4-AMINO-4-OXOBUTANOYL PEPTIDE CYCLIC ANALOGUES, INHIBITORS OF VIRAL REPLICATION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to US Provisional Application Nos. 61/121,378 filed December 10, 2008 and 61/226,323 filed July 17, 2009, both of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention provides 4-amino-4-oxobutanoyl peptide cyclic analogues, useful as antiviral agents. Certain 4-amino-4-oxobutanoyl peptide cyclic analogues disclosed herein are potent and/ or selective inhibitors of viral replication, particularly Hepatitis C viral replication. The invention also provides pharmaceutical compositions containing one or more 4-amino-4-oxobutanoyl peptide cyclic analogues and one or more pharmaceutically acceptable carriers. Such pharmaceutical compositions may contain a 4-amino-4-oxobutanoyl peptide cyclic analogue as the only active agent or may contain a combination of a 4-amino-4-oxobutanoyl peptide cyclic analogue and one or more other pharmaceutically active agents. The invention also provides methods for treating viral infections, including Hepatitis C infections.

BACKGROUND

[0002] An estimated 3% of the world's population is infected with the hepatitis C virus. Of those exposed to HCV, 80% to 85% become chronically infected, at least 30 % develop cirrhosis of the liver and 1-4% develop hepatocellular carcinoma. Hepatitis C Virus (HCV) is one of the most prevalent causes of chronic liver disease in the United States, reportedly accounting for about 15 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and up to 50 percent of cirrhosis, end-stage liver disease, and liver cancer. Chronic HCV infection is the most common cause of liver transplantation in the U.S., Australia, and most of Europe. Hepatitis C causes an estimated 10,000 to 12,000 deaths annually in the United States. While the acute phase of HCV infection is usually associated with mild symptoms, some evidence suggests that only about 15% to 20% of infected people will spontaneously clear HCV.

[0003] HCV is an enveloped, single-stranded RNA virus that contains a positive-stranded genome of about 9.6 kb. HCV is classified as a member of the Hepacivirus genus of the family Flaviviridae. At least 4 strains of HCV, GT-1 – GT-4, have been characterized.

[0004] The HCV lifecycle includes entry into host cells; translation of the HCV genome, polyprotein processing, and replicase complex assembly; RNA replication, and virion assembly and release. Translation of the HCV RNA genome yields a more than 3000 amino acid long polyprotein that is processed by at least two cellular and two viral proteases. The HCV polyprotein is:

NH2-C-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH.

[0005] The cellular signal peptidase and signal peptide peptidase have been reported to be responsible for cleavage of the N-terminal third of the polyprotein (C-E1-E2-p7) from the nonstructural proteins (NS2-NS3-NS4A-NS4B-NS5A-NS5B). The NS2-NS3 protease mediates a first cis cleavage at the NS2-NS3 site. The NS3-NS4A protease then mediates a second cis-cleavage at the NS3-NS4A junction. The NS3-NS4A complex then cleaves at three downstream sites to separate the remaining nonstructural proteins. Accurate processing of the polyprotein is asserted to be essential for forming an active HCV replicase complex.

[0006] Once the polyprotein has been cleaved, the replicase complex comprising at least the NS3-NS5B nonstructural proteins assembles. The replicase complex is cytoplasmic and membrane-associated. Major enzymatic activities in the replicase complex include serine protease activity and NTPase helicase activity in NS3, and RNA-dependent RNA polymerase activity of NS5B. In the RNA replication process, a complementary negative strand copy of the genomic RNA is produced. The negative strand copy is used as a template to synthesize additional positive strand genomic RNAs that may participate in translation, replication, packaging, or any combination thereof to produce progeny virus. Assembly of a functional replicase complex has been described as a component of the HCV replication mechanism. Provisional application 60/669,872 "Pharmaceutical Compositions and Methods of Inhibiting HCV Replication" filed April 11, 2005, is hereby incorporated by reference in its entirety for its disclosure related to assembly of the replicase complex.

[0007] Current treatment of hepatitis C infection typically includes administration of an interferon, such as pegylated interferon (IFN), in combination with ribavirin. The success of current therapies as measured by sustained virologic response (SVR) depends on the strain of

HCV with which the patient is infected and the patient's adherence to the treatment regimen. Only 50% of patients infected with HCV strain GT-1 exhibit a sustained virological response. Direct acting antiviral agents such as ACH-806, VX-950 and NM 283 (prodrug of NM 107) are in clinical development for treatment of chronic HCV. Due to lack of effective therapies for treatment for certain HCV strains and the high mutation rate of HCV, new therapies are needed. The present invention fulfills this need and provides additional advantages, which are described herein.

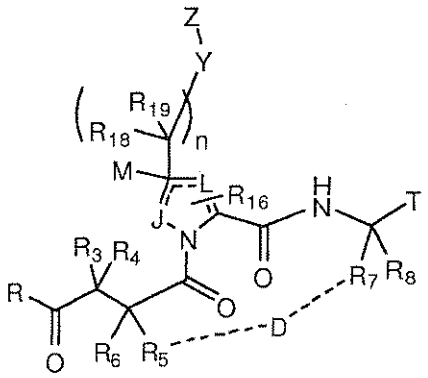
SUMMARY OF THE INVENTION

[0008] The invention provides compounds of Formula I (shown below) and includes 4-amino-4-oxobutanoyl peptides and cyclic analogues thereof. The 4-amino-4-oxobutanoyl peptides and cyclic analogues thereof of Formula I disclosed herein possess antiviral activity. The invention provides compounds of Formula I that are potent and/ or selective inhibitors of Hepatitis C virus replication. The invention also provides pharmaceutical compositions containing one or more compound of Formula I, or a salt, solvate, or acylated prodrug of such compounds, and one or more pharmaceutically acceptable carriers.

[0009] The invention further comprises methods of treating patients suffering from certain infectious diseases by providing to such patients an amount of a compound of Formula I effective to reduce signs or symptoms of the disease or disorder. These infectious diseases include viral infections, particularly HCV infections. The invention particularly includes methods of treating human patients suffering from an infectious disease, but also encompasses methods of treating other animals, including livestock and domesticated companion animals, suffering from an infectious disease.

[0010] Methods of treatment include providing a compound of Formula I as a single active agent or providing a compound of Formula I in combination with one or more other therapeutic agents.

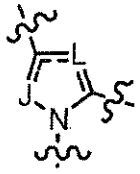
[0011] Thus in a first aspect the invention includes compounds of Formula I pharmaceutically acceptable salts thereof:



(Formula I)

Within Formula I

====== represents a double or single covalent bond, and the group



contains 0 or 1 double bonds.

R is –COOH or C_1-C_6alkylester; or

R is a group of the formula $-NR_1R_2$ and R_1 and R_2 meet one of the following conditions:

(i) R_1 and R_2 are taken together to form a 4-to 7-membered heterocyclic ring containing 0 to 2 additional heteroatoms chosen from N, S, and O, which ring is optionally fused to a 5 to 6-membered heterocyclic ring containing 1 or 2 heteroatoms independently chosen N, S, or O or to a 5- to 6-membered carbocyclic ring to form a bicyclic ring system which is optionally substituted;

(ii) R_1 and R_2 are taken together to form an optionally substituted 5- to 9-membered bridged heterocyclic ring containing 0, 1, or 2 additional N, S, or O atoms, or an optionally substituted 5- to 7-membered heterocyclic ring containing 0 or 1 additional N, S, or O atoms fused to an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring, to form a bicyclic ring system which is bridged;

(iii) R_1 and R_2 are taken together to form an optionally substituted 4- to 7-membered heterocyclic ring containing 0 or 1 additional N, S, or O atoms fused to an optionally substituted 5- to 9-membered bridged carbocyclic or heterocyclic ring;

(iv) R_1 and R_2 are taken together to form an optionally substituted bicyclic system with rings in spiro orientation having a total of 6 to 12 ring atoms with 0, 1 or 2 additional heteroatoms independently chosen from N, O, and S with remaining ring atoms being carbon; or

(v) R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, $-NR_{10}R_{11}$, $-(C=O)NR_{10}R_{11}$, $-(C=S)NR_{10}R_{11}$, $-(C=O)R_{12}$, $-SO_2R_{12}$, $-(C=O)OR_{12}$, $-O(C=O)R_{12}$, $-OR_{12}$, or $-N(C=O)R_{12}$, and R_2 is hydrogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, heterocycloalkyl, or (aryl)C_0-C_4alkyl;

(vi) R_1 is C_1-C_6alkyl or C_3-C_7cycloalkyl, and R_2 is hydrogen; or

R_3, R_4, and R_8 are independently

(a) hydrogen, halogen, or amino, or

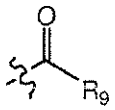
(b) C_1-C_6alkyl, C_2-C_6alkenyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (aryl)C_0-C_4alkyl, (heteroaryl)C_0-C_4alkyl, (C_3-C_7cycloalkenyl)C_0-C_4alkyl, (heterocycloalkyl)C_0-C_4alkyl, C_2-C_6alkanoyl, or mono- or di- C_1-C_6alkylamino, each of which is optionally substituted.

Or, R_3 and R_4 may be joined to form an optionally substituted 3- to 7- membered cycloalkyl ring or an optionally substituted 3– to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms independently chosen from N, S, and O.

R_6 is hydrogen, C_1-C_6alkyl, or (C_3-C_7cycloalkyl)C_0-C_2alkyl.

D is a C_7-C_{11} saturated or unsaturated hydrocarbon chain at R_5 that is (i) covalently bound to R_7, where R_7 is a methylene or methine group or D is a C_7-C_{11} saturated or unsaturated hydrocarbon chain at R_5 that is (ii) covalently bound to an optionally substituted cycloalkyl ring formed by R_7 and R_8 being joined to from a 3- to 7- membered optionally substituted cycloalkyl ring.

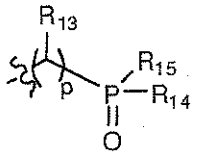
T is a group of the formula:

 where R_9 is one of the following:

R_9 is hydroxyl, amino, -COOH, $-NR_{10}R_{11}$, $-OR_{12}$, $-SR_{12}$, $-NR_{10}(S=O)R_{11}$, $-NR_{10}SO_2R_{11}$, $-NR_{10}SONR_{11}R_{12}$, $-NR_{10}SO_2NR_{11}R_{12}$, $-(C=O)OR_{10}$, $-NR_{10}(C=O)OR_{11}$, or $-CONR_{10}R_{11}$;

R_9 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (C_3-C_7cycloalkenyl)C_0-C_4alkyl, (C_3-C_7cycloalkyl)CH_2SO_2-, (C_3-C_7cycloalkyl)$CH_2SO_2NR_{10}$-, (heterocycloalkyl)C_0-C_4alkyl, (aryl)C_0-C_2alkyl, or (5- to 10-membered heteroaryl)C_0-C_2alkyl, each of which is optionally substituted;

R_9 is a phosphonate of the formula



where p is 0, 1, or 2;

R_9 is $-C_0$-C_4alkylXR_X, where X is –(C=O)NH-, -NH(C=O)- and R_X is aryl or heteroaryl; or

R_9 is $-CH(R_Y)(C_3$-C_7cycloalkyl), $-SO_2CH(R_Y)(C_3$-C_7cycloalkyl), or $-NR_{10}SO_2CH(R_Y)(C_3$-C_7cycloalkyl), where R_Y is halogen or R_Y is C_1-C_6alkyl, C_2-C_6alkanoyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (C_4-C_7cycloalkenyl)C_0-C_4alkyl, (aryl)C_0-C_4alkyl, (aryl)C_0-C_4alkoxy, (heterocycloalkyl)C_0-C_2alkyl, or (5- to 10-membered heteroaryl)C_0-C_4alkyl, each of which is optionally substituted.

R_{10}, R_{11}, and R_{12} are independently at each occurrence hydrogen or trifluoromethyl, or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (aryl)C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, (C_3-C_7cycloalkenyl)C_0-C_2alkyl, (heterocycloalkyl)C_0-C_2alkyl, or (5- to 10-membered heteroaryl)C_0-C_2alkyl, each of which is optionally substituted.

R_{13} is hydrogen or C_1-C_2alkyl.

R_{14} and R_{15} are independently hydrogen, hydroxyl, or C_1-C_2alkyl.

n is 0, 1, or 2.

M is hydrogen, halogen, hydroxyl, C_1-C_2alkyl, or C_1-C_2alkoxy.

Y is absent, $CR_{18}R_{19}$, NR_{20}, S, O, $-O(C=O)(NR_{20})$-, $NH(C=O)(NR_{20})$-, $-NH(S=O)(NR_{20})$-, $-(NR_{20})(C=O)$-, or -O(C=O)-; or Y is taken together with one of J, L, or M to form a ring.

J is CH_2 or J is taken together with Y to form a 3- to 7- membered carbocyclic or heterocyclic ring, which ring is substituted with 0 or 1 or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkoxy, trifluoromethyl, and trifluoromethoxy; when J is taken together with Y to form a ring Z may be absent.

L is CH_2 or L is taken together with Y to form a 3- to 7- membered carbocyclic or heterocyclic ring, which ring is substituted with 0 or 1 or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkoxy, trifluoromethyl, and trifluoromethoxy; when L is taken together with Y to form a ring Z may be absent.

Z is (mono-, bi-, or tri- cyclic aryl)C_0-C_2alkyl or (mono-, bi-, or tri- cyclic heteroaryl)C_0-C_2alkyl, each of which Z is substituted with 0 or 1 or more substituents independently chosen from halogen, hydroxyl, amino, cyano, $-CONH_2$, -COOH, $-SO_2NR_{11}R_{12}$, $-(C=O)NR_{11}R_{12}$,

-$NR_{11}(C=O)R_{12}$, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- and di-C_1-C_4alkylamino, C_1-C_4alkylester, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, and 0 or 1 (C_3-C_7cycloalkyl)C_0C_2alkyl, (phenyl)C_0-C_2alkyl, (phenyl)C_0-C_2alkoxy, (5- or 6-membered heteroaryl)C_0-C_2alkyl, (5- or 6-membered heteroaryl)C_0-C_2alkoxy, naphthyl, indanyl, (5- or 6-membered heterocycloalkyl)C_0-C_2alkyl, or 9- or 10-membered bicyclic heteroaryl, each of which is substituted with 0, 1, or 2 substituents independently chosen from:

(c) halogen, hydroxyl, amino, cyano, nitro, -COOH, $-CONH_2$, $CH_3(C=O)NH$-, =NOH, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4hydroxyalkyl, mono- and di-C_1-C_4alkylamino, $-NR_8SO_2R_{11}$, $-C(O)OR_{11}$, $-NR_8COR_{11}$, $-NR_8C(O)OR_{11}$, trifluoromethyl, and trifluoromethoxy, and

(d) phenyl and 5- or 6-membered heteroaryl, each of which is substituted with 0 or 1 or more of halogen, hydroxyl, C_1-C_4alkyl, and C_1-C_2alkoxy.

R_{16} represents 0 to 4 substituents is independently chosen from halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

R_{18} and R_{19} are independently hydrogen, hydroxyl, halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy,

R_{20} is hydrogen, C_1-C_2alkyl, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy.

[0012] The invention particularly includes compounds of Formula I in which one of the following conditions is met.

[0013] (1) R_1 and R_2 are joined to form a substituted 4-membered heterocyclic ring containing 0 or 1 additional N, S, or O atoms, or an optionally substituted 4-membered heterocyclic ring containing 0 or 1 additional N, S, or O atoms fused to an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring.

[0014] (2) Z is a (tricyclic aryl)C_0-C_2alkyl or (tri cyclic heteroaryl)C_0-C_2alkyl.

[0015] (3) R_1 and R_2 are taken together to form an optionally substituted 5- to 9-membered bridged heterocyclic ring containing 0, 1, or 2 additional N, S, or O atoms, or an optionally substituted 5- to 7-membered heterocyclic ring containing 0 or 1 additional N, S, or O atoms fused to an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring to form a bicyclic ring system which is fused; or R_1 and R_2 are taken together to form an optionally substituted 4- to 7-membered heterocyclic ring containing 0 or 1 additional N, S, or O atoms fused to an optionally substituted 5- to 9-membered bridged carbocyclic or heterocyclic ring; or

[0016] (4) -$(NR_{20})(C=O)$-.

[0017] Certain compounds of Formula I disclosed herein exhibit good activity in an HCV replication assay, such as the HCV replicon assay set forth in Example 6, which follows. Preferred compounds of Formula I exhibit an EC_{50} of about 40 micromolar or less, or more preferably an EC_{50} of about 10 micromolar or less; or still more preferably an EC_{50} of about 5 nanomolar or less in an HCV replicon replication assay

DETAILED DESCRIPTION OF THE INVENTION

CHEMICAL DESCRIPTION AND TERMINOLOGY

[0018] Prior to setting forth the invention in detail, it may be helpful to provide definitions of certain terms to be used herein. Compounds of the present invention are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. Unless clearly contraindicated by the context each compound name includes the free acid or free base form of the compound as well hydrates of the compound and all pharmaceutically acceptable salts of the compound.

[0019] The term "4-amino-4-oxobutanoyl peptide cyclic analogues " encompasses all compounds that satisfy Formula I, including any enantiomers, racemates and stereoisomers, as well as all pharmaceutically acceptable salts of such compounds. The phrase "a compound of Formula I" includes all subgeneric groups of Formula I including Formula IA, and Formula II to VII as well as all forms of such compounds, including salts and hydrates, unless clearly contraindicated by the context in which this phrase is used.

[0020] The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced items. The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to"). Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as"), is intended merely to better illustrate

the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0021] An "active agent" means a compound (including a compound of the invention), element, or mixture that when administered to a patient, alone or in combination with another compound, element, or mixture, confers, directly or indirectly, a physiological effect on the patient. The indirect physiological effect may occur via a metabolite or other indirect mechanism. When the active agent is a compound, then salts, solvates (including hydrates) of the free compound, crystalline forms, non-crystalline forms, and any polymorphs of the compound are included. Compounds may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g., asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, all optical isomers in pure form and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. All forms are contemplated herein regardless of the methods used to obtain them.

[0022] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -(CH_2)C_3-C_8cycloalkyl is attached through carbon of the methylene (CH_2) group.

[0023] "Alkanoyl" indicates an alkyl group as defined herein, attached through a keto (-(C=O)-) bridge. Alkanoyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C_2alkanoyl group is an acetyl group having the formula CH_3(C=O)-.

[0024] A bond represented by a combination of a solid and dashed line, ie. =====, may be either a single or double bond.

[0025] "Alkyl" is a branched or straight chain saturated aliphatic hydrocarbon group, having the specified number of carbon atoms, generally from 1 to about 12 carbon atoms. The term C_1-C_6alkyl as used herein indicates an alkyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms. Other embodiments include alkyl groups having from 1 to 8 carbon atoms, 1 to 4 carbon atoms or 1 or 2 carbon atoms, e.g. C_1-C_8alkyl, C_1-C_4alkyl, and C_1-C_2alkyl. When C_0-C_n alkyl is used herein in conjunction with another group, for example, (aryl)C_0-C_4 alkyl, the indicated group, in this case aryl, is either directly bound by a single covalent bond (C_0), or attached by an alkyl chain having the specified number of carbon atoms, in this case 1, 2, 3, or 4 carbon atoms. C_0-$C_n$alkyl is used in conjunction with heteroaryl, aryl, phenyl, cycloalkyl, and heterocycloalkyl, e.g., (5- to 10-membered heteroaryl)C_0-C_2alkyl, (aryl)C_0-C_2alkyl, (phenyl)C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, and (heterocycloalkyl)C_0-C_4alkyl. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, 3-methylbutyl, t-butyl, n-pentyl, and sec-pentyl.

[0026] "Alkenyl" indicates a straight or branched hydrocarbon chain comprising one or more unsaturated carbon- carbon double bonds, which may occur in any stable point along the chain. Alkenyl groups described herein have the indicated number of carbon atoms. E.g., C_2-C_6alkenyl indicates an alkenyl group of from 2, 3, 4, 5, or 6 carbon atoms. When no number of carbon atoms is indicated, alkenyl groups described herein typically have from 2 to about 12 carbon atoms; in certain embodiments lower alkenyl groups, having 8 or fewer carbon atoms, are preferred. Examples of alkenyl groups include ethenyl, propenyl, and butenyl groups.

[0027] "Alkoxy" indicates an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge (-O-). Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3- pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. When "C_0-$C_n$alkoxy" is used in with another group, for example, (heteroaryl)C_0-C_4alkoxy, the indicated group, in this case heteroaryl, is either attached via a covalently bound oxygen bridge (C_0alkoxy), or attached by an alkoxy group having the specified number of carbon atoms, in this case from 1 to about 4 carbon atoms, that is covalently bound to the group it substitutes via the alkoxy oxygen atom.

[0028] "Mono- and/or di-alkylcarbamate" indicates groups of the formula ($alkyl_1$)-O (C=O)NH- and ($alkyl_1$)-O (C=O)N($alkyl_2$)- in which the $alkyl_1$ and $alkyl_2$ groups are independently chosen alkyl groups as defined above having the indicated number of carbon atoms.

[0029] The term "alkylester" indicates an alkyl group as defined herein attached through an ester linkage. The ester linkage may be in either orientation, e.g. a group of the formula –O(C=O)alkyl or a group of the formula –(C=O)O-alkyl.

