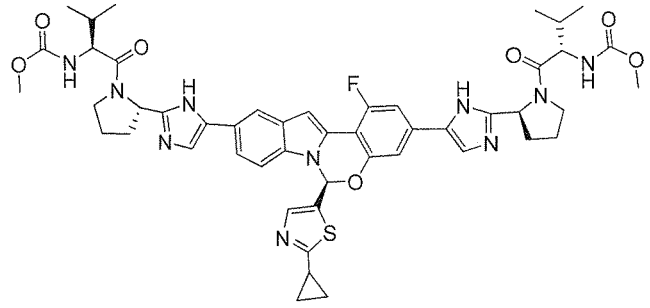


or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the structure:



In another aspect, there is provided a pharmaceutically acceptable salt of the compound having the structure:



The Compounds of Formula (I) (also referred to herein as the "Heterocycle-Substituted Tetracyclic Compounds") and pharmaceutically acceptable salts thereof can be useful, for example, for inhibiting HCV viral replication or replicon activity, and for treating or preventing HCV infection in a patient. Without being bound by any specific theory, it is believed that the Heterocycle-Substituted Tetracyclic Compounds inhibit HCV viral replication by inhibiting HCV NS5A.

Accordingly, the present disclsoure provides methods for treating or preventing HCV infection in a patient, comprising administering to the patient an effective amount of at least one Heterocycle-Substituted Tetracyclic Compound.

~~In another aspect, there is provided any compound numbered 1-547 as described herein or stereoisomer thereof, or a pharmaceutically acceptable salt thereof.~~

In another aspect, there is provided a pharmaceutical composition comprising an effective amount of the compound as defined herein, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In another aspect, there is provided a pharmaceutical composition consisting essentially of the compound as defined herein, or a pharmaceutically acceptable salt thereof, a HCV protease inhibitor, a HCV NS5B polymerase inhibitor and a pharmaceutically acceptable carrier, wherein the amounts of the compound as defined herein, or a pharmaceutically acceptable salt thereof, the HCV protease

inhibitor and the HCV NS5B polymerase inhibitor are together effective to treat HCV infection in a human patient.

In another aspect, there is provided the ~~composition~~ compound as defined herein or a pharmaceutically acceptable salt thereof for use in therapy~~for use in inhibiting HCV replication or for use in treating infection by HCV in a patient in need thereof~~.

In another aspect, there is provided use of ~~(i)~~ the compound as defined herein or a pharmaceutically acceptable salt thereof ~~or (ii) the composition as defined herein,~~ in the manufacture of a medicament for the treatment of ~~a patient infected with~~ HCV infection.

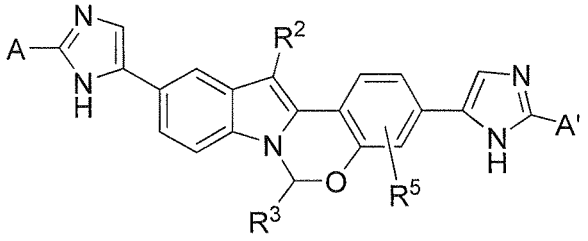
~~In another aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt or prodrug thereof, for use in (i) the inhibition of HCV replication or (ii) the treatment of infection by HCV, in a patient in need thereof.~~

The details of the disclosure are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other embodiments, aspects and features of the present disclosure are either further described in or will be apparent from the ensuing description, examples and appended claims.

WHAT IS CLAIMED IS:

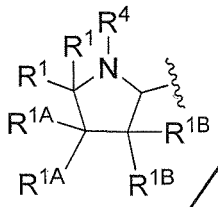
1. A compound having the formula (I):



(I)

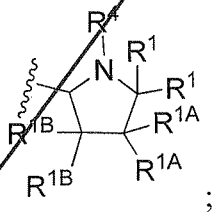
or a pharmaceutically acceptable salt thereof, wherein:

A is:



;

A' is:



