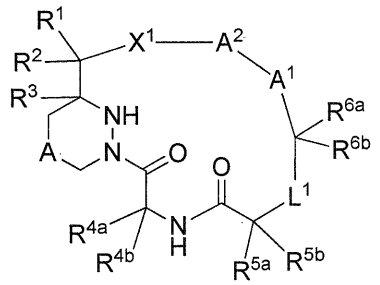
infection are difficult to achieve because of the prodigious amount of daily virus production in chronically infected patients and the high spontaneous mutability of HCV virus (Neumann, et al., *Science* 1998, *282*, 103-7; Fukimoto, et al., *Hepatology*, 1996, *24*, 1351-4; Domingo, et al., *Gene* 1985, *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 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 ~~substituents~~ 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)$_2$ ~~where such an optional substitution is chemically feasible~~;

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 ~~the arylene, heteroarylene, heterocycloalkylene or cycloalkylene moiety of~~ 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 ~~where such an optional substitution is chemically feasible~~;

L^1 is -O-C(O)-, -O-CH$_2$-, ~~-NR^{11}-C(O)-~~, -NR^{10}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;

R^1 and R^2 are independently H, (C$_1$-C$_4$)alkyl, (C$_2$-C$_4$)alkenyl, (C$_2$-C$_4$)alkynyl, halo, cyano or -C(O)-(C$_1$-C$_4$)alkyl; or

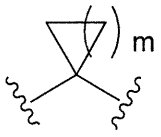
R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-, -C(=S)- or –C(=N(C$_1$-C$_4$)alkyl)-;

R^3 is H or (C$_1$-C$_4$)alkyl which is optionally substituted with halo, cyano, hydroxyl or (C$_1$-C$_4$)alkoxy;

R^{4a} and R^{4b} are independently H, (C$_1$-C$_8$)alkyl, aryl, aryl(C$_1$-C$_4$)alkyl, heterocycloalkyl, heterocycloalkyl(C$_1$-C$_4$)alkyl, cycloalkyl or cycloalkyl(C$_1$-C$_4$)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, ~~amino,~~ mono(C$_1$-C$_8$)alkylamino, di(C$_1$-C$_8$)alkylamino, aryl and heteroaryl ~~where such an optional substitution is chemically feasible~~;

R^{5a} and R^{5b} are independently H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, aryl, heterocycloalkyl, cycloalkyl, aryl$(C_1\text{-}C_4)$alkyl, cycloalkyl$(C_1\text{-}C_4)$alkyl or heterocycloalkyl$(C_1\text{-}C_4)$alkyl, wherein each R^{5a} and R^{5b} is optionally substituted with one or more substituents selected from the group consisting of $-N_3$, cyano, -COOH, halo, hydroxyl, amino, mono$(C_1\text{-}C_8)$alkylamino, di$(C_1\text{-}C_8)$alkylamino, $(C_1\text{-}C_8)$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, $=N(C_1\text{-}C_4)$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 $-S(O)_2R^9$;

R^{6a} and R^{6b} are independently H, hydroxyl, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, $-CH_2CH_2CR^9(=N(C_1\text{-}C_4)\text{alkoxy})$, 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, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono$(C_1\text{-}C_8)$alkylamino, di$(C_1\text{-}C_8)$alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$ and $(C_1\text{-}C_8)$alkanoyl ~~where such an optional substitution is chemically feasible~~; or R^{6a} and R^{6b} together form a spirocycle having Formula (a);

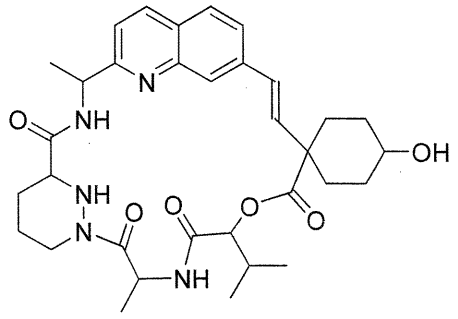
each R^8 is independently H, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl, wherein R^8 is optionally substituted with -OR, $-N(R^9)_2$, $-CON(R^9)_2$ or cyano;

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

each n is independently 0, 1 or 2; and

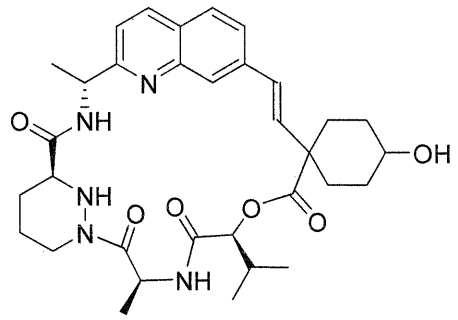
m is 1, 2, 3, 4 or 5.

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



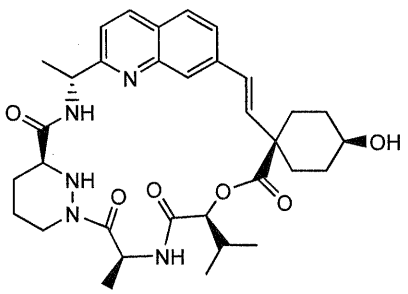
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

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



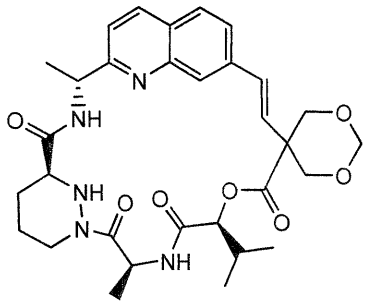
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

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



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

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



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

In another ~~embodiment~~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, 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 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 thereofto a mammal in need thereof. In one ~~aspect 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:

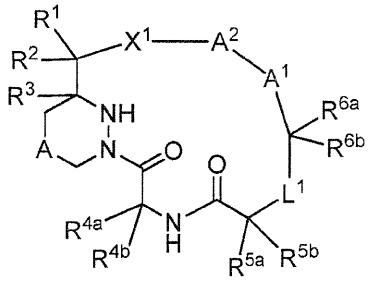
"Alkanoyl" is RC(O)-; "alkanoyloxy" is RC(O)O-; and "alkanoylamino" is RC(O)NR'-; where R is an alkyl group as defined herein, and R' is hydrogen or alkyl.

"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 (-$CH_2CH_2CH_2CH_2CH$=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-).

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 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}-C(O)-, -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;

R^1 and R^2 are independently H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, halo, cyano or -C(O)-$(C_1$-$C_4)$alkyl; or

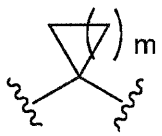
R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-, -C(=S)- or –C(=N$(C_1$-$C_4)$alkyl)-;

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

R^{4a} and R^{4b} are independently H, $(C_1$-$C_8)$alkyl, aryl, aryl$(C_1$-$C_4)$alkyl, heterocycloalkyl, heterocycloalkyl$(C_1$-$C_4)$alkyl, cycloalkyl or cycloalkyl$(C_1$-$C_4)$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, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, aryl, heterocycloalkyl, cycloalkyl, aryl$(C_1$-$C_4)$alkyl, cycloalkyl$(C_1$-$C_4)$alkyl or heterocycloalkyl$(C_1$-$C_4)$alkyl, wherein each R^{5a} and R^{5b} is 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} 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; or R^{6a} and R^{6b} together form a spirocycle having Formula (a);

each R^8 is independently 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;

each n is independently 0, 1 or 2; and

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

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 Claim 1 or 2, wherein A^2 is $-CH(R^8)$-quinolinylene, $-CH(R^8)$-isoquinolinylene, $-CH(R^8)$-naphthyridinylene, $-CH(R^8)$-cinnolinylene, $-CH(R^8)$-quinoxalinylene, $-CH(R^8)$-phenylene or $-CH(R^8)$-halophenylene.

4. The compound of any preceding claim, wherein R^8 is methyl.

5. The compound of any preceding claim, wherein X^1 is -O-, -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)-; and R^3 is H.

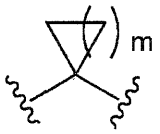
6. The compound of any preceding claim, wherein X^1 is -O-, -NH- or $-N(CH_3)$-; R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-; R^3 is H; one of R^{4a} and R^{4b} is H and the other is methyl; and one of R^{5a} and R^{5b} is H and the other is isopropyl.

7. The compound of any preceding claim, wherein X^1 is -O-, -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; 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)-heteroarylene; and R^8 is methyl.

8. The compound of any preceding claim, 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.

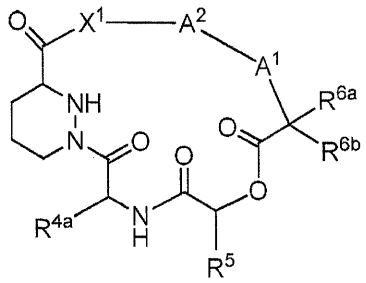
9. The compound of any preceding claim, wherein R^{6a} and R^{6b} together form a spirocycle having Formula (a):



(a),

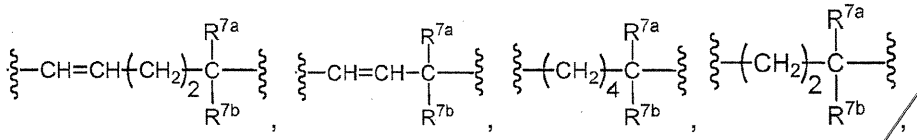
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, $=N(C_1\text{-}C_4)$alkoxy, halo, hydroxyl, $-NH_2$, $(C_1\text{-}C_4)$alkyl,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

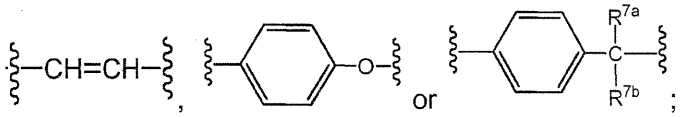
10. The compound of Claim 1, which is a compound of Formula II:



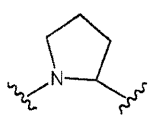
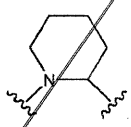
Formula II

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

A^1 is 



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 a bond, -CH_2-, -O-, -NH-, -N(CH_3)-,  or  ;

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

R^5 is H, (C_1-C_4)alkyl, halo(C_1-C_8)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_8)alkyl, cycloalkyl or heterocycloalkyl;

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),

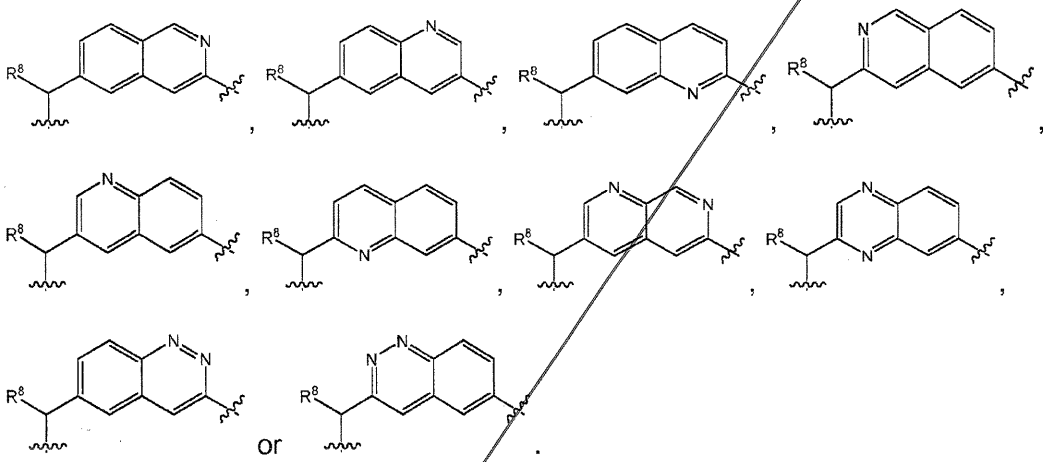
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, =N(C_1-C_4)alkoxy, halo, hydroxyl, -NH_2, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl,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

R^{7a} and R^{7b} are independently H, -OH, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl;

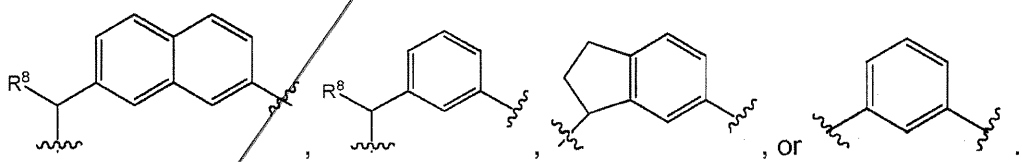
R^8 is H or $(C_1\text{-}C_4)$alky; and

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

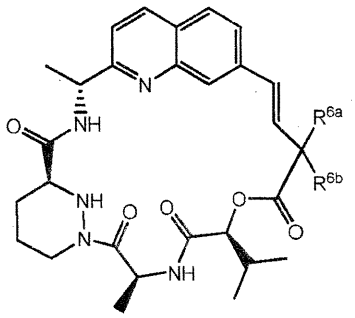
11. The compound of any preceding claim, wherein R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



12. The compound of any preceding claim, wherein R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



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

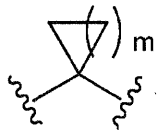


Formula II-c

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

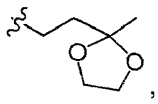


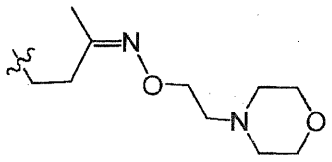
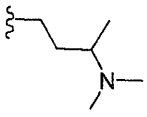
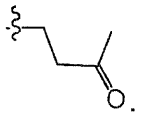
(a),

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

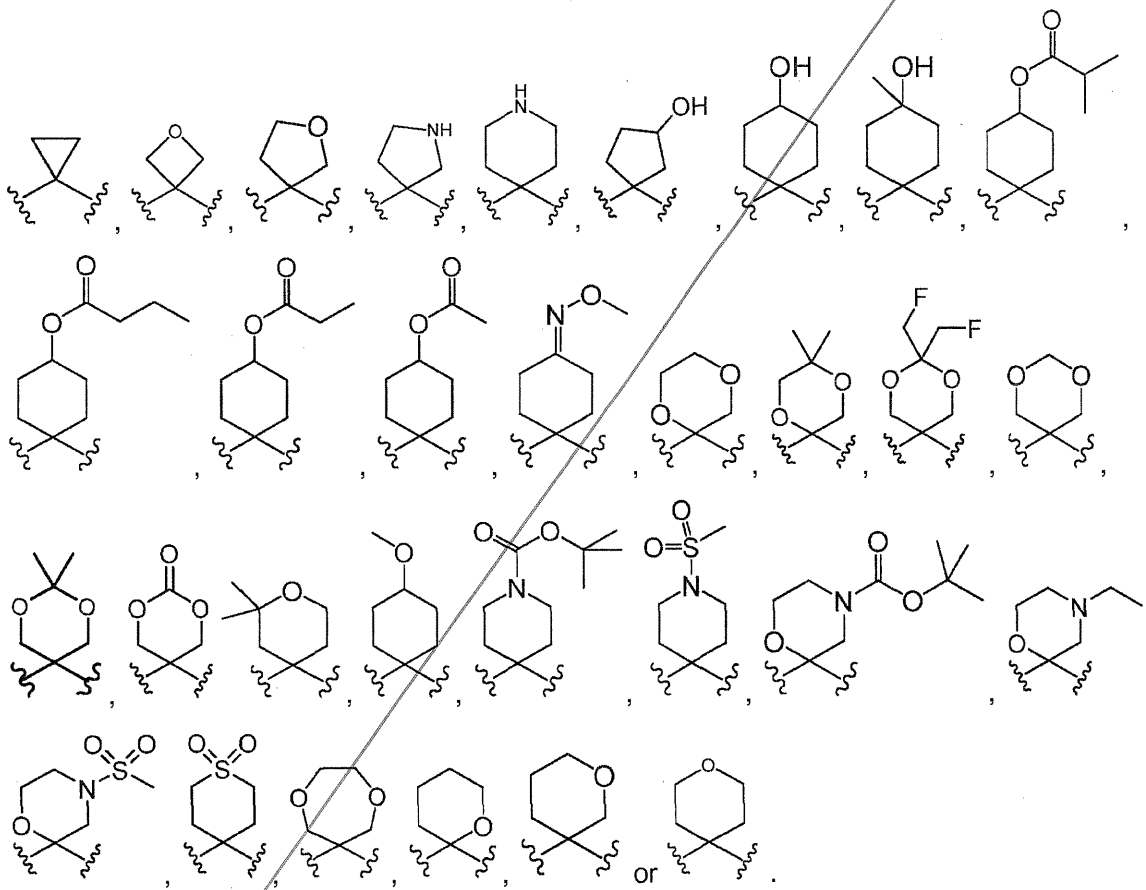
each R^9 is independently H, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl or $(C_2$-$C_4)$alkynyl.

14. The compound of any preceding claim, wherein R^{6a} and R^{6b} are independently H, -OH, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, $(C_1$-$C_8)$alkyl, hydroxy$(C_1$-$C_8)$alkyl, halo$(C_1$-$C_8)$alkyl,

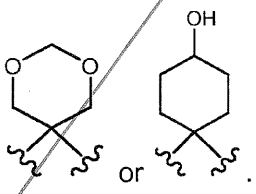
$(C_1$-$C_4)$alkoxy$(C_1$-$C_8)$alkyl, halo$(C_1$-$C_4)$alkoxy$(C_1$-$C_8)$alkyl,  ,

 ,  or  .

