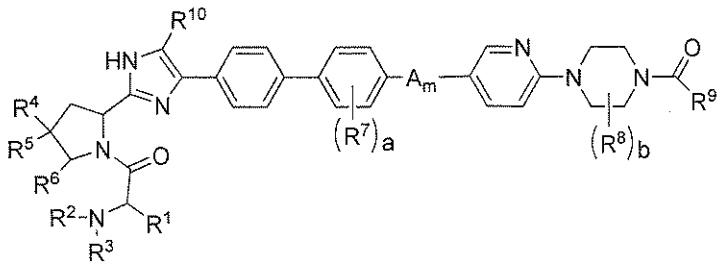
the course of therapy is still lengthy and accompanied by undesirable side effects. Accordingly, there remains a serious unmet need in HCV treatment.

The virus responsible for HCV infection has been identified as a positive-strand RNA virus belonging to the family *Flaviviridae*. The HCV genome encodes a polyprotein that during the viral lifecycle is cleaved into ten individual proteins, including both structural and non-structural proteins. The six non-structural proteins, denoted as NS2, NS3, NS4A, NS4B, NS5A, and NS5B have been shown to be required for RNA replication. In particular, the NS5A protein appears to play a significant role in viral replication, as well as in modulation of the physiology of the host cell. Effects of NS5A on interferon signaling, regulation of cell growth and apoptosis have also been identified. (Macdonald et al., *Journal of General Virology* (2004), 85, 2485-2502.) Compounds which inhibit the function of the NS5A protein are expected to provide a new approach to HCV therapy.

SUMMARY ~~OF THE INVENTION~~

In one ~~aspect~~embodiment, the ~~invention~~ present disclosure provides novel compounds which inhibit replication of the HCV virus.

In one aspect~~Accordingly~~, ~~the invention~~ there is provided~~s~~ a compound of formula (I):



(I)

wherein

R^1 is selected from C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, C_{3-6}cycloalkyl, heterocycle, and heteroaryl, wherein C_{1-6}alkyl is optionally substituted with $-OR^a$, amino, $-SR^e$, heterocycle, or heteroaryl, C_{1-6}alkoxy is optionally substituted with $-OR^a$, and heterocycle is optionally substituted with $-OR^a$, amino, or $-C(O)OC_{1-6}$alkyl, or with one or two C_{1-3}alkyl or =O;

R^2 is selected from hydrogen and C_{1-6}alkyl;

R^3 is selected from hydrogen, C_{1-6}alkyl, $-C(O)OC_{1-6}$alkyl, $-C(O)NR^mR^n$, $-C(O)C_{3-6}$cycloalkyl, and $-S(O)_2C_{1-3}$alkyl;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocycle;

R^4 is selected from C_{1-6}alkyl, -NR^bR^c, -OR^d, -SR^e, -$S(O)C_{1-3}$alkyl, -$S(O)_2C_{1-3}$alkyl, -CN, -$C(O)NR^aR^b$, heterocycle, heteroaryl, and halo, wherein C_{1-6}alkyl is optionally substituted with -OR^a; and R^5 and R^6 are hydrogen;

or R^4 and R^5 are independently C_{1-6}alkyl or halo and R^6 is hydrogen;

or R^4 and R^5 taken together form $-(CH_2)_n-$, wherein *n* is 2, 3, 4, or 5 and R^6 is hydrogen;

or R^4 and R^5 taken together form $-O-(CH_2)_2-O-$ and R^6 is hydrogen;

or R^4 is hydrogen or C_{1-3}alkyl and R^5 and R^6 taken together form $-(CH_2)_m-$, wherein *m* is 1, 2, 3, or 4;

or R^4 and R^5 are each hydrogen and R^6 is C_{1-6}alkyl;

R^7 is selected from halo, C_{1-3}alkyl, and C_{1-3}alkoxy wherein C_{1-3}alkyl and C_{1-3}alkoxy are optionally substituted with one, two, three, four, or five halo;

R^8 is C_{1-3}alkyl, optionally substituted with -OR^h;

R^9 is selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, -NR^fR^g, heteroaryl, heterocycle, and $-CH_2$-heteroaryl;

wherein:

