MACROCYCLIC HEPATITIS C SERINE PROTEASE INHIBITORS

RELATED APPLICATIONS

This application claims the benefit of U.S. provisional patent application Ser. No. 61/191,725, filed September 11, 2008, and U.S. provisional patent application Ser. No. 61/209,689, filed March 10, 2009. The disclosures of the aforementioned patent applications are incorporated herein in their entirety by this reference.

TECHNICAL FIELD

The present invention relates to novel macrocycles having activity against the hepatitis C virus (HCV) and useful in the treatment of HCV infections. More particularly, the invention relates to macrocyclic compounds, compositions containing such compounds and methods for using the same, as well as processes for making such compounds.

BACKGROUND OF THE INVENTION

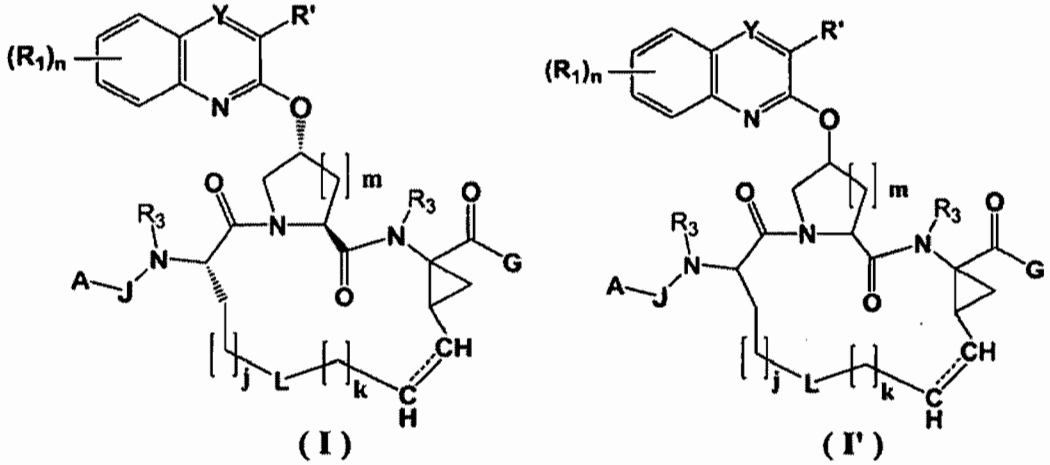
HCV is the principal cause of non-A, non-B hepatitis and is an increasingly severe public health problem both in the developed and developing world. It is estimated that the virus infects over 200 million people worldwide, surpassing the number of individuals infected with the human immunodeficiency virus (HIV) by nearly five fold. HCV infected patients, due to the high percentage of individuals inflicted with chronic infections, are at an elevated risk of developing cirrhosis of the liver, subsequent hepatocellular carcinoma and terminal liver disease. HCV is the most prevalent cause of hepatocellular cancer and cause of patients requiring liver transplantations in the western world.

There are considerable barriers to the development of anti-HCV therapeutics, which include, but are not limited to, the persistence of the virus, the genetic diversity of the virus during replication in the host, the high incident rate of the virus developing drug-resistant mutants, and the lack of reproducible infectious culture systems and small-animal models for HCV replication and pathogenesis. In a majority of cases, given the mild course of the infection and the complex biology of the liver, careful consideration must be given to antiviral drugs, which are likely to have significant side effects.

SUMMARY OF THE INVENTION

The present invention relates to novel macrocyclic compounds and methods of treating a hepatitis C infection in a subject in need of such therapy with said macrocyclic compounds. The compounds of the present invention interfere with the life cycle of the hepatitis C virus and are useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the compounds of the present invention, or pharmaceutically acceptable salts, esters or prodrugs thereof, in combination with a pharmaceutically acceptable carrier or excipient.

In one aspect, the invention provides a compound of formula I or formula I':



(I) (I')

or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein:

J is absent, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, -C(O)-, -O-C(O)-, - $N(R_3)$-C(O)-, -C(S)-, - $C(=NR_4)$-, -S(O)-, $-S(O_2)$-, or $-N(R_3)$-;

A is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted arylalkyl, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted carbocyclic;

Each R_1 is independently selected from

(i) halogen, hydroxy, amino, -CN, $-CF_3$, $-N_3$, $-NO_2$, $-OR_4$, $-SR_4$, $-SOR_4$, $-SO_2R_4$, $-N(R_3)S(O_2)-R_4$, $-N(R_3)S(O_2)NR_3R_4$, $-NR_3R_4$, $-C(O)OR_4$, $-C(O)R_4$, $-C(O)NR_3R_4$, or $-N(R_3)C(O)R_4$;

(ii) optionally substituted aryl;

(iii) optionally substituted heteroaryl;

(iv) optionally substituted heterocyclic;

(v) optionally substituted carbocyclic; or

(vi) optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

G is –E-R_5;

wherein E is absent; optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; or -O-, -S-, -N(R_3)-, -N(R_3)S(O_p)-, -N(R_3)C(O)-, -N(R_3) C(O)S(O_p)-, -OS(O_p)-, -C(O)S(O_p)-, or -C(O)N(R_3)S(O_p)-;

p is 0, 1, or 2;

R_5 is H; optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;

R_3 and R_4 are each independently selected at each occurrence from the following: optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclic; optionally substituted carbocyclic; or hydrogen;

L is absent or is selected from optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

Y is N or –C(R")–;

wherein A, R_1, R' and/or R" can be taken together to form a ring;

j = 0, 1, 2, 3, or 4;

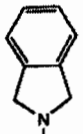
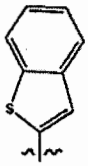
k= 0, 1, 2, or 3;

m = 0, 1, or 2;

n is 0, 1, 2, 3, or 4; and

⁼⁼⁼⁼ denotes a carbon-carbon single or double bond,

wherein if Y is N, then R' is optionally substituted heterocyclic, optionally substituted heteroaryl, optionally substituted aryl or optionally substituted

carbocyclic, and comprises two or more fused rings, and wherein R' is not  or ;

wherein if Y is –C(R")–, then R' and R" taken together with the carbon atoms to which they are attached form an aryl or heteroaryl ring, each said ring is optionally substituted;

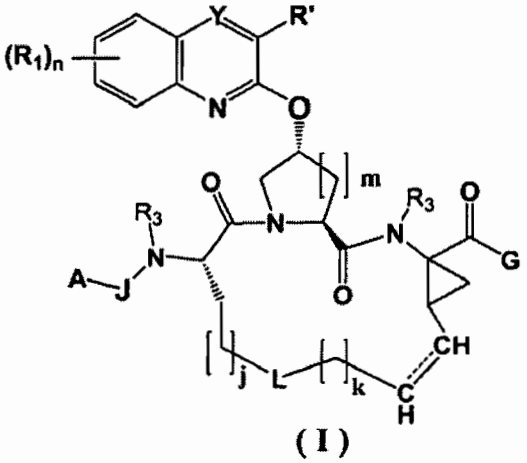
provided that said compound is not tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I or I', or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient.

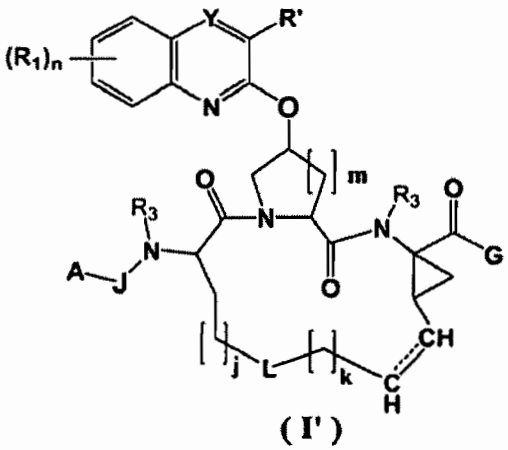
In one aspect, the invention provides a method of treating a viral infection in a subject, comprising administering to the subject a therapeutically effective amount of a compound of formula I or I', or a pharmaceutically acceptable salt, ester or prodrug thereof, or a pharmaceutical composition comprising the same.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a compound of formula I or I':



(I)



(I')

or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein:

J is absent, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, -C(O)-, -O-C(O)-, - $N(R_3)$-C(O)-, -C(S)-, - $C(=NR_4)$-, -S(O)-, -$S(O_2)$-, or –$N(R_3)$-;

A is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted arylalkyl, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted carbocyclic;

Each R_1 is independently selected from

(i) halogen, hydroxy, amino, -CN, -CF_3, -N_3, -NO_2, -OR_4, -SR_4, -SOR_4, -SO_2R_4, –$N(R_3)S(O_2)–R_4$, -$N(R_3)$ $S(O_2)NR_3R_4$, -NR_3R_4, -$C(O)OR_4$, -$C(O)R_4$, -$C(O)NR_3R_4$, or -$N(R_3)C(O)R_4$;

(ii) optionally substituted aryl;

(iii) optionally substituted heteroaryl;

(iv) optionally substituted heterocyclic;

(v) optionally substituted carbocyclic; or

(vi) optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

G is –E-R_5;

wherein E is absent; optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; or -O-, -S-, -$N(R_3)$-, -$N(R_3)S(O_p)$-, -$N(R_3)C(O)$-, -$N(R_3)$ $C(O)S(O_p)$-, -$OS(O_p)$-, -$C(O)S(O_p)$-, or -$C(O)N(R_3)S(O_p)$-;

p is 0, 1, or 2;

R_5 is H; optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;

R_3 and R_4 are each independently selected at each occurrence from the following: optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclic; optionally substituted carbocyclic; or hydrogen;

L is absent or is selected from optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

Y is N or –C(R")–;

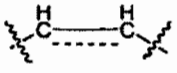
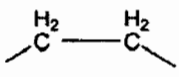
wherein A, R_1, R' and/or R" can be taken together to form a ring;

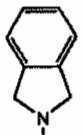
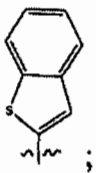
j = 0, 1, 2, 3, or 4;

k= 0, 1, 2, or 3;

m = 0, 1, or 2;

n is 0, 1, 2, 3, or 4; and

 denotes a carbon-carbon single or double bond (i.e.,  means or ),

wherein if Y is N, then R' is optionally substituted heterocyclic, optionally substituted heteroaryl, optionally substituted aryl or optionally substituted carbocyclic, and comprises two or more fused rings, and wherein R' is not  or ;

wherein if Y is –C(R")–, then R' and R" taken together with the carbon atoms to which they are attached form an aryl or heteroaryl ring, each of which is optionally substituted;

provided that said compound is not tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

It is understood that the embodiments of the invention discussed below with respect to the preferred variable selections can be taken alone or in combination with one or more of the other embodiments, or preferred variable selections, of the invention, as if each combination were explicitly listed herein.

In one aspect, the invention provides a compound of formula I or I', or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Y is CR", and R' and R" taken together with the carbon atoms to which they are attached form an optionally substituted aryl or an optionally substituted heteroaryl ring.

In another aspect, the invention provides a compound of formula I or I', or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Y is CR", and R' and R" taken together with the carbon atoms to which they are attached form an optionally substituted aryl ring, preferably phenyl.

Alternatively or additionally, k=3, j=1 and L is absent.

Alternatively or additionally, R' and R", and the atoms to which each is attached, form an aryl which is substituted by $(R_2)_x$, wherein each R_2 is independently selected from halogen, hydroxy, amino, -CN, $-CF_3$, $-N_3$, $-NO_2$, $-OR_4$, $-SR_4$, $-SOR_4$, $-SO_2R_4$, $-N(R_3)S(O_2)-R_4$, $-N(R_3)S(O_2)NR_3R_4$, $-NR_3R_4$, $-C(O)OR_4$, $-C(O)R_4$, $-C(O)NR_3R_4$, or $-N(R_3)C(O)R_4$; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclic; optionally substituted carbocyclic; or optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; and x is 0, 1, 2, 3, or 4.

Alternatively or additionally, R_1 is absent (i.e., n=0) or is halogen, hydroxy, amino, -CN, $-CF_3$, $-N_3$, $-NO_2$, $-OR_4$, $-SR_4$, $-SOR_4$, $-SO_2R_4$, $-N(R_3)S(O_2)-R_4$, $-N(R_3)S(O_2)NR_3R_4$, $-NR_3R_4$, $-C(O)OR_4$, $-C(O)R_4$, $-C(O)NR_3R_4$, or $-N(R_3)C(O)R_4$.

Alternatively or additionally, R' and R", and the atoms to which each is attached, form an aryl which is substituted by $(R_2)_x$, wherein each R_2 is independently absent (i.e., x=0) or halogen.

Alternatively or additionally, R_1 is absent (i.e., n=0) or halogen.

Alternatively or additionally, E is -NH-, $-NHS(O_p)-$, or $-NH(CO)S(O_p)-$, and p is 2.

Alternatively or additionally, E is $-NHS(O_p)-$, and p is 2.

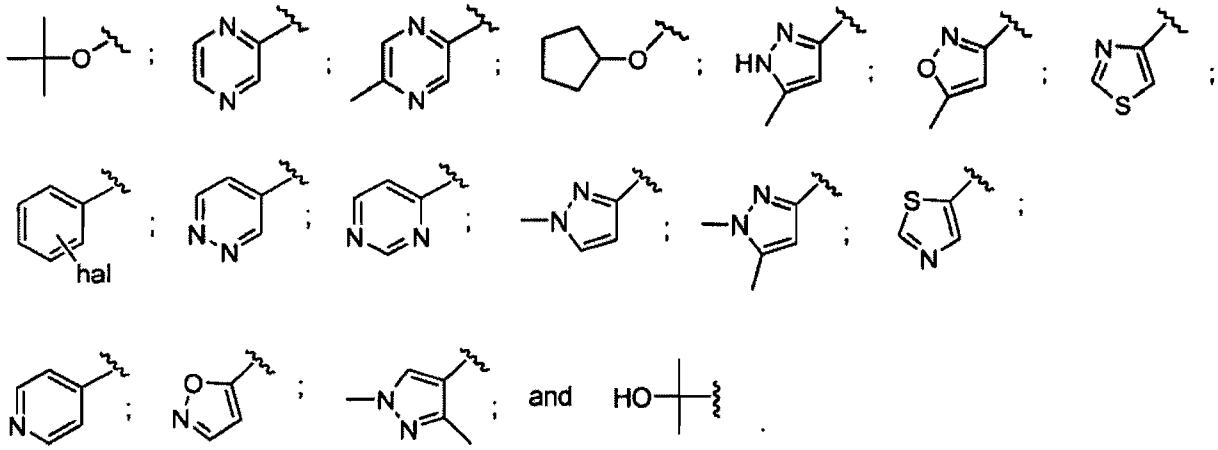
Alternatively or additionally, R_5 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyridinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, or imidazolyl, each of which is optionally substituted. In a further embodiment, R_5 is optionally substituted cyclopropyl or optionally substituted thienyl, preferably cyclopropyl or thienyl.

Alternatively or additionally, J is -C(O)-, -O-C(O)-, -C(S)-, -C(=NR_4)-, -S(O)-, or -S(O_2)-. Preferably, J is -C(O)-.

Alternatively or additionally, m is 1.

Alternatively or additionally, each R_3 is H.

Alternatively or additionally, A is optionally substituted –C_1-C_8 alkyl, containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted –C_1-C_8 alkoxy, optionally substituted heteroaryl, optionally substituted –C_3-C_{12} cycloalkyl, or optionally substituted –C_3-C_{12} heterocycloalkyl. In a further embodiment, A is selected from



Preferably, A is a 5-methyl-pyrazin-2-yl.

In still another aspect, the invention provides a compound of formula I or I', or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Y is CR", and R' and R" taken together with the carbon atoms to which they are attached form an optionally substituted heteroaryl ring. The remaining variables are as defined above, including the alternative or preferred embodiments, as if repeated herein.

The invention also features a compound of formula I or I' (preferably formula I), or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Y is CR", and R' and R" taken together with the carbon atoms to which they are attached form

an aryl or heteroaryl ring, preferably phenyl, which is optionally substituted with one or more R_2;

k=0, j=0, m=1, n=0, 1, 2, 3 or 4, and L is C_3-C_6alkylene, C_3-C_6alkenylene or C_3-C_6alkynylene and is optionally substituted with one or more R_7 (preferably butylene);

J is -C(O)- or -O-C(O)- (preferably -C(O)-);

A is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}carbocyclic, aryl, heteroaryl or heterocyclic comprising 5 to 10 ring atoms, and A is optionally substituted with one or more R_6;

G is –E-R_5, E is -NHS(O_2)-; R_5 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}carbocyclic (preferably cyclopropyl), heteroaryl (preferably thienyl) or heterocyclic comprising 5 to 10 ring atoms, and R_5 is optionally substituted with one or more R_7;

each R_1 and R_2 is independently selected from halogen, hydroxy, amino, -CN, $-CF_3$, $-N_3$, $-NO_2$, $-OR_4$, $-SR_4$, $-S(O)R_4$, $-S(O_2)R_4$, $-NR_3R_4$, $-C(O)OR_4$, $-C(O)R_4$, $-C(O)NR_3R_4$, $-N(R_3)C(O)R_4$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, C_3-C_{10}carbocyclic optionally substituted with one or more R_7, or heterocyclic comprising 5 to 10 ring atoms and optionally substituted with one or more R_7,

wherein each R_6 and R_7 is independently selected at each occurrence from halogen, hydroxy, amino, $-CF_3$, -CN, $-N_3$, $-NO_2$, $-C_1$-C_6alkyl (preferably methyl), C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, or C_2-C_6haloalkynyl (and, preferably, R_1 and R_2 is absent in each instance); and

R_3 and R_4 are each independently selected at each occurrence from hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl and R_3 is preferably hydrogen.

