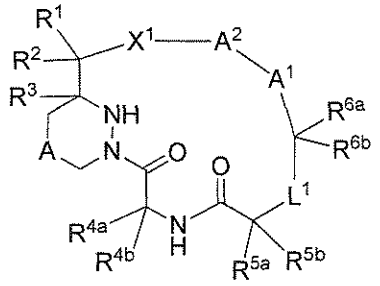
infection are difficult to achieve because of the prodigious amount of daily virus production in chronically infected patients and the high spontaneous mutability of HCV virus (Neumann, et al., *Science* 1998, *282*, 103-7; Fukimoto, et al., *Hepatology*, 1996, *24*, 1351-4; Domingo, et al., *Gene* 1985, *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.

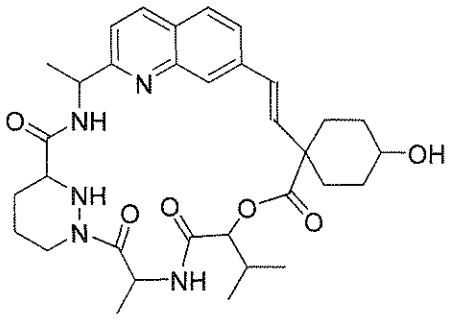
SUMMARY

In one aspect, there is provided a compound of Formula I:



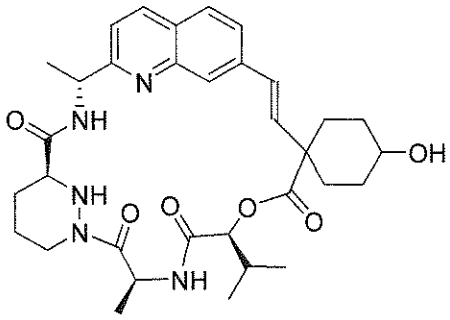
Formula I

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



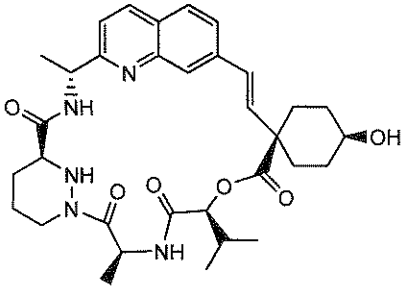
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof.

In one aspect, there is provided a compound which is:



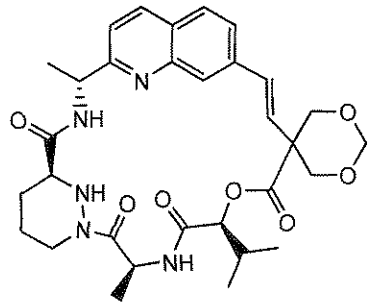
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof.

In one aspect, there is provided a compound which is:



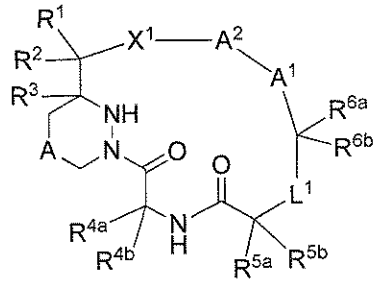
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof.

In one aspect, there is provided a compound which is:



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

In one aspect, there is provided a compound of Formula I:



Formula I

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

A is CH_2;

A^1 is $(C_2\text{-}C_5)$alkenylene, wherein a sp^3 carbon atom of A^1 is optionally replaced by -O-, $-S(O)_n$-, -NH- or $-N((C_1\text{-}C_4)alkyl)$-, and wherein a sp^3 or sp^2 carbon atom of A^1 is optionally substituted with one or more groups selected from the group consisting of halo, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, aryl, heterocycloalkyl, cycloalkyl, aryl$(C_1\text{-}C_4)$alkyl, cycloalkyl$(C_1\text{-}C_4)$alkyl, heterocycloalkyl$(C_1\text{-}C_4)$alkyl, arylheterocycloalkyl$(C_1\text{-}C_4)$alkyl, $-OR^9$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ and $-N(R^9)_2$;

A^2 is $-CH(R^8)$-heteroarylene, wherein A^2 is optionally substituted with one or more substituents selected from the group consisting of $-OR^9$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-N(R^9)_2$, halo, halo$(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkoxy, cyano and $(C_1\text{-}C_8)$alkyl;

L^1 is -O-C(O);

X^1 is -NH- or -N(CH_3)-;

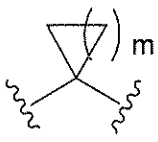
R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-;

R^3 is H or (C_1-C_4)alkyl optionally substituted with halo, cyano, hydroxyl or (C_1-C_4)alkoxy;

R^{4a} and R^{4b} are independently H or (C_1-C_8)alkyl, wherein each R^{4a} and R^{4b} is optionally substituted with one or more substituents selected from the group consisting of cyano, -COOH, halo, hydroxyl, amino, (C_1-C_8)alkoxy, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, aryl and heteroaryl;

R^{5a} and R^{5b} are independently H or (C_1-C_8)alkyl optionally substituted with one or more substituents selected from the group consisting of -N_3, cyano, -COOH, halo, hydroxyl, amino, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, (C_1-C_8)alkoxy, aryl and heteroaryl, or

R^{5a} and R^{5b} together form a spirocycle having Formula (a):



(a),

wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, =N(C_1-C_4)alkoxy, halo, hydroxyl, -NH_2, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, -OC(O)R^9, -C(O)$_2R^9$, and -S(O)$_2R^9$;