[0030] "Alkyloxime" is a group of the formula –C=N-O-alkyl, where the alkyl group is an alkyl group as defined herein, having the indicated number of carbon atoms.

[0031] "Alkylsulfonyl" is alkyl-SO_2- and "Alkylthio" is alkyl-S-, where the alkyl group is an alkyl group as defined herein, having the indicated number of carbon atoms. The point of attachment of the alkylsulfonyl or alkythio substituent is on the sulfur atom.

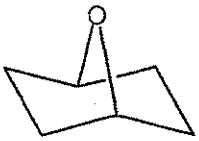
[0032] "Aryl" indicates an aromatic group containing only carbon in the aromatic ring or rings. Such aromatic groups may be further substituted with carbon or non-carbon atoms or groups. Typical aryl groups contain 1 or 2 separate, fused, or pendant rings and from 6 to about 12 ring atoms, without heteroatoms as ring members. Where indicated aryl groups may be substituted. Such substitution may include fusion to a 5 to 7-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently chosen from N, O, and S, to form, for example, a 3,4-methylenedioxy-phenyl group. Aryl groups include, for example, phenyl, naphthyl, including 1-naphthyl and 2-naphthyl, and bi-phenyl.

[0033] In the term "(aryl)alkyl," aryl and alkyl are as defined above, and the point of attachment is on the alkyl group. "(Aryl)C_0-C_4alkyl" indicates an aryl group that is directly attached via a single covalent bond (aryl)C_0alkyl or attached through an alkyl group having from 1 to about 4 carbon atoms. Examples of (aryl)alkyl groups include piperonyl and (phenyl)alkyl groups such as benzyl and phenylethyl. Similarly, the term "(aryl)C_0-C_4alkoxy" indicates an aryl group that is directly attached to the molecule it substitutes via an oxygen bridge, e.g. (aryl)C_0alkoxy, or covalently bound to an alkoxy group having from 1 to 4 carbon atoms.

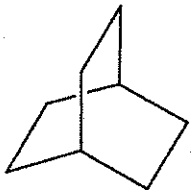
[0034] A "bridged" group is a ring group, typically saturated, in which two non-adjacent ring atoms are covalently bound to the same linking group. The linking group is a methylene, ethylene, or oxygen atom. Examples of bridged groups include:



bicyclo[2.2.1]heptane



7-oxabicyclo[2.2.1]heptane



bicyclo[2.2.2]octane

[0035] A "carbocyclic ring" is a saturated, unsaturated, or aromatic ring group having the indicated number of carbon ring atoms and having only carbon ring atoms.

[0036] "Cycloalkyl" is a saturated hydrocarbon ring group, having the specified number of carbon atoms. Monocyclic cycloalkyl groups typically have from 3 to about 8 carbon ring atoms or from 3 to 7 (3, 4, 5, 6, or 7) carbon ring atoms. Cycloalkyl substituents may be pendant from a substituted nitrogen or carbon atom, or a substituted carbon atom that may have two substituents may have a cycloalkyl group, which is attached as a spiro group. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl as well as bridged or caged saturated ring groups such as norbornane or adamantane. Likewise "cycloalkenyl" is a hydrocarbon ring group having the indicated number of carbon atoms and at least carbon-carbon double between ring carbon atoms.

[0037] The terms "(cycloalkyl)C_0-$C_n$alkyl" indicates a substituent in which the cycloalkyl and alkyl are as defined herein, and the point of attachment of the (cycloalkyl)alkyl group to the molecule it substitutes is either a single covalent bond, (C_0alkyl) or on the alkyl group. (Cycloalkyl)alkyl encompasses, but is not limited to, cyclopropylmethyl, cyclohexylmethyl, and cyclohexylmethyl.

[0038] "Haloalkyl" indicates both branched and straight-chain alkyl groups having the specified number of carbon atoms, substituted with 1 or more halogen atoms, up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0039] "Haloalkoxy" indicates a haloalkyl group as defined herein attached through an oxygen bridge (oxygen of an alcohol radical).

[0040] "Halo" or "halogen" indicates any of fluoro, chloro, bromo, and iodo.

[0041] "Heteroaryl" indicates a stable monocyclic aromatic ring having the indicated number of ring atoms which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a stable

bicyclic or tricyclic system containing at least one 5- to 7-membered aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon. Monocyclic heteroaryl groups typically have from 5 to 7 ring atoms. In some embodiments bicyclic heteroaryl groups are 9- to 10-membered heteroaryl groups, that is, groups containing 9 or 10 ring atoms in which one 5- to 7-member aromatic ring is fused to a second aromatic or non-aromatic ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heteroaryl group is not more than 2. It is particularly preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, oxazolyl, pyranyl, pyrazinyl, pyrazolopyrimidinyl, pyrazolyl, pyridizinyl, pyridyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienylpyrazolyl, thiophenyl, triazolyl, benzo[*d*]oxazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxadiazolyl, dihydrobenzodioxynyl, furanyl, imidazolyl, indolyl, and isoxazolyl.

[0042] A "heterocyclic ring" is a saturated, unsaturated, or aromatic ring group having at least one ring containing a heteroatom chosen from N, O, and S, with remaining ring atoms being carbon.

[0043] Examples of heterocyclic rings include pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl,

quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl.

[0044] By way of example and not limitation, carbon bonded heterocyclic rings are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Carbon bonded heterocyclic rings include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

[0045] By way of example and not limitation, nitrogen bonded heterocyclic rings are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

[0046] The term "heterocycloalkyl" indicates a saturated monocyclic group having the indicated number of ring atoms and containing from 1 to about 3 heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a saturated bicyclic ring system having at least one N, O, or S ring atom with the remaining atoms being carbon. Monocyclic heterocycloalkyl groups usually have from 4 to about 8 ring atoms. In some embodiments monocyclic heterocycloalkyl groups have from 5 to 7 ring atoms. Bicyclic heterocycloalkyl groups typically have from about five to about 12 ring atoms. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl, piperidinyl, and pyrrolidinyl groups.

[0047] The term "(heterocycloalkyl)alkyl" indicates a saturated substituent in which the heterocycloalkyl and alkyl are as defined herein, and the point of attachment of the (heterocycloalkyl)alkyl group to the molecule it substitutes is on the alkyl group. This term encompasses, but is not limited to, piperidylmethyl, piperazinylmethyl, and pyrrolidinylmethyl.

[0048] The term "mono- and/ or di-alkylamino" indicates secondary or tertiary alkyl amino groups, wherein the alkyl groups are independently chosen alkyl groups, as defined herein, having the indicated number of carbon atoms. The point of attachment of the alkylamino group is on the nitrogen. Examples of mono- and di-alkylamino groups include ethylamino, dimethylamino, and methyl-propyl-amino.

[0049] "Mono- and/ or di-alkylcarboxamide" indicates a mono-alkylcarboxamide group of formula ($alkyl_1$)-NH-(C=O)- or a dialkylcarboxamide group of the formula ($alkyl_1$)($alkyl_2$)-N-(C=O)- in which the point of attachment of the mono- or dialkylcarboxamide substituent to the molecule it substitutes is on the carbon of the carbonyl group. The term "mono and/ or di-alkylcarboxamide" also includes groups of the formula ($alkyl_1$)(C=O)NH- and ($alkyl_1$)(C=O)($alkyl_2$)N- in which the point of attachment is the nitrogen atom. The groups $alkyl_1$ and $alkyl_2$ are independently chosen alkyl groups having the indicated number of carbon atoms. Likewise, the term "mono- and/ or di-alkylsulfonamide" indicates mono-alkyl groups of the formula ($alkyl_1$)SO_2NH- and ($alkyl_1$)$NHSO_2$- and di-alkyl groups of the formula ($alkyl_1$)SO_2($alkyl_2$)N- and ($alkyl_1$)N($alkyl_2$)SO_2-.

[0050] "Oxo," means a keto group (C=O). An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of $-CH_2-$ to $-C(=O)-$. An oxo group that is a substituent of an aromatic carbon atom results in a conversion of –CH– to –C(=O)– and a loss of aromaticity.

[0051] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When the substituent is oxo (i.e., =O) then 2 hydrogens on the atom are replaced. When an oxo group substitutes aromatic moieties, the corresponding partially unsaturated ring replaces the aromatic ring. For example a pyridyl group substituted by oxo is a pyridone. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation into an effective therapeutic agent. Unless otherwise specified substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent the point of attachment of this substituent to the core structure is in the alkyl portion.

[0052] Suitable groups that may be present on a "substituted" position include, but are not limited to, e.g., halogen; cyano; hydroxyl; nitro; azido; alkanoyl (such as a C_2-C_6 alkanoyl group such as acyl or the like); carboxamido; alkyl groups (including cycloalkyl groups) having 1 to about 8 carbon atoms, or 1 to about 6 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 8, or 2 to about 6 carbon atoms; alkoxy groups having one or more oxygen linkages and from 1 to about 8, or from 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those having one or more thioether linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those having one or more sulfinyl linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those having one or more sulfonyl linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; aminoalkyl groups including groups having one or more N atoms and from 1 to about 8, or from 1 to about 6 carbon atoms; aryl having 6 or more carbons and one or more rings, (e.g., phenyl, biphenyl, naphthyl, or the like, each ring either substituted or unsubstituted aromatic); arylalkyl having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyl being an exemplary arylalkyl group; arylalkoxy having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyloxy being an exemplary arylalkoxy group; or a saturated, unsaturated, or aromatic heterocyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, pyridyl, pyrazinyl, pyrimidinyl, furanyl, pyrrolyl, thienyl, thiazolyl, triazinyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, and pyrrolidinyl. Such heterocyclic groups may be further substituted, e.g. with hydroxyl, alkyl, alkoxy, halogen and amino.

[0053] A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, capsules, injections, suspensions, liquids, emulsions, creams, ointments, suppositories, inhalable forms, transdermal forms, and the like.

[0054] "Pharmaceutical compositions" are compositions comprising at least one active agent, such as a compound or salt of Formula I, and at least one other substance, such as a carrier. Pharmaceutical compositions meet the U.S. FDA's GMP (good manufacturing practice) standards for human or non-human drugs.

[0055] "Pharmaceutically acceptable salts" includes derivatives of the disclosed compounds in which the parent compound is modified by making inorganic and organic, non-toxic, acid or base addition salts thereof. The salts of the present compounds can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts.

[0056] Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Lists of additional suitable salts may be found, e.g., in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985).

[0057] The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active compound is provided. An excipient is any inert substance added to a drug to prepare a pharmaceutical composition that is generally safe, non-toxic and neither biologically or otherwise undesirable. Excipients that are acceptable for veterinary use as well as human pharmaceutical use are preferred.

[0058] A "patient" is a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder,

prophylactic or preventative treatment, or diagnostic treatment. In some embodiments the patient is a human patient.

[0059] "Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

[0060] "Providing a compound of Formula I with at least one additional active agent" means the compound of Formula I and the additional active agent(s) are provided simultaneously in a single dosage form, provided concomitantly in separate dosage forms, or provided in separate dosage forms for administration separated by some amount of time that is within the time in which both the compound of Formula I and the at least one additional active agent are within the blood stream of a patient. The compound of Formula I and the additional active agent need not be prescribed for a patient by the same medical care worker. The additional active agent or agents need not require a prescription. Administration of the compound of Formula I or the at least one additional active agent can occur via any appropriate route, for example, oral tablets, oral capsules, oral liquids, inhalation, injection, suppositories or topical contact.

[0061] "Treatment," as used herein includes providing a compound of Formula I, either as the only active agent or together with at least one additional active agent sufficient to: (a) prevent or prophylacticly treat a disease or a symptom of a disease from occurring in a patient who may be predisposed to the disease but has not yet been diagnosed as having it (e.g. including diseases that may be associated with or caused by a primary disease (as in liver fibrosis that can result in the context of chronic HCV infection, prophylaxis of HCV-related conditions including liver fibrosis and hepatocellular carcinoma is included in the invention); (b) inhibiting the disease, i.e. arresting its development; and (c) relieving the disease, i.e., causing regression of the disease. "Treating" and "treatment" also means providing a therapeutically effective amount of a compound of Formula I, as the only active agent or together with at least one additional active agent to a patient infected with HCV.

[0062] A "therapeutically effective amount" of a pharmaceutical combination of this invention means an amount effective, when administered to a patient, to provide a therapeutic benefit such as an amelioration of symptoms, e.g., an amount effective to decrease the symptoms of a hepatitis C infection. For example a patient infected with a hepatitis C virus may present elevated levels of certain liver enzymes, including AST and ALT. Normal levels of AST are from 5 to 40 units per liter of serum (the liquid part of the blood) and normal levels of ALT are

from 7 to 56 units per liter of serum. A therapeutically effect amount is thus an amount sufficient to provide a significant reduction in elevated AST and ALT levels or an amount sufficient to provide a return of AST and ALT levels to the normal range. A therapeutically effective amount is also an amount sufficient to prevent a significant increase or significantly reduce the detectable level of virus or viral antibodies in the patient's blood, serum, or tissues. One method of determining treatment efficacy includes measuring HCV RNA levels by a convention method for determining viral RNA levels such as the Roch TaqMan assay. In certain preferred embodiments treatment reduces HCV RNA levels below the limit of quantitation (30 IU/mL, as measured by the Roche TaqMan(R) assay) or more preferably below the limit of detection (10 IU/mL, Roche TaqMan).

[0063] A significant increase or reduction in the detectable level of virus or viral antibodies is any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student's T-test, where $p < 0.05$.

CHEMICAL DESCRIPTION

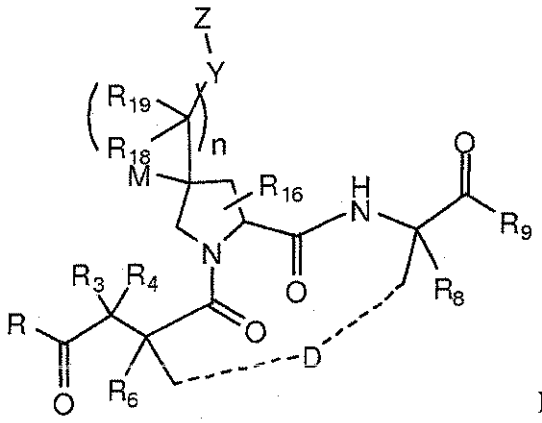
[0064] Formula I includes all subformulae thereof. In certain situations, the compounds of Formula I may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g. asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, it should be understood that all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds being included in the present invention. In these situations, single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example using a chiral HPLC column.

[0065] Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers, but rather includes all tautomeric forms.

[0066] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C.

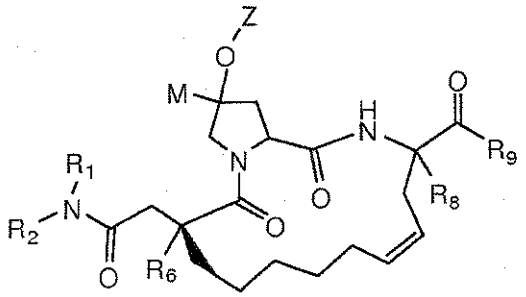
[0067] Certain compounds are described herein using a general formula that includes variables, e.g. R, R_1-R_8, R_{16}, R_{18}, R_{19}, M, n, T, Y, and Z. Unless otherwise specified, each variable within such a formula is defined independently of other variables. Thus, if a group is said to be substituted, e.g. with 0-2 R*, then the group may be substituted with up to two R* groups and R* at each occurrence is selected independently from the definition of R*. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0068] In addition to compounds of Formula I as described above, the invention also includes compounds of Formula II to IV that carry any combination of the variable definitions set forth below that result in a stable compound.

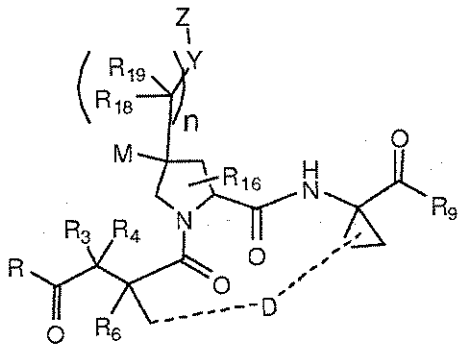


Formula II

[0069] In Formula II D is an alkyl or alkenyl group having 6 to 10 carbon atoms.

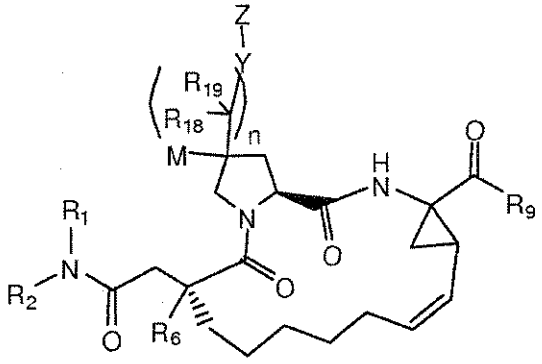


Formula III



Formula IV

[0070] In Formula IV, D is an alkyl or alkenyl group having 6 to 10 carbon atoms.



Formula V

[0071] For example, the invention includes embodiments in which any one or more of the following conditions are met, so long as a stable compound results.

The R_1 and R_2 Substituents

[0072] The invention includes embodiments in which R_1 and R_2 carry any of the following definitions.

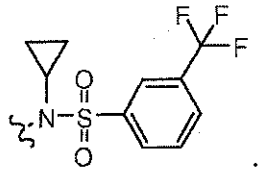
[0073] (a) R_1 and R_2 form an optionally substituted azetidine ring.

[0074] (b) R_1 and R_2 form an optionally substituted azetidine ring, which azetidine ring is unsubstituted, or substituted with 1 or 2 halogen atoms or phenyl substituted with 0 to 3 substituents independently chosen from halogen, methyl, and methoxy.

[0075] (c) R_1 and R_2 are joined to form a 4- to 7- membered heterocycloalkyl ring containing 0 to 2 additional heteroatoms independently chosen from N, O, and S which ring is optionally fused to a 5- or 6- membered heterocyclic ring, containing 1 or 2 heteroatoms independently chosen from N, O, and S, or fused to a 5- or 6-membered carbocyclic ring to form a bicyclic ring system, each of which 5- to 7- membered heterocycloalkyl ring or bicyclic ring system is substituted with 0 to 3 substituents independently chosen from A- and AB-,

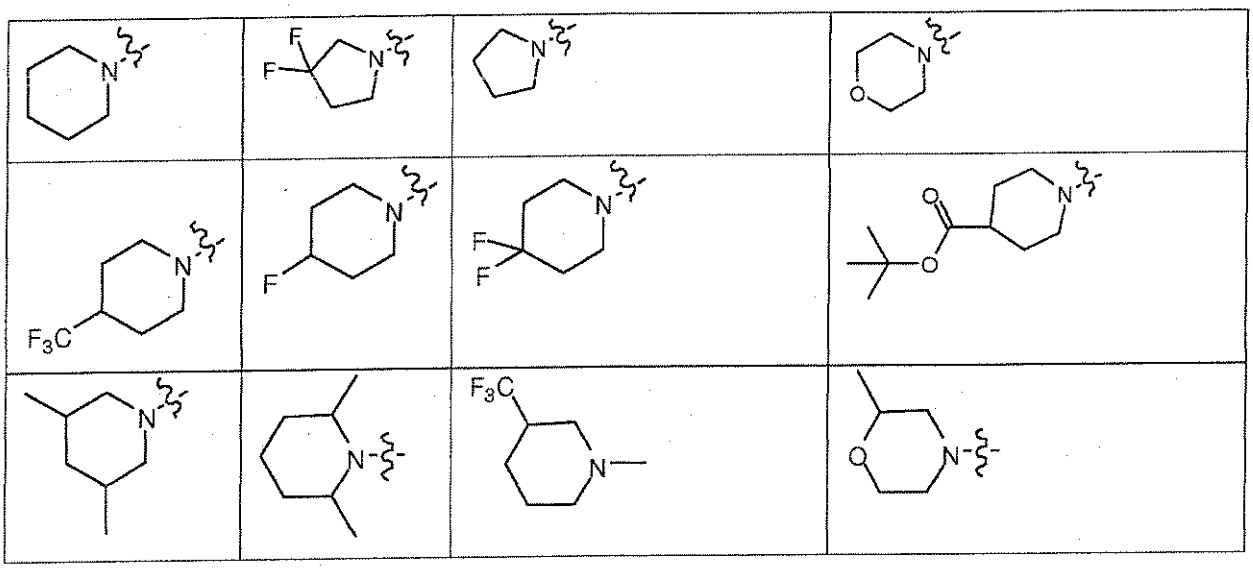
where A is halogen, hydroxyl, amino, cyano, oxo, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- or di-C_1-C_4alkylamino, C_1-C_4alkylester, C_1-C_4alkyloxime, C_3-C_7cycloalkyl-NH-(C=O)-, heterocycloalkyl-(C=O)-, mono- or di-C_1-C_4alkylcarboxamide, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfonamide, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, pyridyl, pyrimidinyl, pyrazine, phenyl, which pyridyl, pyrimidinyl and phenyl are substituted with 0 to 2 substituents independently chosen halogen, methyl and methoxy; and B is C_1-C_4alkyl.

