TITLE OF THE INVENTION
HCV NS3 PROTEASE INHIBITORS

The present invention relates to macrocyclic compounds that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, their synthesis, and their use for treating or preventing HCV infection.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 3.9 million infected people in the United States alone, according to the U.S. Center for Disease Control, roughly five times the number of people infected with the human immunodeficiency virus (HIV). According to the World Health Organization, there are more than 170 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their off-spring.

Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection. The current state of the art in the treatment of HCV infection has been discussed in the following references: B. Dymock, et al., "Novel approaches to the treatment of hepatitis C virus infection," Antiviral Chemistry & Chemotherapy, 11: 79-96 (2000); H. Rosen, et al., "Hepatitis C virus: current understanding and prospects for future therapies," Molecular Medicine Today, 5: 393-399 (1999); D. Moradpour, et al., "Current and evolving therapies for hepatitis C," European J. Gastroenterol. Hepatol., 11: 1189-1202 (1999); R. Bartenschlager, "Candidate Targets for Hepatitis C Virus-Specific Antiviral Therapy," Intervirology, 40: 378-393 (1997); G.M. Lauer and B.D. Walker, "Hepatitis C Virus Infection," N. Engl. J. Med., 345: 41-52 (2001); B.W. Dymock, "Emerging therapies for hepatitis C virus infection," Emerging Drugs, 6: 13-42 (2001); and C. Crabb, "Hard-Won Advances Spark Excitement about Hepatitis C," Science: 506-507 (2001).

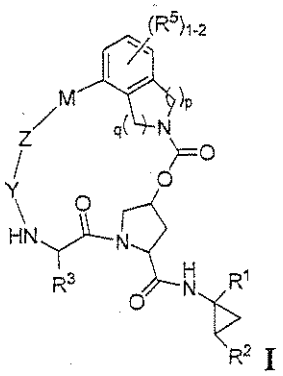
Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3), a helicase (NS3), and an RNA-dependent RNA polymerase (NS5B). The NS3 protease is located in the N-terminal domain of the NS3 protein, and is considered a prime drug target since it is responsible for an intramolecular

cleavage at the NS3/4A site and for downstream intermolecular processing at the NS4A/4B, NS4B/5A and NS5A/5B junctions. Previous research has identified classes of peptides, such as hexapeptides as well as tripeptides discussed in U.S. patent applications US2005/0020503, US2004/0229818, and US2004/00229776, showing degrees of activity in inhibiting the NS3 protease. The aim of the present invention is to provide further compounds which exhibit activity against the HCV NS3 protease.

SUMMARY

The present disclosure relates to novel macrocyclic compounds of formula (**I**) and/or pharmaceutically acceptable salts or hydrates thereof. These compounds are useful in the inhibition of HCV (hepatitis C virus) NS3 (non-structural 3) protease, the prevention or treatment of one or more of the symptoms of HCV infection, either as compounds or their pharmaceutically acceptable salts or hydrates (when appropriate), or as pharmaceutical composition ingredients, whether or not in combination with other HCV antivirals, anti-infectives, immunomodulators, antibiotics or vaccines.

In a first aspect, there is provided a compound of formula (**I**) and/or a pharmaceutically acceptable salt or hydrate thereof:



I

wherein:

p and q are both 1;

R^1 is $CONR^{10}SO_2R^6$;

R^2 is C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein said alkyl or alkenyl is optionally substituted with 1 to 3 halo;

R^3 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl;

R^5 is H;

R^6 is C_3-C_6 cycloalkyl;

Y is C(=O);

Z is O;

M is C_1-C_{12} alkylene or C_2-C_{12} alkenylene; and

each R^{10} is independently H or C_1-C_6 alkyl.

The present disclosure also includes pharmaceutical compositions containing a compound of the present disclosure and methods of preparing such pharmaceutical compositions. The present disclosure further includes methods of treating or preventing one or more symptoms of HCV infection.

In a second aspect, there is provided a pharmaceutical composition comprising an effective amount of a compound as defined above or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier.

In a third aspect, there is provided a compound as defined above or a pharmaceutically acceptable salt or hydrate thereof, for use in therapy.

In a fourth aspect, there is provided a use of a compound as defined above or a pharmaceutically acceptable salt or hydrate thereof, in the preparation of a medicament for preventing or treating infection by HCV in a subject in need thereof.

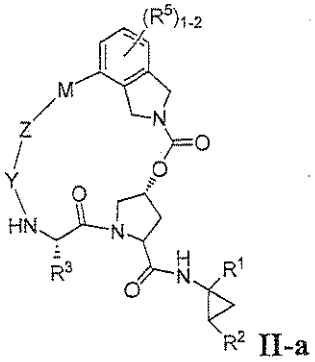
In a fifth aspect, there is provided a compound as defined above for use in a method of preventing or treating HCV.

In a sixth aspect, there is provided a combination of a compound as defined above or a pharmaceutically acceptable salt or hydrate thereof and at least one second therapeutic agent selected from HCV antiviral agents, immunomodulators and anti-infective agents.

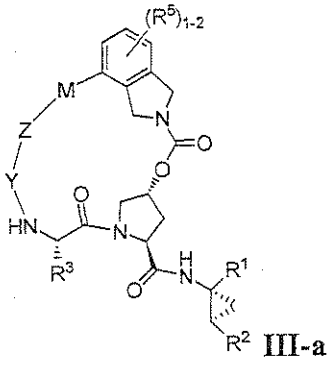
Other embodiments, aspects and features of the present disclosure are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of formula **I** above, and pharmaceutically acceptable salts and/or hydrates thereof. These compounds and their pharmaceutically acceptable salts and/or hydrates are HCV protease inhibitors (e.g., HCV NS3 protease inhibitors). The present invention also includes compounds of formulae **II-a** and **III-a** wherein all variables are as defined for formula **I**.



II-a



III-a

A first embodiment of the present invention is a compound of formula **I**, **II-a** or **III-a**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is $CONHSO_2R^6$, and all other variables are as originally defined (i.e., as defined in the Summary of the Invention). In a first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is C_3-C_5 cycloalkyl; and all other variables are as defined in the first embodiment. In a feature of the first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is cyclopropyl; and all other variables are as defined in the first embodiment.

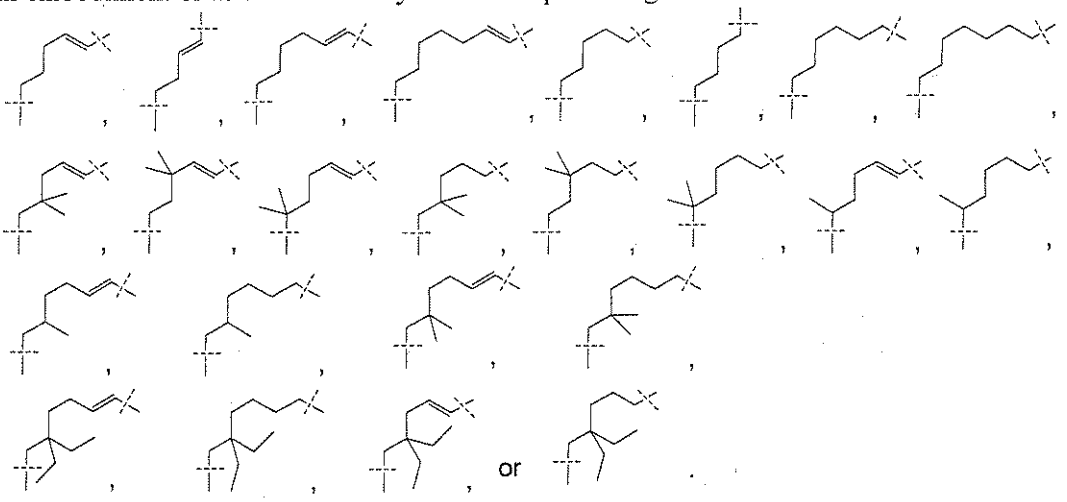
A second embodiment of the present invention is a compound of formula **I**, **II-a** or **III-a**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^2 is C_1-C_6 alkyl or C_2-C_6 alkenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the second embodiment, R^2 is C_1-C_4 alkyl or C_2-C_4 alkenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a second aspect of the second embodiment, R^2 is C_2-C_4 alkenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a feature of the second aspect of the second embodiment, R^2 is vinyl; and all other variables are as defined in the third embodiment or as defined in any one of the preceding embodiments. In a third aspect of the second embodiment, R^2 is C_1-C_4 alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a feature of the third aspect of the third

embodiment, R^2 is ethyl; and all other variables are as defined in the third embodiment or as defined in any one of the preceding embodiments.

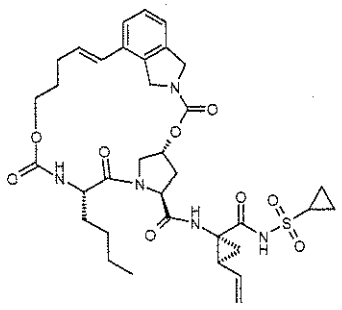
A third embodiment of the present invention is a compound of formula **I**, **II-a** or **III-a**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^3 is C_3-C_8 cycloalkyl or C_1-C_8 alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the third embodiment, R^3 is C_5-C_7 cycloalkyl or C_1-C_8 alkyl; and all other variables are as defined in the third embodiment or as defined in any one of the preceding embodiments. In a second aspect of the third embodiment, R^3 is C_5-C_6 cycloalkyl or C_1-C_8 alkyl; and all other variables are as defined in the third embodiment or as defined in any one of the preceding embodiments. In a third aspect of the third embodiment, R^3 is propyl or butyl; and all other variables are as defined in the third embodiment or as defined in any one of the preceding embodiments. In a feature of the third aspect of the third embodiment, R^3 is i-propyl, n-butyl or t-butyl; and all other variables are as defined in the third embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the third embodiment, R^3 is cyclopentyl or cyclohexyl; and all other variables are as defined in the third embodiment or as defined in any one of the preceding embodiments.

A fourth embodiment of the present invention is a compound of formula **I**, **II-a** or **III-a**, or a pharmaceutically acceptable salt or hydrate thereof, wherein M is C_1-C_{10} alkylene or C_2-C_{10} alkenylene (including linear and branched chain alkylene or alkenylene); and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the fourth embodiment, M is C_1-C_8 alkylene or C_2-C_8 alkenylene (including linear and branched chain alkylene or alkenylene); and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a second aspect of the fourth embodiment, M is C_4 alkylene or C_4 alkenylene (including linear and branched chain alkylene or alkenylene); and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the fourth embodiment, M is C_5 alkylene or C_5 alkenylene (including linear and branched chain alkylene or alkenylene); and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the fourth embodiment, M is C_6 alkylene or C_6 alkenylene (including linear and branched chain alkylene or alkenylene); and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a fifth aspect of the fourth embodiment, M is C_7 alkylene or C_7 alkenylene (including linear and branched chain alkylene or alkenylene); and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a sixth aspect of the fourth embodiment, M is C_8 alkylene or C_8 alkenylene (including linear and branched chain alkylene or alkenylene); and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a seventh aspect of the fourth embodiment, M is C_9 alkylene or C_9 alkenylene (including linear and branched chain alkylene or alkenylene); and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In an eighth aspect of the fourth embodiment, M is C_{10} alkylene or C_{10}

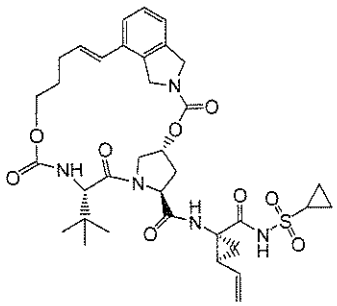
alkenylene (including linear and branched chain alkylene or alkenylene); and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In an nineth aspect of the fourth embodiment, M is selected from the following; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments.



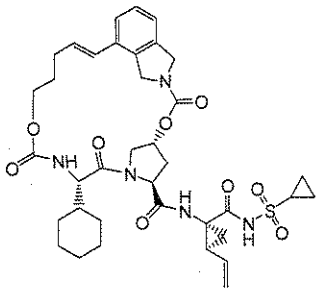
A fifth embodiment of the present invention is a compound, or a pharmaceutically acceptable salt or hydrate thereof, selected from the group consisting of the following compounds.



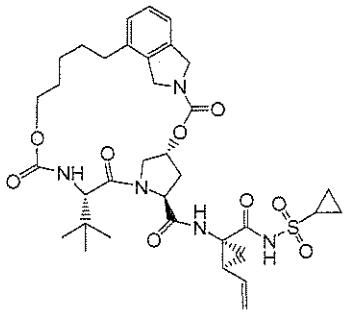
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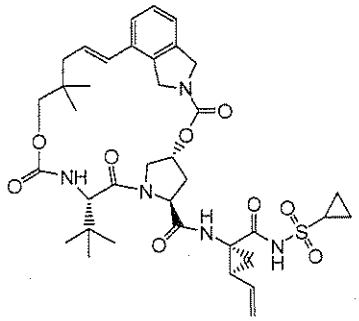
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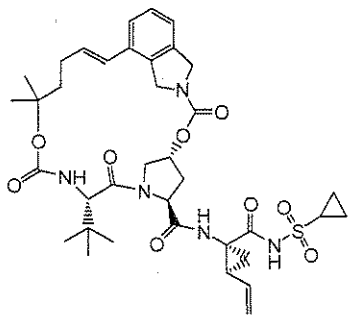
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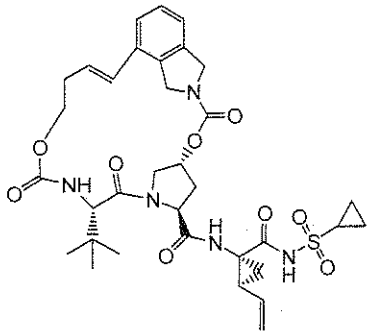
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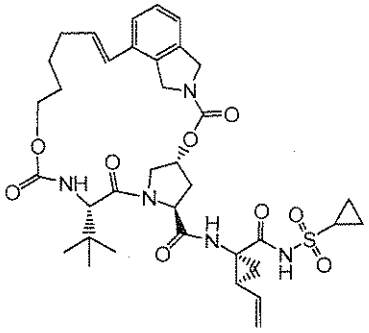
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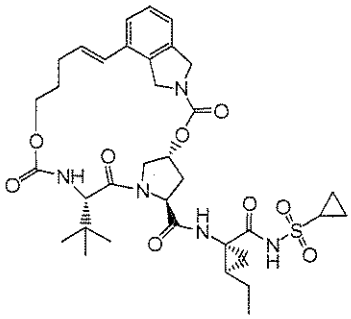
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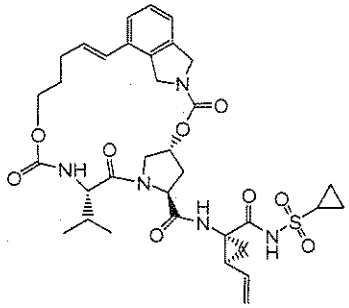
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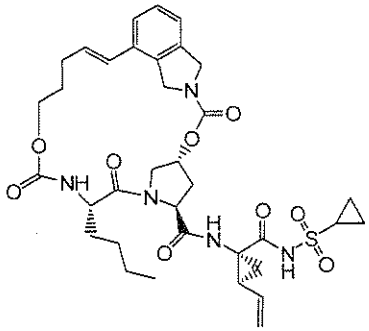
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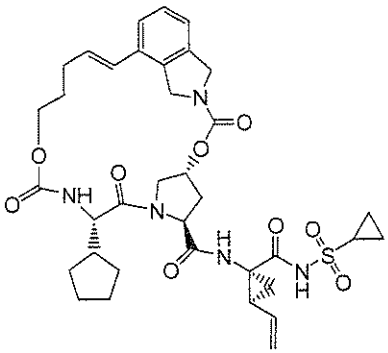
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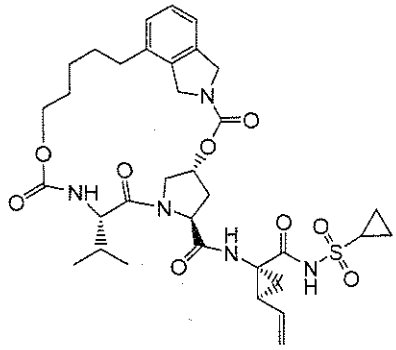
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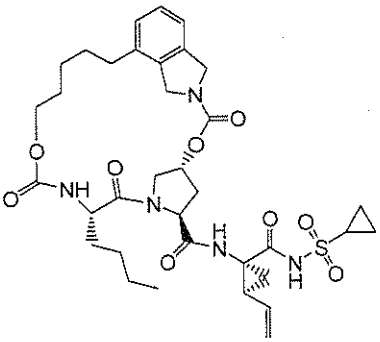
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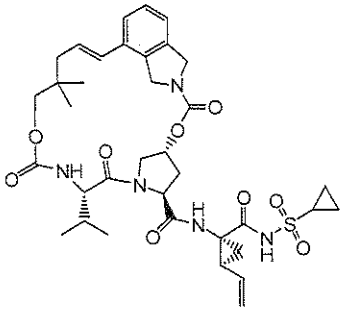
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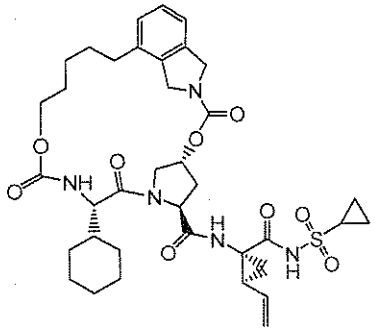
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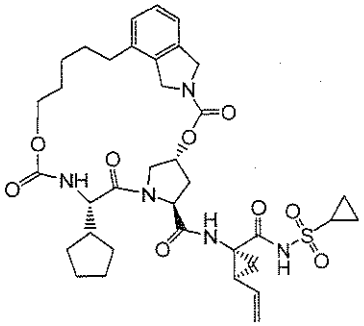
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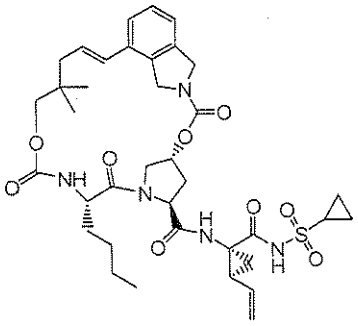
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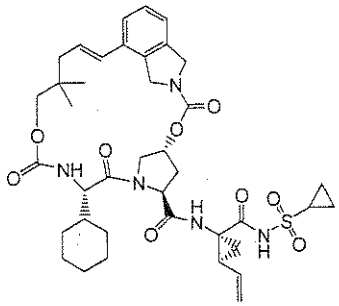
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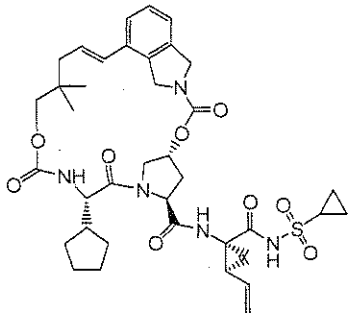
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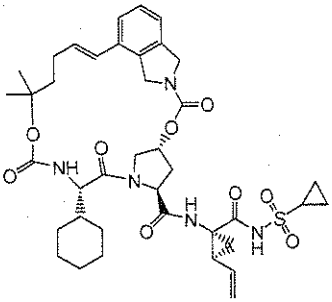
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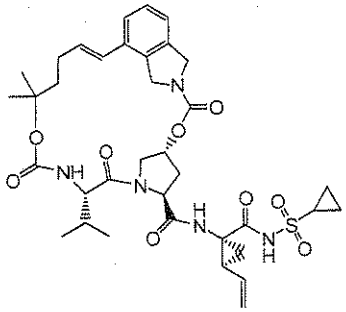
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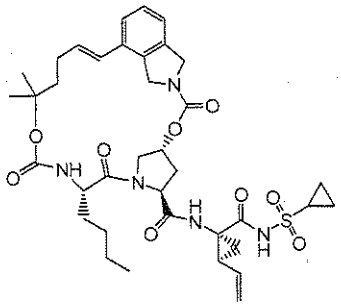
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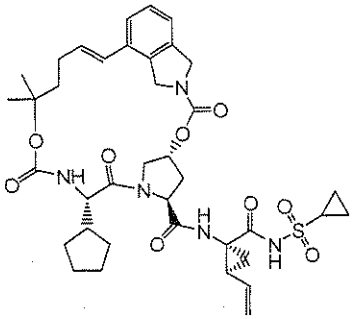
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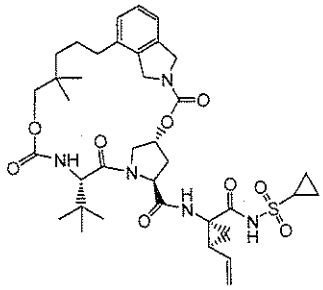
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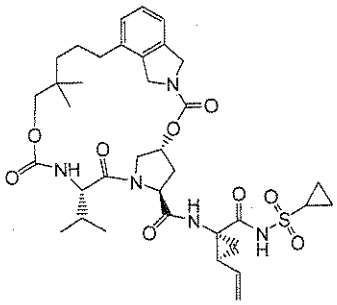
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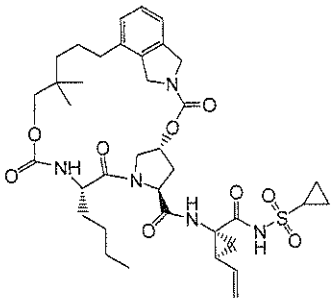
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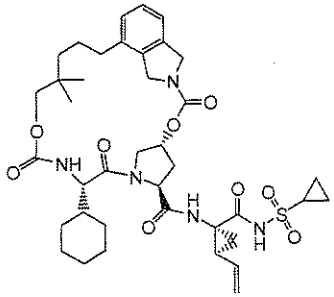
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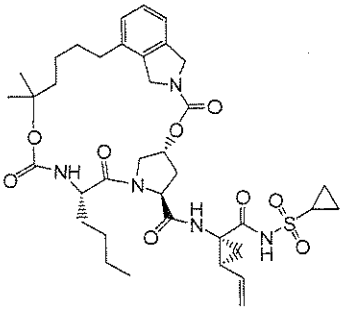
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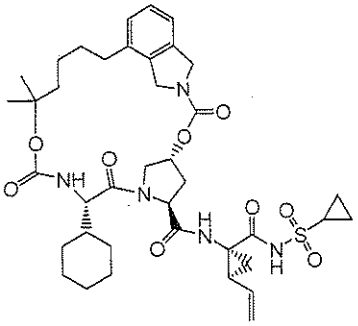
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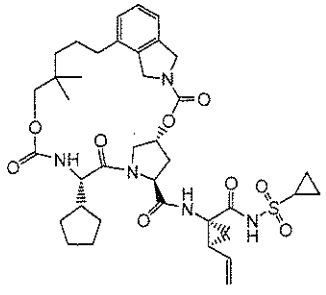
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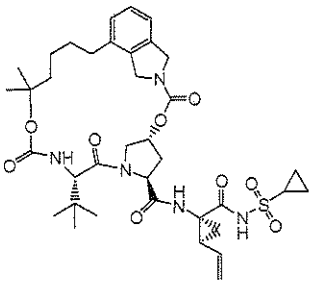


