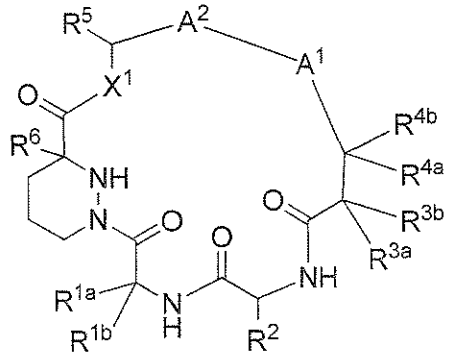
2007, *5*(6), 453-463). A number of HCV treatments are reviewed by Dymock et al. in Antiviral Chemistry & Chemotherapy, 11:2; 79-95 (2000). Virologic cures of patients with chronic HCV infection are difficult to achieve because of the prodigious amount of daily virus production in chronically infected patients and the high spontaneous mutability of HCV virus (Neumann, et al., *Science* 1998, *282*, 103-7; Fukimoto, et al., *Hepatology*, 1996, *24*, 1351-4; Domingo, et al., *Gene* 1985, *40*, 1-8; Martell, et al., *J. Virol.* 1992, *66*, 3225-9.

Currently, there are primarily two antiviral compounds, ribavirin, a nucleoside analog, and interferon-alpha (α) (IFN), that are used for the treatment of chronic HCV infections in humans. Ribavirin alone is not effective in reducing viral RNA levels, has significant toxicity, and is known to induce anemia. The combination of IFN and ribavirin has been reported to be effective in the management of chronic hepatitis C (Scott, L. J., et al. *Drugs* 2002, 62, 507-556) but less than half the patients given this treatment show a persistent benefit. Therefore, there is a need to develop more effective anti-HCV therapies.

The macrocycle sanglifehrin and derivatives are immunomodulatory and bind peptidyl-prolyl cis/trans isomerase (PPIase) cyclophilins in a unique manner (WO 97/02285; WO 98/07743; *J. Am. Chem. Soc* 2003, 125, 3849-3859; *J. Org. Chem.* 2000, 65, 9255-9260; *Angew. Chem. Int. Ed.* 1999, 38, 2443-2446). The cyclophilins are peptidyl-prolyl cis/trans isomerases (PPIase) that regulate protein folding *in vivo* and inhibit hepatitis C virus (Lin et al., WO2006/138507). However, none of the sanglifehrins or their derivatives has become available for human anti-viral therapy. Therefore, there is a continuing need to develop macrocyclic sanglifehrins with anti-*Flaviviridae* virus activity and particularly anti-HCV activity.

SUMMARY

In one ~~embodiment~~aspect, there is provided a compound ~~represented by~~of Formula I:



Formula I

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein:

A^1 is $(C_2\text{-}C_5)$alkylene, $(C_2\text{-}C_5)$alkenylene, $(C_2\text{-}C_5)$alkynylene, -O-$(C_2\text{-}C_4)$alkylene, -O-$(C_2\text{-}C_4)$alkenylene, arylene, aryl$(C_1\text{-}C_2)$alkylene, heterocycloalkylene or heterocycloalkyl$(C_1\text{-}C_2)$alkylene, wherein a sp^3 carbon atom of A^1 is optionally substituted with one or more $(C_1\text{-}C_4)$alkyl;

A^2 is arylene or heteroarylene, wherein A^2 is optionally substituted with halo;

X^1 is -O-, -NH- or -N($(C_1\text{-}C_4)$alkyl)-;

R^{1a} and R^{1b} are independently H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl;

R^2 is H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl;

R^{3a} and R^{3b} are independently H or $(C_1\text{-}C_8)$alkyl;

R^{4a} and R^{4b} are independently H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl;

R^5 is H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl, or

R^5 forms a cyclic moiety along with -N($(C_1\text{-}C_4)$alkyl)- of X^1 or arylene of A^2; and

R^6 is H or $(C_1\text{-}C_4)$alkyl.

In another ~~embodiment~~aspect, there is provided a pharmaceutical composition comprising a therapetucially effective amount of a compound of Formula I as described herein or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof and ~~one or more~~a pharmaceutically acceptable ~~carriers or~~ excipient~~s~~. In one ~~aspect of the~~ embodiment, the pharmaceutical composition further comprises one or more additional therapeutic agents.

