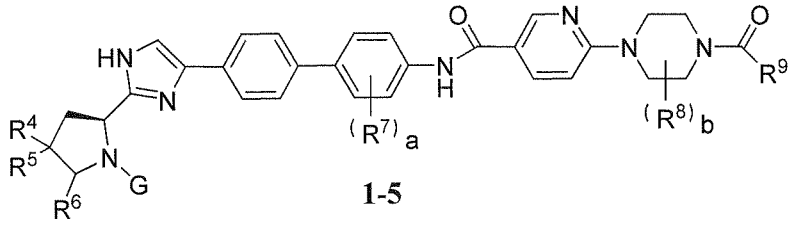
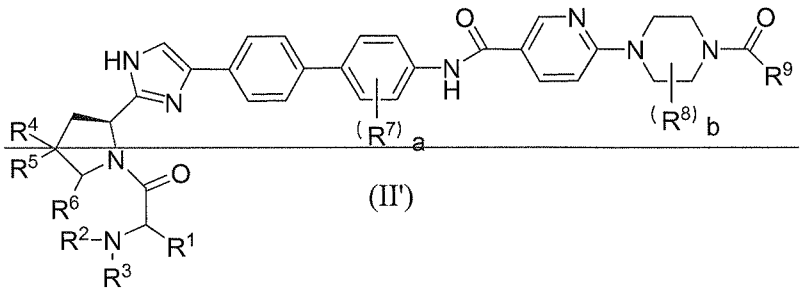
composition of the present disclosure and one or more other therapeutic agents useful for treating hepatitis C viral infections. Further, the present disclosure provides a method of inhibiting replication of the hepatitis C virus in a mammal, the method comprising administering a compound or a pharmaceutical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

In separate and distinct embodiments, the present disclosure also provides synthetic processes and intermediates described herein, which are useful for preparing compounds of the present disclosure. In an aspect, there is provided process for preparing a compound of formula (~~II'~~1-5)

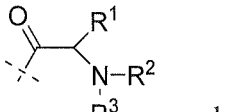


1-5



(II')

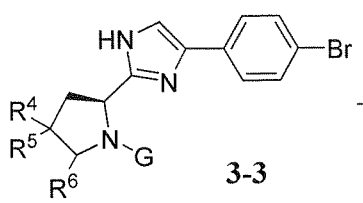
where G represents the group



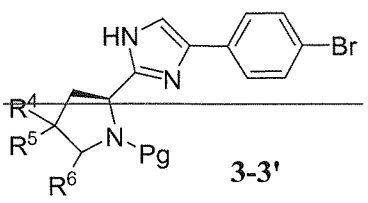
, and

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

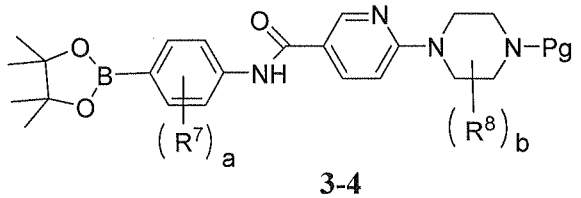


3-3

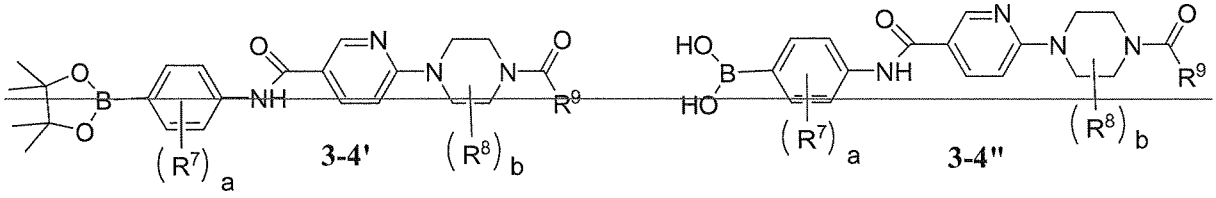


3-3'