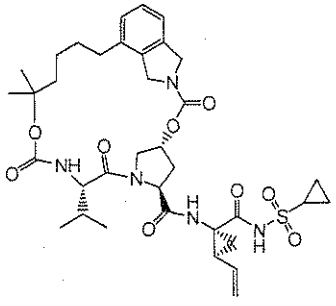
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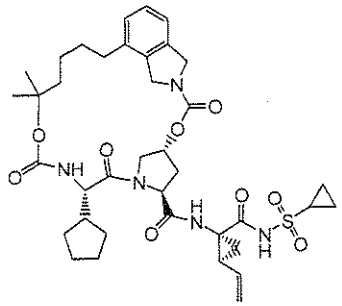
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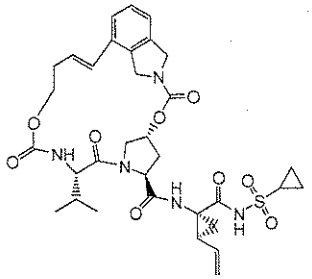




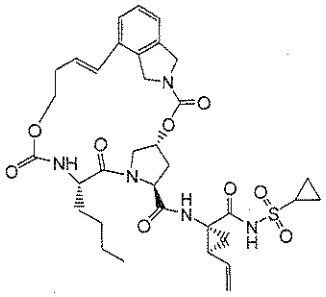
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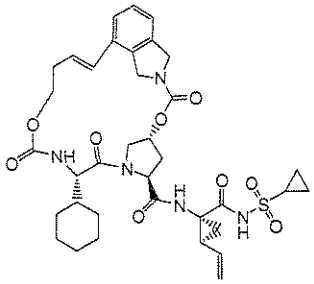
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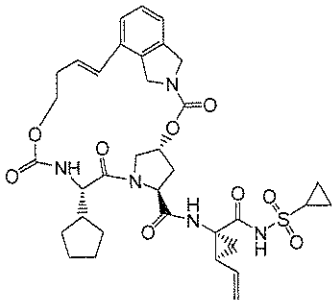
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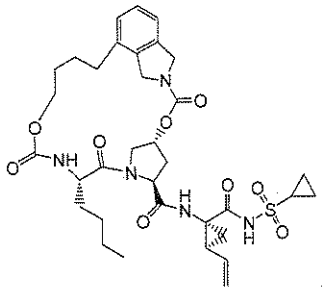
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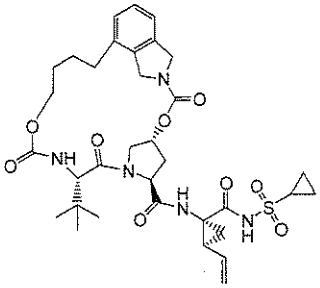
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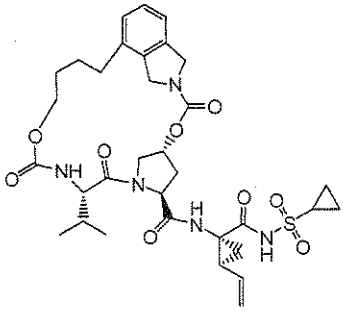
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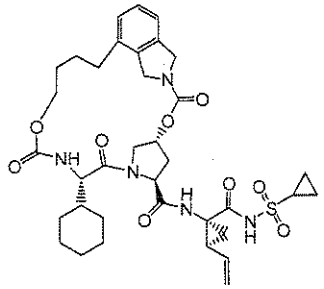
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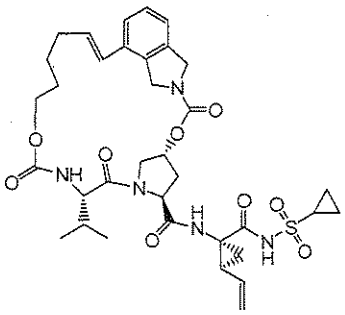
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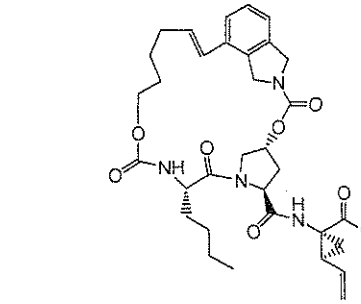
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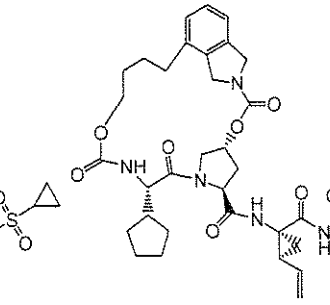
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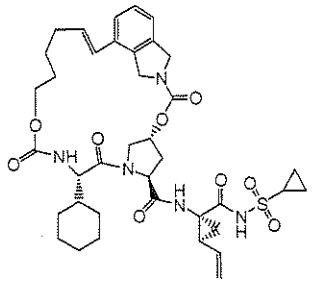
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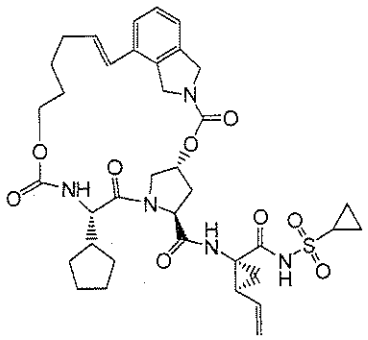
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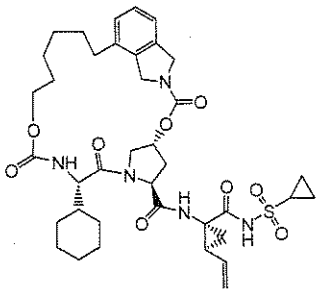
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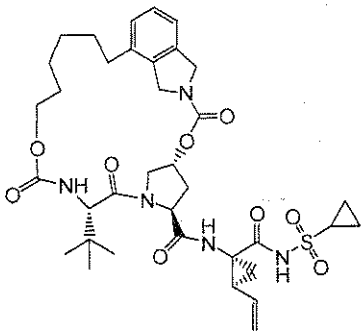
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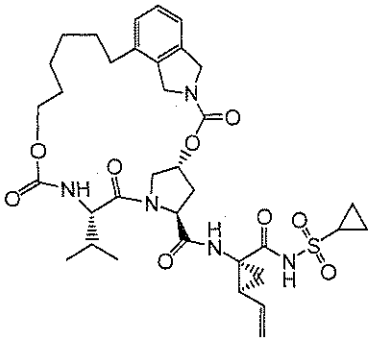
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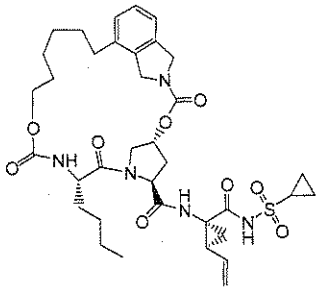
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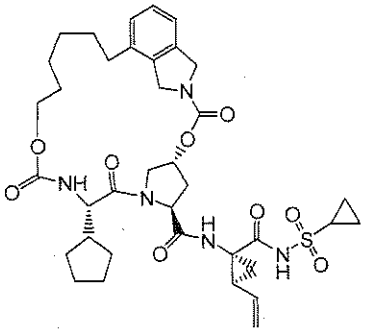
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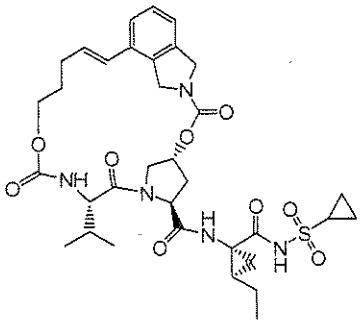
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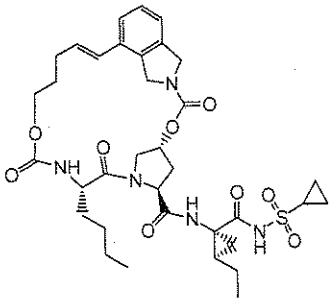
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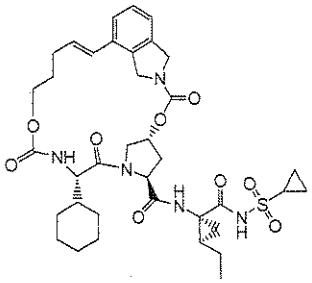
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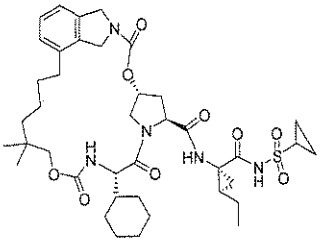
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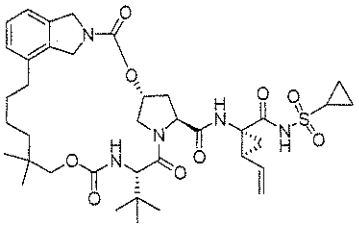
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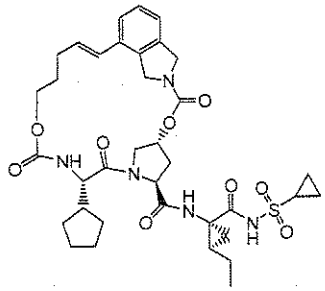
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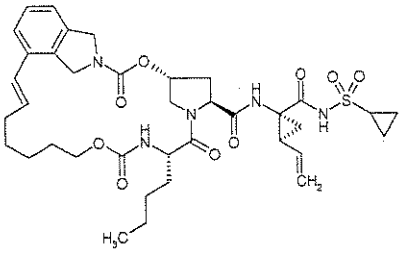
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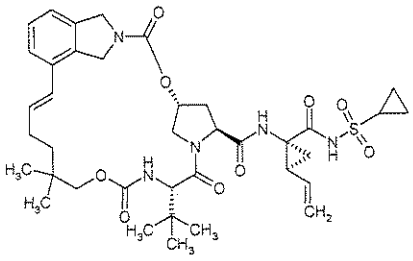
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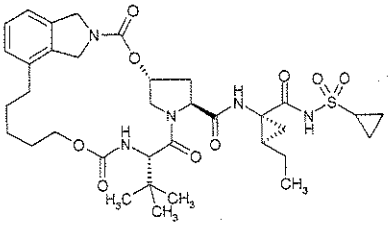
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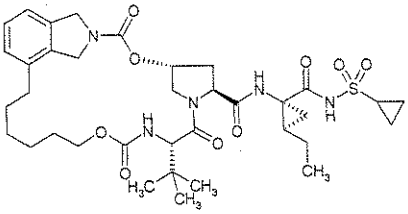
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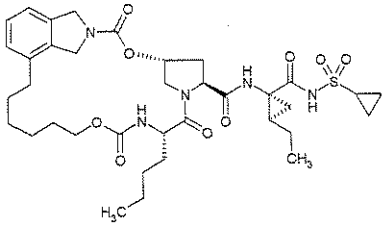
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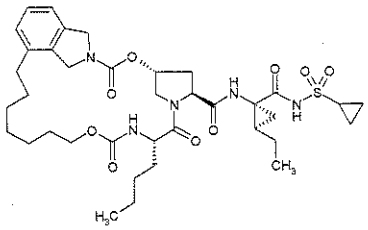
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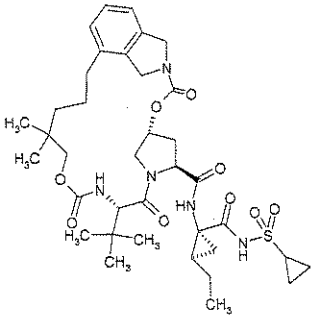
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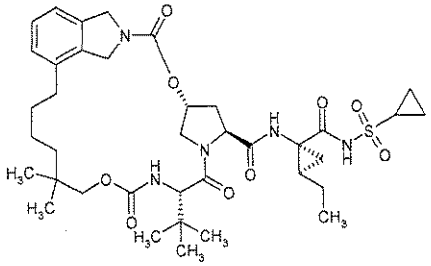
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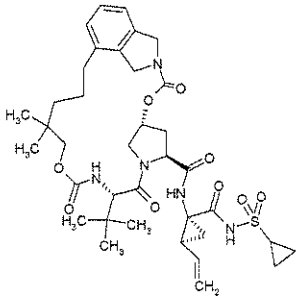
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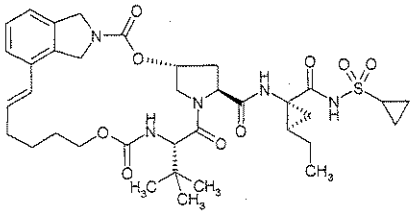
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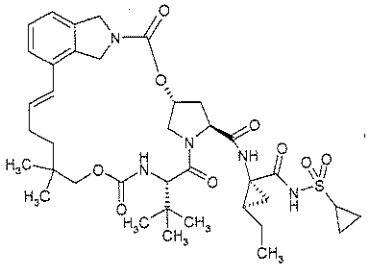
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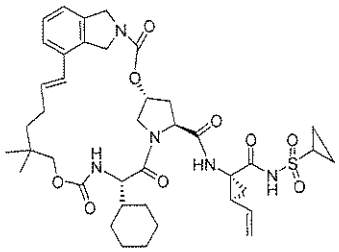
III-206



III-207



III-208



III-225

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of formula **I**, **II-a**, or **III-a** and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

(c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

(d) A pharmaceutical combination which is (i) a compound of formula **I**, **II-a**, or **III-a** and (ii) a second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent; wherein the compound of formula **I**, **II-a**, or **III-a** and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV NS3 protease, or for treating or preventing infection by HCV.