;

each occurrence of R^1 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl and halo;

each occurrence of R^{1A} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl and halo, or one R^{1A} group and an R^1 group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused C_3-C_7 cycloalkyl group, or two R^{1A} groups that are attached to the same carbon atom, and the common carbon atom to which they are attached, can combine to form a spirocyclic C_3-C_7 cycloalkyl group;

each occurrence of R^{1B} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl or halo, or an R^{1B} group and an R^{1A} group that are attached to the same ring, together with the carbon atoms to which they are attached, can combine to form a fused C_3-C_7 cycloalkyl group, or an R^{1B} group and an R^1 group that are attached to the

same ring, can combine to form a bridging group having the formula $-CH_2-$ or $-CH_2CH_2-$;

R^2 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl or halo;

R^3 is thiazolyl or thiadiazolyl wherein said thiazolyl group and said thiadiazolyl group can be optionally substituted on one or more ring carbon atoms with R^6, and wherein said thiazole group or thiadiazole group can optionally be fused to a C_3-C_7 cycloalkyl group;

each occurrence of R^4 is independently selected from $-C(O)-C(R^7)_2NHC(O)O-R^8$;

R^5 represents up to 3 substituents, each independently selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, 4 to 6-membered monocyclic heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, C_6-C_{10} aryl, benzyl and -O-(C_1-C_6 alkyl), wherein said C_3-C_7 cycloalkyl group, said 4 to 6-membered monocyclic heterocycloalkyl group, said 5 or 6-membered monocyclic heteroaryl group, said C_6-C_{10} aryl group, or the phenyl moiety of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, $-(C_1$-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

R^6 represents up to 2 substituents, each independently selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-(C_1-C_6 haloalkyl), C_2-C_6 alkynyl, C_1-C_6 hydroxyalkyl, $-(C_1$-C_6 alkylene)$_m$-O-C_1-C_6 alkyl, $-N(R^6)_2$, C_6-C_{10} aryl, $-(C_1$-C_6 alkylene)$_m$-(C_3-C_7 cycloalkyl), -O-(C_6-C_{10} aryl), 4 to 7-membered monocyclic heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, -O-(5 or 6-membered monocyclic heteroaryl), 8 to 10-membered bicyclic heteroaryl and -O-(8 to 10-membered bicyclic heteroaryl), wherein said C_6-C_{10} aryl group, said C_3-C_7 cycloalkyl group, said 4 to 7-membered monocyclic heterocycloalkyl group, said 5 or 6-membered monocyclic heteroaryl group and said 8 to 10-membered bicyclic heteroaryl group, can be optionally substituted with up to 3 groups, each independently selected from halo, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl and -O-C_1-C_6 alkyl, and wherein said C_6-C_{10} aryl group, said 5 or 6-membered monocyclic heteroaryl group and said 8 to 10-membered bicyclic heteroaryl group, can be optionally fused with a 3 to 6 membered cycloalkyl group;

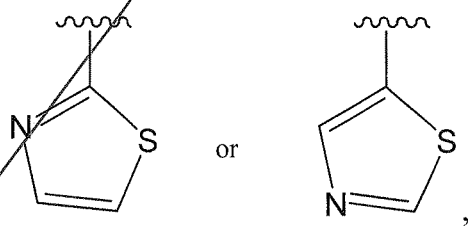
each occurrence of R^7 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl, 4 to 8-membered monocyclic heterocycloalkyl, 6 to 10-

membered bicyclic heterocycloalkyl and C_3-C_7 cycloalkyl, wherein said 4 to 8-membered monocyclic heterocycloalkyl group, said 6 to 10-membered bicyclic heterocycloalkyl group and said C_3-C_7 cycloalkyl group can be optionally substituted with up to 5 groups, each independently selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, -O-C_1-C_6 alkyl, $-N(R^6)_2$ and -O-(C_1-C_6 haloalkyl), and wherein said C_3-C_7 cycloalkyl group can be optionally fused to a 4 to 6-membered monocyclic heterocycloalkyl group, and wherein said 4 to 8-membered monocyclic heterocycloalkyl group and said C_3-C_7 cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic C_3-C_6 cycloalkyl group; and wherein said C_3-C_7 cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic 3 to 6-membered monocyclic heterocycloalkyl group, and wherein two R^7 groups, that are attached to a common carbon atom, together with the common carbon atom to which they are attached, join to form a C_3-C_7 cycloalkyl group;

each occurrence of R^8 is independently C_1-C_6 alkyl, C_3-C_7 cycloalkyl and C_6-C_{10} aryl; and