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



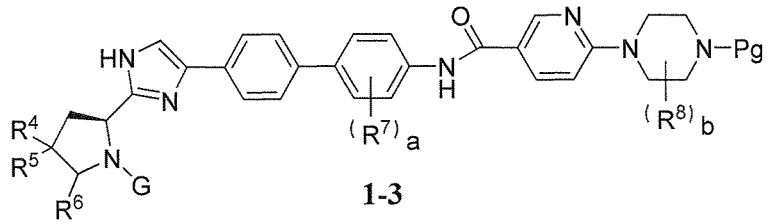
3-4



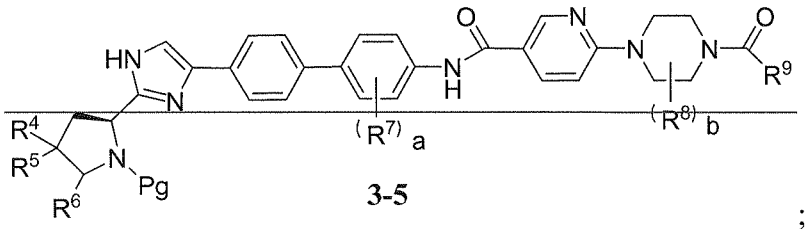
3-4' **3-4"**

wherein Pg is an amino-protecting group,

to provide a protected intermediate ~~3-5~~1-3



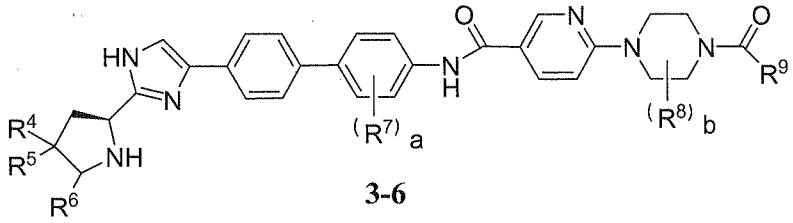
1-3



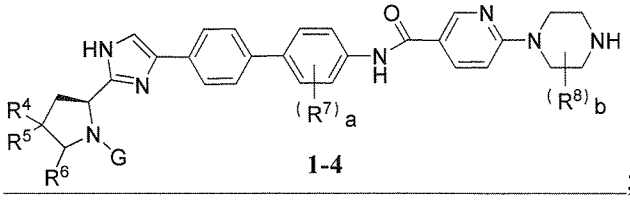
3-5

;

(b) deprotecting intermediate ~~3-5~~ 1-3 to provide a deprotected intermediate ~~3-6~~1-4:



3-6

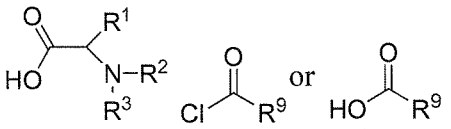


1-4

;

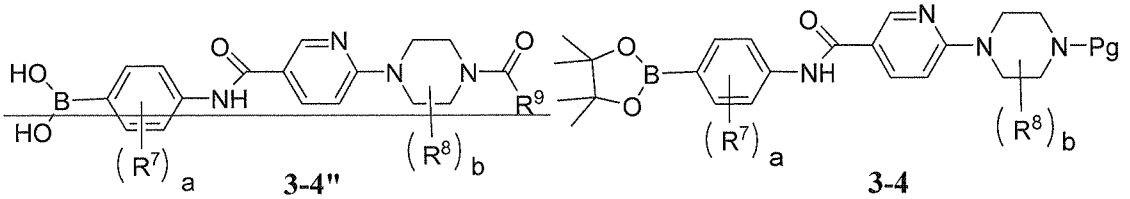
and

(c) reacting intermediate ~~3-6~~ 1-4 with a carboxylic acid or carboxylic acid chloride:



to provide a compound of formula (~~II~~1-5) or a pharmaceutically-acceptable salt or stereoisomer thereof.

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



wherein Pg is an amino-protecting group, 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 provided a compound as described herein for use in medical therapy, as well as the use of a compound 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.