(e) The combination of (d), wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

(f) A method of inhibiting HCV NS3 protease in a subject in need thereof which comprises administering to the subject an effective amount of a compound of formula **I**, **II-a**, or **III-a**.

(g) A method of preventing or treating infection by HCV in a subject in need thereof which comprises administering to the subject an effective amount of a compound of formula **I**, **II-a**, or **III-a**.

(h) The method of (g), wherein the compound of formula **I**, **II-a**, or **III-a** is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

(i) The method of (h), wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

(j) A method of inhibiting HCV NS3 protease in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

(k) A method of preventing or treating infection by HCV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

The present invention also includes a compound of the present invention (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HCV NS3 protease, or (b) preventing or treating infection by HCV. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HCV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the

embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "haloalkyl" refers to an alkyl group wherein a hydrogen has been replaced by a halogen. The term "alkoxy" refers to an "alkyl-O-" group.

The term "alkylene" refers to any linear or branched chain alkylene group having a number of carbon atoms in the specified range. Thus, for example, "-C_{1-6} alkylene-" refers to any of the C_1 to C_6 linear or branched alkylenes. A class of alkylenes of particular interest with respect to the invention is -$(CH_2)_{1-6}$-, and sub-classes of particular interest include -$(CH_2)_{1-4}$-, -$(CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-, and -CH_2-. Also of interest is the alkylene -$CH(CH_3)$-.

The term "alkenylene" refers to any linear or branched chain divalent alkenylene group having a number of carbon atoms in the specified range.

The terms "cycloalkyl" refers to any cyclic ring of an alkane or alkene having a number of carbon atoms in the specified range. Thus, for example, "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "cycloalkoxy" refers to a "cycloalkyl-O-" group.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heteroaryl ring described as containing from "1 to 3 heteroatoms" means the ring can contain 1, 2, or 3 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. The oxidized forms of the heteroatoms N and S are also included within the scope of the present invention.

When any variable (e.g., R^{10}) occurs more than one time in any constituent or in formula **I**, **II-a**, or **III-a** or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (e.g., aryl, a heteroaromatic ring, or a saturated heterocyclic ring) provided such ring substitution is chemically allowed and results in a stable compound. A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain

essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject).

As a result of the selection of substituents and substituent patterns, certain of the compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether isolated or in mixtures, are within the scope of the present invention.

As would be recognized by one of ordinary skill in the art, certain of the compounds of the present invention can exist as tautomers. For the purposes of the present invention a reference to a compound of formula **I**, **II-a**, or **III-a** is a reference to the compound per se, or to any one of its tautomers per se, or to mixtures of two or more tautomers.

The compounds of the present inventions are useful in the inhibition of HCV protease (e.g., HCV NS3 protease) and the prevention or treatment of infection by HCV. For example, the compounds of this invention are useful in treating infection by HCV after suspected past exposure to HCV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HCV protease, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Many of the compounds of the invention carry an acidic moiety, in which case suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (e.g., antiviral agents

useful for treating HCV infection), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or salt (or hydrate) and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients, as well as any product which results, directly or indirectly, from combining the specified ingredients.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition being prevented. The term also includes herein the amount of active compound sufficient to inhibit HCV NS3 protease and thereby elicit the response being sought (i.e., an "inhibition effective amount"). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

For the purpose of inhibiting HCV NS3 protease and preventing or treating HCV infection, the compounds of the present invention, optionally in the form of a salt or a hydrate, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can

be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990.

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention also relates to a method of inhibiting HCV NS3 protease, inhibiting HCV replication, or preventing or treating HCV infection with a compound of the present invention in combination with one or more therapeutic agents and a pharmaceutical composition comprising a compound of the present invention and one or more therapeutic agents selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent. Such therapeutic agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, R7025 (an enhanced interferon (Roche)), interferon-β, interferon-α, pegylated interferon-α (peginterferon-α), a combination of interferon-α and ribavirin, a combination of peginterferon-α and ribavirin, a combination of interferon-α and levovirin, and a combination of peginterferon-α and levovirin. Interferon-α includes, but is not limited to, recombinant interferon-α2a (such as Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon-α2a (Pegasys™), interferon-α2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon-α2b (PegIntron™), a recombinant consensus interferon (such as interferon alphacon-1), albuferon (interferon-α bound to human serum albumin (Human Genome Sciences)), and a

purified interferon-α product. Amgen's recombinant consensus interferon has the brand name Infergen®. Levovirin is the L-enantiomer of ribavirin which has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in WO 01/60379 (assigned to ICN Pharmaceuticals). In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent target for inhibition of HCV replication. Both substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are disclosed in WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, GB-2337262, WO 02/48116, WO 02/48172, and U.S. Patent No. 6,323,180.

Ribavirin, levovirin, and viramidine may exert their anti-HCV effects by modulating intracellular pools of guanine nucleotides via inhibition of the intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting enzyme on the biosynthetic route in *de novo* guanine nucleotide biosynthesis. Ribavirin is readily phosphorylated intracellularly and the monophosphate derivative is an inhibitor of IMPDH. Thus, inhibition of IMPDH represents another useful target for the discovery of inhibitors of HCV replication. Therefore, the compounds of the present invention may also be administered in combination with an inhibitor of IMPDH, such as VX-497, which is disclosed in WO 97/41211 and WO 01/00622 (assigned to Vertex); another IMPDH inhibitor, such as that disclosed in WO 00/25780 (assigned to Bristol-Myers Squibb); or mycophenolate mofetil [see A.C. Allison and E.M. Eugui, Agents Action, 44 (Suppl.): 165 (1993)].

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with the antiviral agent amantadine (1-aminoadamantane) [for a comprehensive description of this agent, see J. Kirschbaum, Anal. Profiles Drug Subs. 12: 1-36 (1983)].

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with the antiviral agent polymerase inhibitor R7128 (Roche).

The compounds of the present invention may also be combined for the treatment of HCV infection with antiviral 2'-*C*-branched ribonucleosides disclosed in R. E. Harry-O'kuru, et al., J. Org. Chem., 62: 1754-1759 (1997); M. S. Wolfe, et al., Tetrahedron Lett., 36: 7611-7614 (1995); U.S. Patent No. 3,480,613 (Nov. 25, 1969); International Publication Number WO 01/90121 (29 November 2001); International Publication Number WO 01/92282 (6 December 2001); and International Publication Number WO 02/32920 (25 April 2002); and International Publication Number WO 04/002999 (8 January 2004); and International Publication Number WO

04/003000 (8 January 2004); and International Publication Number WO 04/002422 (8 January 2004); the contents of each of which are incorporated by reference in their entirety. Such 2'-*C*-branched ribonucleosides include, but are not limited to, 2'-*C*-methyl-cytidine, 2'-*C*-methyl-uridine, 2'-*C*-methyl-adenosine, 2'-*C*-methyl-guanosine, and 9-(2-*C*-methyl-β-D-ribofuranosyl)-2,6-diaminopurine, and the corresponding amino acid ester of the ribose C-2', C-3', and C-5' hydroxyls and the corresponding optionally substituted cyclic 1,3-propanediol esters of the 5'-phosphate derivatives.

The compounds of the present invention may also be combined for the treatment of HCV infection with other nucleosides having anti-HCV properties, such as those disclosed in WO 02/51425 (4 July 2002), assigned to Mitsubishi Pharma Corp.; WO 01/79246, WO 02/32920, WO 02/48165 (20 June 2002), and WO2005003147 (13 Jan. 2005)(including R1656, (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine, shown as compounds 3-6 on page 77) assigned to Pharmasset, Ltd.; WO 01/68663 (20 September 2001), assigned to ICN Pharmaceuticals; WO 99/43691 (2 Sept. 1999); WO 02/18404 (7 March 2002), US2005/0038240 (Feb. 17, 2005) and WO2006021341 (2 March 2006), including 4'-azido nucleosides such as R1626, 4'-azidocytidine, assigned to Hoffmann-LaRoche; U.S. 2002/0019363 (14 Feb. 2002); WO 02/100415 (19 Dec. 2002); WO 03/026589 (3 Apr. 2003); WO 03/026675 (3 Apr. 2003); WO 03/093290 (13 Nov. 2003);: US 2003/0236216 (25 Dec. 2003); US 2004/0006007 (8 Jan. 2004); WO 04/011478 (5 Feb. 2004); WO 04/013300 (12 Feb. 2004); US 2004/0063658 (1 Apr. 2004); and WO 04/028481 (8 Apr. 2004); the content of each is incorporated herein by reference in its entirety.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS5B polymerase. Such HCV NS5B polymerase inhibitors that may be used as combination therapy include, but are not limited to, those disclosed in WO 02/057287, US 6,777,395, WO 02/057425, US 2004/0067901, WO 03/068244, WO 2004/000858, WO 04/003138 and WO 2004/007512; the content of each is incorporated herein by reference in its entirety. Other such HCV polymerase inhibitors include, but are not limited to, valopicitabine (NM-283; Idenix) and 2'-F-2'-beta-methylcytidine (see also WO 2005/003147, assigned to Pharmasset, Ltd.).

In one embodiment, nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS3 protease inhibitors are selected from the following compounds:
4-amino-7-(2-C-methyl-β-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-methylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-dimethylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-vinyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-hydroxymethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-

C-fluoromethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-methyl-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylic acid; 4-amino-5-bromo-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-chloro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2,4-diamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 4-amino-7-(2-C-ethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C,2-O-dimethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 2-amino-5-methyl-7-(2-C, 2-O-dimethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 4-amino-7-(3-deoxy-2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-deoxy-2-C-methyl-β-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-2-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-C-methyl-β-D-xylofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2,4-di-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-deoxy-3-fluoro-2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2 ,3-d]pyrimidine; and the corresponding 5'-triphosphates; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may also be combined for the treatment of HCV infection with non-nucleoside inhibitors of HCV polymerase such as those disclosed in WO 01/77091 (18 Oct. 2001), assigned to Tularik, Inc.; WO 01/47883 (5 July 2001), assigned to Japan Tobacco, Inc.; WO 02/04425 (17 January 2002), assigned to Boehringer Ingelheim; WO 02/06246 (24 Jan. 2002), assigned to Istituto di Ricerche di Biologia Moleculare P. Angeletti S.P.A.; WO 02/20497 (3 March 2002); WO 2005/016927 (in particular JTK003), assigned to Japan Tobacco, Inc.; the content of each is incorporated herein by reference in its entirety; and HCV-796 (Viropharma Inc.).

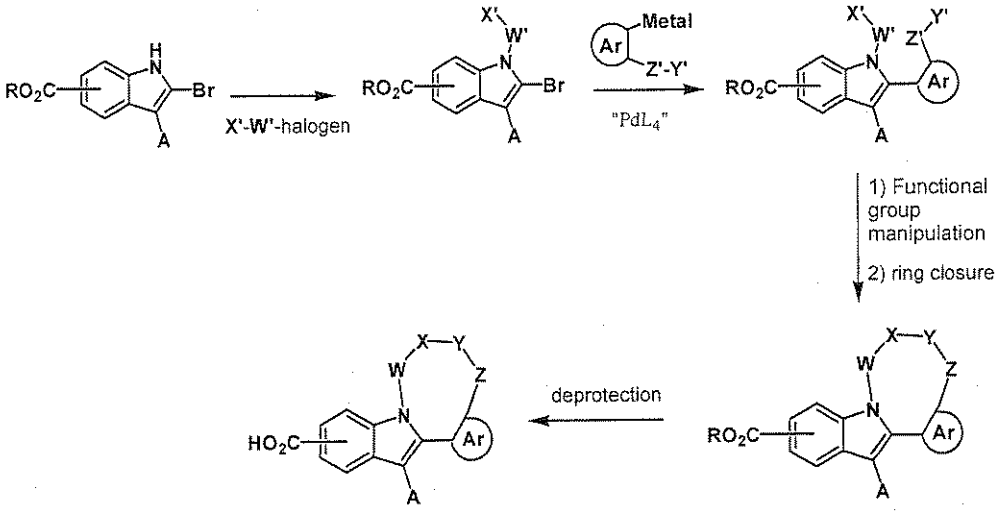
In one embodiment, non-nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS3 protease inhibitors are selected from the following compounds:

14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; methyl ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocin-11-

yl)carbonyl]amino}sulfonyl)acetate; ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 3-chloro-14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine 11-carboxylic acid; *N*'-(11-carboxy-14-cyclohexyl-7,8-dihydro-*6H*-indolo[1,2-e][1,5]benzoxazocin-7-yl)-*N*,*N*-dimethylethane-1,2-diaminium bis(trifluoroacetate); 14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid; 14-cyclohexyl-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[3-(dimethylamino)propyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(diethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(1-methylpiperidin-4-yl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-N-[(dimethylamino)sulfonyl]-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-*N*-[(dimethylamino)sulfonyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 6-allyl-14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 13-cyclohexyl-5-methyl-4,5,6,7-tetrahydrofuro[3',2':6,7][1,4]diazocino[1,8-*a*]indole-10-carboxylic acid; 15-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,6]benzodiazonine-12-carboxylic acid; 15-cyclohexyl-8-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,5]benzodiazonine-12-carboxylic acid; 13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxylic acid; and pharmaceutically acceptable salts thereof.

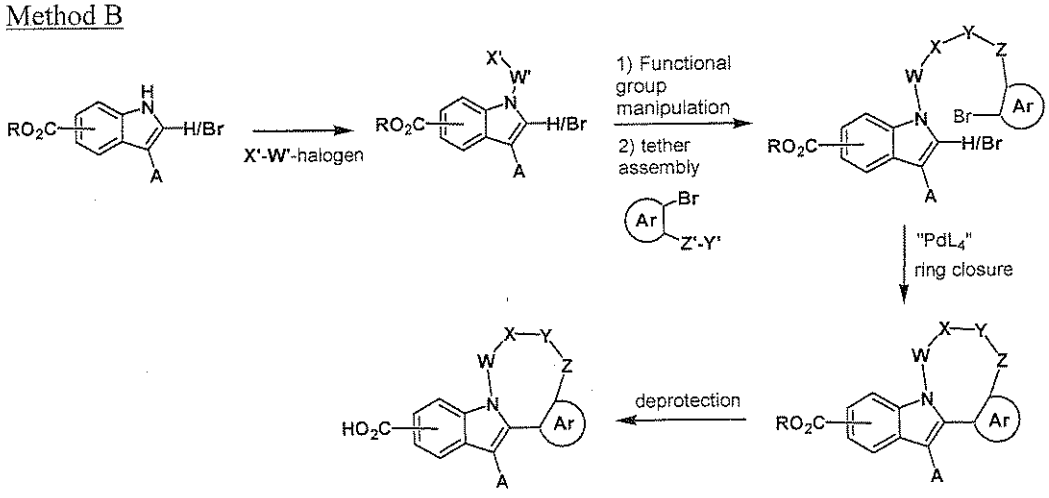
The above tetracyclic indole-based HCV NS5B polymerase inhibitors may be obtained following methods A-E as outlined below, wherein different variables may be selected in accordance with the specific tetracyclic indole compound to be prepared:

Method A



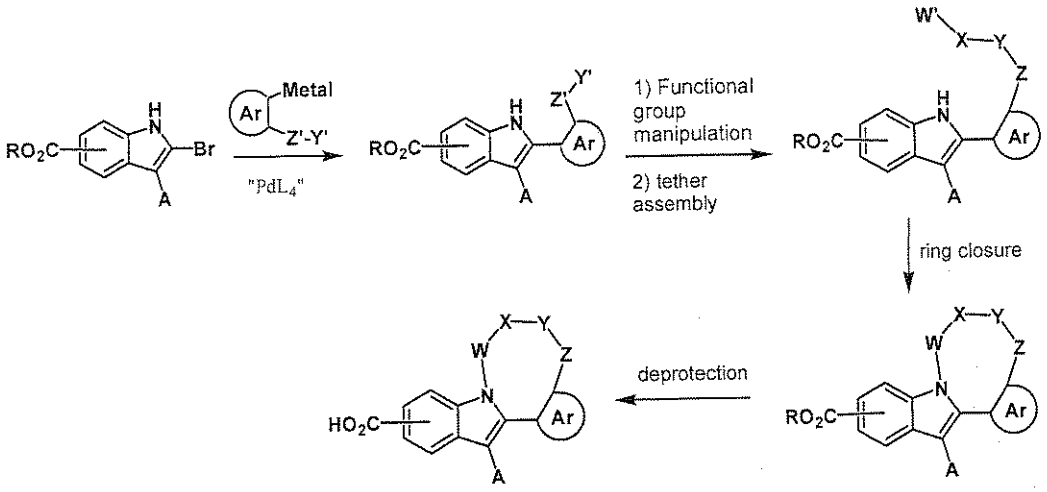
2-Bromoindole intermediate (prepared as described in published International patent application WO2004087714) was functionalized on the indole nitrogen to introduce pre-cursor functionality W'/X' to either or both of the elements W/X of the tether. Pd-mediated cross-coupling methodology (*eg*, Suzuki, Stille *etc*) then brought in the C2 aromatic bearing pre-cursor functionality Z'/Y' to either or both of the elements Z/Y of the tether. Functional group manipulation followed by ring closure afforded the tetracyclic system. Ester deprotection then yielded the target indole carboxylic acids, with the C2 aromatic tethered to the indole nitrogen.

