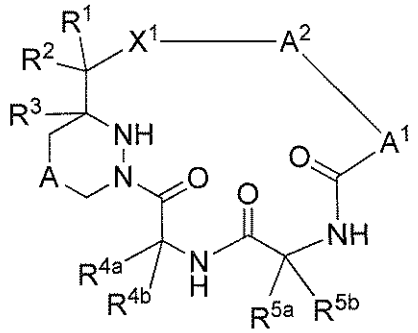
infection are difficult to achieve because of the prodigious amount of daily virus production in chronically infected patients and the high spontaneous mutability of HCV virus (Neumann, *et al.*, *Science* 1998, *282*, 103-7; Fukimoto, *et al.*, *Hepatology*, 1996, *24*, 1351-4; Domingo, *et al.*, *Gene*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

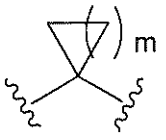


Formula I

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

one or more substituent 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, 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) is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, -NH_2, -C(O)O-(C_1-C_8)alkyl, -C(O)-di(C_1-C_8)alkylamino, -C(O)-(C_1-C_8)alkyl, -C(O)-heterocycloalkyl, -$S(O)_2R^{10}$, –$OSi(R^{10})_3$, (C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_8)alkanoyl and aryl(C_1-C_4)alkyl;

R^{6a}, R^{6b}, R^{7a} and R^{7b} are independently H, hydroxyl, cyano, (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, -$S(O)R^9$, -$S(O)_2R^9$ or -$N(R^9)_2$, wherein each of R^{6a}, R^{6b}, R^{7a} and R^{7b} is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, cyano, (C_1-C_4)alkyl, (C_1-C_8)alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, -NHS(O)R^9, -NHC(O)R^9, -OC(O)-(C_1-C_8)alkyl -C(O)O-(C_1-C_8)alkyl and (C_1-C_8)alkanoyl, wherein each -OC(O)-(C_1-C_8)alkyl or (C_1-C_8)alkoxy is optionally substituted with one or more amino, -OC(O)O-(C_1-C_8)alkyl or -$Si(R^{10})_3$; 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, (C_2-C_4)alkenyl or (C_2-C_4)alkynyl;

each R^{10} is independently H, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, cycloalkyl(C_1-C_4)alkyl or aryl, wherein R^{10} is optionally substituted with one or more halo;

each n is independently 0, 1 or 2; and

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

In one aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein or a pharmaceutically acceptable salt, isotope, stereoisomer, mixture of stereoisomers, tautomer, ester or prodrug thereof and a pharmaceutically acceptable excipient.

In another embodiment, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt, ester or prodrug thereof and one or more pharmaceutically acceptable carriers or excipients. 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, 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, 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.

DETAILED DESCRIPTION

Definitions

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

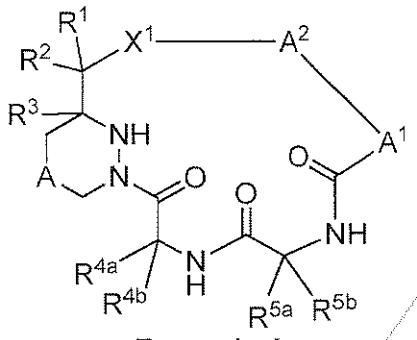
"Alkanoyl" is RC(O)-; "alkanoyloxy" is RC(O)O-; and "alkanoylamino" is RC(O)NR'-; where R is an alkyl group as defined herein, and R' is hydrogen or alkyl.

"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, an 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:

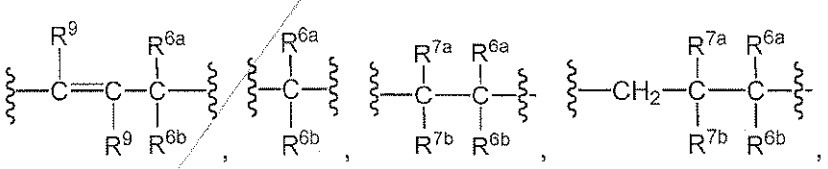
1. A compound of Formula I:

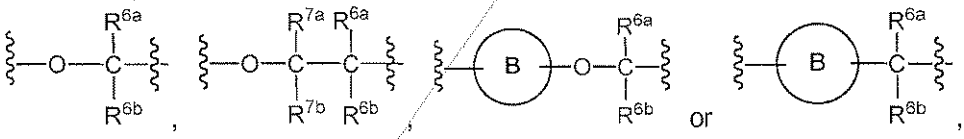


Formula I

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 $-CR^9=CR^9-$, 



wherein B is arylene, heteroarylene, cycloalkylene or heterocycloalkylene;

A^2 is -CH(R^8)-arylene, -CH(R^8)-heteroarylene, -CH(R^8)-heterocycloalkylene, -CH(R^8)-cycloalkylene, arylene, heteroarylene or cycloalkylene, wherein A^2 is optionally substituted with one or more substituents selected from the group consisting of oxo, $-OR^9$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-N(R^9)_2$, halo, halo(C$_1$-C$_4$)alkyl, (C$_1$-C$_4$)alkoxy(C$_1$-C$_4$)alkyl, halo(C$_1$-C$_4$)alkoxy, cyano and (C$_1$-C$_8$)alkyl;

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$_1$-C$_4$)alkanoyl; or

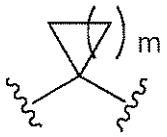
R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-, -C(=S)- or –C(=N(C_1-C_4)alkyl)-;

R^3 is H or (C_1-C_4)alkyl which is optionally substituted with halo, cyano, hydroxy 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 of R^{4a} and R^{4b} is optionally substituted with one or more substituent selected from the group consisting of cyano, (C_1-C_8)alkoxy, -COOH, -C(O)O-(C_1-C_8)alkyl, halo, hydroxyl, amino, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, -C(O)-mono(C_1-C_8)alkylamino, -C(O)-di(C_1-C_8)alkylamino, -C(O)-heterocycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein each substituent is optionally substituted with one or more halo, heterocycloalkyl or aryl;

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 R^{5a} and R^{5b} are independently optionally substituted with one or more substituent 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, 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 sufur atom, and wherein a ring atom of Formula (a) is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, -NH_2, -C(O)O-(C_1-C_8)alkyl, -C(O)-di(C_1-C_8)alkylamino, -C(O)-(C_1-C_8)alkyl, -C(O)-heterocycloalkyl, -$S(O)_2R^{10}$, –$OSi(R^{10})_3$, (C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_8)alkanoyl and aryl(C_1-C_4)alkyl;

R^{6a}, R^{6b}, R^{7a} and R^{7b} are independently H, hydroxyl, cyano, (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, cycloalkyl, -SR^9, -$S(O)R^9$, -$S(O)_2R^9$ or -$N(R^9)_2$, wherein each of R^{6a}, R^{6b}, R^{7a} and R^{7b} is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, cyano, (C_1-C_4)alkyl, (C_1-C_8)alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, -NHS(O)R^9, -NHC(O)R^9, -OC(O)-(C_1-C_8)alkyl -C(O)O-(C_1-C_8)alkyl and

(C_1-C_8)alkanoyl, wherein each -OC(O)-(C_1-C_8)alkyl or (C_1-C_8)alkoxy is optionally substituted with one or more amino, -OC(O)O-(C_1-C_8)alkyl or -Si(R^{10})$_3$; 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, (C_2-C_4)alkenyl or (C_2-C_4)alkynyl;

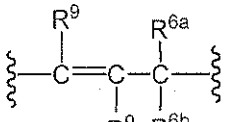
each R^{10} is independently H, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, cycloalkyl(C_1-C_4)alkyl or aryl, wherein R^{10} is optionally substituted with one or more halo;

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 is methylene.

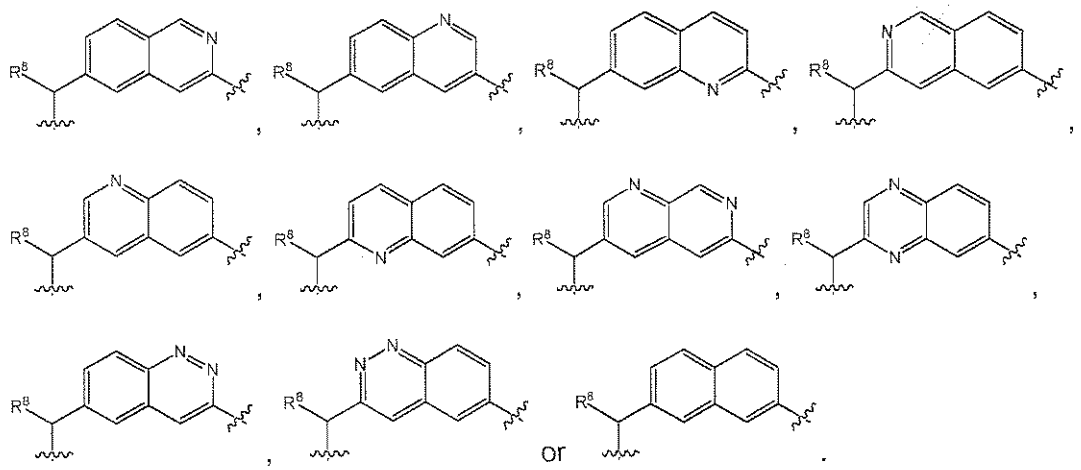
3. The compound of any preceding claim, wherein A^1 is ethenylene, propenylene, ethylene, propylene, oxypropylene, oxypropenylene, pyrazolylene, phenylene or pyrimidinylene.

4. The compound of any preceding claim, wherein A^1 is .

5. The compound of any preceding claim, wherein A^2 is -CH(R^8)-arylene or -CH(R^8)-heteroarylene.

6. The compound of any preceding claim, 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.

7. The compound of any preceding claim, wherein A^2 is



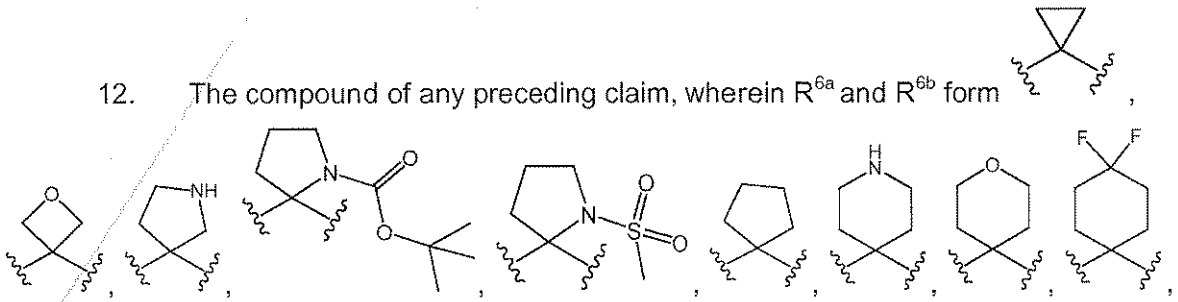
8. The compound of any preceding claim, wherein X^1 is -O- or –NH-.

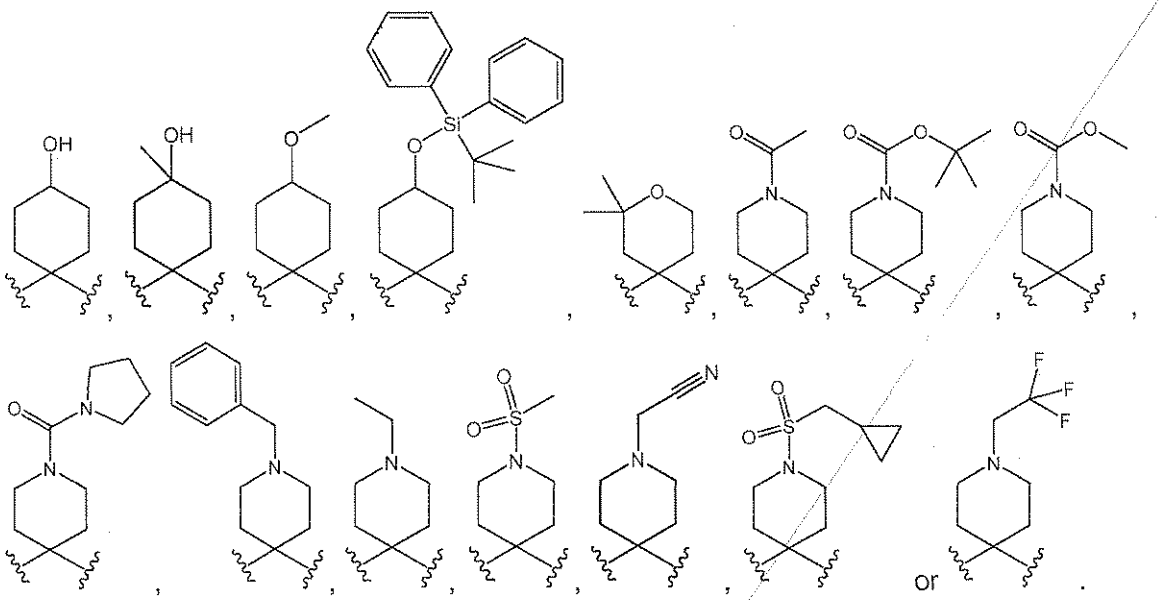
9. The compound of any preceding claim, wherein R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-.

10. The compound of any preceding claim, wherein R^3 is H.

11. The compound of any preceding claim, wherein R^{6a} is H and R^{6b} is H or (C_1-C_4)alkyl, or R^{6a} and R^{6b} together form a spirocycle having Formula (a).

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

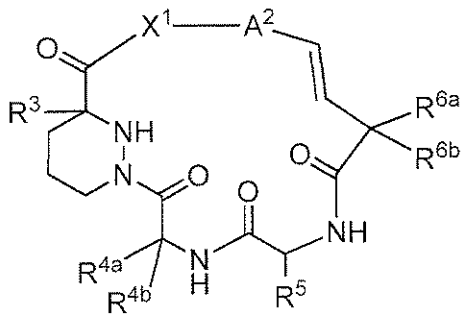




13. The compound of any preceding claim, wherein R^3 is H; R^{5a} is H; R^{5b} is H, (C_1-C_8)alkyl, hydroxy(C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, azido(C_1-C_8)alkyl, aryl, cycloalkyl, aryl(C_1-C_4)alkyl, cycloalkyl(C_1-C_4)alkyl, heterocycloalkyl(C_1-C_4)alkyl or arylheterocycloalkyl(C_1-C_4)alkyl; R^{6a} is H; and R^{6b} is H, (C_1-C_4)alkyl or hydroxy(C_1-C_4)alkyl.

14. The compound of any preceding claim, wherein X^1 is -O- or -NH-; R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-; R^3 is H; R^{4a} is H; R^{4b} is methyl; R^{5a} is H and R^{5b} is iso-propyl, propenyl or propynyl; and R^8 is methyl.

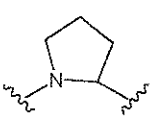
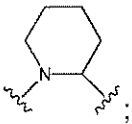
15. The compound of any preceding claim, which is a compound of Formula II:



Formula II

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

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

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

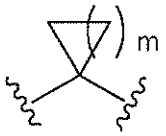
R^3 is H or (C_1-C_4)alkyl;

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

R^5 is (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 R^5 is optionally substituted with one or more substituent selected from -N_3, cyano, -COOH, halo, hydroxyl, amino, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, aryl and heteroaryl,

R^{6a} and R^{6b} are independently H, hydroxyl, cyano, (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, -$S(O)_2R^9$ or -$N(R^9)_2$, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, cyano, (C_1-C_4)alkyl, (C_1-C_8)alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, -NHS(O)R^9, -NHC(O)R^9, -OC(O)-(C_1-C_8)alkyl -C(O)O-(C_1-C_8)alkyl and (C_1-C_8)alkanoyl, wherein each -OC(O)-(C_1-C_8)alkyl or (C_1-C_8)alkoxy is optionally substituted with one or more amino, -OC(O)O-(C_1-C_8)alkyl or -Si(R^{10})$_3$; or

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



(a),

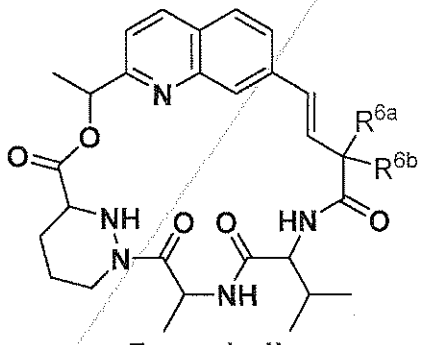
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sufur atom, and wherein a ring atom of Formula (a) is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, $-NH_2$, $-C(O)O-(C_1-C_8)$alkyl, $-C(O)$-di(C_1-C_8)alkylamino, $-C(O)-(C_1-C_8)$alkyl, $-C(O)$-heterocycloalkyl, $-S(O)_2R^{10}$, $-OSi(R^{10})_3$, (C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_8)alkanoyl and aryl(C_1-C_4)alkyl;

R^8 is H or (C_1-C_4)alkyl;

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

each R^{10} is independently H, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, cycloalkyl(C_1-C_4)alkyl or aryl, wherein R^{10} is optionally substituted with one or more halo.