C_{1-6}alkyl is optionally substituted with one or two substituents independently selected from $-OR^h$, -NR^jR^k, -$NHC(O)C_{1-3}$alkyl, -$NHC(O)OC_{1-3}$alkyl, -$NHC(O)C_{3-6}$cycloalkyl, C_{3-6}cycloalkyl, halo, -$NHC(O)C_{1-3}$alkyl$C(O)OR^h$, -$NHC(O)C_{1-3}$alkylOR^h, -$NHC(O)NHC_{1-3}$alkyl, -$NHS(O)_2C_{1-3}$alkyl, and heterocycle;

C_{1-6}alkoxy is optionally substituted with $-OR^h$;

any C_{3-6}cycloalkyl is optionally substituted with one, two, or three substituents independently selected from C_{1-3}alkyl, halo, -NR^aR^b, $-OR^h$, and $-CD_3$, wherein any C_{1-3}alkyl is optionally substituted with one, two, or three halo;

any heterocycle is optionally substituted with one, two, or three substituents independently selected from C_{1-3}alkyl, halo, -$C(O)OC_{1-3}$alkyl, -$C(O)C_{1-6}$alkyl, -$C(O)C_{3-6}$cycloalkyl, $-C(O)NHC_{1-6}$alkyl, -$C(O)NHC_{3-6}$cycloalkyl, $-S(O)_2C_{1-6}$alkyl, and $-C(O)NH_2$;

wherein any $-C(O)C_{1-6}$alkyl is optionally substituted with -$NHC(O)OC_{1-3}$alkyl, -OR^h, -NR^jR^k, or heterocycle,

any -C(O)C_{3-6}cycloalkyl is optionally substituted with one or two C_{1-3}alkyl, and

any –C(O)NHC_{1-6}alkyl is optionally substituted with –OR^h or C_{3-6}cycloalkyl;

any heteroaryl is optionally substituted with one or two C_{1-3}alkyl;

R^a, R^b, R^e, R^h, R^j, R^k, R^m, and R^n are each independently hydrogen or C_{1-3}alkyl;

R^c is hydrogen or C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with –OR^a or amino;

R^d is hydrogen or C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with –OR^h or with heteroaryl optionally substituted with C_{1-3}alkyl;

R^f is hydrogen or C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with –OR^h;

R^g is selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, NR^aR^b, and heterocycle, wherein C_{1-6}alkyl is optionally substituted with –OR^h and heterocycle is optionally substituted with one or two =O;

R^{10} is selected from hydrogen, halo, and C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with one, two, or three halo, or with –OR^h;

A_m is –NHC(O)- or –C(O)NH-

a is 0, 1, or 2; and

b is 0, 1 or 2;

or a pharmaceutically-acceptable salt of stereoisomer thereof.

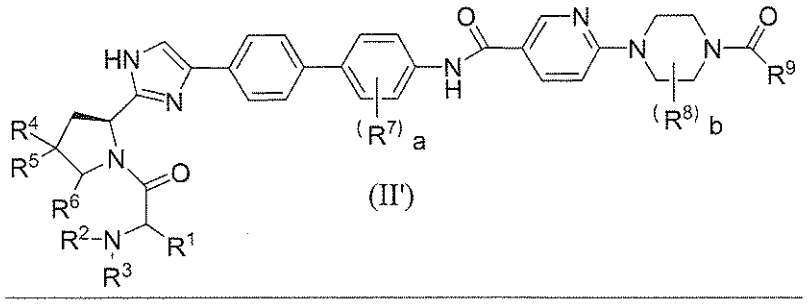
As used hereinafter, the phrase "compound of formula (I)" means a compound of formula (I) or a pharmaceutically acceptable salt thereof; i.e., this phrase means a compound of formula (I) in free base form or in a pharmaceutically acceptable salt form unless otherwise indicated.

In another aspect, there is ~~The invention also~~ provide~~s~~ a pharmaceutical composition comprising a compound of the ~~invention~~ present disclosure and a pharmaceutically-acceptable carrier. In addition, the present disclosure ~~invention~~ provides a pharmaceutical composition comprising a compound of the present disclosure~~invention~~, a pharmaceutically-acceptable carrier and one or more other therapeutic agents useful for treating hepatitis C viral infections.