Method B



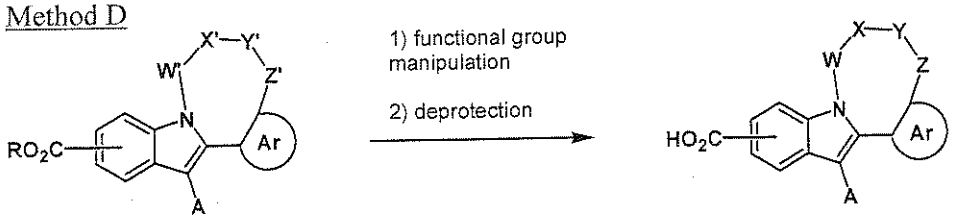
Following tether assembly out to the appropriate 2-haloaromatic, Pd-mediated ring closure afforded the fused tetracyclic system. Ester deprotection then yielded the target indole carboxylic acids, with the C2 aromatic tethered to the indole nitrogen.

Method C



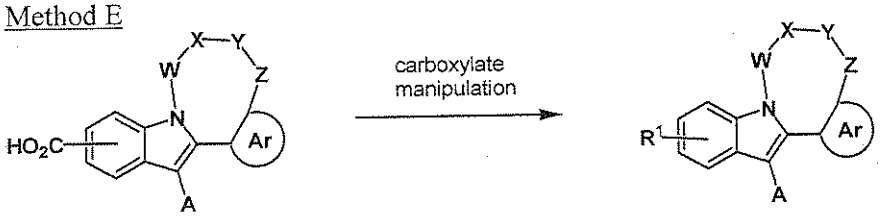
The C2 aromatic was introduced at the outset *via* Pd-mediated cross-coupling methodology (Suzuki, Stille *etc*). The tether was then built up, with cyclisation onto the indole nitrogen finally closing the ring. Ester deprotection then yielded the target indole carboxylic acids, with the C2 aromatic tethered to the indole nitrogen.

Method D



Fused tetracyclic intermediates arising from Methods A-C underwent manipulation of the functionality in the tether prior to ester deprotection to yield the target C2-tethered indole carboxylic acids.

Method E



C2-tethered indole carboxylic acids arising from Methods A-D were further derivatised through manipulation of the carboxylate functionality to give compounds bearing a carboxylate replacement or carboxamide. During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The HCV NS3 protease inhibitory activity of the present compounds may be tested using assays known in the art. One such assay is HCV NS3 protease time-resolved fluorescence

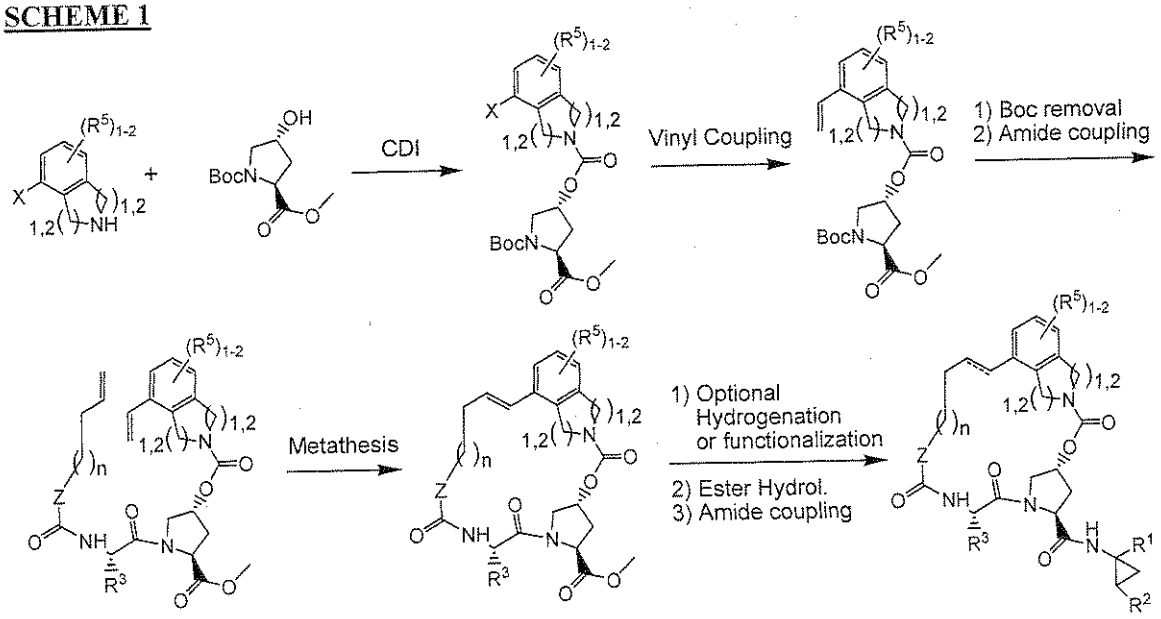
(TRF) assay as described in Example 56. Other examples of such assays are described in e.g., International patent publication WO2005/046712. Compounds useful as HCV NS3 protease inhibitors would have a Ki less than 50 μM, more preferably less than 10 μM, and even more preferably less than 100 nM.

The present invention also includes processes for making compounds of formula **I**, **II-a**, or **III-a**. The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above. The following reaction schemes and examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

General Description of Synthesis:

The compounds of the present invention may be synthesized as outlined in the general Schemes 1 and 2.

SCHEME 1

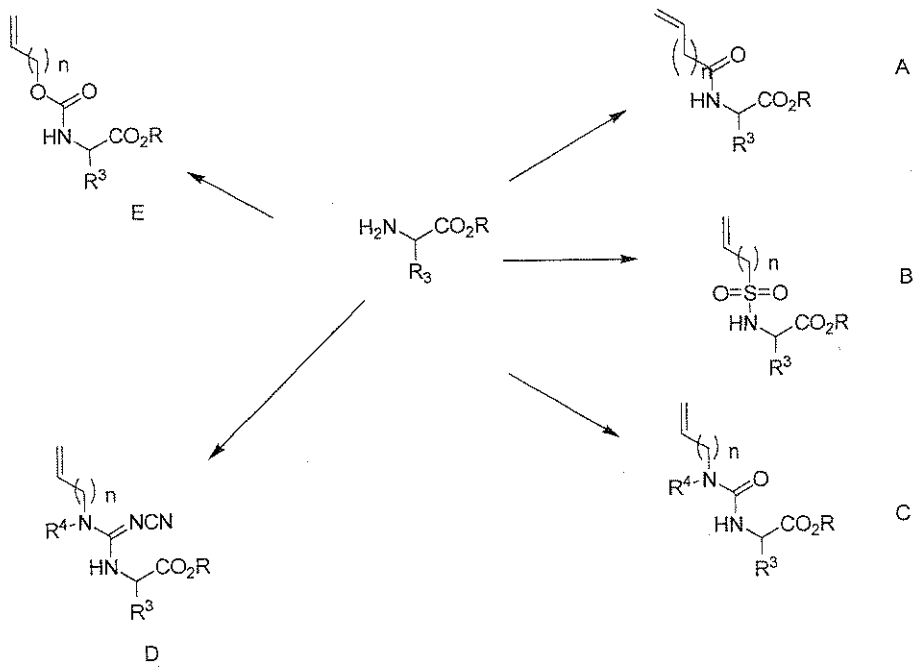


Scheme 1 (n=0-9) outlines the synthesis of a representative molecule. An appropriately protected 4-hydroxyproline derivative (for example, a carbamate protected nitrogen and an ester protected acid can be reacted with carbonyldiimidazole or equivalent reagent and then reacted with an appropriately substituted isoindoline or tetrahydroisoquinoline. The alkenyl functionality may be introduced at this or a later stage by palladium catalyzed reaction of a halide substituent such as chloride, bromide and iodide, or

other functionality such as a triflate with an organometallic reagent such as a vinyl or allyltrialkyltin. Alternatively, the alkenyl functionality may be introduced prior to the reaction with protected prolinol.

Scheme 2 describes the synthesis of the olefin containing amino acid portion. An amino acid (either commercially available or may be prepared readily using known methods in the art) in which the acid functionality is protected as an ester (for example, R=methyl) can be converted to amides A by coupling an olefinic carboxylic acid utilizing a wide range of peptide coupling agents known to those skilled in the art such as DCC, EDC, BOP, TBTU, etc. Preparation of the sulfonamides B can be accomplished by reaction with the appropriate sulfonyl chloride in an organic solvent (e.g., THF) with an amine base as scavenger. Urea derivatives C may be prepared by reacting the aminoester with a reagent such as carbonyldiimidazole, to form an intermediate isocyanate (Catalano et al., WO 03/062192) followed by addition of a second olefin containing amine. Alternatively, phosgene, diphosgene or triphosgene may be used in place of carbonyldiimidazole. Cyanoguanidine derivatives D can be prepared by reaction of the amino acid ester with diphenyl C-cyanocarbonimidate in an organic solvent, followed by addition of a second olefin containing amine. Carbamate derivatives E may be prepared by reacting an olefin containing alcohol with carbonyldiimidazole (or phosgene, triphosgene or diphosgene) in an organic solvent, followed by addition of the amino ester.

SCHEME 2

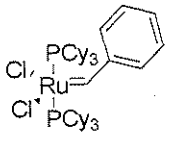


Following functionalization of the amine, the ester can be hydrolyzed under a range of basic conditions known to those skilled in the art (Theodora W. Greene, Protective Groups in Organic Synthesis, Third Edition, John Wiley and Sons, 1999).

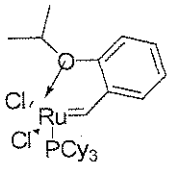
Deprotection of the carbamate protecting group on the proline portion may be carried out by a variety of methods known to persons skilled in the art (Theodora W. Greene, Protective Groups in Organic Synthesis, Third Edition, John Wiley and Sons, 1999).

To complete the synthesis of the compounds of this invention, the amino acid derivative can be coupled to the proline derivative via a wide range of peptide coupling reagents such as DCC, EDC, BOP, TBTU etc (see Scheme 1). Macrocyclization is then achieved by an olefin metathesis using a range of catalysts that have been described in the literature for this purpose. At this stage the olefinic bond produced in the ring closing metathesis may be optionally hydrogenated to give a saturated linkage or functionalized in alternative ways such as cyclopropanation. The proline ester is then hydrolyzed under basic conditions and coupled with the cyclopropylamino acid ester (the appropriate alkenyl or alkylcyclopropane portion of the molecule can be prepared as described previously (Llinas-Brunet et al., US 6,323,180) and subjected to an additional basic hydrolysis step to provide the final compounds. The proline ester can also be hydrolyzed and directly coupled to an appropriately functionalized cyclopropylamino acid acyl sulfonamide (which can be prepared according to Wang X.A. et al. WO2003/099274) to provide the final compounds.

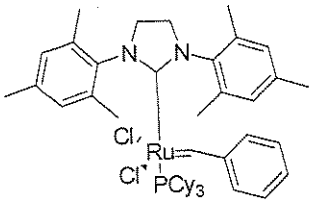
Olefin metathesis catalysts include the following Ruthenium based species: F: Miller et al *J. Am. Chem. Soc* 1996, 118, 9606; G: Kingsbury et al *J. Am. Chem. Soc* 1999, 121, 791; H: Scholl et al Org. Lett. 1999, 1, 953; Hoveyda et al US2002/0107138; K: Furstner et al. J. Org. Chem 1999, 64, 8275. The utility of these catalysts in ring closing metathesis is well known in the literature (e.g. Trnka and Grubbs, *Acc. Chem. Res.* 2001, 34, 18).



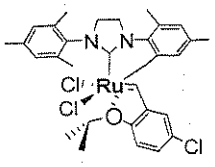
F



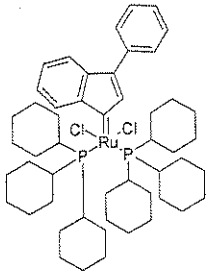
G



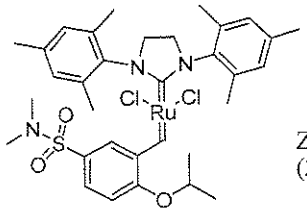
H



J



K



Zhan ruthenium metathesis catalyst RC-303
(Zhan catalyst 1B, RC-303, Zannan Pharma Ltd.)

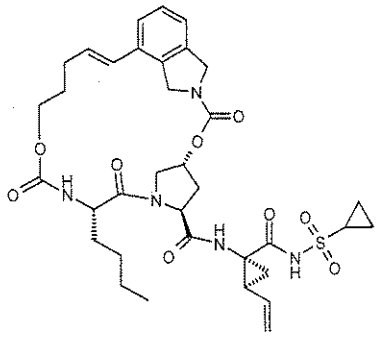
List of Abbreviations

BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate		
DCC	Dicyclohexylcarbodiimide	CH_3CN	Acetonitrile
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene		
DCE	Dichloroethane	DCM	Dichloromethane
DMAP	4-Dimethylamino pyridine	DIPEA	Diisoproylethylamine
DMF	Dimethylformamide	DMSO	Dimethyl sulfoxide
EDC	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide		

Et_3N	Triethylamine	Et_2O	Diethyl ether
EtOAc	Ethyl acetate	EtOH	Ethanol
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate		
HBr	Hydrobromic acid		
HCl	Hydrochloric acid	HOAc	Acetic acid
HOAt	1-Hydroxy-7-azabenzotriazole	LiOH	Lithium hydroxide
MeOH	Methanol	$MgSO_4$	Magnesium Sulfate
$NaHCO_3$	Sodium bicarbonate	Na_2SO_4	Sodium sulfate
NaOH	Sodium hydroxide	NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide	Pd/C	Palladium on carbon
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium (0)		
PhMe	Toluene	PPh_3	Triphenylphosphine
RT	room temperature	THF	Tetrahydofuran
TBTU	*O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate		

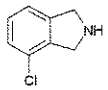
EXAMPLE 1

(5R,7S,10S)-10-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (**III-1**)



III-1

Step 1: 4-Chloroisoindoline

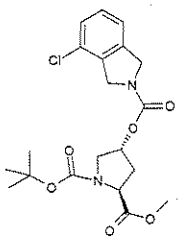


A mixture of 3-chlorophthalic acid anhydride (9 g, 49.2 mmol) and formamide (100 mL) was heated to 125 °C and stirred for 3 h. Water (300 mL) was then added and the mixture was cooled to room temperature. The mixture was filtered and the resulting white solid was washed with water and dried to give 4-chloro-1H-isoindole-1,3(2H)-dione (7.7 g, 86% yield).

To solid 4-chloro-1H-isoindole-1,3(2H)-dione (4.0 g, 22.0 mmol) was added borane-THF complex (1 M/THF, 88.1 mL, 88.1 mmol) dropwise with stirring. When the addition was complete, the reaction mixture was heated to reflux (80 °C) and stirred for 6 h. The reaction mixture was then cooled to

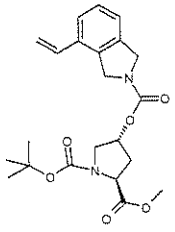
0°C, methanol (2.8 mL, 88.1 mmol) was carefully added dropwise and the reaction mixture was warmed to room temperature. HCl (6 N) was added until the mixture was acidic and then the mixture was concentrated. The crude product was dissolved in 1 M HCl and extracted twice with ethyl ether and twice with dichloromethane. The pH of the aqueous layer was adjusted to pH = 11 with solid NaOH and extracted three times with ethyl acetate. The combined ethyl acetate extracts were dried over Na_2SO_4, filtered and concentrated to give 4-chloroisoindoline (1.8 g, 53% yield). LRMS (ESI) *m/z* 154 $[(M+H)^+$; calcd for C_8H_9ClN: 154].

Step 2: 1-*tert*-Butyl 2-methyl (2S,4R)-4-{[(4-chloro-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy} pyrrolidine-1,2-dicarboxylate



To a solution of *N*-Boc proline methyl ester (2.87 g, 11.7 mmol) in DMF (15 mL) at 0°C was added carbonyldiimidazole (1.9 g, 11.7 mmol). The reaction was warmed to room temperature and stirred for 30 min. A solution of 4-chloroisoindoline (1.8 g, 11.7 mmol) in DMF (10 mL) was then added and the reaction mixture was heated to 50 °C and stirred for 2 h. The reaction mixture was poured onto ethyl ether and 0.5 M HCl and the layers were separated. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated. The crude product was purified on silica gel (gradient elution 10% to 90% ethyl acetate in hexanes) to give 1-*tert*-butyl 2-methyl (2S,4R)-4-{[(4-chloro-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (3.3 g, 66% yield). LRMS (ESI) *m/z* 325 $[(M+H\text{-Boc})^+$; calcd for $C_{15}H_{18}ClN_2O_4$: 325].

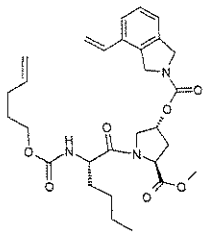
Step 3: 1-*tert*-Butyl 2-methyl (2S,4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy} pyrrolidine-1,2-dicarboxylate



A solution of 1-*tert*-butyl 2-methyl (2S,4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (40 mg, 0.09 mmol), vinyl tributylystannane (36 mg, 0.11 mmol) and cesium fluoride (31 mg, 0.21 mmol) in dioxane (0.5 mL) was degassed with N_2 for 15 min. Bis(tributylphospine)palladium(0) (2 mg, 0.005 mmol) was then added and the reaction vessel was sealed and heated to 100 °C for 18h. After cooling, the reaction mixture was concentrated and purifed by silica gel chromatography (10% to 90% ethyl acetate in hexanes) to give 1-*tert*-butyl 2-methyl (2S,4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (10 mg, 25 % yield).

LRMS (ESI) *m/z* 317 [(M+H-Boc)$^+$; calcd for $C_{17}H_{21}N_2O_4$: 317].

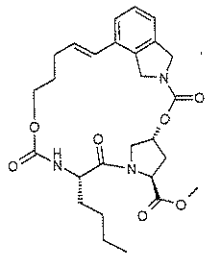
Step 4: Methyl *N*-[(pent-4-enyloxy)carbonyl]-L-norleucyl-(4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate



To a flask containing 1-*tert*-butyl 2-methyl (2S,4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (60 mg, 0.14 mmol) was added a 4 M solution of HCl in dioxane (2 mL). After 1 h, LC-MS analysis indicated complete consumption of the starting material and formation of the desired Boc product. The volatile components were then removed in vacuo, and the crude material was taken up in DMF (2 mL).