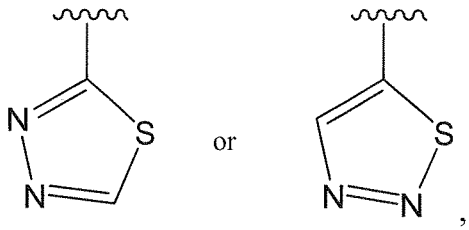
each occurrence of m is independently 0 or 1.

2. The compound of claim 1, wherein R^3 is:



each of which can be optionally substituted with up to two R^6 groups.

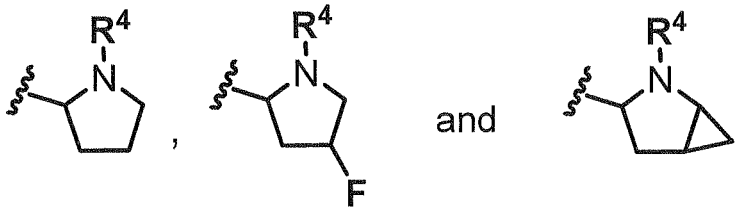
3. The compound of claim 1, wherein R^3 is:



each of which can be optionally substituted with up to two R^6 groups.

4. The compound of any one of claims 1 to 3, wherein A and A'

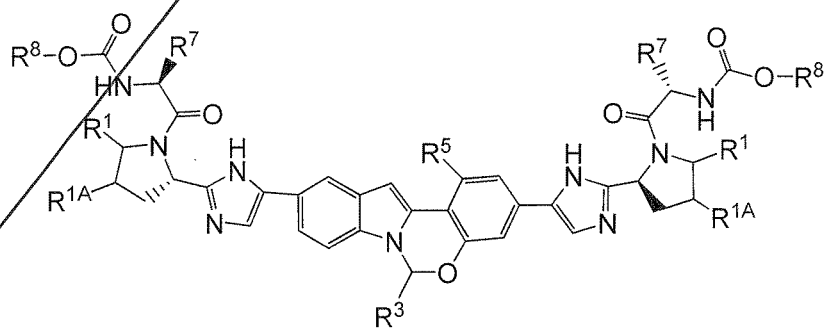
are each independently selected from:



5. The compound of any one of claims 1 to 4, wherein each occurrence of R^4 is independently $-C(O)C(R^7)_2NHC(O)O-R^8$.

6. The compound of claim 5, wherein each occurrence of R^4 is independently $-C(O)CH(R^7)-NHC(O)O-(C_1-C_6$ alkyl) and R^7 is C_1-C_6 alkyl, C_1-C_6 haloalkyl or 4 to 6-membered monocyclic heterocycloalkyl, wherein said 4 to 6-membered monocyclic heterocycloalkyl group can be optionally substituted with up to five C_1-C_6 alkyl groups or said 4 to 6-membered monocyclic heterocycloalkyl group can be optionally substituted on a ring carbon atom with a spirocyclic C_3-C_6 cycloalkyl group.

7. The compound of claim 1 having the formula:



(Ia)