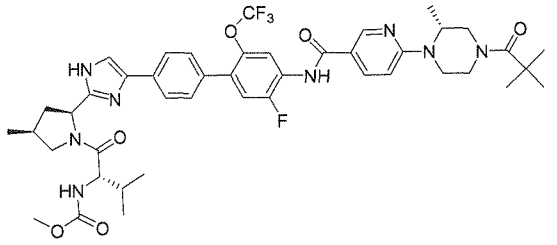
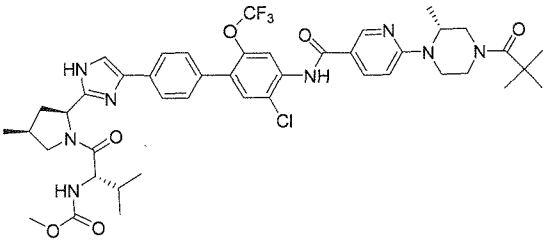
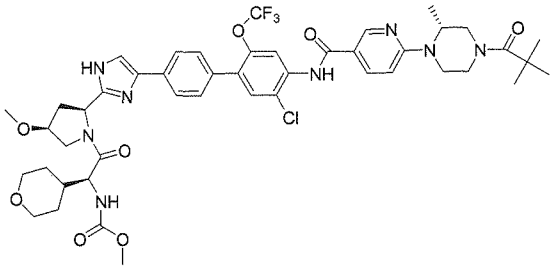
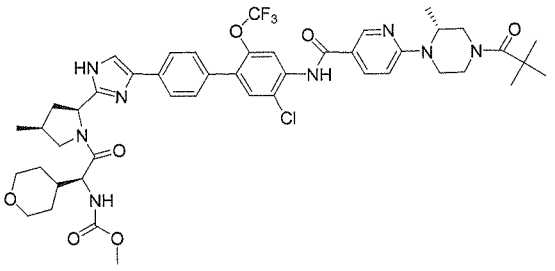
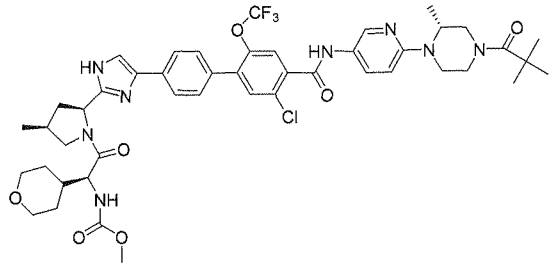
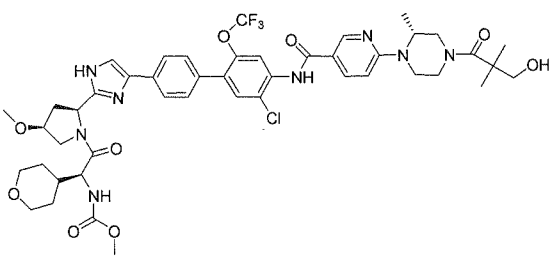
Example No.	Genotype 1a	Genotype 1b
26-4	C	D
26-5	A	
26-6	C	
26-7	C	D
26-8	C	
26-9	C	
26-10	A	
26-11	A	
Table 27		
27-1	D	D
27-2	D	
27-3	D	D
27-4	D	
27-5	D	D
27-6	D	D
27-7	D	
27-8	D	D
Table 28		
28-1	D	D
28-2	D	D
28-3	D	D
28-4	D	
28-5	D	

Example No.	Genotype 1a	Genotype 1b
28-6	D	D
28-7	D	D
28-8	D	
28-9	D	
28-10	D	
28-11	D	D
28-12	D	
28-13	D	
28-14	D	
28-15	D	D
28-16	D	D
28-17	D	D
28-18	D	D
28-19	C	D
28-20	D	D
28-21	D	D
28-22	D	D
28-23	C	
Table 29		
29-1	D	
29-2	C	
29-3	C	
29-4	D	

~~While the present invention has been described with reference to specific aspects or embodiments thereof, it will be understood by those of ordinary skill in the art that various changes can be made or equivalents can be substituted without departing from the true spirit and scope of the invention. Additionally, to the extent permitted by applicable patent statutes and regulations, all publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety as though individually incorporated by reference.~~

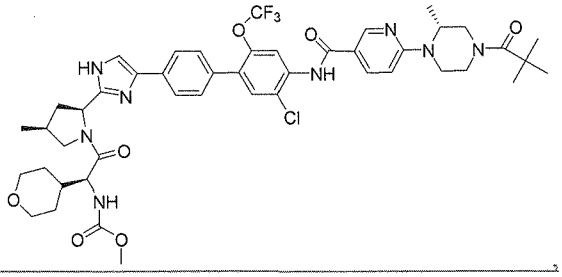
and pharmaceutically-acceptable salts thereof.

11. The compound of Claim 10 wherein the compound is selected from

and pharmaceutically-acceptable salts thereof.