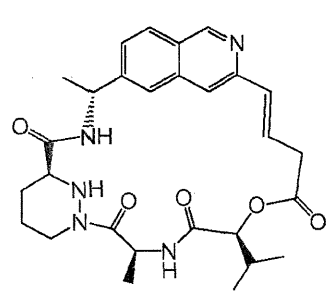
15. The compound of any preceding claim, wherein R^{6a} and R^{6b} together form



16. The compound of any preceding claim, wherein R^{6a} and R^{6b} together form

 .

17. The compound of any preceding claim, which is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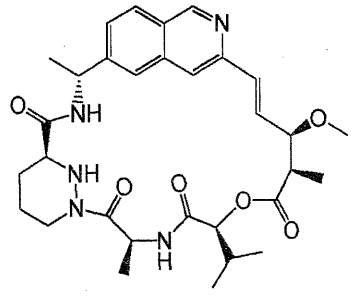
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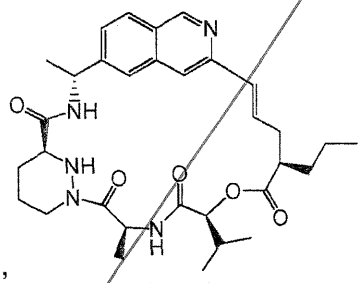
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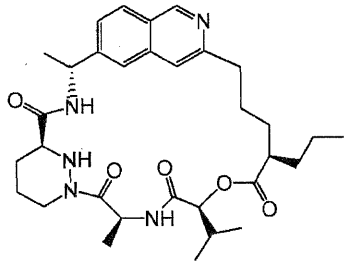
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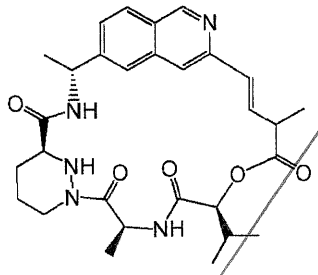
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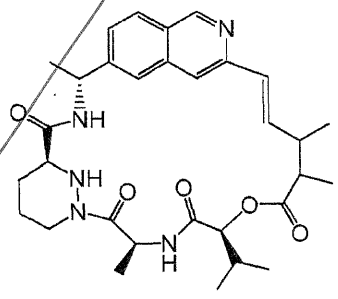
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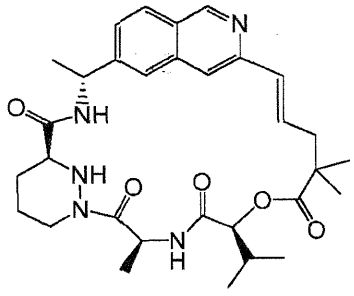
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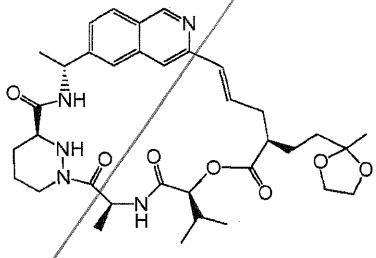
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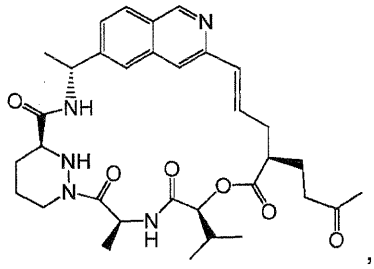
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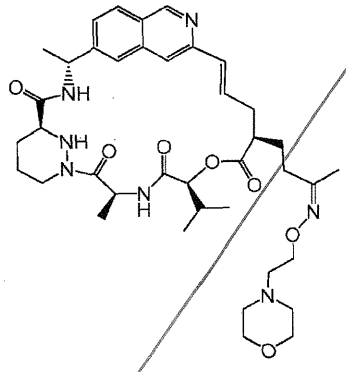
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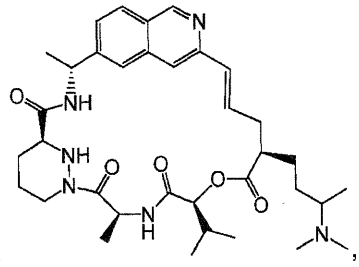
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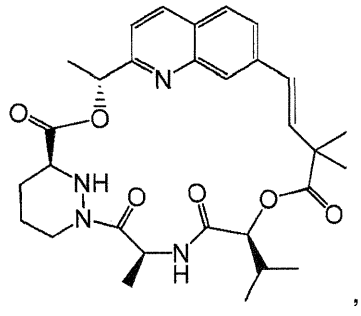

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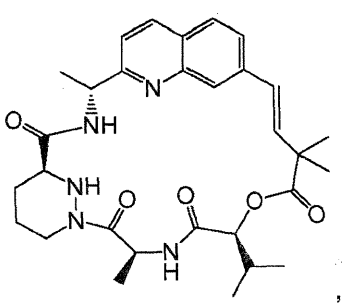
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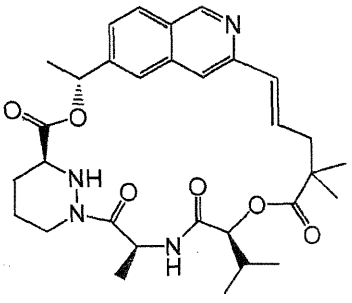
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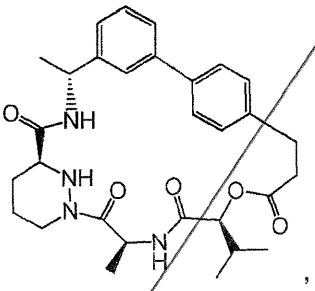
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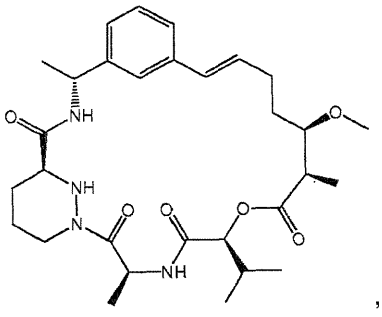
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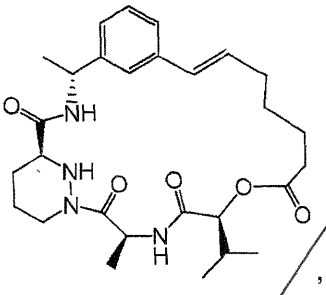
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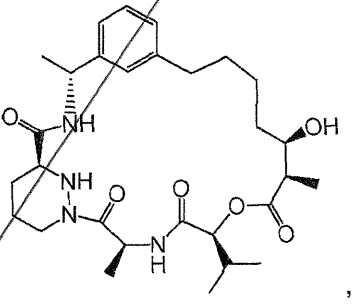
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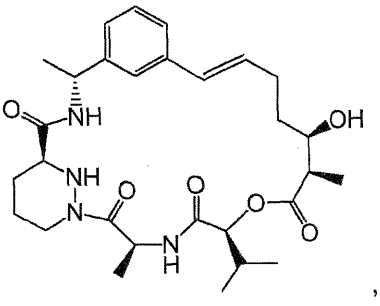
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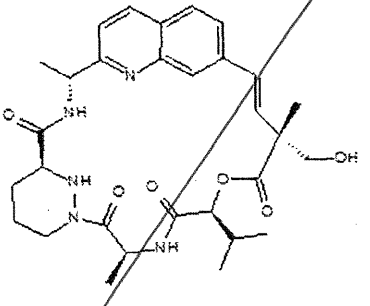
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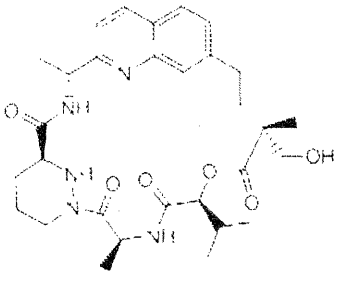
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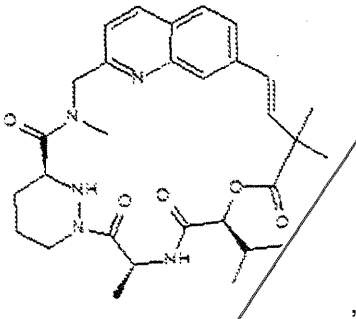
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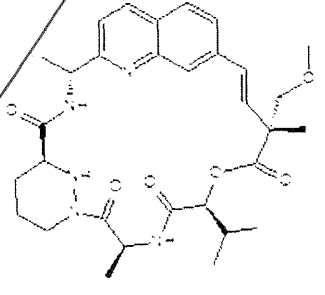
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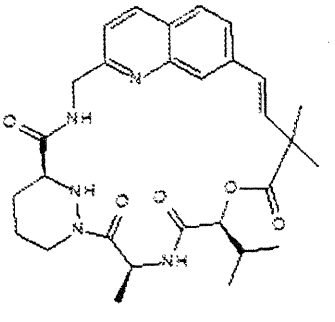
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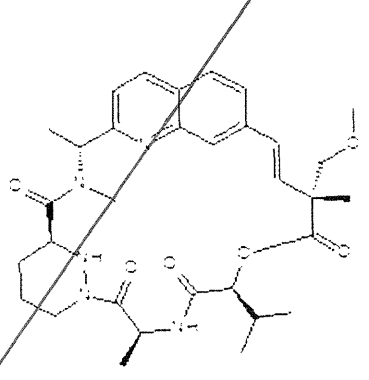
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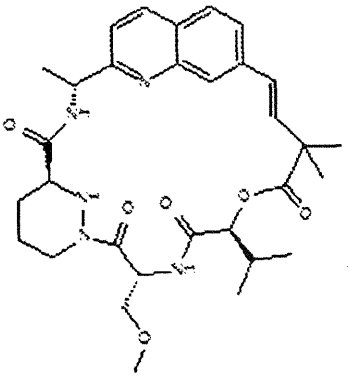
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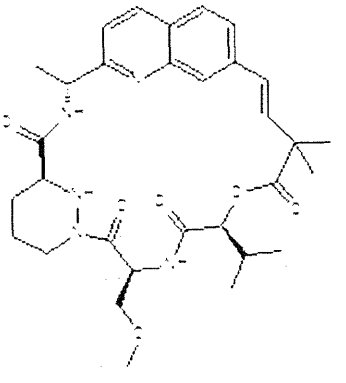
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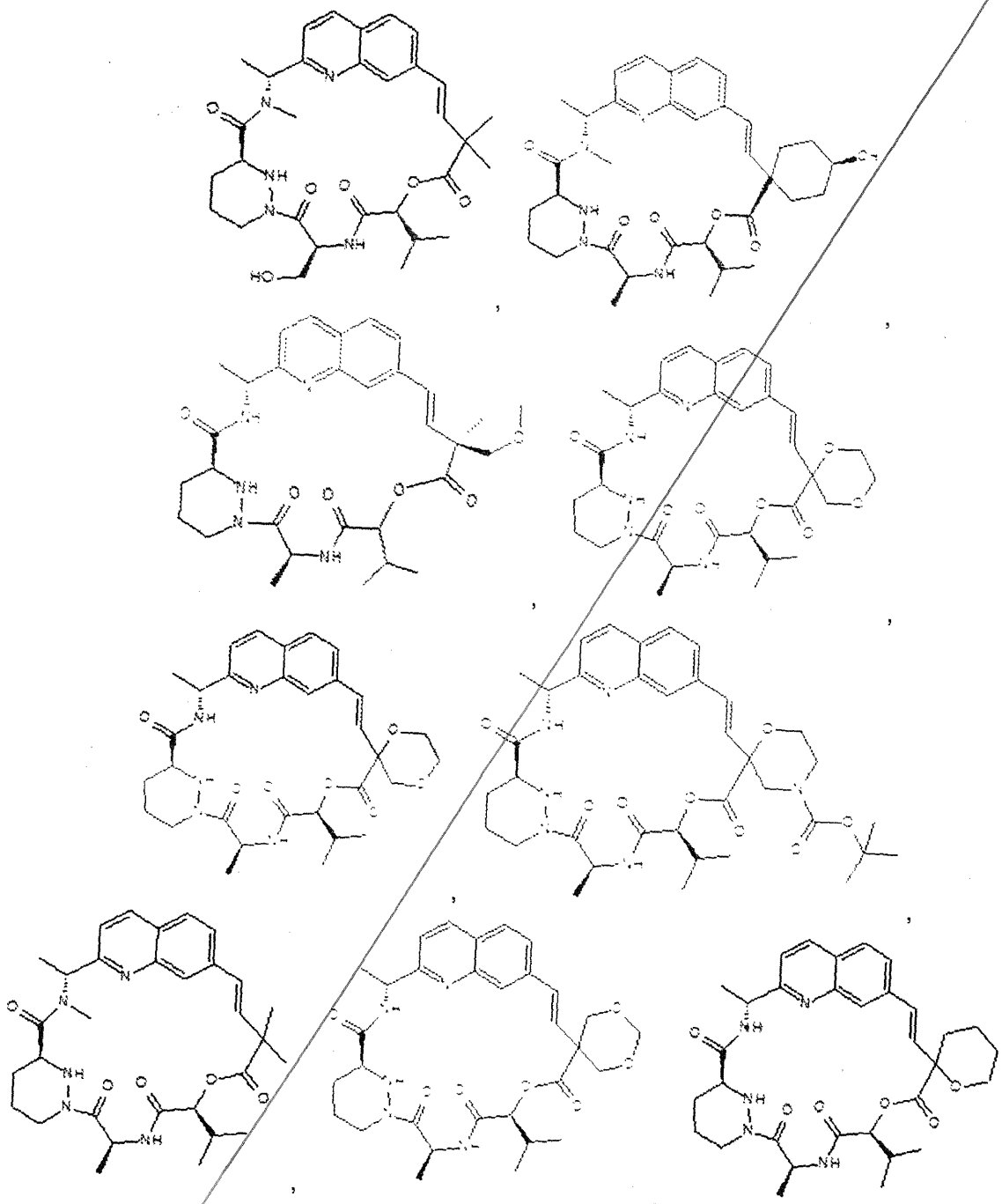