In yet another embodiment, a method for treating *Flaviviridae* viral infection is provided comprising administering a therapeutically effective amount of a compound of Formula I or a

pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof to a mammal in need thereof. In one ~~aspect~~ example of the embodiment, the treatment results in the reduction of the in viral load or clearance of viral RNA in a patient.

In yet another embodiment, a method for treating *Coronaviridae* viral infection is provided comprising administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof to a mammal in need thereof. In one ~~aspect~~ example of the embodiment, the treatment results in the reduction of the in viral load or clearance of viral RNA in a patient.

DETAILED DESCRIPTION

Definitions

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

"Alkanoyl" is RC(O)-; "alkanoyloxy" is RC(O)O-; and "alkanoylamino" is RC(O)NR'-; where R is an alkyl group as defined herein, and R' is hydrogen or alkyl.

"Alkenyl" refers to a straight or branched hydrocarbyl group with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond. In some embodiments, alkenyl is a C_2-C_{20} alkenyl group, a C_2-C_{10} alkenyl group or a C_2-C_6 alkenyl group. Examples of alkenyl group include, but are not limited to, vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), cyclopentenyl (-C_5H_7), and 5-hexenyl (-$CH_2CH_2CH_2CH_2$CH=CH_2).

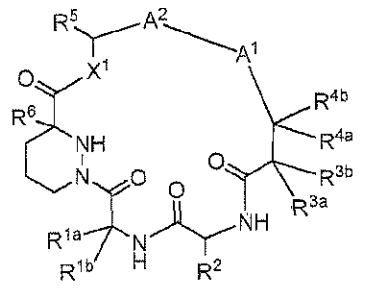
"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, and alkenylene group can have 2 to 20 carbon atoms, 2 to 10 carbon atoms, or 2 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethenylene (-CH=CH-).

"Alkoxy" is RO- where R is alkyl, as defined herein. Non-limiting examples of alkoxy groups include methoxy, ethoxy and propoxy.

"Alkyl" refers to a straight or branched chain hydrocarbyl group. In an embodiment, alkyl has from 1 to 20 carbon atoms (i.e., C_1-C_{20} alkyl). In some embodiments, alkyl is a C_1-C_{10} alkyl

WHAT IS CLAIMED IS:

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein:

A^1 is $(C_2$-$C_5)$alkylene, $(C_2$-$C_5)$alkenylene, $(C_2$-$C_5)$alkynylene, -O-$(C_2$-$C_4)$alkylene, -O-$(C_2$-$C_4)$alkenylene, arylene, aryl$(C_1$-$C_2)$alkylene, heterocycloalkylene or heterocycloalkyl$(C_1$-$C_2)$alkylene, wherein a sp^3 carbon atom of A^1 is optionally substituted with one or more $(C_1$-$C_4)$alkyl;

A^2 is arylene or heteroarylene, wherein A^2 is optionally substituted with halo;

X^1 is -O-, -NH- or -N($(C_1$-$C_4)$alkyl)-;

R^{1a} and R^{1b} are independently H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl or $(C_2$-$C_4)$alkynyl;

R^2 is H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl or $(C_2$-$C_4)$alkynyl;

R^{3a} and R^{3b} are independently H or $(C_1$-$C_8)$alkyl;

R^{4a} and R^{4b} are independently H, -OH, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy or $(C_1$-$C_8)$alkyl;

R^5 is H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl or $(C_2$-$C_4)$alkynyl, or

R^5 forms a cyclic moiety along with -N($(C_1$-$C_4)$alkyl)- of X^1 or arylene of A^2; and

R^6 is H or $(C_1$-$C_4)$alkyl.

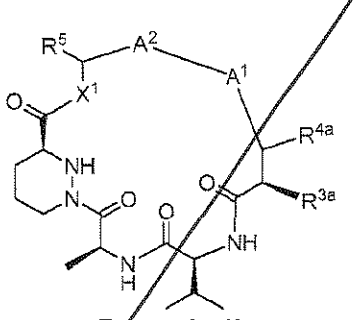
2. The compound of Claim 1, wherein A^1 is ethenylene, propenylene, butenylene, ethylene, propylene, butylene, oxypropylene, oxypropenylene, pyrazolylene, phenylene or pyrimidinylene.