16. The compound of any preceding claim, which is a compound of Formula IIa:

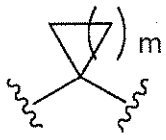


Formula IIa

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, cyano, (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, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ or $-N(R^9)_2$, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, cyano, (C_1-C_4)alkyl, (C_1-C_8)alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$, $-OC(O)-(C_1-C_8)$alkyl $-C(O)O-(C_1-C_8)$alkyl and (C_1-C_8)alkanoyl, wherein each $-OC(O)-(C_1-C_8)$alkyl or (C_1-C_8)alkoxy is optionally substituted with one or more amino, $-OC(O)O-(C_1-C_8)$alkyl or $-Si(R^{10})_3$; 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 sufur atom, and wherein a ring atom of Formula (a) is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, $-NH_2$, $-C(O)O-(C_1-C_8)$alkyl, $-C(O)-di(C_1-C_8)$alkylamino, $-C(O)-(C_1-C_8)$alkyl, $-C(O)$-heterocycloalkyl, $-S(O)_2R^{10}$, $-OSi(R^{10})_3$, (C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_8)alkanoyl and aryl(C_1-C_4)alkyl;

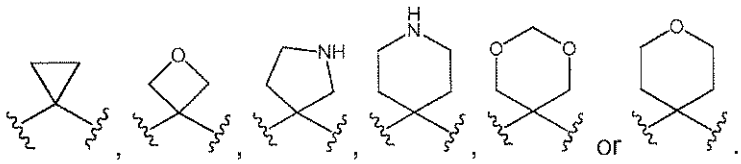
each R^9 is independently H, (C_1-C_4)alkyl, (C_2-C_4)alkenyl or (C_2-C_4)alkynyl; and

each R^{10} is independently H, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, cycloalkyl(C_1-C_4)alkyl or aryl, wherein R^{10} is optionally substituted with one or more halo.

17. The compound of any preceding claim, wherein R^{4a} and R^{4b} are independently H, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl;

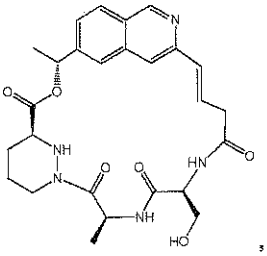
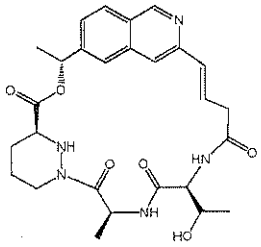
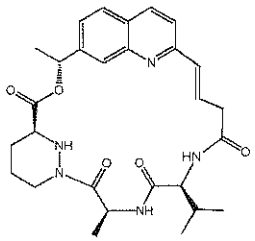
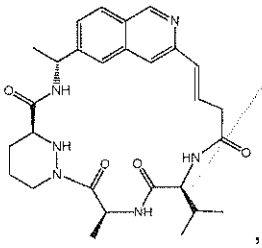
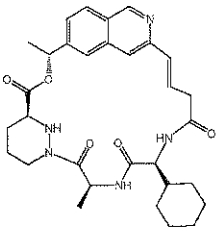
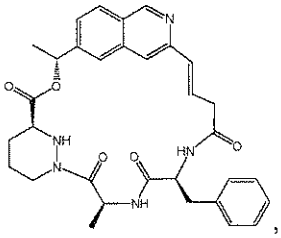
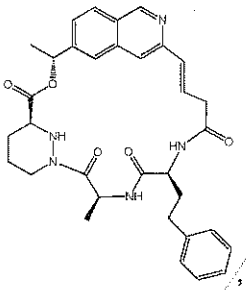
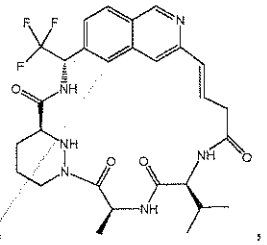
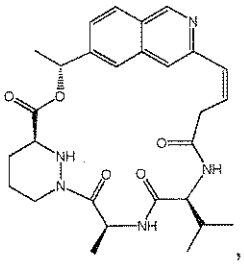
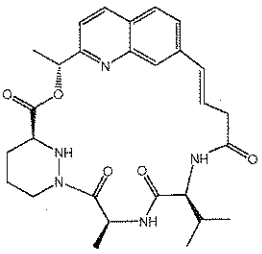
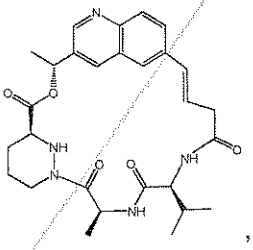
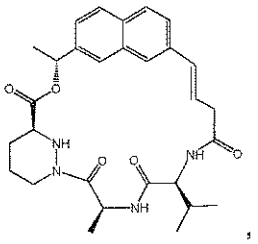
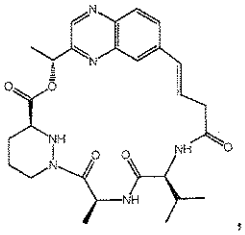
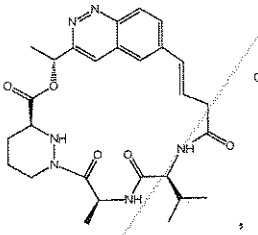
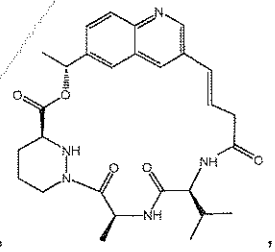
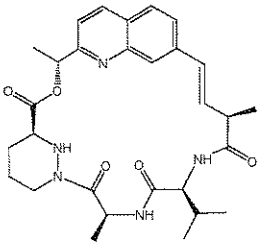
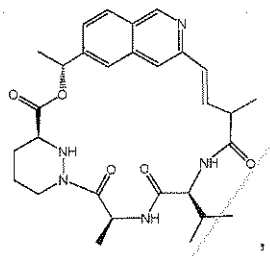
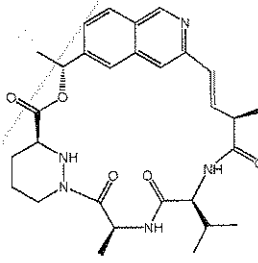
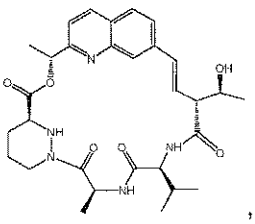
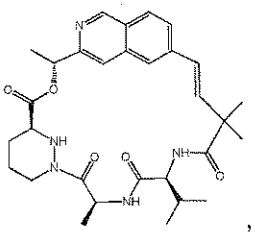
R^5 is H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, aryl, heterocycloalkyl, cycloalkyl, aryl(C_1-C_4)alkyl, cycloalkyl(C_1-C_4)alkyl or heterocycloalkyl(C_1-C_4)alkyl, wherein R^5 is optionally substituted with one or more substituent selected from the group consisting of $-N_3$, halo, hydroxyl, di(C_1-C_8)alkylamino, aryl or heteroaryl; and

R^{6a} and R^{6b} are independently H, -OH, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, (C_1-C_4)alkyl, aryl, cycloalkyl, heterocycloalkyl, di(C_1-C_8)alkylamino and (C_1-C_8)alkanoyl; or

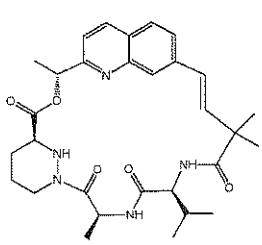
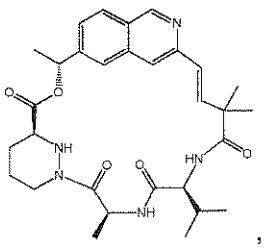
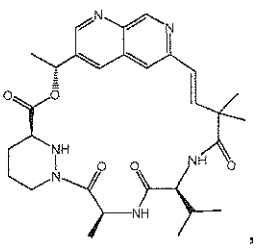
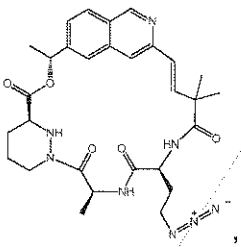
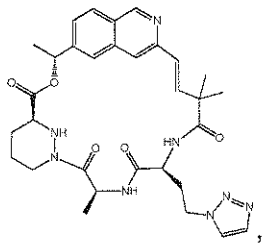
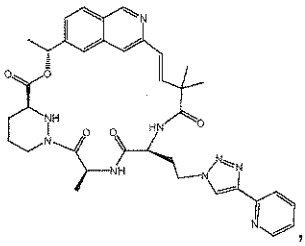
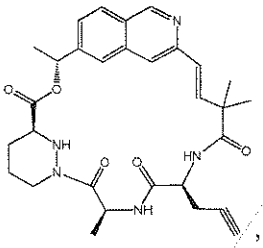
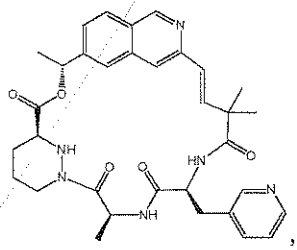
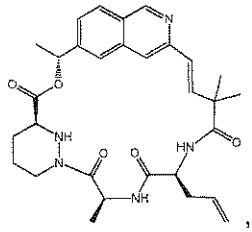
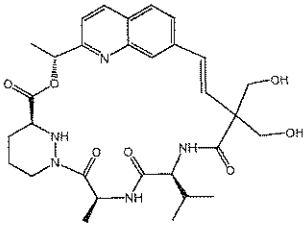
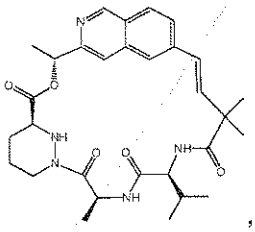
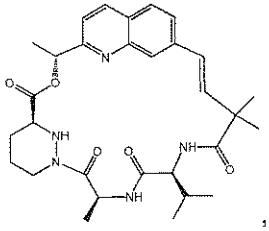
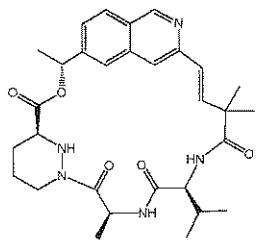
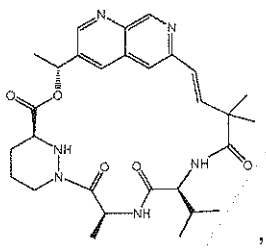
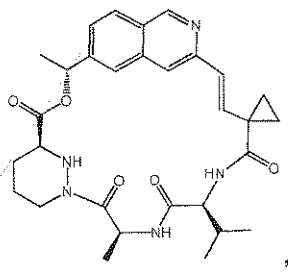
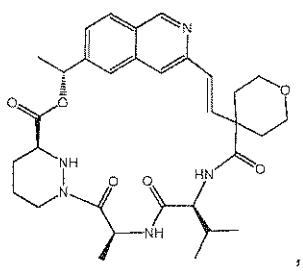
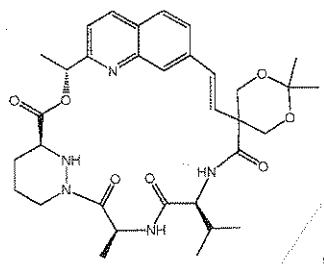
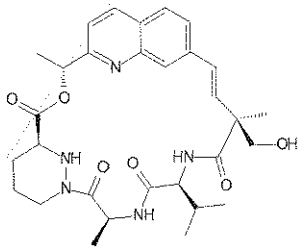
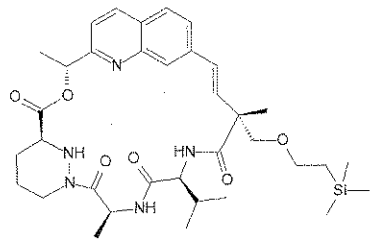
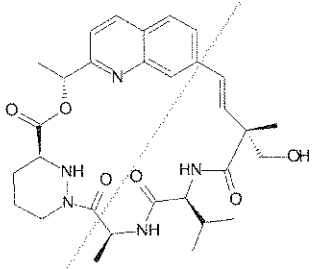
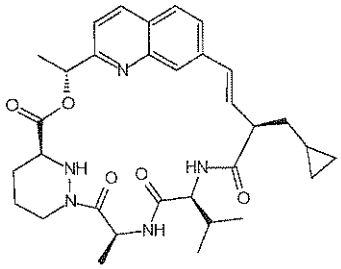
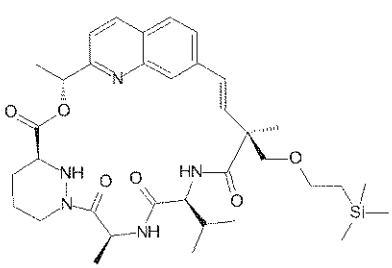
R^{6a} and R^{6b} together form 

or .