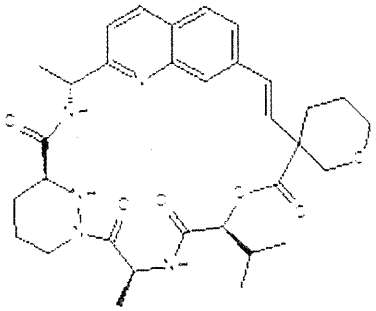
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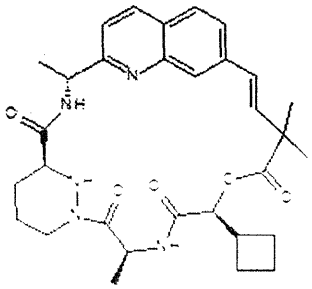
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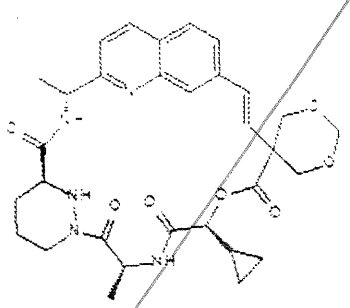
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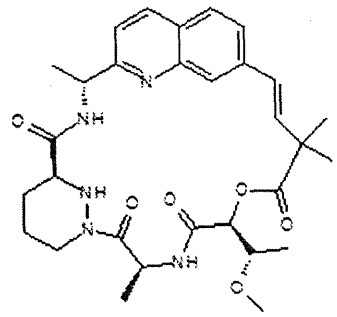
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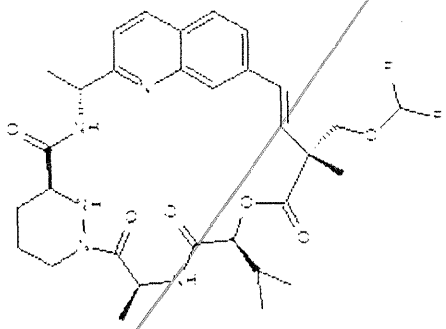
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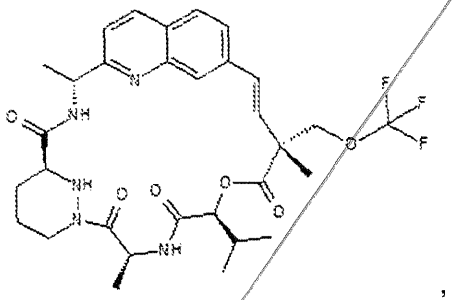
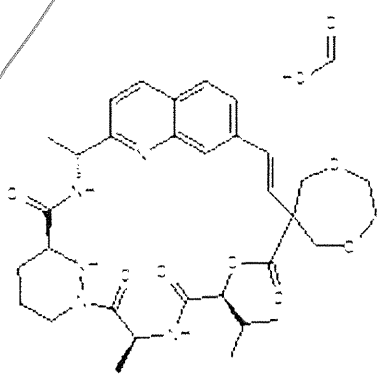
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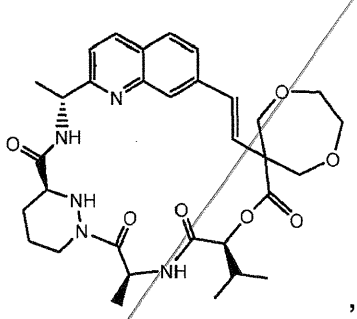
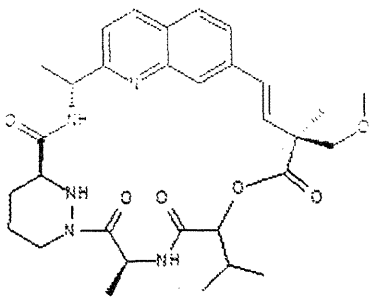
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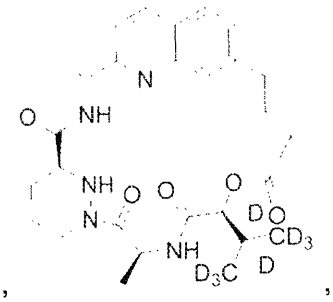
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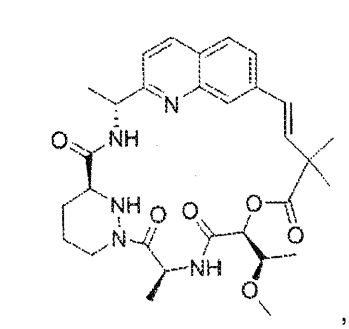
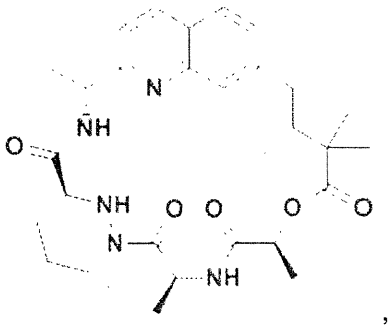
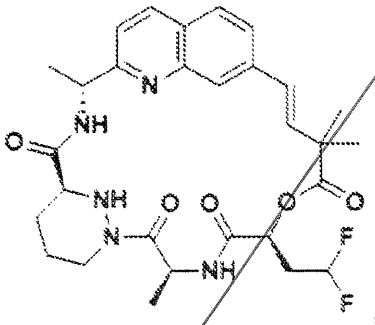
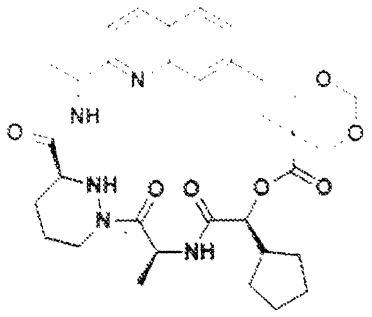
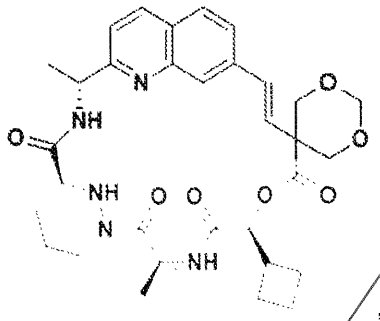
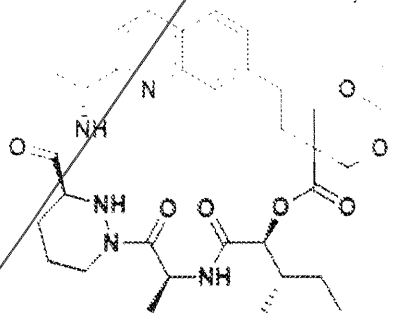
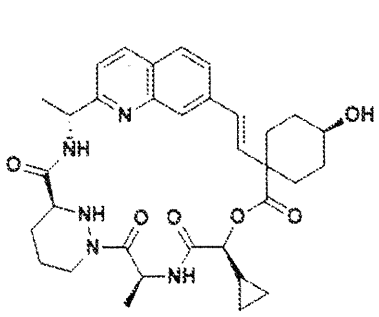
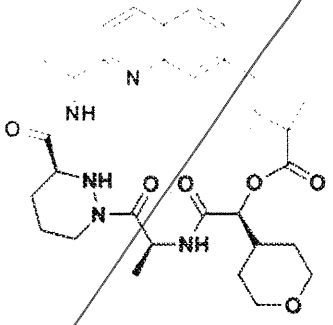
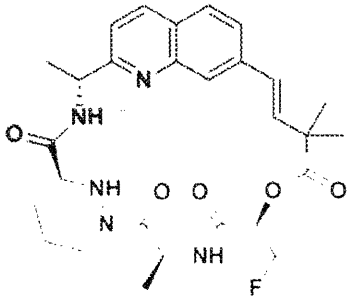
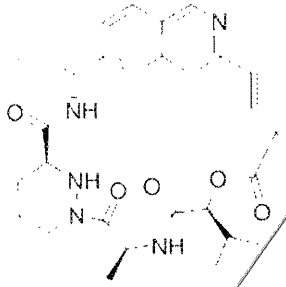
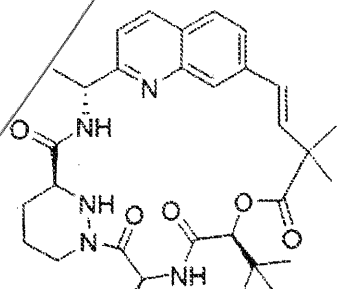
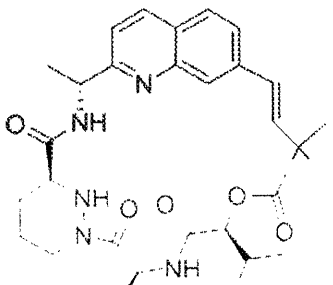
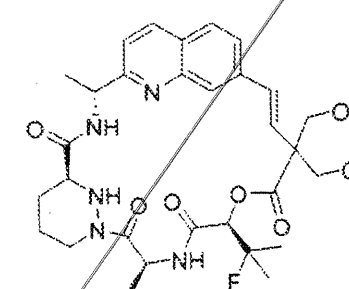
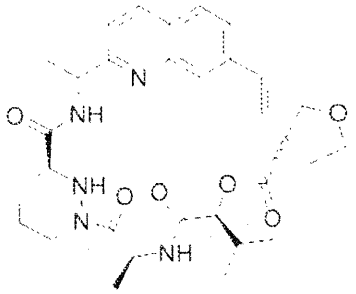
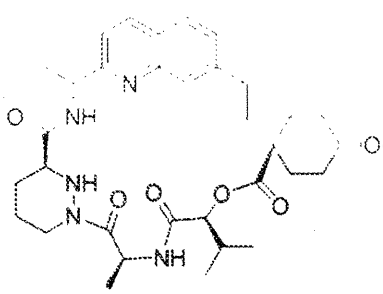
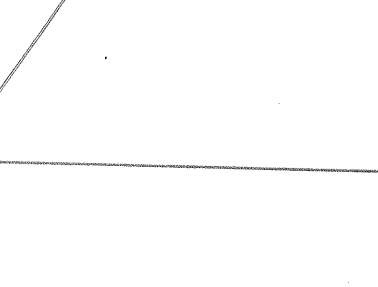
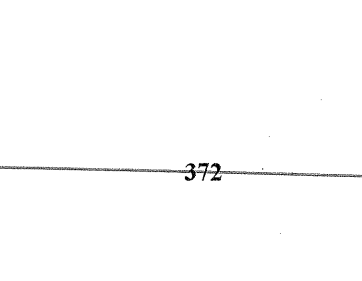
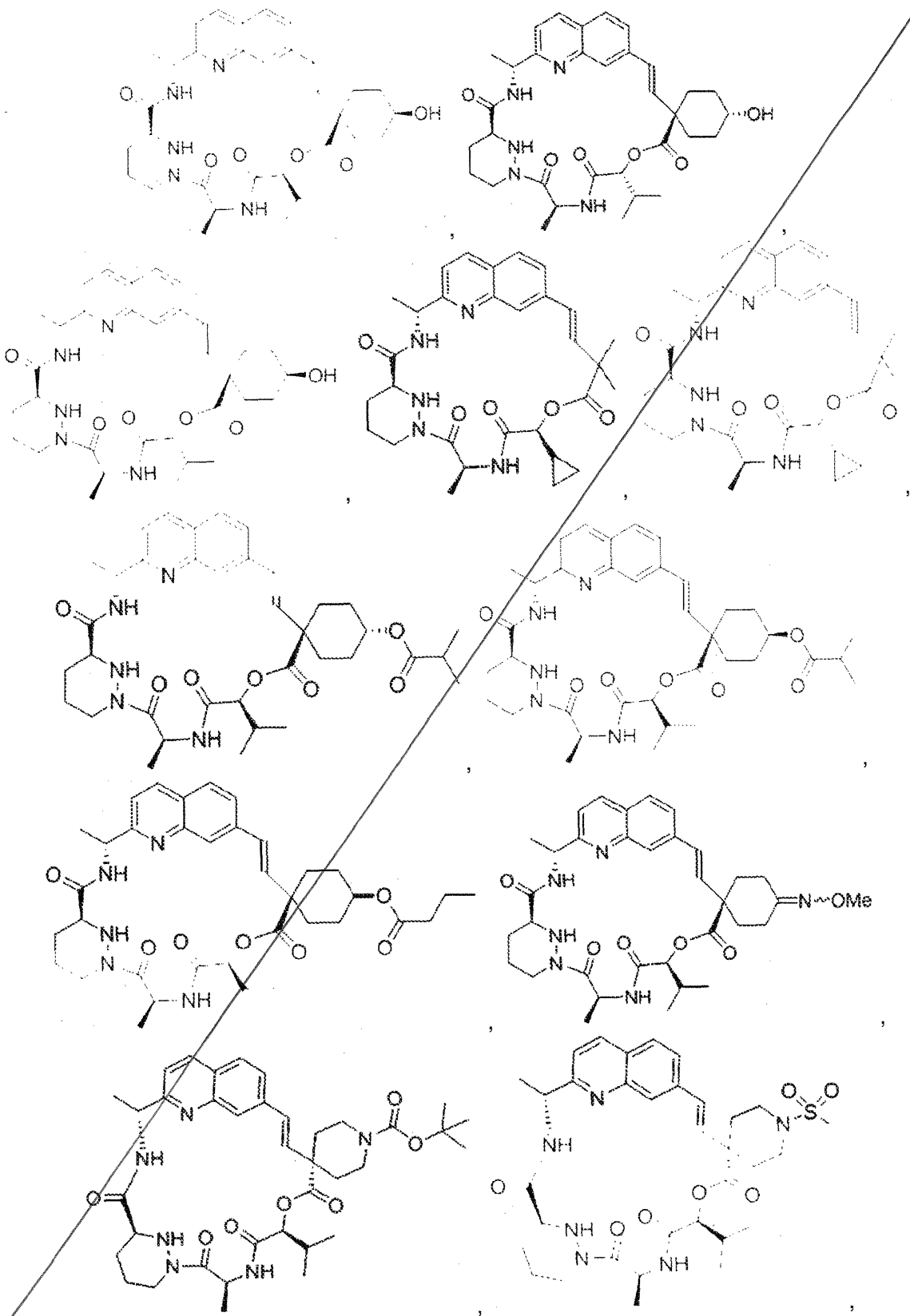
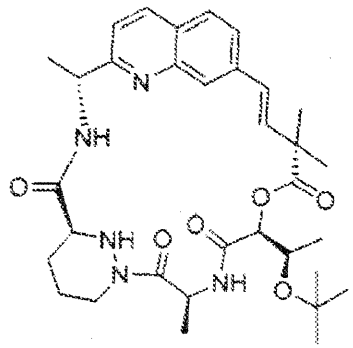
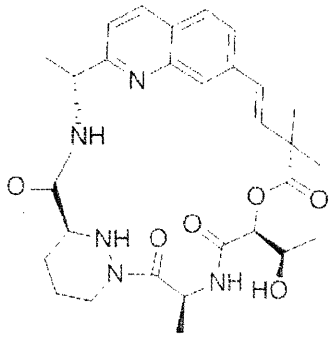
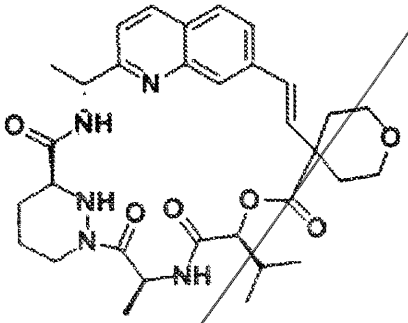
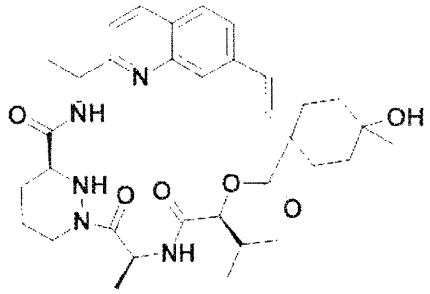
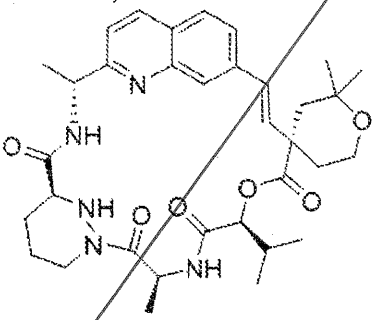
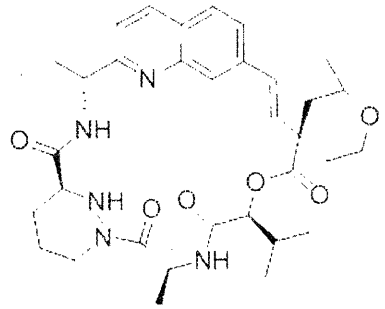
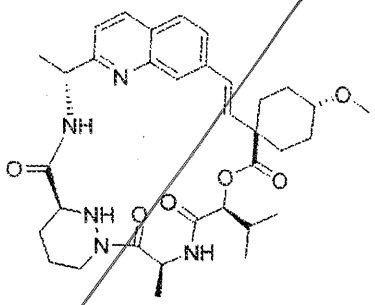
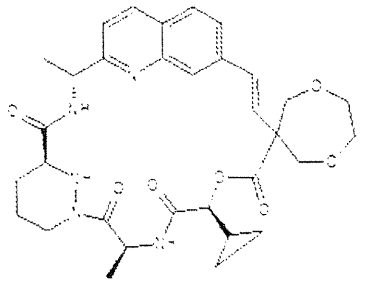
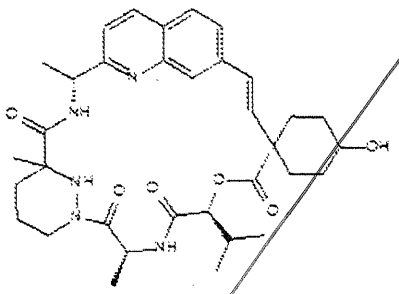
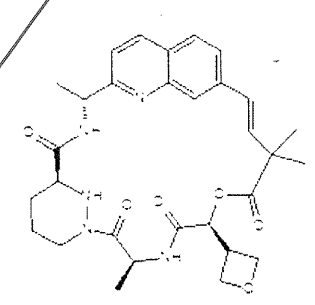
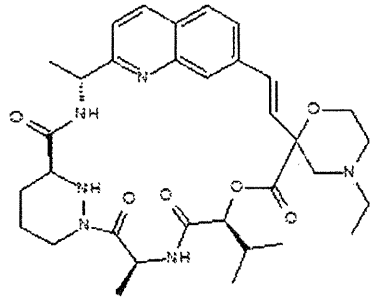
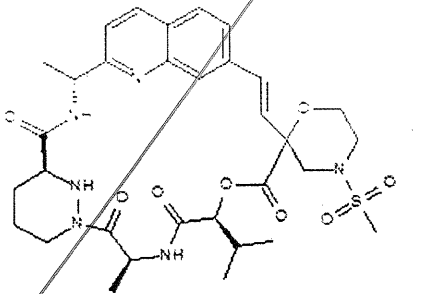
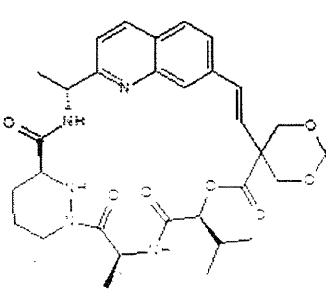
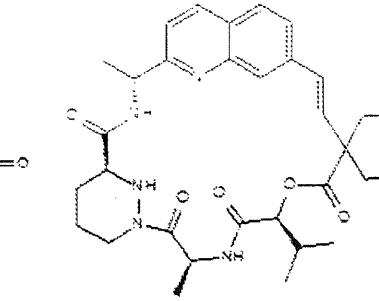
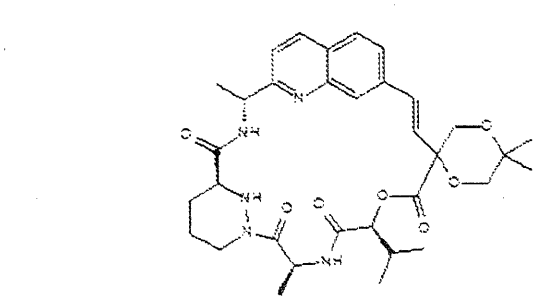
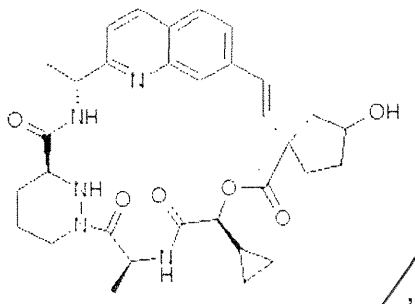
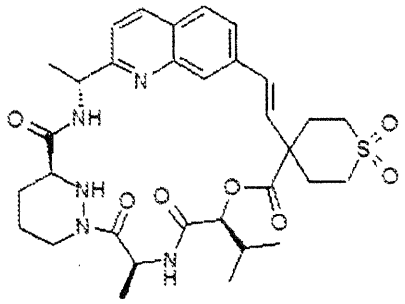
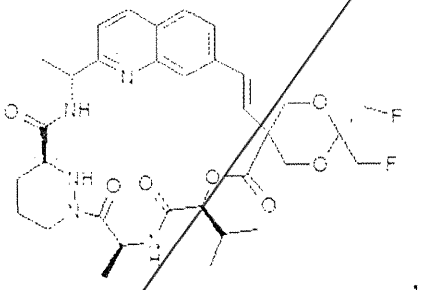
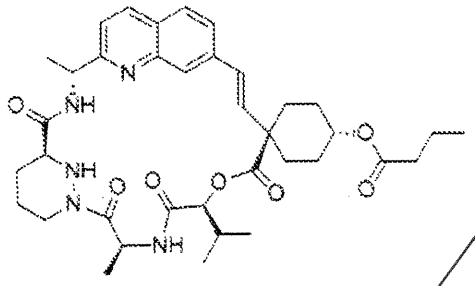
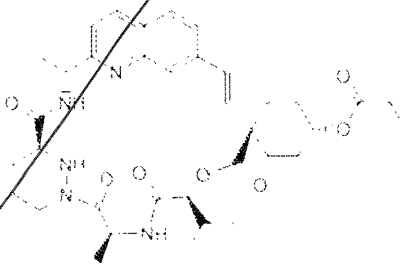
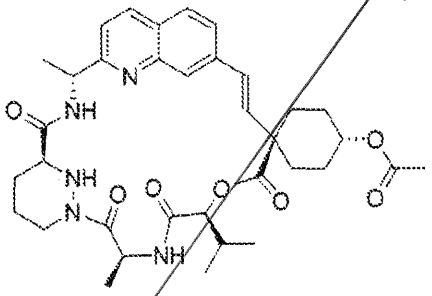
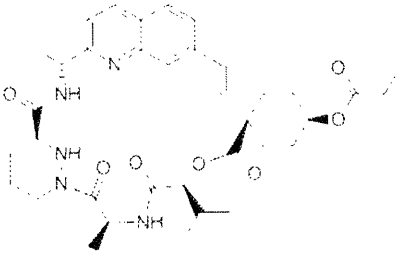
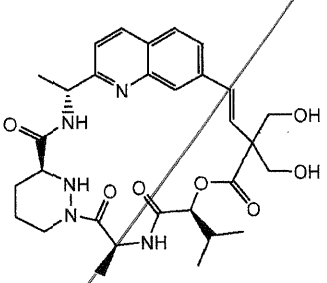
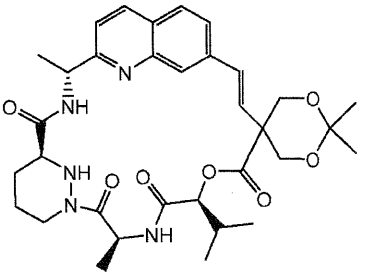
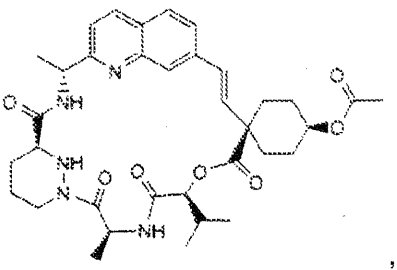




