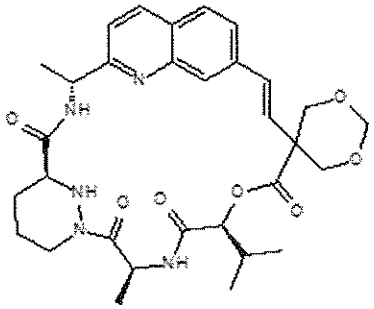
R^{6a} and R^{6b} together form a spirocycle having Formula (a);

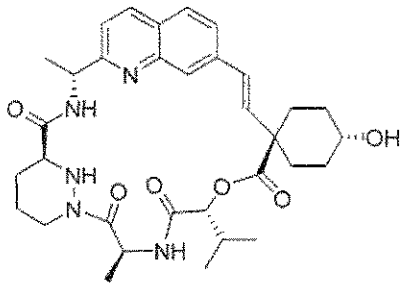
R^8 is H, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl, wherein R^8 is optionally substituted with -OR, -N(R^9)$_2$, -CON(R^9)$_2$, or cyano;

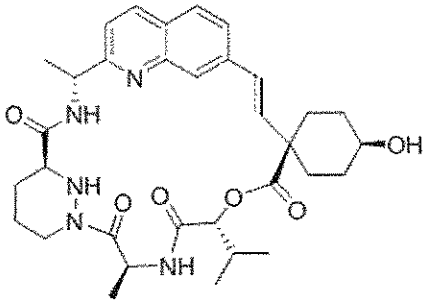
each R^9 is independently H, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_2-C_4)alkenyl or (C_2-C_4)alkynyl; and

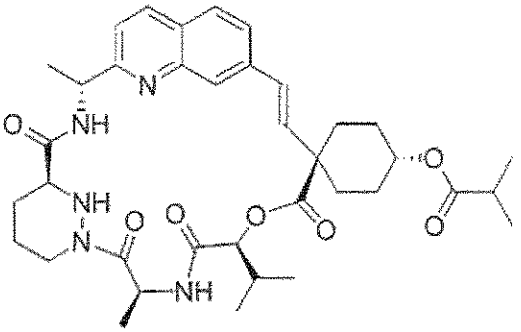
m is 1, 2, 3, 4 or 5.

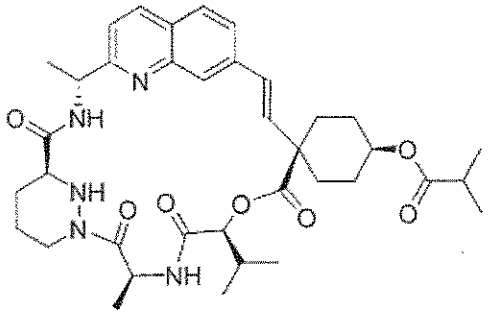
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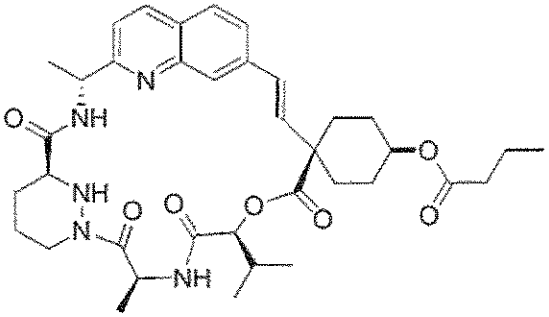