12. The compound of claim 1, which is:



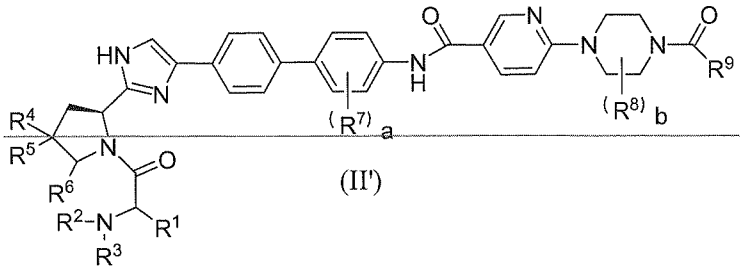
or a pharmaceutically acceptable salt thereof.

~~12~~13. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to ~~11~~12 and a pharmaceutically-acceptable carrier.

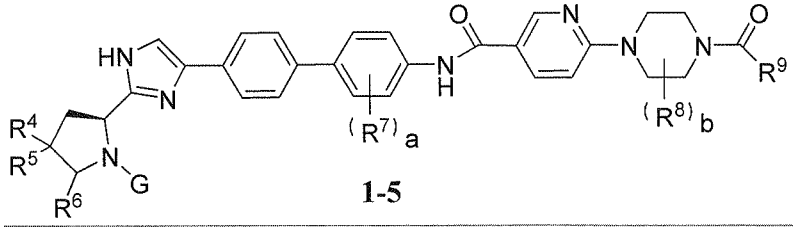
~~13~~14. The pharmaceutical composition of Claim ~~12~~13 further comprising one or more other therapeutic agents useful for treating hepatitis C viral infections.

~~14~~15. The pharmaceutical composition of Claim ~~13~~14 wherein the one or more other therapeutic agents is selected from HCV NS3 protease inhibitors, and HCV NS5B nucleoside and non-nucleoside polymerase inhibitors.

~~15~~16. A process for preparing a compound of formula (~~II~~1-5)

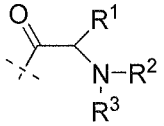


(II')



1-5

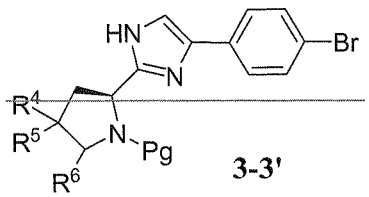
where G represents the group



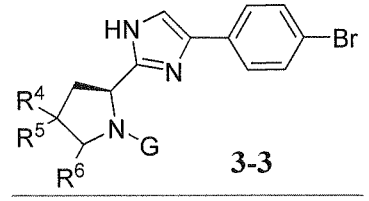
, and

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 in Claim 1, or a pharmaceutically-acceptable salt or stereoisomer thereof, the process comprising:

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

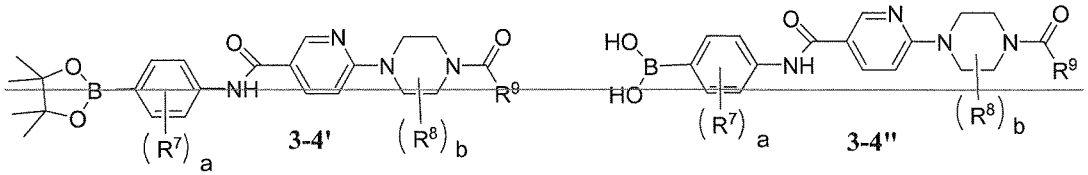


3-3'

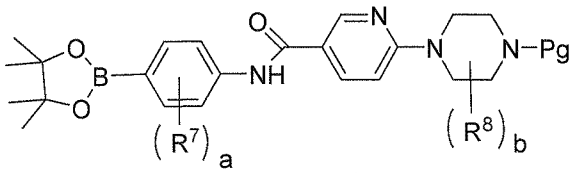


3-3

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



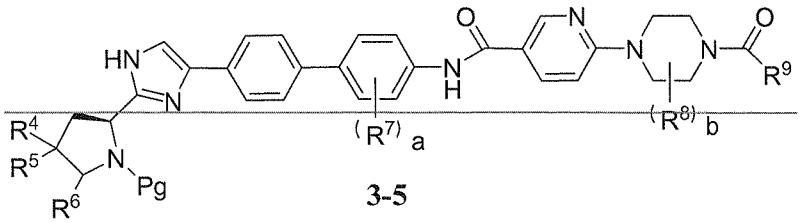
3-4' 3-4"