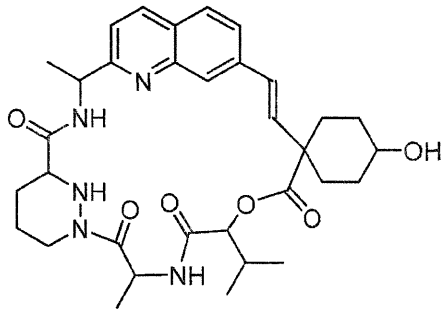















5 , , or ,

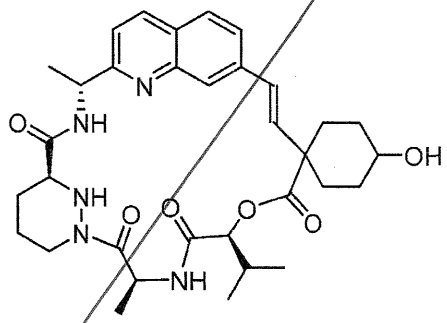
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

18. A compound which is:



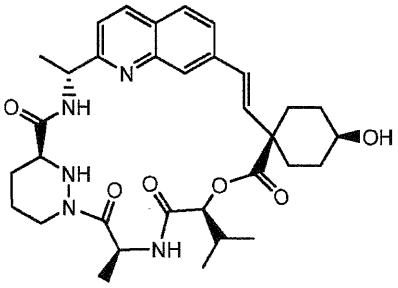
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

19. A compound which is:



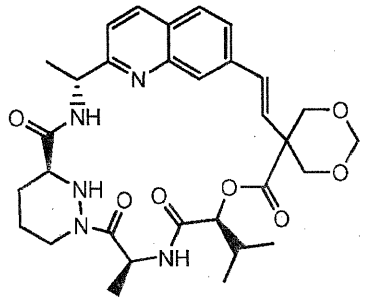
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

20. A compound which is:



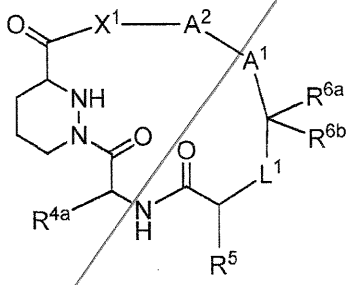
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

21. A compound which is:



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

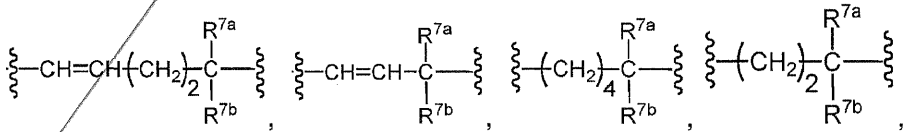
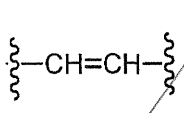
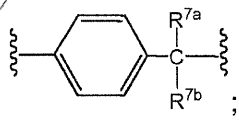
22. The compound of Claim 1, which is a compound of Formula III:



Formula III

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

L^1 is -O-CH_2-, -N(CH_3)-C(O)-, -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;

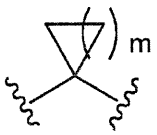
X^1 is -O-, -N(CH_3)- or -NH-;

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

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

R^{6a} and R^{6b} are independently H, hydroxyl, $-CH_2CH_2CR^9(=N(C_1\text{-}C_4)\text{alkoxy})$, $(C_1\text{-}C_8)$alkyl or $(C_1\text{-}C_8)$alkoxy, 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; or

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



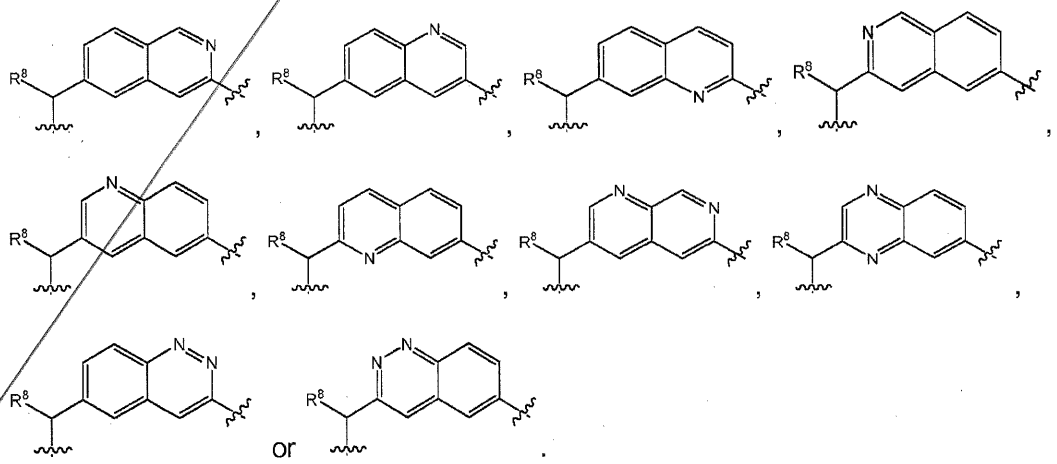
(a),

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, halo, hydroxyl, $-NH_2$, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $-OC(O)R^9$, $-C(O)_2R^9$, and $-S(O)_2R^9$;

R^{7a} and R^{7b} are independently H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl; and

R^8 is H or $(C_1\text{-}C_4)$alkyl.

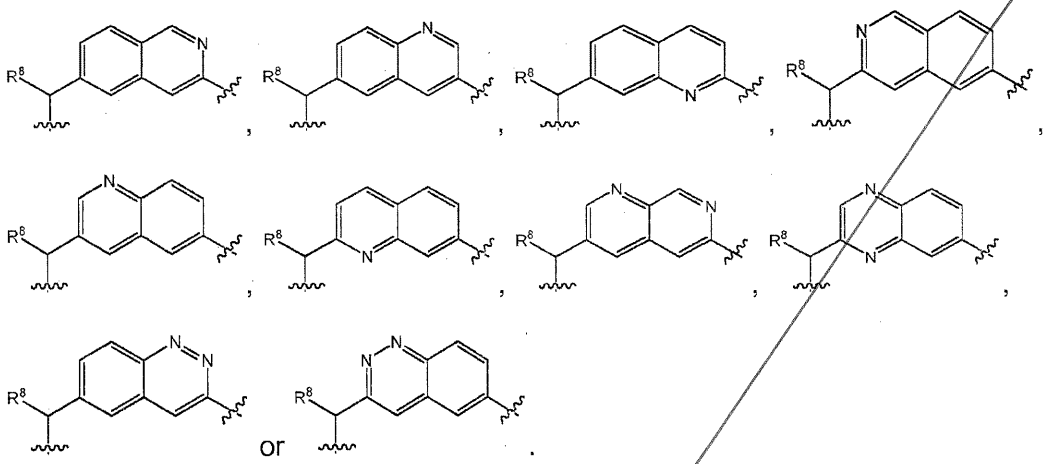
23. The compound of any preceding claim, wherein L^1 is $-NH\text{-}CH_2\text{-}$; R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



or

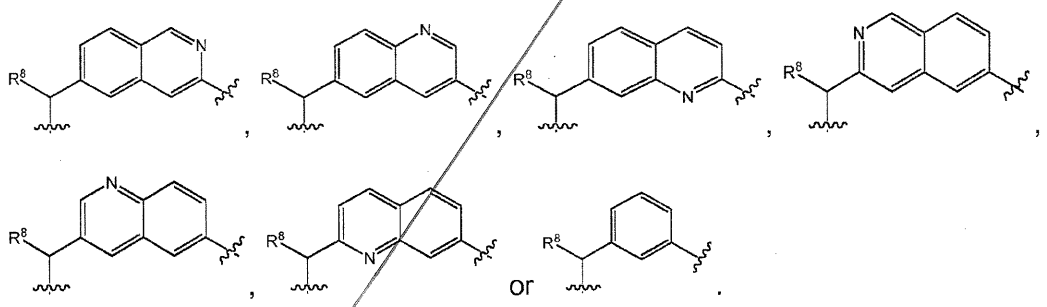
.

24. The compound of any preceding claim, wherein L^1 is -NH-$S(O)_2$-; R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



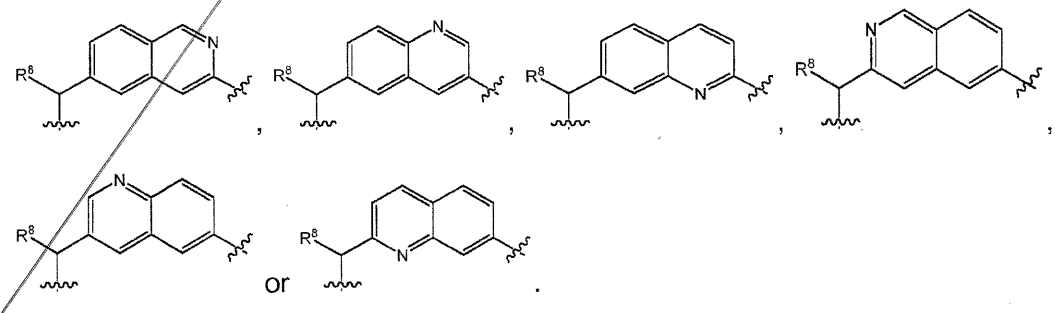
or

25. The compound of any preceding claim, wherein L^1 is -$N(CH_3)$-C(O)-; R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



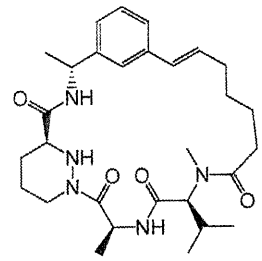
or

26. The compound of any preceding claim, wherein L^1 is -O-CH_2-; R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



or

27. The compound of any preceding claim, which is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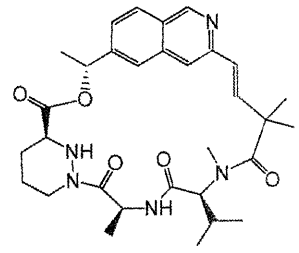
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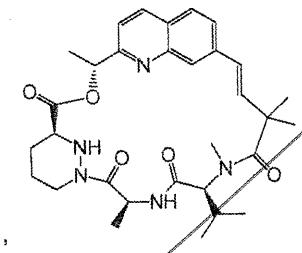
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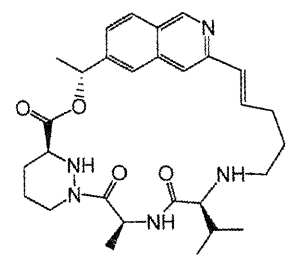
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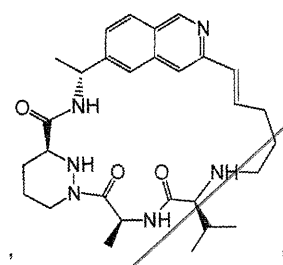
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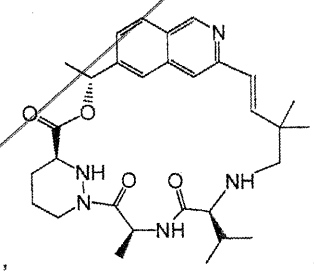
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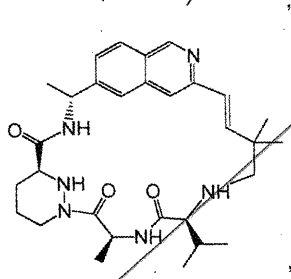
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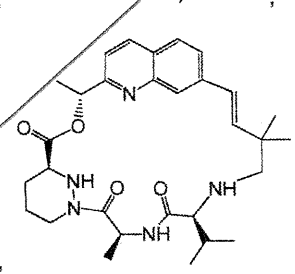
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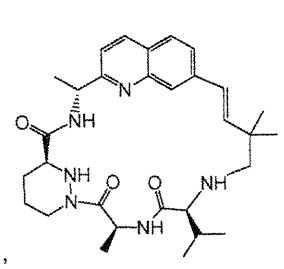
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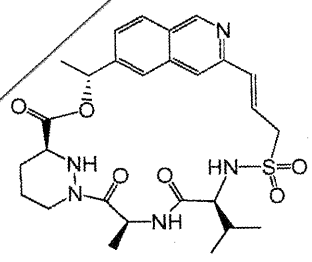
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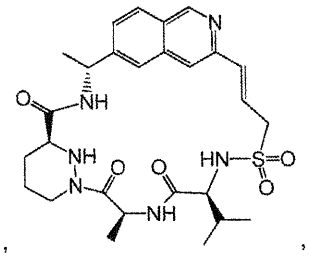
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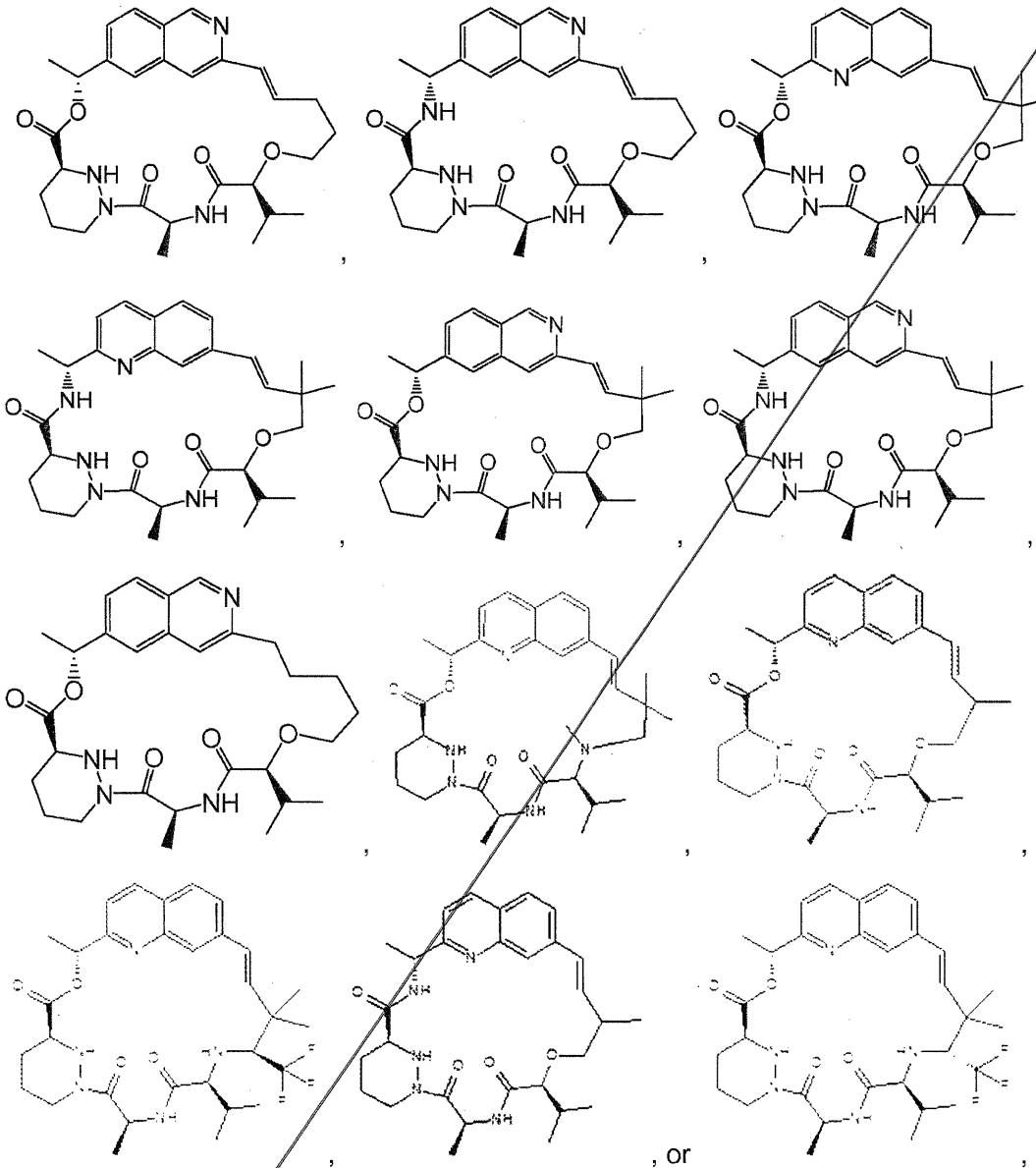


or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

28. 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.