3. The compound of any preceding claim, wherein A^2 is isoquinolinylene, phenylene or halophenylene.

4. The compound of any preceding claim, wherein X^1 is -O- or -NH-; one of R^{1a} and R^{1b} is H and the other is methyl; R^2 is iso-propyl; R^5 is methyl and R^6 is H or methyl.

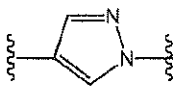
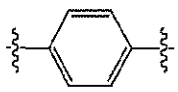
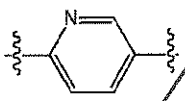
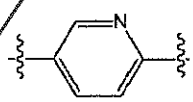
5. The compound of any preceding claim, wherein R^{3a} is H or methyl; R^{3b} is H; R^{4a} is H, -OH, methoxy, trifluoroethoxy; and R^{4b} is H.

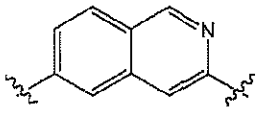
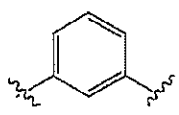
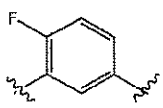
6. The compound of any preceding claim, which is a compound of Formula II:



Formula II

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein:

A^1 is ethenylene, $-CH_2-CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-CH_2-CH_2-$, $-CH=CH-CH_2-C(CH_3)_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-O-CH_2-CH_2-CH_2-$, $-O-CH_2-CH=CH-$,  ,  ,  or  ;

A^2 is  ,  or  ;

X^1 is -O- or -NH-;

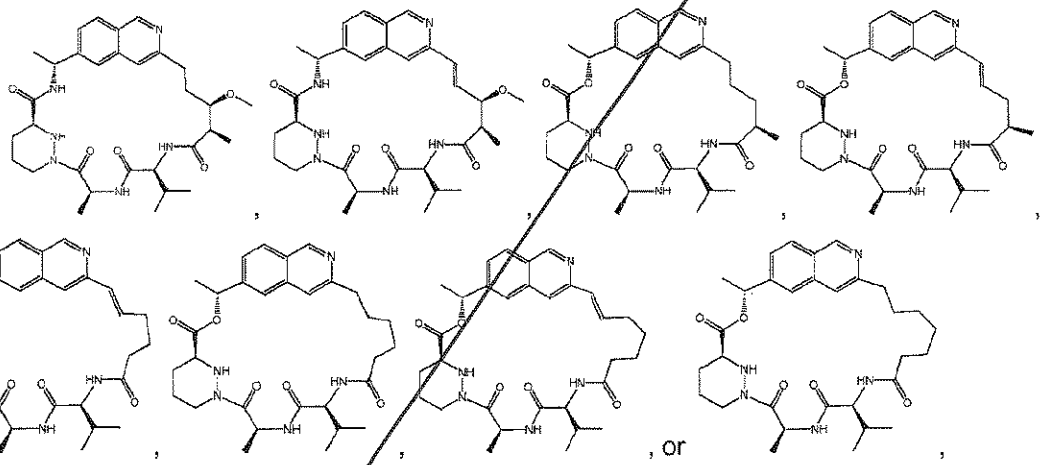
R^{3a} is H or $(C_1$-$C_4)$alkyl;

R^{4a} is H, -OH, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy or $(C_1$-$C_8)$alkyl; and

R^5 is H or $(C_1$-$C_4)$alkyl.

7. The compound of any preceding claim, wherein A^2 is heteroarylene; A^1 is $(C_2$-$C_5)$alkylene, $(C_2$-$C_5)$alkenylene, $(C_2$-$C_5)$alkynylene, wherein A^1 is optionally substituted with one or more $(C_1$-$C_4)$alkyl; R^{3a} is H or $(C_1$-$C_8)$alkyl; and R^{4a} is H, -OH or $(C_1$-$C_4)$alkoxy.