To this mixture was added *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucine (41 mg, 0.17 mmol) (prepared according to the procedure below), DIPEA (0.076 mL, 0.43 mmol), EDC (54 mg, 0.28 mmol) and HOAt (44 mg, 0.28 mmol). After stirring at r.t. for 30 min, complete consumption of the amine was evidenced via LC-MS. The reaction mixture was then worked-up with 0.5 N HCl and EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was then removed in vacuo and the crude product was purified on silica (10-90 % EtOAc/hexanes) to yield 60 mg (79% yield) of methyl *N*-[(pent-4-enyloxy)carbonyl]-L-norleucyl-(4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate. LRMS (ESI) *m/z* 542 [(M+H)$^+$; calcd for $C_{29}H_{40}N_3O_7$: 542].

Step 5: Methyl (5R,7S,10S)-10-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate



A solution of methyl *N*-[(pent-4-enyloxy)carbonyl]-L-norleucyl-(4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate (60 mg, 0.11 mmol) in DCE (20 mL) was degassed with N_2 for 15 min. The Zhan ruthenium metathesis catalyst RC-301 (Zhan Catalyst I (depicted as J on page 43), RC-301, Zannan Pharma Ltd.) (7 mg, 0.01 mmol) was then added. The solution was then heated to 100 °C for 1h. At this time, LC-MS and TLC analysis indicated complete consumption of the starting material and formation of nearly a single product which had the desired mass. The solvent was then removed in vacuo, and the crude product was purified on silica (5-70% EtOAc/hexane) to yield 45 mg (79% yield) of methyl (5R,7S,10S)-10-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-

2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate. LRMS (ESI) *m/z* 514 [(M+H)$^+$; calcd for $C_{27}H_{36}N_3O_7$: 514].

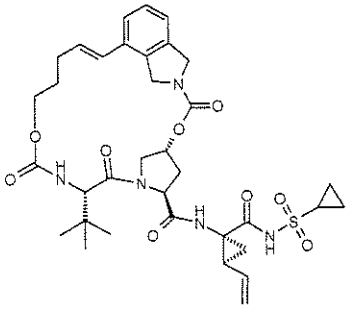
Step 6: (5R,7S,10S)-10-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide

To a solution of methyl (5R,7S,10S)-10-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (45 mg, 0.09 mmol) in THF (2 mL), MeOH (0.5 mL), and water (1 mL) was added LiOH (21 mg, 0.87 mmol). The reaction mixture was heated to 40 °C and stirred for 1 h, at which time complete consumption of the methyl ester starting material was observed by LC-MS. The mixture was then worked-up with 0.5 N HCl and EtOAc. The organic layer was then dried over K_2CO_3, and solvent was removed in vacuo. The crude product was taken up in DMF (1 mL).

To the above solution was added (1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride (Llinas-Brunet et al US03/15755 and Wang et al WO 03/099274) (32 mg, 0.12 mmol), TBTU (51 mg, 0.16 mmol) and DIPEA (0.071 mL, 0.40 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was directly purified by reverse phase HPLC to give (5R,7S,10S)-10-butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (27 mg, 47% yield). ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 10.01 (s , 1 H), 7.27 (m, 2 H), 7.12 (d, 1 H), 7.04 (s, 1 H), 6.40 (d, J = 16.1 Hz, 1 H), 6.08 (m, 1 H), 5.76 (m, 1 H), 5.44 (s, 1 H), 5.36 (d, 1 H), 5.25 (d, 1 H), 5.14 (d, 1 H), 4.80-4.68 (m, 3 H), 4.59 (d, 1 H), 4.44 (m, 2 H), 4.38 (m, 1 H), 4.28 (m, 1 H), 3.95 (m, 1 H), 3.77 (dd, 1 H), 2.94 (m, 1 H), 2.43 (m, 2 H), 2.29 (d, 2 H), 2.06 (m, 2 H), 1.94 (m, 1 H), 1.78 (m, 4 H), 1.45 (m, 1 H), 1.38-1.06 (m, 5 H), 1.04 (d, 2 H), 0.92 (t, 3 H) ppm. LRMS (ESI) *m/z* 712 [(M+H)$^+$; calcd for $C_{35}H_{46}N_5O_9S$: 712].

EXAMPLE 2

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (**III-2**)

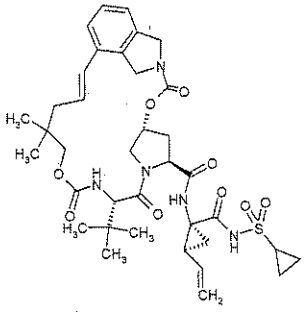


III-2

EXAMPLE 2 was prepared according to the procedure used for EXAMPLE 1 except that 3-methyl-*N*-[(pent-4-enyloxy)carbonyl]-L-valine (prepared according to the procedure below) was used in place of *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucine in Step 4. ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 9.90 (s , 1 H), 7.28 (m, 2 H), 7.13 (m, 2 H), 6.31 (d, J = 15.9 Hz, 1 H), 6.04 (m, 1 H), 5.74 (m, 1 H), 5.45 (m, 2 H), 5.27 (d, 1 H), 5.16 (d, 1 H), 4.77-4.66 (m, 3 H), 4.55 (d, 1 H), 4.48 (t, 1 H), 4.41-4.35 (m, 2 H), 4.27 (m, 1 H), 3.93 (m, 1 H), 3.74 (dd, 1 H), 2.93 (m, 1 H), 2.45 (d, 2 H), 2.32 (m, 2 H), 2.10-1.95 (m, 2 H), 1.74 (m, 1 H), 1.47 (m, 1 H), 1.37 (m, 2 H), 1.07 (s, 9 H) ppm. LRMS (ESI) *m/z* 712 [$(M+H)^+$; calcd for $C_{35}H_{46}N_5O_9S$: 712].

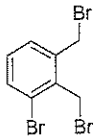
EXAMPLE 3

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (**III-8**)



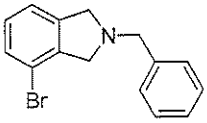
III-8

Step 1: 1-Bromo-2,3-bis(bromomethyl)benzene



A suspension of 3-bromo-o-xylene (196 g, 1.06 mol), *N*-bromosuccinimide (377 g, 2.15 mol) and benzoyl peroxide (0.26 g, 1.0 mmol) in carbon tetrachloride (1800 mL) was heated to reflux under nitrogen for 15 h. The contents of the reaction flask were cooled, filtered, and the filtrate evaporated. Distilled crude material under high vacuum. Major fractions distilled between 88 °C and 152 °C. Recovered 108 g pure material. Recovered 182 g slightly crude material which could be used in the following reaction. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.56 (d, J = 8.0 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.16 (t, J = 8.0 Hz, 1 H), 4.84 (s, 2 H), 4.64 (s, 2 H).

Step 2: 2-Benzyl-4-bromoisoindoline

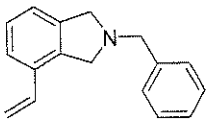


Postassium bicarbonate (204 g, 2.04 mol) was suspended in acetonitrile (12 L) and the mixture was heated to 80 °C. Solutions of 1-bromo-2,3-bis(bromomethyl)benzene (280 g, 0.82 mol in 500

mL acetonitrile) and benzylamine (87.5 g, 0.82 mol in 500 mL acetonitrile) were added concurrently via addition funnels over 1 h. The reaction mixture was stirred at 77 °C for 16h. The contents of the reaction flask were cooled, filtered and the solvent removed by evaporation. The reaction was partitioned between 1M K_2CO_3 and EtOAc. The organics were washed with brine, dried with anhydrous Na_2SO_4, filtered, and evaporated. Flash column chromatography (gradient elution: heptane to 10% EtOAc in heptane) gave after evaporation the title compound as a pale oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.41-7.39 (m, 2 H), 7.37-7.34 (m, 2 H), 7.32-7.27 (m, 2 H), 7.10-7.03 (m, 2 H), 4.02 (s, 2 H), 3.97 (s, 2 H), 3.91 (s, 2 H). LRMS (ESI) *m/z* 289 [$(M+H)^+$; calcd for $C_{15}H_{15}BrN$: 289].

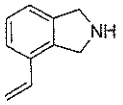
Converted to HCl salt in HCl/MeOH. Added MTBE and filtered solid to give 118 g of product as the HCl salt.

Step 3: 2-Benzyl-4-vinylisoindoline



A solution of 2-benzyl-4-bromoisoindoline (16.7 g, 58.0 mmol) and tributyl(vinyl)tin (20.3 mL, 69.6 mmol) in toluene (400 mL) was degassed by bubbling nitrogen gas through the solution for 0.25h. Tetrakis(triphenylphosphine)palladium (0) (1.30 g, 1.16 mmol) was added and the resulting solution heated in a 100 °C oil bath under nitrogen for 24h. The contents of the reaction flask were cooled, evaporated and subjected to flash column chromatography eluting with hexane/ethyl acetate 95/5 to give after evaporation the title compound as a pale oil that turned pink on standing. LRMS (ESI) *m/z* 236 [$(M+H)^+$; calcd for $C_{17}H_{18}N$: 236].

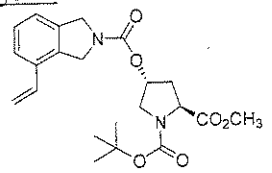
Step 4: 4-Vinylisoindoline



A solution of 2-benzyl-4-vinylisoindoline (58 mmol) in 1,2-dichloroethane (150 mL) was placed in a 1L round bottom flask under nitrogen. To this was attached an addition funnel containing a solution of 1-chloroethyl chloroformate (7.51 mL, 69.6 mmol) in 1,2-dichloroethane. The reaction flask was cooled in an ice bath and the contents of the addition funnel were added dropwise over 20 min keeping the internal reaction temperature <5 °C. After the addition was complete the reaction flask was allowed to warm to room temperature then heated to reflux for 45 min. The contents of the reaction flask were cooled to room temperature then the solvent removed by evaporation. Methanol (200 mL) was added and the contents of the reaction flask were heated to reflux for 30 min. The reaction flask was cooled and the solvent removed by evaporation. Water (200 mL) was added and the resulting mixture washed with ethyl acetate (2 × 250 mL). The aqueous layer was made basic with 2N sodium hydroxide then extracted with methylene chloride (4 × 250 mL). The combined organic extracts were dried with anhydrous sodium sulfate, filtered and the filtrate evaporated. The remaining residue was subjected to flash column chromatography eluting with methylene chloride/methanol/ammonium hydroxide 97/3/0.3 to

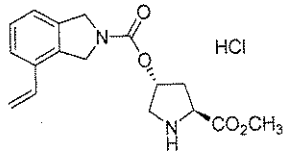
95/5/0.5. Evaporation of fractions gave the title compound as a brown oil, 6.00g (41.4 mmol, 71% yield for two steps). LRMS (ESI) *m/z* 146 [(M+H)$^+$; calcd for $C_{10}H_{12}N$: 146].

Step 5: 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate



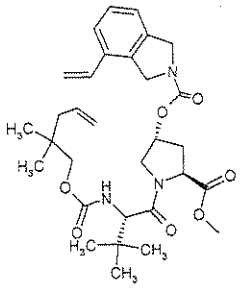
A solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (10.1 g, 41.4 mmol) in DMF (90 mL) under nitrogen was cooled to 0 °C. Solid 1,1'-carbonyldiimidazole (6.70 g, 41.4 mmol) was added to the reaction. The contents of the reaction flask were warmed to room temperature and after 2h a solution of 4-vinylisoindoline (6.00 g, 41.4 mmol) in DMF (10 mL) was added. The reaction was heated in a 60 °C oil bath for 2h then cooled and poured into water and 5% potassium bisulfate. The resulting mixture was extracted with ethyl acetate (4 × 250 mL). Combined organics were washed with brine, dried with anhydrous sodium sulfate, filtered and evaporated. Flash column chromatography eluting with hexane/ethyl acetate 70/30 gave the title compound as a white foam, 13.9 g (33.4 mmol, 81% yield). LRMS (ESI) *m/z* 417 [(M+H)$^+$; calcd for $C_{227}H_{29}N_2O_6$: 417].

Step 6: (3*R*,5*S*)-5-(Methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate Hydrochloride



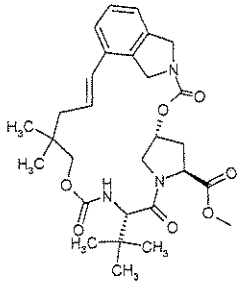
A solution of 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (13.9 g, 33.4 mmol) in ethyl acetate (700 mL) was cooled in an ice bath the saturated with hydrogen chloride gas. The reaction flask was sealed and allowed to warm to room temperature. After 3.5h the solvent was removed by evaporation to give the title compound as a gray solid, 11.2 g, 95% yield). ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 7.47-7.45 (m, 1 H), 7.32-7.31 (m, 1 H), 7.26-7.21 (m, 1 H), 6.79-6.73 (m, 1 H), 5.79 - 5.73 (m, 1 H), 5.46 (s, 1 H), 5.41 - 5.38 (m, 1 H), 4.80 - 4.72 (m, 4 H), 3.91 (s, 3 H), 3.74 - 3.63 (m, 2 H), 2.77 - 2.71(m, 1 H), 2.51-2.46 (m, 1 H). LRMS (ESI) *m/z* 317 [(M+H)$^+$; calcd for $C_{17}H_{21}N_2O_4$: 317].

Step 7: Methyl *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valyl-(4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate



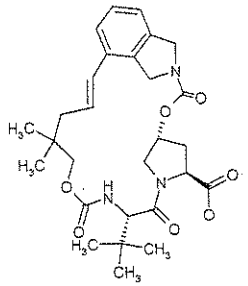
To a solution of (3*R*,5*S*)-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate hydrochloride (2.00 g, 5.67 mmol) and *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine (1.54 g, 5.67 mmol) in DMF (100 mL) was added EDC (1.41 g, 7.37 mmol), HOBt (1.00 g, 7.37 mmol) and DIPEA (3.16 mL, 22.8 mmol). The reaction mixture was stirred at RT for 18 h and then diluted with ethyl acetate and aqueous $NaHCO_3$. The layers were separated and the organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified on silica gel (gradient elution 5% to 50% ethyl acetate in hexanes) to give methyl *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valyl-(4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate (2.75 g, 85% yield) as a white foam. LRMS (ESI) *m/z* 570 $[(M+H)^+$; calcd for $C_{31}H_{44}N_3O_7$: 570].

Step 8: Methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate



A solution of methyl *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valyl-(4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate (2.46 g, 4.32 mmol) in anhydrous dichloromethane (450 mL) was purged with nitrogen for 15 min. A solution of bis(tricyclohexylphosphine)-3-phenyl-1H-indene-1-ylideneruthenium dichloride (Neolyst M1 catalyst purchased from Strem) (0.40 g, 0.43 mmol) in degassed, anhydrous dichloromethane (50 mL) was then added dropwise over 30 min. The reaction mixture was stirred at RT, during which time 0.2 g portions of the catalyst were added approximately every 8-12h. Reaction progress was monitored by HPLC until the reaction was complete at 48h. The residue was purified by flash chromatography on silica gel, eluting with 10-70% EtOAc/Hexane, to give methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (1.85 g, 76% yield). LRMS (ESI) *m/z* 542 $[(M+H)^+$; calcd for $C_{29}H_{40}N_3O_7$: 542].

Step 9: (5R,7S,10S)-10-*tert*-Butyl-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylic acid



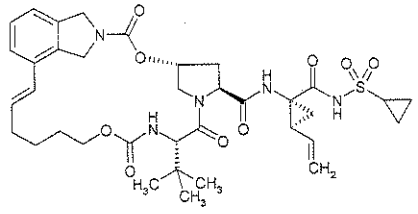
To a solution of methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (0.9 g, 1.67 mmol) in THF:H2O (2:1, 45 mL) was added LiOH (0.40, 16.7 mmol). The reaction mixture was heated to 40 °C and stirred for 1 h. The reaction mixture was diluted with aqueous HCl, and extracted with EtOAc. The combined EtOAc layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The product was used with no further purification. LRMS (ESI) *m/z* 528 $[(M+H)^+$; calcd for $C_{28}H_{38}N_3O_7$: 528].

Step 10: (5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide

A solution of (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylic acid (100 mg, 0.19 mmol), (1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride (Llinas-Brunet et al US03/15755 and Wang et al WO 03/099274) (76 mg, 0.28 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium phosphorushexafluoride (HATU, 108 mg, 0.28 mmol), DIPEA (0.073 mL, 0.42 mmol) and 4-dimethylaminopyridine (2 mg) in dichloromethane (5 mL) was stirred at 40 °C for 1 h. The reaction solution was diluted with aqueous saturated $NaHCO_3$, and extracted with EtOAc. The combined EtOAc layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography eluting with 3% MeOH/CH_2Cl_2, to give (5R,7S,10S)-10-*tert*-butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (80 mg, 57% yield). ^{1}H NMR (400 MHz, ppm, $CDCl_3$) δ 7.48 (s, 1 H), 7.23 (s, 1 H), 7.12 (d, 1 H), 6.23 (d, J = 15.9 Hz, 1 H), 5.94 (m, 1 H), 5.76 (m, 1 H), 5.50 (m, 2 H), 5.43 (s, 1 H), 5.24 (d, J = 16.6 Hz, 1 H), 5.11 (d, 1 H), 4.70 (s, 2 H), 4.61 (d, 1 H), 4.48 (m, 3 H), 4.35 (d, 1 H), 4.14 (d, 1 H), 3.74 (d, 1 H), 3.34 (d, 1 H), 2.89 (m, 1 H), 2.43 (dd, 2 H), 2.06 (m, 1 H), 1.93 (m, 1 H), 1.89 (dd, 1 H), 1.43 (d, 1 H), 1.25 (m, 3 H), 1.09 (s, 3 H), 1.06 (s, 9 H), 0.86 (s, 3 H). LRMS (ESI) *m/z* 740 $[(M+H)^+$; calcd for $C_{37}H_{50}N_5O_9S$: 740].