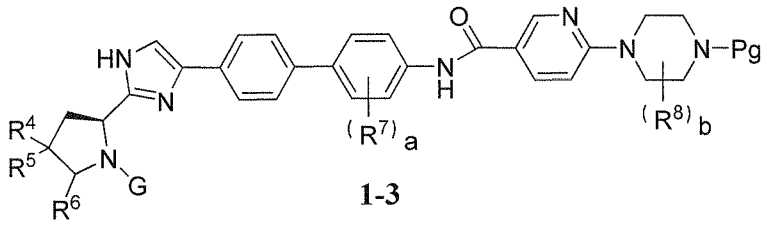
3-4

wherein Pg is an amino-protecting group,

to provide a protected intermediate ~~3-5~~1-3



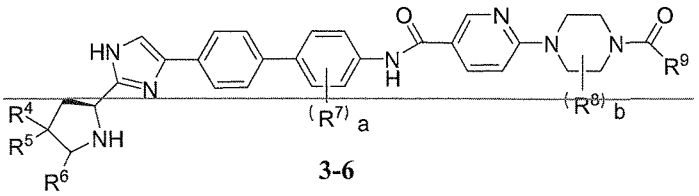
3-5



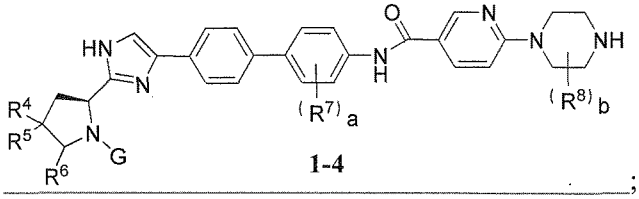
1-3

;

(b) deprotecting intermediate ~~3-5~~1-3 to provide a deprotected intermediate ~~3-6~~1-4:



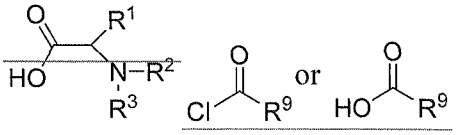
3-6



1-4;

and

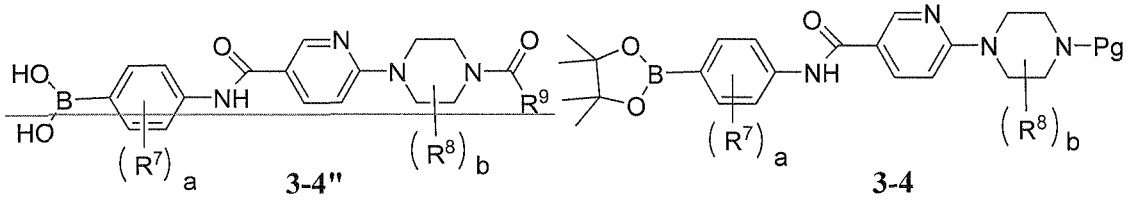
(c) reacting intermediate ~~3-6~~1-4 with a carboxylic acid or carboxylic acid chloride:



to provide a compound of formula (~~II~~1-5) or a pharmaceutically-acceptable salt or stereoisomer thereof.

~~16~~17. The process of Claim ~~15~~16, wherein R^1 is C_{1-6}alkyl or tetrahydropyranyl, R^2 is hydrogen, R^3 is -C(O)OC_{1-6}alkyl, R^4 is methyl or methoxy, R^5 and R^6 are both hydrogen, 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.

~~17~~18. A compound of formula ~~3-4"~~3-4:



3-4" **3-4**

wherein Pg is an amino-protecting group, 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.

~~18. The compound of Claim 17 wherein the compound is crystalline.~~

19. A compound as claimed in any one of Claims 1 to ~~11~~12 for use in therapy.

20. A compound as claimed in any one of Claims 1 to ~~11~~12 for use in the treatment of a hepatitis C viral infection in a mammal.

21. The compound of Claim 20 for use in the treatment of a hepatitis C viral infection in a mammal in combination with one or more other therapeutic agents.

22. The compound of Claim 21 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.

23. A compound as claimed in any one of Claims 1 to ~~11~~ 12 for use in inhibiting replication of the hepatitis C virus in a mammal.

24. The compound of Claim 23 for use in inhibiting replication of the hepatitis C virus in a mammal 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.

25. Use of a compound as claimed in any one of Claims 1 to ~~11~~ 12 for manufacture of a medicament for the treatment of hepatitis C viral infections in a mammal.