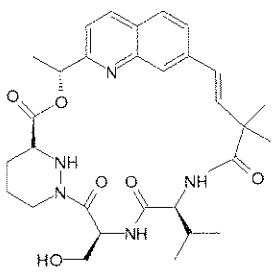
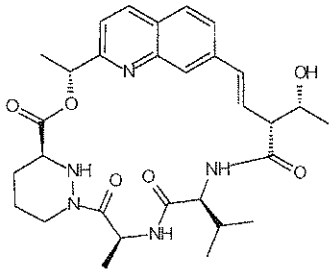
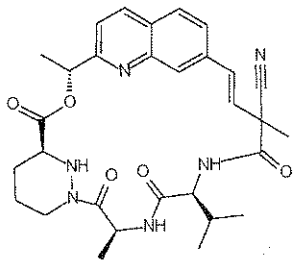
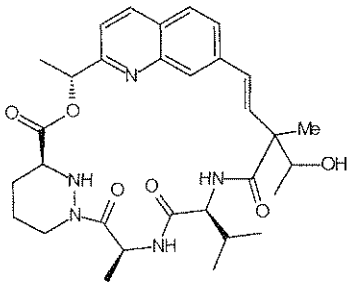
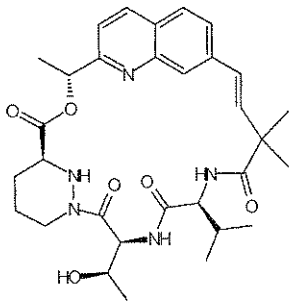
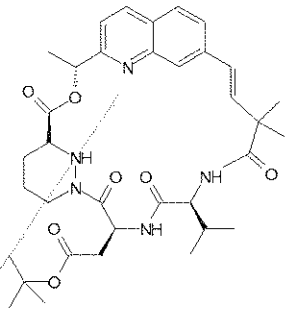
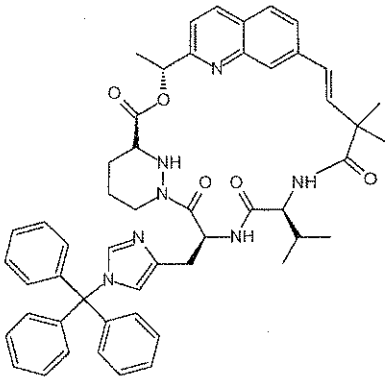
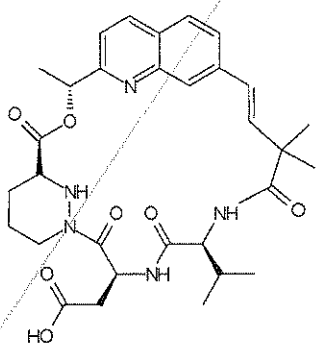
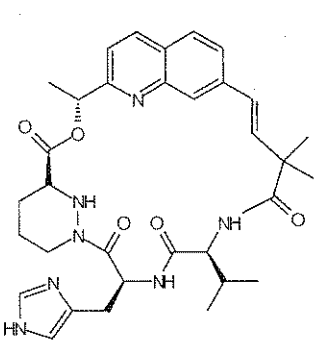
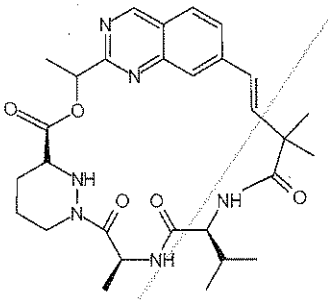
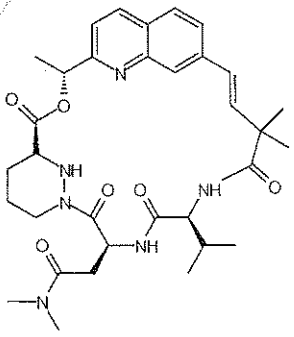
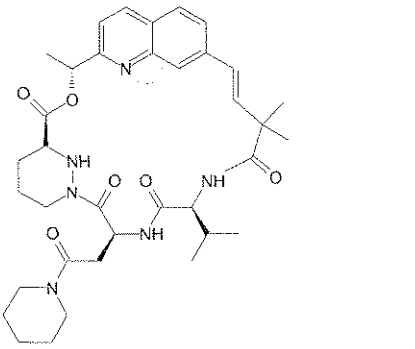
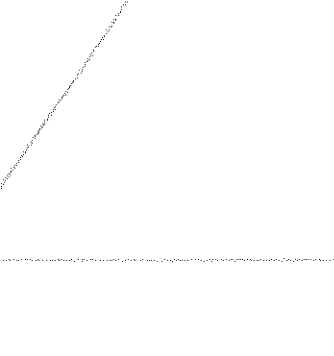
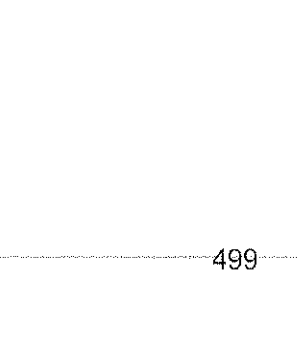
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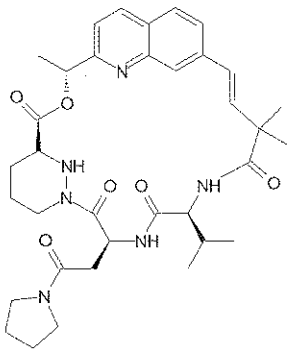
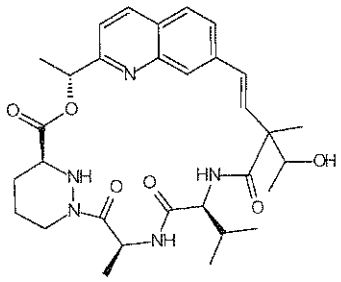
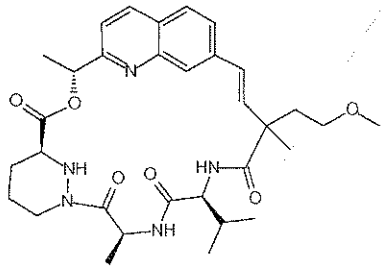
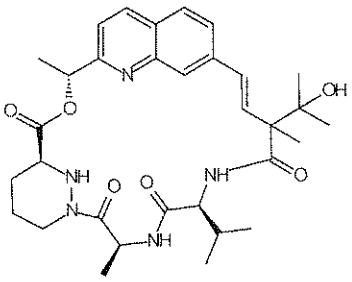
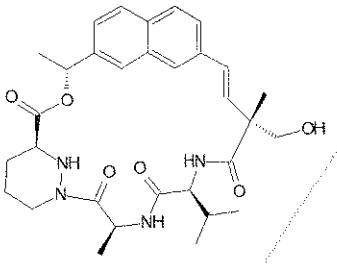
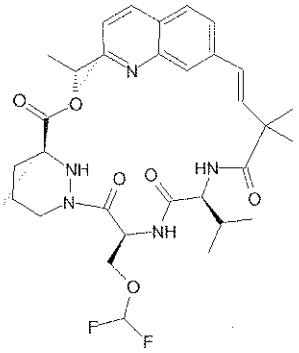
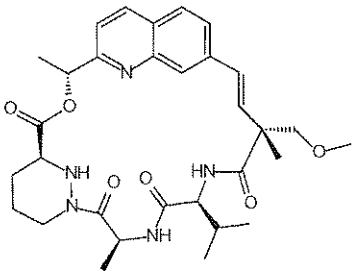
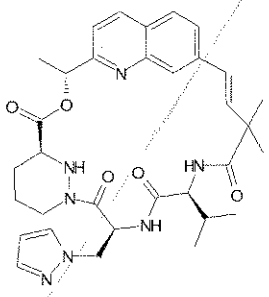
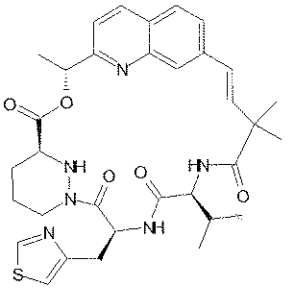
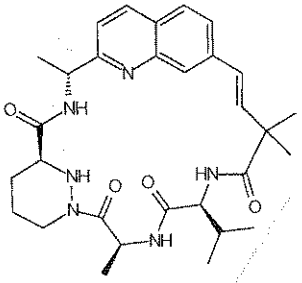
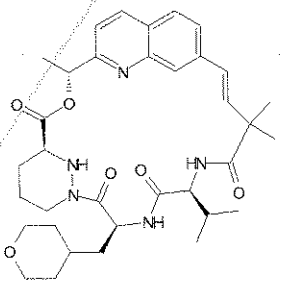
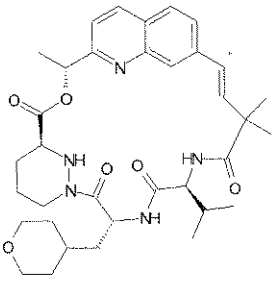

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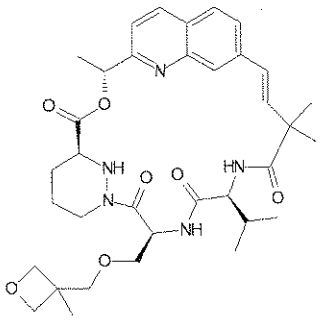
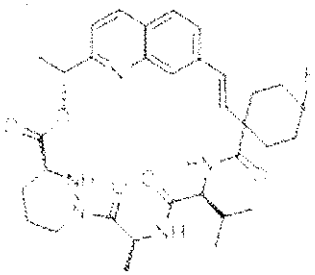
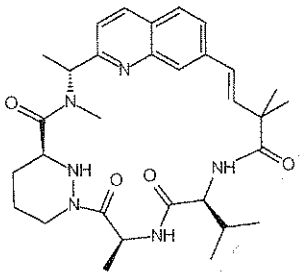
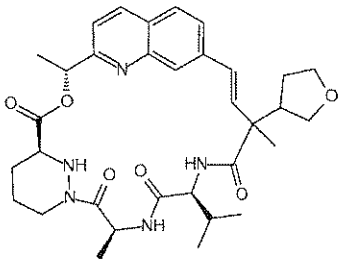
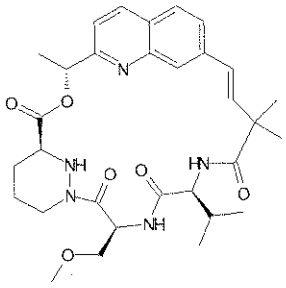
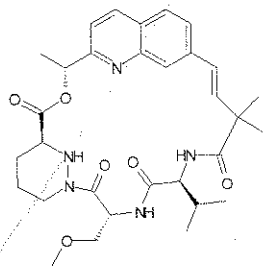
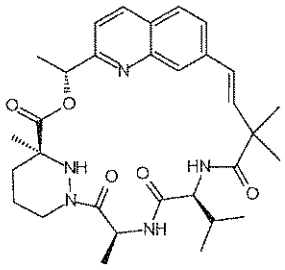
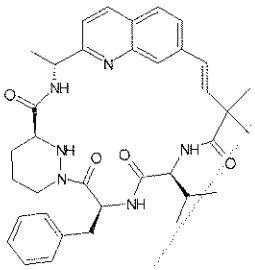
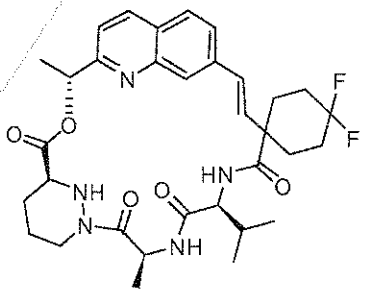
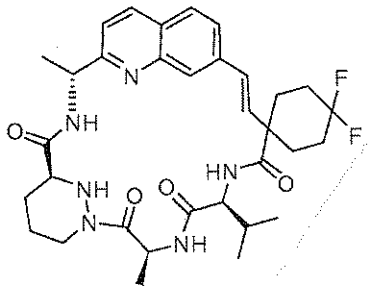
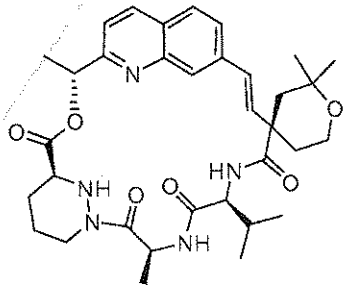
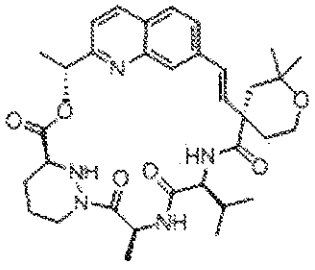
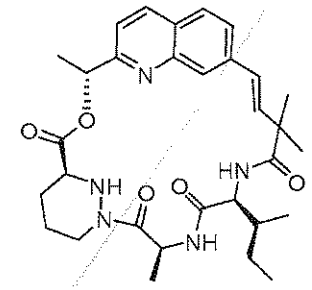
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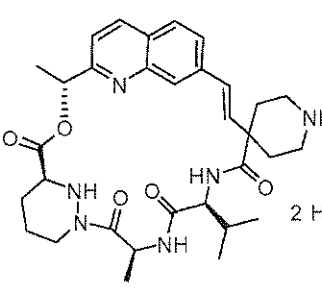
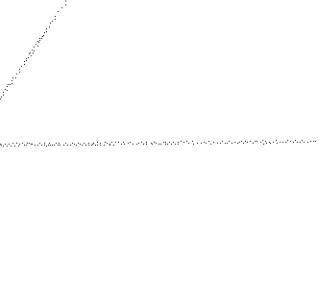
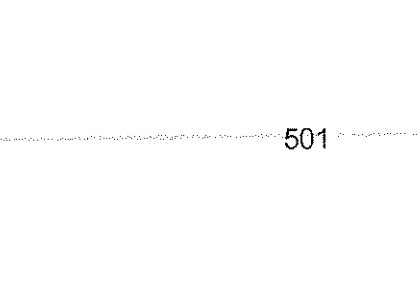

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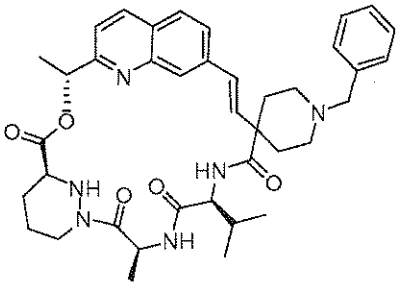
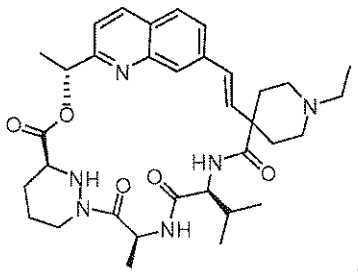
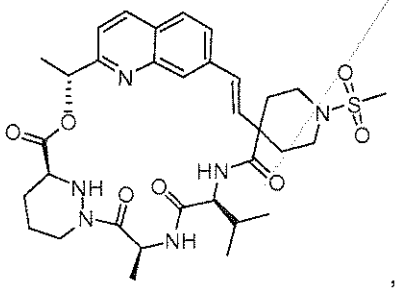
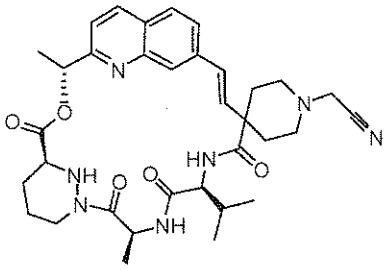
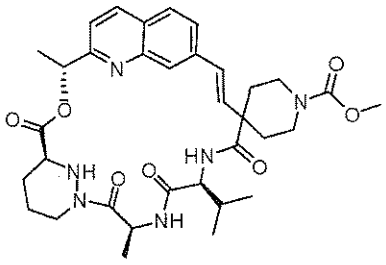
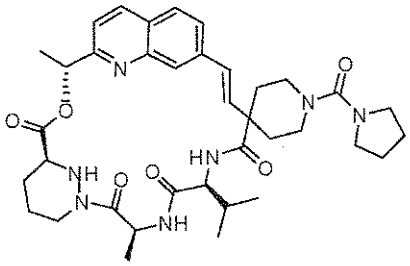
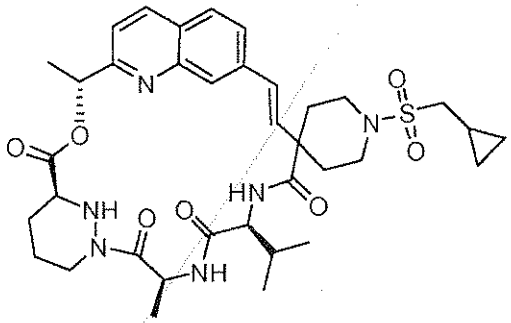
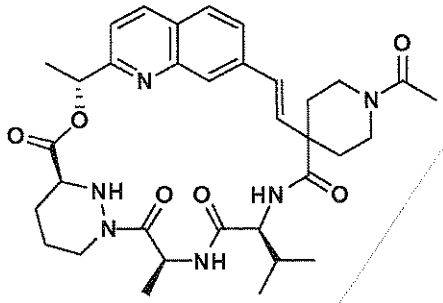
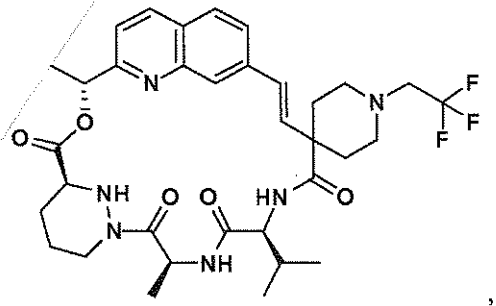
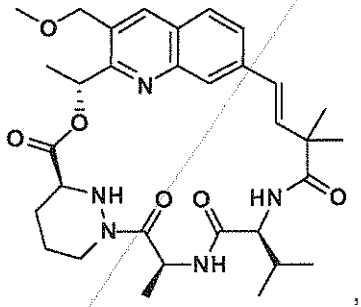
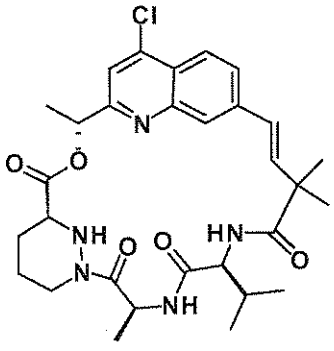
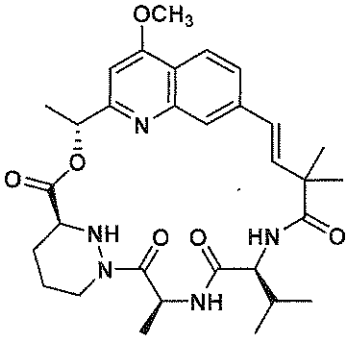

