EXAMPLE 4

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-12**)

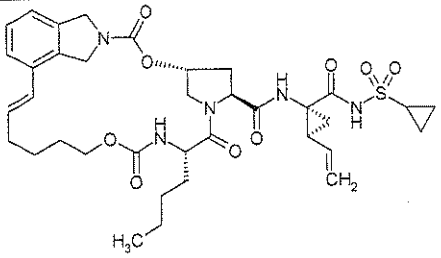


III-12

The title compound was prepared according to the procedure used for EXAMPLE 3 except that 3-methyl-*N*-[(hex-5-enyloxy)carbonyl]-L-valine (prepared according to the procedure below) was used in place of *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine in Step 7. ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 9.13 (s, 1 H), 7.26 (t, 1 H), 7.23 (d, 1 H), 7.16 (d, 1 H), 6.39 (d, J = 16.4 Hz, 1 H), 6.08 (m, 1H), 5.76 (m, 1 H), 5.38 (s, 1 H), 5.29 (d, 1 H), 5.12 (d, 1 H), 4.79 (d, 1 H), 4.73 – 4.63 (m, 4 H), 4.41 (s, 1 H), 4.37 (q, 1 H), 4.24 (d, 1 H), 3.96 (dd, 1 H), 3.77 (quin, 1 H), 2.94 (m, 1 H), 2.51 (q, 1 H), 2.29 – 2.13 (m, 4 H), 1.87 (dd, 1 H), 1.68 (m, 2 H), 1.53 (quin, 2 H), 1.44 (dd, 1 H), 1.25 (m, 2 H), 1.05 (s, 9 H). LRMS (ESI) *m/z* 726 [(M+H)$^+$; calcd for $C_{36}H_{48}N_5O_9S$: 726].

EXAMPLE 5

(5R,7S,10S)-10-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-133**)

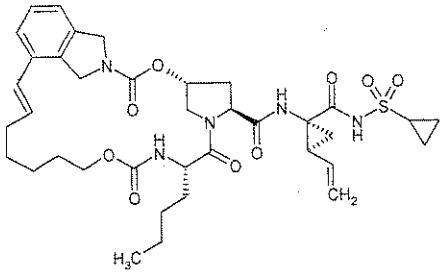


III-133

The title compound was prepared according to the procedure used for EXAMPLE 3 except that 3-methyl-*N*-[(hex-5-enyloxy)carbonyl]-L-norleucine (prepared according to the procedure below) was used in place of *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine in Step 7. ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 7.24 (t, 1 H), 7.23 (d, 1 H), 7.15 (d, 1 H), 6.91 (d, 1 H), 6.37 (d, J = 16.1 Hz, 1 H), 6.07 (m, 1H), 5.75 (m, 1 H), 5.39 (s, 1 H), 5.29 (d, 1 H), 5.12 (d, 1 H), 4.77 (d, 1 H), 4.66 (m, 3 H), 4.57 (m, 1 H), 4.47 (q, 1 H), 4.39 (q, 1 H), 4.27 (d, 1 H), 3.90 (dd, 1 H), 3.77 (quin, 1 H), 2.96 (m, 1 H), 2.49 (q, 1 H), 2.29 (m, 1 H), 2.22 (m, 3 H), 1.88 (dd, 1 H), 1.75 (m, 2 H), 1.64 (m, 2 H), 1.52 (m, 2 H), 1.39 (m, 5 H), 1.27 (m, 1 H), 1.18 (m, 1 H), 1.09 (m, 2 H), 0.94 (t, 3 H). LRMS (ESI) *m/z* 726 [(M+H)$^+$; calcd for $C_{36}H_{48}N_5O_9S$: 726].

EXAMPLE 6

(5R,7S,10S)-10-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,24:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclodocosine-7-carboxamide (**III-198**)

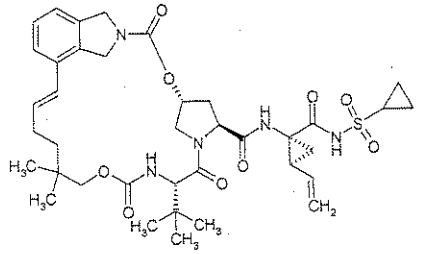


III-198

The title compound was prepared according to the procedure used for EXAMPLE 3 except that *N*-[(hept-6-en-1-yloxy)carbonyl]-L-norleucine (prepared according to the procedure below) was used in place of *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine in Step 7. ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 9.26 (s, 1 H), 7.39 (d, 1 H), 7.24 (t, 1 H), 7.15 (d, 1 H), 6.30 (d, J = 15.9 Hz, 1 H), 6.20 (m, 1H), 5.75 (m, 1 H), 5.53 (s, 1 H), 5.31 (d, 1 H), 5.12 (d, 1 H), 4.70 (m, 4 H), 4.43 (dd, 1 H), 4.34 (m, 2 H), 4.27 (q, 1 H), 3.91 (dd, 1 H), 3.79 (quin, 1 H), 3.31 (m, 1 H), 2.97 (m, 1 H), 2.31 (m, 1 H), 2.22 (m, 3 H), 1.89 (dd, 1 H), 1.74 (m, 2 H), 1.66 (m, 1 H), 1.56 (m, 3 H), 1.38 (m, 8 H), 1.19 (m, 1 H), 1.09 (m, 2 H), 0.94 (t, 3 H). LRMS (ESI) *m/z* 740 [$(M+H)^+$; calcd for $C_{37}H_{50}N_5O_9S$: 740].

EXAMPLE 7

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-199**)

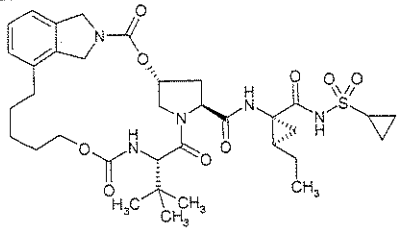


III-199

The title compound was prepared according to the procedure used for EXAMPLE 3 except that *N*-{[(2,2-dimethylhex-5-enyl)oxy]carbonyl}-3-methyl-L-valine (prepared according to the procedure below) was used in place of *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine in Step 7. ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 9.17 (s, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 2 H), 7.16 (d, J = 7.5 Hz, 1 H), 6.38 (d, J = 16 Hz, 1 H), 6.03 (m, 1 H), 5.79 (m, 1 H), 5.32 (m, 2 H), 5.13 (m, 1 H), 4.82-4.77 (m, 1 H), 4.73-4.61 (m, 4 H), 4.48 (s, 1 H), 4.39 (m, 1 H), 4.19 (d, J = 12 Hz, 1 H), 3.96 (m, 1 H), 2.96 (m, 1 H), 2.59-2.55 (m, 1 H), 2.35-2.12 (m, 4 H), 1.89 (m, 1 H), 1.49-1.23 (m, 6 H), 1.51-0.98 (m, 14 H), 0.95-0.85 (m, 4 H). LRMS (ESI) *m/z* 754 [$(M+H)^+$; calcd for $C_{38}H_{52}N_5O_9S$: 754].

EXAMPLE 8

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (**III-200**)

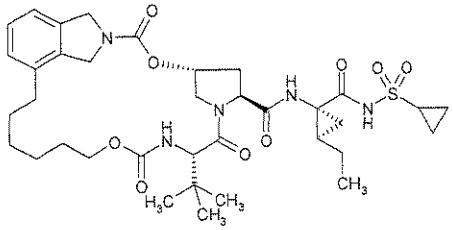


III-200

A solution of EXAMPLE 2 (0.32 mg, 0.45 mmol) and palladium on carbon (10% wt., 0.03 g) in EtOAc (10 mL) was vigorously stirred under a hydrogen balloon for 1 h. The reaction mixture was filtered and concentrated. The residue was purified by reverse-phase HPLC (DeltaPak C18 column), running 40-65% CH_3CN in water (with NH_4OAc 1 g/L). The fractions were concentrated, diluted with aqueous saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 70 mL). The combined CH_2Cl_2 layers were washed with water (50 mL), dried over Na_2SO_4, filtered and concentrated to give (5R,7S,10S)-10-*tert*-butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (0.31 g, 97% yield). ^1H NMR (CD_3OD, ppm) δ 7.23 (t, 1 H), 7.14 (d, 1 H), 7.10 (d, 1 H), 7.02 (d, 1 H), 5.52 (s, 1H), 4.74 - 4.60 (m, 4 H), 4.48 - 4.30 (m, 4 H), 3.88 (d, 1 H), 3.75 (s, 1H), 2.99 (m, 1 H), 2.62 (m, 1 H), 2.41 (m, 2 H), 2.14 (m, 1H), 1.79 (m, 1 H), 1.65 – 1.51 (m, 6 H), 1.47 – 1.19 (m, 5 H), 1.07 (s, 9 H), 0.99 (t, 3 H). LRMS (ESI) *m/z* 716 $[(M+H)^+$; calcd for $C_{35}H_{50}N_5O_9S$: 716].

EXAMPLE 9

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-201**)



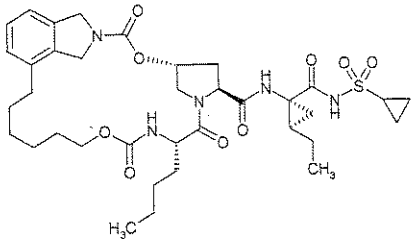
III-201

The title compound was prepared from EXAMPLE 4 using the procedure described for EXAMPLE 8. ^1H NMR (500 MHz, ppm, CD_3OD) δ 7.23 (t, 1 H), 7.14 (d, 1 H), 7.10 (d, 1 H), 7.02 (d, 1 H), 5.36 (s, 1 H), 4.71 (m, 3 H), 4.64 (t, 1 H), 4.56 (m, 1 H), 4.40 (m, 2 H), 4.24 (d, 1 H), 3.96 (dd, 1 H),

3.72 (quin, 1 H), 2.98 (m, 1 H), 2.58 (m, 1 H), 2.49 (m, 2 H), 2.15 (t, 1 H), 1.69 – 1.19 (m, 15 H), 1.09 (m, 1 H), 1.06 (s, 9 H), 0.98 (t, 3 H). LRMS (ESI) *m/z* 730 [(M+H)$^+$; calcd for $C_{36}H_{52}N_5O_9S$: 730].

EXAMPLE 10

(5R,7S,10S)-10-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-202**)

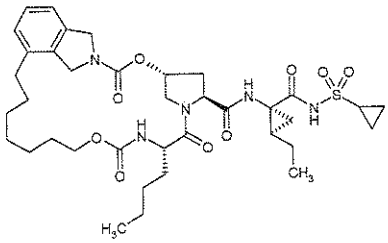


III-202

The title compound was prepared from EXAMPLE 5 using the procedure described for EXAMPLE 8. ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 7.23 (t, 1 H), 7.14 (d, 1 H), 7.09 (d, 1 H), 6.99 (d, 1 H), 5.39 (s, 1 H), 4.76 – 4.61 (m, 4 H), 4.43 (m, 3 H), 4.29 (d, 1 H), 3.92 (dd, 1 H), 3.69 (quin, 1 H), 2.99 (m, 1 H), 2.57 (m, 1 H), 2.51 (m, 2 H), 2.19 (tt, 1 H), 1.77 (m, 1 H), 1.70 – 1.30 (m, 20 H), 1.17 (m, 2 H), 1.10 (m, 2 H), 0.99 (t, 3 H), 0.95 (t, 3 H). LRMS (ESI) *m/z* 730 [(M+H)$^+$; calcd for $C_{36}H_{52}N_5O_9S$: 730].

EXAMPLE 11

(5R,7S,10S)-10-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18,19,20-tetradecahydro-5H-2,24:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclodocosine-7-carboxamide (**III-203**)

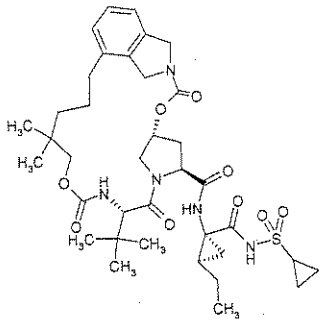


III-203

The title compound was prepared from EXAMPLE 6 using the procedure described for EXAMPLE 8. ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 7.25 (t, 1 H), 7.15 (d, 1 H), 7.11 (d, 1 H), 5.55 (s, 1 H), 4.70 (m, 4 H), 4.49 (m, 1 H), 4.38 (t, 1 H), 4.29 (m, 2 H), 3.94 (dd, 1 H), 3.73 (quin, 1 H), 3.00 (m, 1 H), 2.63 (quin, 1 H), 2.51 (m, 1 H), 2.38 (m, 1 H), 2.20 (tt, 1 H), 1.76 (quin, 1 H), 1.68 – 1.07 (m, 24 H), 1.00 (t, 3 H), 0.95 (t, 3 H). LRMS (ESI) *m/z* 744 [(M+H)$^+$; calcd for $C_{37}H_{54}N_5O_9S$: 744].

EXAMPLE 12

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (**III-204**)

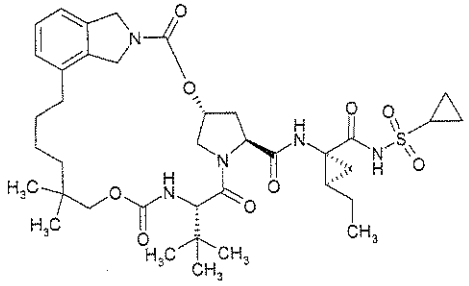


III-204

The title compound was prepared from EXAMPLE 3 using the procedure described for EXAMPLE 8. ^{1}H NMR (400 MHz, ppm, CD_3OD) δ 9.06 (s, 1 H), 7.22 (dd, 1 H), 7.13 (d, 1 H), 7.07 (d, 1 H), 5.51 (s, 1 H), 4.72 (d, 2 H), 4.68 (d, 2 H), 4.44 (d, 2 H), 4.28 (m, 2 H), 3.87 (dd, 1 H), 3.28 (m, 1 H), 2.98 (d, 1 H), 2.85 (m, 3 H), 2.52 (m, 1 H), 2.43 (m, 2 H), 2.15 (m, 1 H), 1.15-1.17 (m, 3 H), 1.41 (m, 2 H), 1.30 (m, 1 H), 1.21 (m, 4 H), 1.08 (m, 1 H), 1.06 (s, 3 H), 1.05 (s, 9 H), 0.98 (t, 3 H), 0.81 (s, 3 H). LRMS (ESI) *m/z* 744 [$(M+H)^+$; calcd for $C_{37}H_{54}N_5O_9S$: 744].

EXAMPLE 13

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-205**)

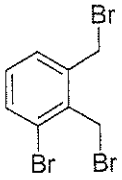


III-205

The title compound was prepared from EXAMPLE 7 using the procedure described for EXAMPLE 8. ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 9.09 (s, 1 H), 7.24 (t, J = 7.5 Hz, 1 H), 7.15 (d, J = 7.5 Hz, 1 H), 7.10 (d, J = 7.5 Hz, 1 H), 5.53 (s, 1 H), 4.75 - 4.59 (m, 4 H), 4.44 - 4.37 (m, 3 H), 4.20 (d, J = 12 Hz, 1 H), 3.95 - 3.91 (m, 1 H), 3.31 (m, 2 H), 2.99 - 2.96 (m, 1 H), 2.62 - 2.46 (m, 3 H), 2.17 - 2.13 (m, 1 H), 1.67 - 1.50 (m, 6 H), 1.37 - 1.18 (m, 7 H), 1.15 - 0.96 (m, 16 H), 0.80 (s, 3 H). LRMS (ESI) *m/z* 758 [$(M+H)^+$; calcd for $C_{38}H_{56}N_5O_9S$: 758].

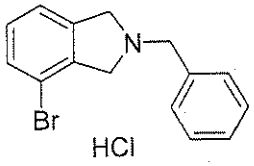
Alternative Preparation:

Step 1: 1-Bromo-2,3-bis(bromomethyl)benzene



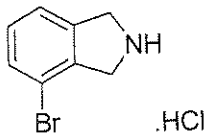
To a suspension of 3-bromo-o-xylene (999 g, 5.40 mol) in chlorobenzene (9 L) at RT was added *N*-bromosuccinimide (1620 g, 9.1 mol) and benzoyl peroxide (2.6 g, 10.8 mmol). The reaction mixture was heated to 80 °C and stirred under nitrogen for 18 h. The reaction mixture was cooled to 70 °C and an additional portion of NBS (302 g, 1.7 mol) was added. The reaction mixture was heated to 80 °C and stirred under nitrogen for 22 h. The reaction mixture was cooled to RT, diluted with heptane (6 L) and filtered. The filter cake was washed with heptane (4 L) and the combined filtrates were evaporated. The crude product was dissolved in heptane (2 L) and chloroform (200 mL) and filtered through basic alumina (500 g). The alumina pad was washed with heptane (4 L) and the combined filtrates were evaporated to give 1-bromo-2,3-bis(bromomethyl)benzene (1760 g, crude weight) which was used without further purification. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.56 (d, J = 8.0 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.16 (t, J = 8.0 Hz, 1 H), 4.84 (s, 2 H), 4.64 (s, 2 H).