29. The pharmaceutical composition of Claim 28, 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.

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

31. 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 any one of Claims 1-27 or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

32. The method of Claim 31, wherein the viral infection is caused by a Hepatitis B virus or a Hepatitis C virus.

33. The method of Claim 32, 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.

34. 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 any one of Claims 1-27 or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

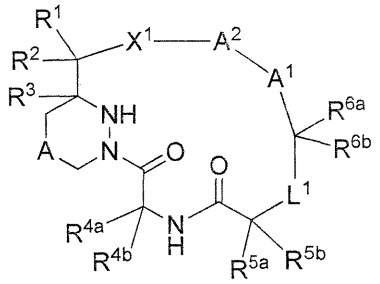
35. The method of Claim 34, wherein the viral infection is caused by a SARS coronarirus.

36. The method of Claim 35, 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.

37. A method for providing immunomodulation to a human patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound any one of Claims 1-27 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 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;

R^1 and R^2 are independently H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, halo, cyano or -C(O)-$(C_1$-$C_4)$alkyl; or

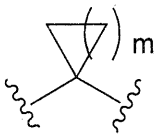
R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-, -C(=S)- or –C(=N$(C_1$-$C_4)$alkyl)-;

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

R^{4a} and R^{4b} are independently H, $(C_1$-$C_8)$alkyl, aryl, aryl$(C_1$-$C_4)$alkyl, heterocycloalkyl, heterocycloalkyl$(C_1$-$C_4)$alkyl, cycloalkyl or cycloalkyl$(C_1$-$C_4)$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, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, aryl, heterocycloalkyl, cycloalkyl, aryl$(C_1$-$C_4)$alkyl, cycloalkyl$(C_1$-$C_4)$alkyl or heterocycloalkyl$(C_1$-$C_4)$alkyl, wherein each R^{5a} and R^{5b} is 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} 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; or R^{6a} and R^{6b} together form a spirocycle having Formula (a);

each R^8 is independently 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;

each n is independently 0, 1 or 2; and

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

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 Claim 1 wherein A^2 is $-CH(R^8)$-quinolinylene, $-CH(R^8)$-isoquinolinylene, $-CH(R^8)$-naphthyridinylene, $-CH(R^8)$-cinnolinylene, $-CH(R^8)$-quinoxalinylene, $-CH(R^8)$-phenylene or $-CH(R^8)$-halophenylene.

4. The compound of claim 1 wherein R^8 is methyl.

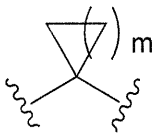
5. The compound of claim 1, wherein X^1 is -O-, -NH- or $-N(CH_3)$-; R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-; and R^3 is H.

6. The compound of claim 1, wherein X^1 is -O-, -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; 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.

7. The compound of claim 1, wherein X^1 is -O-, -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; 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 $-CH(R^8)$-heteroarylene; and R^8 is methyl.

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.

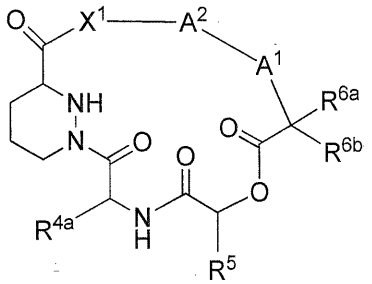
9. The compound of claim 1, wherein R^{6a} and R^{6b} together form a spirocycle having Formula (a):



(a),

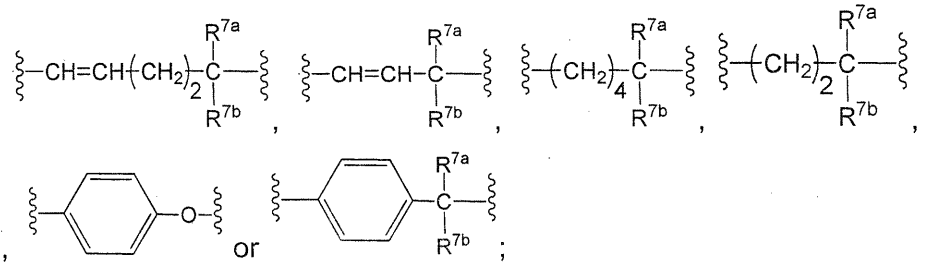
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, $=N(C_1\text{-}C_4)$alkoxy, halo, hydroxyl, $-NH_2$, $(C_1\text{-}C_4)$alkyl,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

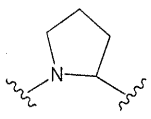
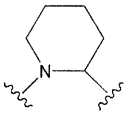


Formula II

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

A^1 is 

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

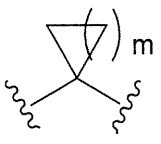
X^1 is a bond, -CH_2-, -O-, -NH-, -N(CH_3)-,  or  ;

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

R^5 is H, (C_1-C_4)alkyl, halo(C_1-C_8)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_8)alkyl, cycloalkyl or heterocycloalkyl;

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),

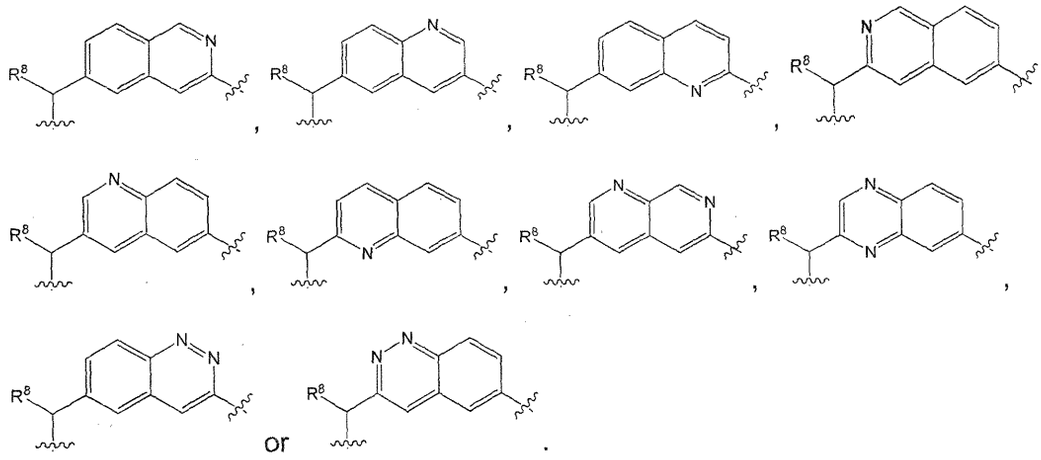
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, =N(C_1-C_4)alkoxy, halo, hydroxyl, -NH_2, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl,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

R^{7a} and R^{7b} are independently H, -OH, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl;

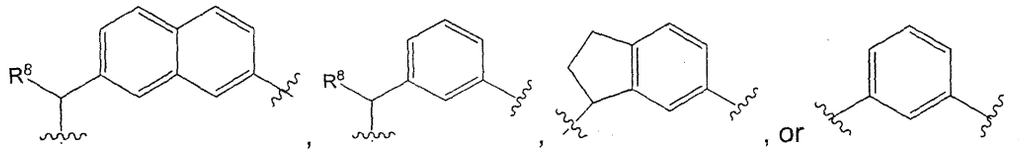
R^8 is H or $(C_1\text{-}C_4)$alky; and

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

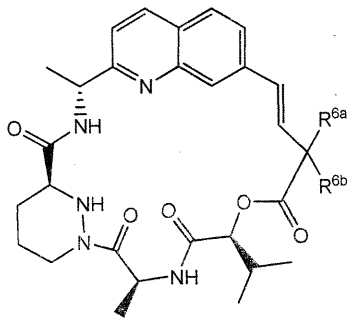
11. The compound of claim 1, wherein R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



12. The compound of claim 10, wherein R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



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

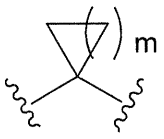


Formula II-c

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

R^{6a} and R^{6b} are independently H, hydroxyl, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, $-CH_2CH_2CR^9(=N(C_1\text{-}C_4)\text{alkoxy})$, 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, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono$(C_1\text{-}C_8)$alkylamino, di$(C_1\text{-}C_8)$alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$ and $(C_1\text{-}C_8)$alkanoyl where such an optional substitution is chemically feasible; or R^{6a} and R^{6b} together form a spirocycle having Formula (a); or

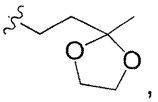
R^{6a} and R^{6b} together form a spirocycle having Formula (a):

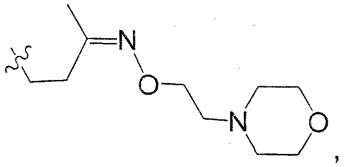
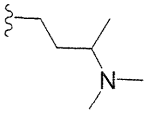
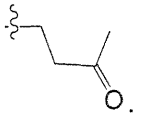


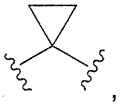
(a),

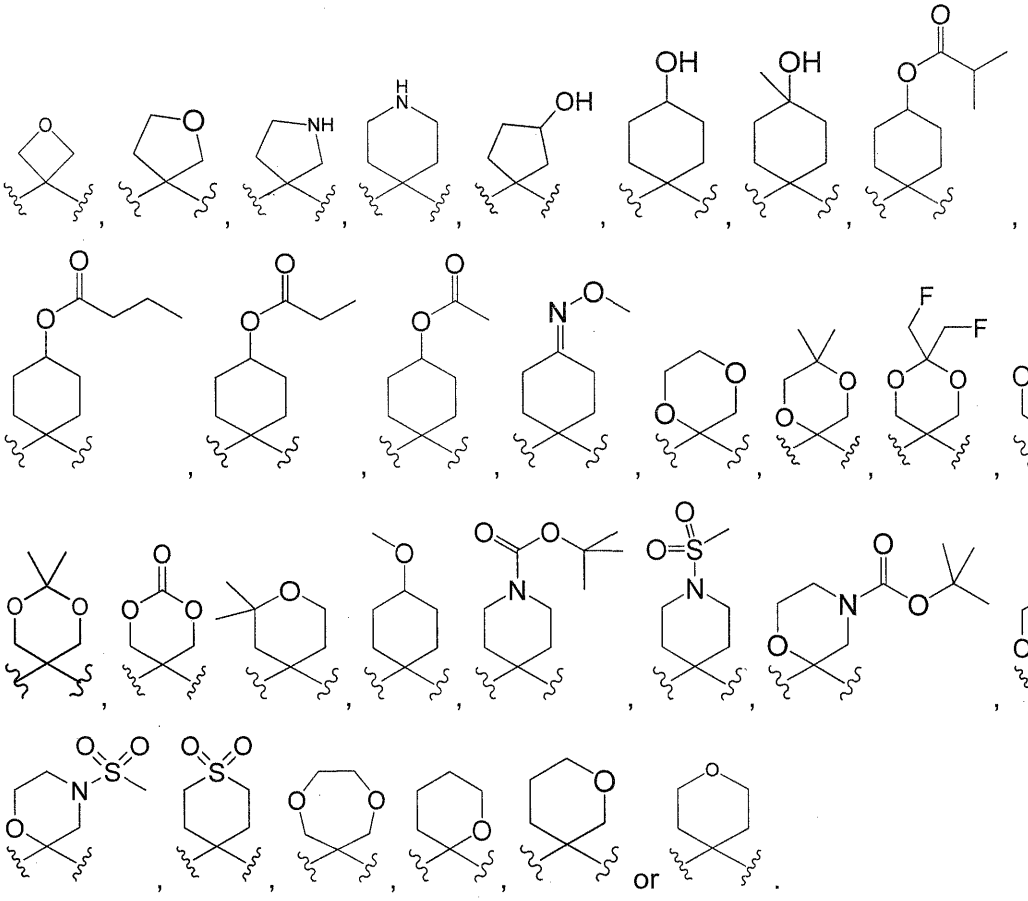
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) optionally has one or more substituents selected from the group consisting of oxo, $=N(C_1\text{-}C_4)$alkoxy, halo, hydroxyl, $-NH_2$, $(C_1\text{-}C_4)$alkyl,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

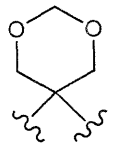
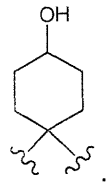
each R^9 is independently H, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl.

14. The compound of claim 13, wherein R^{6a} and R^{6b} are independently H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_8)$alkyl, hydroxy$(C_1\text{-}C_8)$alkyl, halo$(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_4)$alkoxy$(C_1\text{-}C_8)$alkyl, halo$(C_1\text{-}C_4)$alkoxy$(C_1\text{-}C_8)$alkyl,  ,

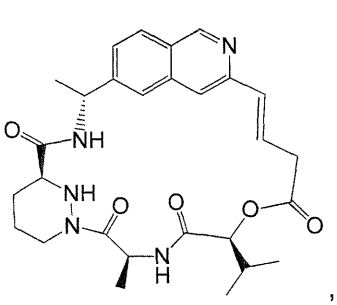
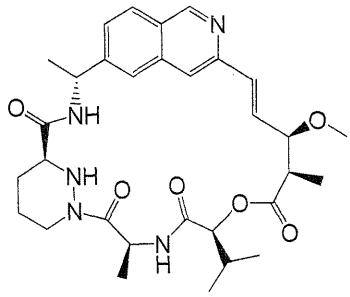
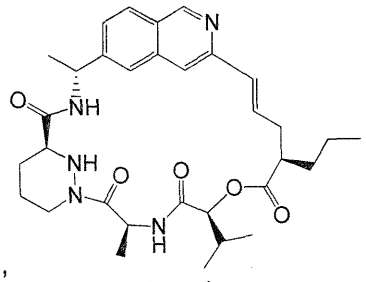
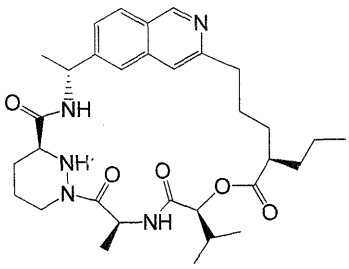
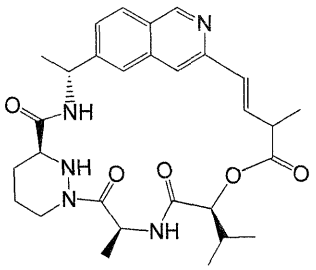
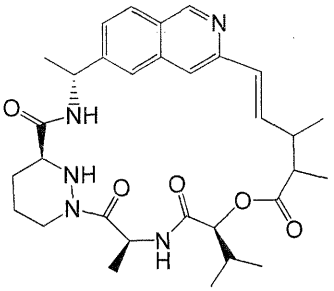
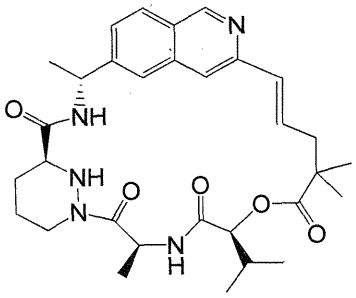
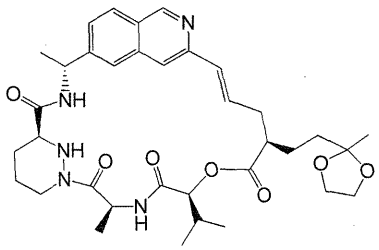
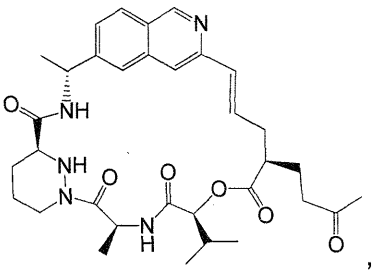
 ,  or  .