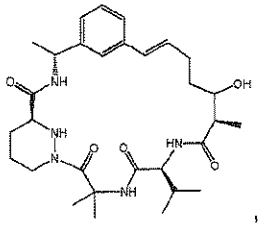
8. The compound of any preceding claim, which is



or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

9. The compound of any preceding claim, wherein A^2 is arylene; and A^1 is $(C_2$-$C_5)$alkylene, $(C_2$-$C_5)$alkenylene, $(C_2$-$C_5)$alkynylene, -O-$(C_2$-$C_5)$alkylene, -O-$(C_2$-$C_4)$alkenylene, wherein A^1 is optionally substituted with one or more $(C_1$-$C_4)$alkyl; R^{3a} is H or $(C_1$-$C_4)$alkyl; and R^{4a} is H, -OH, $(C_1$-$C_4)$alkoxy or halo$(C_1$-$C_4)$alkoxy.

10. The compound of any preceding claim, which is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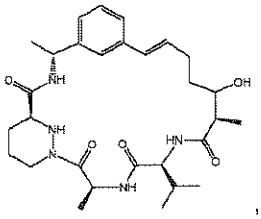
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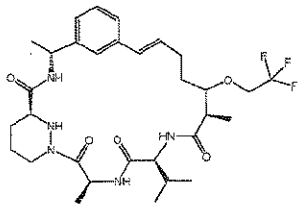
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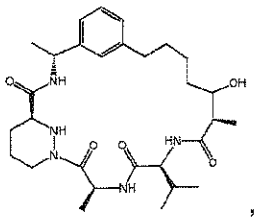
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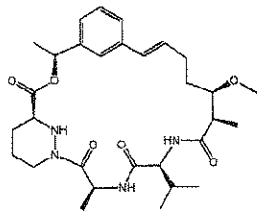
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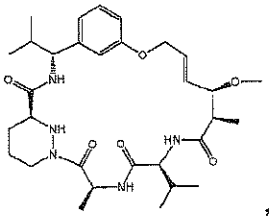
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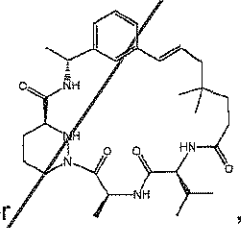
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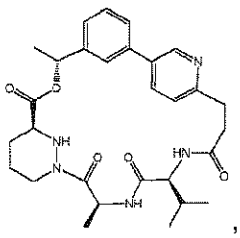
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

11. The compound of any preceding claim, wherein A^2 is arylene; and A^1 is pyrazolylene, phenylene or pyrimidinylene.

12. The compound of any preceding claim, which is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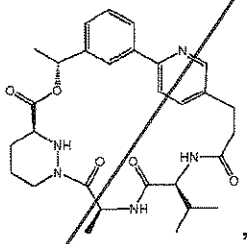
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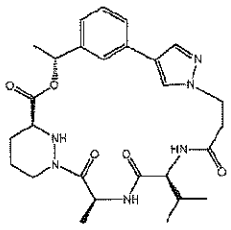
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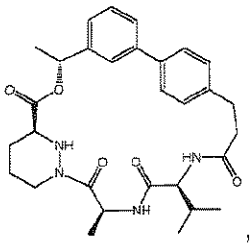
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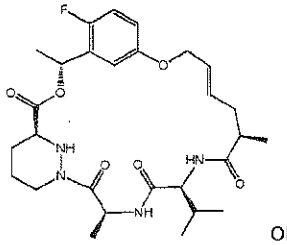
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

13. The compound of any preceding claim, wherein A^2 is haloarylene; and A^1 is -O-(C_2-C_5)alkylene or -O-(C_2-C_4)alkenylene.

14. The compound of any preceding claim, which is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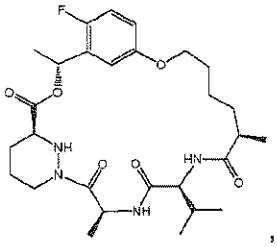
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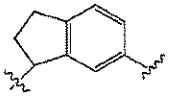
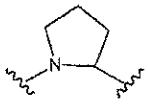
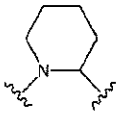
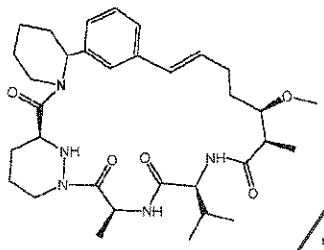
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

15. The compound of any preceding claim, wherein A^1 is $(C_2$-$C_5)$alkylene or $(C_2$-$C_5)$alkenylene; R^5 is methyl, or R^5 form  along with arylene of A^2, or R^5 form  or  along with $-N((C_1$-$C_4)$alkyl$)$- or X^1; and R^6 is H or methyl.