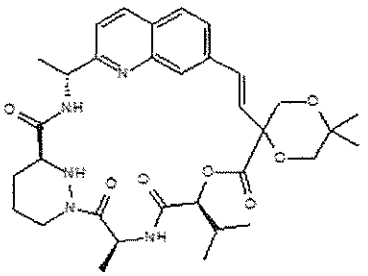


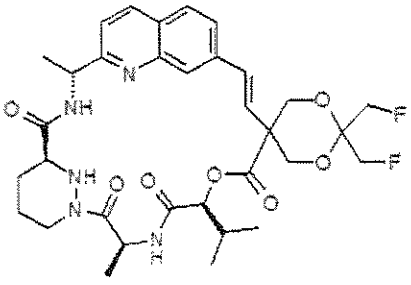


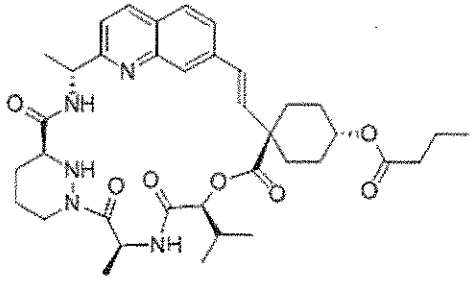
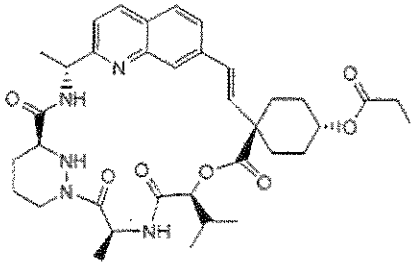
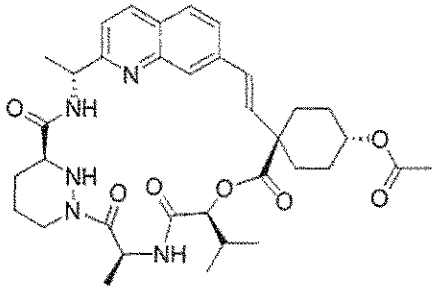
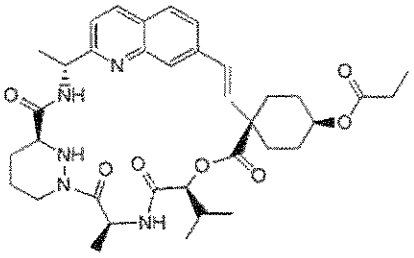
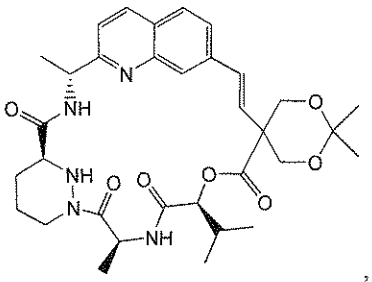
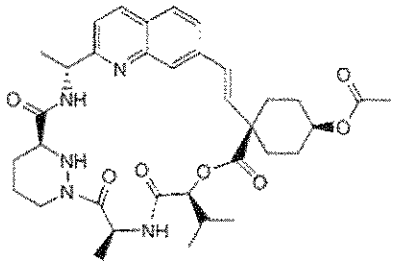
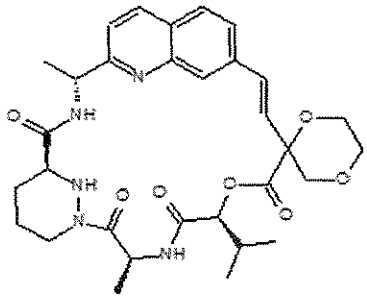
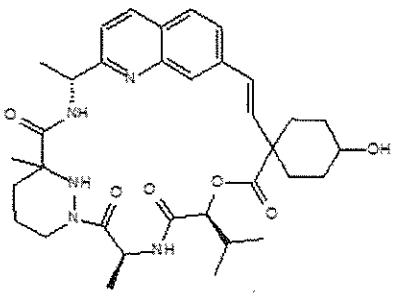
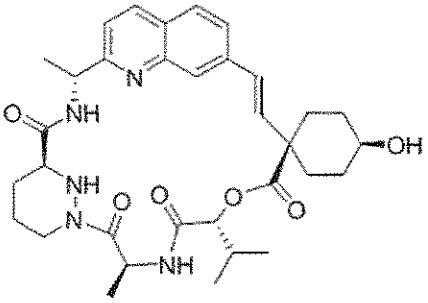








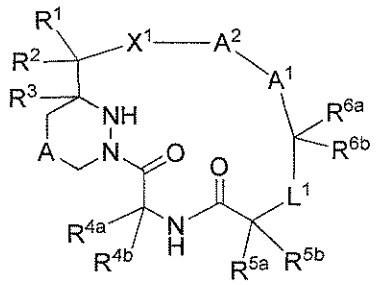



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In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I as described above or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof and a pharmaceutically acceptable

What is claimed is:

1. A compound of Formula I:



Formula I

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

A is a bond, -O-, -S(O)$_n$-, -NH-, -N((C$_1$-C$_4$)alkyl)- or (C$_1$-C$_2$)alkylene;

A^1 is (C$_1$-C$_5$)alkylene, (C$_2$-C$_5$)alkenylene, (C$_2$-C$_5$)alkynylene, arylene, heteroarylene, cycloalkylene, heterocycloalkylene, aryl(C$_1$-C$_2$)alkylene, heteroaryl(C$_1$-C$_2$)alkylene, cycloalkyl(C$_1$-C$_2$)alkylene or heterocycloalkyl(C$_1$-C$_2$)alkylene, wherein a sp^3 carbon atom of A^1 is optionally replaced by -O-, -S(O)$_n$-, -NH- or -N((C$_1$-C$_4$)alkyl)-, and wherein a sp^3 or sp^2 carbon atom of A^1 is optionally substituted with one or more groups selected from the group consisting of halo, (C$_1$-C$_8$)alkyl, (C$_2$-C$_8$)alkenyl, (C$_2$-C$_8$)alkynyl, aryl, heterocycloalkyl, cycloalkyl, aryl(C$_1$-C$_4$)alkyl, cycloalkyl(C$_1$-C$_4$)alkyl, heterocycloalkyl(C$_1$-C$_4$)alkyl, arylheterocycloalkyl(C$_1$-C$_4$)alkyl, -OR^9, -SR^9, -S(O)R^9, -S(O)$_2$R^9 and -N(R^9)$_2$;

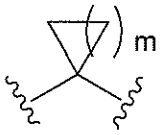
A^2 is -CH(R^8)-arylene, -CH(R^8)-heteroarylene, -CH(R^8)-heterocycloalkylene, -CH(R^8)-cycloalkylene, arylene, cycloalkylene, (C$_1$-C$_3$)alkylene, (C$_2$-C$_3$)alkenylene or (C$_2$-C$_3$)alkynylene, wherein A^2 is optionally substituted with one or more substituents selected from the group consisting of -OR^9, -SR^9, -S(O)R^9, -S(O)$_2$R^9, -N(R^9)$_2$, halo, halo(C$_1$-C$_4$)alkyl, halo(C$_1$-C$_4$)alkoxy, cyano and (C$_1$-C$_8$)alkyl;

L^1 is -O-C(O)-, -O-CH$_2$-, -NR^{11}-CH$_2$-, -NH-C(R^{10})$_2$- or -NH-S(O)$_2$-, wherein each R^{10} is independently H, (C$_1$-C$_4$)alkyl, halo(C$_1$-C$_4$)alkyl, (C$_1$-C$_4$)alkenyl or cycloalkyl; and R^{11} is (C$_1$-C$_4$)alkyl, halo(C$_1$-C$_4$)alkyl, (C$_1$-C$_4$)alkenyl or cycloalkyl;

X^1 is a bond, -O-, -NH-, -N((C$_1$-C$_4$)alkyl)- or heterocycloalkylene;

8. The compound of claim 1, wherein one of R^{6a} and R^{6b} is H; and the other H, hydroxyl, $-CH_2CH_2CR^9(=N(C_1\text{-}C_4)alkoxy)$, $(C_1\text{-}C_8)$alkyl or $(C_1\text{-}C_8)$alkoxy, wherein R^{6a} or R^{6b} is optionally substituted with one or more substituents selected from the group consisiting of halo, hydroxyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, heterocycloalkyl, $(C_1\text{-}C_4)$alkanoyl or di$(C_1\text{-}C_4)$alkylamino.