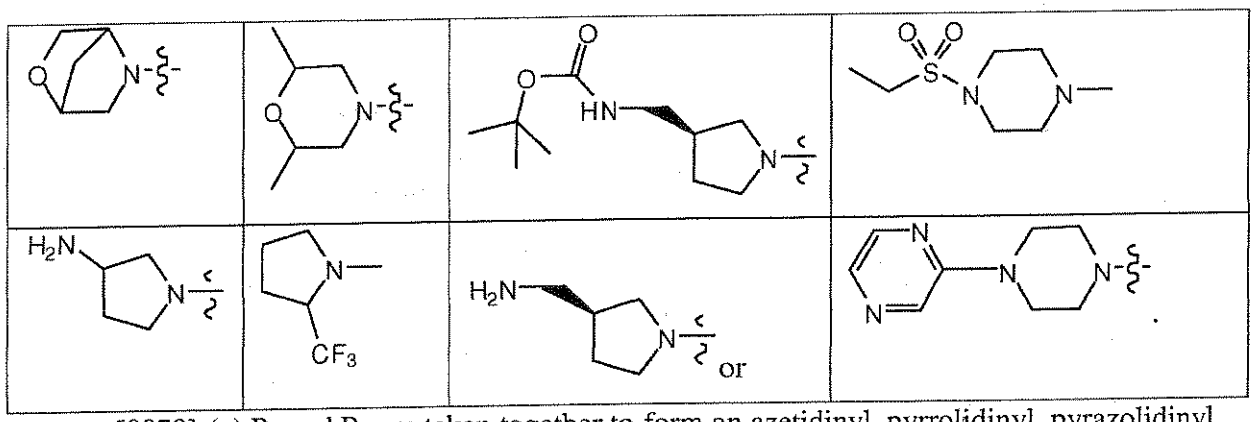
[0076] (d) Any heterocycloalkyl ring formed by R_1 and R_2 may be substituted with 0 to 2 substituents independently chosen from chloro, fluoro, hydroxyl, COOH, -$CONH_2$, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, mono- or di-C_1-C_4alkylamino, trifluoromethyl, (mono- or di-C_1-C_4alkylcarbamate)C_0-C_2alkyl-, C1-C_4alkylester, mono- or di-C_1-C_4alkylcarboxamide phenyl, benzyl, pyridyl, 5-fluorobenzo[d]imidazol-2-yl, and a group of the formula

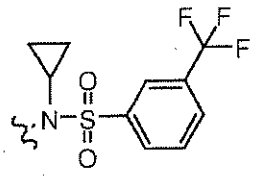


[0077] (e) R_1 and R_2 are joined to form a pyrrolidine, morpholine, piperidine, or piperazine ring, each of which is optionally substituted with 0 to 2 substituents independently chosen from fluoro, amino, hydroxyl, methyl, and trifluoromethyl.

[0078] (f) R_1 and R_2 are taken together to form a group of the formula





[0079] (g) R_1 and R_2 are taken together to form an azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl, octohydroquinolinyl, octohydroisoquinolinyl, dihydroquinolinyl, dihydroisoquinolinyl, octohydroindolyl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, or octohydroisoindolyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from chloro, fluoro, hydroxyl, COOH, -$CONH_2$, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, mono- or di-C_1-C_4alkylamino, trifluoromethyl, (mono- or di-C_1-C_4alkylcarbamate)C_0-C_2alkyl-, C_1-C_4alkylester, mono- or di-C_1-C_4alkylcarboxamide phenyl, benzyl, pyridyl, 5-fluorobenzo[d]imidazol-2-yl, and a group of the formula  .

[0080] (h) R_1 and R_2 are taken together to form an optionally substituted 5- to 9-membered bridged heterocyclic ring wherein the bridged ring is a pyrrolidinyl, morpholinyl, piperazinyl, piperidinyl, octohydroindolyl, or octohydroisoindolyl group, each of which is bridged with one of methylene, ethylene, oxoethyl, and oxo, each of which 5- to 9-membered bridged heterocyclic ring is substituted with 0, 1, or 2 substituents independently chosen from chloro, fluoro, hydroxyl, COOH, -$CONH_2$, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, mono- or di-C_1-C_4alkylamino, trifluoromethyl, and C_1-C_4alkylester.

The R_3 to R_8 Substituents

[0081] (a) R_3 and R_4 are independently (1) hydrogen, or (2) C_1-C_4alkyl or (C_3-C_7cycloalkyl) C0-C_4alkyl, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxyl, amino, cyano, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0082] (b) R_3 is hydrogen or methyl and R_4 is hydrogen, C_1-C_4alkyl, or (C_3-C_7cycloalkyl) C0-C_4alkyl.

[0083] (c) R_3 is hydrogen or methyl and R_4 is hydrogen or C_1-C_4alkyl.

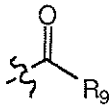
[0084] (d) R_3 and R_4 are independently hydrogen or methyl.

[0085] (e) R_3 is hydrogen or C_1-C_4alkyl, or (C_3-C_6cycloalkyl)C_0-C_2alkyl, and R_4 is hydrogen.

[0086] (f) In certain embodiments R_3, R_4, R_6, and R_8 are independently hydrogen or methyl; and R_5 is a C_7-C_{11} saturated or unsaturated hydrocarbon chain that is covalently bound to R_7, where R_7 is a methylene or methine group.

[0087] (g) The invention also includes compounds and salts in which R_3, R_4, and R_6 are independently hydrogen or methyl; and R_5 is a C_7-C_{11} saturated or unsaturated hydrocarbon chain that is covalently bound to an optionally substituted cycloalkyl ring formed by R_7 and R_8 being joined to from a 3- to 7- membered optionally substituted cycloalkyl ring.

T and R_9 Substituents

[0088] The invention includes compounds and salts of Formula I in which T is a group of the formula  and R_9 carries any of the definitions which follow.

[0089] (a) R_9 is hydroxyl, amino, -COOH, $-NR_{10}R_{11}$, $-OR_{12}$, $-SR_{12}$, $-NR_{10}(S=O)R_{11}$, $-NR_{10}SO_2R_{11}$, $-NR_{10}SONR_{11}R_{12}$, $-NR_{10}SO_2NR_{11}R_{12}$, $-(C=O)OR_{10}$, $-NR_{10}(C=O)OR_{11}$, or $-CONR_{10}R_{11}$.

R_9 is hydroxyl, $-OR_{12}$, $-NR_{10}SO_2R_{11}$, or $-NR_{10}SO_2NR_{11}R_{12}$.

[0090] (b) R_9 is $-NR_{10}SO_2R_{11}$.

[0091] (c) The invention includes compounds of Formula I including compounds in which R_9 carries the definitions (a) and (b) set forth immediately above in which R_{10} and R_{12} are independently hydrogen or methyl and R_{11} is trifluormethyl or C_1-C_6alkyl or R_{11} is C_3-C_6cycloalkyl, phenyl, or benzyl, each of which is substituted with 0 to 2 substituents independently chosen from halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, and (phenyl)C_0-C_2alkyl.

[0092] (d) In certain embodiments R_{10} is hydrogen or methyl and R_{11} is cyclopropyl.

The Y, n, J, and L Variables and M Substituent

[0093] The invention includes compounds and salts of Formula I in which any of the following conditions are met for Y, n, J, L, and M.

[0094] (a) In certain embodiments n is 0; and Y is absent, O or -O(C=O)-.

[0095] (b) In certain other embodiments n is 0 and Y is O.

[0096] (c) The invention includes embodiments in which n is 0; and Y is $-(NR_{20})(C=O)-$, where R_{20} is hydrogen or methyl.

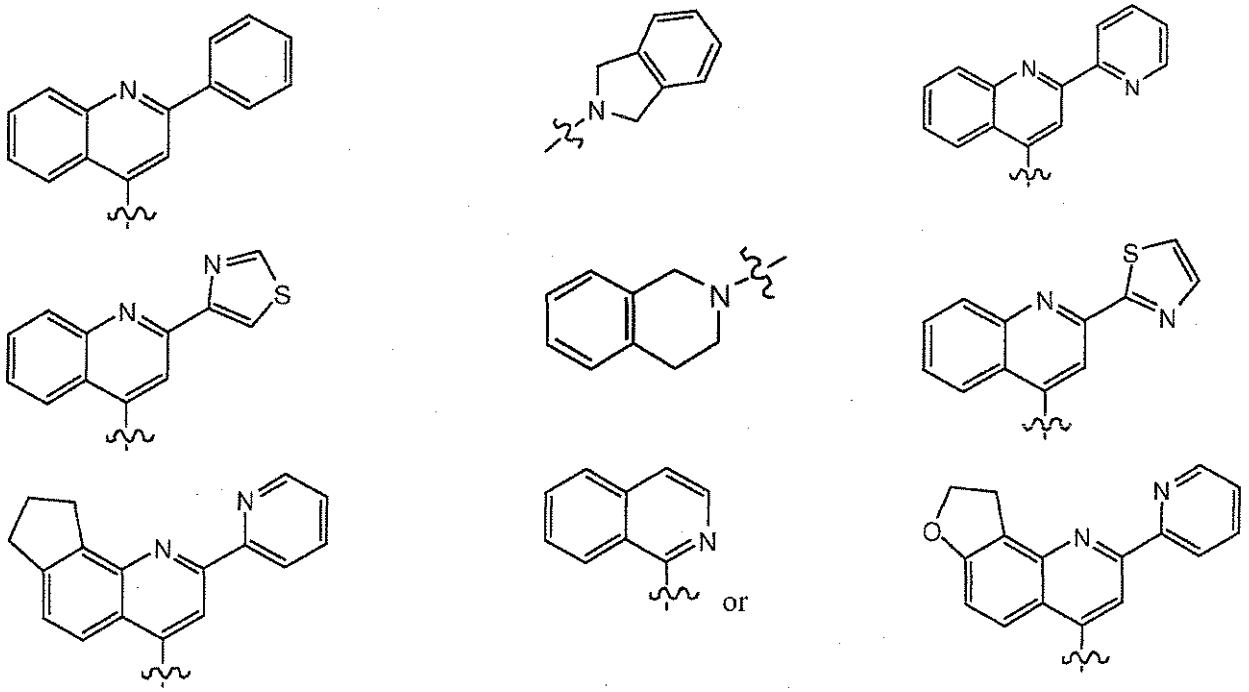
[0097] (d) M is hydrogen.

[0098] (e) J and L are both CH_2.

The Z Substituent

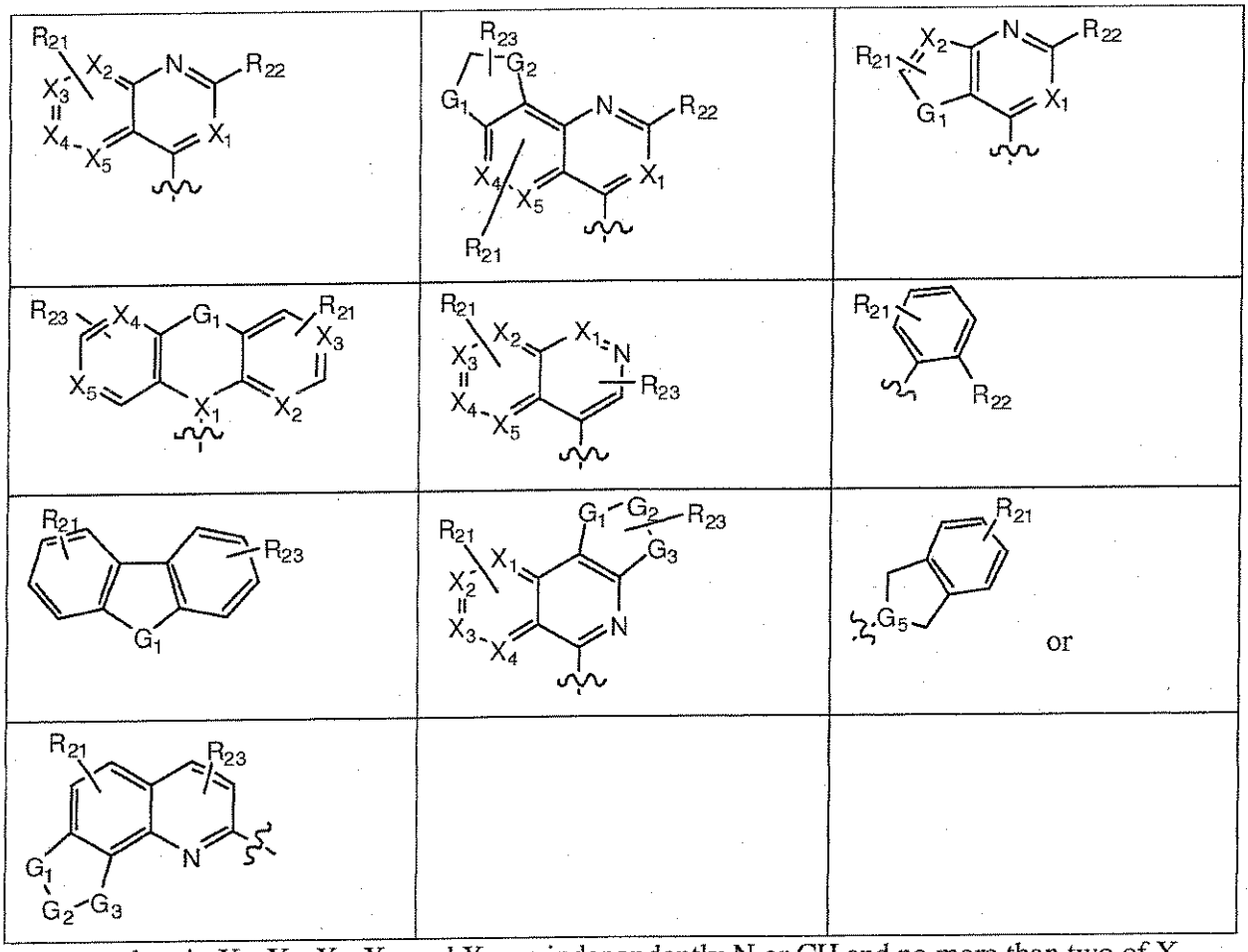
[0099] The Z Substituent may have any of the following definitions.

[0100] (a) Z is a group of the formula:



each of which is substituted by 0, 1, 2, or 3 substituents independently chosen from halogen, C_1-C_4alkyl, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

[0101] (b) Z is a group of the formula



wherein X_1, X_2, X_3, X_4, and X_5 are independently N or CH and no more than two of X_1–X_5 are N;

G_1, G_2, G_3, and G_4 are independently CH_2, O, S, or NR_{26}, wherein no more than two of G_1 to G_4 are other than hydrogen; G_5 is N or CH;

R_{21} represents from 0 to 3 groups independently chosen from halogen, hydroxyl, amino, cyano, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy,

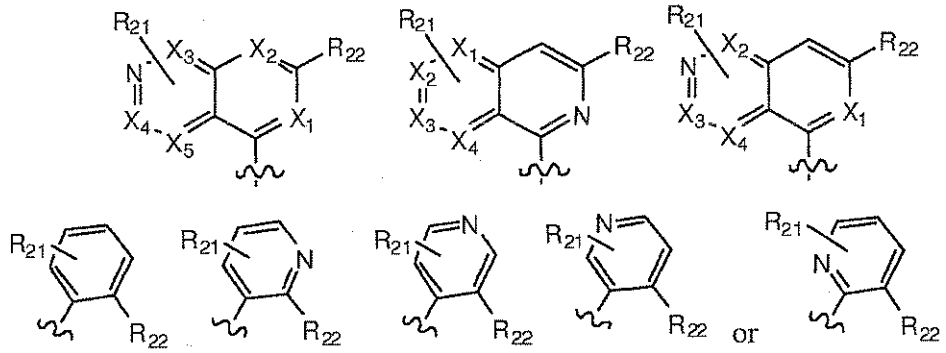
R_{22} is hydrogen, halogen, hydroxyl, amino, cyano, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- and di-C_1-C_4alkylamino, C_1-C_4alkylester, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, or

R_{22} is (phenyl)C_0-C_2alkyl, (phenyl)C_0-C_2alkoxy, (pyridyl)C_0-C_2alkyl, (5- or 6-membered heteroaryl)C_0-C_2alkoxy, naphthyl, indanyl, (thiazolyl)C_0-C_2alkyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from

halogen, hydroxyl, amino, cyano, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, trifluoromethyl, and trifluoromethoxy; and

R_{23} is 0 to 2 substituents independently chosen from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0102] (c) Z is a group of the formula



wherein

X_1, X_2, X_3, and X_4, are independently N or CH and no more than two of X_1–X_4 are N;

R_{21} represents from 0 to 3 groups independently chosen from halogen, hydroxyl, amino, cyano, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy,

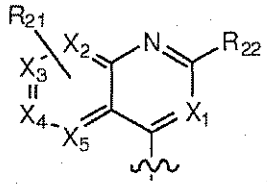
R_{22} is hydrogen, halogen, hydroxyl, amino, cyano, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- and di-C_1-C_4alkylamino, C_1-C_4alkylester, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, or

R_{22} is (C_3-C_7cycloalkyl)C_0-C_2alkyl, (phenyl)C_0-C_2alkyl, (phenyl)C_0-C_2alkoxy, (5- or 6-membered heteroaryl)C_0-C_2alkyl, (5- or 6-membered heteroaryl)C_0-C_2alkoxy, naphthyl, indanyl, (5- or 6-membered heterocycloalkyl)C_0-C_2alkyl, or 9- or 10 membered bicyclic heteroaryl, each of which is substituted with 0, 1, or 2 substituents independently chosen from

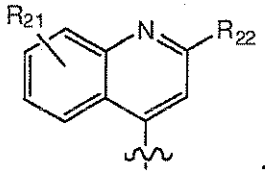
(1) halogen, hydroxyl, amino, cyano, nitro, -COOH, -$CONH_2$, CH_3(C=O)NH-, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4hydroxyalkyl, mono- and di-C_1-C_4alkylamino, -$NR_8SO_2R_{11}$, -$C(O)OR_{11}$,
-NR_8COR_{11}, -$NR_8C(O)OR_{11}$, trifluoromethyl, and trifluoromethoxy, and

(2) phenyl and 5- or 6-membered heteroaryl, each of which is substituted with 0 or 1 or more of halogen, hydroxyl, C_1-C_4alkyl, C_1-C_2alkoxy.

[0103] (c) Z is a group of the formula



[0104] (d) Z is a quinoline of the formula



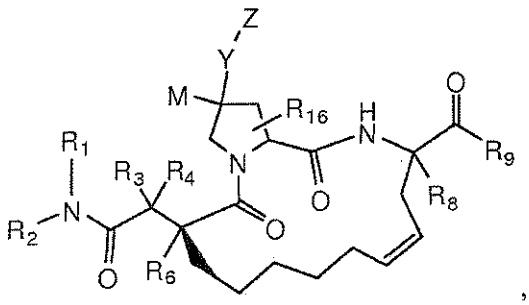
[0105] (e) In certain embodiments the variables R_{21} and R_{22} in Z carry the following definitions:

R_{21} represents a substituent at the 7-position of the quinoline, and 0 to 2 additional substituents independently chosen from halogen, hydroxyl, amino, cyano, $-CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy; and

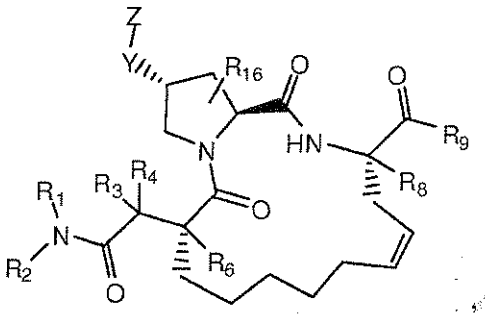
R_{22} is phenyl, pyridyl, or thiazolyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from halogen, hydroxyl, amino, cyano, -COOH, $-CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, trifluoromethyl, and trifluoromethoxy.

[0106] (f) In other embodiments R_{21} is a methoxy or ethoxy substituent at the 7-position of the quinoline and R_{22} is phenyl pyridyl, or thiazolyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from methyl, methoxy, chloro, C_1-C_4alkyl, mono and di- C_1-C_4alkylamino.

[0107] The invention includes compounds of Formula VI, VII, and VIII (which are subgeneric groups of Formula I)

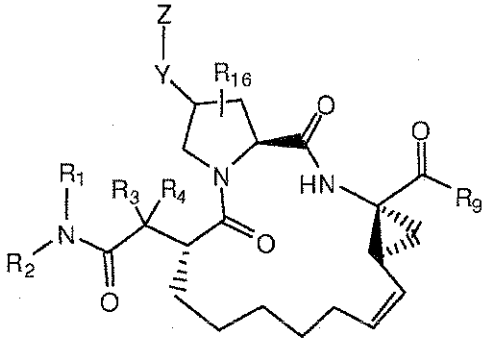


,



, or

Formula VI



Formula VII

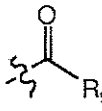
Formula VIII

[0108] Within Formula VI, VII, and VIII the following conditions are met.

[0109] R_1 and R_2 are joined to form an azetidine, pyrrolidine, morpholine, piperidine, or piperazine ring, each of which is substituted with 0 to 3 substituents independently chosen from fluoro, amino, hydroxyl, C_1-C_2alkyl, and trifluoromethyl, and each of which is substituted with 0 or 1 substituent chosen from methoxyimino, aminoC_1-C_4alkyl, C_1-C_2alkylsulfonyl, and pyrazinyl.

[0110] R_3 is hydrogen and R_4 is hydrogen, C_1-C_4alkyl, or (C_3-C_7cycloalkyl)C_0-C_2alkyl.