The invention further features a compound of formula I or I' (preferably formula I), or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Y is CR", R' and R" taken together with the carbon atoms to which they are attached form a phenyl optionally substituted with one or more R_2;

k=3, j=1, m=1, n=0,1, 2, 3, or 4, and L is absent;

J is -C(O)- or -O-C(O)-;

A is C_1-C_6alkyl, aryl, heteroaryl, C_5-C_6carbocyclic or heterocyclic comprising 5 to 6 ring atoms, and is optionally substituted with one or more R_6;

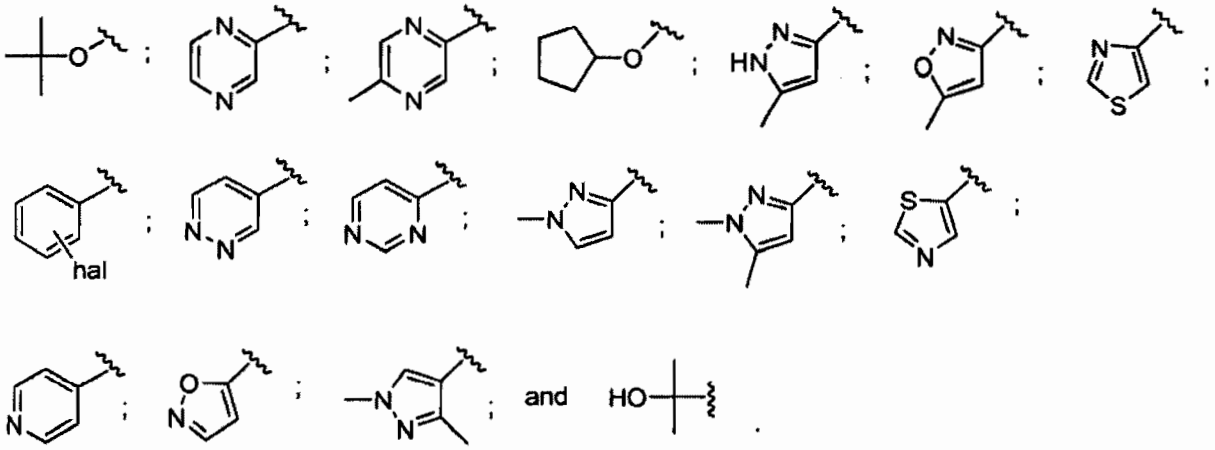
G is –E-R_5, E is -NHS(O_2)-; R_5 is C_3-C_6carbocyclic or heteroaryl, and is optionally substituted with one or more R_7; in one embodiment, R_5 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyridinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, or imidazolyl, each of which is optionally substituted with one or more R_7; preferably, R_5 is cyclopropyl;

each R_1 and R_2 is independently selected from halogen, hydroxy, amino, -CN, -N_3, -CF_3, -NO_2, -OR_4, -SR_4, -S(O)R_4, -S(O_2)R_4, -NR_3R_4, -C(O)OR_4, -C(O)R_4, -C(O)NR_3R_4, -N(R_3)C(O)R_4, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, or C_2-C_6haloalkynyl;

R_3 is hydrogen; and each R_4 is independently selected from hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl;

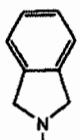
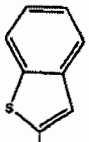
R_6 and R_7 is independently selected at each occurrence from halogen, hydroxy, amino, -CF_3, -CN, -N_3, -NO_2, -C_1-C_6alkyl (preferably methyl), C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, or C_2-C_6haloalkynyl;

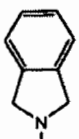
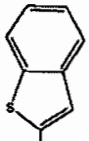
A can be, for example, selected from the following groups, each group optionally substituted with one or more R_6:



In yet another aspect, the invention provides a compound of formula I or I', or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein R' is optionally substituted heterocyclic, optionally substituted heteroaryl, optionally substituted aryl

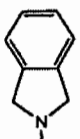
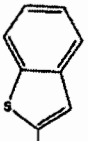
or optionally substituted carbocyclic, and comprises two or more fused rings, and

wherein R' is not  or  ; and Y is N.

In still another aspect, the invention provides a compound of formula I or I', or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein R' is an optionally substituted heterocyclic or optionally substituted heteroaryl, comprises two or more fused rings, and wherein R' is not  or  ; and Y is N. Preferably, R' is an optionally substituted fused bicyclic heterocyclic or fused bicyclic heteroaryl. Alternatively or additionally, R' is an optionally substituted with one or more R_2, and preferably with an alkyl or aryl.

The remaining variables are as defined above, including in the preferred and alternative embodiments.

In another aspect, the invention provides a compound of formula I or I' or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein R' is optionally substituted heterocyclic, optionally substituted heteroaryl, optionally substituted aryl or optionally substituted carbocyclic, and comprises two or more fused rings, and

wherein R' is not  or  , and Y is N; wherein k=3, j=1 and L is absent.

Preferably, the compound has formula I.

Alternatively or additionally, m is 1.

Alternatively or additionally, each R_3 is H.

Alternatively or additionally, R_1 and R_2 are independently hydrogen or halogen.

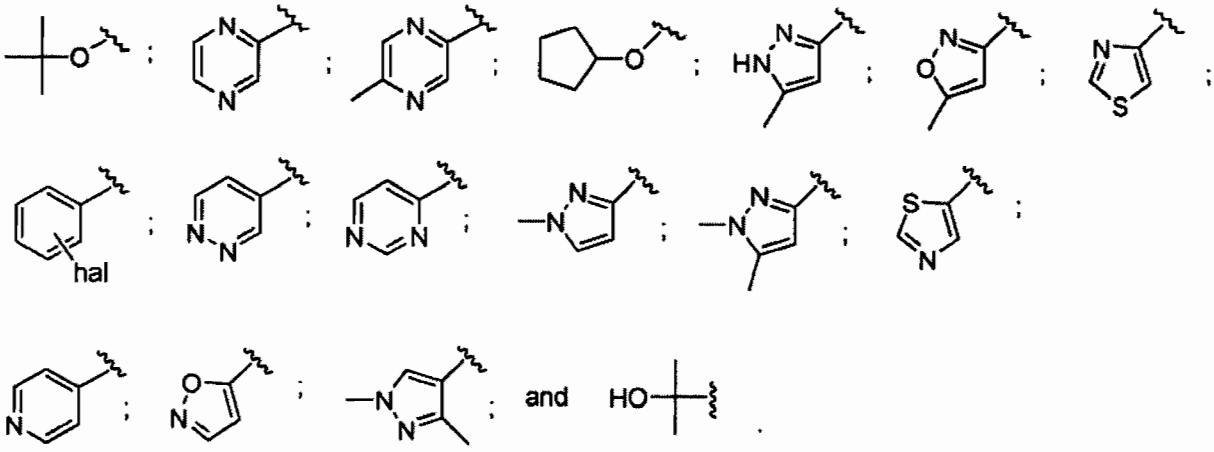
Alternatively or additionally, E is $-NHS(O_p)-$, and p is 2.

Alternatively or additionally, R_5 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyridinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, or imidazolyl, each of which is

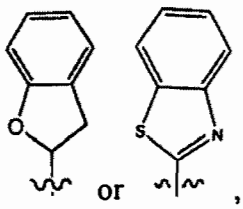
optionally substituted. In a further embodiment, R_5 is optionally substituted cyclopropyl or optionally substituted thienyl, and preferably cyclopropyl or thienyl.

Alternatively or additionally, J is -C(O)-.

Alternatively or additionally, A is optionally substituted $-C_1$-C_8 alkyl, containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted $-C_1$-C_8 alkoxy, optionally substituted heteroaryl, optionally substituted $-C_3$-C_{12} cycloalkyl, or optionally substituted $-C_3$-C_{12} heterocycloalkyl. In a further embodiment, A is selected from

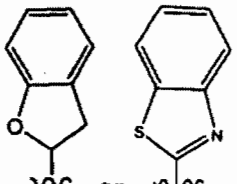


In another aspect, the invention provides a compound of formula I or I' or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Y is N, and R' is



, and is optionally substituted; provided that said compound is not tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

The invention also features a compound of formula I or formula I' (preferably formula I), or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Y



is N, and R' is  or , and is optionally substituted with one or more R_2;

k=0, j=0, m=1, n=0,1, 2, 3, or 4, and L is C_3-C_6alkylene, C_3-C_6alkenylene or C_3-C_6alkynylene and is optionally substituted with one or more R_7;

J is -C(O)- or -O-C(O)-;

A is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}carbocyclic, aryl, heteroaryl, or heterocyclic comprising 5 to 10 ring atoms, and A is optionally substituted with one or more R_6;

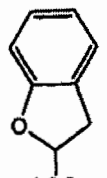
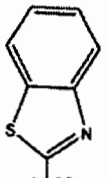
G is –E-R_5, E is -NHS(O_2)-; R_5 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}carbocyclic, aryl, heteroaryl, or heterocyclic comprising 5 to 10 ring atoms, and R_5 is optionally substituted with one or more R_7;

each R_1 and R_2 is independently selected from halogen, hydroxy, amino, -CN, -CF_3, -N_3, -NO_2, -OR_4, -SR_4, -S(O)R_4, -S(O_2)R_4, -NR_3R_4, -C(O)OR_4, -C(O)R_4, -C(O)NR_3R_4, -N(R_3)C(O)R_4, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, C_3-C_{10}carbocyclic optionally substituted with one or more R_7, or heterocyclic comprising 5 to 10 ring atoms and optionally substituted with one or more R_7,

wherein each R_6 and R_7 is independently selected from halogen, hydroxy, amino, -CN, -CF_3,-N_3, -NO_2, -C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, or C_2-C_6haloalkynyl; and R_3 or R_4 are each independently selected at each occurrence from hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl;

provided that said compound is not tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

The invention further features a compound of formula I or formula I' (preferably formula I), or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein Y is N, and R' is  or , and is optionally substituted with one or more R_2;

k=0, j=0, m=1, n=0,1, 2, 3, or 4, and L is C_3-C_6alkylene, C_3-C_6alkenylene or C_3-C_6alkynylene and is optionally substituted with one or more halo;

J is -C(O)- or -O-C(O)-; A is C_1-C_6alkyl, aryl, heteroaryl, C_3-C_{10}carbocyclic or heterocyclic comprising 5 to 10 ring atoms, and is optionally substituted with one or more R_6;

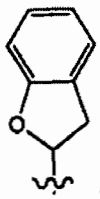
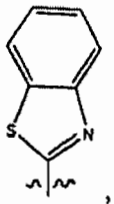
G is –E-R_5, E is -NHS(O_2)-; R_5 is C_3-C_{10}carbocyclic or heteroaryl, and is optionally substituted with one or more R_7;

each R_1 and R_2 are independently selected from halogen, hydroxy, amino, -CN, -CF_3, -N_3, -NO_2, -OR_4, -SR_4, -S(O)R_4, -S(O_2)R_4, -NR_3R_4, -C(O)OR_4, -C(O)R_4, -C(O)NR_3R_4, -N(R_3)C(O)R_4, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, C_3-C_{10}carbocyclic optionally substituted with one or more R_7, or heterocyclic comprising 5 to 10 ring atoms and optionally substituted with one or more R_7,

wherein each R_6 and R_7 is independently selected from halogen, hydroxy, amino, -CN, -CF_3, -N_3, -NO_2, - C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, or C_2-C_6haloalkynyl; R_3 is hydrogen; and each R_4 is independently selected from hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl;

provided that said compound is not tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

In addition, the invention features a compound of formula I or formula I' (preferably formula I), or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein Y is N, and R' is  or , and is optionally substituted with one or more R_2;

k=3, j=1, m=1, n=0,1, 2, 3, or 4, and L is absent; J is -C(O)- or -O-C(O)-; A is C_5-C_6carbocyclic or a heterocyclic comprising 5 to 6 ring atoms, and is optionally substituted with one or more R_6;

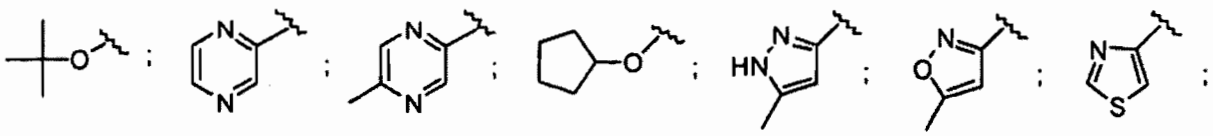
G is –E-R_5, E is -NHS(O_2)-; R_5 is C_3-C_6carbocyclic or heteroaryl, and is optionally substituted with one or more R_7;

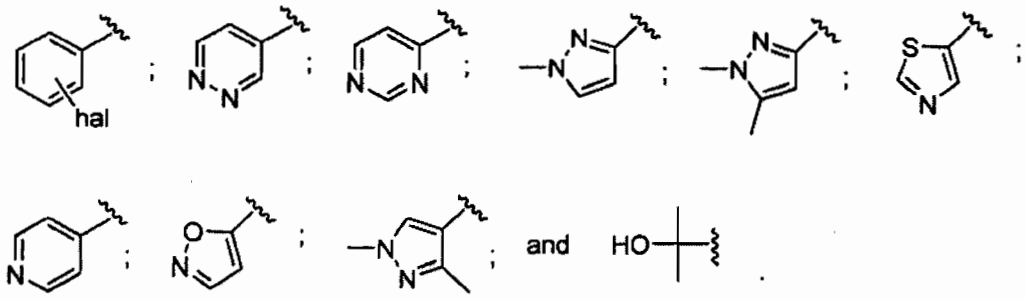
each R_1 and R_2 are independently selected from halogen, hydroxy, amino, -CN, -CF_3, -N_3, -NO_2, -OR_4, -SR_4, -S(O)R_4, -S(O_2)R_4, -NR_3R_4, -C(O)OR_4, -C(O)R_4, -C(O)NR_3R_4, -N(R_3)C(O)R_4, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, or C_2-C_6haloalkynyl;

R_3 is hydrogen; and each R_4 is independently selected from hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl and R_6 and R_7 are as defined above;

provided that said compound is not tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

In one embodiment, R_5 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyridinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, or imidazolyl, each of which is optionally substituted with one or more R_7. Preferably, R_5 is cyclopropyl. A can be, for example, selected from the the following groups and optionally substituted with one or more R_6:





Representative compounds include, but are not limited to, the following compounds:

(1) tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(2) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(isonicotinamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(3) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(2-fluorobenzamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15, 16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(4) N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide;

(5) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(6) N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)isoxazole-5-carboxamide;

(7) N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)thiazole-4-carboxamide;

(8) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(9) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(10) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1,3-dimethyl-1H-pyrazole-4-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(11) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(3-fluorobenzamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(12) tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(13) N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide;

(14) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(15) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(16) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(17) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(18) tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(19) N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide;

(20) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(21) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(22) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(23) (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(24) tert-butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-

5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(25) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyrazine-2-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(26) Cyclopentyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(27) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(28) N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide;

(29) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(30) N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)thiazole-5-carboxamide;

(31) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-fluorobenzamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(32) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyridazine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(33) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(34) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(35) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-hydroxy-2-methylpropanamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(36) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(37) Cyclopentyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(2-fluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(38) tert-Butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(2,9-difluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a- hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(39) tert-butyl (2R,6S,13aR,14aR,16aS)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(40) Cyclopentyl (2R,6S,13aR,14aR,16aS)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(41) tert-Butyl (2R,6S,13aR,14aR,16aS)-5,16-dioxo-2-(phenanthridin-6-yloxy)-14a-(thiophen-2-ylsulfonylcarbamoyl)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(42) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(43) Cyclopentyl (1aR,3aS,5R,9S,16aS,Z)-1a-(cyclopropylsulfonylcarbamoyl)-5-(2-fluoro phenanthridin-6-yloxy)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexa decahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(44) tert-butyl (1aR,3aS,5R,9S,16aS,Z)-1a-(cyclopropylsulfonylcarbamoyl)-5-(9-fluoro phenanthridin-6-yloxy)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadeca hydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(45) tert-butyl (1aR,3aS,5R,9S,16aS,Z)-1a-(cyclopropylsulfonylcarbamoyl)-5-(8-fluoro phenanthridin-6-yloxy)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadecahydro cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(46) (1aR,3aS,5R,9S,16aR,Z)-5-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropyl sulfonyl)-9-(isonicotinamido)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-1a-carboxamide;