16. The compound of any preceding claim, which is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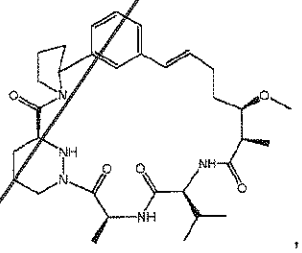
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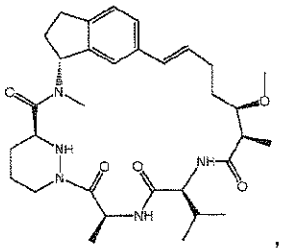
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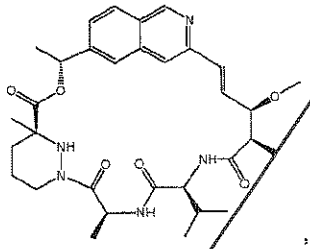
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or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

17. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any preceding claim or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof and a pharmaceutically acceptable excipient.

18. The pharmaceutical composition of Claim 17, further comprising at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin, HCV NS3 protease inhibitors, HCV NS5a inhibitors, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, and TLR-7 agonists; or a mixture thereof.

19. The pharmaceutical composition of Claim 18, wherein the at least one addition therapeutic agent is ribavirin, telaprevir, boceprevir or sofosbuvir.

20. A method for treating a *Flaviviridae* viral infection in a human patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of Claims 1-16 or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

21. The method of Claim 20, wherein the viral infection is caused by a Hepatitis B virus or a Hepatitis C virus.

22. The method of Claim 21, wherein the viral infection causes a disease selected from the group consisting of dengue fever, yellow fever, hepatitis C, Japanese encephalitis, Kyasanur forest disease, Murray valley encephalitis, St. Louis encephalitis, tick-borne encephalitis or West Nile encephalitis.

23. A method for treating a *Coronaviridae* viral infection in a human patient in need thereof, comprising administering to the patient a therapeutically effective amount of a

compound of any one of Claims 1-16 or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

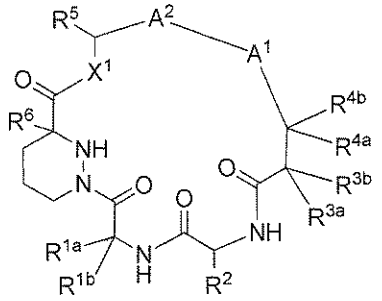
24. The method of Claim 23, wherein the viral infection is caused by a SARS coronarirus.

25. The method of Claim 24, wherein the viral infection causes a disease selected from the group consisting of severe acute respiratory syndrome (SARS), cancer, inflammation, obesity, acquired immune deficiency syndrome (AIDS), or cirrhosis.

26. A method for providing immunomodulation to a human patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of Claims 1-16 or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein:

A^1 is $(C_2\text{-}C_5)$alkylene, $(C_2\text{-}C_5)$alkenylene, $(C_2\text{-}C_5)$alkynylene, -O-$(C_2\text{-}C_4)$alkylene, -O-$(C_2\text{-}C_4)$alkenylene, arylene, aryl$(C_1\text{-}C_2)$alkylene, heterocycloalkylene or heterocycloalkyl$(C_1\text{-}C_2)$alkylene, wherein a sp^3 carbon atom of A^1 is optionally substituted with one or more $(C_1\text{-}C_4)$alkyl;

A^2 is arylene or heteroarylene, wherein A^2 is optionally substituted with halo;

X^1 is -O-, -NH- or -N($(C_1\text{-}C_4)$alkyl)-;

R^{1a} and R^{1b} are independently H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl;

R^2 is H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl;

R^{3a} and R^{3b} are independently H or $(C_1\text{-}C_8)$alkyl;

R^{4a} and R^{4b} are independently H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl;

R^5 is H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl, or

R^5 forms a cyclic moiety along with -N($(C_1\text{-}C_4)$alkyl)- of X^1 or arylene of A^2; and

R^6 is H or $(C_1\text{-}C_4)$alkyl.