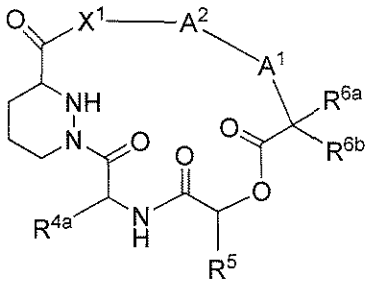
9. The compound of claim 1, wherein R^{6a} and R^{6b} together form a spirocycle having Formula (a):



(a),

wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, $=N(C_1\text{-}C_4)$alkoxy, halo, hydroxyl, $-NH_2$, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $-OC(O)R^9$, $-C(O)_2R^9$, and $-S(O)_2R^9$.

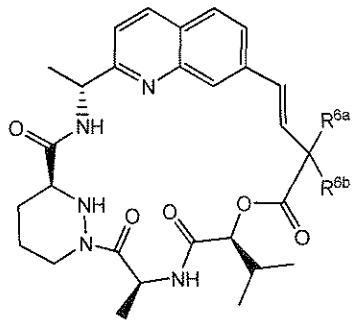
10. The compound of Claim 1, which is a compound of Formula II:



Formula II

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

13. The compound of Claim 1, which is a compound of Formula II-c:

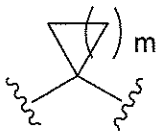


Formula II-c

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

R^{6a} and R^{6b} are independently H, hydroxyl, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $-CH_2CH_2CR^9(=N(C_1$-$C_4)$alkoxy), aryl, heterocycloalkyl, cycloalkyl, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ and $-N(R^9)_2$, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, cyano, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono$(C_1$-$C_8)$alkylamino, di$(C_1$-$C_8)$alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$ and $(C_1$-$C_8)$alkanoyl where such an optional substitution is chemically feasible; or R^{6a} and R^{6b} together form a spirocycle having Formula (a); or

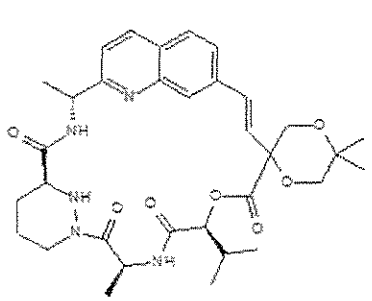
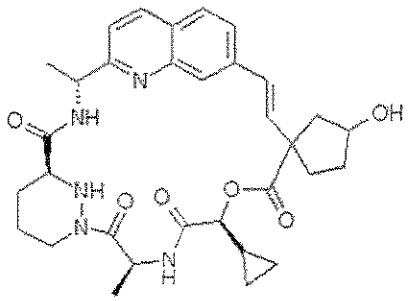
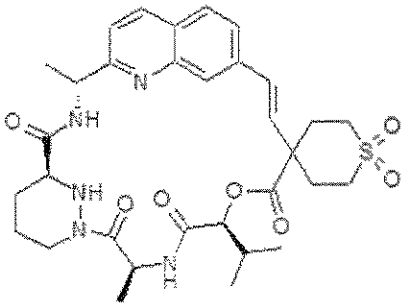
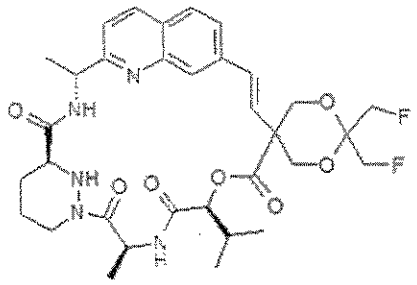
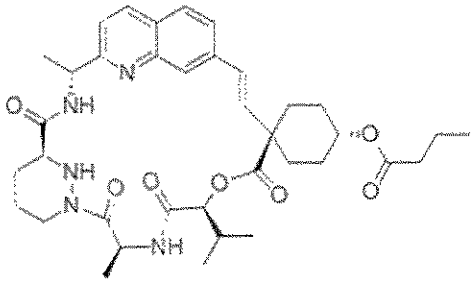
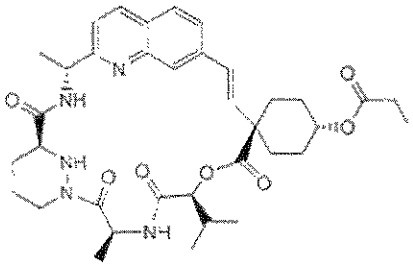
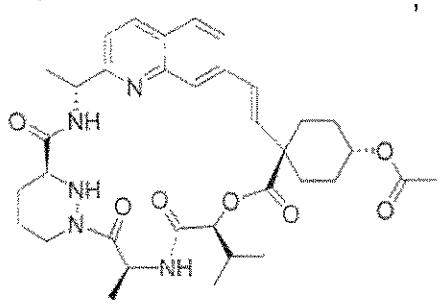
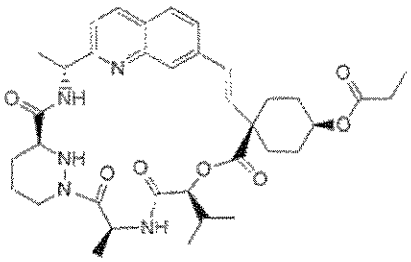
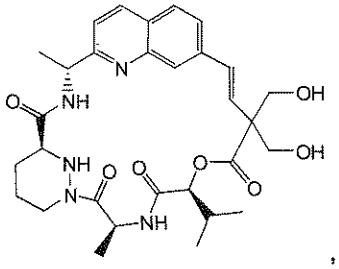
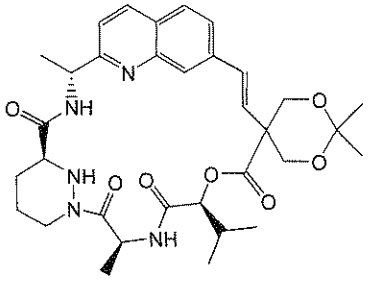
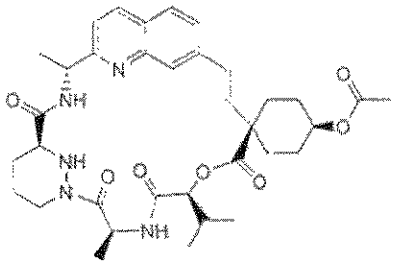
R^{6a} and R^{6b} together form a spirocycle having Formula (a):