(47) (1aR,3aS,5R,9S,16aR,Z)-5-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropyl sulfonyl)-9-(5-methylpyrazine-2-carboxamido)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11, 12,13,14,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-1a-carboxamide;

(48) cyclopentyl (2R,6S,13aR,14aR,16aS)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

(49) tert-butyl (1aR,3aS,5R,9S,16aS,Z)-1a-(cyclopropylsulfonylcarbamoyl)-5-(2,9-difluoro phenanthridin-6-yloxy)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadecahydro cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(50) tert-butyl (1aR,3aS,5R,9S,16aS,Z)-1a-(cyclopropylsulfonylcarbamoyl)-5-(2,10-difluoro phenanthridin-6-yloxy)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadecahydro cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(51) tert-butyl (1aR,3aS,5R,9S,16aR,Z)-1a-(cyclopropylsulfonylcarbamoyl)-5-(3-(naphthalen-2-yl)quinoxalin-2-yloxy)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadecahydro cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(52) tert-butyl (1aR,3aS,5R,9S,16aR,Z)-1a-(cyclopropylsulfonylcarbamoyl)-5-(3-(naphthalen-1-yl)quinoxalin-2-yloxy)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadecahydro cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(53) tert-butyl (1aR,3aS,5R,9S,16aR,Z)-5-(3-(1H-indol-5-yl)quinoxalin-2-yloxy)-1a-(cyclo propylsulfonylcarbamoyl)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadeca hydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(54) tert-butyl (1aR,3aS,5R,9S,16aR,Z)-5-(3-(1H-indol-6-yl)quinoxalin-2-yloxy)-1a-(cyclo propylsulfonylcarbamoyl)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadeca hydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(55) tert-butyl (1aR,3aS,5R,9S,16aR,Z)-1a-(cyclopropylsulfonylcarbamoyl)-3,8-dioxo-5-(3-(quinolin-3-yl)quinoxalin-2-yloxy)-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadeca hydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(56) tert-butyl (1aR,3aS,5R,9S,16aR,Z)-5-(3-(benzo[d][1,3]dioxol-5-yl)quinoxalin-2-yloxy)-1a-(cyclopropylsulfonylcarbamoyl)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate;

(57) (1aR,3aS,5R,9S,16aR,Z)-5-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropyl sulfonyl)-9-(5-methylpyrazine-2-carboxamido)-3,8-dioxo-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14, 16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-1a-carboxamide; and

(58) tert-butyl (1aR,3aS,5R,9S,16aS,Z)-1a-(cyclopropylsulfonylcarbamoyl)-3,8-dioxo-5-(thiazolo[4,5-c]quinolin-4-yloxy)-1,1a,2,3,3a,4,5,6,8,9,10,11,12,13,14,16a-hexadecahydro cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-9-ylcarbamate; and

(59) tert-Butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(3,9-difluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a- hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I or I'described herein, or the embodiments described above, or a pharmaceutically

acceptable salt, ester, or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient.

According to another embodiment, the pharmaceutical compositions of the present invention may further contain one or more other anti-HCV agents. Examples of anti-HCV agents include, but are not limited to, α-interferon; β-interferon; pegylated interferon-α; pegylated interferon-lambda; ribavirin; viramidine; R-5158; nitazoxanide; amantadine; Debio-025, NIM-811; HCV polymerase inhibitors such as R7128, R1626, R4048, T-1106, PSI-7851, PF-00868554, ANA-598, IDX184, IDX102, IDX375, GS-9190, VCH-759, VCH-916, MK-3281, BCX-4678, MK-3281, VBY708, ANA598, GL59728 or GL60667; BMS-790052; BMS-791325; BMS-650032; HCV entry, helicase or internal ribosome entry site inhibitors; or other HCV replication inhibitors such as GS-9132, ACH-1095, AP-H005, A-831, A-689, AZD2836. For further details see S. Tan, A. Pause, Y. Shi, N. Sonenberg, Hepatitis C Therapeutics: Current Status and Emerging Strategies, *Nature Rev. Drug Discov.*, **1**, 867-881 (2002); WO 00/59929 (2000); WO 99/07733 (1999); WO 00/09543 (2000); WO 99/50230 (1999); US5861297 (1999); and US2002/0037998 (2002).

According to an additional embodiment, the pharmaceutical compositions of the present invention may further contain another HCV protease inhibitor, such as telaprevir, boceprevir, ITMN-191, BI-201335, TMC-435, MK-7009, VBY-376, VX-500, VX-813, PHX-B, ACH-1625, IDX136, or IDX316.

In other embodiments, the invention provides a pharmaceutical composition further comprising pegylated interferon, another anti-viral, anti-bacterial, anti-fungal or anti-cancer agent, or an immune modulator, and/or further comprising a cytochrome P450 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof. In certain embodiments, the cytochrome P450 monooxygenase inhibitor is ritonavir.

In another aspect, the invention provides for the use of a compound of the invention to manufacture an agent for preventing or treating viral infection. In another aspect, the invention provides for the use of a compound of the invention to manufacture an agent for preventing or treating hepatitis C infection. The present invention also contemplates the use of a solvate (e.g., hydrate) of a compound of the invention to manufacture pharmaceutical compositions for preventing or treating hepatitis C infection. As used herein, "solvate" refers to the physical association of a

compound of the invention with one or more solvent molecule, whether organic or inorganic. This physical association often includes hydrogen bonding. In certain instances, the solvate is capable of isolation, for example, when one or more solvate molecules are incorporated in the crystal lattice of the crystalline solid.

In another embodiment, the compounds or pharmaceutical compositions of the invention are administered with ritonavir, either simultaneously or sequentially. In certain embodiments, a compound or a pharmaceutical composition of the invention is administered in the same composition as ritonavir. In another embodiment, a compound or a pharmaceutical composition thereof of the invention is administered in a different composition than ritonavir.

According to yet another embodiment, the pharmaceutical compositions of the present invention may further comprise inhibitor(s) of other targets in the HCV life cycle, including, but not limited to, helicase, polymerase, metalloprotease, CD81, NS5A, cyclophilin, and internal ribosome entry site (IRES).

In one aspect, the invention provides a method of treating a viral infection in a subject, comprising administering to the subject a therapeutically effective amount of a compound of formula I or I' described herein, or a pharmaceutically acceptable salt, ester or prodrug thereof, or a pharmaceutical composition comprising the same.

According to a further embodiment, the present invention includes methods of treating hepatitis C infections in a subject in need of such treatment by administering to said subject an anti-HCV virally effective amount or an inhibitory amount of the compounds or pharmaceutical compositions of the present invention.

According to another embodiment, the present invention includes methods of treating hepatitis C infections in a subject in need of such treatment by administering to said subject a compound or a pharmaceutical composition of the present invention. The methods can further include administration of an additional therapeutic agent, including another antiviral agent or an anti-HCV agent as described hereinabove. The additional agent can be co-administered (such as concurrently administered or sequentially administered) with a compound (a pharmaceutically acceptable salt, ester or prodrug thereof) or a pharmaceutical composition of the present invention. The additional agent(s) and a compound (or a pharmaceutically acceptable salt, ester or prodrug thereof) of the present invention can be formulated in the same composition, or in different compositions but co-administered concurrently or sequentially. The methods herein can further include the step of identifying that the subject is in need of

treatment for hepatitis C infection. The identification can be by subjective (e.g., health care provider determination) or objective (e.g., diagnostic test) means.

In one aspect, the invention provides a method of inhibiting the replication of hepatitis C virus, the method comprising contacting a hepatitis C virus with an effective amount of a compound or pharmaceutical composition of the invention.

In another embodiment, the invention provides a method as described above, further comprising administering an additional anti-hepatitis C virus agent. Examples of anti-hepatitis C virus agents include, but are not limited to, α-interferon; β-interferon; pegylated interferon-α; pegylated interferon-lambda; ribavirin; viramidine; R-5158; nitazoxanide; amantadine; Debio-025, NIM-811; HCV polymerase inhibitors such as R7128, R1626, R4048, T-1106, PSI-7851, PF-00868554, ANA-598, IDX184, IDX102, IDX375, GS-9190, VCH-759, VCH-916, MK-3281, BCX-4678, MK-3281, VBY708, ANA598, GL59728 or GL60667; BMS-790052; BMS-791325; BMS-650032; HCV entry, helicase or internal ribosome entry site inhibitors; or other HCV replication inhibitors such as GS-9132, ACH-1095, AP-H005, A-831, A-689, AZD2836. For further details see S. Tan, A. Pause, Y. Shi, N. Sonenberg, Hepatitis C Therapeutics: Current Status and Emerging Strategies, *Nature Rev. Drug Discov.*, **1**, 867-881 (2002); WO 00/59929 (2000); WO 99/07733 (1999); WO 00/09543 (2000); WO 99/50230 (1999); US5861297 (1999); and US2002/0037998 (2002). Preferably, a compound or a pharmaceutical composition of the present invention is co-administered with, or used in combination with, pegylated interferon (e.g., pegylated interferon alpha-2a or 2b) and ribavirin. Ritonavir or another cytochrome P450 monooxygenase inhibitor can also be used to enhance the pharmacokinetics of the compound of the present invention. The patient being treated is preferably infected with HCV genotype-1 (e.g., genotype 1a or 1b). Patients infected with other HCV genotypes, such as genotypes 2, 3, 4, 5 or 6, can also be treated with a compound or a pharmaceutical composition of the present invention.

In another embodiment, the invention provides a method as described above, further comprising administering another HCV protease inhibitor, an HCV polymerase inhibitor, an HCV helicase inhibitor, or an internal ribosome entry site (IRES)inhibitor, such as telaprevir, boceprevir, ITMN-191, BI-201335, TMC-435, MK-7009, VBY-376, VX-500, VX-813, PHX-B, ACH-1625, IDX136, IDX316, pegylated interferon, another anti-viral, anti-bacterial, anti-fungal or anti-cancer

agent, or an immune modulator, and/or further comprising a cytochrome P450 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof. In certain embodiments, the cytochrome P450 monooxygenase inhibitor is ritonavir.

An additional embodiment of the present invention includes methods of treating biological samples by contacting the biological samples with the compounds of the present invention.

Yet another aspect of the present invention is a process of making any of the compounds delineated herein employing any of the synthetic means delineated herein.

Definitions

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group. The number of carbon atoms in a hydrocarbyl substituent can be indicated by the prefix "C_x-C_y," where x is the minimum and y is the maximum number of carbon atoms in the substituent.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen radicals. For example, "haloalkyl" means an alkyl substituent wherein at least one hydrogen radical is replaced with a halogen radical.

If a linking element in a depicted structure is "absent", then the left element in the depicted structure is directly linked to the right element in the depicted structure. For example, if a chemical structure is depicted as X–L–Y wherein L is absent, then the chemical structure is X–Y.

The term "alkyl" as used herein, refers to a saturated, straight- or branched-chain hydrocarbon radical typically containing from 1 to 20 carbon atoms. For example, "C_1-C_6 alkyl" or "C_1-C_8 alkyl" contains from one to six, or from one to eight, carbon atoms, respectively. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl, heptyl, octyl radicals and the like.

The term "alkenyl" as used herein, denotes a straight- or branched-chain hydrocarbon radical containing one or more double bonds and typically from 2 to 20 carbon atoms. For example, "C_2-C_6 alkenyl" or "C_2-C_8 alkenyl" contains from two to six, or from two to eight carbon atoms, respectively. Alkenyl groups include, but are

not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

The term "alkynyl" as used herein, denotes a straight- or branched-chain hydrocarbon radical containing one or more triple bonds and typically from 2 to 20 carbon atoms. For example, "C_2-C_6 alkynyl" or "C_2-C_8 alkynyl" contains from two to six, or from two to eight, carbon atoms, respectively. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl and the like.

The term "alkylene" refers to a divalent group derived from a straight or branched saturated hydrocarbyl chain typically containing from 1 to 20 carbon atoms, more typically from 1 to 8 carbon atoms, and even more typically from 1 to 6 carbon atoms. Representative examples of alkylene include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, and -$CH_2CH(CH_3)CH_2$-.

The term "alkenylene" refers to a divalent unsaturated hydrocarbyl group which may be linear or branched and which has at least one carbon-carbon double bond. An alkenylene group typically contains 2 to 20 carbon atoms, more typically from 2 to 8 carbon atoms, and even more typically from 2 to 6 carbon atoms. Non-limiting examples of alkenylene groups include —C(H)=C(H)—, —C(H)=C(H)—CH_2—, —C(H)=C(H)—CH_2—CH_2—, —CH_2—C(H)=C(H)—CH_2—, —C(H)=C(H)—$CH(CH_3)$—, and —CH_2—C(H)=C(H)—$CH(CH_2CH_3)$—.

The term "alkynylene" refers to a divalent unsaturated hydrocarbon group which may be linear or branched and which has at least one carbon-carbon triple bond. Representative alkynylene groups include, by way of example, -C≡C-, -C≡C-CH_2-, -C≡C-CH_2-CH_2-, -CH_2-C≡C-CH_2-, -C≡C-$CH(CH_3)$-, and -CH_2-C≡C-$CH(CH_2CH_3)$-.

The term "cycloalkyl" denotes a monovalent group derived from a monocyclic or polycyclic saturated carbocyclic ring compound. Examples of cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl and the like.

The terms "carbocycle" or "carbocyclic" or "carbocyclyl" refer to a saturated (e.g., "cycloalkyl"), partially saturated (e.g., "cycloalkenyl" or "cycloalkynyl") or completely unsaturated (e.g., "aryl") ring system containing zero heteroatom ring atom and typically from 3 to 18 carbon ring atoms. A carbocyclyl may be, without limitation, a single ring, or two or more fused rings, or bridged or spiro rings. A

carbocyclyl may contain, for example, from 3 to 14 ring members (i.e., C_3-C_{14}carbocyclyl, such as C_3-C_{14}cycloalkyl), from 3 to 10 ring members (i.e., C_3-C_{10}carbocyclyl, such as C_3-C_{10}cycloalkyl), from 3 to 8 ring members (i.e., C_3-C_8carbocyclyl, such as C_3-C_8cycloalkyl), or from 3 to 6 ring members (i.e., C_3-C_6carbocyclyl, such as C_3-C_6cycloalkyl). A substituted carbocyclyl may have either cis or trans geometry. Representative examples of carbocyclyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclopentadienyl, cyclohexadienyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, cyclohexenyl, phenyl, naphthyl, fluorenyl, indanyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, isoindenyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), decalinyl, and norpinanyl and the like. A carbocyclyl group can be attached to the parent molecular moiety through any substitutable carbon atom of the group.

The term "aryl" refers to an aromatic carbocyclyl containing from 6 to 14 carbon ring atoms. Non-limiting examples of aryls include phenyl, naphthalenyl, anthracenyl, and indenyl and the like. An aryl group can be connected to the parent molecular moiety through any substitutable carbon atom of the group.

The term "aralkyl" or "arylalkyl" refers to an alkyl residue attached to an aryl ring. Examples of aralkyl include, but are not limited to, benzyl, phenethyl and the like.

The term "heteroaryl" means an aromatic heterocyclyl typically containing from 5 to 18 ring atoms. A heteroaryl may be a single ring, or two or more fused rings. Non-limiting examples of five-membered heteroaryls include imidazolyl; furanyl; thiophenyl (or thienyl or thiofuranyl); pyrazolyl; oxazolyl; isoxazolyl; thiazolyl; 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-oxadiazolyl; and isothiazolyl. Non-limiting examples of six-membered heteroaryls include pyridinyl; pyrazinyl; pyrimidinyl; pyridazinyl; and 1,3,5-, 1,2,4-, and 1,2,3-triazinyl. Non-limiting examples of 6/5-membered fused ring heteroaryls include benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl. Non-limiting examples of 6/6-membered fused ring heteroaryls include quinolinyl; isoquinolinyl; and benzoxazinyl (including cinnolinyl and quinazolinyl).

The term "heteroaralkyl" or "heteroarylalkyl" refers to an alkyl residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term "heterocycloalkyl" refers to a non-aromatic 3-, 4-, 5-, 6- or 7-membered ring or a bi- or tri-cyclic group fused system, where (i) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above rings may be fused to a benzene ring. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl and the like.