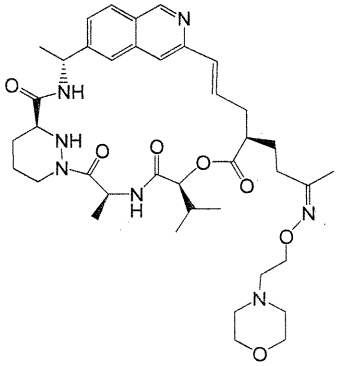
15. The compound of claim 13, wherein R^{6a} and R^{6b} together form  ,



16. The compound of claim 13, wherein R^{6a} and R^{6b} together form  or  .

17. The compound of claim 13, which is

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,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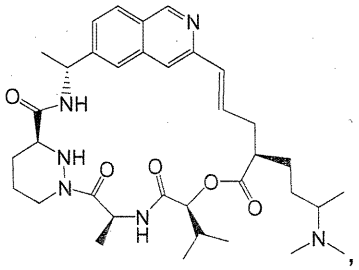
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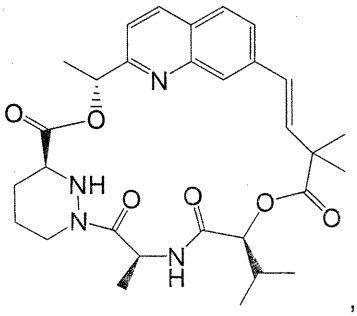
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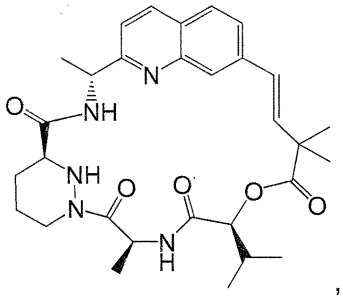
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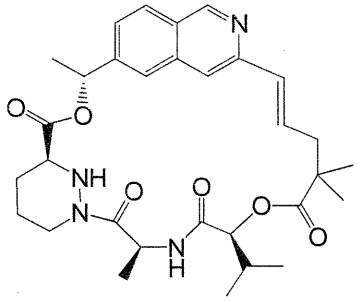
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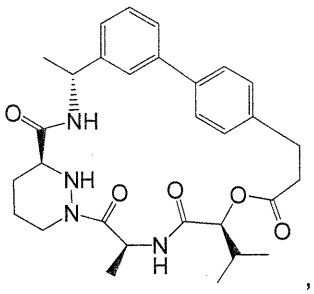
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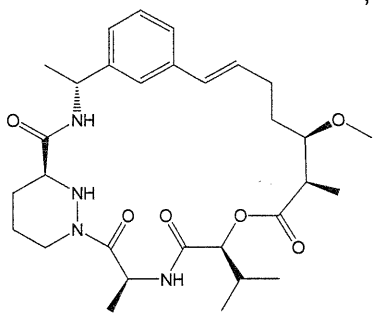
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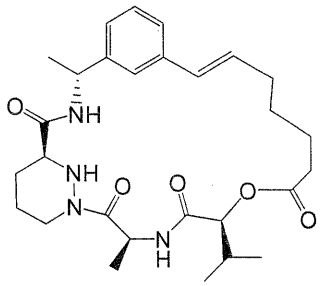
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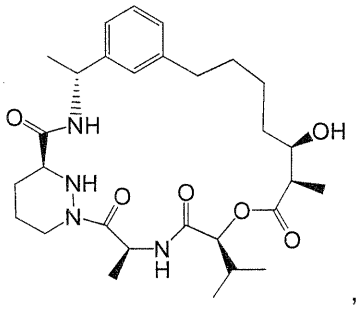
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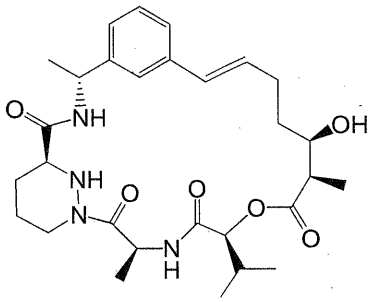
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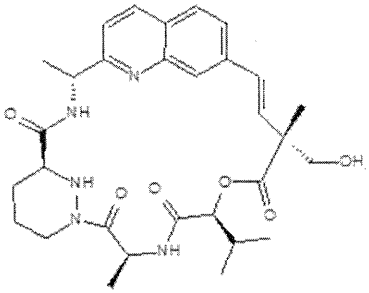
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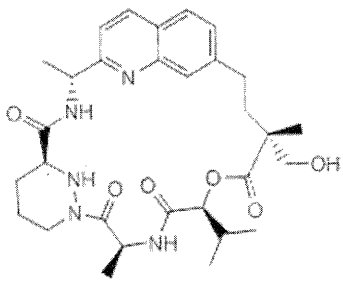
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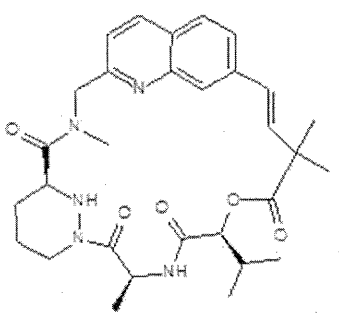
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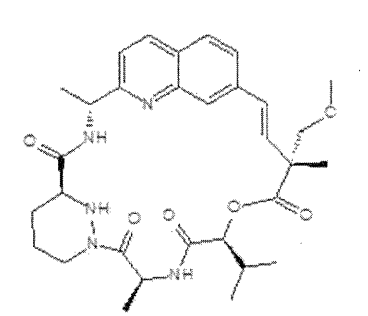
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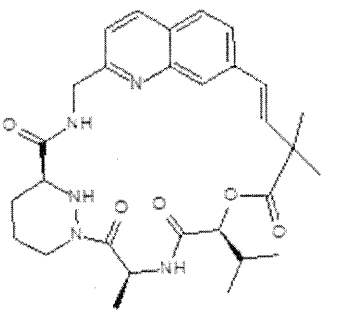
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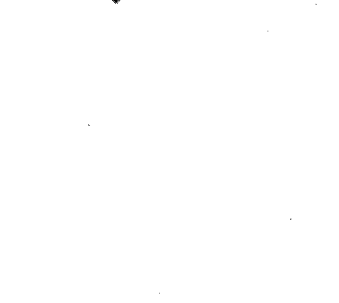
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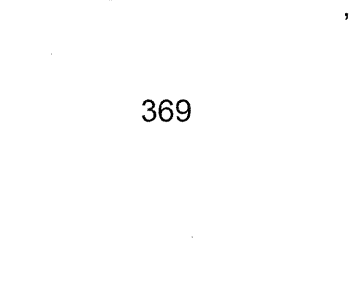
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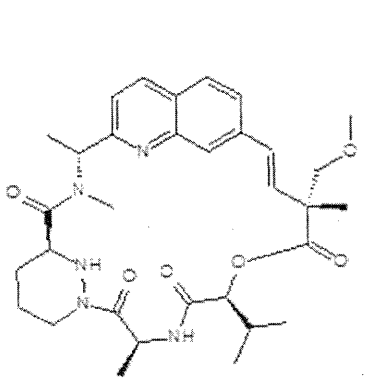
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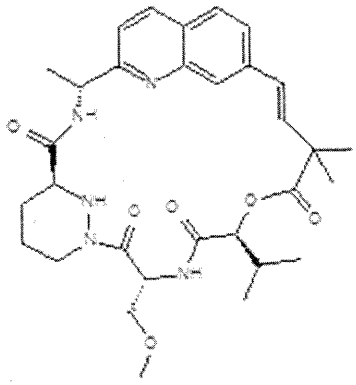
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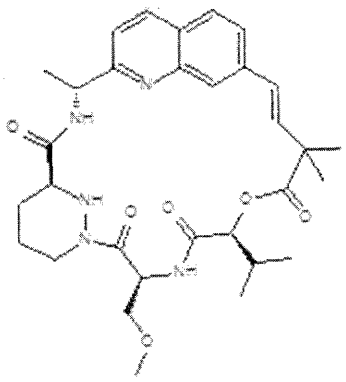
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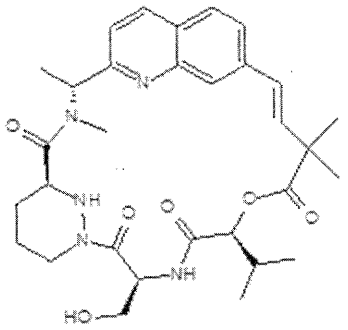
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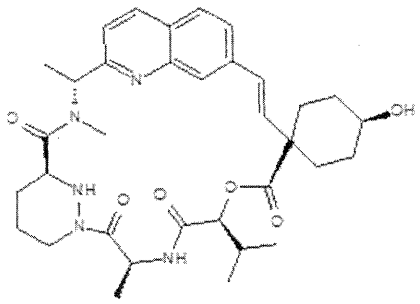
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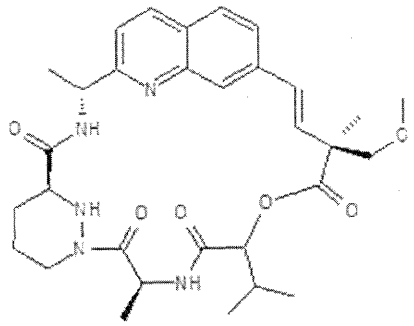
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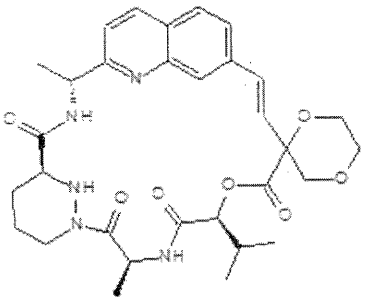
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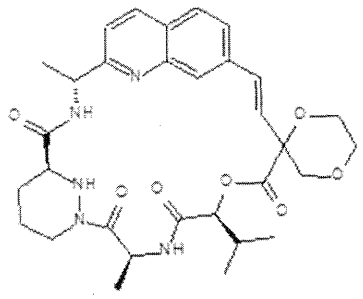
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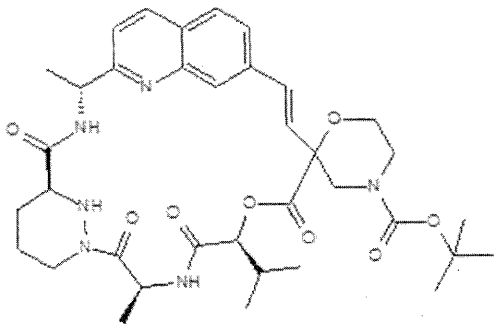