(a),

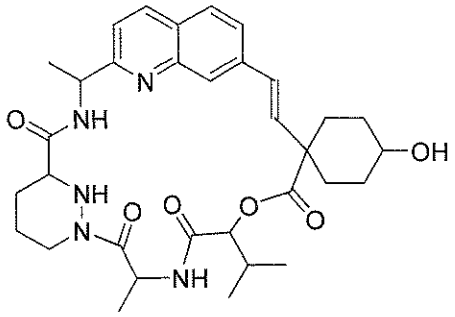
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, $=N(C_1$-$C_4)$alkoxy, halo, hydroxyl, $-NH_2$, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $-OC(O)R^9$, $-C(O)_2R^9$, and $-S(O)_2R^9$; and

each R^9 is independently H, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl or $(C_2$-$C_4)$alkynyl.


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or

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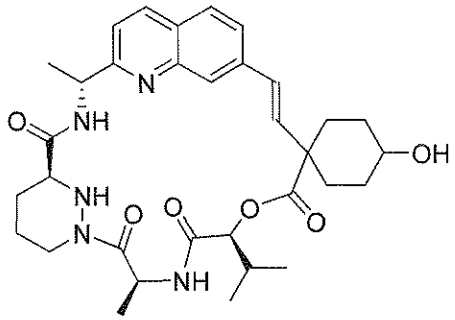
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof.

18. A compound which is:



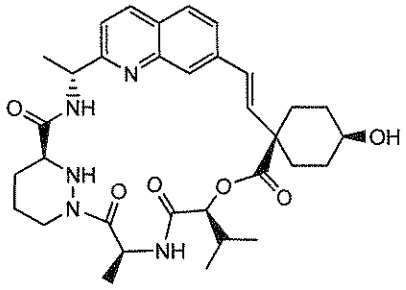
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof.

19. A compound which is:



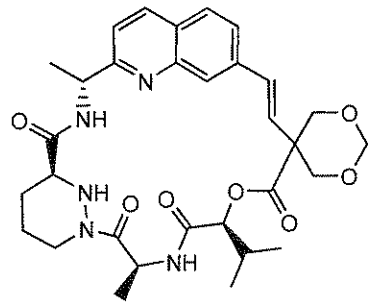
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof.

20. A compound which is:



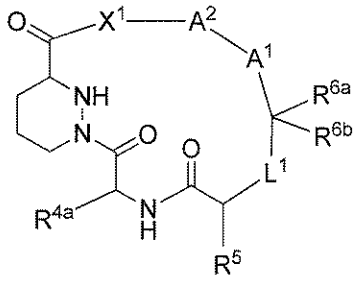
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof.

21. A compound which is:



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

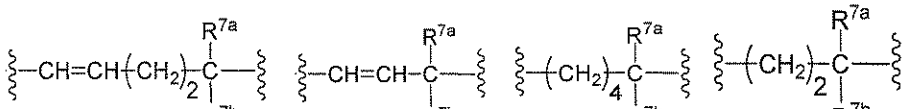
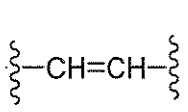
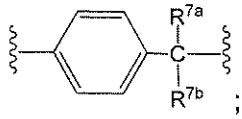
22. The compound of Claim 1, which is a compound of Formula III:



Formula III

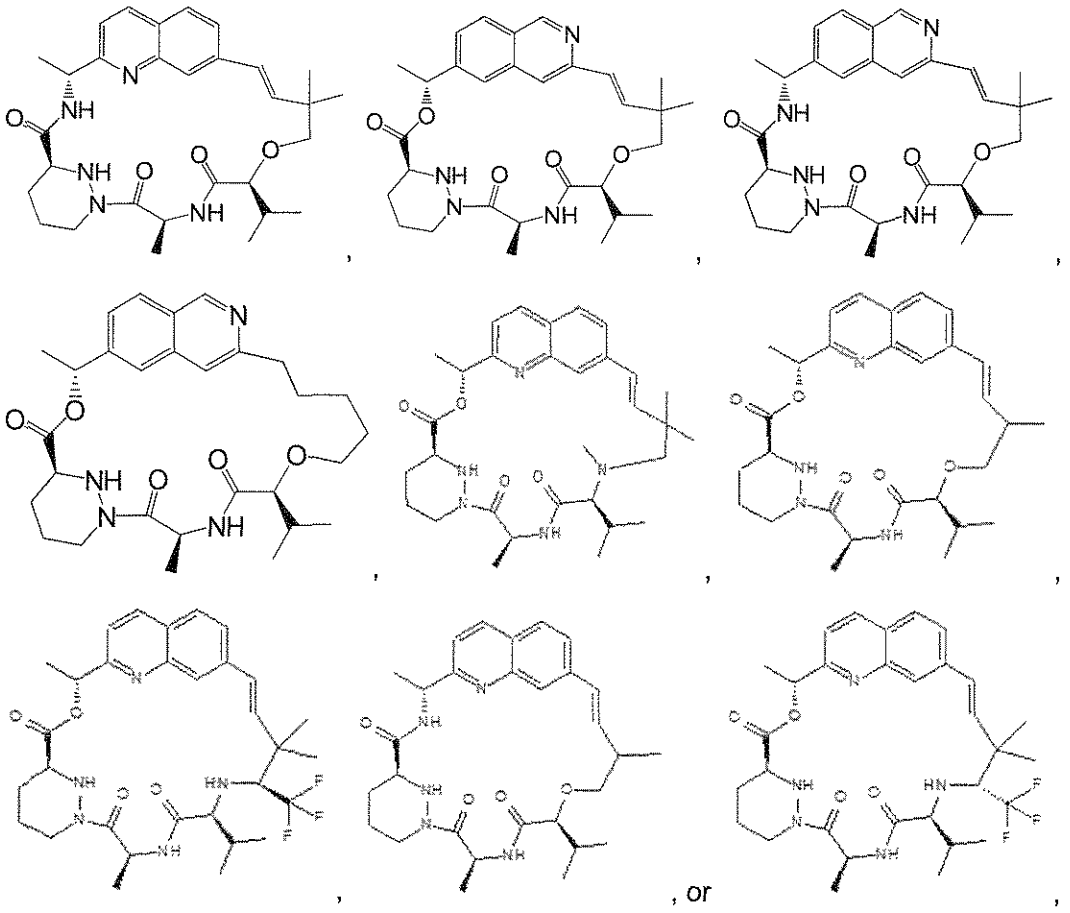
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof, wherein

L^1 is -O-CH_2-, -NH-CH_2-, -N(CH_3)-CH_2-, -NH-CH(CF_3)- or -NH-S(O)$_2$-;

A^1 is ,  or ;

A^2 is -CH(R^8)-arylene, -CH(R^8)-heteroarylene, -CH(R^8)-heterocycloalkylene, -CH(R^8)-cycloalkylene, arylene or cycloalkylene;

X^1 is -O-, -N(CH_3)- or -NH-;



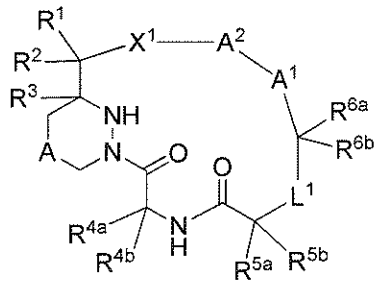
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof.

27. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof and a pharmaceutically acceptable excipient.

28. The pharmaceutical composition of Claim 27, 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.

29. The pharmaceutical composition of Claim 28, wherein the at least one addition therapeutic agent is ribavirin, telaprevir, boceprevir or sofosbuvir.

30. A compound of Formula I:



Formula I

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

A is CH_2;

A^1 is $(C_2$-$C_5)$alkenylene, wherein a sp^3 carbon atom of A^1 is optionally replaced by -O-, $-S(O)_n$-, -NH- or $-N((C_1$-$C_4)$alkyl)-, and wherein a sp^3 or sp^2 carbon atom of A^1 is optionally substituted with one or more groups selected from the group consisting of halo, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, aryl, heterocycloalkyl, cycloalkyl, aryl$(C_1$-$C_4)$alkyl, cycloalkyl$(C_1$-$C_4)$alkyl, heterocycloalkyl$(C_1$-$C_4)$alkyl, arylheterocycloalkyl$(C_1$-$C_4)$alkyl, $-OR^9$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ and $-N(R^9)_2$;

A^2 is $-CH(R^8)$-heteroarylene, wherein A^2 is optionally substituted with one or more substituents selected from the group consisting of $-OR^9$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-N(R^9)_2$, halo, halo$(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkoxy, cyano and $(C_1$-$C_8)$alkyl;

L^1 is -O-C(O);

X^1 is -NH- or $-N(CH_3)$-;

R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-;

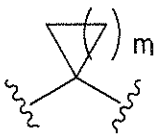
R^3 is H or $(C_1$-$C_4)$alkyl optionally substituted with halo, cyano, hydroxyl or $(C_1$-$C_4)$alkoxy;

R^{4a} and R^{4b} are independently H or $(C_1$-$C_8)$alkyl, wherein each R^{4a} and R^{4b} is optionally substituted with one or more substituents selected from the group consisting of cyano, -COOH,

halo, hydroxyl, amino, $(C_1$-$C_8)$alkoxy, mono$(C_1$-$C_8)$alkylamino, di$(C_1$-$C_8)$alkylamino, aryl and heteroaryl;

R^{5a} and R^{5b} are independently H or $(C_1$-$C_8)$alkyl optionally substituted with one or more substituents selected from the group consisting of $-N_3$, cyano, -COOH, halo, hydroxyl, amino, mono$(C_1$-$C_8)$alkylamino, di$(C_1$-$C_8)$alkylamino, $(C_1$-$C_8)$alkoxy, aryl and heteroaryl, or

R^{5a} and R^{5b} together form a spirocycle having Formula (a):



(a),

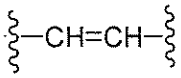
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, $=N(C_1$-$C_4)$alkoxy, halo, hydroxyl, $-NH_2$, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $-OC(O)R^9$, $-C(O)_2R^9$, and $-S(O)_2R^9$;

R^{6a} and R^{6b} together form a spirocycle having Formula (a);

R^8 is H, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl, wherein R^8 is optionally substituted with -OR, $-N(R^9)_2$, $-CON(R^9)_2$, or cyano;

each R^9 is independently H, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl or $(C_2$-$C_4)$alkynyl; and

m is 1, 2, 3, 4 or 5.