The terms "heterocyclic" or "heterocyclo" or "heterocyclyl" refer to a saturated (e.g., "heterocycloalkyl"), partially unsaturated (e.g., "heterocycloalkenyl" or "heterocycloalkynyl") or completely unsaturated (e.g., "heteroaryl") ring system typically containing from 3 to 18 ring atoms, where at least one of the ring atoms is a heteroatom (i.e., nitrogen, oxygen or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur. A heterocyclyl group can be linked to the parent molecular moiety via any substitutable carbon or nitrogen atom in the group, provided that a stable molecule results. A heterocyclyl may be, without limitation, a single ring, which typically contains from 3 to 14 ring atoms, from 3 to 8 ring atoms, from 3 to 6 ring atoms, or from 5 to 6 ring atoms. Non-limiting examples of single-ring heterocyclyls include furanyl, dihydrofuranyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazoly, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, triazinyl, isoxazinyl, oxazolidinyl, isoxazolidinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, or diazepinyl. A heterocyclyl may also include, without limitation, two or more rings fused together, such as, for example, naphthyridinyl, thiazolpyrimidinyl, thienopyrimidinyl, pyrimidopyrimidinyl, or pyridopyrimidinyl. A heterocyclyl may comprise one or more sulfur atoms as ring members; and in some cases, the sulfur atom(s) is oxidized to SO or SO_2. The nitrogen heteroatom(s) in a heterocyclyl may or may not be quaternized, and may or

may not be oxidized to N-oxide. In addition, the nitrogen heteroatom(s) may or may not be N-protected.

The terms "optionally substituted", "optionally substituted alkyl," "optionally substituted "optionally substituted alkenyl," "optionally substituted alkynyl", "optionally substituted carbocyclic," "optionally substituted aryl", " optionally substituted heteroaryl," "optionally substituted heterocyclic," and any other optionally substituted group as used herein, refer to groups that are substituted or unsubstituted by independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to:

-F, -Cl, -Br, -I,

-OH, protected hydroxy, alkoxy, oxo, thiooxo,

$-NO_2$, -CN, CF_3, N_3,

$-NH_2$, protected amino, -NH alkyl, -NH alkenyl, -NH alkynyl, -NH cycloalkyl, -NH -aryl, -NH -heteroaryl, -NH -heterocyclic, -dialkylamino, -diarylamino, -diheteroarylamino,

-O- alkyl, -O- alkenyl, -O- alkynyl, -O- cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocyclic,

-C(O)- alkyl, -C(O)- alkenyl, -C(O)- alkynyl, -C(O)- cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl,

$-CONH_2$, -CONH- alkyl, -CONH- alkenyl, -CONH- alkynyl, -CONH-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl,

$-OCO_2$- alkyl, $-OCO_2$- alkenyl, $-OCO_2$- alkynyl, $-OCO_2$- cycloalkyl, $-OCO_2$-aryl, $-OCO_2$-heteroaryl, $-OCO_2$-heterocycloalkyl, $-OCONH_2$, -OCONH- alkyl, -OCONH- alkenyl, -OCONH- alkynyl, -OCONH- cycloalkyl, -OCONH- aryl, -OCONH- heteroaryl, -OCONH- heterocycloalkyl,

-NHC(O)- alkyl, -NHC(O)- alkenyl, -NHC(O)- alkynyl, -NHC(O)-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, $-NHCO_2$- alkyl, $-NHCO_2$- alkenyl, $-NHCO_2$- alkynyl, $-NHCO_2$ -cycloalkyl, $-NHCO_2$-aryl, $-NHCO_2$- heteroaryl, $-NHCO_2$- heterocycloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, -NHC(O)NH- alkenyl, -NHC(O)NH- alkenyl, -NHC(O)NH- cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, $NHC(S)NH_2$, -NHC(S)NH- alkyl, -NHC(S)NH- alkenyl, -NHC(S)NH- alkynyl, -NHC(S)NH- cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, $-NHC(NH)NH_2$, -NHC(NH)NH- alkyl, -NHC(NH)NH- -alkenyl, -

NHC(NH)NH- alkenyl, -NHC(NH)NH- cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)- alkyl, -NHC(NH)- alkenyl, -NHC(NH)- alkenyl, -NHC(NH)- cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl,

-C(NH)NH- alkyl, -C(NH)NH- alkenyl, -C(NH)NH- alkynyl, -C(NH)NH-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl,

-S(O)- alkyl, - S(O)- alkenyl, - S(O)- alkynyl, - S(O)- cycloalkyl, - S(O)-aryl, - S(O)-heteroaryl, - S(O)-heterocycloalkyl $-SO_2NH_2$, $-SO_2NH$- alkyl, $-SO_2NH$- alkenyl, $-SO_2NH$- alkynyl, $-SO_2NH$- cycloalkyl, $-SO_2NH$- aryl, $-SO_2NH$- heteroaryl, $-SO_2NH$-heterocycloalkyl,

$-NHSO_2$- alkyl, $-NHSO_2$- alkenyl, - $NHSO_2$- alkynyl, $-NHSO_2$- cycloalkyl, - $NHSO_2$-aryl, $-NHSO_2$-heteroaryl, $-NHSO_2$-heterocycloalkyl,

$-CH_2NH_2$, $-CH_2SO_2CH_3$, -alkyl, -alkenyl, -alkynyl, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -cycloalkyl, -carbocyclic, -heterocyclic, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S- alkyl, -S- alkenyl, -S- alkynyl, -S- cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl.

It is understood that the aryls, heteroaryls, carbocyclics, heterocyclics, alkyls, and the like can be further substituted.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The term "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be either a patient or a healthy human.

The term "hydroxy activating group", as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxy group so that it will depart during synthetic procedures such as in a substitution or elimination reactions. Examples of hydroxy activating group include, but not limited to, mesylate, tosylate, triflate, p-nitrobenzoate, phosphonate and the like.

The term "leaving group," or "LG", as used herein, refers to any group that leaves in the course of a chemical reaction involving the group and includes but is not limited to halogen, brosylate, mesylate, tosylate, triflate, p-nitrobenzoate, phosphonate groups, for example.

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxy group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the are described generally in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxy protecting groups include benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, methoxycarbonyl, tert-butoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-furfuryloxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl, para-methoxybenzyldiphenylmethyl, triphenylmethyl(trityl), tetrahydrofuryl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2,2,2-triehloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, and the like. Preferred hydroxy protecting groups for the present invention are acetyl (Ac or -C(O)CH_3), benzoyl (Bz or -C(O)C_6H_5), and trimethylsilyl (TMS or -$Si(CH_3)_3$).

The term "amino protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the are described generally in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, and the like.

The term "protected amino," as used herein, refers to an amino group protected with an amino protecting group as defined above.

The term "alkylamino" refers to a group having the structure -N(R_aR_b), where R_a and R_b are independent H or alkyl.

The term "acyl" includes residues derived from acids, including but not limited to carboxylic acids, carbamic acids, carbonic acids, sulfonic acids, and phosphorous acids. Examples include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfinyls, aliphatic sulfinyls, aromatic phosphates and aliphatic phosphates. Examples of aliphatic carbonyls include, but are not limited to, acetyl, propionyl, 2-fluoroacetyl, butyryl, 2-hydroxy acetyl, and the like.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts, or salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, or magnesium

salts, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the compounds formed by the process of the present invention which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to afford any compound delineated by the formulae of the instant invention. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991); Bundgaard, et al., Journal of Drug Deliver Reviews, 8:1-38(1992); Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

This invention also encompasses pharmaceutical compositions containing, and methods of treating viral infections through administering, pharmaceutically acceptable prodrugs of compounds of the invention. For example, compounds of the

invention having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxyysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxy carbonyls, as outlined in Advanced Drug Delivery Reviews, 1996, 19, 1 15. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in J. Med. Chem. 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the

term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water, alcohol or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, polysorbate, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), mono- or di-glycerides, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, antioxidants, sweetening, flavoring, and perfuming agents. The liquid dosage form can also be encapsulated in a gelatin capsule, wherein a compound of the present invention can be dissolved in a pharmaceutically acceptable carrier containing, for example, one or more solubilizating agents (e.g., polysorbate 80 and mono and diglycerides), and other suitable excipients (e.g., an antioxidants such as ascorbyl palmitate, or a sweetening or flavoring agent).

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Immediate release forms are also contemplated by the present invention.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present invention, viral infections are treated or prevented in a subject, such as a human or another animal, by administering to the subject a therapeutically effective amount of a compound of the invention (or a pharmaceutically acceptable salt, ester or prodrug thereof), in such amounts and for such time as is necessary to achieve the desired result. The term "therapeutically effective amount" of a compound of the invention, as used herein, means a sufficient amount of the compound so as to decrease the viral load in a subject and/or decrease the subject's HCV symptoms. As is well understood in the medical arts a therapeutically effective amount of a compound of this invention will be at a reasonable benefit/risk ratio applicable to any medical treatment.

Antiviral Activity

An inhibitory amount or dose of the compounds of the present invention may range from about 0.1 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50 mg/Kg. Inhibitory amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

According to the methods of treatment of the present invention, viral infections are treated or prevented in a subject such as a human or lower mammal by administering to the subject an anti-hepatitis C virally effective amount or an inhibitory amount of a compound of the present invention, in such amounts and for

such time as is necessary to achieve the desired result. An additional method of the present invention is the treatment of biological samples with an inhibitory amount of a compound of composition of the present invention in such amounts and for such time as is necessary to achieve the desired result.

The term "anti-hepatitis C virally effective amount" of a compound of the invention, as used herein, means a sufficient amount of the compound so as to decrease the viral load in a biological sample or in a subject. As well understood in the medical arts, an anti-hepatitis C virally effective amount of a compound of this invention will be at a reasonable benefit/risk ratio applicable to any medical treatment.

The term "inhibitory amount" of a compound of the present invention means a sufficient amount to decrease the hepatitis C viral load in a biological sample or a subject. It is understood that when said inhibitory amount of a compound of the present invention is administered to a subject it will be at a reasonable benefit/risk ratio applicable to any medical treatment as determined by a physician. The term "biological sample(s)," as used herein, means a substance of biological origin intended for administration to a subject. Examples of biological samples include, but are not limited to, blood and components thereof such as plasma, platelets, subpopulations of blood cells and the like; organs such as kidney, liver, heart, lung, and the like; sperm and ova; bone marrow and components thereof; or stem cells. Thus, another embodiment of the present invention is a method of treating a biological sample by contacting said biological sample with an inhibitory amount of a compound or pharmaceutical composition of the present invention.

Upon improvement of a subject's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the disorder being

treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

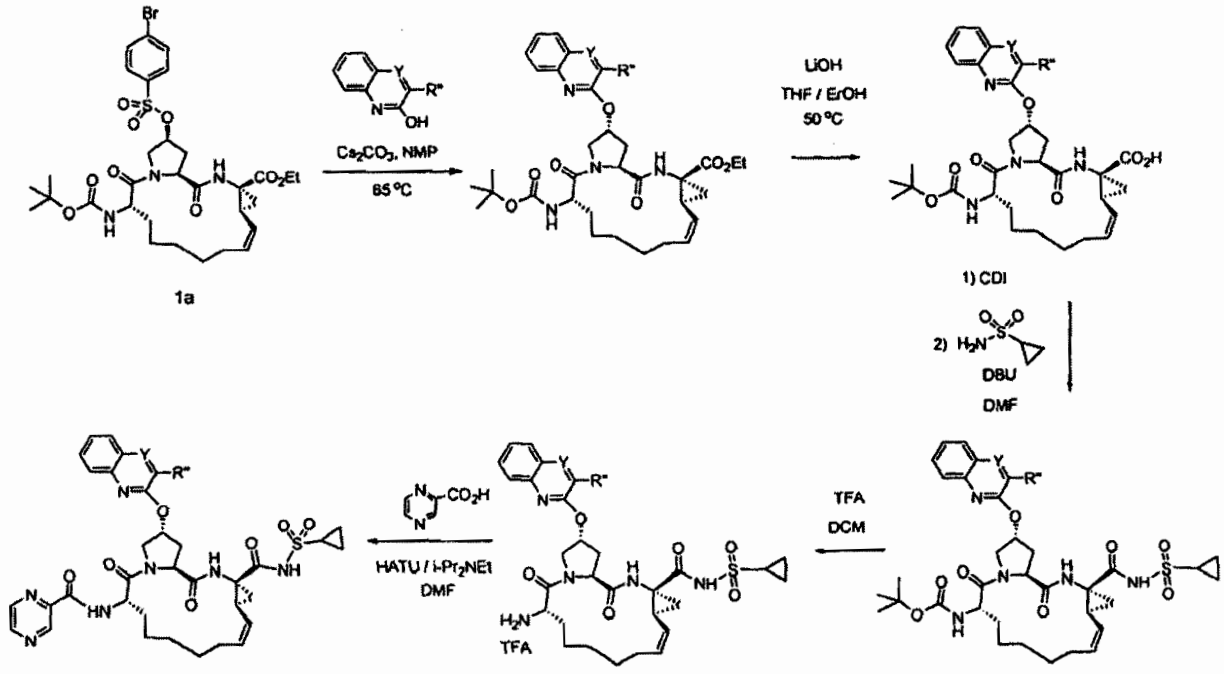
The total daily inhibitory dose of the compounds of this invention administered to a subject in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In one embodiment, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses. In another embodiment, the treatment regimen comprises administration to a patient in need of such treatment from about 25 mg to about 6000 mg of a compound(s) of this invention per day in single or multiple doses, either with or without a cytochrome P450 monooxygenase inhibitor such as ritonavir. The suitable daily dose for the co-administered cytochrome P450 monooxygenase inhibitor (e.g., ritonavir) can range, without limitation, from 10 to 200 mg. Preferably, a compound(s) of the present invention, or a combination of a compound(s) of the invention and ritonavir, is administered once daily or twice daily to achieve the desired daily dose amount. For instance, when used without ritonavir, a compound of the present invention can be administered to a patient twice a day with a total daily dose of 4000, 4200, 4400, 4600, 4800 or 5000 mg. For another instance, when used in combination with ritonavir, a compound of the present invention can be administered to a patient once or twice a day with a total daily dose of 200, 400, 600 or 800 mg, where the amount of ritonavir can be 25, 50 or 100 mg per administration.

Synthetic Methods

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared.

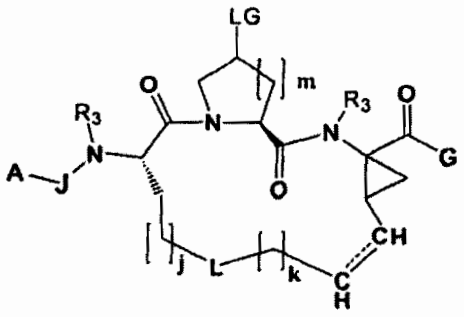
Definitions of variables in the structures in the schemes herein are commensurate with those of corresponding positions in the formulae delineated herein.

Scheme 1



Scheme 1 describes the synthesis of various compounds of the invention. The starting material was displaced at the leaving groups by reaction with a nucleophile to provide a nucleophile substituted macrocycle. Base hydrolysis of the ester to the acid was followed by coupling of a sulfonamide derivative. The protected nitrogen was then deprotected and substituted with another group.