[0111] R_6 and R_8 are independently hydrogen or methyl;

[0112] T is a group of the formula ; and

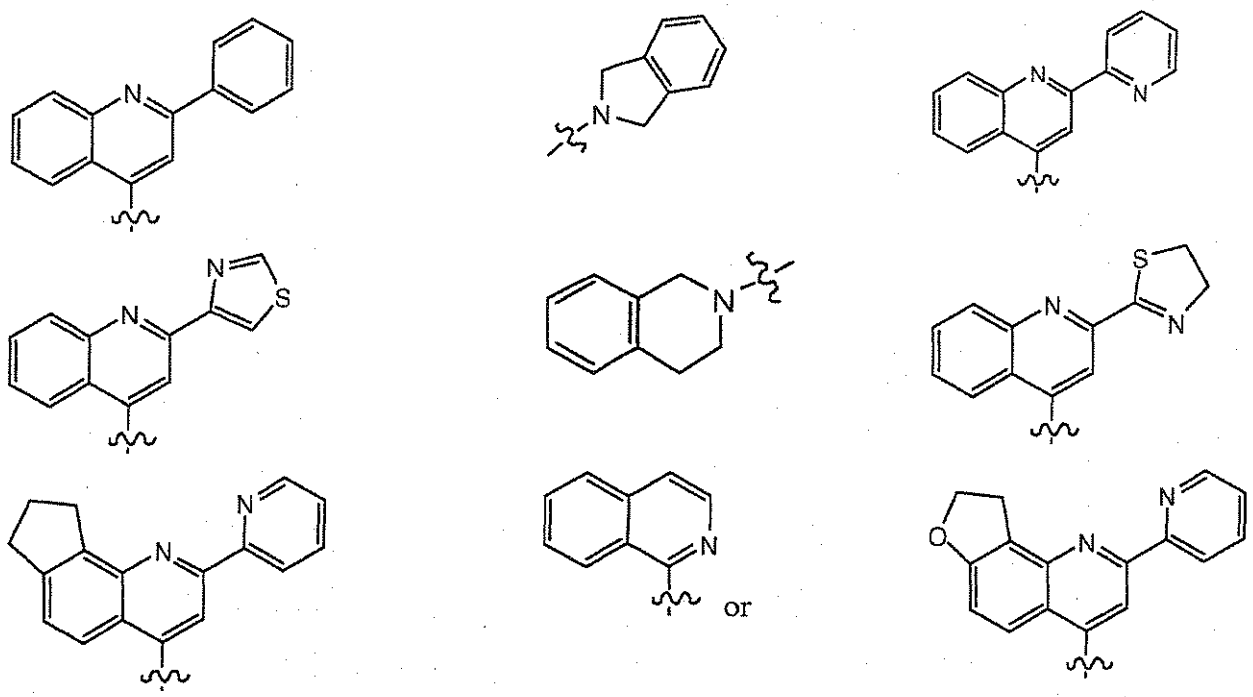
[0113] R_9 is hydroxyl, -OR_{12}, or -$NR_{10}SO_2R_{11}$, where R_{10} is hydrogen or methyl: R_{11} is C_1-C_6alkyl or C_3-C_7cycloalkyl; and R_{12} is C_1-C_4alkyl;

[0114] R_{16} is 0 to 2 substituents independently chosen from halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0115] M is hydrogen or methyl.

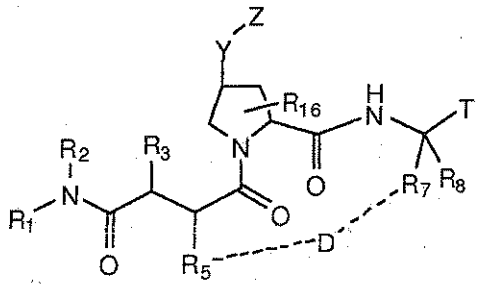
[0116] Y is O, -O(C=O)-, or –(NH)(C=O)-.

[0117] Z is a group of the formula:



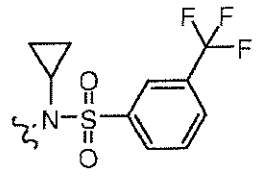
each of which is substituted by 0, 1, 2, or 3 substituents independently chosen from halogen, C_1-C_4alkyl, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

[0118] The invention includes compounds and salts of Formula IA



Formula IA

[0119] Within Formula IA, R_1 and R_2 are taken together to form an azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl, octohydroquinolinyl, octohydroisoquinolinyl, dihydroquinolinyl, dihydroisoquinolinyl, octohydroindolyl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, or octohydroisoindolyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from chloro, fluoro, hydroxyl, COOH, -$CONH_2$, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, mono- or di-C_1-C_4alkylamino, trifluoromethyl, (mono- or di-C_1-C_4alkylcarbamate)C_0-C_2alkyl-, C_1-C_4alkylester, mono- or di-C_1-

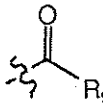
C_4alkylcarboxamide phenyl, benzyl, pyridyl, 5-fluorobenzo[d]imidazol-2-yl, and a group of the formula 

[0120] R_1 and R_2 are taken together to form an optionally substituted 5- to 9-membered bridged heterocyclic ring wherein the bridged ring is a pyrrolidinyl, morpholinyl, piperazinyl, piperidinyl, octohydroindolyl, or octohydroisoindolyl group, each of which is bridged with one of methylene, ethylene, oxoethyl, and oxo, each of which 5- to 9-membered bridged heterocyclic ring is substituted with 0, 1, or 2 substituents independently chosen from chloro, fluoro, hydroxyl, COOH, -$CONH_2$, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, mono- or di-C_1-C_4alkylamino, trifluoromethyl, and C_1-C_4alkylester.

[0121] R_3 is hydrogen or C_1-C_4alkyl, or (C_3-C_6cycloalkyl)C_0-C_2alkyl.

[0122] D is a C_7-C_{11} saturated or unsaturated hydrocarbon chain at R_5 that is (i) covalently bound to R_7, where R_7 is a methylene group or D is a C_7-C_{11} saturated or unsaturated hydrocarbon chain at R_5 that is (ii) covalently bound to a cycloalkyl ring formed by R_7 and R_8 being joined to from a 3- to 6- membered cycloalkyl ring.

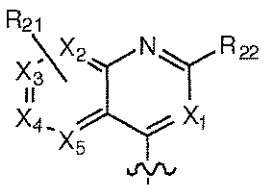
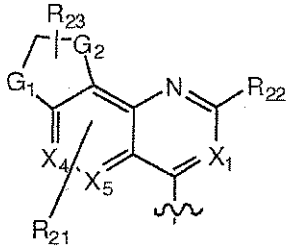
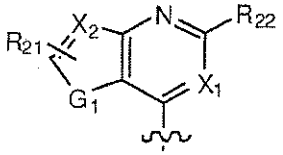
[0123] T is a group of the formula:

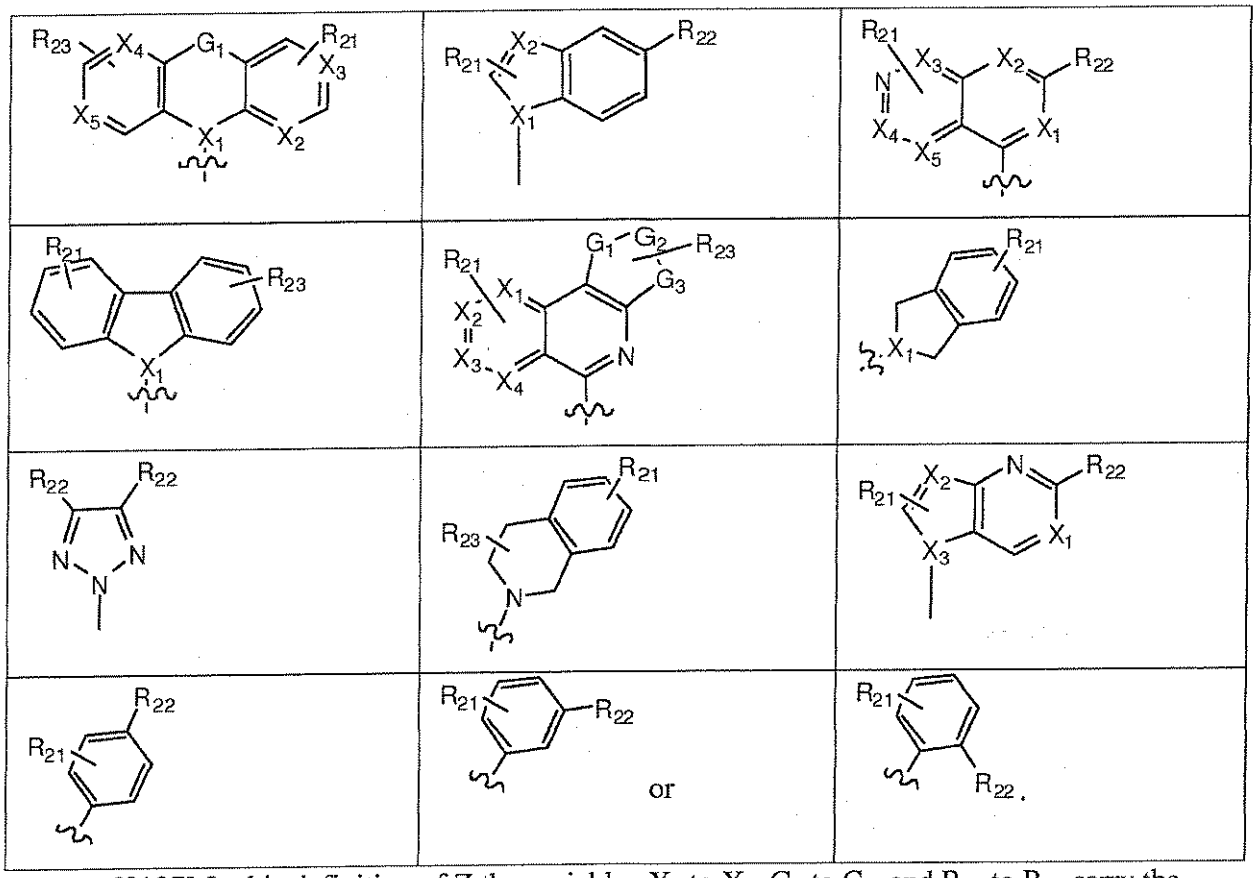
 Where, R_9 is hydroxyl, amino, -COOH, -$NR_{10}R_{11}$, -OR_{12}, -$NR_{10}SO_2R_{11}$, or -$NR_{10}SO_2NR_{11}R_{12}$, where R_{10}, R_{11}, and R_{12} are independently at each occurrence hydrogen, trifluoromethyl, C_1-C_6alkyl, C_2-C_6alkenyl, (phenyl)C_0-C_2alkyl, or (C_3-C_7cycloalkyl)C_0-C_2alkyl.

[0124] R_{16} represents 0 to 2 substituents is independently chosen from halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0125] R_{20} is hydrogen, C_1-C_2alkyl, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy.

[0126] Z is a group of the formula



[0127] In this definition of Z the variables X_1 to X_5, G_1 to G_4, and R_{21} to R_{23} carry the following definitions.

[0128] X_1, X_2, X_3, X_4, and X_5 are independently N or CH and no more than two of X_1 – X_5 are N.

[0129] G_1, G_2, G_3, and G_4 are independently CH_2, O, S, or NR_{26}, wherein no more than two of G_1 to G_4 are other than hydrogen.

[0130] R_{21} represents from 0 to 2 groups independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

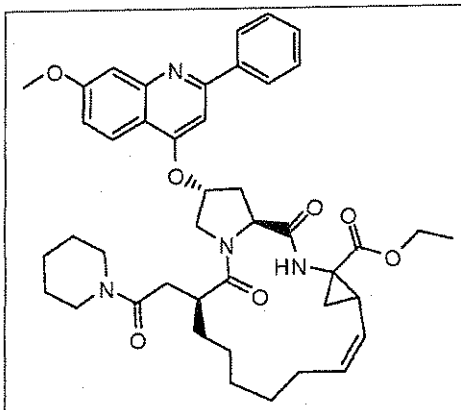
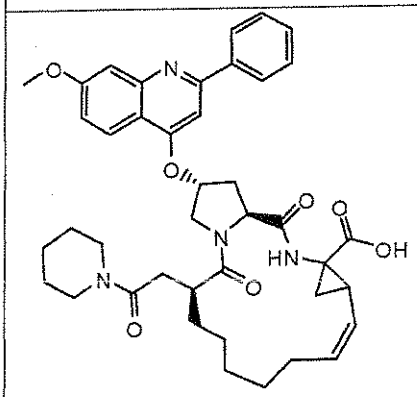
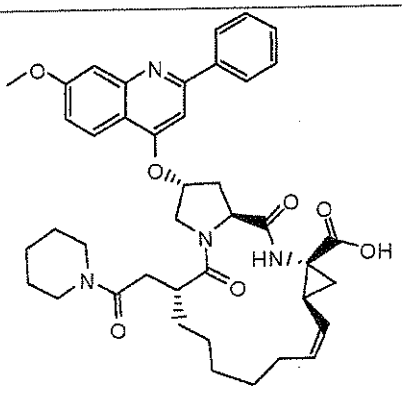
[0131] R_{22} is hydrogen, halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- or di-C_1-C_4alkylamino, C_1-C_4alkylester, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy, or R_{22} is chosen from (C_3-C_7cycloalkyl)C_0-C_2alkyl, (phenyl)C_0-C_2alkyl, (pyridyl)C_0-C_2alkyl, (phenyl)C_0--C_2alkoxy, and (thiazolyl)C_0-C_2alkyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from halogen, hydroxyl, amino, cyano, nitro, -COOH, -$CONH_2$,

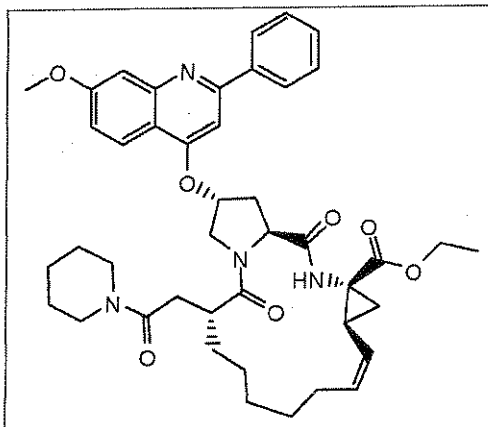
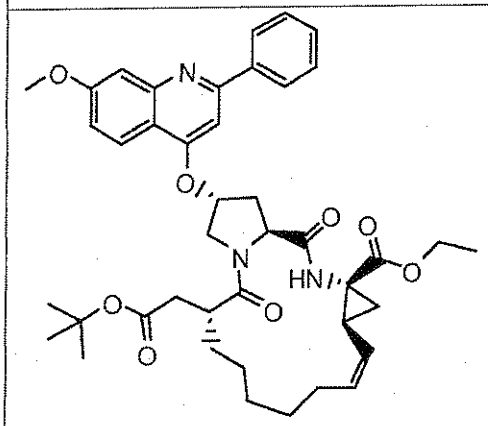
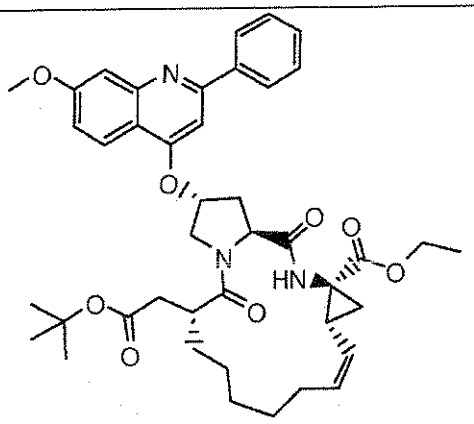
$CH_3(C=O)NH$-, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4hydroxyalkyl, mono- and di-C_1-C_4alkylamino, trifluoromethyl, and trifluoromethoxy.

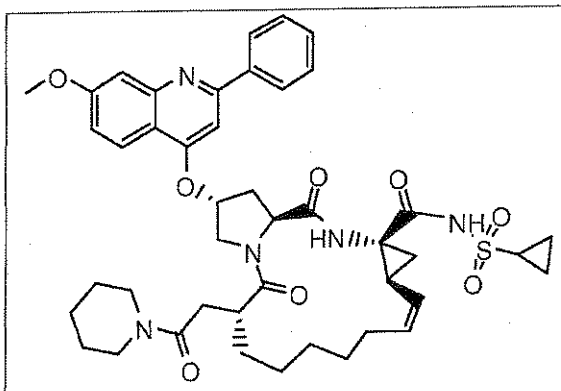
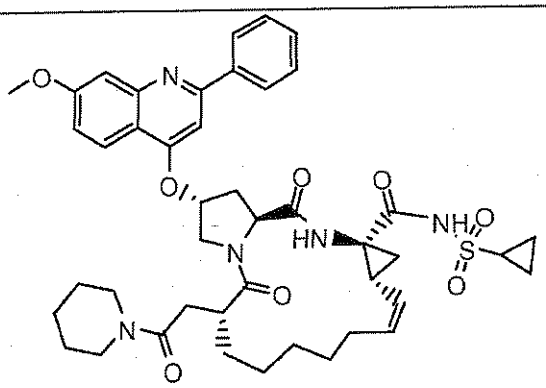
[0132] R_{23} is 0 to 2 substituents independently chosen from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0133] Any of the definitions for the variables, e.g. R_1, R_2, R_3, R_4, R_6, R_8, R_{16}, Y, Z, and T, used for Formula IA may be used for Formula I or other subgeneric formulae of Formula I so long as a stable compound results.

[0134] The following compounds are removed by proviso:

	(2R,6S,16aS,Z)-ethyl 2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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
	(2R,6S,16aS,Z)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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
	(2R,6R,13aS,14aR,16aS,Z)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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

	(2R,6R,13aS,14aR,16aS,Z)-ethyl 2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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
	(2R,6R,13aS,14aR,16aS,Z)-ethyl 6-(2-tert-butoxy-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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
	(2R,6R,13aR,14aS,16aS,Z)-ethyl 6-(2-tert-butoxy-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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

	(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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
	(2R,6R,13aR,14aS,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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

PHARMACEUTICAL PREPARATIONS

[0135] Compounds of the invention can be administered as the neat chemical, but are preferably administered as a pharmaceutical composition. Accordingly, the invention provides pharmaceutical compositions comprising a compound or pharmaceutically acceptable salt of the Formula I, together with at least one pharmaceutically acceptable carrier. The pharmaceutical composition may contain a compound or salt of Formula I as the only active agent, or may contain one or more additional active agents.

[0136] Compounds of the invention may be administered orally, topically, parenterally, by inhalation or spray, sublingually, transdermally, via buccal administration, rectally, as an ophthalmic solution, or by other means, in dosage unit formulations containing conventional pharmaceutically acceptable carriers. The pharmaceutical composition may be formulated as any pharmaceutically useful form, e.g., as an aerosol, a cream, a gel, a pill, a capsule, a tablet, a syrup, a transdermal patch, or an ophthalmic solution. Some dosage forms, such as tablets and capsules, are subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

[0137] Carriers include excipients and diluents and must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the patient being treated. The carrier can be inert or it can possess pharmaceutical benefits of its own. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound.

[0138] Classes of carriers include, but are not limited to binders, buffering agents, coloring agents, diluents, disintegrants, emulsifiers, flavorants, glidents, lubricants, preservatives, stabilizers, surfactants, tableting agents, and wetting agents. Some carriers may be listed in more than one class, for example vegetable oil may be used as a lubricant in some formulations and a diluent in others. Exemplary pharmaceutically acceptable carriers include sugars, starches, celluloses, powdered tragacanth, malt, gelatin, talc, and vegetable oils. Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the compound of the present invention.

[0139] Pharmaceutical compositions formulated for oral administration are often preferred. These compositions contain between 0.1 and 99% of a compound of the invention and usually at least about 5% (weight %) of a compound of the invention. Some embodiments contain from about 25% to about 50% or from 5% to 75 % of a compound of invention.

METHODS OF TREATMENT

[0140] The invention includes methods of preventing and treating hepatitis C infections, by providing an effective amount of a compound of the invention to patient at risk for hepatitis C infection or infected with a hepatitis C virus. A compound of the invention may be provided as the only active agent or may be provided together with one or more additional active agents.

[0141] The pharmaceutical combinations disclosed herein are useful for preventing and treating hepatitis C infections in patients.

[0142] An effective amount of a pharmaceutical combination of the invention may be an amount sufficient to (a) prevent hepatitis C or a symptom of a hepatitis C from occurring in a patient who may be predisposed to hepatitis C but has not yet been diagnosed as having it or prevent diseases that may be associated with or caused by a primary hepatitis C infection (such as liver fibrosis that can result in the context of chronic HCV infection); (b) inhibit the progression of hepatitis C; and (c) cause a regression of the hepatitis C infection. An amount of

a pharmaceutical composition effect to inhibit the progress or cause a regression of hepatitis C includes an amount effective to stop the worsening of symptoms of hepatitis C or reduce the symptoms experienced by a patient infected with the hepatitis C virus. Alternatively a halt in progression or regression of hepatitis C may be indicated by any of several markers for the disease. For example, a lack of increase or reduction in the hepatitis C viral load or a lack of increase or reduction in the number of circulating HCV antibodies in a patient's blood are markers of a halt in progression or regression of hepatitis C infection. Other hepatitis C disease markers include aminotransferase levels, particularly levels of the liver enzymes AST and ALT. Normal levels of AST are from 5 to 40 units per liter of serum (the liquid part of the blood) and normal levels of ALT are from 7 to 56 units per liter of serum. These levels will typically be elevated in a HCV infected patient. Disease regression is usually marked by the return of AST and ALT levels to the normal range.