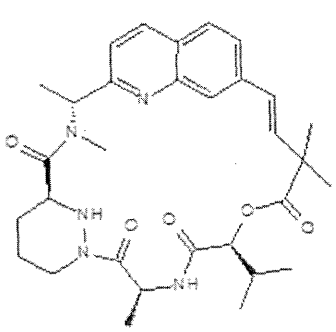
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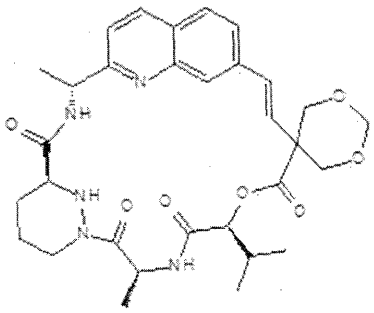
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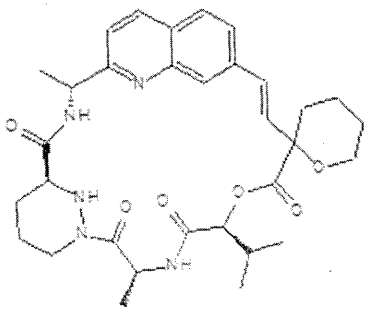
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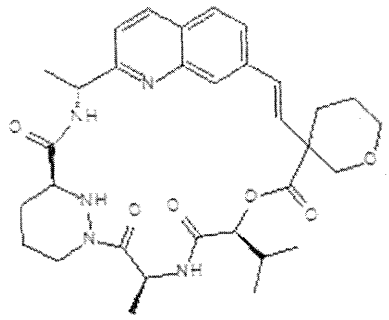
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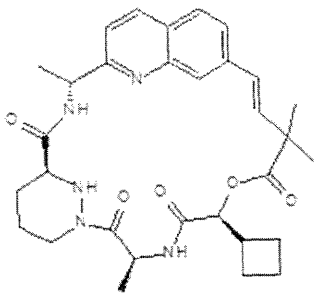
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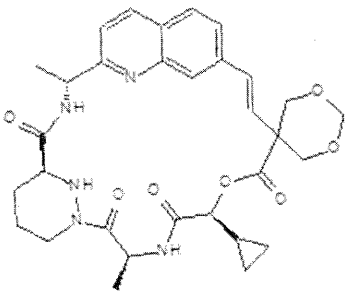
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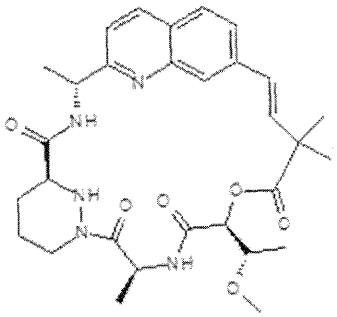
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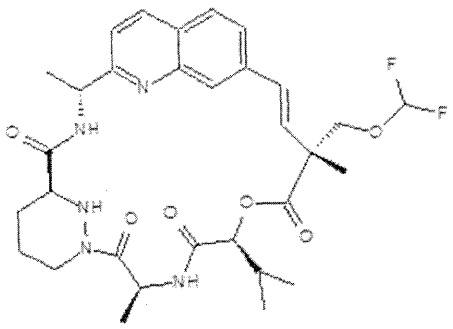
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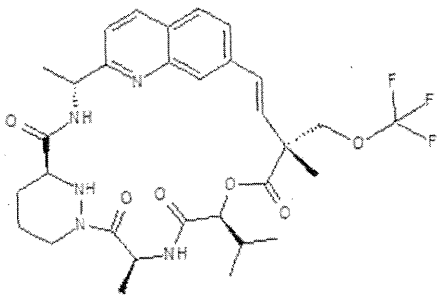
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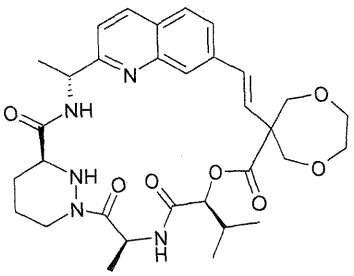
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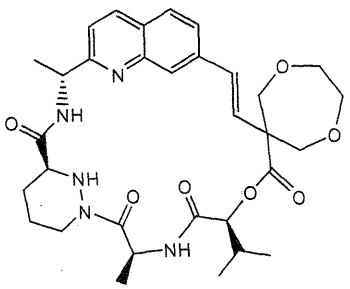
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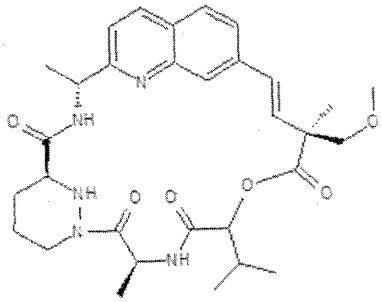
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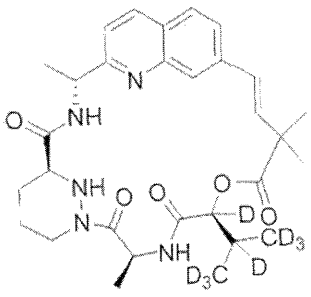
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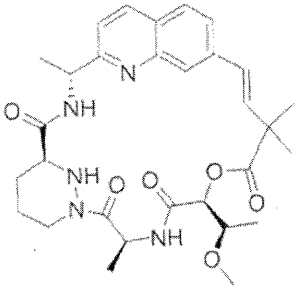
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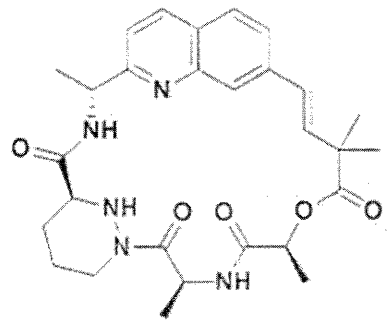
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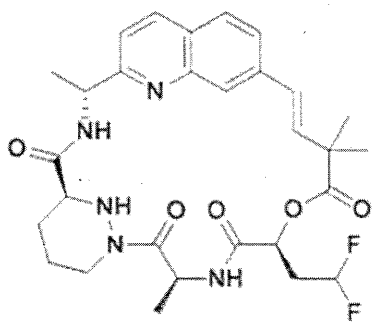
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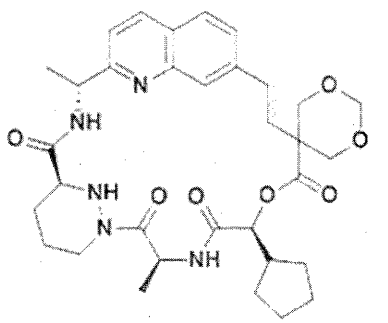
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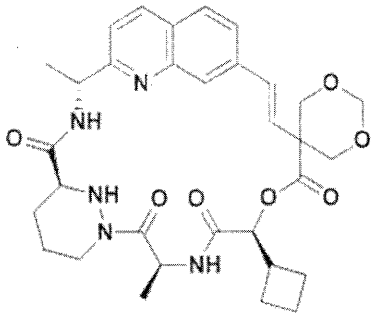
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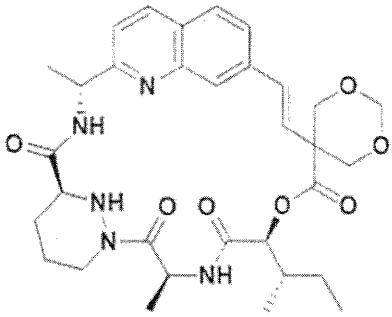
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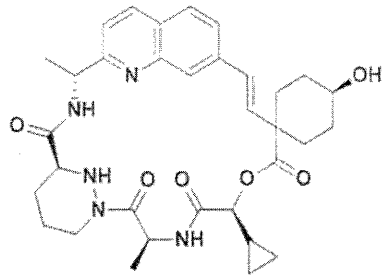
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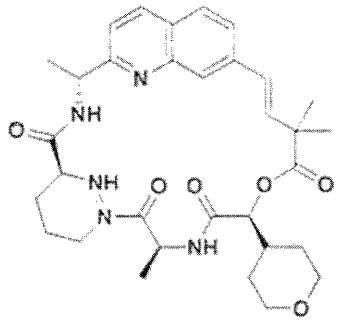
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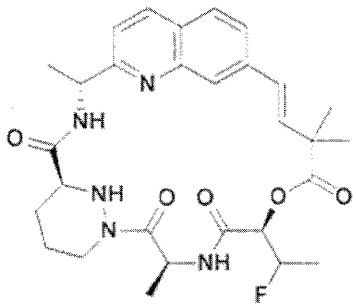
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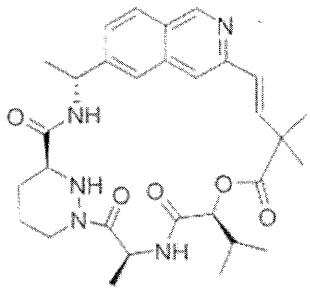
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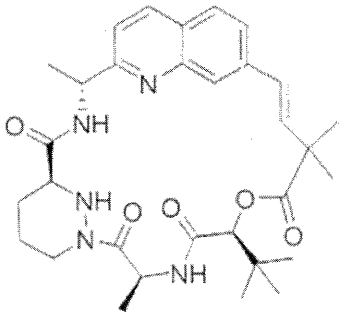
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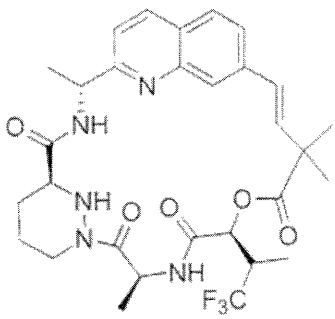
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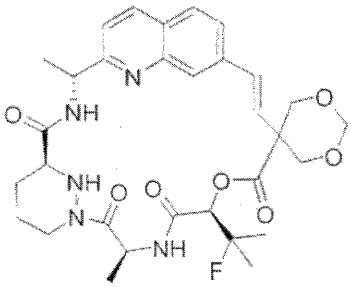
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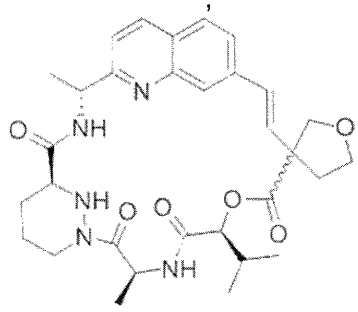
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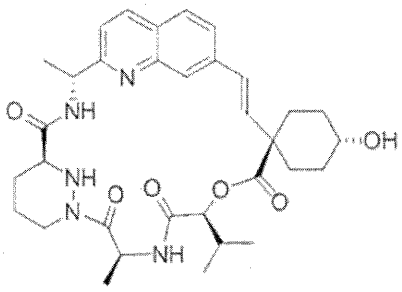
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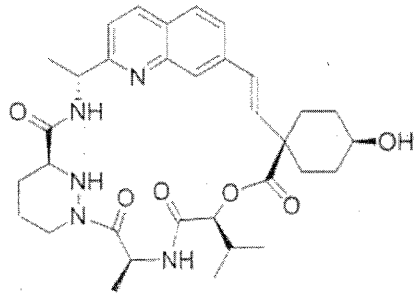
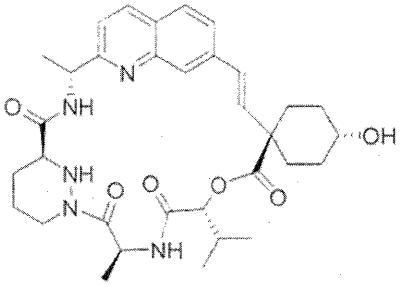
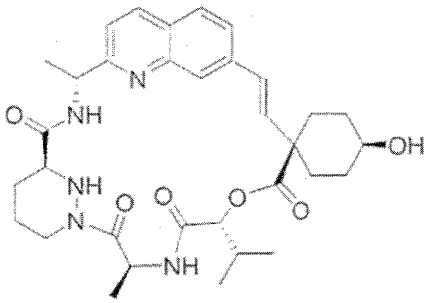
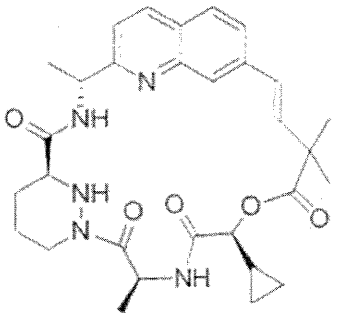
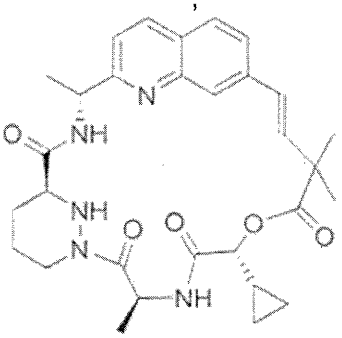
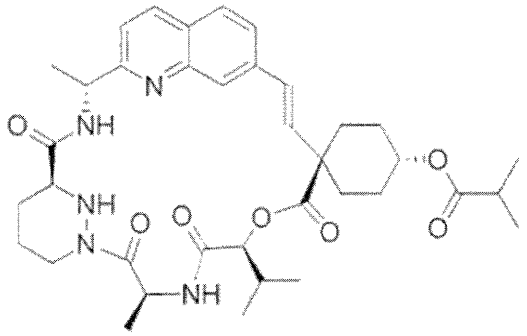
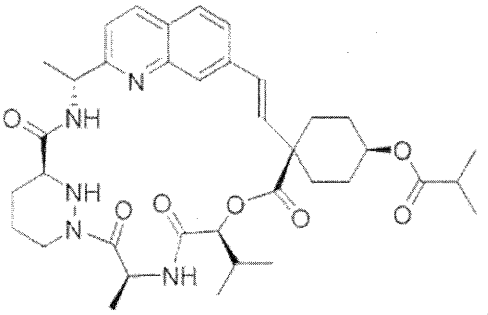
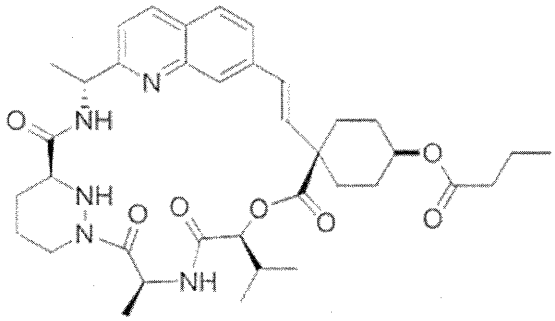
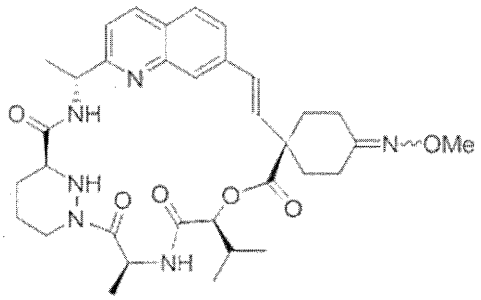
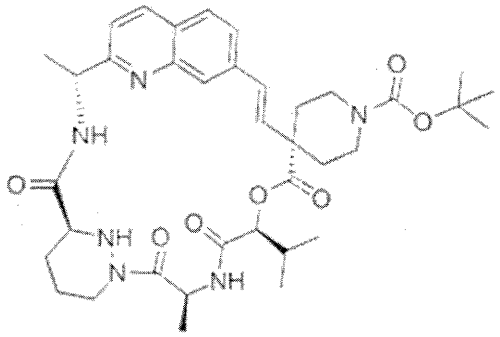
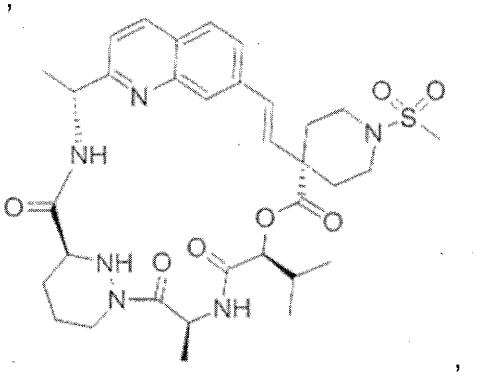

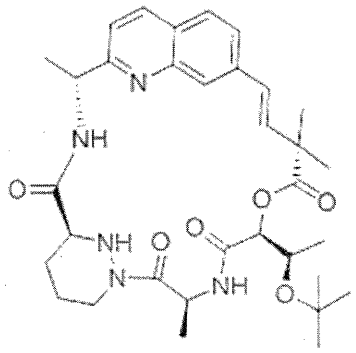
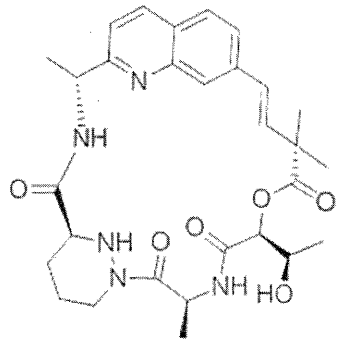
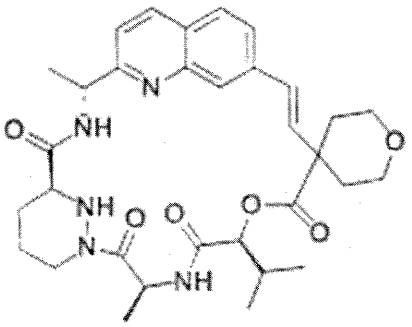
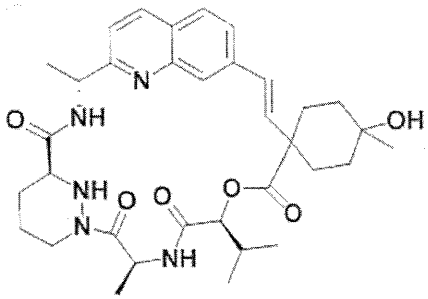
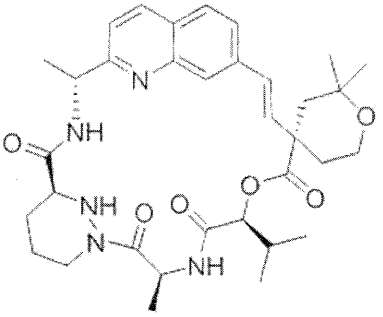
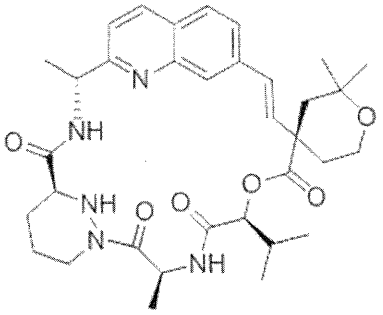
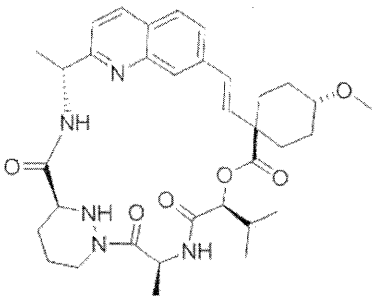
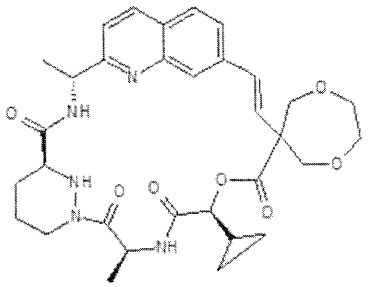
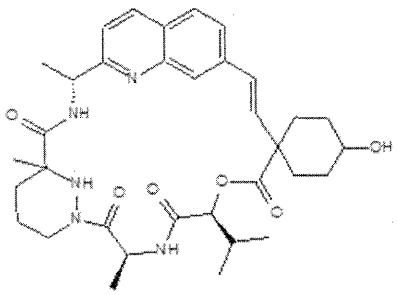
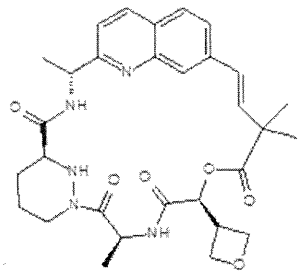
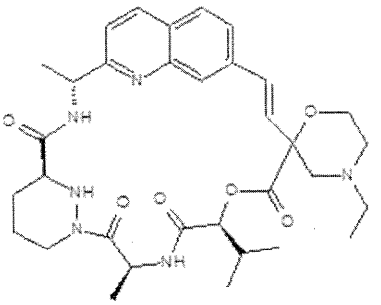
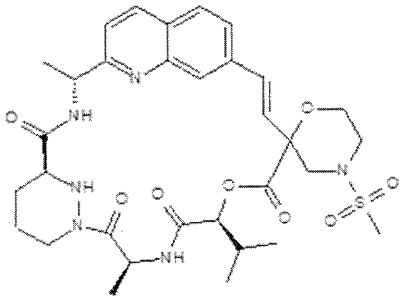
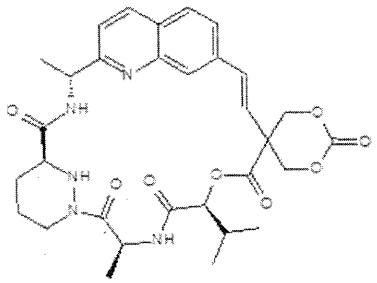
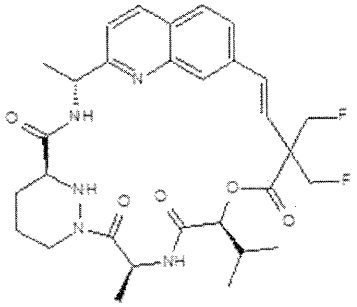