Step 2: 2-Benzyl-4-bromoisoindoline hydrochloride



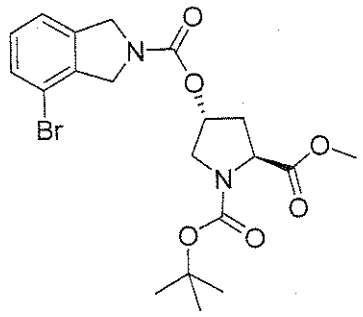
Potassium bicarbonate (657 g, 6.56 mol) was suspended in MeCN (17 L) and the mixture was heated to 80 °C. Solutions of crude 1-bromo-2,3-bis(bromomethyl)benzene (900 g, 2.63 mol in 1 L MeCN) and benzylamine (281 g, 2.63 mol in 1 L MeCN) were added concurrently via addition funnels over 2 h. The reaction mixture was stirred at 77 °C for 2 h and then cooled to RT and stirred for 16 h. The contents of the reaction flask were cooled, filtered and the solvent removed by evaporation. The reaction was partitioned between water (6 L) and EtOAc (2 L). The pH was adjusted to >9 by the addition of 1M K_2CO_3, the layers were separated and the aqueous phase extracted with an additional portion of EtOAc (2 L). The combined organics were washed with brine, dried with anhydrous Na_2SO_4, filtered, and evaporated. The crude oil was diluted with EtOH (300 mL) and cooled to 0 °C. Methanolic HCl was added until the mixture was acidic, followed by MTBE (700 mL) and the mixture sonicated, then stirred for 15 h. MTBE (1 L) was added and the mixture was filtered and washed with 20% EtOH in MTBE followed by MTBE. The solid was air dried to give 2-benzyl-4-bromoisoindoline hydrochloride (211g). An additional portion of product (86 g) was isolated by concentration of the mother liquors. LRMS (ESI) *m/z* 289 [$(M+H)^+$; calcd for $C_{15}H_{15}BrN$: 289].

Step 3: 4-Bromoisoindoline



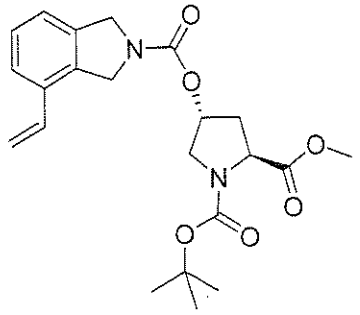
To a solution of 2-benzyl-4-bromoisoindoline hydrochloride (11 g, 30.96 mmol) in 200 mL EtOAc was added 1M NaOH (100 mL) and the mixture stirred for 30 min. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and solvent evaporated to an oil which was azeotroped once with toluene (50 mL). The oil was dissolved in chlorobenzene (50 mL) and 4A molecular sieves (5 g) added to the stirred solution. After 10 min, 1-chloroethylchloroformate (5.6 mL, 51 mmol) was added dropwise over 5 min. The reaction mixture was then heated to 90 °C for 2 h, cooled to room temperature and filtered. The solids were washed with chlorobenzene (5 mL) and methanol (40 mL). The filtrate was heated to 70 °C for 1 h., allowed to cool and stirred at room temperature overnight. The solids were filtered, washed with chlorobenzene (2 mL) and hexane and dried to give 6.84 g of title compound. LRMS (ESI) *m/z* 198.1 $[(M+H)^+$; calcd for C_8H_9BrN: 198.0].

Step 4: 1-t-Butyl 2-methyl (2S,4R)-4-{[(4-bromo-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate



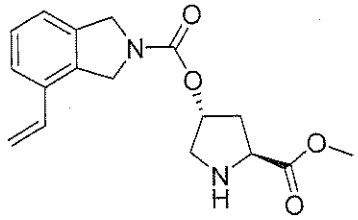
To a solution of (2S,4R)-BOC-4-hydroxyproline methyl ester (126.3 g, 515 mmol) in DMF (960 mL) at 0 °C was added N,N'-carbonyldiimidazole (83.51 g, 515 mmol). The reaction mixture was stirred at room temperature for 3 h. 4-Bromoisoindoline hydrochloride (120 g, 515 mmol) and diisopropylethylamine (96.3 mL, 540 mmol) were added and the reaction mixture heated to 50 °C for 6 h then allowed to cool to room temperature and stirred overnight. The reaction mixture was partitioned between EtOAc (3 L) and 10% aqueous $KHSO_4$ (6 L), the aqueous re-extracted with EtOAc (2 L) and the combined organic phases washed with 10% aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and solvent evaporated to a foam (239 g). LRMS (ESI) *m/z* 471.0 $[(M+H)^+$; calcd for $C_{20}H_{26}BrN_2O_6$: 471.1].

Step 5: 1-t-Butyl 2-methyl (2S,4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate



To a solution of 1-t-butyl 2-methyl (2S,4R)-4-{[(4-bromo-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (10.0 g, 21.3 mmol) in ethanol (200 mL) was added potassium vinyltrifluoroborate (4.28 g, 32 mmol) and triethylamine (4.5 mL, 32 mmol) followed by dichloro[1,1-bis(diphenylphosphino)ferrocene]palladium (II) chloride dichloromethane adduct (175 mg, 0.21 mmol). The reaction mixture was heated to reflux for 6 h, cooled to room temperature, diluted with 10% aqueous $KHSO_4$ and the ethanol removed by evaporation in vacuo. The aqueous residue was extracted with EtOAc and the organic phase washed with brine, dried over Na_2SO_4, solvent evaporated and crude product purified by chromatography on silica eluting with 40-60% EtOAc/ hexane to give, after evaporation, the title compound (8.18 g). LRMS (ESI) *m/z* 417.2 $[(M+H)^+$; calcd for $C_{22}H_{29}N_2O_6$: 417.2].

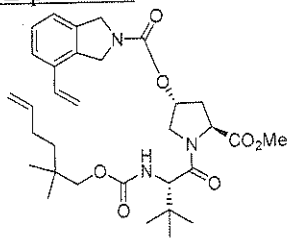
Step 6: (3*R*,5*S*)-5-(Methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate hydrochloride



.HCl

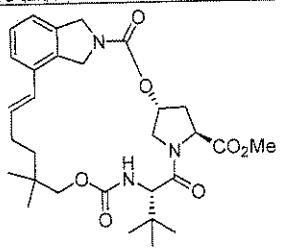
A mixture of 1-t-butyl 2-methyl (2S,4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (18.0 g, 43.2 mmol) and HCl/dioxane (4 M) (43.2 mL, 173 mmol) was stirred at RT for 2h. The reaction mixture was concentrated to remove the dioxane followed by concentration from Et_2O to give (3*R*,5*S*)-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate hydrochloride as an off-white solid (15 g) which was used without further purifcation. LRMS (ESI) *m/z* 317 $[(M+H)^+$; calcd for $C_{17}H_{21}N_2O_4$: 317].

Step 7: Methyl *N*-{[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate



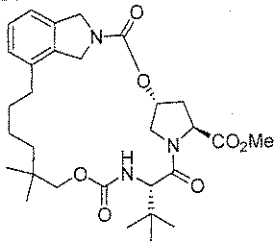
To a solution of (3*R*,5*S*)-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate hydrochloride (5.0 g, 14.2 mmol) and *N*-{[(2,2-dimethylhex-5-enyl)oxy]carbonyl}-3-methyl-L-valine (4.0 g, 14.2 mmol) in DMF (20 ml) at RT was added DIPEA (2.5 mL, 14.2 mmol), EDC (5.5 g, 28.4 mmol), and HOAt (1.9 g, 14.2 mmol). After 18 h the reaction mixture was poured into Et_2O, and extracted with 1 N HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with 1 N HCl, water, $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified on silica (30% EtOAc in hexanes) to yield 4.2 g of the title compound as a thick oil. LRMS (ESI) *m/z* 584.4 $[(M+H)^+$; calcd for $C_{32}H_{46}N_3O_7$: 584.3].

Step 8: Methyl (5*R*,7*S*,10*S*,18*E*)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylate



To a solution of methyl *N*-{[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (4.7 g, 8.05 mmol) in degassed (nitrogen bubbling for 30 min) DCM (1410 mL) was added Zhan 1B catalyst (Zhan catalyst 1B, RC-303, Zannan Pharma Ltd.) (0.591 g, 0.805 mmol). The mixture was then stirred at RT under an N_2 atmosphere. After 19 h, the reaction was complete and DMSO (57 µL, 0.805 mmol) was added. The mixture was stirred for 2 h and the mixture was concentrated in vacuo to ~70 mL. The crude product was then directly purified on silica (gradient elution, 0-50% EtOAc in hexanes) to yield 4.4 g of the title compound as an oil. LRMS (ESI) *m/z* 556.3 $[(M+H)^+$; calcd for $C_{30}H_{42}N_3O_7$: 556.3].

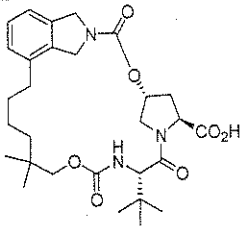
Step 9: Methyl (5*R*,7*S*,10*S*)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18, 19-dodecahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylate



To a solution of methyl (5*R*,7*S*,10*S*,18*E*)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriaza-cyclohenicosine-7-carboxylate (4.4 g, 7.92 mmol) in EtOAc (79 mL) was added Pd/C (0.421 g, 0.396 mmol). A H_2 balloon was then placed on the reaction flask. The flask was evacuated quickly and filled with H_2. After 17 h, the reaction was complete as determined by LC-MS. The Pd/C was filtered through

glass wool, and the crude product was purified on silica (gradient elution, 0-60% EtOAc in hexanes) to yield 4.01 g of the title compound as a white powder. LRMS (ESI) *m/z* 558.4 [$(M+H)^+$; calcd for $C_{30}H_{44}N_3O_7$: 558.3].

Step 10: (5*R*,7*S*,10*S*)-10-*tert*-Butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylic acid



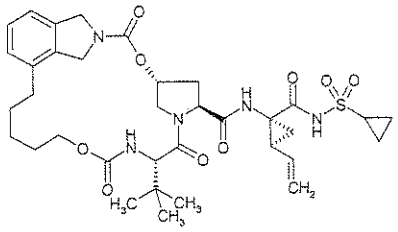
To a solution of methyl (5*R*,7*S*,10*S*)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylate (5.76 g, 10.33 mmol) in THF (41.3 mL), MeOH (41.3 mL), and water (20.7 mL) at RT was added LiOH (4.33 g, 103 mmol). After full conversion (45 min), as judged by LC-MS, the reaction was worked up by partitioning between Et_2O and 1N HCl. The aqueous layer was then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo to yield 5.53 g of the title compound, which was used without further purification. LRMS (ESI) *m/z* 544.4 [$(M+H)^+$; calcd for $C_{29}H_{42}N_3O_7$: 544.3].

Step 11: (5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-205**)

To a solution of (5*R*,7*S*,10*S*)-10-*tert*-Butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylic acid (5.53 g, 10.17 mmol) and (1*R*,2*R*)-1-amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride (3.28 g, 12.21 mmol) in DMF (50.9 mL) was added DIPEA (7.11 ml, 40.7 mmol) and HATU (5.03 g, 13.22 mmol). After full conversion (1h), the reaction mixture was partitioned between EtOAc and 1N HCl. The organic layer was washed with brine three times, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude material was then purified on silica (gradient elution, 20-80% EtOAc in hexanes) to yield 5.8 g of the title compound as a white powder.

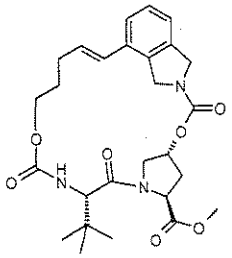
EXAMPLE 14

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (**III-5**)



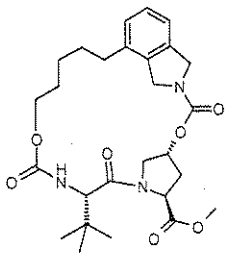
III-5

Step 1: Methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate



Methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate was prepared according to the procedure used for methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (EXAMPLE 3, Step 8) except that 3-methyl-*N*-[(pent-4-enyloxy)carbonyl]-L-valine (prepared according to the procedure below) was used in place of *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine in Step 7. LRMS (ESI) *m/z* 514 $[(M+H)^+$; calcd for $C_{27}H_{36}N_3O_7$: 514].

Step 2: Methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate



To a solution of methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (0.10 g, 0.20 mmol) in ethyl acetate (7 mL) was added 10% palladium on carbon (0.01 g). The reaction mixture was stirred under a balloon of hydrogen for 5 h at room temperature. Contents of the reaction flask were filtered through celite and the filtrate evaporated. The crude product was used with no further purification (0.09g, 90% yield). LRMS (ESI) *m/z* 516 $[(M+H)^+$; calcd for $C_{27}H_{38}N_3O_7$: 516].

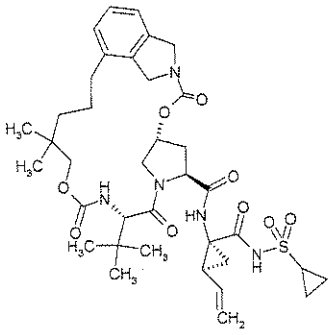
Step 3: (5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide

To a solution of methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (90 mg, 0.18 mmol) in THF (2 mL) and MeOH (0.5 mL), was added LiOH (1N 1.75 mL, 1.75 mmol). The reaction mixture was heated to 40 °C and stirred for 1 h, at which time complete consumption of the methyl ester starting material was observed by LC-MS. The mixture was then worked-up with 0.5 N HCl and EtOAc. The organic layer was then dried over K_2CO_3, and solvent was removed in vacuo. The crude product was taken up in DMF (1 mL).

To the above solution was added (1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride (51 mg, 0.19 mmol), TBTU (77 mg, 0.24 mmol) and DIPEA (0.07 mL, 0.40 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was directly purified by reverse phase HPLC to give (5R,7S,10S)-10-*tert*-butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (34 mg, 28% yield). ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 9.14 (s, 1 H), 7.23 (t, 1 H), 7.13 (d, 1 H), 7.10 (d, 1 H), 5.75 (quin, 1H), 5.53 (s, 1 H), 5.29 (d, 1 H), 5.12 (d, 1H), 4.75 – 4.59 (m, 5 H), 4.42 (m, 2 H), 4.34 (s, 1 H), 4.30 (d, 1 H), 3.88 (dd, 1 H), 3.75 (m, 1 H), 3.60 (q, 2 H), 2.95 (m, 1 H), 2.63 (m, 1 H), 2.41 (m, 2 H), 2.26 – 2.12 (m, 2H), 1.88 (dd, 1 H), 1.79 (m, 1 H), 1.56 (m, 3 H), 1.41 (m, 3 H), 1.25 (m, 2 H), 1.17 (t, 2 H), 1.06 (s, 9 H). LRMS (ESI) *m/z* 714 $[(M+H)^+$; calcd for $C_{35}H_{48}N_5O_9S$: 714].

EXAMPLE 15

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16,17,18-dodecahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (**III-206**)



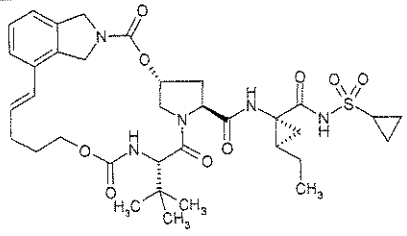
III-206

The title compound was prepared according to the procedure used for EXAMPLE 14 (using steps 2 and 3) except that methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-

1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (EXAMPLE 3, Step 1) was used in place of methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate in Step 2. ^{1}H NMR (400 MHz, ppm, $CDCl_3$) δ 9.91 (s, 1 H), 7.22 (t, 1 H), 7.09 (d, 2 H), 7.05 (d, 1 H), 5.77 (m, 1 H), 5.60 (s, 1 H), 5.45 (d, 1 H), 5.29 (s, 1 H), 5.15 (d, 1 H), 4.72 (q, 2 H), 4.40-4.55 (m, 4 H), 4.30 (d, 1 H), 4.25 (d, 1 H), 3.78 (dd, 1 H), 3.26 (d, 1 H), 2.91 (m, 1 H), 2.50 (m, 3 H), 2.39 (m, 3 H), 2.11 (m, 1 H), 1.98 (m, 2 H), 1.51 (m, 2 H), 1.38 (m, 4 H), 1.18(m, 1 H), 1.04 (s, 9 H), 1.01 (t, 3 H), 0.79 (s, 3 H). LRMS (ESI) *m/z* 742 [(M+H)$^+$; calcd for $C_{37}H_{52}N_5O_9S$: 742].

EXAMPLE 16

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (**III-16**)



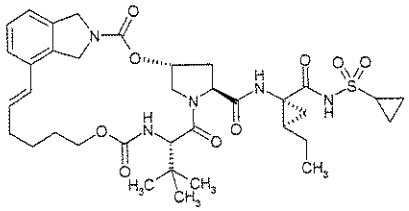
III-16

To a solution of methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (EXAMPLE 14, Step 1) (60 mg, 0.12 mmol) in THF (1 mL) and MeOH (0.5 mL) was added LiOH (1N 1.17 mL, 1.17 mmol). The reaction mixture was heated to 40 °C and stirred for 1 h, at which time complete consumption of the methyl ester starting material was observed by LC-MS. The mixture was then worked-up with 0.5 N HCl and EtOAc. The organic layer was then dried over K_2CO_3, and solvent was removed in vacuo. The crude product was taken up in DMF (1 mL).

To the above solution was added (1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropanaminium chloride (32 mg, 0.12 mmol), TBTU (48 mg, 0.15 mmol) and DIPEA (0.044 mL, 0.25 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was directly purified by reverse phase HPLC to give (5R,7S,10S)-10-*tert*-butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxamide (55 mg, 67% yield). ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 7.33 (d, 1 H), 7.26 (t, 1 H), 7.16 (d, 1 H), 6.39 (d, J = 15.7 Hz, 1 H), 6.13 (m, 1H), 5.37 (s, 1 H), 4.69 (m, 4 H), 4.47 – 4.28 (m, 4 H), 3.89 (m, 1 H), 3.83 (d, 1 H), 2.98 (m, 1 H), 2.40 (m, 2 H), 2.31 (m, 1 H), 2.11 (t, 1 H), 1.99 (s, 1 H), 1.73 (s, 1 H), 1.60 (m, 2 H), 1.52 (m, 1 H), 1.29 – 1.15 (m, 3 H), 1.08 (s, 9 H), 0.98 (t, 3 H). LRMS (ESI) *m/z* 714 [(M+H)$^+$; calcd for $C_{35}H_{48}N_5O_9S$: 714].

