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

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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.

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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.

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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)).

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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.

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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.

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SUMMARY OF THE INVENTION

In one aspect, the present invention-disclosure provides a Compounds of Formula (I):

5 with up to 5 groups, each independently selected from halo, -CN, C₁-C₆ alkyl, C₁-C₆
haloalkyl, C₃-C₇ cycloalkyl, -O-C₁-C₆ alkyl, -N(R⁶)₂ and -O-(C₁-C₆ haloalkyl), and
wherein said C₃-C₇ 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 C₃-C₇ cycloalkyl group can be substituted on a ring
10 carbon atom with a spirocyclic C₃-C₆ cycloalkyl group; and wherein said C₃-C₇
cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic 3 to 6-
membered monocyclic heterocycloalkyl group, and wherein two R⁷ groups, that are
attached to a common carbon atom, together with the common carbon atom to which
they are attached, join to form a C₃-C₇ cycloalkyl group;
15 each occurrence of R⁸ is independently C₁-C₆ alkyl, C₃-C₇ cycloalkyl
and C₆-C₁₀ aryl; and
each occurrence of m is independently 0 or 1.

The Compounds of Formula (I) (also referred to herein as the
20 “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.

25 Accordingly, the present ~~invention~~ disclosure 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
30 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 and a
pharmaceutically acceptable carrier.

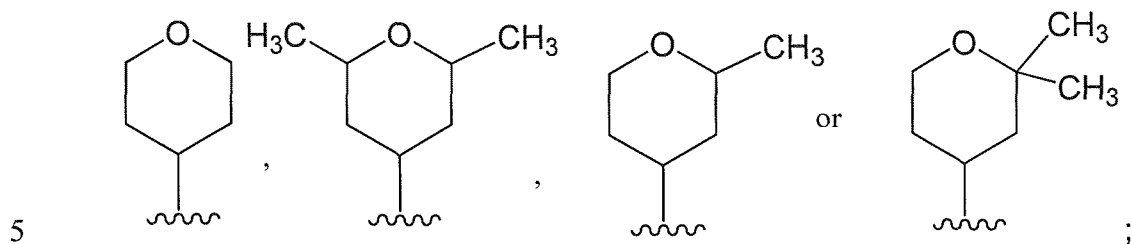
In another aspect, there is provided the composition as defined herein
35 for use in inhibiting HCV replication or for use in treating infection by HCV in a
patient in need thereof.

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

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
10 HCV replication or (ii) the treatment of infection by HCV, in a patient in need thereof.

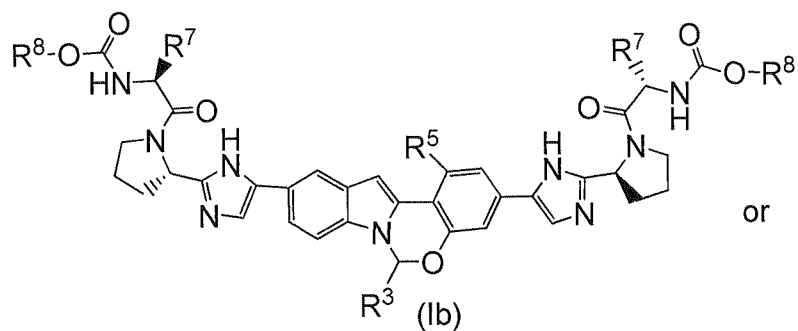
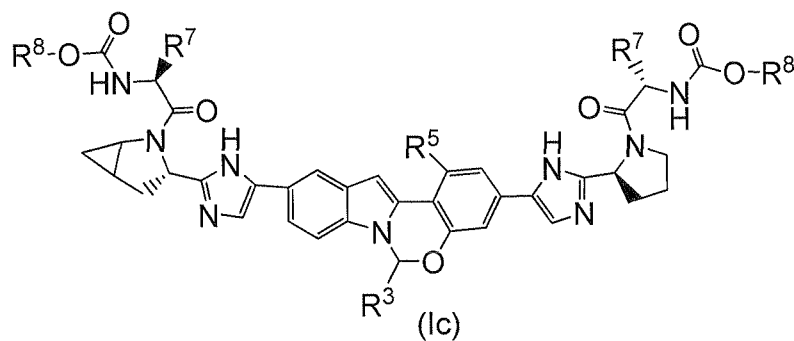
 The details of the ~~invention~~ disclosure are set forth in the accompanying detailed description below.

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



and each occurrence of R^8 is methyl.

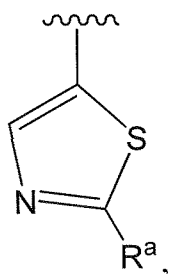
9. The compound of claim 7, having the formula:



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or a pharmaceutically acceptable salt thereof,
wherein:

R^3 is:



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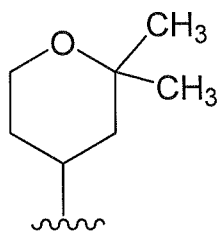
R^a is C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl;

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

5 optionally substituted with up to 5 groups, each independently selected from halo, C₁-C₆ alkyl and C₃-C₇ cycloalkyl, and wherein said tetrahydropyranyl group can be optionally substituted on a ring carbon atom with a spirocyclic cyclopropyl group; and each occurrence of R⁸ is methyl.

10 10. The compound of claim 9, wherein, R^a is cyclopropyl, cyclobutyl, cyclopentyl, n-propyl, isopropyl, isobutyl or t-butyl; R⁵ is F and each occurrence of R⁷ is independently selected from isopropyl, -CF(CH₃)₂ or:



15 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.

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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.

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

16. ~~Use of A method of treating a patient infected with HCV comprising the step of administering an amount of (i) the compound according to any of claims 1 to 11 or~~

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5 (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 effective to treat infection by HCV in said patient.

10 ~~17. 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.~~

15 ~~17. The method-use according to claim 16 or 17, further comprising the use step of administering ribavirin to said patient.~~

20 ~~18. The method-use according to claim 16 or 17, further comprising the use step of administering from one to three additional therapeutic agents to said patient, wherein the additional therapeutic agents are each independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.~~

25 ~~19. The method-use according to claim 1918, wherein the one to three additional therapeutic agents comprises MK-5172.~~

~~20. The method-use according to claim 19-18 or 2019, wherein the one to three additional therapeutic agents comprises sofosbuvir.~~

30 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.

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

5 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.

10 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.

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