[0143] Symptoms of hepatitis C that may be affected by an effective amount of a pharmaceutical combination of the invention include decreased liver function, fatigue, flu-like symptoms: fever, chills, muscle aches, joint pain, and headaches, nausea, aversion to certain foods, unexplained weight loss, psychological disorders including depression, tenderness in the abdomen, and jaundice.

[0144] "Liver function" refers to a normal function of the liver, including, but not limited to, a synthetic function including synthesis of proteins such as serum proteins (e.g., albumin, clotting factors, alkaline phosphatase, aminotransferases (e.g., alanine transaminase, aspartate transaminase), 5'-nucleosidase, y glutaminyltranspeptidase, etc.), synthesis of bilirubin, synthesis of cholesterol, and synthesis of bile acids; a liver metabolic function, including carbohydrate metabolism, amino acid and ammonia metabolism, hormone metabolism, and lipid metabolism; detoxification of exogenous drugs; and a hemodynamic function, including splanchnic and portal hemodynamics.

[0145] An effective amount of a combination described herein will also provide a sufficient concentration of the active agents in the concentration when administered to a patient. A sufficient concentration of an active agent is a concentration of the agent in the patient's body necessary to prevent or combat the infection. Such an amount may be ascertained experimentally, for example by assaying blood concentration of the agent, or theoretically, by calculating bioavailability. The amount of an active agent sufficient to inhibit viral infection in

vitro may be determined with a conventional assay for viral infectivity such as a replicon based assay, which has been described in the literature.

[0146] The invention also includes using pharmaceutical combinations comprising a compound of the invention in prophylactic therapies. In the context of prophylactic or preventative treatment an effective amount of a compound of the invention is an amount sufficient to significantly decrease the patient's risk of contracting a hepatitis C infection.

[0147] The invention includes a method of inhibiting HCV replication *in vivo* comprising providing a compound or salt of the invention to a patient infected with HCV a concentration of the compound or salt sufficient to inhibit HCV replicon replication *in vitro*. In this instance the concentration includes an *in vivo* concentration, such as a blood or plasma concentration. The concentration of compound sufficient to inhibit HCV replicon replication *in vitro* includes may be determined from an assay of replicon replication such as the assay provided in Example 6, herein.

[0148] Methods of treatment include providing certain dosage amounts of a compound of the invention to a patient. Dosage levels of each active agent of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the patient treated and the particular mode of administration. Dosage unit a compound of the invention. In certain embodiments 25 mg to 500 mg, or 25 mg to 200 mg of a compound of the invention are provided daily to a patient. Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most infectious disorders, a dosage regimen of 4 times daily or less is preferred and a dosage regimen of 1 or 2 times daily is particularly preferred.

[0149] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the patient undergoing therapy.

PACKAGED FORMULATIONS

[0150] The invention comprises providing a compound or salt of Formula I in a container together with instructions for using the composition to treat a patient suffering from Hepatitis C infection.

[0151] The invention includes packaged pharmaceutical combinations. Such packaged combinations include a compound of Formula I in a container. The container may additionally include instructions for using the combination to treat or prevent a viral infection, such as a hepatitis C infection, in a patient.

[0152] The packaged pharmaceutical combination may include one or more additional active agents.

COMBINATION METHODS

[0153] The invention includes pharmaceutical compositions and methods of treatment in which a compound or salt of the invention is provided together with one or more additional active agents. In certain embodiments the active agent (or agents) is an HCV protease inhibitor or HCV polymerase inhibitor. For example the protease inhibitor may be telaprevir (VX-950) and the polymerase inhibitor may be valopicitabine, or NM 107, the active agent which valopicitabine is converted into in vivo. In certain embodiments the second active agent is ribavirin, interferon, or Peg-interferon alpha conjugate.

[0154] According to the methods of the invention, the compound of the invention and an additional active agent may be: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by any other combination therapy regimen known in the art. When delivered in alternation therapy, the methods of the invention may comprise administering or delivering the compound of The invention and an additional active agent sequentially, e.g., in separate solution, emulsion, suspension, tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e., serially, whereas in simultaneous therapy, effective dosages of two or more active ingredients are administered together. Various sequences of intermittent combination therapy may also be used.

[0155] In certain embodiments method of treatment includes providing a patient with a compound of Formula I and an interferon such as a pegylated interferon or interferon gamma.

The interferon may be the only compound provided with the compound of the invention or may be provided with an additional active agent that is not an interferon.

[0156] The invention methods of treatment and pharmaceutical combinations including compounds of the invention any one or combination of the following compounds and substances as an additional active agent:

Caspase inhibitors: IDN 6556 (Idun Pharmaceuticals)

Cyclophilin Inhibitors: NIM811 (Novartis) and DEBIO-025 (Debiopharm)

Cytochrome P450 monooxygenase inhibitors: ritonavir (WO 94/14436), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole

Glucocorticoids: hydrocortisone, cortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, paramethasone, betamethasone, and dexamethasone

Hematopoietins: hematopoietin-1 and hematopoietin-2. Other members of the hematopoietin superfamily such as the various colony stimulating factors (e.g. (e.g. G-CSF, GM-CSF, M-CSF), Epo, and SCF (stem cell factor)

Homeopathic Therapies: Milk Thistle, silymarin, ginseng, glycyrrhizin, licorice root, schisandra, vitamin C, vitamin E, beta carotene, and selenium

Immunomodulatory compounds: thalidomide, IL-2, hematopoietins, IMPDH inhibitors, for example Merimepodib (Vertex Pharmaceuticals Inc.), interferon, including natural interferon (such as OMNIFERON, Viragen and SUMIFERON, Sumitomo, a blend of natural interferons), natural interferon alpha (ALFERON, Hemispherx Biopharma, Inc.), interferon alpha nl from lymphblastoid cells (WELLFERON, Glaxo Wellcome), oral alpha interferon, Peg-interferon, Peg-interferon alfa 2a (PEGASYS, Roche), recombinant interferon alfa 2a (ROFERON, Roche), inhaled interferon alpha 2b (AERX, Aradigm), Peg-interferon alpha 2b (ALBUFERON, Human Genome Sciences/ Novartis, PEGINTRON, Schering), recombinant interferon alfa 2b (INTRON A, Schering), pegylated interferon alfa 2b (PEG-INTRON, Schering, VIRAFERONPEG, Schering) ,interferon beta-1a (REBIF, Serono, Inc. and Pfizer), consensus interferon alpha (INFERGEN, Valeant Pharmaceutical), interferon gamma-1b (ACTIMMUNE, Intermune, Inc.),

un-pegylated interferon alpha, alpha interferon, and its analogues, and synthetic thymosin alpha 1 (ZADAXIN, SciClone Pharmaceuticals Inc.)

Immunosupressants: sirolimus (RAPAMUNE, Wyeth)

Interleukins: (IL-1, IL-3, IL-4, IL-5, IL-6, IL-10, IL-11, IL-12), LIF, TGF-beta, TNF-alpha) and other low molecular weight factors (e.g. AcSDKP, pEEDCK, thymic hormones, and minicytokines)

Interferon Enhancers: EMZ702 (Transition Therapeutics)

IRES inhibitors: VGX-410C (VGX Pharma)

Monoclonal and Polyclonal antibodies: XTL-6865 (XTL), HuMax-HepC (Genmab), Hepatitis C Immune Globin (human) (CIVACIR, Nabi Biopharmceuticals)

Nucleoside analogues: Lamivudine (EPIVIR, 3TC, GlaxoSmithKline), MK-0608 (Merck), zalcitabine (HIVID, Roche US Pharmaceuticals), ribavirin (including COPEGUS (Roche), REBETOL (Schering), VILONA (ICN Pharmaceuticals, and VIRAZOLE (ICN Pharmaceuticals), and viramidine (Valeant Pharmaceuticals), an amidine prodrug of ribavirin. Combinations of nucleoside analogues may also be employed.

Non-nucleoside inhibitors: PSI-6130 (Roche/ Pharmasset), delaviridine (RESCRIPTOR, Pfizer), and HCV-796 (Viropharm)

P7 protein inhibitor: amantadine (SYMMETREL, Endo Pharmaceuticals, Inc.)

Polymerase inhibitors: NM283 (valopicitabine) (Idenix) and NM 107 (Idenix).

Protease inhibitors: BILN-2061 (Boehringer Ingelheim), GW-433908 (prodrug of Amprenavir, Glaxo/ Vertex), indinavir (CRIXIVAN, Merck), ITMN-191 (Intermune/ Array Biopharma), VX950 (Vertex) and combinations comprising one or more of the foregoing protease inhibitors

RNA interference: SIRNA-034 RNAi (Sirna Therapeutics)

Therapeutic Vaccines: IC41 (Intercell), IMN-0101 (Imnogenetics), GI 5005 (Globeimmune), Chronvac-C (Tripep/ Inovio), ED-002 (Imnogenetics), Hepavaxx C (ViRex Medical)

TNF agonists: adalimumab (HUMIRA, Abbott), entanercept (ENBREL, Amgen and Wyeth), infliximab (REMICADE, Centocor, Inc.)

Tubulin inhibitors: Colchicine

Sphingosine-1-phosphate receptor modulators: FTY720 (Novartis)

TLR agonists: ANA-975 (Anadys Pharmaceuticals), TLR7 agonist (Anadys Pharmaceuticals), CPG10101(Coley), and TLR9 agonists including CPG 7909 (Coley)

Cyclophilin Inhibitors: NIM811 (Novartis) and DEBIO-025 (Debiopharm)

[0157] Patients receiving hepatitis C medications are typically given interferon together with another active agent. Thus methods of treatment and pharmaceutical combinations in which a compound of the invention is provided together with an interferon, such as pegylated interferon alfa 2a, as the additional active agents are included as embodiments. Similarly methods and pharmaceutical combinations in which ribavirin is an additional active agent are provided herein.

EXAMPLES

[0158] This invention is further illustrated by the following examples that should not be construed as limiting.

[0159] Compounds provided herein may generally be prepared using standard synthetic methods. Starting materials are generally readily available from commercial sources, such as Sigma-Aldrich Corp. (St. Louis, MO). For example, a synthetic route similar to that shown in Example 1 or 2 may be used. It will be apparent that the final product and any intermediate(s) shown in the following schemes may be extracted, dried, filtered and/or concentrated, and may be further purified (*e.g.,* by chromatography). Each variable (*e.g.,* "R") in the following Schemes, refers to any group consistent with the description of the compounds provided herein. An individual skilled in the art may find modifications of one or several of the synthetic steps described herein without diverting significantly from the overall synthetic scheme. Further experimental details for synthesis of representative compounds via these schemes are provided in Examples 1-5, herein.

ABBREVIATIONS

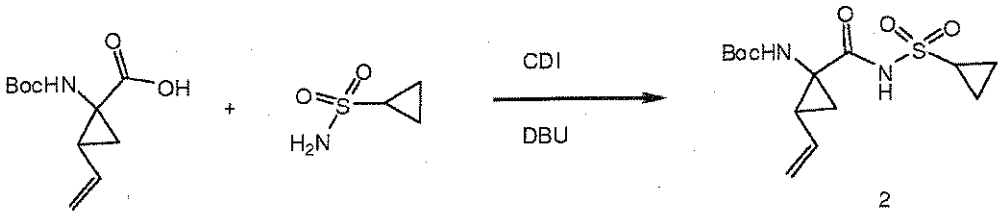
[0160] The following chemical abbreviations are used in Example 1. Additional abbreviations used in these examples will be familiar to those of skill in the art of organic chemical synthesis.

CDI	1,1'-Carbonyldiimidazole
DBU	Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIEA	N, N-Diisopropylethyl amine

DMF	Dimethyl formamide
HATU	O-(7-azabenotriazol-1-yl)-1,1,3,3-tetramethyluronium
HBTU	O-(1*H*-Benzotriazol-1-yl) *N, N,N',N'*-tetramethyluronium hexafluorophosphate
NMM	N-methylmorpholine
RCM	Ring-closing metathesis
TEA	Triethylacetate
TFA	Trifluoroacetic acid

EXAMPLE 1. SYNTHESIS OF (2S,4R)-N-(1-(CYCLOPROPYLSULFONYLCARBAMOYL)-2-VINYLCYCLOPROPYL)-4-(7-METHOXY-2-PHENYLQUINOLIN-4-YLOXY)PYRROLIDINE-2-CARBOXAMIDE (Compound **4**)

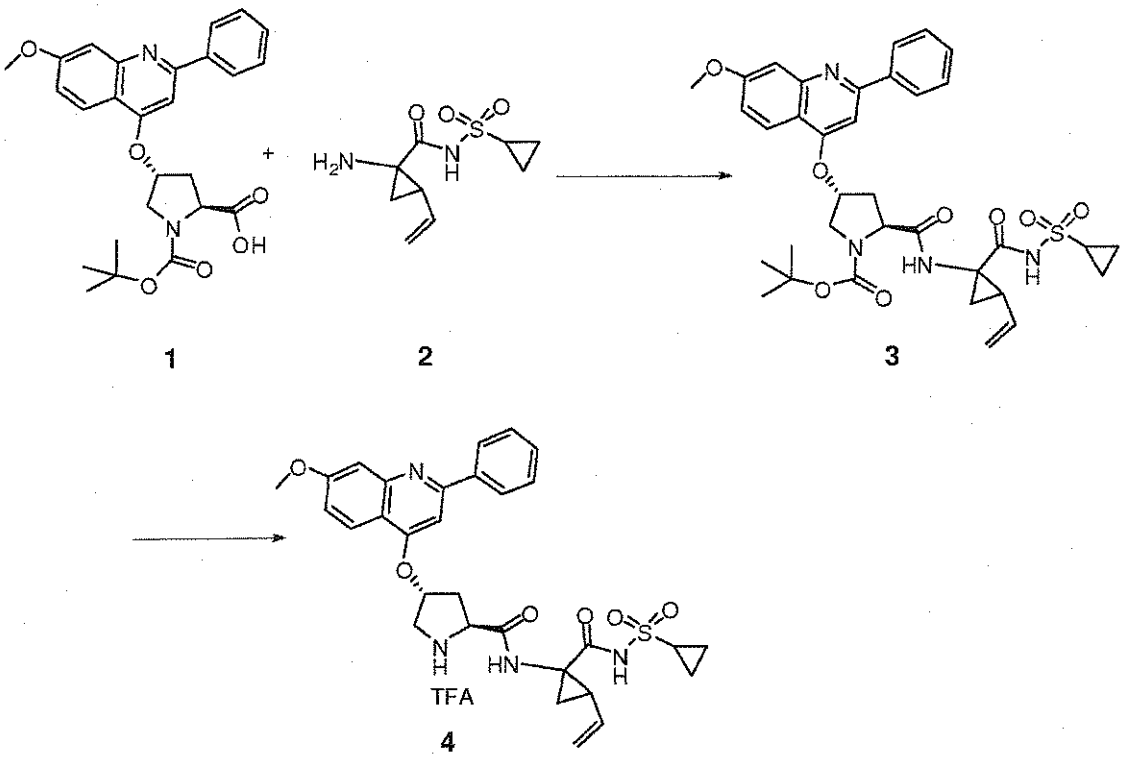
Step 1. Preparation of N-(cyclopropylsulfonyl)-1-(BOC-amino)-2-vinylcyclopropanecarboxamide



2

[0161] CDI (2.98 g, 18.4 mm, 1.1 eq) is dissolved in ethyl acetate. N-Boc-cyclopropylvinyl acid (3.8 g, 16.7 mm, 1.0 eq), prepared via the procedure given by Beaulieu, P.L. et al. (J. Org. Chem. 70: 5869-79 (2005)) is added to the CDI/ ethyl acetate mixture and stirred at RT until the starting material is consumed. Cyclopropyl sulfonamine (2.2 g, 18.4 mm, 1.1 eq) is added to this mixture followed by DBU (2.1 ml, 20.5 mm, 1.23 eq) and the mixture is stirred at RT for 2 h. Workup and purification by silica gel chromatography provides 2g of compound 2.

Step 2. Preparation of (2S,4R)-tert-butyl 2-(1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)-4-(7-methoxy-2-phenylquinolin-4-yloxy)pyrrolidine-1-carboxylate and (2S,4R)-N-(1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)-4-(7-methoxy-2-phenylquinolin-4-yloxy)pyrrolidine-2-carboxamide



[0162] Compound **1** (4.3g, 9.3mmol, 1.1 eq), prepared according to the method given in WO 02/060926, in which DMF is stirred with O-(Benzotriazol-1yl)-N,N,N',N'-Tetramethyluronium hexafluorophosphate (4.1g, 10.5mmol, 1.3eq) for 30 minutes, followed by addition of cyclopropylamine **2** (1.92g, 8.3mmol, 1.0eq) and N-methylmorpholine (2.52g, 25.0mmol,3.0eq). The mixture is stirred over night and the solvent removed under reduced pressure. The resulting residue is diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$. The organic solvent is dried over $MgSO_4$ and concentrated under reduced pressure to afford crude **3**, which is used for next step without further purification.

[0163] Compound **3** in 10 ml dry CH_2Cl_2 is treated with 5 mL TFA and stirred over night. The solvent is removed and the residue recrystallized from ethyl acetate to afford 4.12 g Compound **4** (61% yield two steps).

EXAMPLE 2. SYNTHESIS OF MACROCYCLIC COMPOUNDS

Procedure 1. DeProtection Reaction (Conversion of N-Boc to N-amine or t-butyl ester to carboxylic acid)

[0164] TFA (3~4ml) is added to a solution of Boc protected starting material (1mmol) or t-butyl ester in anhydrous DCM (7 ml) at room temperature. The reaction is monitored with LC/MS and TLC. After 1~3 hrs, the reaction mixture is evaporated reduced pressure to dryness.

The crude product is used for next step reaction without further purification.

Procedure 2. Amide formation

[0165] N-methylmorpholine (2mmol) and HBTU (1.2mmol) are added in one portion at room temperature to a solution of acid (1mmol) in anhydrous DMF (10ml). After stirring at room temperature overnight, amino (1 mmol) is added in one portion and then stirred overnight. The reaction mixture is poured into ice water and extracted with ethyl acetate (100ml). The organic layer is washed with H_2O, brine, and dried over anhydrous $MgSO_4$. The residue is filtered and evaporated in vacuum to dryness. The crude product is purified by flash chromatography on silica gel (hexane-ethyl acetate 100:0 to 50:50) to give the desired product.

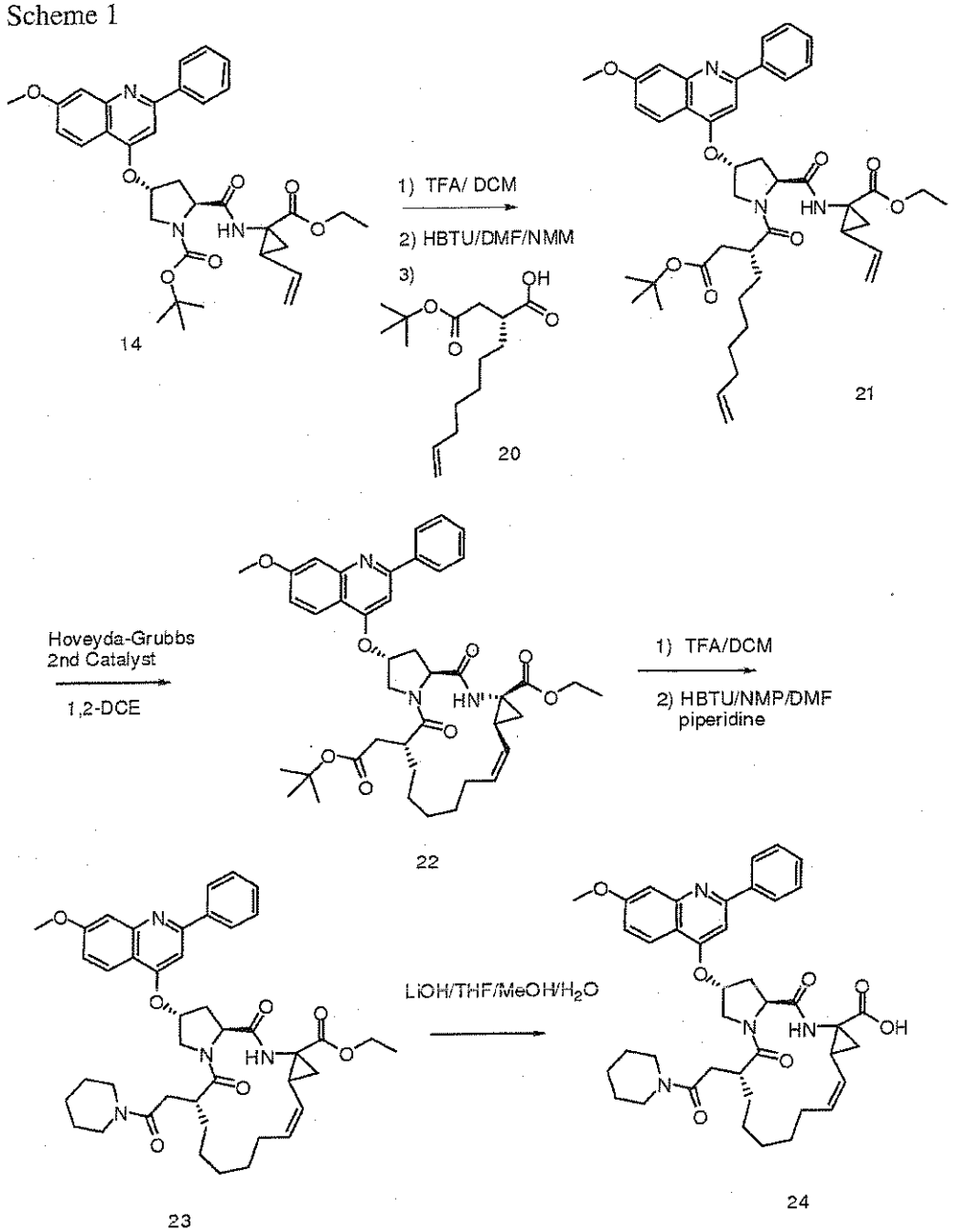
Procedure 3. RCM catalyzed by Grubbs 2nd (CAS Reg. No. 246047-72-3) or Hoveyda-Grubbs 2nd catalyst (CAS Reg. No. 301224-40-8)

[0166] A mixture of starting material (di-olefin, 1mmol), catalyst (5~30mol%) in 1,2-dichloroethane is degassed and heated to 110 °C for 12~24hrs under atmosphere of argon. The reaction is monitored by LC/MS and TLC. The reaction mixture is evaporated to dryness under reduced pressure. The crude product is purified by flash chromatography on silica gel (hexane-ethyl acetate 100:0 to 50:50) to give the desired product.