In one aspect, the invention provides a method of producing a compound of formula I, comprising the step of reacting a compound of formula II:



(II);

wherein,

J is absent, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, -C(O)-, -O-C(O)-, - $N(R_3)$-C(O)-, -C(S)-, - $C(=NR_4)$-, -S(O)-, -$S(O_2)$-, or –$N(R_3)$-;

A is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl, optionally substituted arylalkyl, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted carbocyclic;

G is -E-R_5;

wherein E is absent; optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; or -O-, -S-, -$N(R_3)$-, -$N(R_3)S(O_p)$-, - $N(R_3)C(O)$-, -$N(R_3)$ $C(O)S(O_p)$-, -$OS(O_p)$-, -$C(O)S(O_p)$-, or -$C(O)N(R_3)S(O_p)$-;

p is 0, 1, or 2;

R_5 is H; optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;

Each R_3 and R_4 is independently selected at each occurrence from the following: optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclic; optionally substituted carbocyclic; or hydrogen;

L is absent or is selected from optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

j = 0, 1, 2, 3, or 4;

k= 0, 1, 2, or 3;

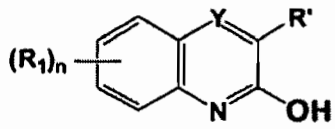
m = 0, 1, or 2;

n is 0, 1, 2, 3, or 4; and

$\equiv\equiv$ denotes a carbon-carbon single or double bond; and

LG is a leaving group;

with a compound of formula III:



(III);

wherein:

Each R_1 is independently selected from

(i) halogen, hydroxy, amino, -CN, -CF_3, -N_3, -NO_2, -OR_4, -SR_4, -SOR_4, -SO_2R_4, –$N(R_3)S(O)_2–R_4$, -$N(R_3)(SO_2)NR_3R_4$, -NR_3R_4, -$C(O)OR_4$, -$C(O)R_4$, -$C(O)NR_3R_4$, or -$N(R_3)C(O)R_4$;

(ii) optionally substituted aryl;

(iii) optionally substituted heteroaryl;

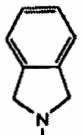
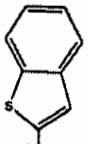
(iv) optionally substituted heterocyclic;

(v) optionally substituted carbocyclic; or

(vi) optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N;

R_3 and R_4 are each independently selected at each occurrence from the following: optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted heterocyclic; optionally substituted carbocyclic; or hydrogen;

Y is N or C(R");

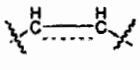
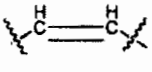
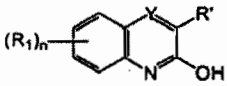
wherein if Y is N, then R' is optionally substituted heterocyclic, optionally substituted heteroaryl, optionally substituted aryl or optionally substituted carbocyclic, and comprises two or more fused rings, and wherein R' is not  or  ; further provided that said compound is not tert-butyl

(2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate;

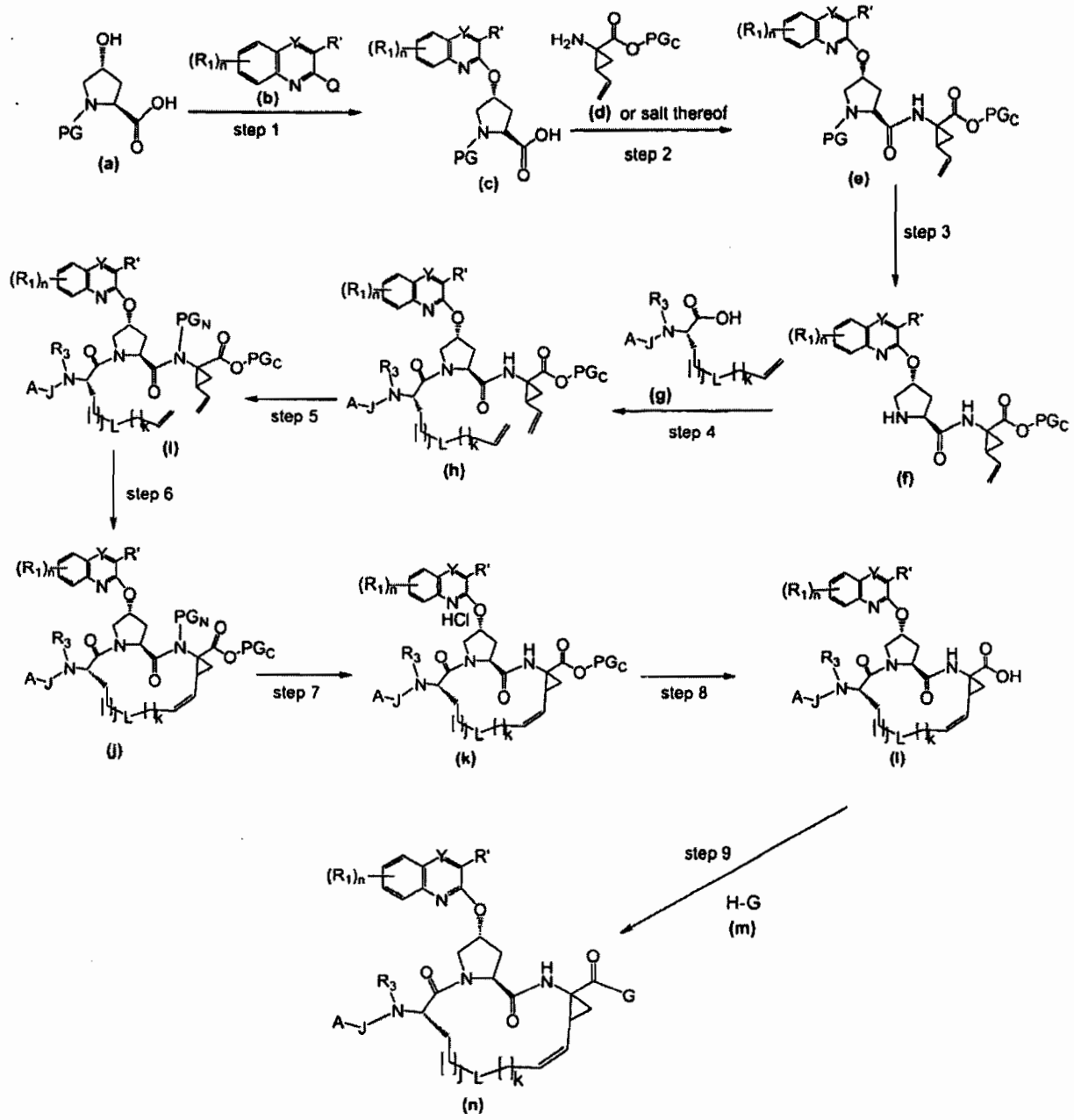
wherein if Y is –C(R")–, then R' and R" taken together with the carbon atoms to which they are attached form an aryl or heteroaryl ring, each said ring is optionally substituted;

wherein A, R_1, R' and/or R" can be taken together to form a ring;

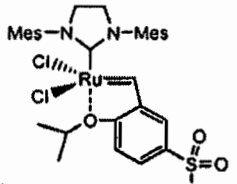
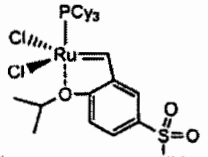
to thereby produce a compound of formula I or I'.

A compound of formula I can also be prepared according to the process depicted in Scheme 2, wherein A, J, L, G, Y, R' R_1, R_3, n, m, j, and k are defined hereinabove, and  is , and wherein Q is halogen or a leaving group, PG and PG_N are each independently an amino protecting group, and PG_C is a carboxylic acid protecting group. Compound **(b)** can be prepared by reacting  with a halogenation agent such as $POCl_3$. Non-limiting examples of amino protecting group include C_1-C_6alkoxycarbonyl (e.g., tert-butoxycarbonyl or Boc), carboxybenzyl, p-methoxybenzyl carbonyl, 9-fluorenylmethyloxycarbonyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, p-methoxyphenyl, benzoyl, or tosyl or other suitable sulfonamides. Non-limiting examples of carboxylic acid protecting group include C_1-C_6alkyl (e.g., tert-butyl, methyl or ethyl), benzyl, or silyl, all of which protect carboxylic acid moieties in the form of esters.

Scheme 2



In step 1, compound **(a)** reacts with compound **(b)** to form compound **(c)**, where the reaction can be conducted, as a non-limiting example, in the presence of sodium tert-butoxide or potassium tert-butoxide. Preferably, the reaction is conducted in the absence of lanthanum chloride. Also preferably, the yield of this reaction is at least 50%. More preferably, the yield of the reaction is at least 60%, 70%, or 80%. Highly preferably, the yield of the reaction is at least 90% or 95%. Preferred PG is C_1-C_6alkoxycarbonyl, such as tert-butoxycarbonyl or Boc.

Compound **(c)** can then be reacted with compound **(d)**, or a salt thereof such as TsOH salt, to form compound **(e)** (step 2), followed by de-protection of the amino group to create compound **(f)** or a salt thereof (e.g., HCl salt) (step 3). Preferred PG_C includes, but is not limited to, C_1-C_6alkyl such as ethyl. Compound **(f)** can then be reacted with compound **(g)** to form compound **(h)** (step 4), which is subsequently amino-protected to form compound **(i)** (step 5) and then subjected to ring-closing metathesis to form compound **(j)** (step 6). Preferred PG_N includes, but is not limited to, C_1-C_6alkoxycarbonyl, such as tert-butoxycarbonyl or Boc. General processes for ring-closing metathesis (RCM) are well known in the art. Preferred processes involve the use of transition metal catalysts, such as those described in U.S. Patent No. 6,921,753 and U.S. Patent Application Publication No. 20070043180. Non-limiting examples of suitable catalysts include Zhan Catalyst-1B (, where Mes is 2,4,6-trimethylphenyl; also known as Zhan-B) and Zhan Catalyst-1C (, where Cy is cyclohexyl), both of which are commercially available from Zannan Pharma, Ltd. (Shanghai, China). De-protection of the amino moiety in compound **(j)** leads to compound **(k)** (or its free-base) (step 7). In certain cases, compound **(h)** can directly undergo the ring-closing metathesis reaction to make compound **(k)** (or its free-base), without the amino protecting and de-protecting steps.

The carboxylic acid moiety in compound **(k)** can then be deprotected to form compound **(l)** (step 8), which reacts with compound **(m)** to form compound **(n)** (step 9). G in compound **(m)** is defined as –E-R_5, wherein E and R_5 are defined hereinabove.

A compound of formula I', as described herein, can be similarly prepared according to Scheme 2.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- , or as (D)- or (L)- for

amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al., Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, etc. delineated herein are for purposes of illustration only and one of ordinary skill in the art will recognize that variation of the reaction conditions can produce the desired bridged macrocyclic products of the present invention. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds of this invention may be modified by appending various functionalities via any synthetic means delineated herein to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

Examples

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not to limit the scope of the invention. The following examples can be prepared according to either Scheme 1 or Scheme 2 as described above. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1. tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 1a. (2S,6S,13aS,14aR,16aS,Z)-ethyl 2-(4-bromophenylsulfonyloxy)-6-(tert-butoxycarbonylamino)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate

A solution of (2S,6S,13aS,14aR,16aS,Z)-ethyl 6-(tert-butoxycarbonylamino)-2-hydroxy-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate and DABCO in toluene was stirred at room temperature (rt). To this solution was added a solution of 4-bromobenzene-1-sulfonyl chloride in toluene. After the addition was complete the reaction mixture was quenched with 10% aqueous sodium carbonate and the mixture stirred for 15 min. Tetrahydrofuran was added and the mixture was washed with 0.5 M HCl, water, and then saturated aqueous sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure and dried to provide the title compound.

Example 1b.

(2R,6S,13aR,14aR,16aS,Z)-ethyl 6-(tert-butoxycarbonylamino)-2-(3-chloroquinoxalin-2-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate (1b)

To a solution of compound 1a (15.0 g, 21.0 mmol) in NMP (55 ml) was added 3-chloroquinoxalin-2-ol (4.56 g, 25.3 mmol) followed by Cs_2CO_3 (17.1 g, 52.6 mmol). The resulting mixture was heated to 70°C for 18 hours. The reaction mixture was cooled to room temperature, and then partitioned between ethyl acetate (300 ml) and 1 N HCl (100 ml). The organic layer was separated, washed with brine (100 ml), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain the crude product as a solid. The solid was purified by column chromatography on silica gel (EtOAc-hexane gradient) to obtain the title compound as a solid (6.2 g., 45% yield); MS(ESI): *m/z* = 656.3 [M+H]

Example 1c.

(2R,6S,13aR,14aR,16aS,Z)-ethyl 6-(tert-butoxycarbonylamino)-5,16-dioxo-2-(3-phenylquinoxalin-2-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate(1c)

To a microwave vessel was added the product from 1b (700 mg. 1.07 mmole), 2-(tributylstannyl)benzo[d]thiazole (905 mg., 2.13 mmole), palladium-tetrakis(triphenylphosphine) (113 mg., .11 mmole) and dioxane (5 ml.). The vessel was evacuated and nitrogen introduced, which was repeated twice. The mixture was reacted in a microwave reactor at 110 degrees C for 1 hr. The reaction was diluted with MeCN and washed 3 times with hexane. The MeCN layer was evaporated and purified by column chromatography on silica gel (CHCl3-EtOAc gradient) to obtain the title compound (692 mg., 86% yield). MS(ESI): *m/z* = 755.2 [M+H].

Example 1d.

(2R,6S,13aR,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-6-(tert-butoxycarbonylamino)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid(1d)

To a solution of the product of Example 1c (692 mg, 0.95 mmol) in tetrahydrofuran (5 ml) / ethanol (2.5 ml) / water (2.5 ml.) was added lithium hydroxide monohydrate (154 mg., 3.7 mmole). The resulting mixture was heated to 50°C for one hour and cooled to room temperature. The organic solvents were mostly removed under reduced pressure, EtOAc (100 ml.) was added and then washed with 1 N HCl (30 ml.). The organic layer was separated, washed with brine (20 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford 666 mg of product 1d.

Example 1f.

To a solution of product of Example 1d (666 mg, 0.92mmol) in 1,2-dichloroethane (9 ml) was added 1,1'-carbonyldiimidazole (246 mg, 1.52 mmol). The reaction mixture was stirred at 40 degrees C for 2 hours. To the above solution was then added the cyclopropanesulfonamide (184 mg, 1.52 mmol) followed by DBU (0.23ml, 1.52 mmol). The resulting mixture was stirred at 40 degrees C for 1 hour. The reaction mixture was diluted with EtOAc (100 ml) and washed with 1 N HCl (20 ml.) then saturated sodium chloride (20 ml). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue

was purified by column chromatography on silica gel ($CHCl_3$ /EtOAc gradient) to obtain the title compound (322 mg, 38% yield). MS (ESI): *m/z* = 830.0 [M+H].

Example 2. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(isonicotinamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 2a.
(2R,6S,13aS,14aR,16aS,Z)-6-amino-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

To a suspension of the product of Example 1 (320 mg, 0.39 mmol) in EtOAc (3 mL) was added a 4 M solution of HCl in dioxane (1.9 mL, 7.7 mmol). The reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure and the resulting solid dried under vacuum to provide (2R,6S,13aR,14aR,16aS,Z)-6-amino-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, Hydrochloric Acid (295 mg, quant. yield).

Example 2b.

To a solution of Example 2a (28 mg, 0.037 mmol) in dichloromethane (0.5 mL) was added isonicotinic acid (5.0 mg, 0.040 mmol), HATU (16.7 mg, 0.044 mmol) and diisopropylethylamine (0.021 mL, 0.12 mmol). The reaction mixture was stirred at 25 °C for 2 hrs. and evaporated. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound. MS (ESI): *m/z* = 835.0 [M+H].

Example 3. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(2-fluorobenzamido)-5,16-dioxo-

1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 3 was prepared according to the procedure utilized for the preparation of Example 2, replacing isonicotinic acid with 2-fluorobenzoic acid. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound.

MS (ESI): *m/z* = 851.9 [M+H].

Example 4. N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide

Example 4 was prepared according to the procedure utilized for the preparation of Example 2, replacing isonicotinic acid with 5-methylisoxazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound.

MS (ESI): *m/z* = 838.9 [M+H].

Example 5. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 5 was prepared according to the procedure utilized for the preparation of Example 2, replacing isonicotinic acid with 5-methylpyrazine-2-carboxylic acid. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound.

MS (ESI): *m/z* = 849.9 [M+H].

Example 6. N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)isoxazole-5-carboxamide

Example 6 was prepared according to the procedure utilized for the preparation of Example 2, replacing isonicotinic acid with isoxazole-5-carboxylic acid. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound. MS (ESI): *m/z* = 824.9 [M+H].

Example 7. N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)thiazole-4-carboxamide

Example 7 was prepared according to the procedure utilized for the preparation of Example 2, replacing isonicotinic acid with thiazole-4-carboxylic acid. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound. MS (ESI): *m/z* = 840.9 [M+H].

Example 8. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 8 was prepared according to the procedure utilized for the preparation of Example 2, replacing isonicotinic acid with 1-methyl-1H-pyrazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound. MS (ESI): *m/z* = 838.0 [M+H].

Example 9. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 9 was prepared according to the procedure utilized for the preparation of Example 2, replacing isonicotinic acid with pyrimidine-4-carboxylic acid.

Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound. MS (ESI): *m/z* = 835.9[M+H].

Example 10. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1,3-dimethyl-1H-pyrazole-4-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 10 was prepared according to the procedure utilized for the preparation of Example 2, replacing isonicotinic acid with 1,3-dimethyl-1H-pyrazole-4-carboxylic acid. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound. MS (ESI): *m/z* = 852.0[M+H].

Example 11. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(3-fluorobenzamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 11 was prepared according to the procedure utilized for the preparation of Example 2, replacing isonicotinic acid with 3-fluorobenzoyl chloride. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound. MS (ESI): *m/z* = 838.0 [M+H].

Example 12. tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 12a. tert-butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-hydroxy-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

To a solution of tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(9H-fluoren-9-ylideneaminooxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate (20.0 g, 26.8 mmol) in acetic acid (80 ml) stirring at 40 °C was zinc dust (10.52 g, 166 mmol). After the addition was complete the reaction mixture was stirred at 40 °C for 1 hour. The mixture was then cooled to room temperature, diluted with toluene, and filtered through Celite. The mother liquor was washed with water, 1 N HCl, and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and filtered. The filtrate was then evaporated under reduced pressure to provide the title compound 12a (14.8 g, 97% yield).

Example 12b. tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-chloroquinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate.

A solution of compound 12a (10.0 g, 17.6 mmol), cesium carbonate (17.2, 52.8 mmol), and 2,3-dichloroquinoxaline (3.50 g, 17.6 mmol) in dimethylformamide (175 ml) was heated to 70°C for 18 hours. An additional portion of 2,3-dichloroquinoxaline (0.70 g, 3.5 mmol) was added and the reaction mixture was stirred at 70 °C for 18 hours. The reaction mixture was cooled to room temperature, and then partitioned between ethyl acetate (300 ml) and 1 N HCl (100 ml). The organic layer was separated, washed with brine (100 ml), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain the crude product as a solid. The solid was purified by column chromatography on silica gel (EtOAc-hexane gradient) to obtain the title compound as a solid (4.7 g., 37% yield); MS(ESI): *m/z* = 731.1 [M+H].