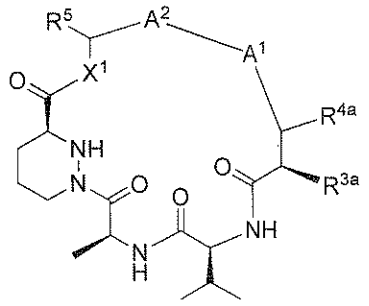
2. The compound of Claim 1, wherein A^1 is ethenylene, propenylene, butenylene, ethylene, propylene, butylene, oxypropylene, oxypropenylene, pyrazolylene, phenylene or pyrimidinylene.

3. The compound of any preceding claim, wherein A^2 is isoquinolinylene, phenylene or halophenylene.

4. The compound of any preceding claim, wherein X^1 is -O- or -NH-; one of R^{1a} and R^{1b} is H and the other is methyl; R^2 is iso-propyl; R^5 is methyl and R^6 is H or methyl.

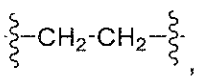
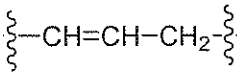
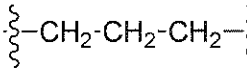
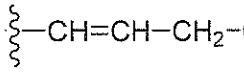
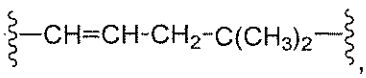
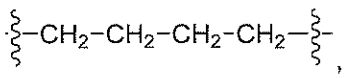
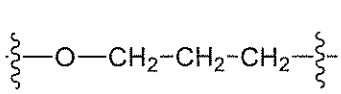
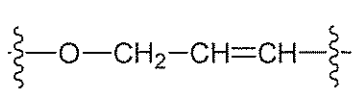
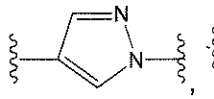
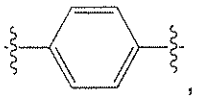
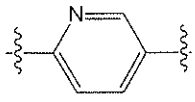
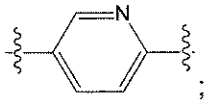
5. The compound of any preceding claim, wherein R^{3a} is H or methyl; R^{3b} is H; R^{4a} is H, -OH, methoxy, trifluoroethoxy; and R^{4b} is H.

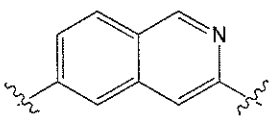
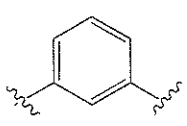
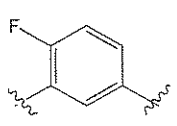
6. The compound of any preceding claim, which is a compound of Formula II:



Formula II

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof, wherein:

A^1 is ethenylene,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  ;

A^2 is  ,  or  ;

X^1 is -O- or -NH-;

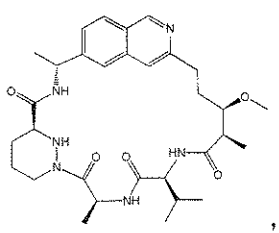
R^{3a} is H or $(C_1\text{-}C_4)$alkyl;

R^{4a} is H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl; and

R^5 is H or $(C_1\text{-}C_4)$alkyl.

7. The compound of any preceding claim, wherein A^2 is heteroarylene; A^1 is $(C_2\text{-}C_5)$alkylene, $(C_2\text{-}C_5)$alkenylene, $(C_2\text{-}C_5)$alkynylene, wherein A^1 is optionally substituted with one or more $(C_1\text{-}C_4)$alkyl; R^{3a} is H or $(C_1\text{-}C_8)$alkyl; and R^{4a} is H, -OH or $(C_1\text{-}C_4)$alkoxy.