31. The compound of claim 30, wherein A^1 is .

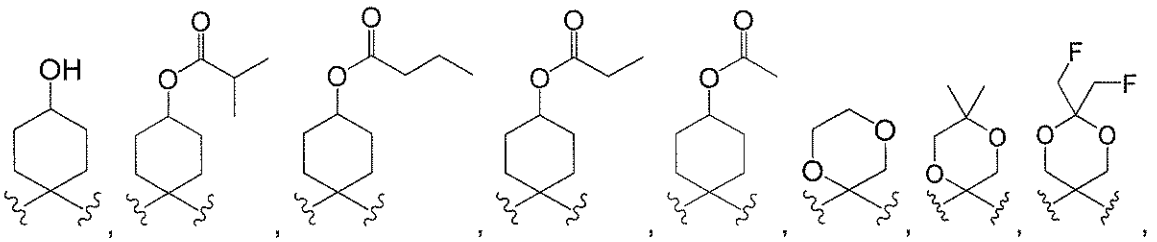
32. The compound of claim 30 or 31, wherein A^2 is $-CH(R^8)$-quinolinylene.

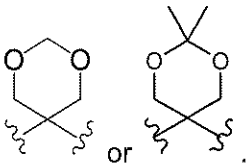
33. The compound of any one of claims 30 to 32 wherein R^8 is methyl.

34. The compound of any one of claims 30 to 33 wherein R^3 is H or methyl; one of R^{4a} and R^{4b} is H and the other is methyl; and one of R^{5a} and R^{5b} is H and the other is isopropyl.

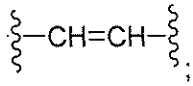
35. The compound of any one of claims 30 to 33 wherein R^3 is H or methyl; one of R^{4a} and R^{4b} is H and the other is methyl; one of R^{5a} and R^{5b} is H and the other is isopropyl; A^2 is $-CH(R^8)$-quinolinylene; and R^8 is methyl.

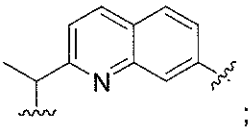
36. The compound of any one of claims 30 to 35, wherein R^{6a} and R^{6b} together form





37. The compound of claim 30, wherein:

A^1 is ;

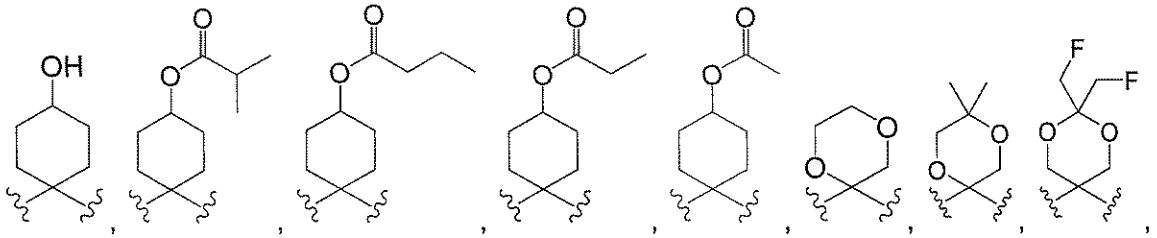
A^2 is ;

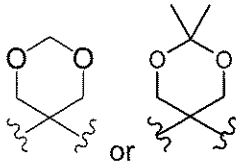
R^3 is H or methyl;

R^{4a} is methyl;

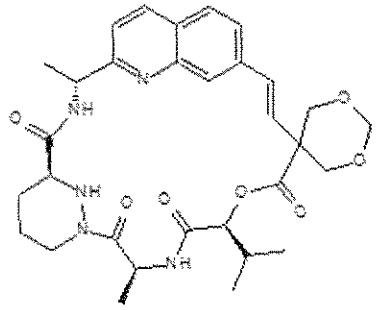
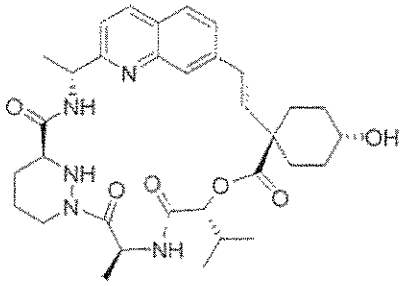
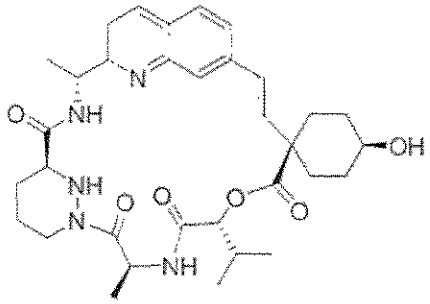
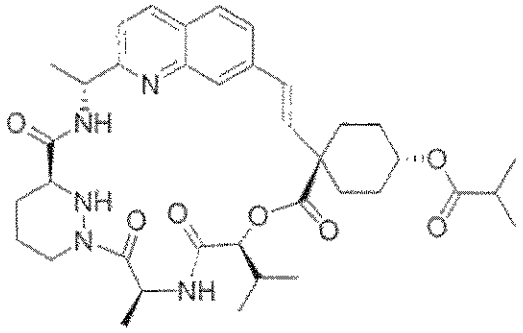
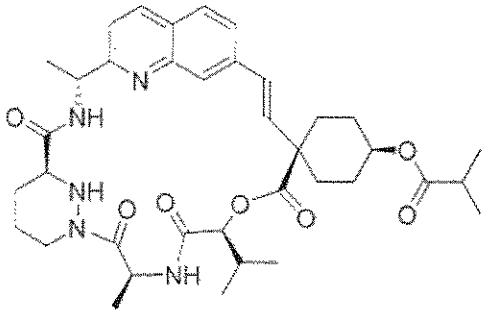
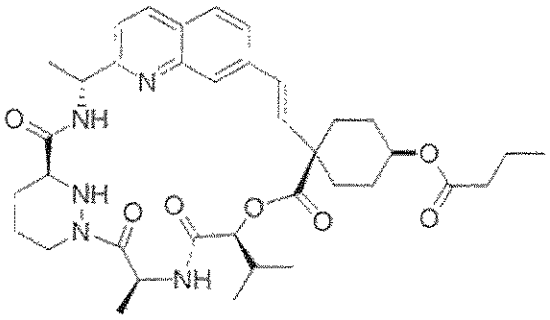
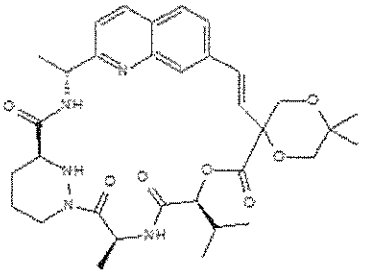
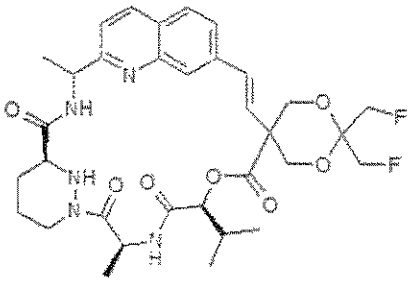
R^5 is iso-propyl; and