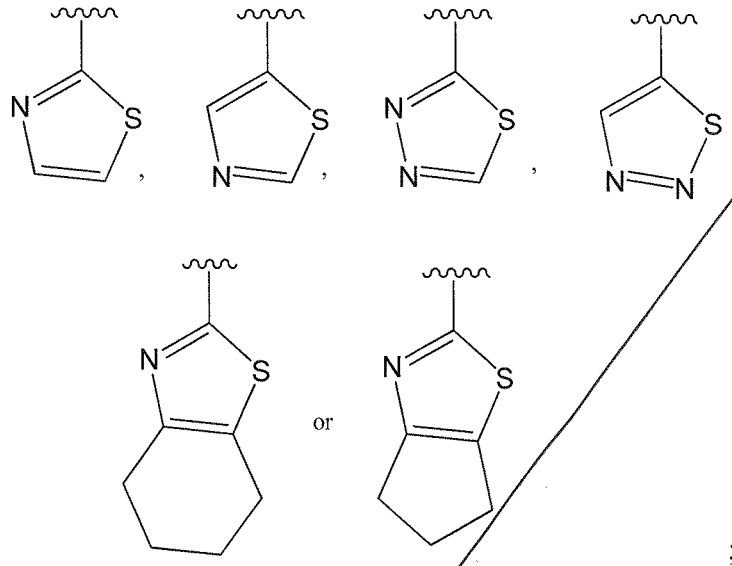
or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is H;

each R^{1A} is H, or an R^{1A} group and an R^1 group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused cyclopropyl group;

R^3 is:



;

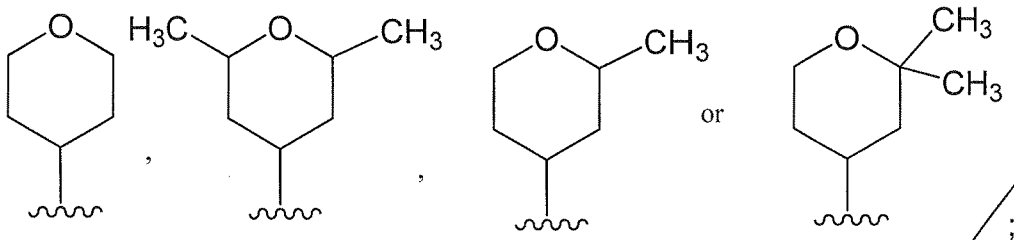
wherein R^3 can be optionally substituted on one or more ring carbon atoms with a group selected from methyl, ethyl, n-propyl, isopropyl, t-butyl, $-CF_3$, cyclopropyl, $-CH_2$-cyclopropyl, cyclobutyl, cyclopentyl, methoxy, -O-(halo-substituted phenyl), $-OCF_3$, $-C(CH_3)_2OH$, $-CH_2CH_2OCH_3$, halo-substituted phenyl and -CN;

each occurrence of R^5 is independently selected from H, methyl and F;

each occurrence of R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl and 4 to 6-membered monocyclic heterocycloalkyl, wherein said 4 to 6-membered monocyclic heterocycloalkyl group can be optionally substituted with up to 5 groups, each independently selected from halo, C_1-C_6 alkyl and C_3-C_7 cycloalkyl, and wherein said 4 to 6-membered monocyclic heterocycloalkyl group can be optionally substituted on a ring carbon atom with a spirocyclic C_3-C_6 cycloalkyl group;

each occurrence of R^8 is independently C_1-C_6 alkyl.

8. The compound of claim 7, wherein each occurrence of R^7 is isopropyl, $-CF(CH_3)_2$,

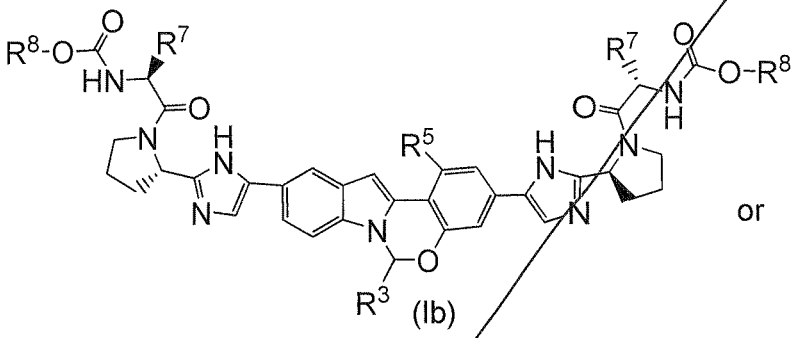


or

;