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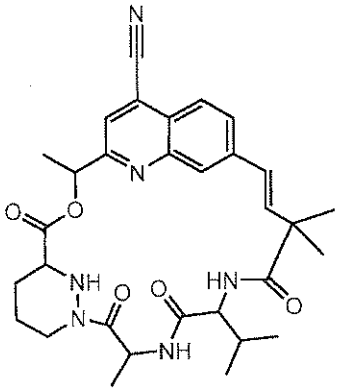
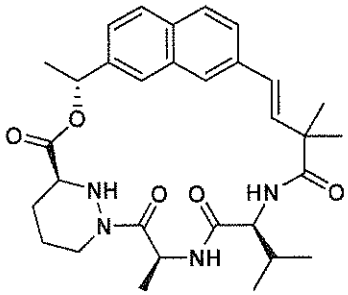
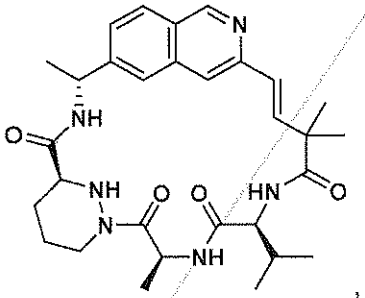
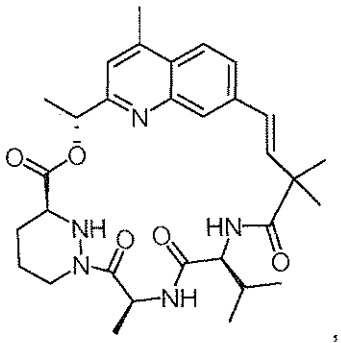
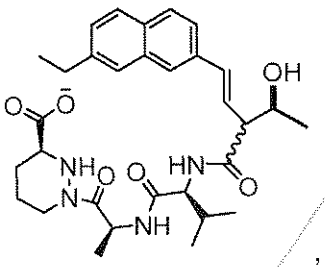
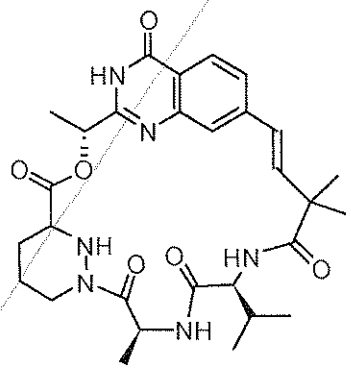
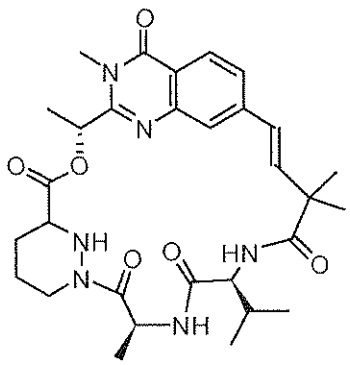
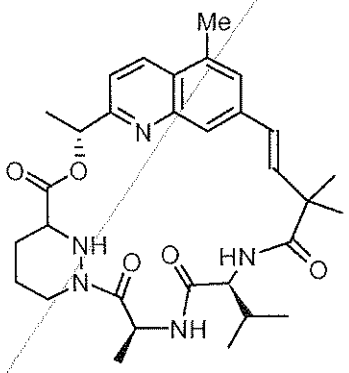
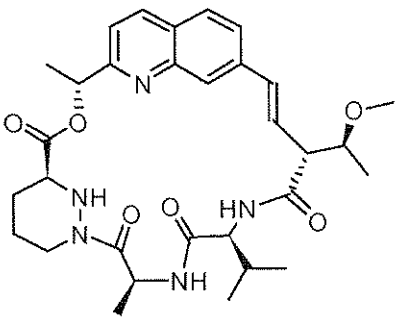
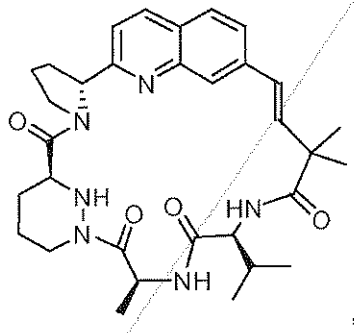
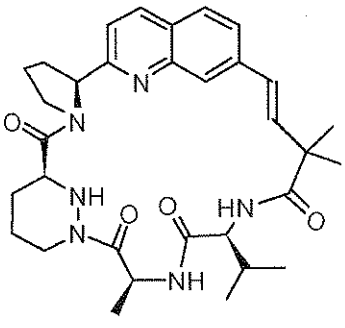
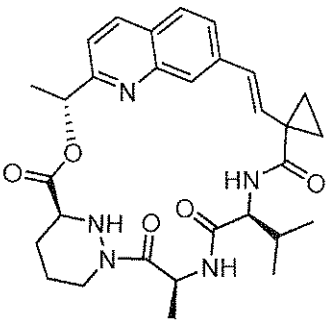

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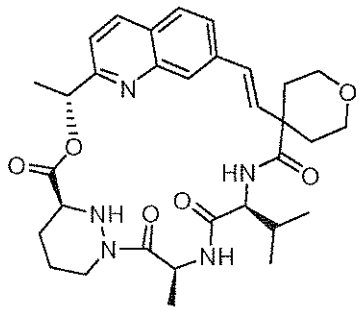
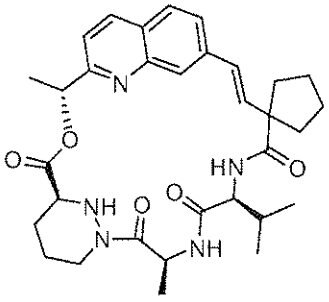
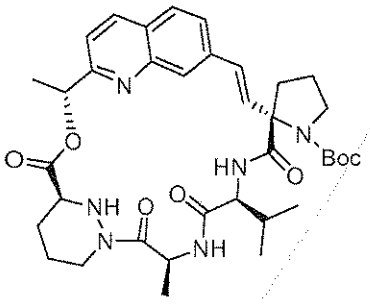
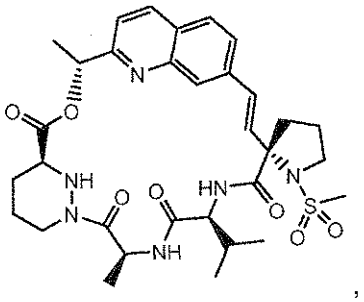
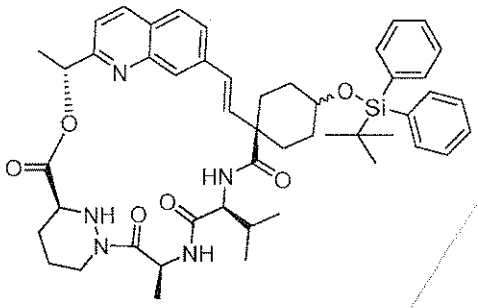
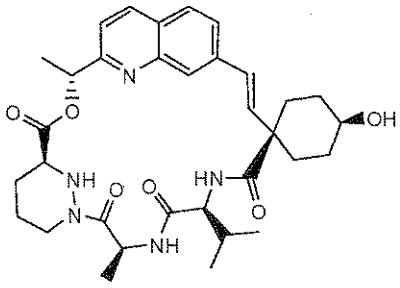
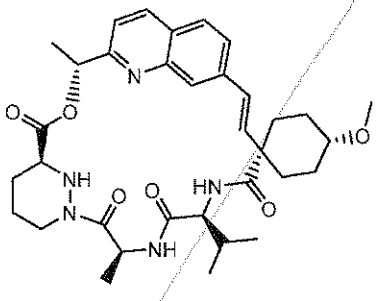
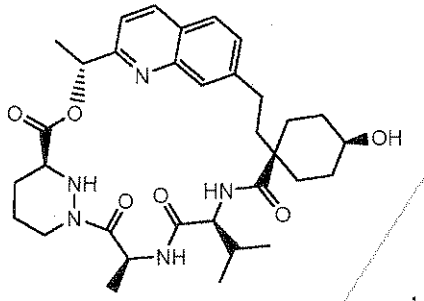
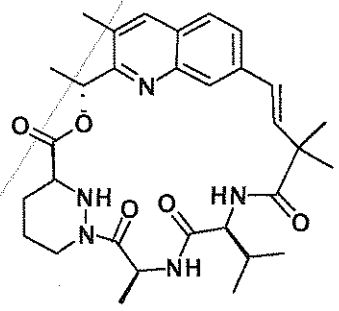
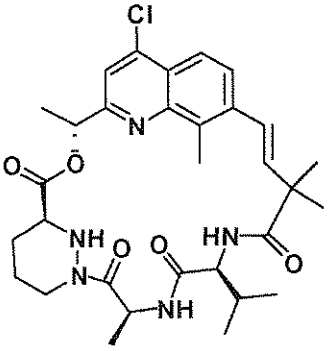
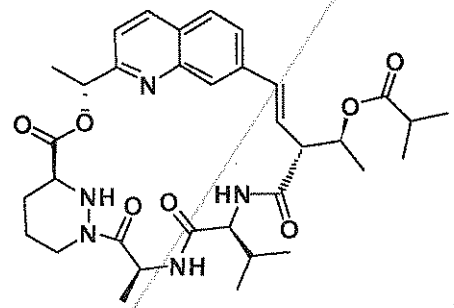
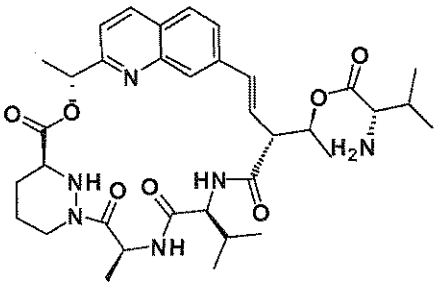
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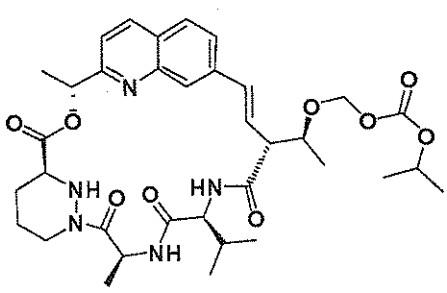
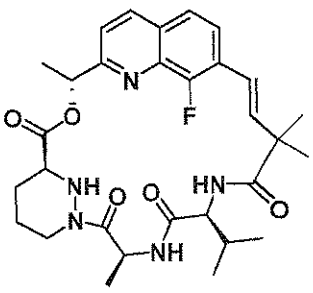
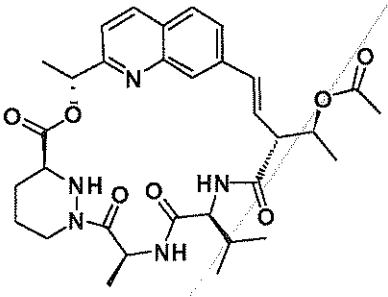
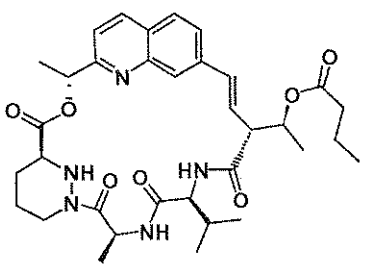
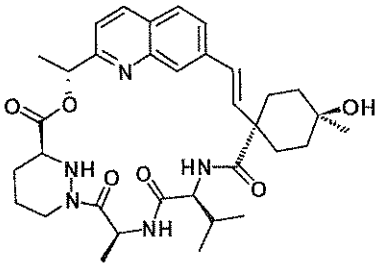
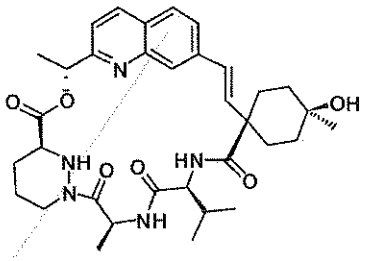
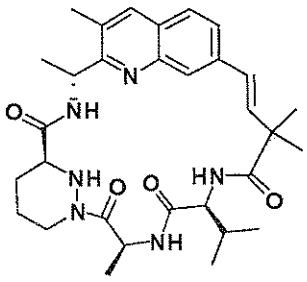

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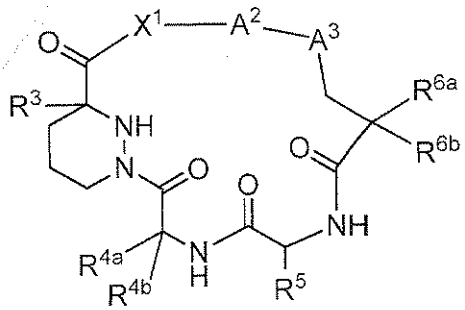

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or

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

19. The compound of any preceding claim, 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

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

A^3 is -CH_2- or -O-;

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

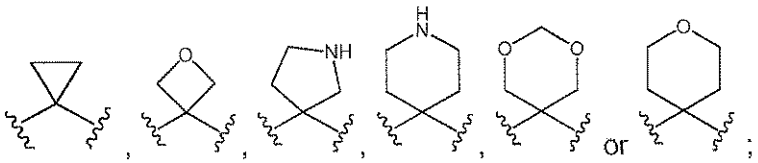
R^3 is H or (C_1-C_4)alkyl;

R^{4a} is H;

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

R^5 is H, (C_1-C_8)alkyl, hydroxy(C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, azido(C_1-C_8)alkyl, cycloalkyl, aryl(C_1-C_4)alkyl, cycloalkyl(C_1-C_4)alkyl, heterocycloalkyl(C_1-C_4)alkyl or heteroarylheteroaryl(C_1-C_4)alkyl;

R^{6a} and R^{6b} are independently H, -OH, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, (C_1-C_4)alkyl, aryl, cycloalkyl, heterocycloalkyl, di(C_1-C_8)alkylamino and (C_1-C_8)alkanoyl; or

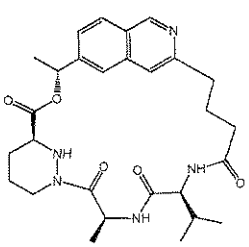
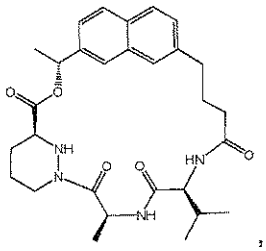
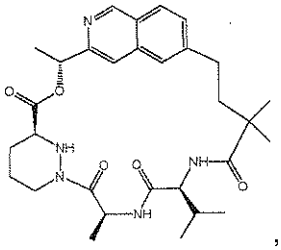
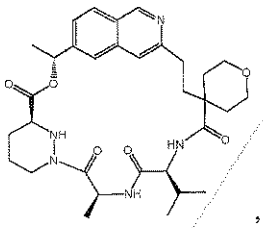
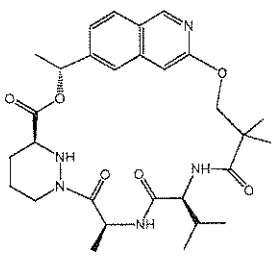
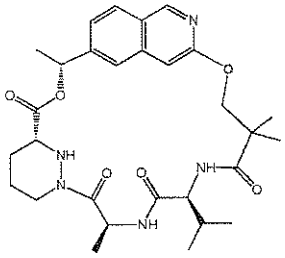
R^{6a} and R^{6b} together form ; and

R^8 is H or (C_1-C_4)alkyl.

20. The compound of any preceding claim, wherein A^2 is -CH(R^8)-arylene or -CH(R^8)-heteroarylene; R^3 is H; and A^3 is -CH_2-.

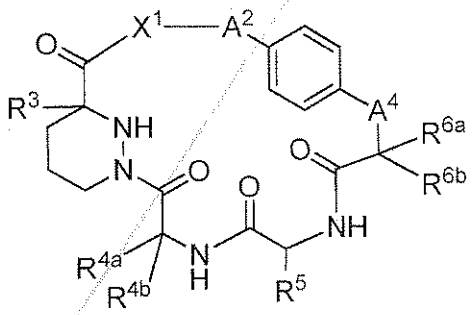
21. The compound of any preceding claim, wherein A^2 is -CH(R^8)-arylene or -CH(R^8)-heteroarylene; R^3 is H; and A^3 is -O-.

22. The compound of any preceding claim, which is


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

23. The compound of any preceding claim, which is a compound of Formula IV:



Formula IV

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

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

A^4 is bond or -O-.

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

R^3 is H or (C_1-C_4)alkyl;

R^{4a} is H;

R^{4b} 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, $(C_1\text{-}C_8)$alkyl, hydroxy$(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, azido$(C_1\text{-}C_8)$alkyl, cycloalkyl, aryl$(C_1\text{-}C_4)$alkyl, cycloalkyl$(C_1\text{-}C_4)$alkyl, heterocycloalkyl$(C_1\text{-}C_4)$alkyl or heteroarylheteroaryl$(C_1\text{-}C_4)$alkyl;

R^{6a} and R^{6b} are independently H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, $(C_1\text{-}C_4)$alkyl, aryl, cycloalkyl, heterocycloalkyl, di$(C_1\text{-}C_8)$alkylamino and $(C_1\text{-}C_8)$alkanoyl; and

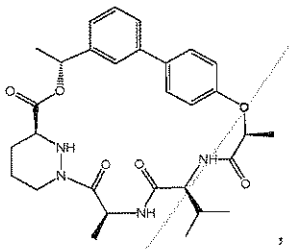
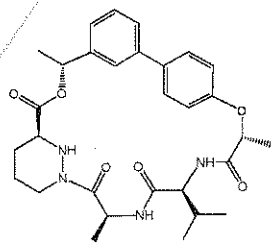
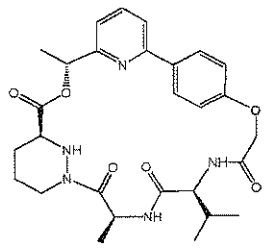
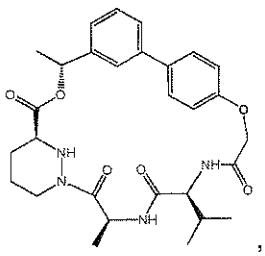
R^8 is H or $(C_1\text{-}C_4)$alkyl.