8. The compound of any preceding claim, which is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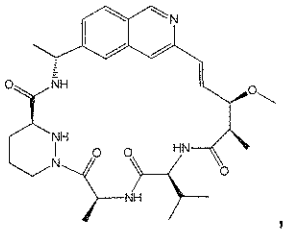
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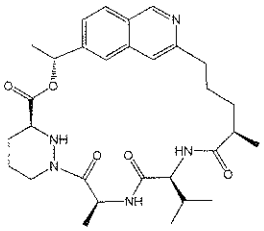
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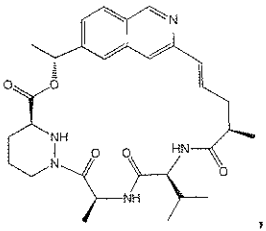
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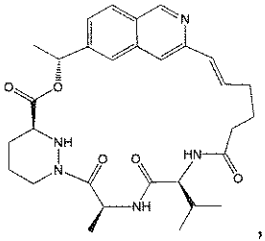
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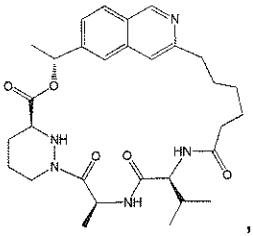
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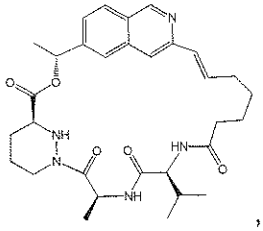
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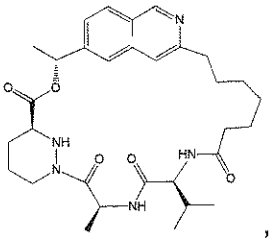
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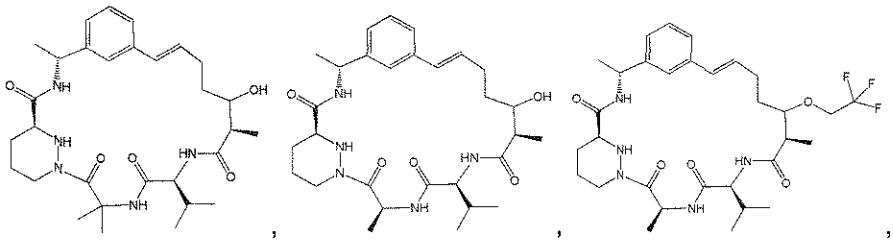
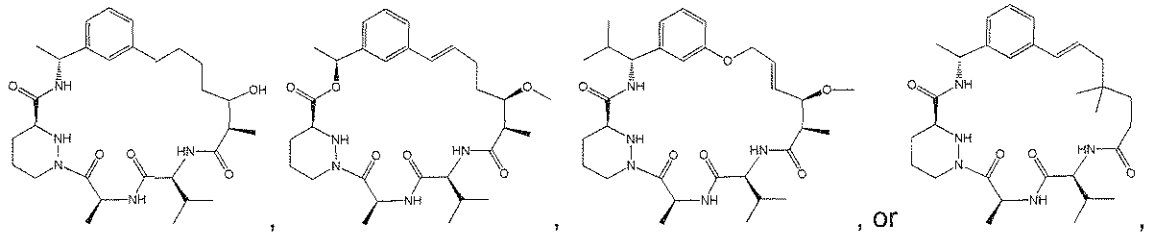
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

9. The compound of any preceding claim, wherein A^2 is arylene; and A^1 is $(C_2\text{-}C_5)$alkylene, $(C_2\text{-}C_5)$alkenylene, $(C_2\text{-}C_5)$alkynylene, -O-$(C_2\text{-}C_5)$alkylene, -O-$(C_2\text{-}C_4)$alkenylene, wherein A^1 is optionally substituted with one or more $(C_1\text{-}C_4)$alkyl; R^{3a} is H or $(C_1\text{-}C_4)$alkyl; and R^{4a} is H, -OH, $(C_1\text{-}C_4)$alkoxy or halo$(C_1\text{-}C_4)$alkoxy.