The present disclosure ~~invention~~ also provides a method of treating a hepatitis C viral infection in a mammal, the method comprising administering to the mammal a therapeutically effective amount of a compound or of a pharmaceutical composition of the present disclosure~~invention~~. In addition, the present disclosure ~~invention~~ provides a method of treating a hepatitis C viral infection in a mammal, the method comprising administering to the mammal a compound or a pharmaceutical

composition of the present disclosure ~~invention~~ and one or more other therapeutic agents useful for treating hepatitis C viral infections. Further, the present disclosure ~~invention~~ provides a method of inhibiting replication of the hepatitis C virus in a mammal, the method comprising administering a compound or a pharmaceutical composition of the present disclosure~~invention~~.

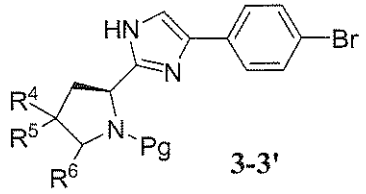
In separate and distinct ~~aspects~~embodiments, the present disclosure ~~invention~~ also provides synthetic processes and intermediates described herein, which are useful for preparing compounds of the present disclosure~~invention~~. In an aspect, there is provided process for preparing a compound of formula (II')



(II')

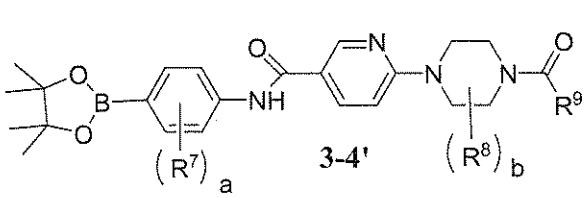
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, *a*, and *b* are defined as above, or a pharmaceutically-acceptable salt or stereoisomer thereof, the process comprising:

(a) reacting a compound of formula 3-3'

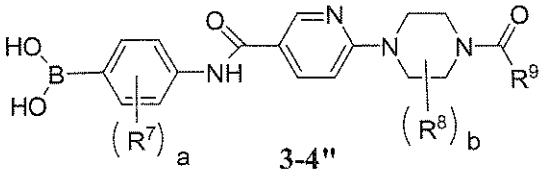


3-3'

wherein Pg is an amino-protecting group, with a compound of formula 3-4' or 3-4"

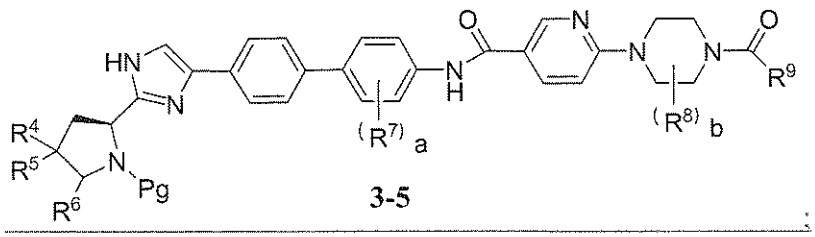


3-4'



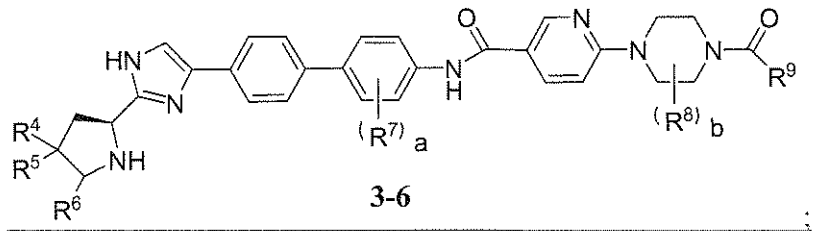
3-4"

to provide a protected intermediate 3-5



3-5

(b) deprotecting intermediate 3-5 to provide a deprotected intermediate 3-6:

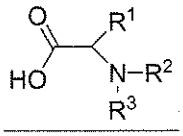


3-6

;

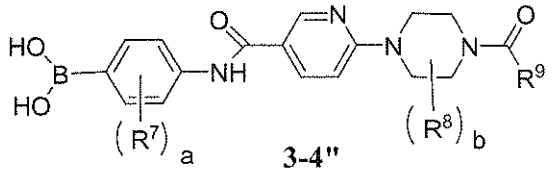
and

(c) reacting intermediate 3-6 with a carboxylic acid:



to provide a compound of formula (II') or a pharmaceutically-acceptable salt or stereoisomer thereof.