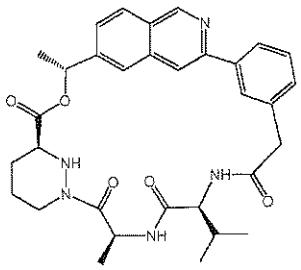
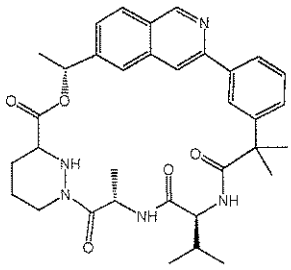
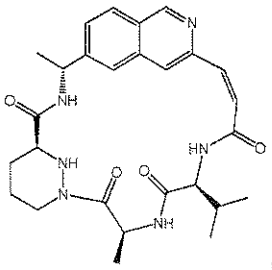
24. The compound of any preceding claim, wherein A^2 is -CH(R^8)-arylene or -CH(R^8)-heteroarylene; R^3 is H; and A^4 is -O-

25. The compound of any preceding claim, wherein A^2 is -CH(R^8)-arylene or -CH(R^8)-heteroarylene; R^3 is H; and A^4 is bond.

26. The compound of any preceding claim, wherein A^1 is ethenylene; A^2 is -CH(R^8)-arylene, -CH(R^8)-heteroarylene, -CH(R^8)-heterocycloalkylene, -CH(R^8)-cycloalkylene or cycloalkylene; X^1 is -O-, -NH- or -N((C1-C4)alkyl)-.

27. The compound of any preceding claim, which is


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or


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 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.

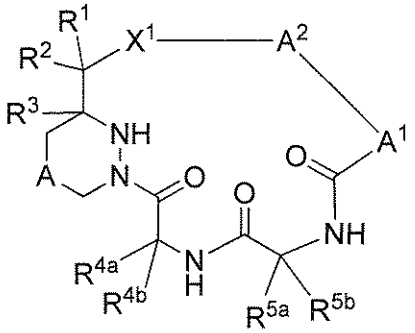
35. The method of Claim 34, wherein the viral infection is caused by a SARS coronarirus.

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:

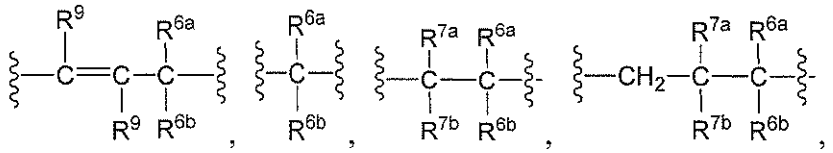
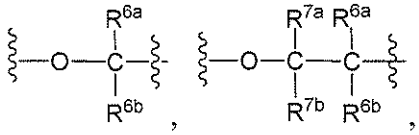
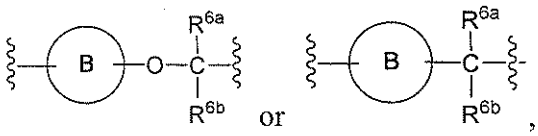
1. A compound of Formula I:



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 –CR^9=CR^9–, , , ,  or ,

wherein B is arylene, heteroarylene, cycloalkylene or heterocycloalkylene;

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

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 $(C_1$-$C_4)$alkanoyl; or

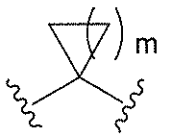
R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-, -C(=S)- or –C(=N(C_1-C_4)alkyl)-;

R^3 is H or $(C_1$-$C_4)$alkyl which is optionally substituted with halo, cyano, hydroxy 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 of R^{4a} and R^{4b} is optionally substituted with one or more substituent selected from the group consisting of cyano, $(C_1$-$C_8)$alkoxy, -COOH, -C(O)O-$(C_1$-$C_8)$alkyl, halo, hydroxyl, amino, mono$(C_1$-$C_8)$alkylamino, di$(C_1$-$C_8)$alkylamino, -C(O)-mono$(C_1$-$C_8)$alkylamino, -C(O)-di$(C_1$-$C_8)$alkylamino, -C(O)-heterocycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein each substituent is optionally substituted with one or more halo, heterocycloalkyl or aryl;

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 R^{5a} and R^{5b} are independently optionally substituted with one or more substituent 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, 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) is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, -NH_2, -C(O)O-$(C_1$-$C_8)$alkyl, -C(O)-di$(C_1$-$C_8)$alkylamino, -C(O)-$(C_1$-$C_8)$alkyl, -C(O)-heterocycloalkyl, -$S(O)_2R^{10}$, –$OSi(R^{10})_3$, $(C_1$-$C_4)$alkyl, cyano$(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_8)$alkanoyl and aryl$(C_1$-$C_4)$alkyl;

R^{6a}, R^{6b}, R^{7a} and R^{7b} are independently H, hydroxyl, cyano, $(C_1\text{-}C_8)$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, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ or $-N(R^9)_2$, wherein each of R^{6a}, R^{6b}, R^{7a} and R^{7b} is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, cyano, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_8)$alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono$(C_1\text{-}C_8)$alkylamino, di$(C_1\text{-}C_8)$alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$, $-OC(O)\text{-}(C_1\text{-}C_8)$alkyl $-C(O)O\text{-}(C_1\text{-}C_8)$alkyl and $(C_1\text{-}C_8)$alkanoyl, wherein each $-OC(O)\text{-}(C_1\text{-}C_8)$alkyl or $(C_1\text{-}C_8)$alkoxy is optionally substituted with one or more amino, $-OC(O)O\text{-}(C_1\text{-}C_8)$alkyl or $-Si(R^{10})_3$; 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, $(C_2\text{-}C_4)$alkenyl or $(C_2\text{-}C_4)$alkynyl;

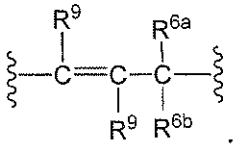
each R^{10} is independently H, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, cycloalkyl$(C_1\text{-}C_4)$alkyl or aryl, wherein R^{10} is optionally substituted with one or more halo;

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 is methylene.

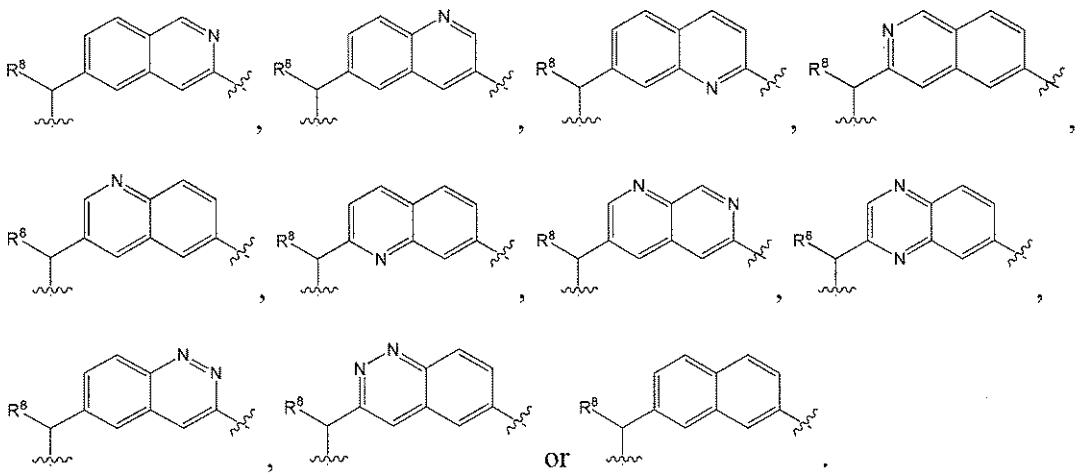
3. The compound of Claim 1, wherein A^1 is ethenylene, propenylene, ethylene, propylene, oxypropylene, oxypropenylene, pyrazolylene, phenylene or pyrimidinylene.

4. The compound of Claim 1, wherein A^1 is .

5. The compound of Claim 1, wherein A^2 is $-CH(R^8)$-arylene or $-CH(R^8)$-heteroarylene.

6. 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.

7. The compound of Claim 1, wherein A^2 is



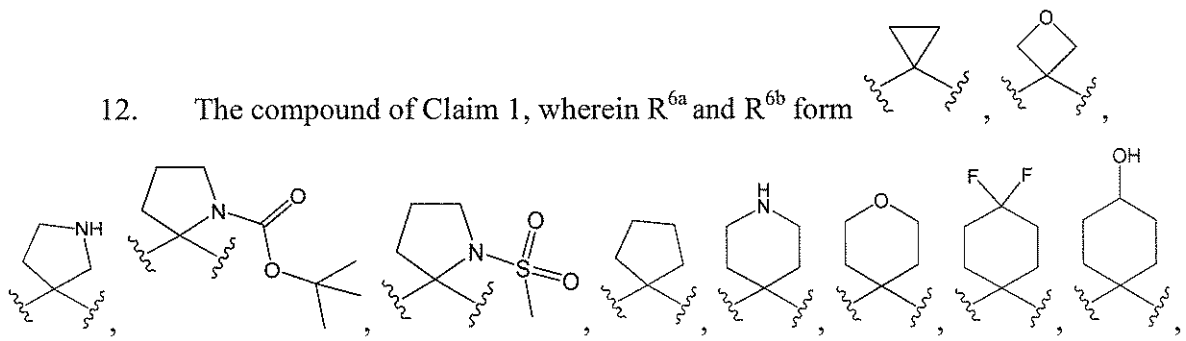
8. The compound of Claim 1, wherein X^1 is -O- or –NH-.

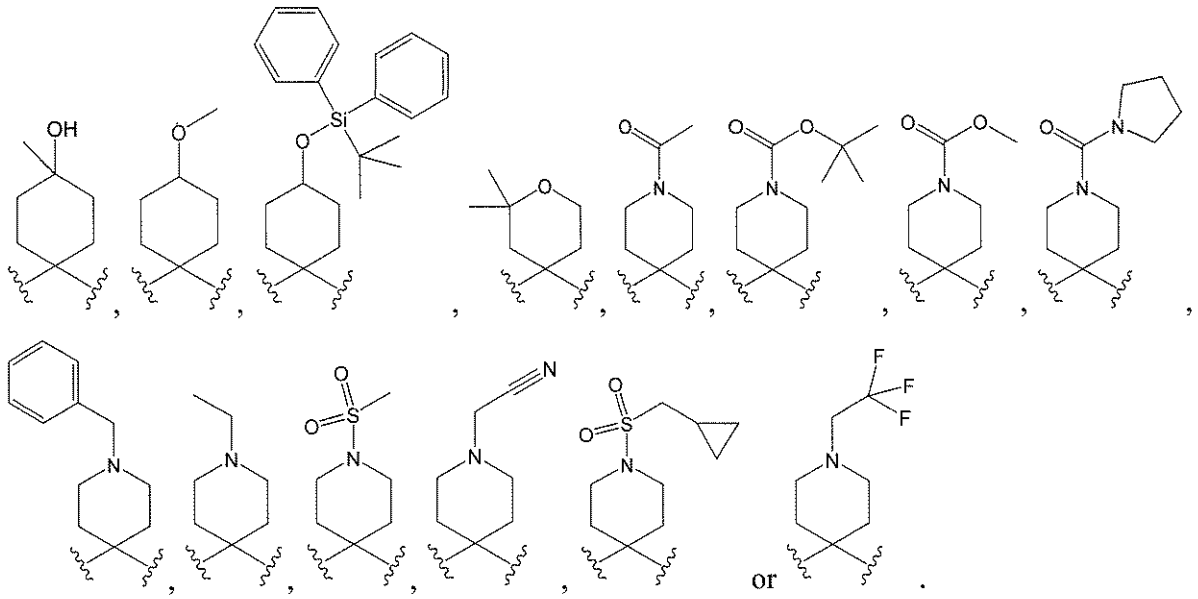
9. The compound of Claim 1, wherein R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-.

10. The compound of Claim 1, wherein R^3 is H.

11. The compound of Claim 1, wherein R^{6a} is H and R^{6b} is H or $(C_1\text{-}C_4)$alkyl, or R^{6a} and R^{6b} together form a spirocycle having Formula (a).

12. The compound of Claim 1, wherein R^{6a} and R^{6b} form

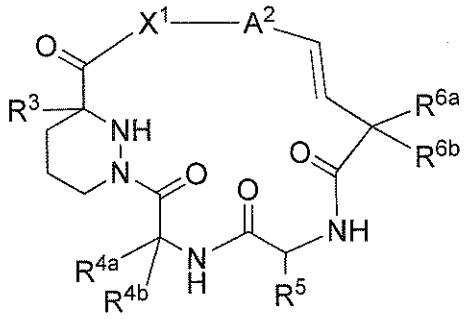




13. The compound of Claim 1, wherein R^3 is H; R^{5a} is H; R^{5b} is H, $(C_1\text{-}C_8)$alkyl, hydroxy$(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, azido$(C_1\text{-}C_8)$alkyl, aryl, cycloalkyl, aryl$(C_1\text{-}C_4)$alkyl, cycloalkyl$(C_1\text{-}C_4)$alkyl, heterocycloalkyl$(C_1\text{-}C_4)$alkyl or arylheterocycloalkyl$(C_1\text{-}C_4)$alkyl; R^{6a} is H; and R^{6b} is H, $(C_1\text{-}C_4)$alkyl or hydroxy$(C_1\text{-}C_4)$alkyl.

14. The compound of Claim 1, wherein X^1 is -O- or -NH-; R^1 and R^2, when taken together with the carbon to which they are both attached, form -C(=O)-; R^3 is H; R^{4a} is H; R^{4b} is methyl; R^{5a} is H and R^{5b} is iso-propyl, propenyl or propynyl; and R^8 is methyl.

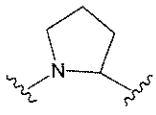
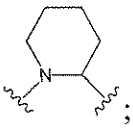
15. The compound of Claim 1, which is a compound of Formula II:



Formula II

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

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

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

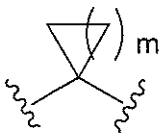
R^3 is H or (C_1-C_4)alkyl;

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

R^5 is (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 R^5 is optionally substituted with one or more substituent selected from -N_3, cyano, -COOH, halo, hydroxyl, amino, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, aryl and heteroaryl,

R^{6a} and R^{6b} are independently H, hydroxyl, cyano, (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, -$S(O)_2R^9$ or -N(R^9)$_2$, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, cyano, (C_1-C_4)alkyl, (C_1-C_8)alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, -NHS(O)R^9, -NHC(O)R^9, -OC(O)-(C_1-C_8)alkyl -C(O)O-(C_1-C_8)alkyl and (C_1-C_8)alkanoyl, wherein each -OC(O)-(C_1-C_8)alkyl or (C_1-C_8)alkoxy is optionally substituted with one or more amino, -OC(O)O-(C_1-C_8)alkyl or -Si(R^{10})$_3$; or

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



(a),

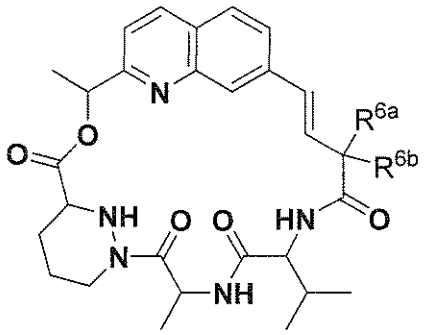
wherein one or more carbon ring atoms of Formula (a) is optionally replaced by a nitrogen, oxygen or sulfur atom, and wherein a ring atom of Formula (a) is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, $-NH_2$, $-C(O)O-(C_1-C_8)$alkyl, $-C(O)$-di(C_1-C_8)alkylamino, $-C(O)-(C_1-C_8)$alkyl, $-C(O)$-heterocycloalkyl, $-S(O)_2R^{10}$, $-OSi(R^{10})_3$, (C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_8)alkanoyl and aryl(C_1-C_4)alkyl;

R^8 is H or (C_1-C_4)alkyl;

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

each R^{10} is independently H, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, cycloalkyl(C_1-C_4)alkyl or aryl, wherein R^{10} is optionally substituted with one or more halo.

16. The compound of Claim 1, which is a compound of Formula IIa:

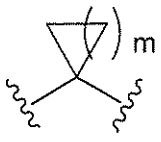


Formula IIa

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, cyano, (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, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$ or $-N(R^9)_2$, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, cyano, (C_1-C_4)alkyl, (C_1-C_8)alkoxy, aryl, cycloalkyl, heterocycloalkyl, mono(C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, $-NHS(O)R^9$, $-NHC(O)R^9$, $-OC(O)-(C_1-C_8)$alkyl $-C(O)O-(C_1-C_8)$alkyl and (C_1-C_8)alkanoyl, wherein each $-OC(O)-(C_1-C_8)$alkyl or (C_1-C_8)alkoxy is optionally substituted with one or more amino, $-OC(O)O-(C_1-C_8)$alkyl or $-Si(R^{10})_3$; 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) is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, $-NH_2$, $-C(O)O-(C_1-C_8)$alkyl, $-C(O)$-di(C_1-C_8)alkylamino, $-C(O)-(C_1-C_8)$alkyl, $-C(O)$-heterocycloalkyl, $-S(O)_2R^{10}$, $-OSi(R^{10})_3$, (C_1-C_4)alkyl, cyano(C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_8)alkanoyl and aryl(C_1-C_4)alkyl;

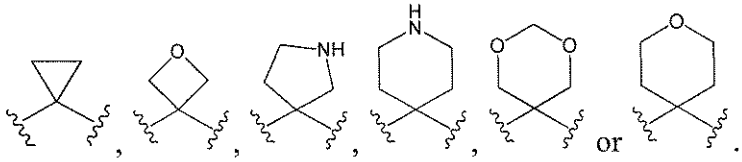
each R^9 is independently H, (C_1-C_4)alkyl, (C_2-C_4)alkenyl or (C_2-C_4)alkynyl; and

each R^{10} is independently H, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, cycloalkyl(C_1-C_4)alkyl or aryl, wherein R^{10} is optionally substituted with one or more halo.