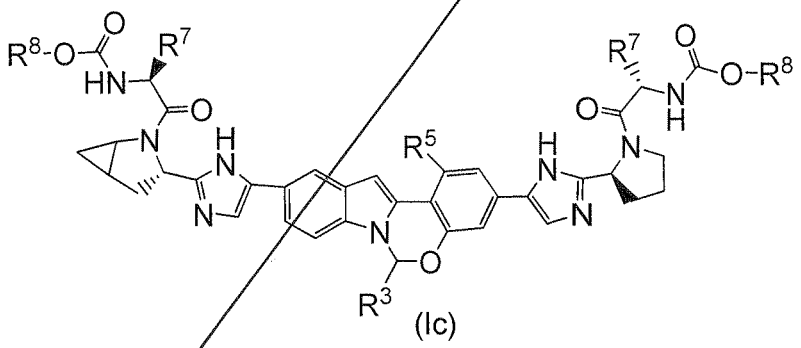
and each occurrence of R^8 is methyl.

9. The compound of claim 7, having the formula:



(Ib)

or

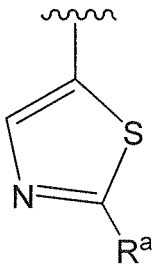


(Ic)

or a pharmaceutically acceptable salt thereof,

wherein:

R^3 is:



,

R^a is C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

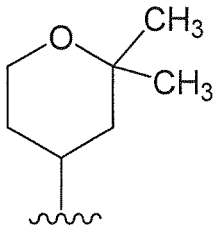
R^5 is H or F;

each occurrence of R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl or tetrahydropyranyl, wherein said tetrahydropyranyl group can be

optionally substituted with up to 5 groups, each independently selected from halo, C_1-C_6 alkyl and C_3-C_7 cycloalkyl, and wherein said tetrahydropyranyl group can be optionally substituted on a ring carbon atom with a spirocyclic cyclopropyl group; and

each occurrence of R^8 is methyl.

10. The compound of claim 9, wherein, R^a is cyclopropyl, cyclobutyl, cyclopentyl, n-propyl, isopropyl, isobutyl or t-butyl; R^5 is F and each occurrence of R^7 is independently selected from isopropyl, $-CF(CH_3)_2$ or:



11. Any compound numbered 1-547 as described in the above specification or stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising an effective amount of the compound of any of claims 1 to 11 and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition according to claim 12 further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

14. The pharmaceutical composition according to claim 13, further comprising a third therapeutic agent selected from the group consisting of HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

15. The composition according to any of claims 12-14 for use in inhibiting HCV replication or for use in treating infection by HCV in a patient in need thereof.

16. Use of (i) the compound according to any of claims 1 to 11 or

(ii) the composition according to any of claims 12 to 14, in the manufacture of a medicament for the treatment of a patient infected with HCV.

17. The use according to claim 16, further comprising the use of ribavirin.

18. The use according to claim 16, further comprising the use of one to three additional therapeutic agents, wherein the additional therapeutic agents are each independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

19. The use according to claim 18, wherein the one to three additional therapeutic agents comprises MK-5172.

20. The use according to claim 18 or 19, wherein the one to three additional therapeutic agents comprises sofosbuvir.

21. A compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt or prodrug thereof, for use in (i) the inhibition of HCV replication or (ii) the treatment of infection by HCV, in a patient in need thereof.

22. The compound according to claim 21, further comprising ribavirin.

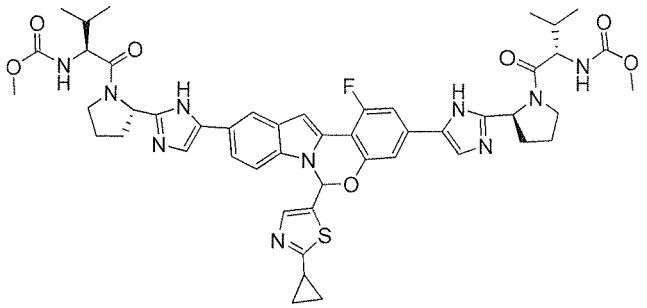
23. The compound according to claim 21, further comprising one to three additional therapeutic agents, wherein the additional therapeutic agents are each independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

24. The compound according to claim 24, wherein the one to three additional therapeutic agents comprises MK-5172.

25. The compound according to claim 23 or 24, wherein the one to three additional therapeutic agents comprises sofosbuvir.