Procedure 4. Hydrolysis of esters

[0167] LiOH hydrate (6 equiv.) is added in one portion at room temperature to the solution of ester (1mmol) in THF (5ml), methanol (2.5ml), and water (2.5ml), and then the reaction mixture is stirred overnight. After the reaction is complete (by LC/MS), it is cooled to 0°C and acidified to pH~2 and extracted with DCM (20ml x 2). The reaction is dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure. The crude product is purified by flash chromatography on silica gel (hexane-ethyl acetate 100:0 to 20:80) to give the desired product.

Scheme 1



Compound **21** is prepared by procedures 1 and 2 from starting material **14** and amino acid **20**. MS (M^++1) 754.

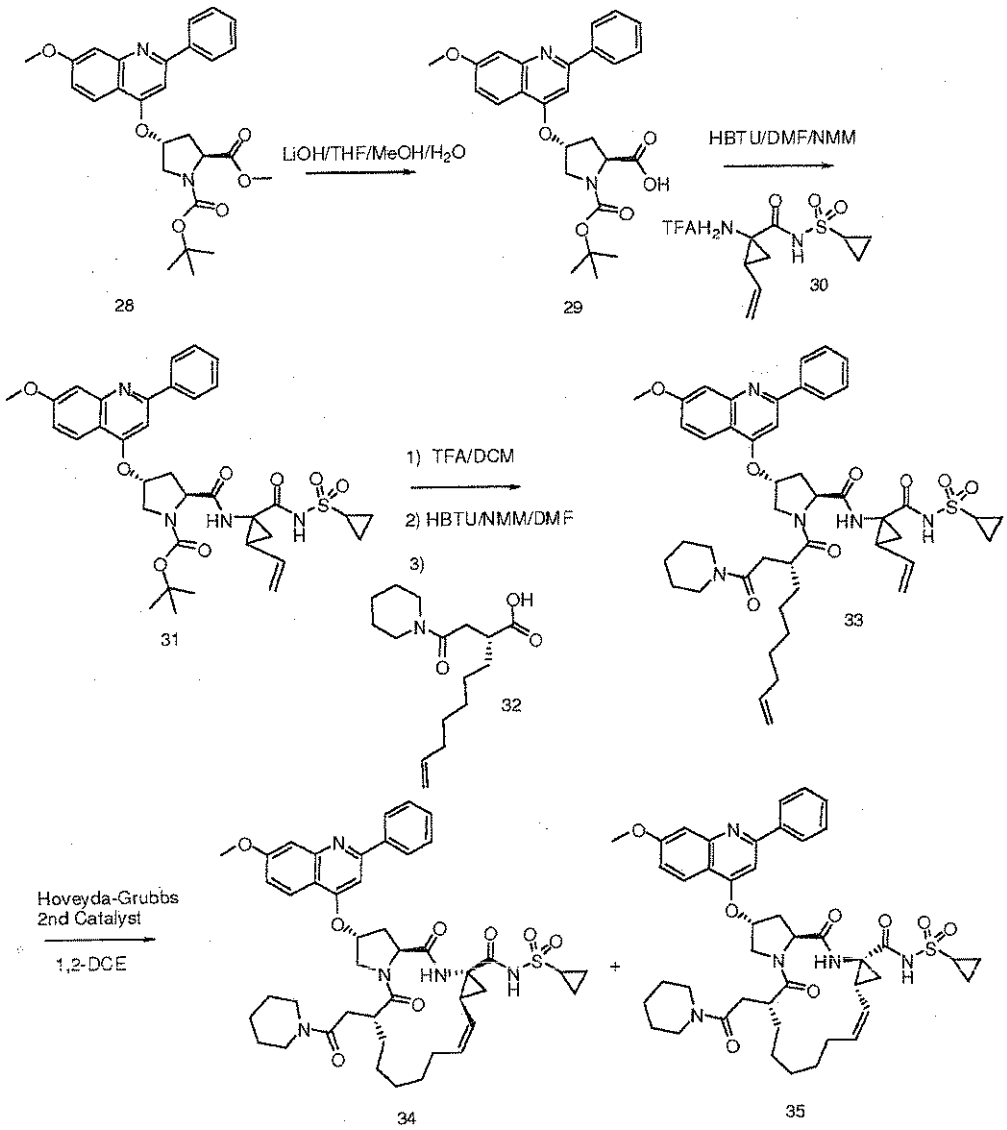
Compound **22** is prepared by procedure step 3. MS (M^++1) 726.

Compound **23** is prepared by procedures 1 and 2. MS (M^++1) 737.

Compound **24** is prepared by procedure 4. MS (M^++1) 709.

EXAMPLE 3. SYNTHESIS OF COMPOUNDS 34 AND 35

Scheme 2. Synthesis of Compounds 34 and 35



Compound **29** is prepared by procedure 4 from starting material **28**.

Compound **30** is prepared by procedure set forth in step 2 with starting material **29**.

Compound **31** is prepared by procedure set forth in steps 1 and 2 with starting material **30**.

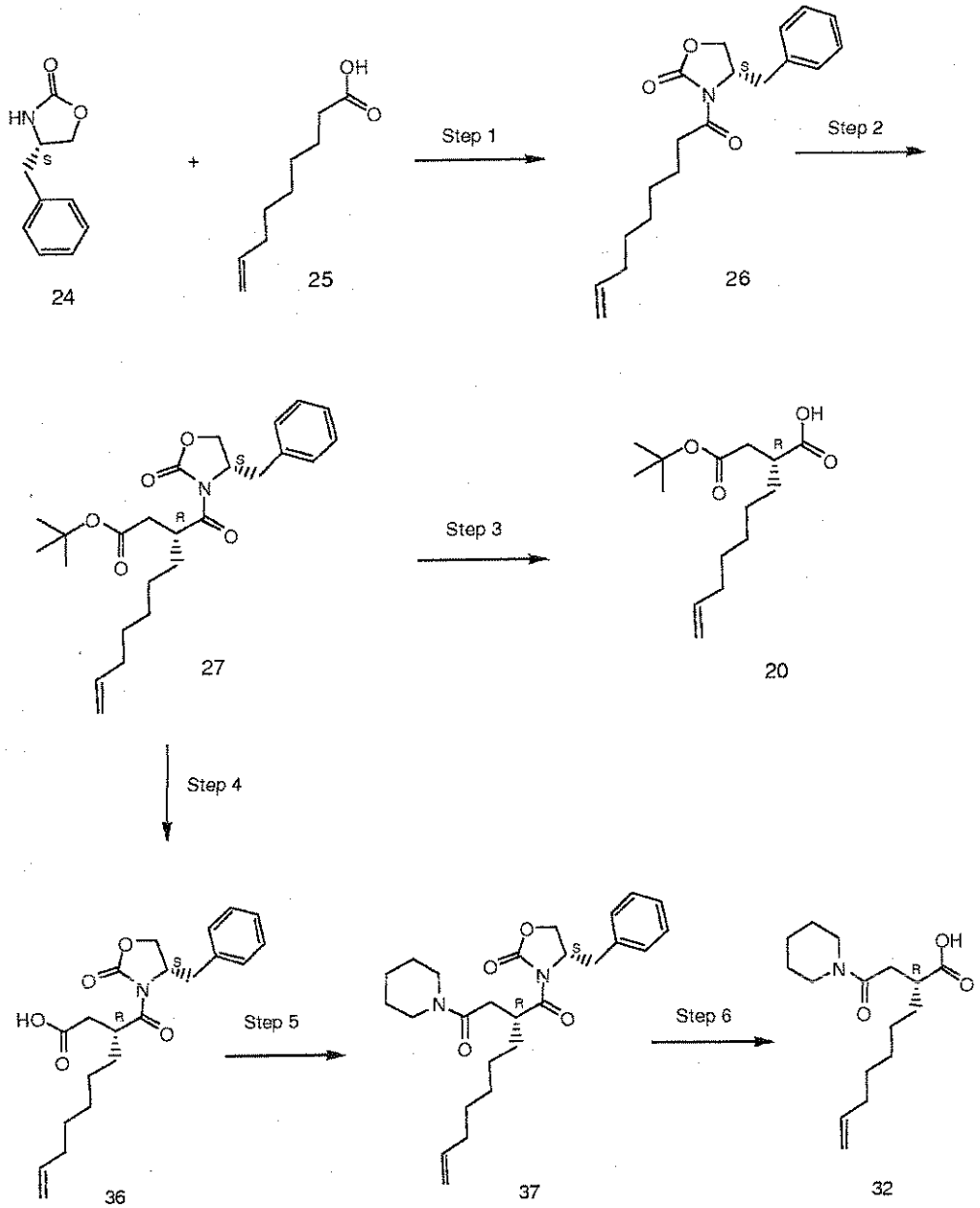
Compound **33** is prepared by procedure set forth in step 4 with starting material **28** and **32**.

Compounds **34** and **35** are prepared by the procedure set forth in step 3. After RCM, the reaction mixture is separated by prep-TLC (hexane –ethyl acetate 1:1) to afford compounds **34** and **35**.

MS (M^++1) = 812

EXAMPLE 4. PREPARATION OF INTERMEDIATES

Preparation of intermediates **20** and **32**



[0168] Step 1. 8-nonenoic acid (1.56g, 10mmol) is placed in a 100ml flask, anhydrous ether (35ml) is added under N_2, cooled to 0°C, TEA (1.6g, 16mmol) is added, followed by pivaloyl chloride (1.26g, 10.5mmol) dropwise. The ice-bath is removed and the reaction mixture is stirred at room temperature for 1hr. The resulting suspension is cooled to 0°C and filtered into a 250 ml flask under N_2 (washed twice with anhydrous ether10ml x 2). The filtrate is cooled to -78°C and diluted with anhydrous THF (25ml).

[0169] A few crystals of 1,10-phenathroline are added o a solution of (S)(-)-4-benzyl-2-oxazolidinone in THF (25ml). The solution is cooled to -78°C and a solution of *n*-BuLi (1.6M in hexane, 6.5ml, 10.4mmol) is added dropwise until the red color persists for 10 min. This solution is added to the above cooled mixed anhydride solution at -78°C over 20 min via cannula. The resulting mixture is stirred at -78°C for additional 30min, then poured into sat. NH_4Cl, the organic layer is separated, the aqueous layer is extracted with ether (50 ml, 3X). The combined organic layers are washed with brine and dried over $MgSO_4$, filtered, concentrated in reduced pressure to dryness. The crude product is purified by flash chromatography (hexane-ethyl acetate 100:0~100:20) to give 3.01g of **26** (95%).

[0170] Step 2. A solution of **26** (3.01g, 9.6mmol) in anhydrous THF is cooled to -78°C, then 2.0m solution of $NaN(TMS)_2$ in hexane (5.76ml) was added dropwise over 10min. After 30min, t-Butyl bromoacetate was added dropwise at -78°C. The reaction mixture was stirred at –78 °C for 2 hrs. LC/MS and TLC monitored the reaction. The reaction was quenched with 10% $KHSO_4$ to pH~4~6, extracted with ethyl acetate, organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtered, evaporated in reduced pressure to dryness. The crude product was purified by chromatography on silica gel (hexane –ethyl acetate 100:0~100:20) to give compound **14**.

[0171] Step 3. H_2O_2 (50%, 0.9 ml) is added dropwise over 5 min. at 0 °C, followed by a solution of LiOH (0.2g in 2ml of H_2O). The reaction mixture is added to a solution of **27** (1.05g, 2.44 mmol) in THF/H2O (5:1, 24 ml). The mixture is stirred at 0 °C for 1h and then quenched by dropwise addition of an aqueous solution of sodium thiosulphate (10 ml) while keeping the temperature below 20°C. The mixture is extracted with ethyl acetate (discarded) and the aqueous phase was acidified to pH~2 with solid citric acid and extracted with ethyl acetate. The combined organic phase is washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The residue is purified by column chromatography on silica gel, eluting with a gradient system of hexane:ethyl acetate (100:0) to 50:50 to afford the desired compound **20** (503 mg).

[0172] Step 4. Compound **36** is prepared by procedure 1.

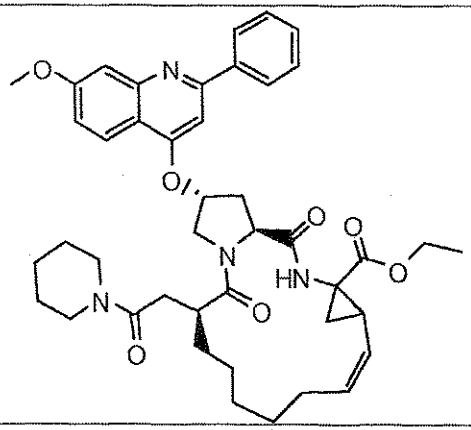
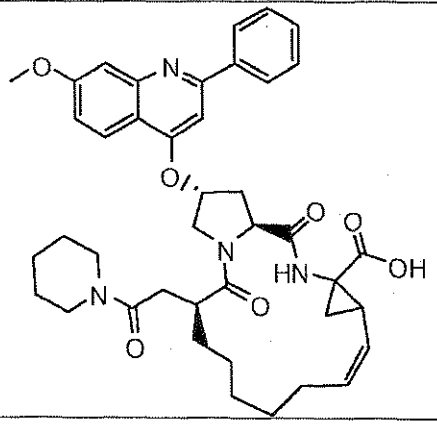
[0173] Step 5. Compound **37** is prepared by procedure 2.

[0174] Step 6. Compound **32** is prepared from **37** by the procedure given in step 3 for the preparation of compound **20**.

EXAMPLE 5. ADDITIONAL COMPOUNDS

[0175] The compounds disclosed in Table I below are prepared by the methods set forth in Examples 1-4 above.

TABLE I

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
42.		(2R,6S,16aS,Z)-ethyl 2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	**		
43.		(2R,6S,16aS,Z)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	**		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
44.		(2R,6R,13aS,14aR,16aS,Z)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	*		
45.		(2R,6R,13aS,14aR,16aS,Z)-ethyl 2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	*		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
46.		(2R,6R,13aS,14aR,16aS,Z)-ethyl 6-(2-tert-butoxy-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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	*		
47.		(2R,6R,13aR,14aS,16aS,Z)-ethyl 6-(2-tert-butoxy-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
48.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	**		
49.		(2R,6R,13aR,14aS,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	**		
50.		(2R,6R,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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-2-yl 4-fluoroisoindoline-2-carboxylate	***	3.85	742

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
51.		(2R,6R,13aR,14aR,16aS)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide	***	4.07	814
52.		(3S,13R,17R,18aS)-N-(cyclopropylsulfonyl)-17-(7-methoxy-2-phenylquinolin-4-yloxy)-1,14-dioxo-13-(2-oxo-2-(piperidin-1-yl)ethyl)octadecahydropyrrolo[1,2-a][1,4]diazacyclohexadecine-3-carboxamide	**	3.01	816
53.		(3S,4S,12R,16R,17aS)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-4-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)hexadecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide	**	4.01	816

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
54.		(3R,12R,16R,17aS)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-3-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)hexadecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide	***	4.21	816
55.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-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	***	3.95	798
56.		(3R,12R,16R,17aS,Z)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide	**	3.92	800

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
57.		(3S,12R,16R,17aS,Z)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide	**	3.99	800
58.		tert-butyl 2-((2R,6R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetate	0	3.24	801
59.		2-((2R,6R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetic acid	***	3.57	745

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
60.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-6-(2-morpholino-2-oxoethyl)-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	***	2.63	814
61.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***	2.72	848
62.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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	***	3.26	880

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
63.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***	3.01	834
64.		(12R,16R,17aS,Z)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-3-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxylic acid	**	2.87	711
65.		(3R,12R,16R,17aS,Z)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-3-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide	**	2.9	814

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
66.		(3S,12R,16R,17aS,Z)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-3-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide	**	2.94	814
67.		tert-butyl 4-(2-((2R,6R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetyl)piperazine-1-carboxylate	***	3.04	913

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
68.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,5-dimethylpiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***	2.89	840
69.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(2,6-dimethylpiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***	2.82	840

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
70.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4-fluoropiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***	3.12	830
71.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(3-(trifluoromethyl)piperidin-1-yl)ethyl)-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	***	3.41	880
72.		(2R,6R,13aS,14aR,16aS,Z)-6-(2-(tert-butylamino)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***	2.97	800

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
73.		(2R,6R,13aS,14aR,16aS,Z)-6-(2-(cyclopentylamino)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***	3.06	812
74.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	***	3.16	813.5
75.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-6-(2-(2-methylmorpholino)-2-oxoethyl)-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	***	2.96	828

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
76.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(2,6-dimethylmorpholino)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***	2.83	842
77.		(2R,6R,13aS,14aR,16aS,Z)-6-(2-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***	2.58	826
78.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-6-(2-(3-methylpiperidin-1-yl)-2-oxoethyl)-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	***	3.1	826

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
79.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-5,16-dioxo-2-(2-phenylquinoline-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	***	1.98	
80.		(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-2-(2-phenylquinoline-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		2.1	

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
81.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-2-(2-phenylquinoline-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	***		
82.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-5,16-dioxo-2-(2-(pyridin-2-yl)-8,9-dihydrofuro[2,3-h]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]diazacyclopentadecine-14a-carboxamide	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
83.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-2-(2-(pyridin-2-yl)-8,9-dihydrofuro[2,3-h]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]diazacyclopentadecine-14a-carboxamide	***		
84.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-2-(2-(pyridin-2-yl)-8,9-dihydrofuro[2,3-h]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]diazacyclopentadecine-14a-carboxamide	*		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
85.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(pyrrolidine-1-carbonyl)piperazin-1-yl)ethyl)-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	***		
86.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4-(ethylsulfonyl)piperazin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
87.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(pyrazin-2-yl)piperazin-1-yl)ethyl)-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	***		
88.		tert-butyl 2-((2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-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)acetate	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
89.		2-((2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-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)acetic acid	***		
90.		(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
91.		(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-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	***		
92.		(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
93.		(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-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	***		
94.		(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
95.		(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(2-(trifluoromethyl)pyrrolidin-1-yl)ethyl)-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	***		
96.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(6-methoxy-2-(pyridin-2-yl)quinoline-4-carboxamido)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
97.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-2-(6-methoxy-2-(pyridin-2-yl)quinoline-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	***		
98.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl)-2-(6-methoxy-2-(pyridin-2-yl)quinoline-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
99.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-((2R,6S)-2,6-dimethylpiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***		
100.		(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3-fluoropiperidin-1-yl)-2-oxoethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
101.		(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(4-fluoropiperidin-1-yl)-2-oxoethyl)-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	***		
102.		(2R,6R,14aR,16aS,Z)-6-(2-((S)-3-aminopyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
103.		tert-butyl ((3S)-1-(2-((2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetyl)pyrrolidin-3-yl)methylcarbamate	***		
104.		tert-butyl ((3S)-1-(2-((2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetyl)pyrrolidin-3-yl)methylcarbamate	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
105.		(2R,6R,14aR,16aS,Z)-6-(2-((S)-3-(aminomethyl)pyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***		
106.		(2R,6R,14aR,16aS,Z)-6-(2-((R)-3-aminopyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
107.		(2R,6R,14aR,16aS,Z)-6-(2-((R)-3-(2-aminopropan-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***		
108.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-((S)-3-hydroxypyrrolidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
109.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-((R)-pyrrolidin-3-ylamino)ethyl)-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	***		
110.		(2R,6R,14aR,16aS,Z)-6-(2-((Z)-3-(aminomethyl)-4-(methoxyimino)-3-methylpyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
111.		(2R,6R,14aR,16aS,Z)-6-(2-((S)-3-(2-aminopropan-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide	***		
112.		(2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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-2-yl 3,4-dihydroisoquinoline-2(1H)-carboxylate	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
113.		(2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-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-2-yl 3,4-dihydroisoquinoline-2(1H)-carboxylate	***		
114.		(2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-6-(2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl)-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-2-yl 3,4-dihydroisoquinoline-2(1H)-carboxylate	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
115.		(2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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-2-yl 3,4-dihydroisoquinoline-2(1H)-carboxylate	***		
116.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-8-methyl-2-(pyridin-2-yl)quinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
117.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-8-methyl-2-(pyridin-2-yl)quinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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	*		
118.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
119.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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	***		
120.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(6-methoxy-3-phenylnaphthalen-1-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
121.		(2R,6R,13aS,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(2-(isopropylamino)thiazol-4-yl)-7-methoxy-8-methylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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	***		
122.		(2R,6R,13aS,16aS,Z)-2-(5-chloro-6-methoxyisoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
123.		(2R,6R,13aS,16aS,Z)-2-(5-chloro-6-methoxyisoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-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	*		
124.		(2R,6R,13aS,16aS,Z)-2-(5-chloro-6-methoxyisoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
125.		(2R,6R,13aS,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-2-(2-(pyridin-2-yl)-8,9-dihydro-7H-cyclopenta[h]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]diazacyclopentadecine-14a-carboxamide	***		
126.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
127.		(2R,6R,13aS,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-5,16-dioxo-2-(2-(pyridin-2-yl)-8,9-dihydro-7H-cyclopenta[h]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]diazacyclopentadecine-14a-carboxamide	*		
128.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-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-carboxamide	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
129.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-8-methyl-2-(pyridin-3-yl)quinolin-4-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-carboxamide	*		
130.		(2R,6R,14aR,16aS,Z)-2-(5-chloro-6-methoxy-3-(pyridin-2-yl)isoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
131.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-8-methyl-2-(pyridin-3-yl)quinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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	***		
132.		(2R,6R,14aR,16aS,Z)-2-(5-chloro-6-methoxy-3-(pyridin-2-yl)isoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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	***		

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
133.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-2-(2-(2-isopropylthiazol-4-yl)-7-methoxy-8-methylquinolin-4-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-carboxamide	***		
134.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluorocyclohexyl)-2-oxoethyl)-2-(2-(2-(isopropylamino)thiazol-4-yl)-7-methoxy-8-methylquinolin-4-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-carboxamide			

Cpd.	STRUCTURE	Name	EC50	rt	MS+1
135.		(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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			
136.		(2R,6R,13aS,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3-fluoropiperidin-1-yl)-2-oxoethyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-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-carboxamide			

*** (EC_{50} < 1 micromolar), ** (EC_{50} between 1 micromolar and 10 micromolar) and * (EC_{50} greater than 10 micromolar).