Example 12c.

To a microwave vessel was added the product from 12b (0.40 g 0.547 mmole), benzofuran-2-yltributylstannane (0.245 g., 0.602 mmole), tris(dibenzylideneacetone)dipalladium(0) (50 mg, 0.055 mmol), 1,3,5,7-tetramethyl-

2,4,8-trioxa-6-phenyl-6-phospha-adamantane (32 mg, 0.11 mmol), sodium bicarbonate (46 mg, 0.547 mmol) and dioxane (3 mL). The vessel was evacuated and nitrogen introduced. The mixture was reacted in a microwave reactor at 110 degrees C for 1 hr. The reaction mixture was diluted with ethyl acetate, washed with 1 N HCl followed by saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The mixture was filtered through Celite and evaporated under reduced pressure. The residue was dissolved in acetonitrile and washed with hexane (five times) and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$-EtOAc gradient) to obtain the title compound (386 mg., 87% yield). MS(ESI): *m/z* = 813.0 [M+H].

Example 13. N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide.

Example 13a.

(2R,6S,13aS,14aR,16aS,Z)-6-amino-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride

The product of Example 12 (0.386 g, 0.475 mmol) was dissolved in a mixture of ethyl acetate (2.4 mL) and 4 N HCl in dioxane (2.4 mL) and stirred at room temperature for one hour. The mixture was then evaporated under reduced pressure to provide the title compound (0.338 mg, 100% yield).

Example 13b.

A mixture of the product of Example 13a (30 mg, 0.040 mmol), 5-methylisoxazole-3-carboxylic acid (5.1 mg, 0.040 mmol), N-ethyl-N-isopropylpropan-2-amine (15.6 mg, 0.12 mmol), and HATU (18.3 mg, 0.048 mmol) in dichloromethane (0.5 mL) was stirred at room temperature for one hour and then evaporated. Purification of the

crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound (14 mg, 42% yield). MS (ESI): *m/z* = 822.0[M+H].

Example 14. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 14 was prepared according to the procedure utilized for the preparation of Example 13, replacing 5-methylisoxazole-3-carboxylic acid with 5-methylpyrazine-2-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 833.0 [M+H].

Example 15. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 15 was prepared according to the procedure utilized for the preparation of Example 13, replacing 5-methylisoxazole-3-carboxylic acid with 1-methyl-1H-pyrazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 821.1 [M+H].

Example 16. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 16 was prepared according to the procedure utilized for the preparation of Example 13, replacing 5-methylisoxazole-3-carboxylic acid with 1,5-dimethyl-1H-pyrazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 835.0 [M+H].

Example 17. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzofuran-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 17 was prepared according to the procedure utilized for the preparation of Example 13, replacing 5-methylisoxazole-3-carboxylic acid with pyrimidine-4-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 818.9 [M+H].

Example 18. tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 18 was prepared according to the procedure utilized for the preparation of Example 12, replacing benzofuran-2-yltributylstannane with benzo[b]thiophen-2-yltributylstannane. Purification of the crude material via silica gel chromatography eluting with hexane/ethyl acetate (1:2) provided the title compound.
MS (ESI): *m/z* = 829.1 [M+H].

Example 19. N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide

Example 19a.

(2R,6S,13aS,14aR,16aS,Z)-6-amino-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride

The product of Example 18 (0.296 g, 0.357 mmol) was dissolved in a mixture of ethyl acetate (1.7 mL) and 4 N HCl in dioxane (1.7 mL) and stirred at room temperature for one hour. The mixture was then evaporated under reduced pressure to provide the title compound (0.262 mg, 96% yield).

Example 19b.

A mixture of the product of Example 19a (30 mg, 0.039 mmol), 5-methylisoxazole-3-carboxylic acid (5.0 mg, 0.039 mmol), N-ethyl-N-isopropylpropan-2-amine (15.2 mg, 0.118 mmol), and HATU (17.9 mg, 0.047 mmol) in dichloromethane (0.5 mL) was stirred at room temperature for one hour and then evaporated. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound (18 mg, 53% yield). MS (ESI): *m/z* = 837.9[M+H].

Example 20. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 20 was prepared according to the procedure utilized for the preparation of Example 19, replacing 5-methylisoxazole-3-carboxylic acid with 5-methylpyrazine-2-

carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 848.7 [M+H].

Example 21. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 21 was prepared according to the procedure utilized for the preparation of Example 19, replacing 5-methylisoxazole-3-carboxylic acid with 1-methyl-1H-pyrazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 836.9 [M+H].

Example 22. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 22 was prepared according to the procedure utilized for the preparation of Example 19, replacing 5-methylisoxazole-3-carboxylic acid with 1,5-dimethyl-1H-pyrazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 851.0 [M+H].

Example 23. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[b]thiophen-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 23 was prepared according to the procedure utilized for the preparation of Example 19, replacing 5-methylisoxazole-3-carboxylic acid with pyrimidine-4-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound. .

MS (ESI): *m/z* = 835.1 [M+H].

Example 24. tert-butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 24a.

(2S,6S,13aS,14aR,16aS,Z)-ethyl 2-(4-bromophenylsulfonyloxy)-6-(tert-butoxycarbonylamino)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate

A solution of (2S,6S,13aS,14aR,16aS,Z)-ethyl 6-(tert-butoxycarbonylamino)-2-hydroxy-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate (22.1 g, 44.8 mmol) and DABCO (8.5 g, 76.7 mmol) in toluene (88 mL) was stirred at room temperature. To this solution was added a solution of 4-bromobenzene-1-sulfonyl chloride 17.2 g, 67.2 mmol) in toluene (44 mL). After the addition was complete the reaction mixture was quenched with 10% aqueous sodium carbonate (110 mL) and the mixture stirred for 15 min. Tetrahydrofuran (44 mL) was added and the mixture was washed with 0.5 M HCl, water, and then saturated aqueous sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure and dried to provide the title compound (27.7 g, 87% yield), which was used without further purification.

Example 24b

(2R,6S,13aS,14aR,16aS,Z)-ethyl 6-(tert-butoxycarbonylamino)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate

To a solution of the compound of Example 24a (11.0 g, 15.4 mmol) in NMP (100 ml) was added phenanthridine-6(*5H*)-one (3.15 g, 16.2 mmol) followed by Cs_2CO_3 (7.53 g, 23.1 mmol). The resulting mixture was heated to 55°C for four hours. The reaction mixture was cooled to room temperature, and then partitioned between ethyl acetate (250 ml) and 5 % aqueous sodium bicarbonate solution (200 ml). The organic layer was separated, washed with 5 % aqueous sodium bicarbonate solution (200 ml) followed by brine (150 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the crude product as a solid. The solid was then dissolved in methyl t-butyl ether (200 ml), the resulting suspension was stirred at room temperature for 1 hour and filtered. The filtrate contained the desired product was concentrated under reduced pressure to obtain 7.95 g of product 24b as a solid; MS-DCI / NH_3: 671 $(M+H)^+$.

Example 24c

(2R,6S,13aS,14aR,16aS,Z)-6-(tert-butoxycarbonylamino)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid (24c)

To a solution of the product of Example 24b (7.8 g, 11.6 mmol) in tetrahydrofuran (40 ml) /ethanol (40 ml) was added an aqueous lithium hydroxide solution (0.84 g of lithium hydroxide in 40 ml of H_2O). The resulting mixture was heated to 50°C for two hours and cooled to room temperature. The organic solvents were mostly removed under reduced pressure, and the resulting residue was acidified with 10 % citric acid aqueous solution and extracted with ethyl acetate (200 ml). The organic layer was separated, washed with brine (200 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a light yellow solid, which was further dried in a vacuum oven at 45°C for 18 h to afford 7.5 g of product 24c as a light yellow solid; MS-DCI / NH_3: 643 $(M+H)^+$.

Example 24d.

tert-butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

To a solution of product of Example 24c (7.46 g, 11.6 mmol) in DMF (80 ml) was added 1,1'-carbomyldiimidazole (5.64 g, 34.8 mmol). The reaction mixture was stirred at room temperature for 6 hours. To the above solution was then added cyclopropanesulfonamide (4.21 g, 34.8 mmol) followed by DBU (5.73 ml, 36.0 mmol). The resulting mixture was stirred at room temperature for 14 hours. To the reaction mixture was added EtOAc (200 ml),10 % aqueous citric acid solution (200 ml) and saturated aqueous sodium chloride (50 ml). The organic layer was separated, washed with saturated aqueous sodium chloride (100 ml), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate / heptane gradient) to obtain the title compound as a white solid (6.40 g, 74% yield). MS (ESI): *m/z* = 746.1 [M+H].

Example 25. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phen anthridin-6-yloxy)-6-(pyrazine-2-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 25a

(2R,6S,13aS,14aR,16aS,Z)-6-amino-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide hydrochloride

To a suspension of the product of Example 24 (0.35 g, 0.47 mmol) in acetonitrile (5 mL) was added a 4 M solution of HCl in dioxane (0.6 mL, 2.4 mmol). The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure and the resulting solid dried under vacuum to provide the title compound (0.32 g, quant. yield).

Example 25b.
(2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyrazine-2-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

To a solution of Example 25a (320 mg, 0.47 mmol) in dimethylformamide (5 mL) was added pyrazinecarboxylic acid (0.065 g, 0.52 mmol), HATU (214 mg, 0.56 mmol) and diisopropylethylamine (0.2 mL, 1.18 mmol). The reaction mixture was stirred at 25 °C for 2 h and then partitioned between 5% aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was purified by crystallization from ethyl acetate / hexane to give the desired product (155 mg, 44% yield) as an off-white solid. MS (ESI): *m/z* = 752.0 [M+H].

Example 26. Cyclopentyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 26a
(2R,6S,13aS,14aR,16aS,Z)-ethyl 6-(cyclopentyloxycarbonylamino)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate

Example 26a was prepared according to the procedure utilized for the preparation of Example 24b, replacing the compound of Example 24a with compound (2S,6S,13aS,14aR,16aS,Z)-ethyl 2-(4-bromophenylsulfonyloxy)-6-(cyclopentyloxycarbonylamino)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate, to provide the title compound.
MS (DCI/NH_3): *m/z* = 683.0 [M+H]

Example 26b

(2R,6S,13aS,14aR,16aS,Z)-6-(cyclopentyloxycarbonylamino)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid

Example 26b was prepared according to the procedure utilized for the preparation of Example 24c, replacing compound 24b with compound 26a, to provide the title compound.

MS (DCI/NH_3): *m/z* = 655.0 [M+H].

Example 26c.

Cyclopentyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

The title compound of Example 26 was prepared according to the procedure utilized for the preparation of Example 24, replacing compound 24c with compound 26b, to provide the title compound.

MS (DCI/NH_3): *m/z* = 758.0 [M+H].

Example 27. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 27 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with 5-methyl-1H-pyrazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound.

MS (ESI): *m/z* = 754.2 [M+H].

Example 28. N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide

Example 28 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with 5-methylisoxazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatrography eluting with acetonitrile/water/TFA provided the title compound.

MS (ESI): *m/z* = 755.1 [M+H].

Example 29. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 29 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with 5-methylpyrazine-2-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.

MS (ESI): *m/z* = 766.1 [M+H].

Example 30. N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)thiazole-5-carboxamide

Example 30 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with thiazole-5-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.

MS (ESI): *m/z* = 757.1 [M+H].

Example 31. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-fluorobenzamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 31 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with 2-fluorobenzoic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 768.1 [M+H].

Example 32. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyridazine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 32 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with pyridazine-4-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 752.1 [M+H].

Example 33. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 33 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with pyrimidine-4-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 752.1 [M+H].

Example 34. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 34 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with 1-methyl-1H-pyrazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 754.2 [M+H].

Example 35. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-hydroxy-2-methylpropanamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 35 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with 2-hydroxy-2-methylpropanoic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.
MS (ESI): *m/z* = 732.2 [M+H].

Example 36. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 36 was prepared according to the procedure utilized for the preparation of Example 25, replacing 2-pyrazinecarboxylic acid with 1,5-dimethyl-1H-pyrazole-3-carboxylic acid. Purification of the crude material via reverse phase chromatography eluting with acetonitrile/water/TFA provided the title compound.

MS (ESI): *m/z* = 768.1 [M+H].

Example 37. Cyclopentyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(2-fluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a, 14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 37a.

5'-Fluoro-2'-nitrobiphenyl-2-carboxylate

To a microwave vessel was added 2-(methoxycarbonyl)phenylboronic acid (63.4 mg, 0.352 mmol), 2-bromo-4-fluoro-1-nitrobenzene (77 mg, 0.35 mmol), diacetoxypalladium (0.93 mg, 4.1 μmol) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (3.47 mg, 8.45 μmol). Ethanol (1760 μl) and sodium carbonate (176 μl, 0.352 mmol) were added and the mixture was reacted in a microwave reactor at 100 °C for 30 min. The reaction mixture was diluted with dichloromethane, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (eluant: 9:1 hexane/ethyl acetate) to provide methyl 5'-fluoro-2'-nitrobiphenyl-2-carboxylate (37a, 54.8 mg, 0.199 mmol, 56.6 % yield).

Example 37b.

2-fluoro-5-hydroxyphenanthridin-6(5H)-one

To a solution of the product of Example 37a (methyl 5'-fluoro-2'-nitrobiphenyl-2-carboxylate, 56.79 mg, 0.206 mmol) in methanol (9 mL) was added 10% palladium on carbon (15.6 mg, 0.015 mmol). The flask was fitted with a hydrogen balloon and de-gassed three times with hydrogen. The reaction mixture was stirred, diluted with dimethylformamide, and filtered. The filtrate was concentrated to provide 2-fluoro-5-hydroxyphenanthridin-6(5H)-one (37b, 46.36 mg, 0.202 mmol, 98 % yield).

Example 37c.

2-Fluorophenanthridin-6(5H)-one

A mixture of the product of Example 37b (2-fluoro-5-hydroxyphenanthridin-6(5H)-one, 46.4 mg, 0.202 mmol), acetic acid (3 mL), and zinc (99 mg, 1.517 mmol) was heated under reflux at 130 ^{o}C for 1 h. The mixture was diluted with dimethylformamide and filtered and the filtrate was concentrated to give a tan solid (100 mg). The solid was partitioned between dichloromethane/dimethylformamide (2/1, 50 mL) and sodium carbonate (10 ml). The organic layer was washed with water (2 x 10ml) and concentrated to provide 2-fluorophenanthridin-6(5H)-one (37c, 38.2 mg, 88% yield).

Example 37d.

(2R,6S,13aS,14aR,16aS,Z)-ethyl 6-(cyclopentyloxycarbonylamino)-2-(2-fluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate

Example 37d was prepared according to the procedure used for the preparation of Example 37b, substituting (2S,6S,13aS,14aR,16aS,Z)-ethyl 2-(4-bromophenylsulfonyloxy)-6-(cyclopentyloxycarbonylamino)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate for 1a, and substituting 2-fluorophenanthridin-6(5H)-one (80c) for phenanthridin-6(5H)-one, to provide the title compound in 48% yield.

Example 37e.

(2R,6S,13aS,14aR,16aS,Z)-6-(cyclopentyloxycarbonylamino)-2-(2-fluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid

Example 37e was prepared according to the procedure used for the preparation of Example 67c, substituting the product of Example 37d for the product of Example 24b.

Example 37f.

Cyclopentyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(2-fluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a, 14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbama

The compound of Example 37 was prepared according to the procedure used for the preparation of Example 24, substituting the product of Example 37e for the product of Example 24c (14.6 mg, 78% yield).

MS (ESI): *m/z* = 776.1 [M+H].

Example 38. tert-Butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(2,9-difluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a, 15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 38a.

Methyl 5,5'-difluoro-2'-nitrobiphenyl-2-carboxylate

To 2-bromo-4-fluoro-1-nitrobenzene (185.16 mg, 0.842 mmol) was added Pd_2dba_3 (23.12 mg, 0.025 mmol) and copper powder (271 mg, 4.26 mmol). Dimethylsulfoxide (2.3 ml) and methyl 2-bromo-4-fluorobenzoate (0.122 ml, 0.842 mmol) were added and the mixture was stirred vigorously at 100 °C for 2 h. The mixture was cooled to room temperature, diluted with ethyl acetate (20 ml), and filtered. The filtrate was washed with water and dried (anhydrous Na_2SO_4) and concentrated to give a yellow oil (279.8 mg). This oil was utilized without purification for the preparation of Example 38b.

Example 38b.