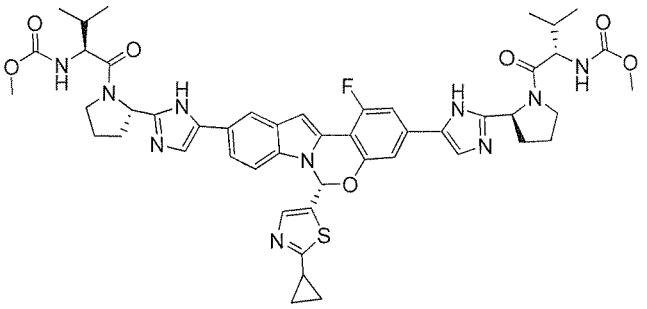
WHAT IS CLAIMED IS:

1. A compound having the structure:



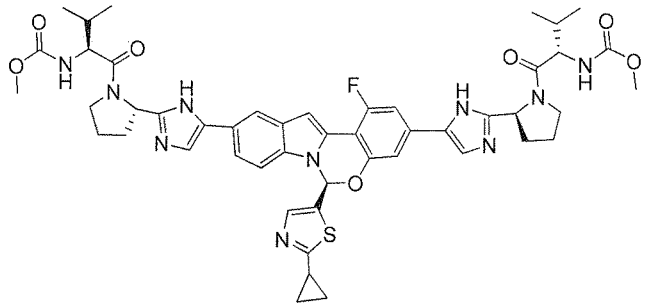
or a pharmaceutically acceptable salt thereof.

2. A compound having the structure:

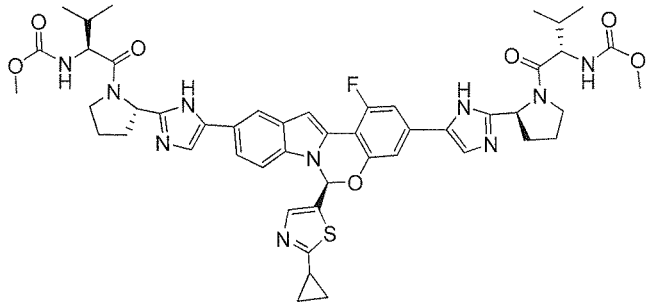


or a pharmaceutically acceptable salt thereof.

3. A compound having the structure:



4. A pharmaceutically acceptable salt of the compound having the structure:

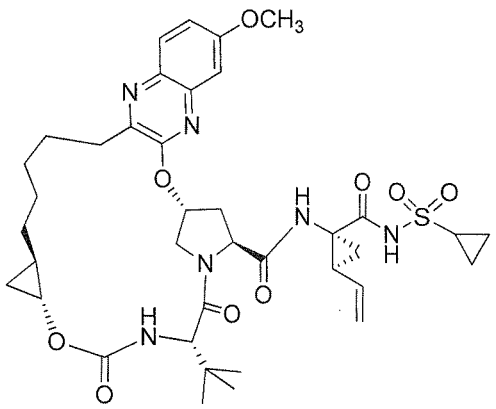


5. A pharmaceutical composition comprising an effective amount of the compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

6. The pharmaceutical composition of claim 5, further comprising one or more additional therapeutic agents, wherein the additional therapeutic agents are each independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

7. A pharmaceutical composition consisting essentially of the compound of claim 1, or a pharmaceutically acceptable salt thereof, a HCV protease inhibitor, a HCV NS5B polymerase inhibitor and a pharmaceutically acceptable carrier, wherein the amounts of the compound of claim 1, or a pharmaceutically acceptable salt thereof, the HCV protease inhibitor and the HCV NS5B polymerase inhibitor are together effective to treat HCV infection in a human patient.