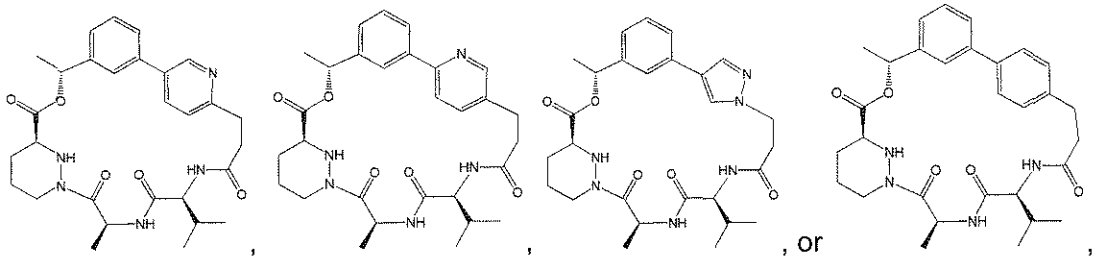
10. The compound of any preceding claim, which is

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

11. *The compound of any preceding claim, wherein* A^2 *is arylene; and* A^1 *is* pyrazolylene, phenylene or pyrimidinylene.

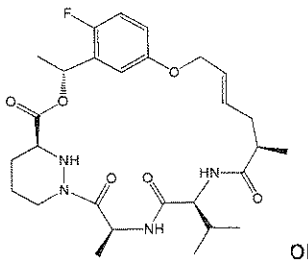
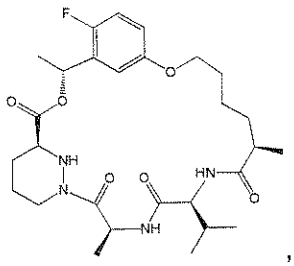
12. The compound of any preceding claim, which is



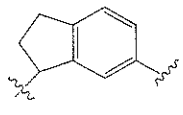
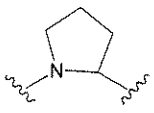
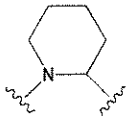
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

13. The compound of any preceding claim, wherein A^2 is haloarylene; and A^1 is -O-(C_2-C_5)alkylene or -O-(C_2-C_4)alkenylene.

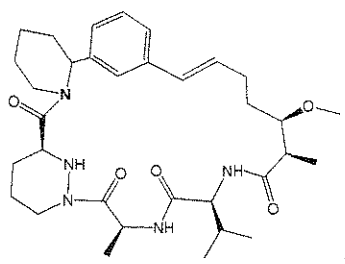
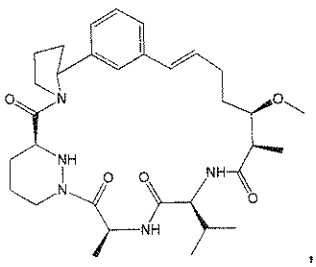
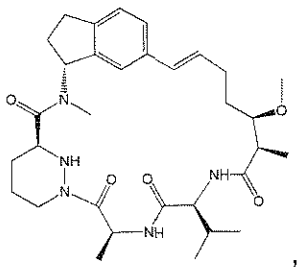
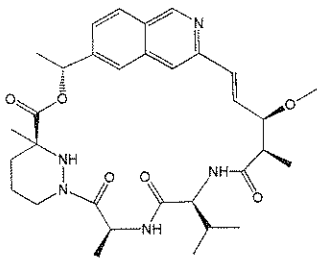
14. The compound of any preceding claim, which is

 or  ,

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

15. The compound of any preceding claim, wherein A^1 is $(C_2$-$C_5)$alkylene or $(C_2$-$C_5)$alkenylene; R^5 is methyl, or R^5 form  along with arylene of A^2, or R^5 form  or  along with $-N((C_1$-$C_4)alkyl)-$ of X^1; and R^6 is H or methyl.

16. The compound of any preceding claim, which is

 ,  ,  , or  ,

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

17. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any preceding claim or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof and a pharmaceutically acceptable excipient.

18. The pharmaceutical composition of Claim 17, further comprising at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin, HCV NS3 protease inhibitors, HCV NS5a inhibitors, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, and TLR-7 agonists; or a mixture thereof.

19. The pharmaceutical composition of Claim 18, wherein the at least one addition therapeutic agent is ribavirin, telaprevir, boceprevir or sofosbuvir.