2,9-Difluoro-5-hydroxyphenanthridin-6(5H)-one

To the product of Example 38a (279.8 mg) was added methanol (7.5 mL) and 10% palladium on carbon (76 mg, 0.071 mmol). The flask was fitted with a hydrogen balloon and the mixture was de-gased and back-filled with hydrogen three times. The

mixture was stirred under hydrogen for 16 h, diluted with dimethylformamide and filtered. The filtrate was concentrated to give a red solid. This material was triturated with dichloromethane/hexane (9/1) and filtered to provide the title compound (Example 38b, 43.15 mg, 0.175 mmol, quantitative yield).

Example 38c.

2,9-Difluorophenanthridin-6(5H)-one

Example 38c was prepared according to the procedure used for the preparation of Example 37c, substituting the product of Example 38b for the product of Example 80b.

Example 38d.

(2R,6S,13aS,14aR,16aS,Z)-ethyl 6-(tert-butoxycarbonylamino)-2-(2,9-difluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate

Example 38d was prepared according to the procedure used for the preparation of Example 24c, substituting the product of Example 38c for phenanthridine-6(*5H*)-one.

Example 38e.

(2R,6S,13aS,14aR,16aS,Z)-6-(tert-butoxycarbonylamino)-2-(2,9-difluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylic acid

Example 38e was prepared according to the procedure used for the preparation of Example 24c, substituting the product of Example 38d for the product of Example 24b.

Example 38f.

tert-Butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(2,9-difluorophenanthridin-6-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,

15,16,16a- hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 38 was prepared according to the procedure used for the preparation of Example 24, substituting the product of Example 38e for the product of Example 24c.
MS (ESI): *m/z* = 782.1 [M+H].

Example 39. tert-butyl (2R,6S,13aR,14aR,16aS)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Argon degassed ethanol (0.8 ml) was added to the product of Example 24 (79.1 mg, 0.106 mmol) and Crabtree's Catalyst (3.45 mg, 4.24 μmol) (4 mole %) in a 4 mL pressure bottle. The vessel was sparged three times with argon and then pressurized with hydrogen (50 psi). The mixture was heated to 50 °C under hydrogen and stirred for 4.5 hr at 50 °C.
The reaction mixture was concentrated and purified by reverse phase chromatography, eluting with an acetonitrile(1% TFA)/water gradient to provide the title compound as a white solid (70.41 mg, 0.094 mmol, 89 % yield).
MS (ESI): *m/z* = 748.2 [M+H].

Example 40. Cyclopentyl (2R,6S,13aR,14aR,16aS)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 40 was prepared according to the procedure utilized for the preparation of Example 39, replacing the product of Example 24 with the product of Example 26.
MS (ESI): *m/z* = 760.2 [M+H].

Example 41. tert-Butyl (2R,6S,13aR,14aR,16aS)-5,16-dioxo-2-(phenanthridin-6-yloxy)-14a-(thiophen-2-ylsulfonylcarbamoyl)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

Example 41 was prepared according to the procedure utilized for the preparation of Example 24, replacing cyclopropanesulfonamide with thiophene-2-sulfonamide. MS (ESI): *m/z* = 788.0 [M+H].

Example 42. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-methylpyrimidine-5-carboxamido)-5,16-dioxo-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 42a.

(S)-2-(2-methylpyrimidine-5-carboxamido)non-8-enoic acid.

Boc–2(*S*)-amino-non-8-eoic acid dicyclohexylamine salt can be suspended in isopropyl acetate, washed several times with an aqueous citric acid solution and then once with water. The washed product, concentrated and then re-diluted in isopropyl acetate, can be reacted with HCl to produce 2(*S*)-amino-non-8-eoic acid HCl salt. 2-Methylpyrimidine-5-carboxylic acid, N,N'-disuccinimidyl carbonate, and N,N-dimethylaminopyridine can be dissolved in N-methyl-2-pyrrolidone (NMP) and stirred. 2(*S*)-Amino-non-8-eoic acid HCl salt is subsequently added, followed by triethylamine, and stirred to produce the title compound of Example 42a, which can be crystallized out by adding HCl followed by water.

Example 42b.

(1R,2S)-ethyl-1-((2S,4R)-N-(tert-butoxycarbonyl)-1-((S)-2-(2-methylpyrimidine-5-carboxamido)non-8-enoyl)-4-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate

(2S,4R)-N-Boc-4-hydroxyproline can be reacted with 2-chloro-3-(thiophen-2-yl)quinoxaline in NMP, in the presence of sodium *t*-butoxide, to produce (2S,4R)-1-(tert-butoxycarbonyl)-4-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)pyrrolidine-2-carboxylic acid. Methyl tertiary butyl ether (MTBE) and water can then be added. The aqueous layer is separated, washed, and then HCl is added, followed by

extraction with MTBE. The extracted product can be mixed with diisopropylethylamine (DIPEA) and HATU (CAS # 148893-10-1), and then reacted with (1R,2S)-ethyl-1-amino-2-vinylcyclopropanecarboxylate tosylate salt in dimethylformide (DMF) and toluene. The reaction produces (2S,4R)-tert-butyl 2-((1R,2S)-1-(ethoxycarbonyl)-2-vinylcyclopropylcarbamoyl)-4-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)pyrrolidine-1-carboxylate, which can be extracted with MTBE and washed with HCl, further extracted, washed, dried, and dissolved in 2-propanol.

HCl can be added to the 2-propanol solution to produce (1R,2S)-ethyl 1-((2S,4R)-4-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, which can be crystallized out by neutralizing with NaOH.

(1R,2S)-ethyl 1-((2S,4R)-4-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, the title compound of Example 42a, N-hydroxy-5-norbornene-2,3-dicarboximide, and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride can be mixed and stirred in DMF for hours, followed by addition of N,N-dimethylethylene diamine. The reaction produces (1R,2S)-ethyl 1-((2S,4R)-1-((S)-2-(2-methylpyrimidine-5-carboxamido)non-8-enoyl)-4-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, which can be dissolved in isopropyl acetate and extracted with aqueous H_3PO_4, and then extracted with aqueous K_2HPO_4. The product can be reacted with di-tert-butyldicarbonate in the presence of dimethylaminopyridine, followed by extraction with a mixture of a citric acid solution and a sodium chloride solution, to produce the title compound of Example 42b.

Example 42c.

(2R,6S,13aS,14aR,16aS,Z)-ethyl-6-(2-methylpyrimidine-5-carboxamido)-5,16-dioxo-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate hydrochloride

The product of Example 42b can be subject to ring-closing metathesis in the presence of Zhan-B catalyst in toluene to produce (2R,6S,13aS,14aR,16aS,Z)-15-tert-butyl

14a-ethyl 6-(2-methylpyrimidine-5-carboxamido)-5,16-dioxo-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-2,3,5,6,7,8,9,10,11,13a,14,14a,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a,15(1H)-dicarboxylate. The catalyst can be quenched with imidazole after the reaction.

The ring-closed product in toluene can be solvent switched to acetonitrile, followed by addition of hydrogen chloride in dioxane and heated to produce the title compound of Example 42c.

Example 42d.
(2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-methylpyrimidine-5-carboxamido)-5,16-dioxo-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

The isolated product of Example 42c can be mixed with tetrahydrofuran, water and $LiOH \cdot H_2O$, and then heated and stirred. The reaction mixture can be later cooled, added with aqueous H_3PO_4, aqueous NaCl and 2-methyl tetrahydrofuran, and the organic layer is separated, washed and filtered. MeCN is added to the concentrated organic layer, heated and cooled, and then diethylamine is added. The slurry is heated and cooled to form (2R,6S,13aS,14aR,16aS,Z)-6-(2-methylpyrimidine-5-carboxamido)-5,16-dioxo-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate diethylamine salt, which can be further washed and dried.

The diethylamine salt can be mixed with tetrahydrofuran, 2-methyl tetrahydrofuran and aqueous H3PO4. The organic layer is separated, washed with aqueous NaCl, and then concentrated and/or purified. The product can be subsequently mixed with NMP, followed by addition of carbonyldiimidazole (CDI) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Cyclopropylsulfonamide can be subsequently added. The reaction mixture is stirred for hours. Isopropyl acetate can then be added, followed by aqueous KH_2PO_4 and then aqueous H_3PO_4. The organic

layer can be isolated, washed, and purified to produce the title compound of Example 42d.

Example 43. N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-3-methylisoxazole-5-carboxamide

Example 43 can be prepared according to the procedure described for the preparation of Example 42, replacing 2-methylpyrimidine-5-carboxylic acid from Example 42a with 3-methylisoxazole-5-carboxylic acid in Example 43a to produce (S)-2-(3-methylisoxazole-5-carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 42 to produce Example 43.

Example 44. N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide

Example 44 can be prepared according to the procedure described for the preparation of Example 42, replacing 2-methylpyrimidine-5-carboxylic acid from Example 42a with 5-methylisoxazole-3-carboxylic acid in Example 44a to produce (S)-2-(5-methylisoxazole-3-carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 42 to produce Example 44.

Example 45. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(3-fluorobenzamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 45 can be prepared according to the procedure described for the preparation of Example 42, replacing 2-methylpyrimidine-5-carboxylic acid from Example 42a with 3-fluorobenzoic acid in Example 45a to produce (S)-2-(3-fluorobenzamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 42 to produce Example 45.

Example 46. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(pyrimidine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 46 can be prepared according to the procedure described for the preparation of Example 42, replacing 2-methylpyrimidine-5-carboxylic acid from Example 42a with pyrimidine-4-carboxylic acid in Example 46a to produce (S)-2-(pyrimidine-4-carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 42 to produce Example 46.

Example 47. N-((2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)isoxazole-5-carboxamide

Example 47 can be prepared according to the procedure described for the preparation of Example 42, replacing 2-methylpyrimidine-5-carboxylic acid from Example 42a with isoxazole-5-carboxylic acid in Example 47a to produce (S)-2-(isoxazole-5-carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 42 to produce Example 47.

Example 48. (2R,6S,13aS,14aR,16aS,Z)-2-(3-(benzo[d]thiazol-2-yl)quinoxalin-2-yloxy)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 48 can be prepared according to the procedure described for the preparation of Example 42, replacing 2-methylpyrimidine-5-carboxylic acid from Example 42a with 5-methylpyrazine-2-carboxylic acid in Example 48a to produce (S)-2-(5-methylpyrazine-2--carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 42 to produce Example 48.

Example 49. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 49a.

(S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoic acid.

Boc–2(*S*)-amino-non-8-eoic acid dicyclohexylamine salt can be suspended in isopropyl acetate, washed several times with an aqueous citric acid solution and then once with water. The washed product, concentrated and then re-diluted in isopropyl acetate, can be reacted with HCl to produce 2(*S*)-amino-non-8-eoic acid HCl salt. 5-Methyl-2-pyrazinecarboxylic acid, N,N'-disuccinimidyl carbonate, and N,N-dimethylaminopyridine can be dissolved in N-methyl-2-pyrrolidone (NMP) and stirred. 2(*S*)-Amino-non-8-eoic acid HCl salt is subsequently added, followed by triethylamine, and stirred to produce the title compound of Example 49a, which can be crystallized out by adding HCl followed by water.

Example 49b.

(1R,2S)-ethyl-1-((2S,4R)-N-(tert-butoxycarbonyl)-1-((S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoyl)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate

(2S,4R)-N-Boc-4-hydroxyproline can be reacted with 6-chlorophenanthridine in NMP, in the presence of sodium *t*-butoxide, to produce (2S,4R)-1-(tert-butoxycarbonyl)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxylic acid. Methyl tertiary butyl ether (MTBE) and water can then be added. The aqueous layer is separated, washed, and then HCl is added, followed by extraction with MTBE. The extracted product can be mixed with diisopropylethylamine (DIPEA) and HATU (CAS # 148893-10-1), and then reacted with (1R,2S)-ethyl-1-amino-2-vinylcyclopropanecarboxylate tosylate salt in dimethylformide (DMF) and toluene. The reaction produces (2S,4R)-tert-butyl 2-((1R,2S)-1-(ethoxycarbonyl)-2-vinylcyclopropylcarbamoyl)-4-(phenanthridin-6-yloxy)pyrrolidine-1-carboxylate, which can be extracted with MTBE and washed with HCl, further extracted, washed, dried, and dissolved in 2-propanol.

HCl can be added to the 2-propanol solution to produce (1R,2S)-ethyl 1-((2S,4R)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, which can be crystallized out by neutralizing with NaOH.

(1R,2S)-ethyl 1-((2S,4R)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, the title compound of Example 49a, N-hydroxy-5-norbornene-2,3-dicarboximide, and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride can be mixed and stirred in DMF, followed by addition of N,N-dimethylethylene diamine. The reaction produces (1R,2S)-ethyl 1-((2S,4R)-1-((S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoyl)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, which can be dissolved in isopropyl acetate and extracted with aqueous H_3PO_4, and then extracted with aqueous K_2HPO_4. The product can be reacted with di-tert-butyldicarbonate in the presence of dimethylaminopyridine, followed by extraction with a mixture of a citric acid solution and a sodium chloride solution, to produce the title compound of Example 49b.

Example 49c.

(2R,6S,13aS,14aR,16aS,Z)-ethyl-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate hydrochloride

The product of Example 49b can be subject to ring-closing metathesis in the presence of Zhan-B catalyst in toluene to produce (2R,6S,13aS,14aR,16aS,Z)-15-tert-butyl 14a-ethyl 6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-2,3,5,6,7,8,9,10,11,13a,14,14a,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a,15(1H)-dicarboxylate. The catalyst can be quenched with imidazole after the reaction.

The ring-closed product in toluene can be solvent switched to acetonitrile, followed by addition of hydrogen chloride in dioxane and heated to produce the title compound of Example 49c.

Example 49d.
(2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

The isolated product of Example 49c can be mixed with tetrahydrofuran, water and $LiOH \cdot H_2O$, and then heated and stirred. The reaction mixture can be later cooled, added with aqueous H_3PO_4, aqueous NaCl and 2-methyl tetrahydrofuran, and the organic layer is separated, washed and filtered. MeCN is added to the concentrated organic layer, heated and cooled, and then diethylamine is added. The slurry is heated and cooled to form (2R,6S,13aS,14aR,16aS,Z)-6-(5-Methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate diethylamine salt, which can be further washed and dried.

The diethylamine salt can be mixed with tetrahydrofuran, 2-methyl tetrahydrofuran and aqueous H3PO4. The organic layer is separated, washed with aqueous NaCl, and then concentrated and/or purified. The product can be subsequently mixed with NMP, followed by addition of carbonyldiimidazole (CDI) and then 1,8-

diazabicyclo[5.4.0]undec-7-ene (DBU). Cyclopropylsulfonamide can be subsequently added. The reaction mixture is stirred for hours. Isopropyl acetate can then be added, followed by aqueous KH_2PO_4 and then aqueous H_3PO_4. The organic layer can be isolated, washed, and purified to produce the title compound of Example 49d. The isolated product can be further dissolved in isopropyl acetate and then the solution is diluted with ethanol. Water can be added to the resulting solution in portion-wise manner with adequate hold-times after each addition to ensure de-super-saturation. Water addition is terminated just as the ternary solvent system becomes bi-phasic due to the partial immiscibility of isopropyl acetate, ethanol, water solvent system. The slurry can be stirred for hours and then the solid is isolated via filtration and drying to produce the crystalline hydrate of the title compound.

Example 50. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 50 can be prepared according to the procedure described for the preparation of Example 49, replacing 5-methylpyrazine-2-carboxylic acid from Example 49a with -(1,5-dimethyl-1H-pyrazole-3-carboxylic acid in Example 50a to produce (S)-2-(1,5-dimethyl-1H-pyrazole-3--carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 49 to produce Example 50.

Example 51. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 51 can be prepared according to the procedure described for the preparation of Example 49, replacing 5-methylpyrazine-2-carboxylic acid from Example 49a with 5-methyl-1H-pyrazole-3-carboxylic acid in Example 51a to produce (S)-2-(5-methyl-

1H-pyrazole-3-carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 49 to produce Example 51.

Example 52. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-fluorobenzamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

Example 52 can be prepared according to the procedure described for the preparation of Example 49, replacing 5-methylpyrazine-2-carboxylic acid from Example 49a with 2-fluorobenzoic acid in Example 52a to produce (S)-2-(2-fluorobenzamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 49 to produce Example 52.