EXAMPLE 6. ASSAY FOR IDENTIFYING COMPOUNDS WHICH INHIBIT HCV REPLICATION

[0174] Compounds claimed herein are tested for the ability to inhibit viral replication of the Hepatitis C replicon in cultured cells in which the HCV replicon construct has been incorporated. The HCV replicon system was described by Bartenschlager, et. al (Science, 285, pp. 110-113 (1999)). The replicon system is predictive of in vivo anti-HCV activity; compounds that are active in humans uniformly evidence activity in the replicon assay.

[0175] In this assay HCV replicon containing cells are treated with different concentrations of the test compound to ascertain the ability of the test compound to suppress replication of the HCV replicon. As a positive control, HCV replicon-containing cells are treated with different concentrations of interferon alpha, a known inhibitor of HCV replication. The replicon assay system includes Neomycin Phosphotransferase (NPT) as a component of the replicon itself in order to detect the transcription of replicon gene products in the host cell. Cells in which the HCV replicon is actively replicating have high levels of NPT; the level of NPT is proportional to HCV replication. Cells in which the HCV replicon is not replicating also have low levels of NPT and thus do not survive when treated with Neomycin. The NPT level of each sample is measured using a captured ELISA.

[0176] A protocol for testing compounds for the ability to inhibit viral replication of the Hepatitis C replicon cultured cells in which the replicon construct has been incorporated, follows.

6A. HCV Replicon and Replicon Expression

[0177] The HCV genome consists of a single ORF that encodes a 3000 amino acid polyprotein. The ORF is flanked on the 5' side by an untranslated region that serves as an internal ribosome entry site (IRES) and at the 3' side by a highly conserved sequence necessary for viral replication (3'-NTR). The structural proteins, necessary for viral infection, are located near the 5' end of the ORF. The non-structural proteins, designated NS2 to NS5B comprise the remainder of the ORF.

[0178] The HCV replicon contains, 5'-3', the HCV-IRES, the neomycin phosphotransferase (neo) gene, the IRES of encephalomyocarditis virus, which directs translation of HCV sequences NS3 to NS5B, and the 3'-NTR. The sequence of the HCV replicon has been deposited in GenBank (Accession no. AJ242652).

[0179] The replicon is transfected into Huh-7 cells using standard methods such as electroporation.

6B. Cell Maintenance

[0180] The equipment and materials include, but are not limited to, Huh-7 HCV replicon-containing cells, maintenance media (DMEM (Dulbecco's modified Eagle media) supplemented with 10% FBS, L-glutamine, non-essential amino acids, penicillin (100 units/ml), streptomycin (100 micrograms/ml), and 500 micrograms/ml of Geneticin (G418), screening media (DMEM supplemented with 10% FBS, L-glutamine, non-essential amino acids, penicillin (100 units/ml) and streptomycin (100 micrograms/ml)), 96 well tissue culture plates (flat bottom), 96 well plates (U bottom for drug dilution), Interferon alpha for positive control, fixation reagent (such as methanol: acetone), primary antibody (rabbit anti-NPTII), secondary antibody: Eu-N1 l, and enhancement solution.

[0181] HCV replicon-containing cells support high levels of viral RNA replicon replication when their density is suitable. Over-confluency causes decreased viral RNA replication. Therefore, cells must be kept growing in log phase in the presence of 500 micrograms/ml of G418. Generally, cells should be passed twice a week at 1: 4-6 dilution. Cell maintenance is conducted as follows:

[0182] HCV replicon-containing cells are examined under a microscope to ensure that cells growing well. Cells are rinsed once with PBS and 2 ml trypsin is added. The cell/ trypsin mixture is incubated at 37 °C in a CO_2 incubator for 3-5 minutes. After incubation 10 ml of complete media is added to stop the trypsinization reaction. Cells are blown gently, put into a 15 ml tube, and spun at 1200 rpm for 4 minutes. The trypsin/ medium solution is removed. Medium (5 ml) is added and the cells are mixed carefully. The cells are counted.

[0183] The cells are then seeded onto 96-well plates at a density of 6000-7500 cells/100 microliters/ well (6-7.5 x 10^5 cells/10 ml/plate). The plates are then incubated at 37 °C in a 5% CO_2 incubator.

[0184] Cells are examined under a microscope approximated 24 hours after seeding and prior to adding drugs. If counting and dilution were performed correctly, cells are 60-70% confluent and nearly all cells should attach and spread evenly in the well.

6C. Treatment of HCV-replicon containing cells with Test Compound

[0185] HCV replicon-containing cells are rinsed with once PBS once; 2 mls of trypsin are then added. Cells are incubated at 37°C in a 5% CO_2 incubator for 3-5 minutes. 10 mls of complete medium is added to stop the reaction. Cells are blown gently, put into a 15 ml tube, and spun at 1200 rpm for four minutes. The trypsin/medium solution is removed and 5 mls of medium (500 ml DMEM (high glucose)) from BRL catalog #12430-054; 50 mls 10% FBS, 5% Geneticin G418 (50 mg/ml, BRL catalog #10131-035), 5 ml MEM non-essential amino acids (100x BRL #11140-050) and 5 ml pen-strep (BRL #15140-148) is added. The cells and media are mixed carefully

[0186] Cells are plated with screening medium (500 ml DMEM (BRL #21063-029), 50 ml FBS (BRL #10082-147) and 5 ml MEM non-essential amino acid (BRL #11140-050) at 6000-7500 fcells/100 µl/well of 96 well plate (6-7.5x105 cells/10 ml/plate). Plates are placed into 37°C 5% CO_2 incubator overnight.

6D. Assay

[0187] The following morning, drugs (test compounds or interferon alpha) are diluted in 96 well U bottom plates with media or DMSO/media, depending on the final concentration chosen for screening. Generally for 6 concentrations of each test compounds ranging from 10 micromolar to 0.03 micromolar are applied. 100 µl of the test compound dilution is placed in wells of the 96 well plate containing the HCV replicon cells. Media without drug is added to some wells as a negative controls. DMSO is known to affect cell growth. Therefore, if drugs diluted in DMSO are used, all wells, including negative control (media only) and positive control (interferon alpha) wells, must contain the same concentration of DMSO, for single dose screening. The plates are incubated at 37°C in a humidified 5% CO_2 environment for three days.

[0188] On day four, the NTPII assay is quantitated. The medium is poured from the plates and the plates are washed once in 200 µl of PBS. The PBS is then decanted and the plates tapped in a paper towel to remove any remaining PBS. Cells are fixed in situ with 100 µl/well of pre-cooled (-20°C) methanol: acetone (1:1) and the plates are placed at -20°C for 30 minutes.

[0189] The fixing solution is poured from the plates and the plates allowed to air-dry completely (approximately one hour). The appearance of the dried cell layer is recorded and the density of the cells in the toxic wells is scored with the naked eye. Alternatively cell viability may be assessed using the MTS assay described below.

[0190] The wells are blocked with 200 µl of blocking solution (10% FBS; 3% NGS in PBS) for 30 minutes at room temperature. The blocking solution is removed and 100 µl of rabbit anti-NPTII diluted 1:1000 in blocking solution is added to each well. The plates are then incubated 45-60 minutes at room temperature. After incubation, wells are washed six times with PBS-0.05% Tween-20 solution. 100 µl of 1:15,000 diluted Europium (EU)-conjugated goat anti-rabbit in blocking buffer is added to each well and incubated at room temperature for 30-45 minutes. The plates are washed again and 100 µl of enhancement solution (Perkin Elmer #4001-0010) is added to each well. Each plate is shaken (approx. 30 rpm) in a plate shaker for three minutes. 95 µl is transferred from each well to a black plate; the EU signal is quantitated in a Perkin-Elmer VICTOR plate reader (EU-Lance).

[0191] When tested in this assay Compounds 11, 16, 25, 33, 38, 39, and 40 exhibit EC50 values of about 10 micromolar or less.

EXAMPLE 7. CYTOTOXICITY ASSAYS

[0192] To insure that the decrease in replicon replication is due to compound activity against the HCV replicon rather than nonspecific toxicity assays are used to quantitate compound cytotoxicity.

7A. Cellular protein albumin assay for cytotoxicity

[0193] Cellular protein albumin measurements provide one marker of cytotoxicity. The protein levels obtained from cellular albumin assays may also be used to provide a normalization reference for antiviral activity of compounds. In the protein albumin assay HCV replicon-containing cells are treated for three days with different concentrations of helioxanthin; a compound that is known to be cytotoxic at high concentrations. The cells are lysed and the cell lysate used to bind plate-bound goat anti-albumin antibody at room temperature (25 °C to 28 °C) for 3 hours. The plate is then washed 6 times with 1X PBS. After washing away the unbound proteins, mouse monoclonal anti-human serum albumin is applied to bind the albumin on the plate. The complex is then detected using phosphatase-labeled anti-mouse IgG as a second antibody.

7B. MTS Assay for Cytotoxicity

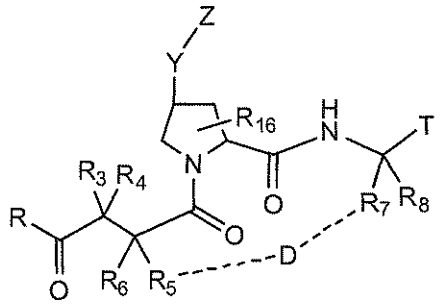
[0194] Cell viability may also be determined by CELLTITER 96 AQUEOUS ONE Solution Cell Proliferation Assay (Promega, Madison WI), a colorimetric assay for determining

the number of viable cells. In this method, before fixing the cells, 10-20 µl MTS reagent is added to each well according to manufacturer's instructions, plates are incubated at 37°C and read at OD 490 nm. During the incubation period living cells covert the MTS reagent to a formazan product which absorbs at 490 nm. Thus the 490 nm absorbance is directly proportional to the number of living cells in culture.

[0195] A direct comparison of the Cellular Albumin and MTS methods for determining cytotoxicity may be obtained as follows: Cells are treated with different concentrations of test compound or Helioxanthin for a three day-period. Prior to lysis for detection albumin as described above, the MTS reagent is added according to manufacturer's instruction to each well and incubate at 37 °C and read at OD 490 nm. The cellular albumin quantitation is then performed as described above.

CLAIMS

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, where

R is $-NR_1R_2$ and

R_1 and R_2 are joined to form a 4- to 7- membered heterocycloalkyl ring containing 0 to 2 additional heteroatoms independently chosen from N, O, and S which ring is optionally fused to a 5- or 6- membered heterocyclic ring, containing 1 or 2 heteroatoms independently chosen from N, O, and S, or optionally fused to a 5- or 6-membered carbocyclic ring to form a bicyclic ring system, each of which 5- to 7- membered heterocycloalkyl ring or bicyclic ring system is optionally substituted; or

R_1 and R_2 are taken together to form an optionally substituted 5- to 9-membered bridged heterocyclic ring containing 0, 1, or 2 additional N, S, or O atoms;

R_3, R_4, and R_8 are independently

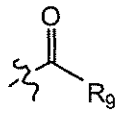
(a) hydrogen, halogen, or amino, or

(b) C_1-C_6alkyl, C_2-C_6alkenyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (aryl)C_0-C_4alkyl, (heteroaryl)C_0-C_4alkyl, (C_3-C_7cycloalkenyl)C_0-C_4alkyl, (heterocycloalkyl)C_0-C_4alkyl, C_2-C_6alkanoyl, or mono- or di- C_1-C_6alkylamino, each of which is optionally substituted;

R_6 is hydrogen, C_1-C_6alkyl, or (C_3-C_7cycloalkyl)C_0-C_2alkyl;

D is an alkyl or alkenyl group having 6 to 10 carbon atoms that is (i) covalently bound to R_7, where R_7 is a methylene or methine group or (ii) covalently bound to an optionally substituted cycloalkyl ring formed by R_7 and R_8 being joined to form a 3- to 7- membered optionally substituted cycloalkyl ring;

T is a group of the formula:



R_9 is $-NR_{10}SO_2R_{11}$ and

R_{10} and R_{11} are independently at each occurrence

hydrogen or trifluoromethyl, or

C_1-C_6alkyl, C_2-C_6alkenyl, (aryl)C_0-C_2alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, (heterocycloalkyl)C_0-C_2alkyl, or (5- to 10-membered heteroaryl)C_0-C_2alkyl, each of which is optionally substituted;

Y is –O-, -O(C=O)- or -(NR_{20})(C=O)-;

Z is (mono- , bi-, or tri- cyclic heteroaryl)C_0-C_2alkyl,

each of which Z is substituted with

0 or 1 or more substituents independently chosen from halogen, hydroxyl, amino, cyano, $-CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, and

0 or 1 (C_3-C_7cycloalkyl)C_0C_2alkyl, (phenyl)C_0-C_2alkyl, or (5- or 6-membered heteroaryl)C_0-C_2alkyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from:

halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, trifluoromethyl, and trifluoromethoxy,

R_{16} represents 0 to 4 substituents is independently chosen from halogen, C_1-C_2alkyl, and C_1-C_2alkoxy; and

R_{20} is hydrogen, C_1-C_2alkyl, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy, wherein the compound is not

(2R,6S,16aS,Z)-ethyl 2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6S,16aS,Z)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,14aR,16aS,Z)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,14aR,16aS,Z)-ethyl 2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,14aR,16aS,Z)-ethyl 6-(2-tert-butoxy-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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;

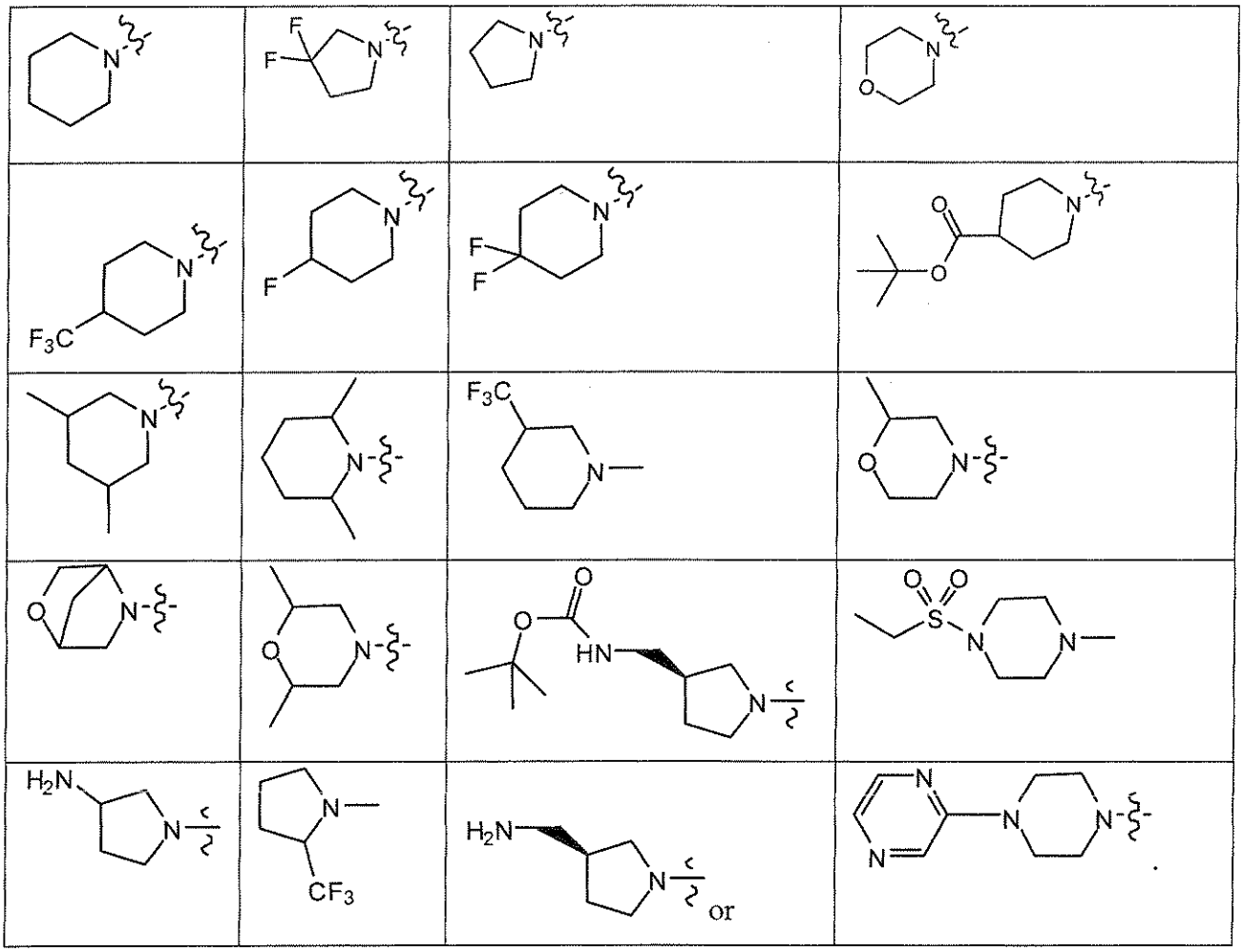
(2R,6R,13aR,14aS,16aS,Z)-ethyl 6-(2-tert-butoxy-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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; and

(2R,6R,13aR,14aS,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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.

2. The compound or salt of Claim 1, wherein R_1 and R_2 are joined to form a pyrrolidine, morpholine, piperidine, or piperazine ring, each of which is substituted with 0 to 2 substituents independently chosen from fluoro, amino, hydroxyl, methyl, and trifluoromethyl.

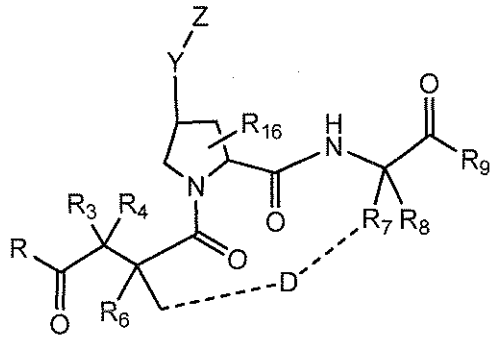
3. The compound or salt of Claim 1 in which R_1 and R_2 are taken together to form a group of the formula



4. A compound or salt of Claim 2, wherein R_3 is hydrogen or methyl and R_4 is hydrogen or C_1-C_4alkyl.

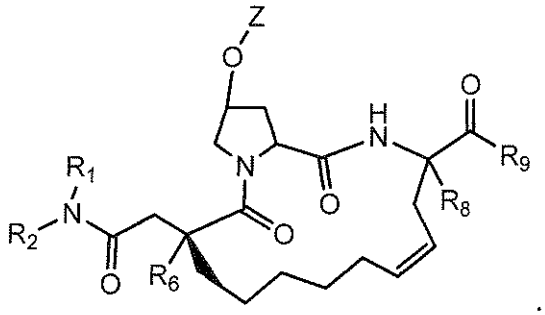
5. A compound or salt of Claim 4, wherein R_3 and R_4 are independently hydrogen or methyl.