17. The compound of Claim 15, wherein R^{4a} and R^{4b} are independently H, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl;

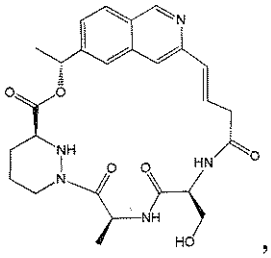
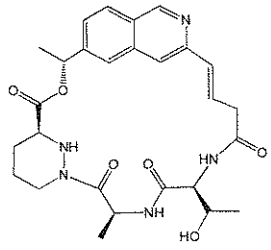
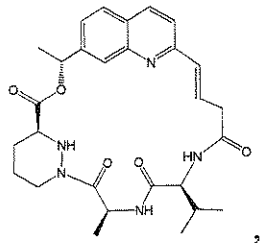
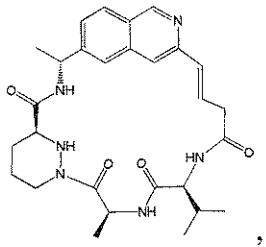
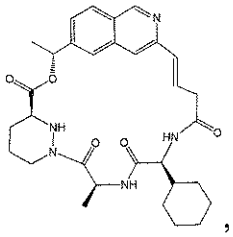
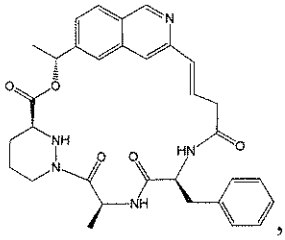
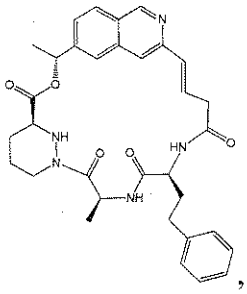
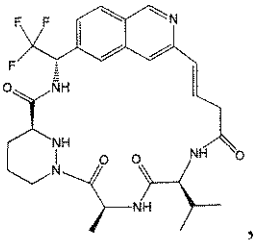
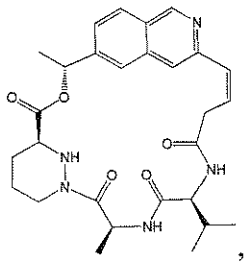
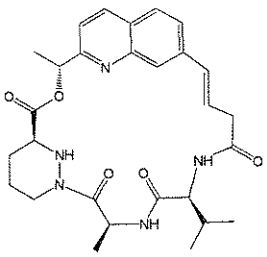
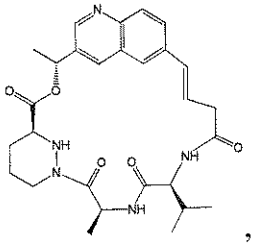
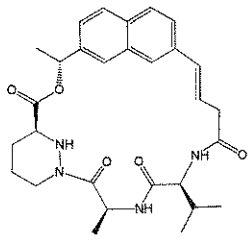
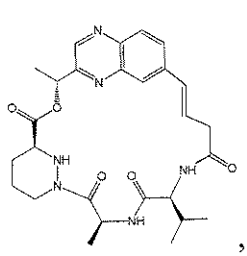
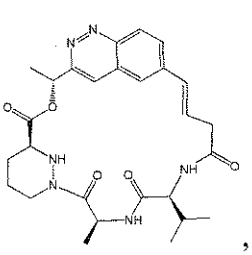
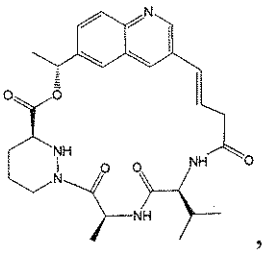
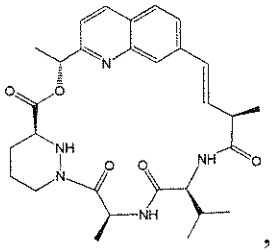
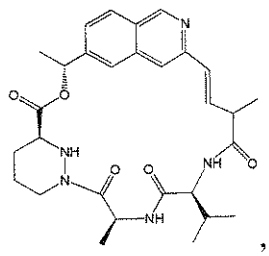
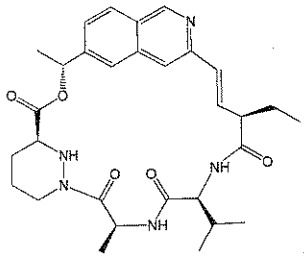
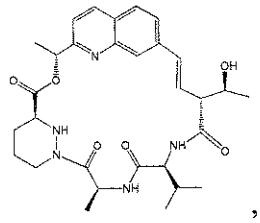
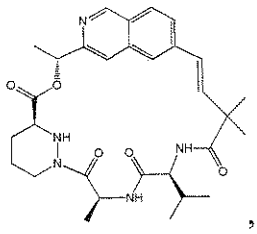
R^5 is H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, aryl, heterocycloalkyl, cycloalkyl, aryl(C_1-C_4)alkyl, cycloalkyl(C_1-C_4)alkyl or heterocycloalkyl(C_1-C_4)alkyl, wherein R^5 is optionally substituted with one or more substituent selected from the group consisting of $-N_3$, halo, hydroxyl, di(C_1-C_8)alkylamino, aryl or heteroaryl; and

R^{6a} and R^{6b} are independently H, -OH, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, hydroxyl, (C_1-C_4)alkyl, aryl, cycloalkyl, heterocycloalkyl, di(C_1-C_8)alkylamino and (C_1-C_8)alkanoyl; or

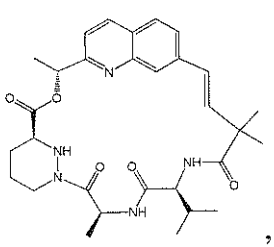
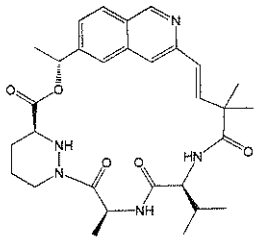
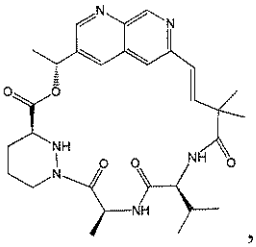
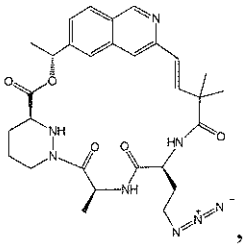
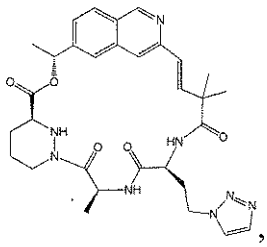
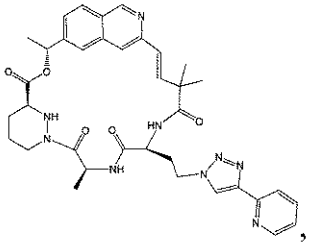
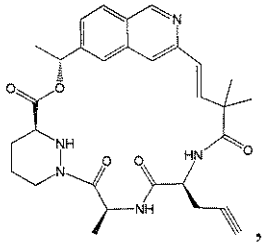
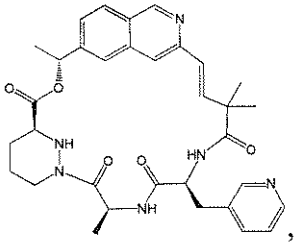
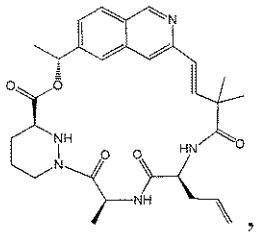
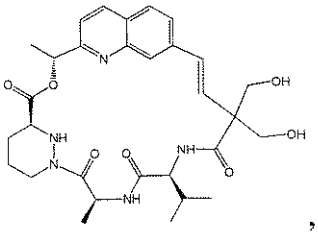
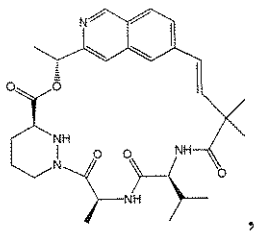
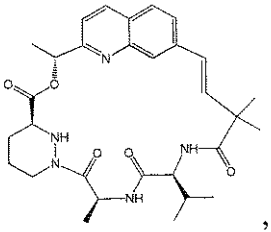
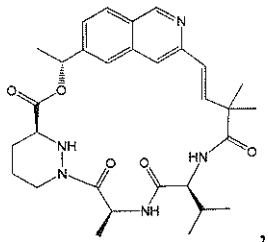
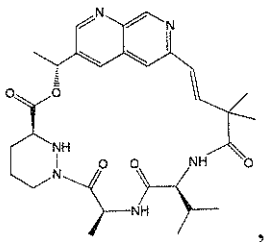
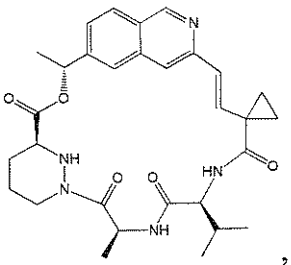
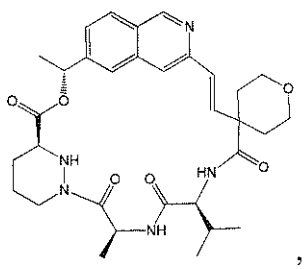
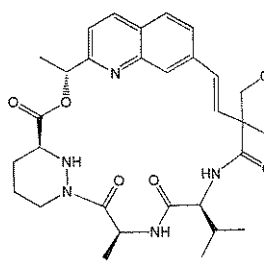
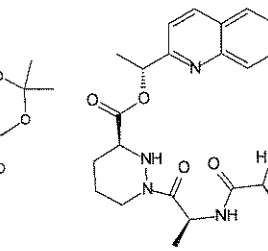
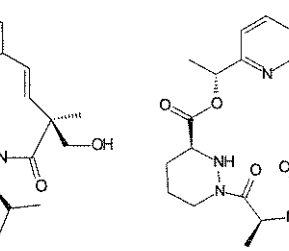
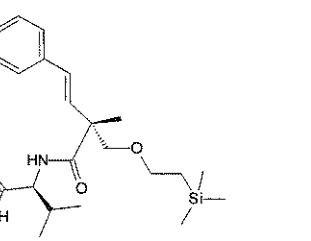
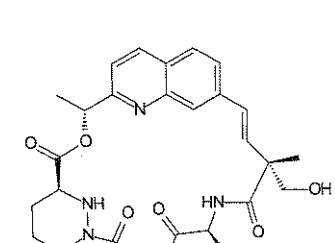
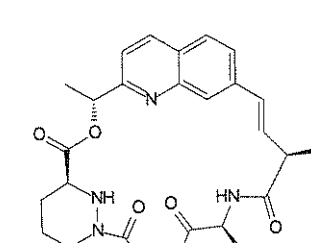
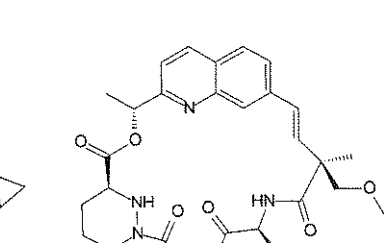
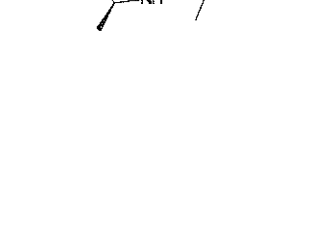
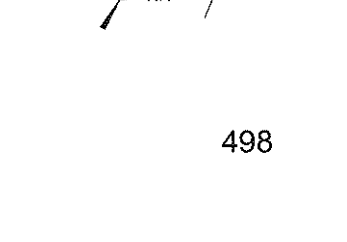
R^{6a} and R^{6b} together form 

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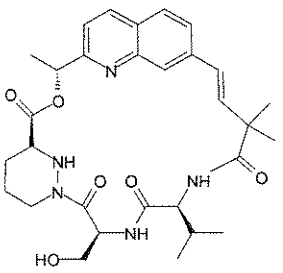
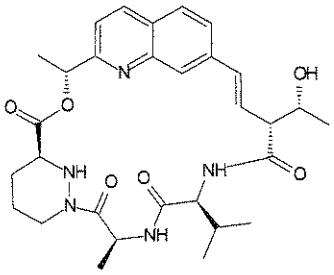
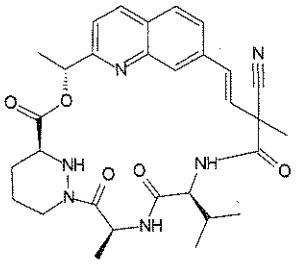
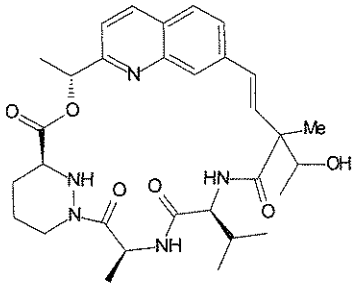
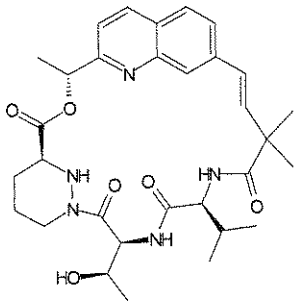
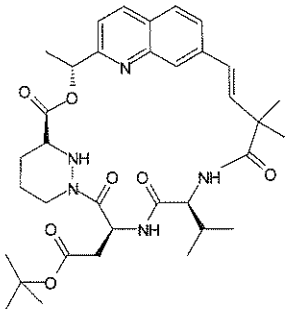
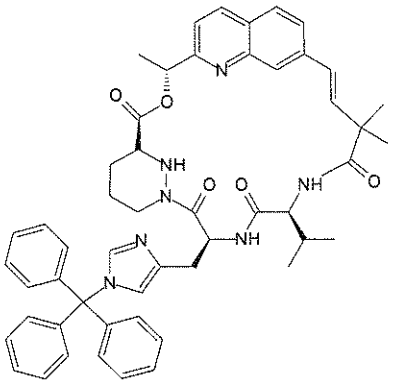
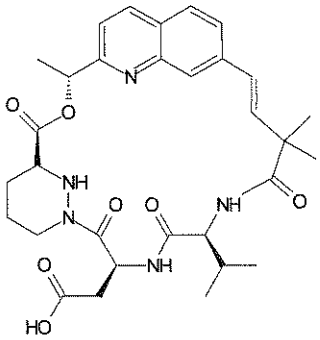
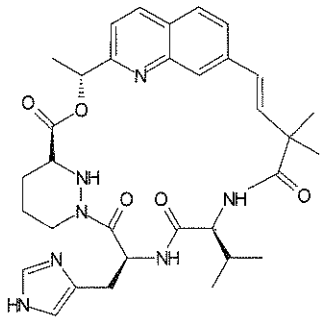
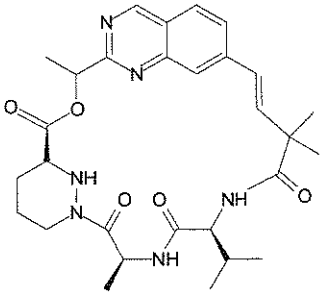
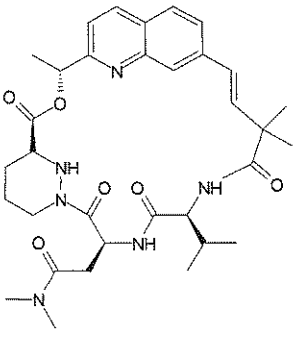
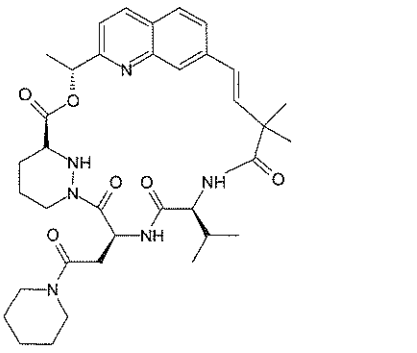
18. The compound of Claim 1, which is