In another aspect, there is provided a compound of formula 3-4":



3-4"

wherein R^7 is fluoro, chloro, or $-OCF_3$, R^8 is methyl, R^9 is *tert*-butyl or 3-hydroxy-2,2-dimethylpropyl, *a* is 1 or 2, and *b* is 1.

In aspects, there are ~~The invention also~~ provideds a compound ~~of the invention~~ as described herein for use in medical therapy, as well as the use of a compound ~~of the invention~~ as described herein in the manufacture of a formulation or medicament for treating a hepatitis C viral infection in a mammal. In another aspect, there is provided a compound as described herein for use in the treatment of a hepatitis C viral infection in a mammal. In another aspect, there is provided a compound as described herein for use in inhibiting replication of the hepatitis C virus in a mammal.

BRIEF DESCRIPTION OF THE DRAWING

The figure shows a powder x-ray diffraction (PXPD) pattern of crystalline (*R*)-5-chloro-4-(6-(2-methyl-4-pivaloylpiperazin-1-yl)nicotinamido)-2-(trifluoromethoxy)-phenylboronic acid.

DETAILED DESCRIPTION OF THE INVENTION

Among other aspects, the invention provides inhibitors of HCV replication of formula (I), pharmaceutically-acceptable salts thereof, and intermediates for the preparation thereof. The following substituents and values are intended to provide representative examples of various aspects of this invention. These representative values are intended to further define such aspects and are not intended to exclude other values or limit the scope of the invention.

In a specific aspect, R^1 is selected from C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, C_{3-6}cycloalkyl, heterocycle, and heteroaryl, wherein C_{1-6}alkyl is optionally substituted with $-OR^a$, amino, $-SR^e$, heterocycle, or heteroaryl, C_{1-6}alkoxy is optionally substituted with $-OR^a$, and heterocycle is optionally substituted with $-OR^a$, amino, or $-C(O)OC_{1-6}$alkyl, or with one or two C_{1-3}alkyl or =O.

In another specific aspect, R^1 is selected from C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, C_{3-6}cycloalkyl, heterocycle, and heteroaryl, wherein C_{1-6}alkyl is optionally substituted with $-OR^a$, amino, $-SR^e$, heterocycle, or heteroaryl, C_{1-6}alkoxy is optionally substituted with $-OR^a$, and heterocycle is optionally substituted with $-OR^a$, amino, or $-C(O)OC_{1-6}$alkyl, or with one or two C_{1-3}alkyl, wherein R^a is hydrogen or C_{1-3}alkyl.

22. The compound of Claim 21 for use in combination with one or more other therapeutic agents.

23. The compound of Claim 22 wherein the one or more other therapeutic agents is selected from HCV NS3 protease inhibitors, HCV NS5B nucleoside and non-nucleoside polymerase inhibitors, interferons and pegylated interferons, cyclophilin inhibitors, HCV NS5A inhibitors, and ribavirin and related nucleoside analogs.

24. A compound as claimed in any one of Claims 1 to 12 for use in inhibiting replication of the hepatitis C virus in a mammal.

25. The compound of Claim 24 for use in combination with one or more other therapeutic agents selected from HCV NS3 protease inhibitors, HCV NS5B nucleoside and non-nucleoside polymerase inhibitors, interferons and pegylated interferons, cyclophilin inhibitors, HCV NS5A inhibitors, and ribavirin and related nucleoside analogs.

26. Use of a compound as claimed in any one of Claims 1 to 12 for manufacture of a medicament for the treatment of hepatitis C viral infections in a mammal.

~~27. A method of treating hepatitis C viral infection in a mammal, the method comprising administering to the mammal a pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 12 and a pharmaceutically-acceptable carrier.~~

~~28. The method of Claim 27 wherein the method further comprises administering one or more other therapeutic agents useful for treating hepatitis C viral infections.~~

~~29. A method of inhibiting replication of the hepatitis C virus in a mammal, the method comprising administering to the mammal a pharmaceutical composition comprising a~~

~~compound as claimed in any one of Claims 1 to 12 and a pharmaceutically acceptable carrier.~~

~~30. The method of Claim 29 wherein the method further comprises administering to the mammal one or more other therapeutic agents useful for inhibiting replication of the hepatitis C virus in a mammal.~~