6. The compound or salt of Claim 5, of the formula

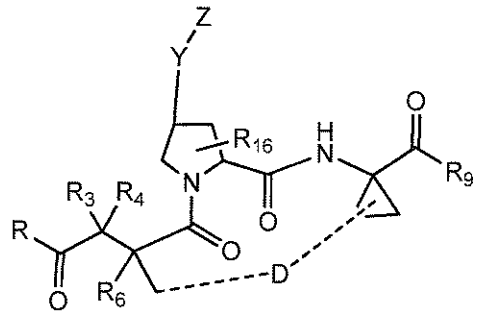


where R_3, R_4, R_6, and R_8 are independently hydrogen or C_1-C_4alkyl.

7. The compound or salt of Claim 6, of the formula

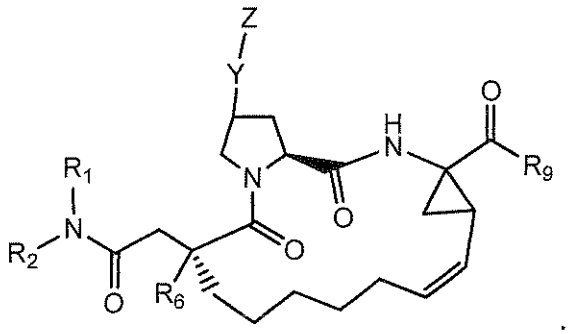


8. The compound or salt of Claim 1, having the formula



where D is an alkyl or alkenyl group having 6 to 10 carbon atoms; and R_3, R_4, and R_6 are independently hydrogen or C_1-C_4alkyl.

9. The compound or salt according to Claim 8, of the formula



10. The compound or salt of Claim 2, wherein

R_9 is $-NR_{10}SO_2R_{11}$; and

R_{11} is C_1-C_4alkyl, C_3-C_6cycloalkyl, phenyl, or benzyl, each of which is substituted with 0 to 2 substituents independently chosen from halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, and (phenyl)C_0-C_2alkyl.

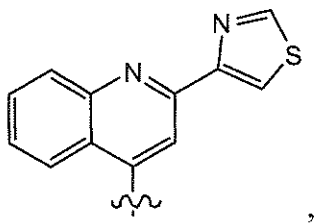
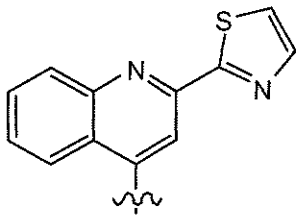
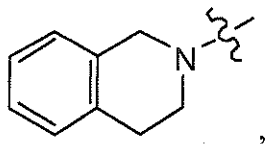
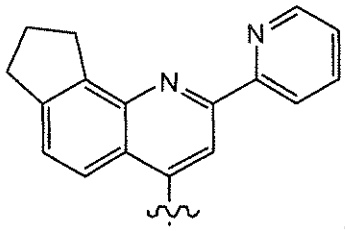
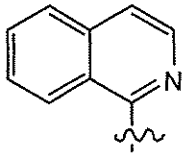
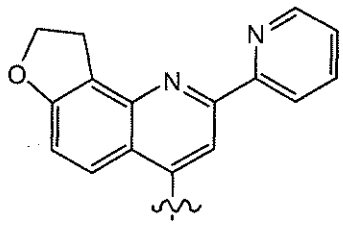
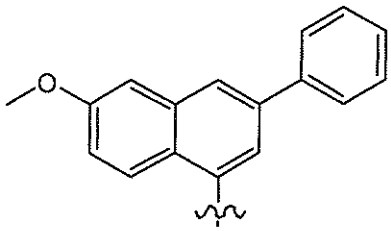
11. The compound or salt of Claim 10 wherein

R_{10} is hydrogen or methyl; and R_{11} is C_1-C_4alkyl or cyclopropyl.

12. The compound or salt of Claim 2 wherein Y is O, -O(C=O)-, or $-(NR_{20})(C=O)-$; and

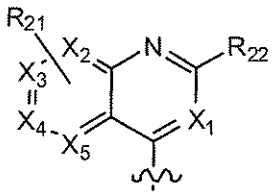
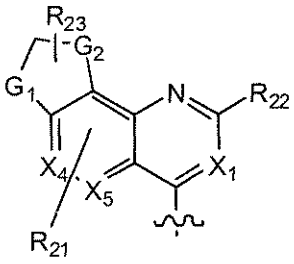
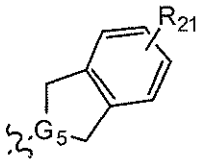
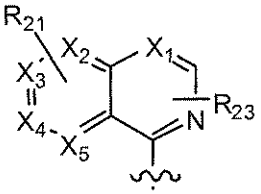
R_{20} is hydrogen or methyl.

13. The compound or salt of Claim 2 wherein Z is


,

,

,

,

,

or


each of which is substituted by 0, 1, 2, or 3 substituents independently chosen from halogen, C_1-C_4alkyl, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

14. The compound or salt of Claim 2, wherein Z is a group of the formula




or


wherein

X_1, X_2, X_3, X_4, and X_5 are independently N or CH and no more than two of X_1–X_5 are N;

G_1 and G_2 are independently CH_2, O, S, or NR_{26}, G_5 is N or CH;

R_{21} represents from 0 to 3 groups independently chosen from halogen, hydroxyl, amino, cyano, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy,

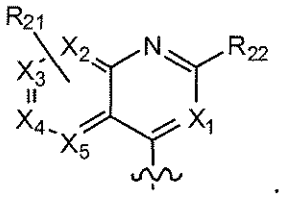
R_{22} is hydrogen, halogen, hydroxyl, amino, cyano, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, C_1-C_4alkylthio, mono- or di-C_1-C_4alkylamino, C_1-C_4alkylester, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy, or

R_{22} is (phenyl)C_0-C_2alkyl, (phenyl)C_0-C_2alkoxy, (pyridyl)C_0-C_2alkyl, or (thiazolyl)C_0-C_2alkyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from

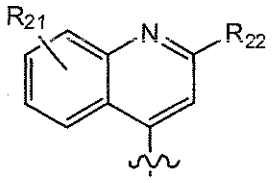
halogen, hydroxyl, amino, cyano, -COOH, -$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, trifluoromethyl, and trifluoromethoxy; and

R_{23} is 0 to 2 substituents independently chosen from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

15. The compound or salt according to Claim14, wherein Z is a group of the formula



16. The compound or salt of Claim 15, where Z is a quinoline of the formula



, wherein

R_{21} represents a substituent at the 7-position of the quinoline, and 0 to 2 additional substituents independently chosen from halogen, hydroxyl, amino, cyano, -$CONH_2$, -COOH, C_1-C_4alkyl, C_2-C_4alkanoyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy; and

R_{22} is phenyl, pyridyl, or thiazolyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from halogen, hydroxyl, amino, cyano, -COOH, -

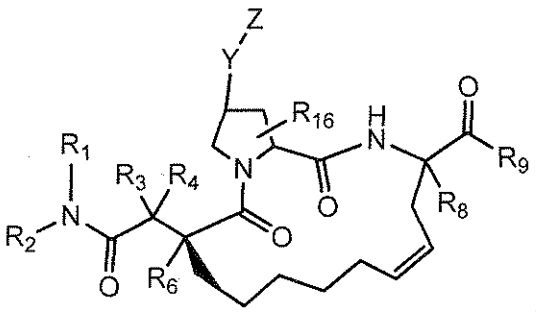
$CONH_2$, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, trifluoromethyl, and trifluoromethoxy.

17. The compound or salt of Claim 15, wherein

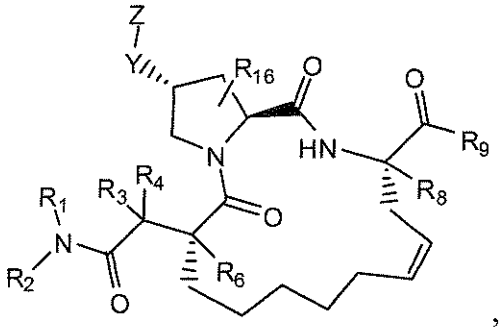
R_{21} is a methoxy or ethoxy substituent at the 7-position of the quinoline, and optionally an additional halogen substituent at the 8-position of the quinoline; and

R_{22} is phenyl, pyridyl, or thiazolyl, each of which is substituted with 0, 1, or 2 substituents independently chosen from methyl, methoxy, chloro, C_1-C_4alkyl, C_1-C_4mono and di-alkyl amino.

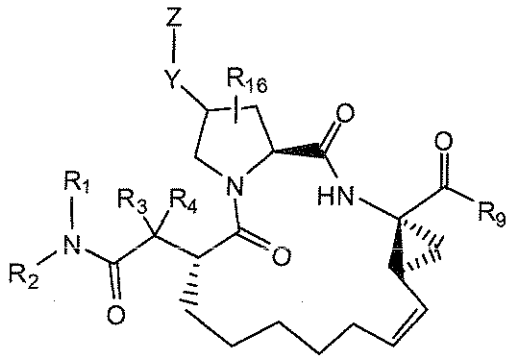
18. A compound or salt of Claim 1 of the formula



,



, or



wherein

R_1 and R_2 are joined to form an azetidine, pyrrolidine, morpholine, piperidine, or piperazine ring,

each of which is substituted with 0 to 3 substituents independently chosen from fluoro, amino, hydroxyl, C_1-C_2alkyl, and trifluoromethyl, and

also substituted with 0 or 1 substituent chosen from methoxyimino, aminoC_1-C_4alkyl, C_1-C_2alkylsulfonyl, and pyrazinyl;

R_3 is hydrogen;

R_4 is hydrogen, C_1-C_4alkyl, or (C_3-C_7cycloalkyl)C_0-C_2alkyl;

R_6 and R_8 are independently hydrogen or methyl;

R_9 is $-NR_{10}SO_2R_{11}$;

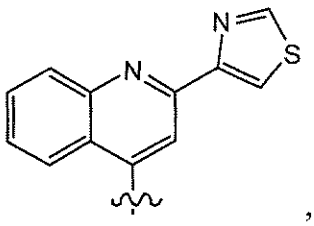
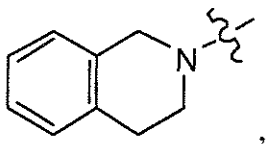
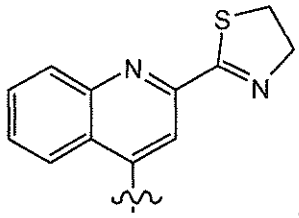
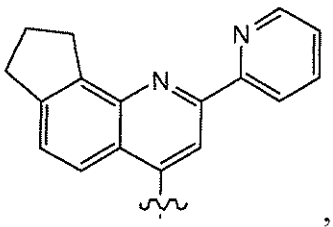
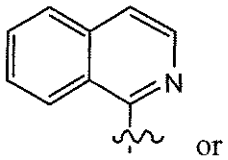
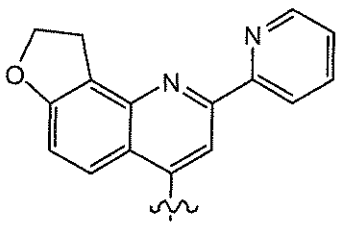
R_{10} is hydrogen or methyl; and

R_{11} is C_1-C_4alkyl or C_3-C_7cycloalkyl; and R_{12} is C_1-C_4alkyl;

R_{16} is 0 to 2 substituents independently chosen from halogen, C_1-C_2alkyl, and C_1-C_2alkoxy;

Y is O, -O(C=O)-, or –(NH)(C=O)-; and

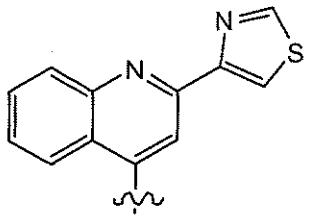
Z is a group of the formula:


,

,

,

,

or


each of which is substituted by 0, 1, 2, or 3 substituents independently chosen from halogen, C_1-C_4alkyl, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

19. A pharmaceutical composition comprising a therapeutically effective amount of one or more compounds or salts of Claim 18 and at least one pharmaceutically acceptable carrier.

20. A compound or salt of Claim 18 wherein Z is a group of the formula



which is substituted by 0, 1, 2, or 3 substituents independently chosen from halogen, C_1-C_4alkyl, C_1-C_4alkoxy, and mono- and di-C_1-C_4alkylamino.

21. A compound or salt of Claim 1, wherein the compound is

(2R,6R,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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-2-yl 4-fluoroisoindoline-2-carboxylate;

(2R,6R,13aR,14aR,16aS)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)octadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(3S,13R,17R,18aS)-N-(cyclopropylsulfonyl)-17-(7-methoxy-2-phenylquinolin-4-yloxy)-1,14-dioxo-13-(2-oxo-2-(piperidin-1-yl)ethyl)octadecahydropyrrolo[1,2-a][1,4]diazacyclohexadecine-3-carboxamide;

(3S,4S,12R,16R,17aS)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-4-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)hexadecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide;

(3R,12R,16R,17aS)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-3-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)hexadecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-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;

(3R,12R,16R,17aS,Z)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-

2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide;

(3S,12R,16R,17aS,Z)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide;

tert-butyl 2-((2R,6R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetate;

2-((2R,6R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetic acid;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-6-(2-morpholino-2-oxoethyl)-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;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(12R,16R,17aS,Z)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-3-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxylic acid;

(3R,12R,16R,17aS,Z)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-3-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide;

(3S,12R,16R,17aS,Z)-N-(cyclopropylsulfonyl)-16-(7-methoxy-2-phenylquinolin-4-yloxy)-3-methyl-1,13-dioxo-12-(2-oxo-2-(piperidin-1-yl)ethyl)-2,3,4,7,8,9,10,11,12,13,15,16,17,17a-tetradecahydro-1H-pyrrolo[1,2-a][1,4]diazacyclopentadecine-3-carboxamide;

tert-butyl 4-(2-((2R,6R,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetyl)piperazine-1-carboxylate;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,5-dimethylpiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(2,6-dimethylpiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4-fluoropiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(3-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-6-(2-(2-methylmorpholino)-2-oxoethyl)-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;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(2,6-dimethylmorpholino)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,13aS,14aR,16aS,Z)-6-(2-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-6-(2-(3-methylpiperidin-1-yl)-2-oxoethyl)-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;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-5,16-dioxo-2-(2-phenylquinoline-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;

(2R,6R,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-2-(2-phenylquinoline-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-2-(2-phenylquinoline-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-5,16-dioxo-2-(2-(pyridin-2-yl)-8,9-dihydrofuro[2,3-h]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]diazacyclopentadecine-14a-carboxamide;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-2-(2-(pyridin-2-yl)-8,9-dihydrofuro[2,3-h]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]diazacyclopentadecine-14a-carboxamide;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-2-(2-(pyridin-2-yl)-8,9-dihydrofuro[2,3-h]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]diazacyclopentadecine-14a-carboxamide;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(pyrrolidine-1-carbonyl)piperazin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4-(ethylsulfonyl)piperazin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(pyrazin-2-yl)piperazin-1-yl)ethyl)-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;

tert-butyl 2-((2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-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)acetate;

2-((2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-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)acetic acid;

(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-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;

(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-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;

(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl)-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;

(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(2-(trifluoromethyl)pyrrolidin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(6-methoxy-2-(pyridin-2-yl)quinoline-4-carboxamido)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-

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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)-2-(6-methoxy-2-(pyridin-2-yl)quinoline-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl)-2-(6-methoxy-2-(pyridin-2-yl)quinoline-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-((2R,6S)-2,6-dimethylpiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3-fluoropiperidin-1-yl)-2-oxoethyl)-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;

(2R,6R,14aR,16aS,Z)-2-(8-chloro-7-methoxy-2-(pyridin-2-yl)quinolin-4-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(4-fluoropiperidin-1-yl)-2-oxoethyl)-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;

(2R,6R,14aR,16aS,Z)-6-(2-((S)-3-aminopyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

tert-butyl ((3S)-1-(2-((2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetyl)pyrrolidin-3-yl)methylcarbamate;

tert-butyl ((3S)-1-(2-((2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-2-(7-methoxy-2-phenylquinolin-4-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-yl)acetyl)pyrrolidin-3-yl)methylcarbamate;

(2R,6R,14aR,16aS,Z)-6-(2-((S)-3-(aminomethyl)pyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-6-(2-((R)-3-aminopyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-6-(2-((R)-3-(2-aminopropan-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-((S)-3-hydroxypyrrolidin-1-yl)-2-oxoethyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-6-(2-((Z)-3-(aminomethyl)-4-(methoxyimino)-3-methylpyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-6-(2-((S)-3-(2-aminopropan-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-N-(cyclopropylsulfonyl)-2-(7-methoxy-2-phenylquinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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-2-yl 3,4-dihydroisoquinoline-2(1H)-carboxylate;

(2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-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-2-yl 3,4-dihydroisoquinoline-2(1H)-carboxylate;

(2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-6-(2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl)-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-2-yl 3,4-dihydroisoquinoline-2(1H)-carboxylate;

(2R,6R,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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-2-yl 3,4-dihydroisoquinoline-2(1H)-carboxylate;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-8-methyl-2-(pyridin-2-yl)quinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-8-methyl-2-(pyridin-2-yl)quinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(6-methoxy-3-phenylnaphthalen-1-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(2-(isopropylamino)thiazol-4-yl)-7-methoxy-8-methylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,16aS,Z)-2-(5-chloro-6-methoxyisoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,16aS,Z)-2-(5-chloro-6-methoxyisoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-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;

(2R,6R,13aS,16aS,Z)-2-(5-chloro-6-methoxyisoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,16aS,Z)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-2-(2-(pyridin-2-yl)-8,9-dihydro-7H-cyclopenta[h]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]diazacyclopentadecine-14a-carboxamide;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,13aS,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-5,16-dioxo-2-(2-(pyridin-2-yl)-8,9-dihydro-7H-cyclopenta[h]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]diazacyclopentadecine-14a-carboxamide;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-2-(7-methoxy-8-methyl-2-(pyridin-3-yl)quinolin-4-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-carboxamide;

(2R,6R,14aR,16aS,Z)-2-(5-chloro-6-methoxy-3-(pyridin-2-yl)isoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(7-methoxy-8-methyl-2-(pyridin-3-yl)quinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-2-(5-chloro-6-methoxy-3-(pyridin-2-yl)isoquinolin-1-yloxy)-N-(cyclopropylsulfonyl)-5,16-dioxo-6-(2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)-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;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluoropiperidin-1-yl)-2-oxoethyl)-2-(2-(2-isopropylthiazol-4-yl)-7-methoxy-8-methylquinolin-4-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-carboxamide;

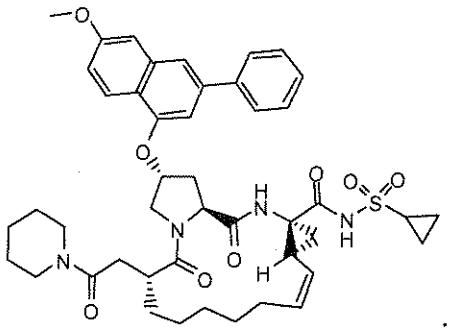
(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3,3-difluorocyclohexyl)-2-oxoethyl)-2-(2-(2-(isopropylamino)thiazol-4-yl)-7-methoxy-8-methylquinolin-4-yloxy)-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide;

(2R,6R,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy)-5,16-dioxo-6-(2-oxo-2-(piperidin-1-yl)ethyl)-

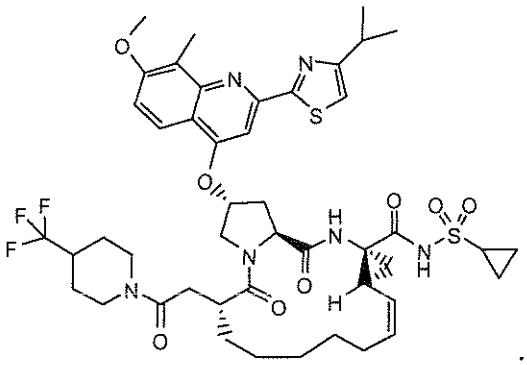
1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide; or

(2R,6R,13aS,16aS,Z)-N-(cyclopropylsulfonyl)-6-(2-(3-fluoropiperidin-1-yl)-2-oxoethyl)-2-(2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-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-carboxamide.

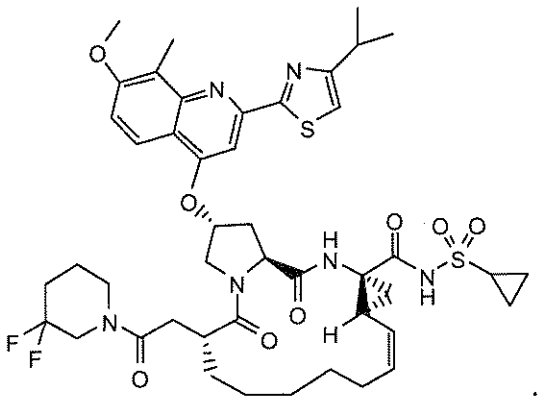
22. A compound or salt thereof of Claim 1, wherein the compound is



23. A compound or salt thereof of Claim 1, wherein the compound is



24. A compound or salt thereof of Claim 1, wherein the compound is



25. A compound or salt thereof of Claim 1, wherein the compound is