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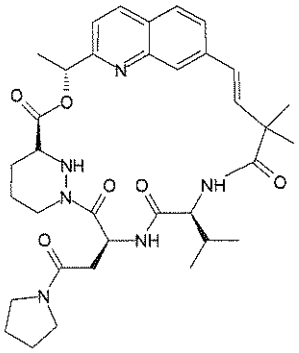
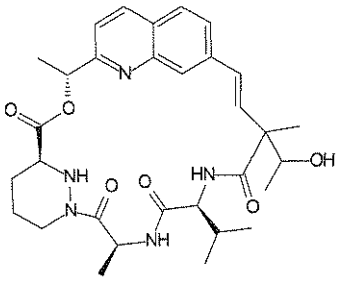
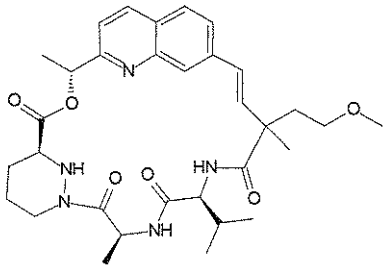
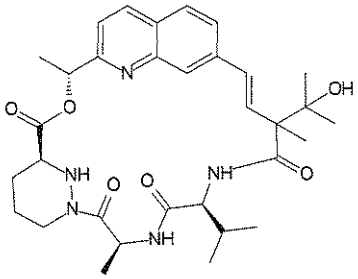
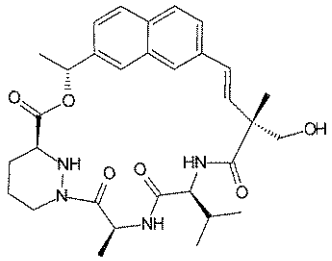
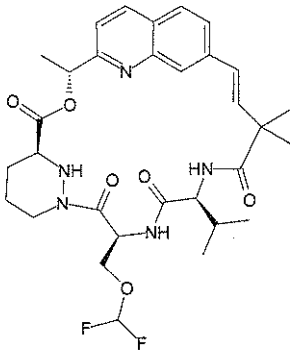
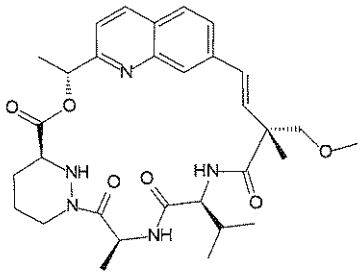
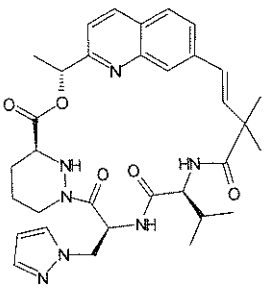
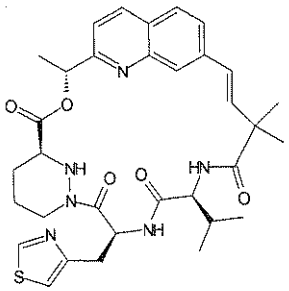
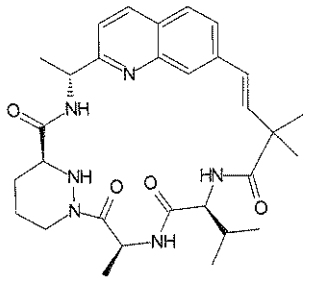
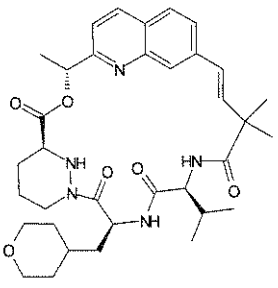
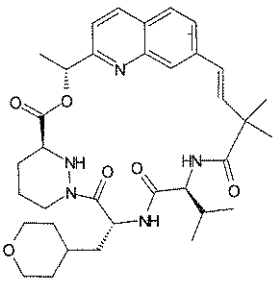
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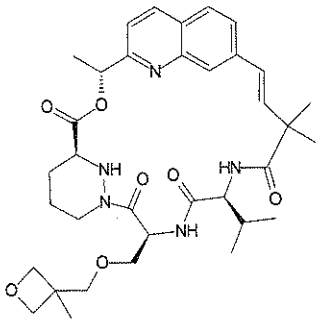
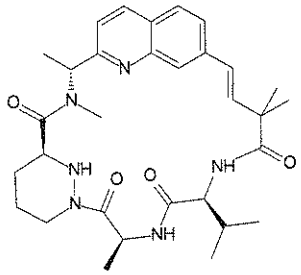
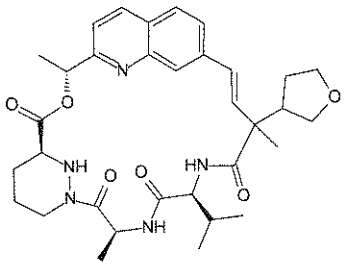
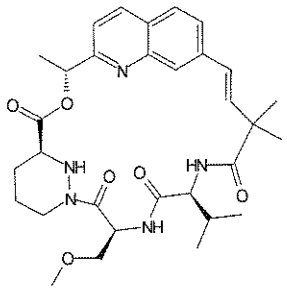
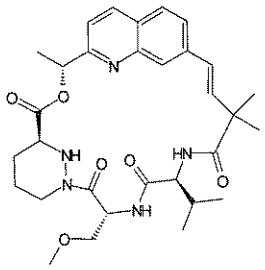
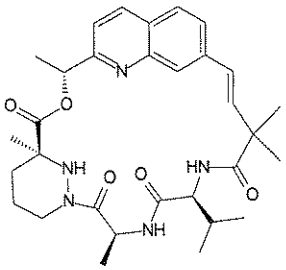
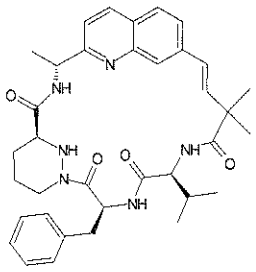
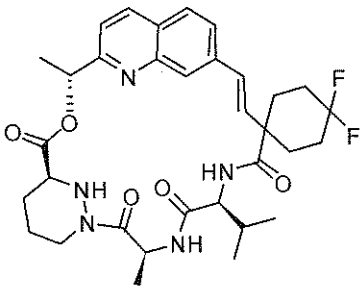
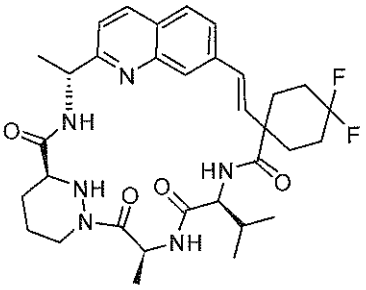
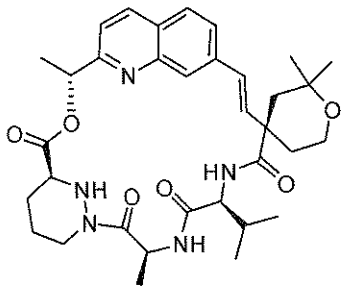
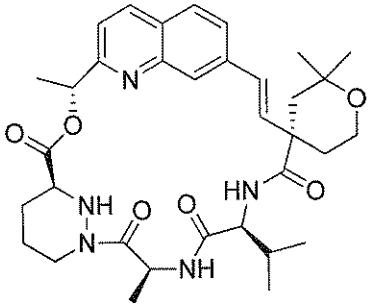
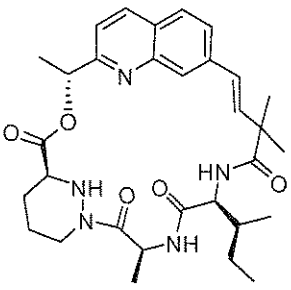
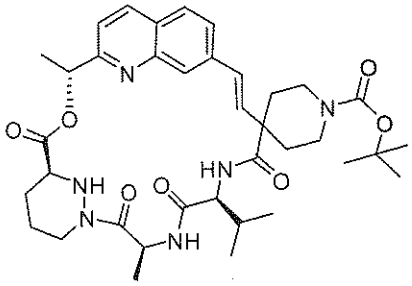
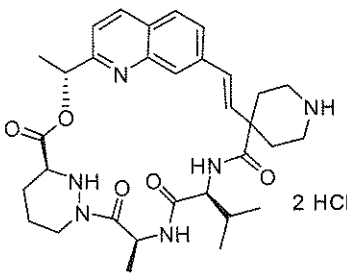
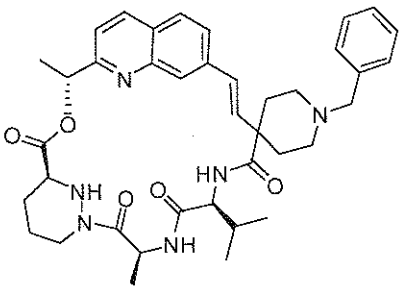