8. The pharmaceutical composition of claim 7, wherein the HCV protease inhibitor is the compound having the structure:



9. The pharmaceutical composition of claim 8, wherein the HCV NS5B polymerase inhibitor is a nucleoside.

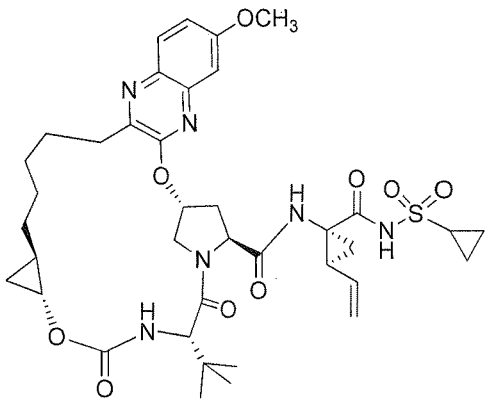
10. The compound of claim 1, or a pharmaceutically acceptable salt thereof for use in therapy.

11. Use of compound of claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of HCV infection.

12. The use of claim 11, further comprising one or more additional therapeutic agents, wherein the additional therapeutic agents are each independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

13. The use of claim 12, wherein the one or more additional therapeutic agents comprise a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

14. The use of claim 13, wherein the HCV protease inhibitor is the compound having the structure:



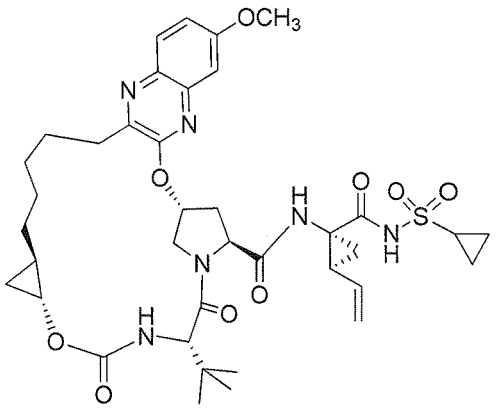
15. The use of claim 14, wherein the HCV NS5B polymerase inhibitor is a nucleoside.

16. A pharmaceutical composition comprising an effective amount of the compound of claim 3 and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, further comprising one or more additional therapeutic agents, wherein the additional therapeutic agents are each independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

18. A pharmaceutical composition consisting essentially of the compound of claim 3, a HCV protease inhibitor, a HCV NS5B polymerase inhibitor and a pharmaceutically acceptable carrier, wherein the amounts of the compound of claim 3, the HCV protease inhibitor and the HCV NS5B polymerase inhibitor are together effective to treat HCV infection in a human patient.

19. The pharmaceutical composition of claim 18, wherein the HCV protease inhibitor is the compound having the structure:



20. The pharmaceutical composition of claim 19, wherein the HCV NS5B polymerase inhibitor is a nucleoside.

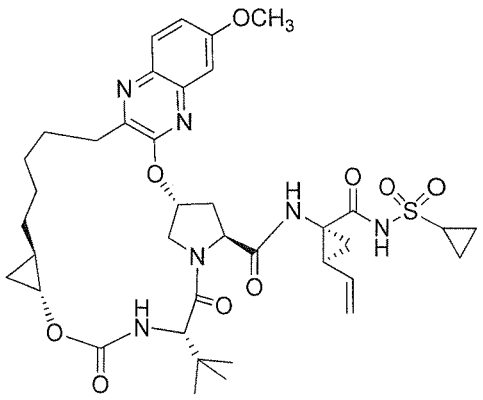
21. The compound of claim 3 for use in therapy.

22. Use of compound of claim 3 in the manufacture of a medicament for treating infection by HCV.

23. The use of claim 22, further comprising one or more additional therapeutic agents, wherein the additional therapeutic agents are each independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

24. The use of claim 23, wherein the one or more additional therapeutic agents comprise a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

25. The use of claim 24, wherein the HCV protease inhibitor is the compound having the structure:



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26. The use of claim 25, wherein the HCV NS5B polymerase inhibitor is a nucleoside.