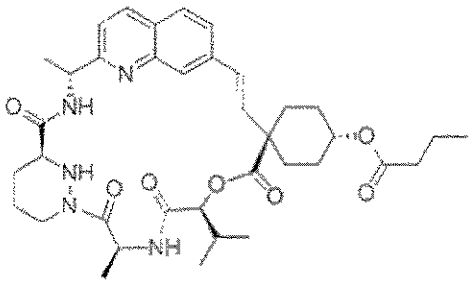
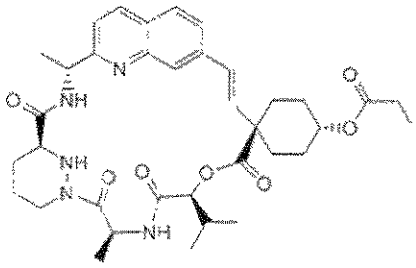
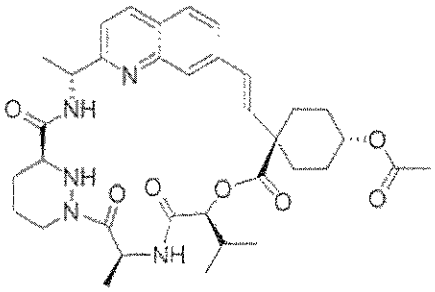
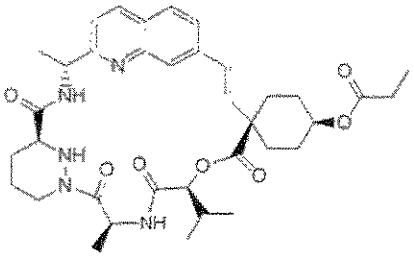
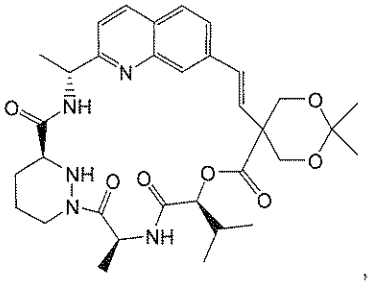
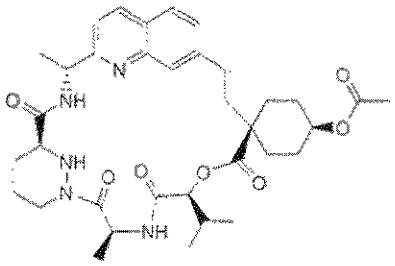
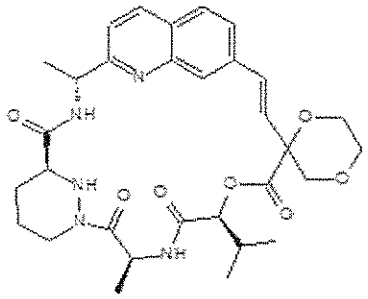
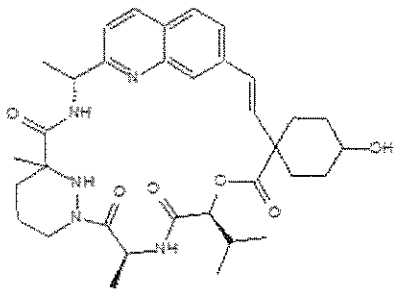
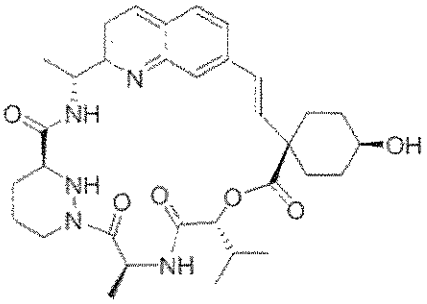
R^{6a} and R^{6b} together form





38. A compound selected from:


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39. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 30 to 38 or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, or ester thereof and a pharmaceutically acceptable excipient.

40. The pharmaceutical composition of claim 39, 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.

41. The pharmaceutical composition of claim 40, wherein the at least one additional therapeutic agent is ribavirin, telaprevir, boceprevir or sofosbuvir.