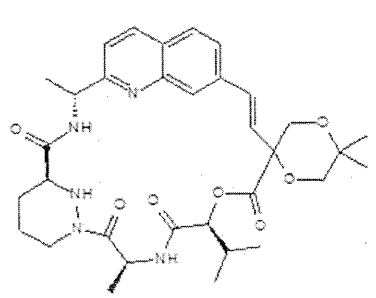
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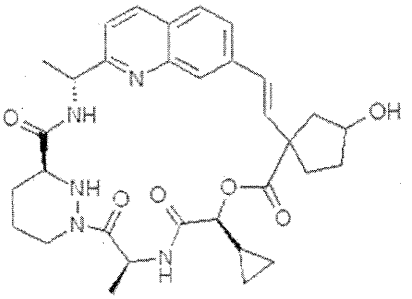
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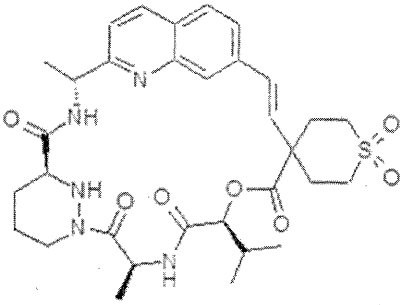
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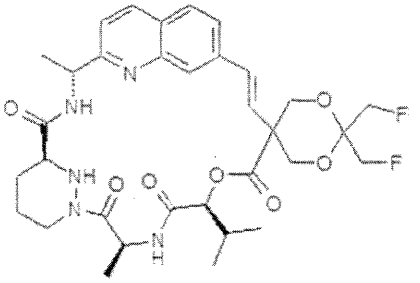
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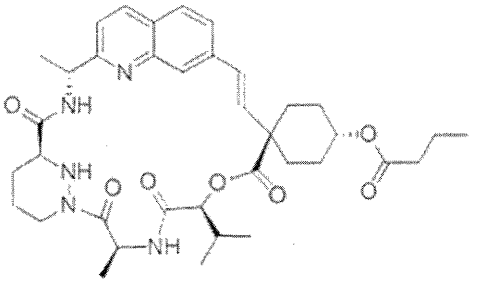
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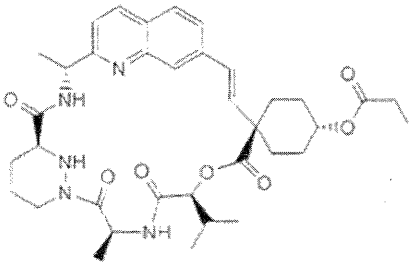
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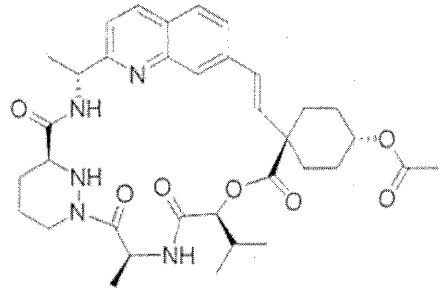
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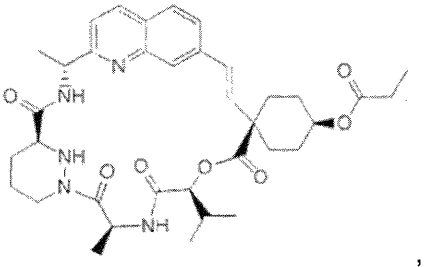
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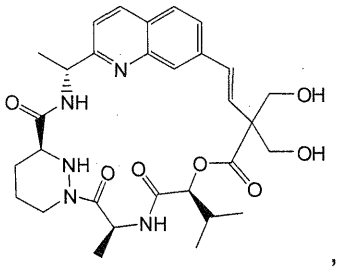
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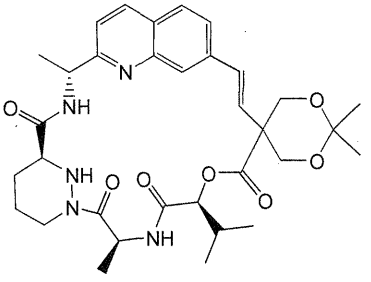
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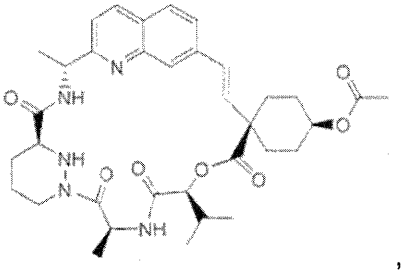
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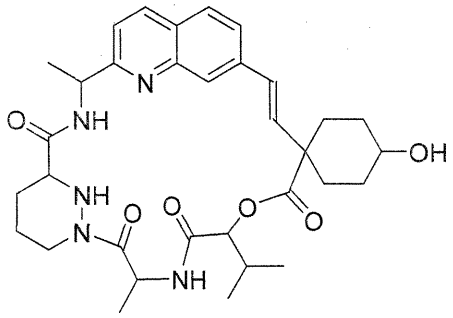
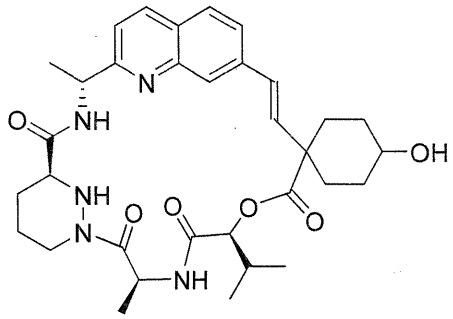
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

18. A compound which is:



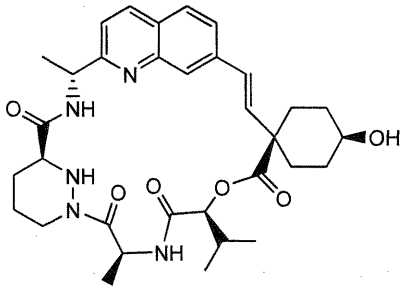
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

19. A compound which is:



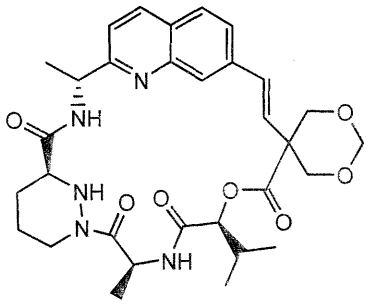
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

20. A compound which is:



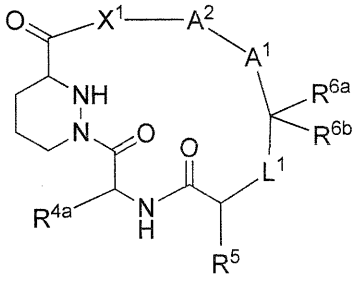
or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

21. A compound which is:



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

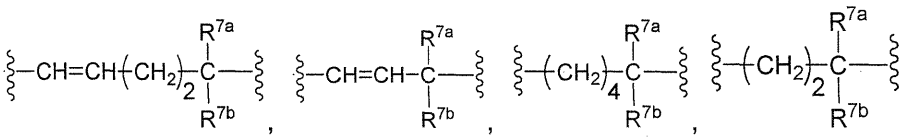
22. The compound of Claim 1, which is a compound of Formula III:

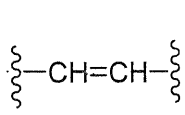
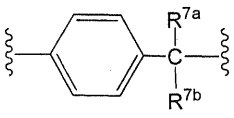


Formula III

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

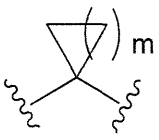
X^1 is -O-, $-N(CH_3)-$ or -NH-;

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

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

R^{6a} and R^{6b} are independently H, hydroxyl, $-CH_2CH_2CR^9(=N(C_1\text{-}C_4)\text{alkoxy})$, $(C_1\text{-}C_8)$alkyl or $(C_1\text{-}C_8)$alkoxy, 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; or

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



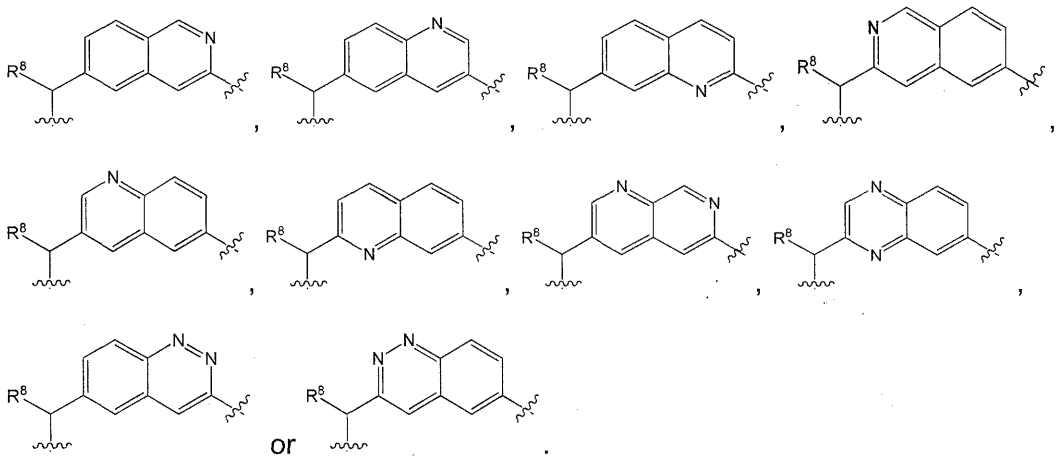
(a),

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, halo, hydroxyl, $-NH_2$, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $-OC(O)R^9$, $-C(O)_2R^9$, and $-S(O)_2R^9$;

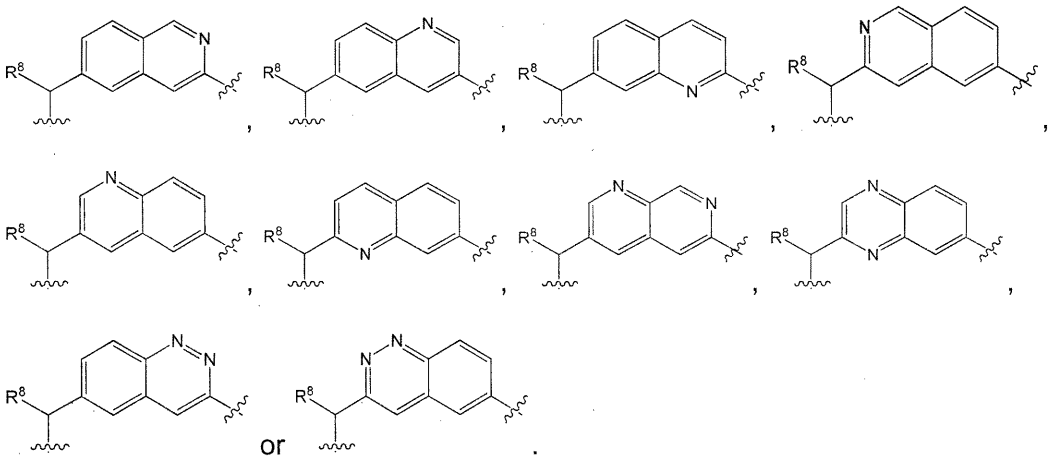
R^{7a} and R^{7b} are independently H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl; and

R^8 is H or $(C_1\text{-}C_4)$alkyl.

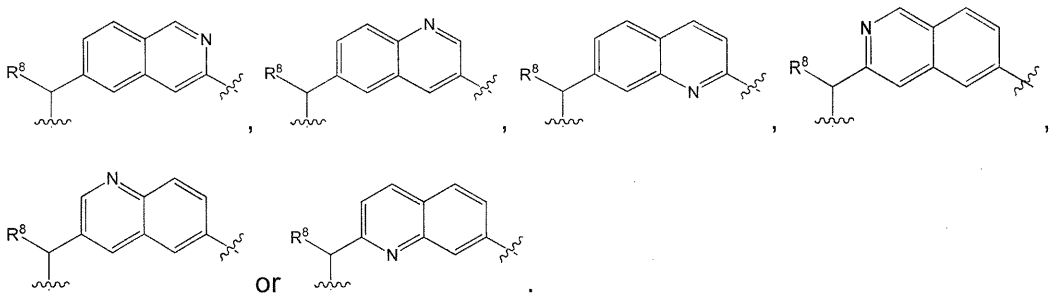
23. The compound of claim 22, wherein L^1 is $-NH\text{-}CH_2\text{-}$; R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



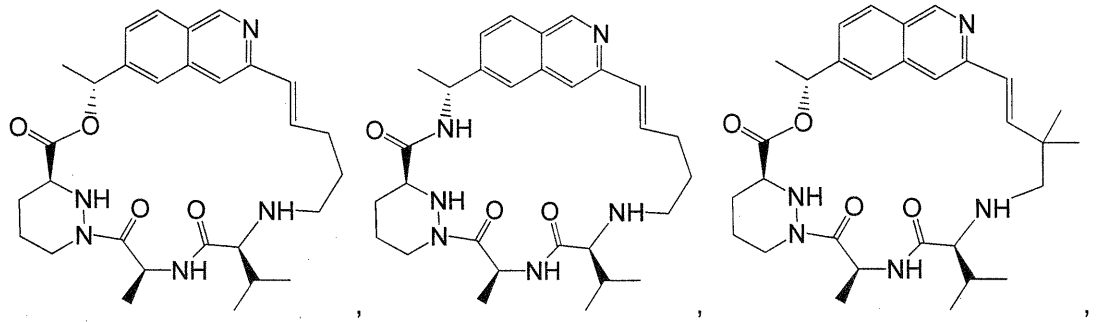
24. The compound of claim 23, wherein L^1 is -NH-$S(O)_2$-; R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is

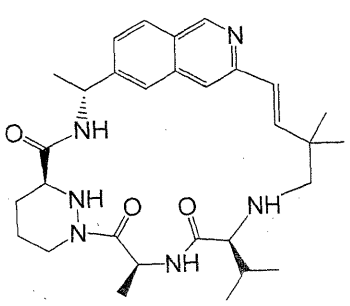


25. The compound of claim 23, wherein L^1 is -O-CH_2-; R^{4a} is methyl; R^5 is isopropyl; R^8 is methyl; and A^2 is



26. The compound of any preceding claim, which is

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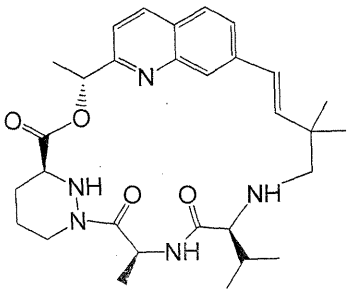
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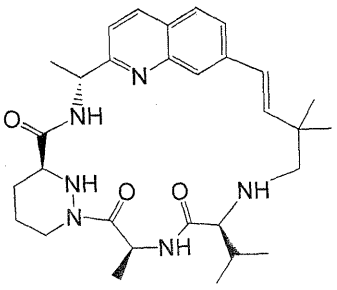
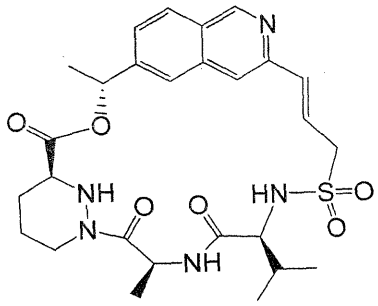
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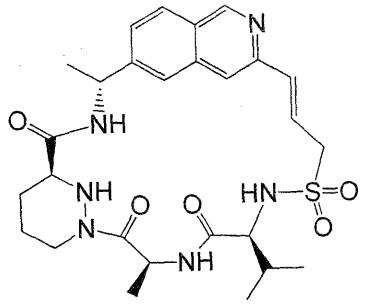
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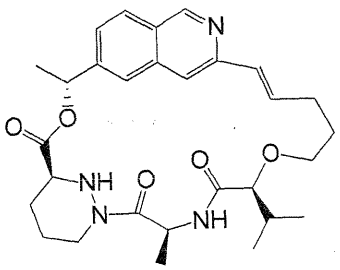
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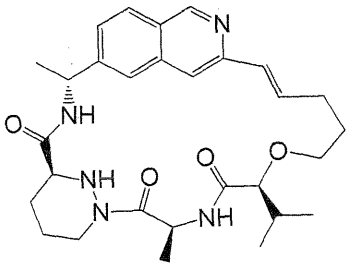
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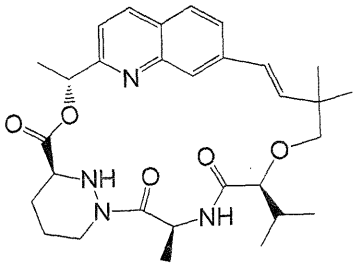
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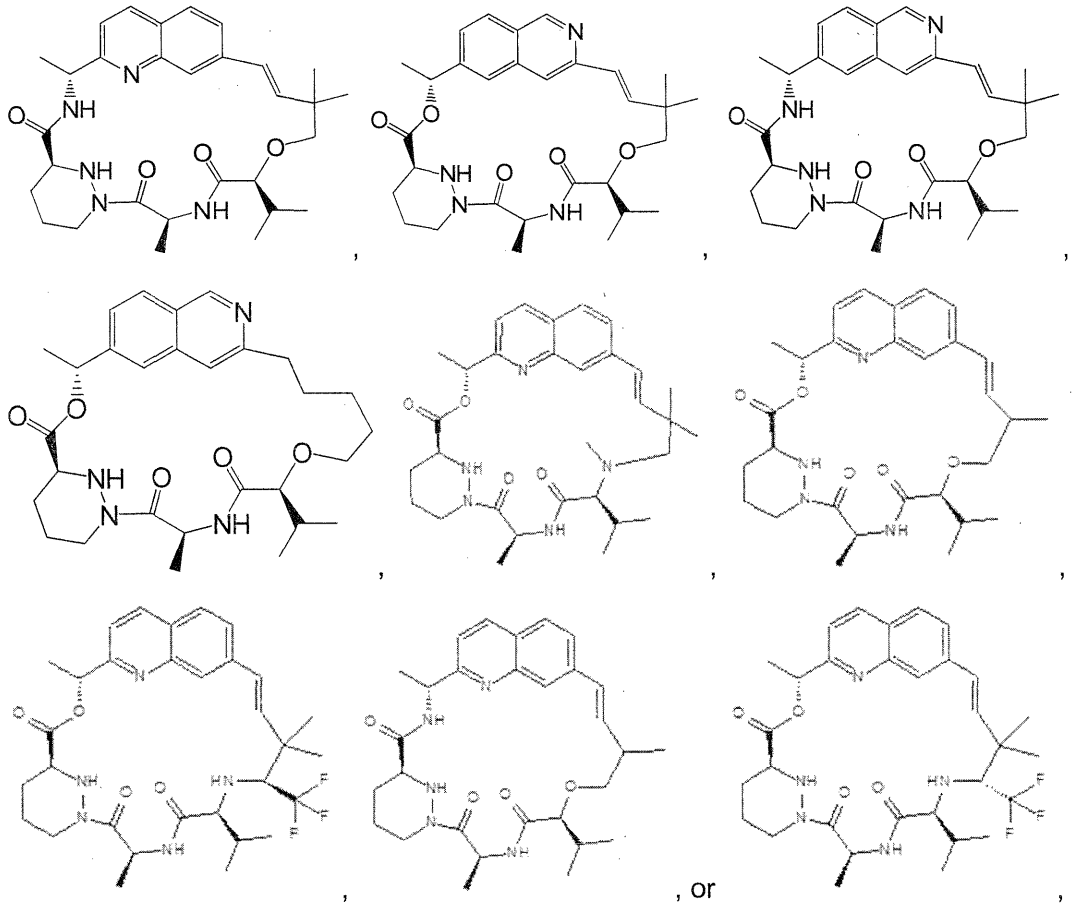

or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof.

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, ester or prodrug 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.