Example 53. (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phen anthridin-6-yloxy)-6-(pyrazine-2-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide

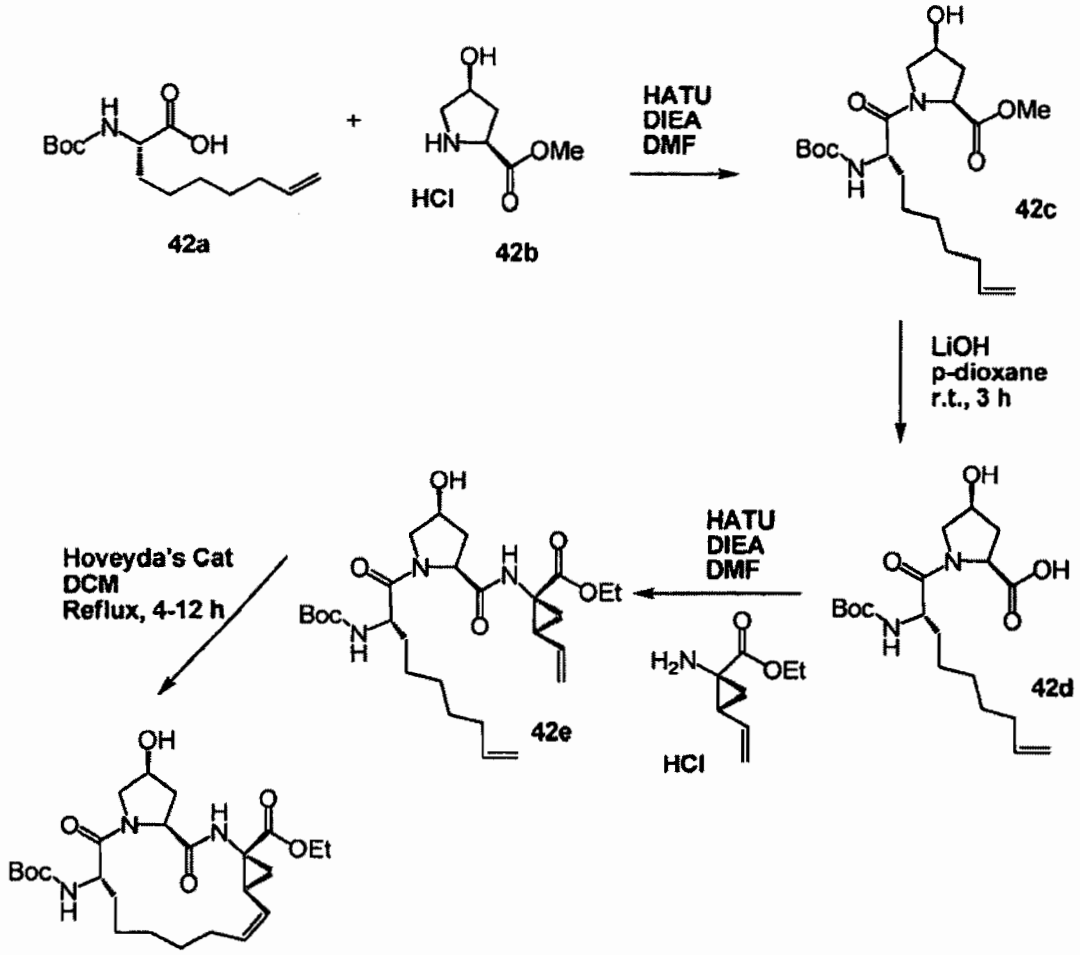
Example 53 can be prepared according to the procedure described for the preparation of Example 49, replacing 5-methylpyrazine-2-carboxylic acid from Example 49a with pyrazine carboxylic acid in Example 53a to produce (S)-2-(pyrazine-2-carboxamido)non-8-enoic acid. All subsequent steps should proceed in a similar fashion to Example 49 to produce Example 53.

Example 54 tert-butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-2-(thiazolo[4,5-c]quinolin-4-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-ylcarbamate

A mixture of 5-bromothiazole-4-carboxylic acid methyl ester (0.521 g, 2.35 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.514 g, 2.35 mmol), 1,1'-bis(di-t-butylphosphino)ferrocene palladium chloride (0.060 g, 0.094 mmol), and sodium carbonate (1.17 mL of 2M aqueous solution) in tetrahydrofuran (12 mL) was stirred under nitrogen at rt for 48 h. The reaction mixture was then heated at 50 °C for an additional 16 h. The reaction mixture was then cooled to rt, diluted with dichoromethane (120 mL) and dimethylformamide (40 mL) and washed with water (20 mL). The resulting solid was isolated by vacuum filtration to provide the title compound (0.251 mg, 53% yield, thiazolo[4,5-c]quinolin-4(5H)-one).

Example 55

Synthesis of the cyclic peptide precursor



To a solution of Boc-L-2-amino-8-nonenoic acid **42a** (1.36g, 5 mol) and the commercially available cis-L-hydroxyproline methyl ester **42b** (1.09g, 6 mmol) in 15 ml DMF, was added DIEA (4 ml, 4eq.) and HATU (4g, 2eq). The coupling was

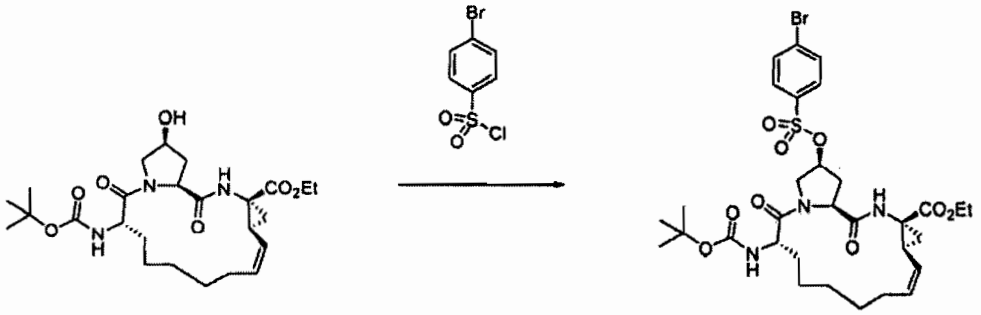
carried out at 0 °C over a period of 1 hour. The reaction mixture was diluted with 100 mL EtOAc, and followed by washing with 5% citric acid 2x 20 ml, water 2x20 ml, 1M $NaHCO_3$ 4x20 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and then was evaporated, affording the dipeptide **42c** (1.91g, 95.8%) that was identified by HPLC (Retention time = 8.9 min, 30-70%, 90%B), and MS (found 421.37, $M+Na^+$).

The dipeptide **42c** (1.91g) was dissolved in 15 mL of dioxane and 15 mL of 1 N LiOH aqueous solution and the hydrolysis reaction was carried out at room temperature for 4 hours. The reaction mixture was acidified by 5% citric acid and extracted with 100 mL EtOAc, and followed by washing with water 2x20 ml, and brine 2x20 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and then removed in vacuum, yielding the free carboxylic acid compound **42d** (1.79g, 97%), which was used for next step synthesis without need for further purification.

To a solution of the free acid obtained above (1.77, 4.64 mmol) in 5 ml DMF, D-β-vinyl cyclopropane amino acid ethyl ester (0.95g, 5 mmol), DIEA (4 ml, 4eq.) and HATU (4g, 2eq) were added. The coupling was carried out at 0 °C over a period of 5 hours. The reaction mixture was diluted with 80 mL EtOAc, and followed by washing with 5% citric acid 2x 20 ml, water 2x20 ml, 1M $NaHCO_3$ 4x20 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and then evaporated. The residue was purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (5:1→3:1→1:1→1:2→1:5). The linear tripeptide **42e** was isolated as an oil after removal of the elution solvents (1.59g, 65.4%), identified by HPLC (Retention time = 11.43 min) and MS (found 544.84, $M+Na^+$).

A solution of the linear tripeptide **42e** (1.51g, 2.89 mmol) in 200 ml dry DCM was deoxygenated by bubbling N_2. Hoveyda's 1st generation catalyst (5 mol% eq.) was then added as solid. The reaction was refluxed under N_2 atmosphere 12 hours. The solvent was evaporated and the residue was purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1→1:2→1:5). The cyclic peptide precursor was isolated as a white powder after removal of the elution solvents (1.24g, 87%), identified by HPLC (Retention time = 7.84 min, 30-70%, 90%B), and MS (found 516.28, $M+Na^+$).

(2S,6S,13aS,14aR,16aS,Z)-ethyl 2-(4-bromophenylsulfonyloxy)-6-(tert-butoxycarbonylamino)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate



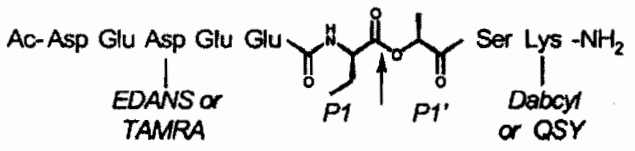
1a

A solution of (2S,6S,13aS,14aR,16aS,Z)-ethyl 6-(tert-butoxycarbonylamino)-2-hydroxy-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate (22.1 g, 44.8 mmol) and DABCO (8.5 g, 76.7 mmol) in toluene (88 mL) was stirred at room temperature. To this solution was added a solution of 4-bromobenzene-1-sulfonyl chloride 17.2 g, 67.2 mmol) in toluene (44 mL). After the addition was complete the reaction mixture was quenched with 10% aqueous sodium carbonate (110 mL) and the mixture stirred for 15 min. Tetrahydrofuran (44 mL) was added and the mixture was washed with 0.5 M HCl, water, and then saturated aqueous sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure and dried to provide the title compound (27.7 g, 87% yield), which was used without further purification.

Example 56

Measurement of potency of inhibition with purified NS3 protease enzyme

The activity of recombinant HCV NS3 proteases derived from isolates representing genotypes 1, 2, 3 or 4 is measured by cleavage of the following peptide substrate:



The substrate is labeled with a fluor and a fluorescence quencher. Cleavage results in release of the quencher and an increase in fluorescence. NS3 protease is incubated with a dilution series of inhibitor in 150 mM NaCl, 10% Glycerol, 5 mM DTT, with or without 0.01% dodecyl maltoside for either 30 minutes or 300 minutes. Substrate is added at a concentration of 5 uM to initiate the reaction, and fluorescence is measured at 2 minute intervals for 30 minutes. Enzyme concentrations range from 10 to 100 nM in the absence of detergent, or 10-fold lower in the presence of detergent. Substrate peptides are labeled with either EDANS and DABCYL (excitation 355 nm, emission 485 nm) or TAMRA and QSY (excitation 544 nm, emission 590 nm). For routine IC50 determination, 3-fold serial dilutions starting with initial concentrations of 100 μM, 200 μM, or 2 mM are used. For compounds with K_i values approaching or lower than the enzyme concentration, a tight-binding calculation format is used, with 24 dilutions of inhibitor covering a range of 0 to 100 nM inhibitor. K_i values are calculated using the tight binding assay format, according to the following equation:

$V = A\{[(K + I - E)^2 + 4KE])^{1/2} - (K + I - E)\}$, where I = total inhibitor concentration, E = active enzyme concentration, K = apparent K_i value and $A = [k_{cat})S/2][K_m = (S)]$.

Replicon cell lines

Two subgenomic replicon cell lines can be used for compound characterization in cell culture: one derived from genotype 1a and one derived from genotype 1b. Both replicon constructs are bicistronic subgenomic replicons essentially similar to those described by Bartenschlager and coworkers (Lohmann et al., *Science* (1999) **285**(5424):110-113). The genotype 1a replicon construct contains the NS3-NS5B coding region derived from the H77 strain of HCV (1a-H77) (Blight et al., *J Virol* (2003) 77(5):3181-3190). The first cistron of the construct consists of the first 36 nucleotides of the HCV 1a-H77 core gene fused to a firefly luciferase reporter and a neomycin phosphotransferase (Neo) selectable marker. The luciferase and Neo coding regions are separated by the FMDV 2a protease. The second cistron contains the NS3-NS5B coding region derived from 1a-H77 with the addition of adaptive mutations E1202G in NS3, K1691R in NS4A, and K2040R and S2204I in NS5A. The 1b-Con-1 replicon construct is identical to the 1a-H77 replicon, except that the 5' and 3' NTRs and the NS3-NS5B coding region can be derived from the 1b-Con-1

strain (Blight et al., *Science* (2000) **290**(5498):1972-1974), and the adaptive mutations are E1202G and T1280I in NS3 and S2204I in NS5A.

Replicon compound testing

Replicon cell lines can be maintained in Dulbecco's modified Eagles medium (DMEM) containing 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen), 200 mg/ml G418 (Invitrogen) and 10% (v/v) fetal bovine serum (FBS). Replicon-containing cells can be seeded into 96 well plates at a density of 5000 cells per well in 100 µl DMEM containing 5% FBS. The next day, the compound can be initially diluted in dimethyl sulfoxide (DMSO) to generate a 200x stock of the inhibitor in a series of 8 half-log dilutions. The dilution series can then be diluted 100-fold in the medium containing 5% FBS. One hundred microliters of medium with the inhibitor can be added to each well of the overnight cell culture plate already containing 100 µl of DMEM with 5% FBS. In assays where the protein binding effect on inhibitor potency is assessed, the medium from the overnight cell culture plates can be replaced with 200 µl DMEM containing 40% human plasma (Innovative Research) plus 5% FBS as well as compound. The cells can be grown for 4 days in tissue culture incubators. The inhibitory effects of compounds against the replicons can be determined by measuring either the level of luciferase or HCV RNA. The luciferase assay can be conducted using a Luciferase Assay System kit (Promega) following the manufacturer's instructions. Briefly, the cell culture medium is removed and wells are washed with 200 µl of phosphate-buffered saline. To each well Passive Lysis buffer (Promega, WI) is added and the plates are incubated for 30 min with rocking to lyse the cells. Luciferin solution (50 µl, Promega) is added, and luciferase activity is measured with a Victor II luminometer (Perkin-Elmer). To determine HCV RNA levels, RNA extractions can be performed using the CellsDirect kit (Invitrogen), and the HCV RNA copy number can be measured using the SuperScript III Platinum One-Step qRT-PCR system (Invitrogen) and primers specific to the HCV 5' nontranslated region. Cytotoxicity can be determined by the 3-[4,5-dimethythiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay as follows. Replicon cells is plated in 96-well plates (4000 cells per well), the next day compound dilutions are added as in the activity assay, and the cells are grown in the presence of the inhibitors for 4 days. The MTT solution is diluted in DMEM containing 5% FBS and 60 µl of the solution is added to the cells. After 4 hrs, the cells are solubilized by the addition

of 30 µl SDS (20% in 0.02 N HCl). The plates are incubated overnight and the optical density can be measured at 570nm. To determine compounds' EC_{50} and TD_{50}, luciferase, RNA inhibition and MTT data can be analyzed using the GraphPad Prism 4 software (equation: sigmoidal dose-response – variable slope).

Mutants in transient replicons

Mutations detected in resistance selection studies can be introduced into wild type transient replicon constructs based on genotypes 1a-H77 and 1b-N. Both replicons are bicistronic sub-genomic constructs containing a firefly luciferase reporter similar to those described above, but they do not contain a Neo selectable marker and are therefore only suitable for transient replication assays. The 1a-H77 replicon for transient assays further differs from the replicon in the stable cell line in that it contains NS2 through NS5B in the second cistron. The 1b-N strain replicon contains NS3 through NS5B in the second cistron, with adaptive mutations E1202G in NS3 and S2204I in NS5A. Mutagenesis can be performed using the Stratagene QuikChange XL II site-directed mutagenesis kit. Mutants' sequences can be confirmed, plasmids can be linearized with *Xba* I restriction enzyme and used as template for in vitro transcription reactions to make mutant replicon RNA for transient transfections. In vitro transcription can be performed with the T7 Megascript kit (Ambion).

Transient replicon transfections can be performed essentially as described by Mo et al. (*Antimicrob Agents Chemother* (2005) **49**(10):4305-4314) with slight modifications. Fifteen micrograms of template RNA can be used to electroporate 3×10^6 cells in a 200 µl volume in a 0.2 cm cuvette. The cells used for transient transfections can be Huh7 cells obtained by curing replicon-containing cells with IFN (Mo et al., *supra*). Electroporation can be done with a Gene Pulser II (Bio-Rad, CA) at 480V and 25µF, using two manual pulses. Transfected cells can be diluted to 7.5×10^4 cells/ml and plated in 96 well plates at 7.5×10^3 cells per well in DMEM with 5% FBS and 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen). Four hours post-transfection, one plate is harvested for luciferase measurement; this plate may provide a measure of the amount of input RNA that can be translated, and thus of transfection efficiency. To the remaining plates, test compound serial dilutions in DMSO can be added (0.5% DMSO final concentration), and plates are incubated for 4 days.

Exemplary compounds of the present invention were tested for their anti-HCV activities. Many of the compounds tested showed unexpected anti-HCV activities, including excellent activities in biochemical assays against HCV proteases representing various HCV genotypes, superior activities in standard HCV replicon assays including activity against 1a-H77 and 1b-con1 HCV strains in the absence or presence of 40% human plasma, and/or excellent activities in transient replicon assays against drug-resistant mutants in a number of different HCV genetic backgrounds.

The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. Such equivalents are intended with be encompassed by the following claims.

Claims:

1. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyrazine-2-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16, 16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.

2. A compound: N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonyl carbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)-5-methylisoxazole-3-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.

3. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.

4. A compound: N-((2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonyl carbamoyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl)thiazole-5-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.

5. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-2-(phenanthridin-6-yloxy)-6-(pyridazine-4-carboxamido)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16, 16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.

6. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(1,5-dimethyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.

7. A compound: (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methyl-1H-pyrazole-3-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating HCV infection in a subject.