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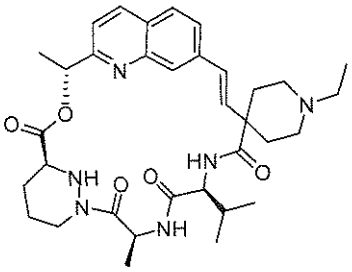
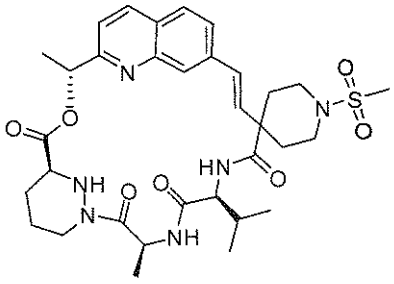
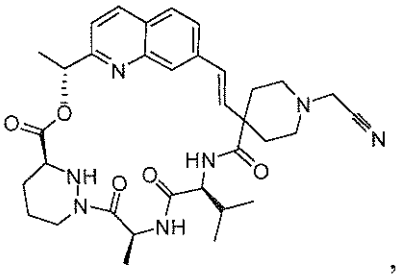
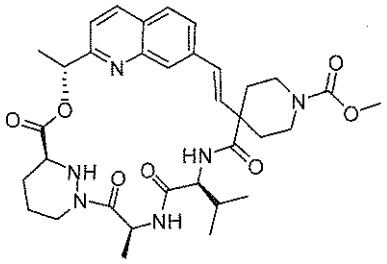
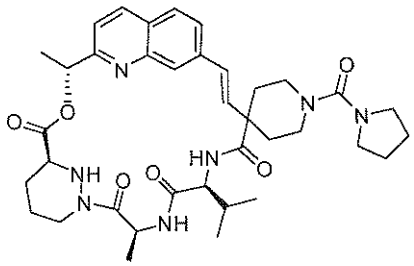
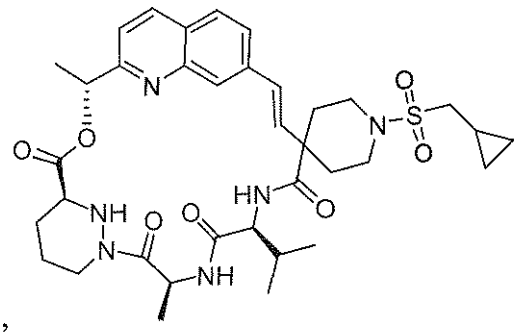
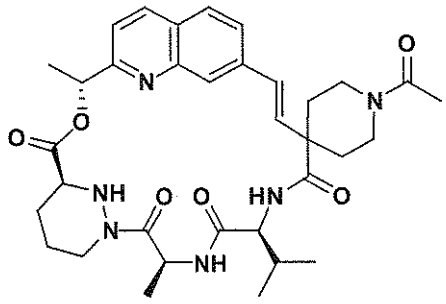
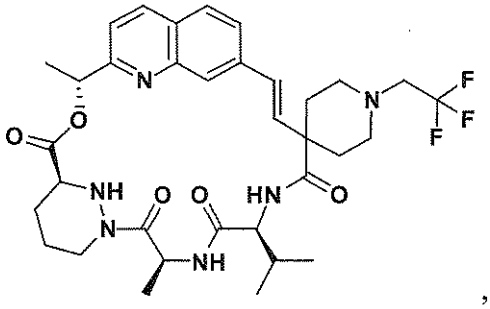
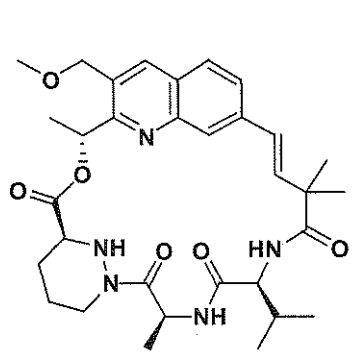
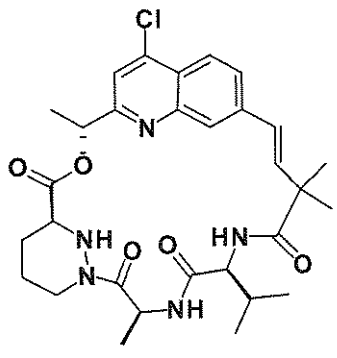
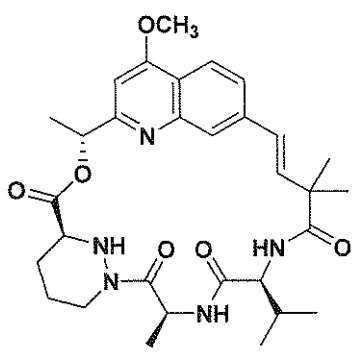
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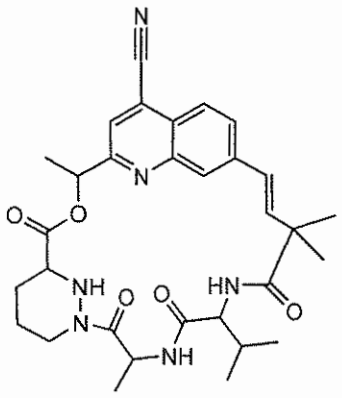
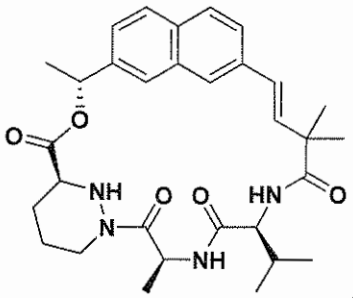
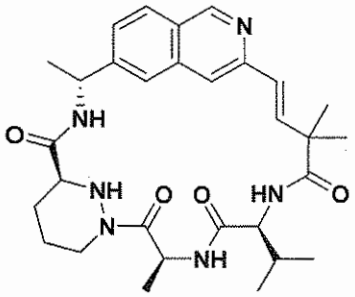
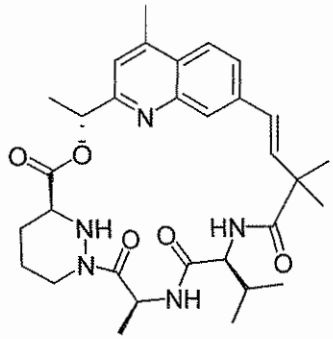
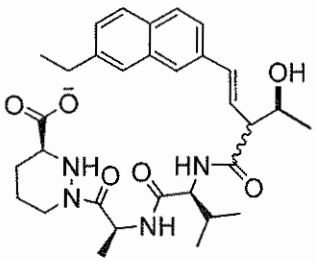
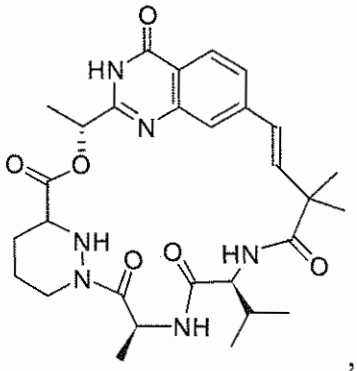
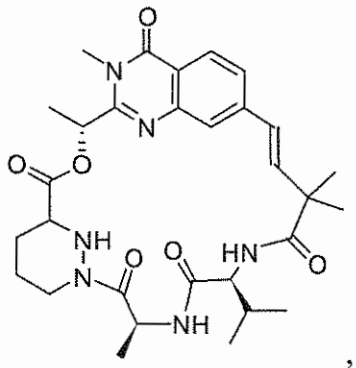
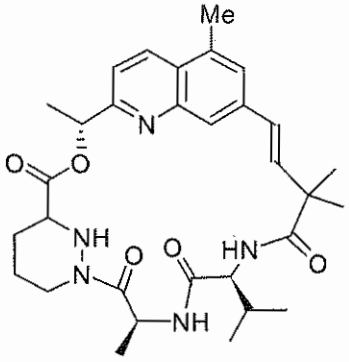
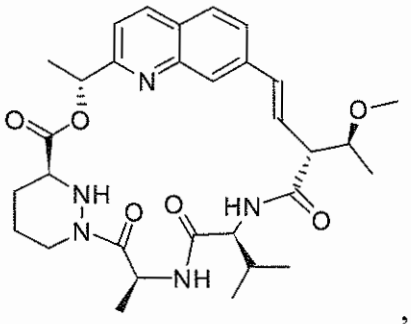
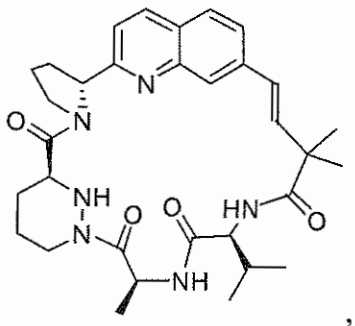
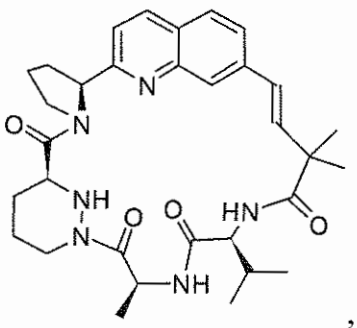
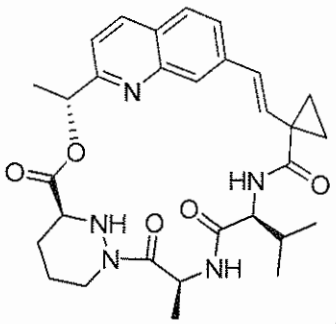
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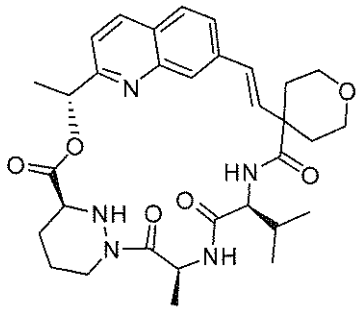
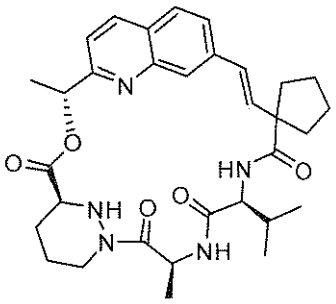
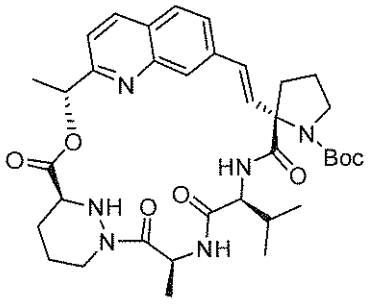
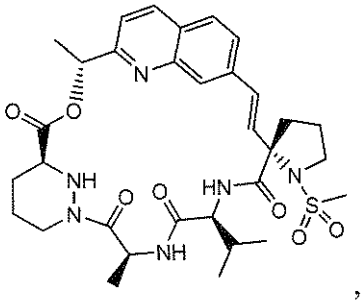
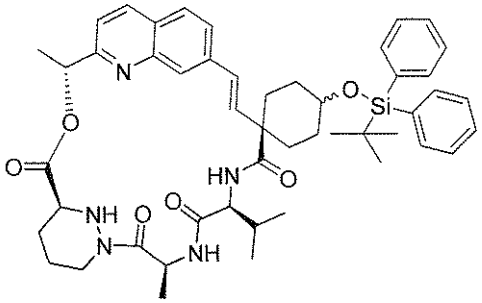
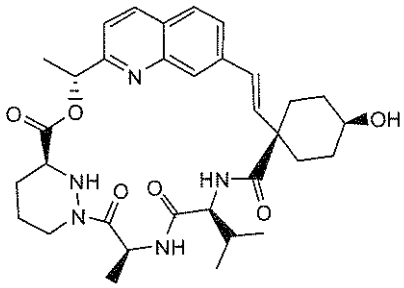
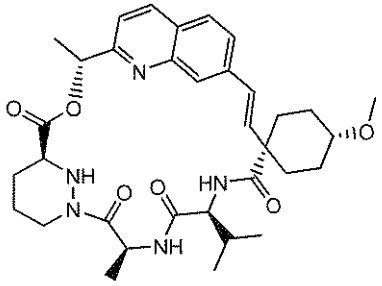
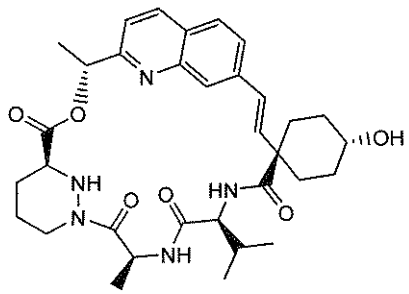
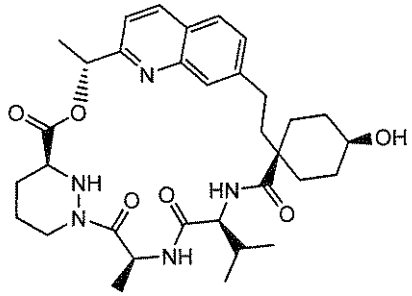
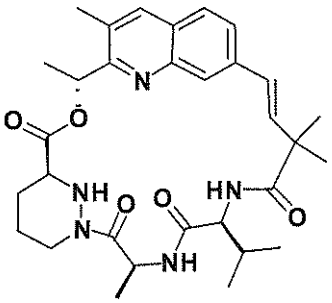
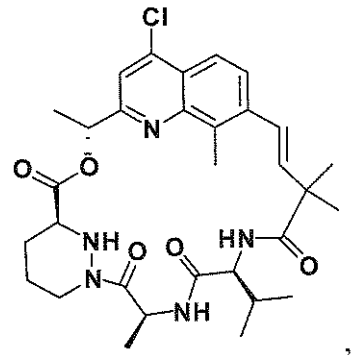
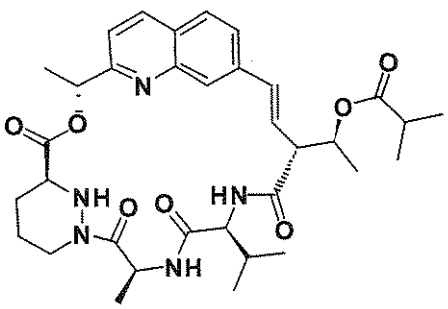
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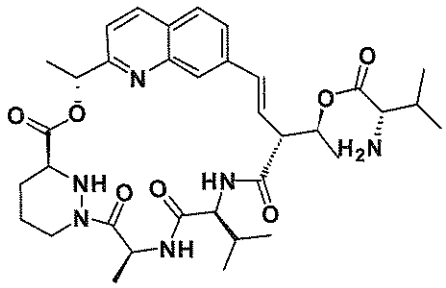
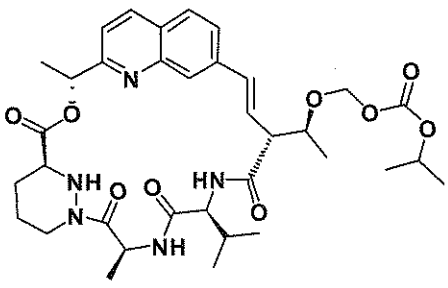
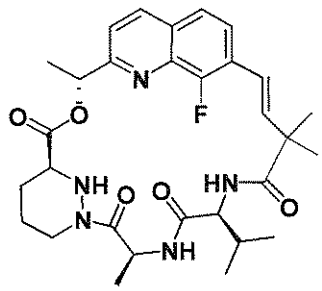
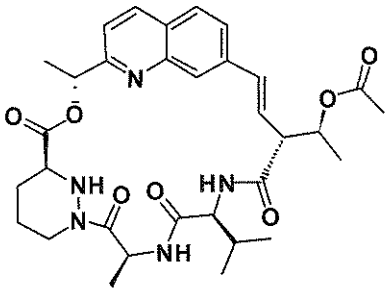
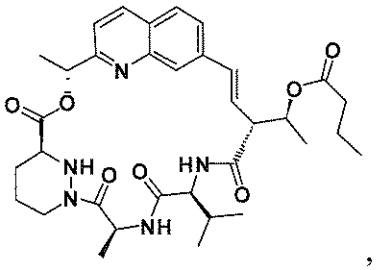
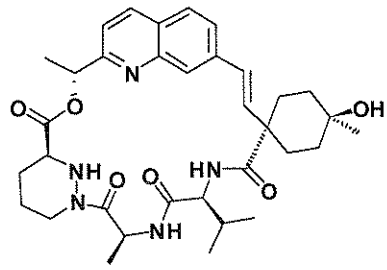
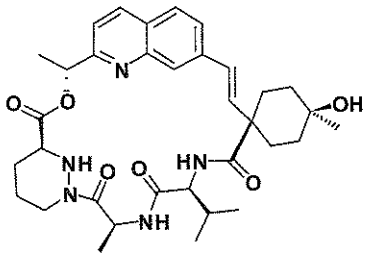
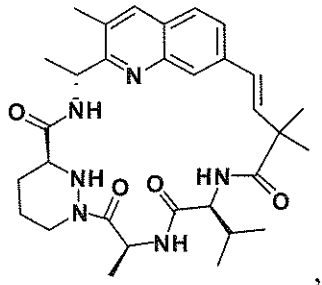

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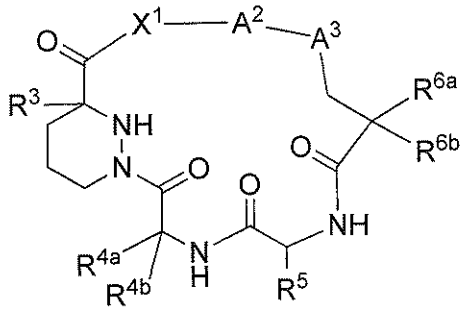

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or

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

19. 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

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

A^3 is -CH_2- or -O-;

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

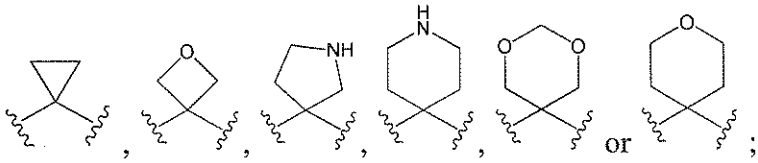
R^3 is H or (C_1-C_4)alkyl;

R^{4a} is H;

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

R^5 is H, (C_1-C_8)alkyl, hydroxy(C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, azido(C_1-C_8)alkyl, cycloalkyl, aryl(C_1-C_4)alkyl, cycloalkyl(C_1-C_4)alkyl, heterocycloalkyl(C_1-C_4)alkyl or heteroarylheteroaryl(C_1-C_4)alkyl;

R^{6a} and R^{6b} are independently H, -OH, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy or (C_1-C_8)alkyl, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, (C_1-C_4)alkyl, aryl, cycloalkyl, heterocycloalkyl, di(C_1-C_8)alkylamino and (C_1-C_8)alkanoyl; or

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

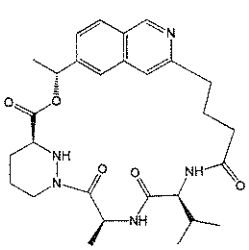
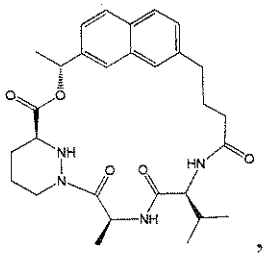
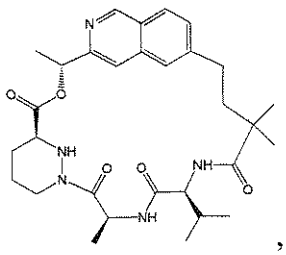
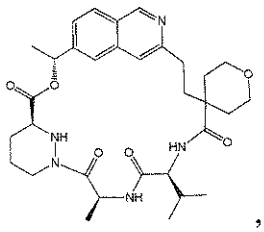
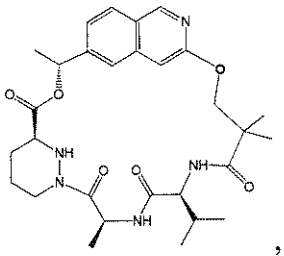
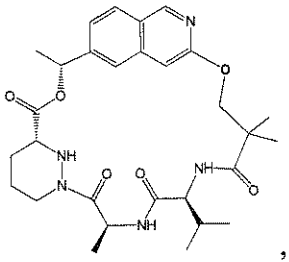
; and

R^8 is H or (C_1-C_4)alkyl.

20. The compound of Claim 19, wherein A^2 is -CH(R^8)-arylene or -CH(R^8)-heteroarylene; R^3 is H; and A^3 is -CH_2-.

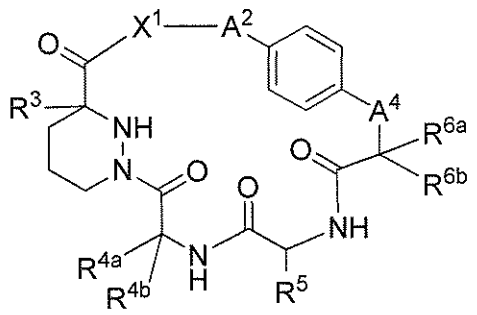
21. The compound of Claim 19, wherein A^2 is -CH(R^8)-arylene or -CH(R^8)-heteroarylene; R^3 is H; and A^3 is -O-.

22. The compound of Claim 19, which is


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, or

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

23. The compound of Claim 1, which is a compound of Formula IV:



Formula IV

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

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

A^4 is bond or -O-;

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

R^3 is H or (C_1-C_4)alkyl;

R^{4a} is H;

R^{4b} 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, $(C_1\text{-}C_8)$alkyl, hydroxy$(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, azido$(C_1\text{-}C_8)$alkyl, cycloalkyl, aryl$(C_1\text{-}C_4)$alkyl, cycloalkyl$(C_1\text{-}C_4)$alkyl, heterocycloalkyl$(C_1\text{-}C_4)$alkyl or heteroarylheteroaryl$(C_1\text{-}C_4)$alkyl;

R^{6a} and R^{6b} are independently H, -OH, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_8)$alkyl, wherein each of R^{6a} and R^{6b} is optionally substituted with one or more substituent selected from the group consisting of halo, $(C_1\text{-}C_4)$alkyl, aryl, cycloalkyl, heterocycloalkyl, di$(C_1\text{-}C_8)$alkylamino and $(C_1\text{-}C_8)$alkanoyl; and

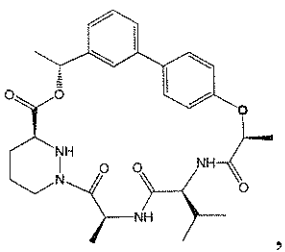
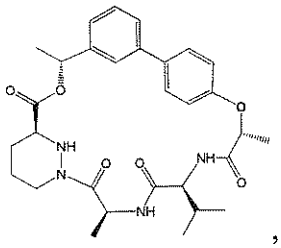
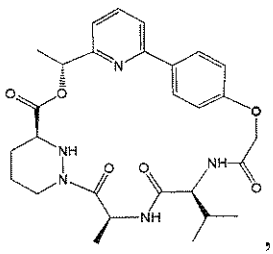
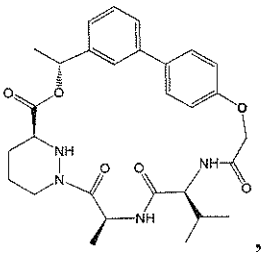
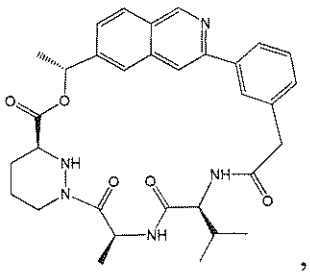
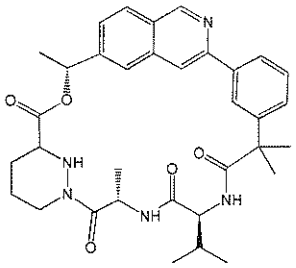
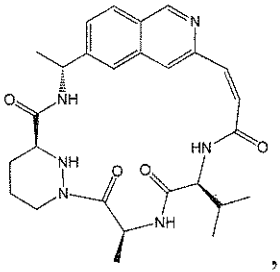
R^8 is H or $(C_1\text{-}C_4)$alkyl.

24. The compound of Claim 23, wherein A^2 is -CH(R^8)-arylene or -CH(R^8)-heteroarylene; R^3 is H; and A^4 is -O-.

25. The compound of Claim 23, wherein A^2 is -CH(R^8)-arylene or -CH(R^8)-heteroarylene; R^3 is H; and A^4 is bond.

26. The compound of Claim 23, wherein A^1 is ethenylene; A^2 is -CH(R^8)-arylene, -CH(R^8)-heteroarylene, -CH(R^8)-heterocycloalkylene, -CH(R^8)-cycloalkylene or cycloalkylene; X^1 is -O-, -NH- or -N((C1-C4)alkyl)-.

27. The compound of Claim 23, which is


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or

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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 Claim 1 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.