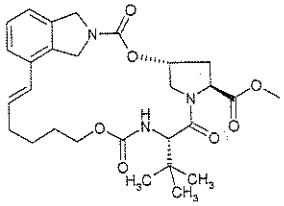
EXAMPLE 17

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-207**)



III-207

Step 1: Methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylate



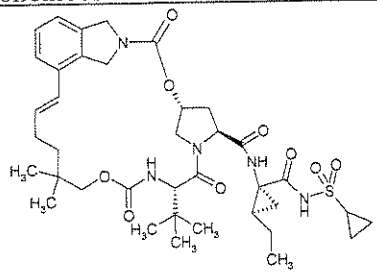
Methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylate was prepared according to the procedure used for methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (EXAMPLE 3, Step 8) except that 3-methyl-*N*-[(hex-5-enyloxy)carbonyl]-L-valine (prepared according to the procedure below) was used in place of *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine in Step 7. LRMS (ESI) *m/z* 528 [(M+H)$^+$; calcd for $C_{28}H_{38}N_3O_7$: 528].

Step 2: (5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide

EXAMPLE 17 was prepared according to the procedure used for EXAMPLE 16 except using methyl (5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylate in place of methyl-(5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (EXAMPLE 14, Step 1). ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 9.06 (s, 1 H), 7.27 (t, 1 H), 7.24 (d, 1 H), 7.18 (d, 1 H), 6.40 (d, J = 16.4 Hz, 1 H), 6.11 (m, 1H), 5.39 (t, 1 H), 4.80 (d, 1 H), 4.69 (m, 4 H), 4.42 (s, 1 H), 4.25 (d, 1 H), 3.97 (dd, 1 H), 3.79 (quin, 1 H), 2.98 (m, 1 H), 2.50 (q, 1 H), 2.78 (m, 2 H), 2.15 (m, 1 H), 1.77 – 1.54 (m, 8 H), 1.32 – 1.19 (m, 4 H), 1.11 (m, 1 H), 1.07 (s, 9 H), 0.98 (t, 3 H). LRMS (ESI) *m/z* 728 [(M+H)$^+$; calcd for $C_{36}H_{50}N_5O_9S$: 728].

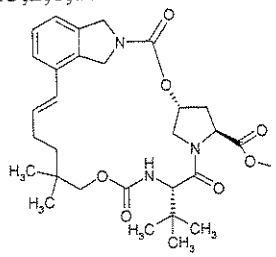
EXAMPLE 18

(5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-208**)



III-208

Step 1: Methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylate

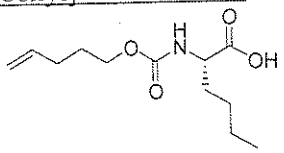


Methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylate was prepared according to the procedure used for methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (EXAMPLE 3, Step 8) except that *N*-{[(2,2-dimethylhex-5-enyl)oxy]carbonyl}-3-methyl-L-valine (prepared according to the procedure below) was used in place of *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine in Step 7. LRMS (ESI) *m/z* 556 [$(M+H)^+$; calcd for $C_{30}H_{42}N_3O_7$: 556].

Step 2: (5R,7S,10S)-10-*tert*-Butyl-*N*-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide

EXAMPLE 18 was prepared according to the procedure used for EXAMPLE 16 except using methyl (5R,7S,10S)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylate in place of methyl-(5R,7S,10S)-10-*tert*-butyl-3,9,12-trioxo-1,6,7,9,10,11,12,14,15,16-decahydro-5H-2,22:5,8-dimethano-4,13,2,8,11-benzodioxatriazacycloicosine-7-carboxylate (EXAMPLE 14, Step 1). ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 10.05 (s, 1 H), 7.24 (m, 2 H), 7.17 (d, 1 H), 7.11 (d, 1 H), 6.61 (s, 1 H), 6.28 (d, J = 16.4 Hz, 1 H), 5.95 (m, 1 H), 5.58 (m, 1 H), 5.31 (s, 1 H), 4.71 (m, 2 H), 4.55 (m, 2 H), 4.46 (d, 2 H), 4.29 (dd, 1 H), 4.17 (d, 1 H), 3.89 (d, 1 H), 3.32 (d, 1 H), 2.92 (m, 1 H), 2.59 (m, 1 H), 2.21-2.30 (m, 2 H), 2.08 (m, 1 H), 1.60-1.78 (m, 6 H), 1.22-1.31 (m, 5 H), 1.06 (s, 9 H), 1.04 (t, 3 H), 0.093 (t, 3 H), 0.87 (s, 3 H). LRMS (ESI) *m/z* 756 [$(M+H)^+$; calcd for $C_{38}H_{54}N_5O_9S$: 756].

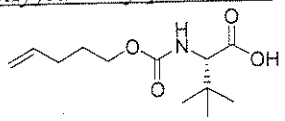
Preparation of *N*-[(Pent-4-e*N*-1-yloxy)carbonyl]-L-norleucine:



To a solution of 1-penten-4-ol (0.95 g, 11.0 mmol) in DMF (15 mL) at 0°C was added carbonyldiimidazole (1.79 g, 11.0 mmol). The reaction mixture was warmed to room temperature and stirred for 30 min. L-norleucine methyl ester hydrochloride (2.0 g, 11.0 mmol) was then added, the reaction mixture was heated to 50 °C and stirred for 15 min. Upon cooling, the reaction mixture was diluted with ethyl ether and washed twice with water. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography (gradient elution 10 to 90% ethyl acetate in hexanes) to afford 2.1 g (74% yield) methyl *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucinate as a clear oil.

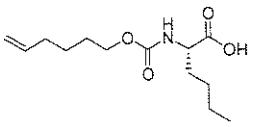
To a stirred solution of methyl *N*-[(pent-4-enyloxy)carbonyl]-L-norleucinate (8.50g, 33.03 mmol) in THF (20 mL) was added 1N NaOH (20 mL). This reaction solution was stirred at room temperature for 3 h, then acidified to pH 3 with 1N HCl and extracted with (3 x 250 mL) EtOAc. The combined EtOAc layer was washed with 50 mL water, 50 mL brine, dried over sodium sulfate, filtered and concentrated to give 7.09 g (88% yield) of the title product as clear oil. LRMS (ESI) *m/z* 244 $[(M+H)^+$; calcd for $C_{12}H_{22}NO_4$: 244].

Preparation of 3-Methyl-*N*-[(pent-4-enyloxy)carbonyl]-L-valine:



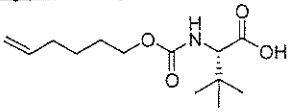
A solution of 4-pentenol (7.22 g, 83.8 mmol) and triphosgene (11.3 g, 38.1 mmol) in dioxane (160 mL) was cooled to 0 °C followed by a dropwise addition of DIPEA (9.85 g, 76.2 mL). The white suspension was stirred vigorously for 1 h at 25 °C, then cooled to 0 °C. A 1 N solution of NaOH (76.2 mL) and t-butylglycine (10.0 g, 76.2 mmol) were added. The resulting suspension was warmed to 25 °C and stirred for 18 h. Approximately half of the dioxane was removed *in vacuo*, the solution was poured into 1 N NaOH (100 mL) and washed with dichloromethane (3 x 150 mL). The aqueous layer was acidified with 6 N HCl and the desired product was extracted with dichloromethane (3 x 150 mL). The combined organics were dried over $MgSO_4$ and concentrated to give 13.7 g (73.9% yield) of 3-methyl-*N*-[(pent-4-enyloxy)carbonyl]-L-valine as a colorless oil. LRMS (ESI) *m/z* 244 $[(M+H)^+$; calcd for $C_{12}H_{22}NO_4$: 244].

Preparation of *N*-[(Hex-5-en-1-yloxy)carbonyl]-L-norleucine:



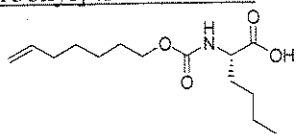
N-[(Hex-5-en-1-yloxy)carbonyl]-L-norleucine was prepared according to the procedure for *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucine by using 5-hexenol instead of 4-pentenol. LRMS (ESI) *m/z* 258 $[(M+H)^+$; calcd for $C_{13}H_{24}NO_4$: 258].

Preparation of 3-Methyl-*N*-[(hex-5-enyloxy)carbonyl]-L-valine:



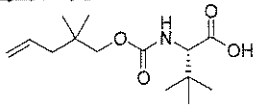
3-Methyl-*N*-[(hex-5-enyloxy)carbonyl]-L-valine was prepared according to the procedure for 3-methyl-*N*-[(pent-4-enyloxy)carbonyl]-L-valine by using 5-hexenol instead of 4-pentenol. LRMS (ESI) *m/z* 258 $[(M+H)^+$; calcd for $C_{13}H_{24}NO_4$: 258].

Preparation of *N*-[(Hept-6-en-1-yloxy)carbonyl]-L-norleucine:

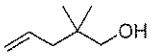


N-[(Hept-6-en-1-yloxy)carbonyl]-L-norleucine was prepared according to the procedure for *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucine by using 6-heptenol instead of 4-pentenol. LRMS (ESI) *m/z* 272 $[(M+H)^+$; calcd for $C_{14}H_{26}NO_4$: 272].

Preparation of *N*-{[(2,2-Dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine:



Step 1: 2,2-Dimethylpent-4-en-1-ol



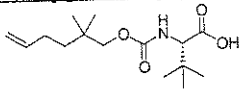
A solution of 2,2-dimethyl 4-pentenoic acid (6.0 g, 46.8 mmol) in anhydrous THF was cooled in an ice bath to 0 °C. A slow stream of 1M lithium aluminum hydride in THF (56.2 mL, 56.2 mmol) was added and the reaction was allowed to warm to 25°C. The reaction mixture was stirred for 1h before pouring into 1N HCl and diethyl ether. The organic layer was separated, dried over $MgSO_4$ and concentrated to provide 2,2-dimethylpent-4-en-1-ol as a clear oil (4.7 g, 87.9% yield).

Step 2: *N*-{[(2,2-Dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine

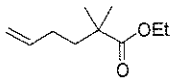
DIPEA (2.48 g, 19.2 mmol) was added dropwise to a 0 °C solution of 2,2-dimethylpent-4-en-1-ol (2.24 g, 19.6 mmol) and triphosgene (2.56 g, 8.64 mmol) in 60 mL dioxane. The resulting white suspension was stirred for 5 min at 0 °C, then allowed to warm to 25 °C over 1 h. The suspension was

cooled to 0 °C with an ice bath, followed by addition of 1 N NaOH (19.2 mL) and *L-tert*-butylglycine (2.52 g, 19.2 mmol). The reaction mixture was warmed to 25 °C and stirred for 72 h. The dioxane was removed *in vacuo* and the reaction mixture was basified to pH 12 with 1 N NaOH. The aqueous layer was extracted with dichloromethane (3x 150 mL), then acidified to pH~1 with 6 N HCl. The aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give *N*-{[(2,2-dimethylpent-4-enyl)oxy]carbonyl}-3-methyl-L-valine as a white powder (4.26 g, 827% yield). LRMS (ESI) *m/z* 272 $[(M+H)^+$; calcd for $C_{14}H_{26}NO_4$: 272].

Preparation of *N*-{[(2,2-Dimethylhex-5-enyl)oxy]carbonyl}-3-methyl-L-valine:



Step 1: Ethyl 2,2-dimethylhex-5-enoate



To a stirred solution of diisopropylamine (13.38 mL, 94.70 mmol) in anhydrous THF (50 mL), at -70°C and under nitrogen, was slowly added 2.5 M n-BuLi in ether (36.50 mL, 91.25 mmol). Stirred for 15 minutes, to this reaction solution was then added dropwise ethyl isobutyrate (11.51 mL, 86.09 mmol) in THF (50 mL), stirred for 20 minutes before added dropwise 4-bromo-1-butene (9.79 mL, 96.42 mmol) in HMPA (20 mL). The reaction solution was then stirred to -50°C in 5 hours, quenched with 1M HCl (10 mL) and water (100 mL), then extracted with (3 x 125 mL) ether. The combined ether layer was washed with water (4 x 70 mL), aqueous saturated $NaHCO_3$ (2 x 70 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was flash chromatographed on 120 g silica gel 60, eluting with 1 - 20% EtOAc / Hexane to give the title product as clear oil (11.01g, 75% yield). LRMS (ESI) *m/z* 171 $[(M+H)^+$; calcd for $C_{10}H_{19}O_2$: 171].

Step 2: 2,2-Dimethylhex-5-en-1-ol



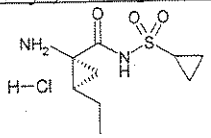
To a stirred solution of 1M LAH in ether (142.14 mL, 142.14 mmol), at 0°C and under nitrogen, was added dropwise ethyl 2,2-dimethylhex-5-enoate (11.00 g, 64.61 mmol) dissolved in 100 mL anhydrous ether over 1 hour. This reaction solution was stirred at 22°C for 20 hours, then quenched with water (3 mL), 1M NaOH (11 mL) and water (9 mL), dried over Na_2SO_4, filtered and concentrated to give the title product (7.22 g, 87.09%). ^1H NMR (500 MHz, $CDCl_3$) δ 5.85-5.77 (m, 1 H); 5.01 (d, 1 H); 4.93 (d, 1 H); 3.33 (d, 2 H); 2.03 (m, 2 H); 1.34 (m, 2 H); 0.89 (m, 6 H) ppm.

Step 3: *N*-{[(2,2-Dimethylhex-5-enyl)oxy]carbonyl}-3-methyl-L-valine

To a stirred solution of 2,2-dimethylhex-5-en-1-ol (10.75 g, 83.85 mmol) in anhydrous 1,4-dioxane (100 mL), at 0°C and under nitrogen, was added triphosgene (13.69 g, 46.12 mmol) and then DIPEA (14.61 mL, 83.85 mmol) cautiously. This reaction solution was stirred at 22°C for 1 hour, cooled to 0 °C and added slowly 1N NaOH (83.85 mL, 83.85 mmol) and L-*tert*-leucine (11.00 g, 83.85 mmol),

then stirred at 22°C for 20 hours. The reaction solution was basified to pH 10 with 1N NaOH, washed with CH_2Cl_2 (3x 100 mL), acidified to pH 5 with 1N HCl and extracted with CH_2Cl_2 (3 x 150 mL). The combined CH_2Cl_2 layer was washed with water (100 mL), dried over Na_2SO_4, filtered and concentrated to give the title product (20.26 g, 84.66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85-5.77 (m, 1 H); 5.24 (d, 1 H); 5.01 (d, 1 H); 4.93 (d, 1 H); 4.20 (d, 1 H); 3.86 (d, 1 H); 3.79 (d, 1 H); 2.01 (m, 2 H); 1.36 (m, 2 H); 1.04 (s, 9 H); 0.92 (m, 6 H) ppm. LRMS (ESI) *m/z* 286 [$(M+H)^+$; calcd for $C_{15}H_{28}NO_4$: 286].

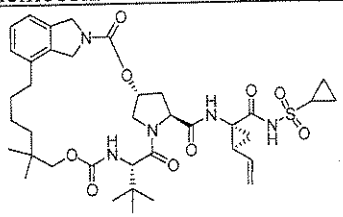
Preparation of (1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropanaminium chloride:



A mixture of (1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride (Llinas-Brunet et al US03/15755 and Wang et al WO 03/099274) (0.05 g, 0.187 mmol) and palladium on carbon (10% wt., 0.01g) in EtOAc (5 mL) was vigorously stirred under hydrogen atmosphere provided by a hydrogen balloon for 1 hour. The reaction mixture was filtered and concentrated to give (1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropanaminium chloride (0.045 g, 89% yield).

EXAMPLE 19

(5*R*,7*S*,10*S*)-10-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-210**)

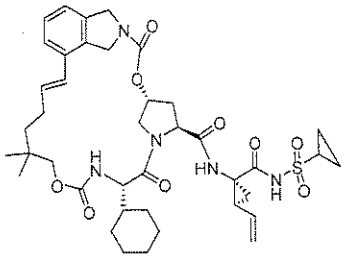


III-210

EXAMPLE 19 was prepared from (5*R*,7*S*,10*S*)-10-*tert*-butyl-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxylic acid (EXAMPLE 13 Alternative Preparation, Step 4) using the procedure for EXAMPLE 3, Step 10. ^{1}H NMR (500 MHz, CD_3OD, ppm) δ 7.25-7.09 (m, 3 H), 5.82-5.74 (m, 1 H), 5.35-5.29 (m, 2 H), 5.15-5.12 (m, 1 H), 4.75-4.59 (m, 3 H), 4.45-4.38 (m, 2 H), 4.21-4.12 (m, 1 H), 4.13-4.09 (m, 1 H), 3.95-3.92 (m, 1 H), 2.98-2.94 (m, 1 H), 2.62-2.54 (m, 1 H), 2.49-2.46 (m, 2 H), 2.25-2.21 (m, 1 H), 2.19-2.13 (m, 1 H), 1.90-1.88 (m, 1 H), 1.52 (m, 2 H), 1.48-1.45 (m, 1 H), 1.40-1.18 (m, 6 H), 1.15-1.00 (m, 14 H), and 0.81 (m, 4 H). LRMS (ESI) *m/z* 756.4 [$(M+H)^+$; calcd for $C_{38}H_{53}N_5O_9S$: 755.9].

EXAMPLE 20

(5*R*,7*S*,10*S*,18*E*)-10-Cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17-decahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-225**)

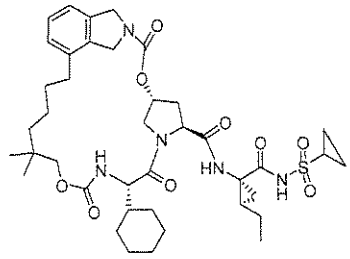


III-225

EXAMPLE 20 was prepared using the procedures from EXAMPLE 13 Alternate Preparation, Steps 1, 2, 4 and 5 using (2*S*)-cyclohexyl({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino)acetic acid in Step 1 and (1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride in Step 5. ^{1}H NMR (500 MHz, CD_3OD, ppm) δ 7.26 (m, 1 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.15 (d, J = 9.5 Hz, 1 H), 6.38 (d, J = 9.5 Hz, 1 H), 5.99–6.02 (m, 1 H), 5.74–5.80 (m, 1 H), 5.29–5.34 (m, 2 H), 5.11–5.14 (m, 1 H), 4.79–4.81 (m, 2 H), 4.64–4.72 (m, 3 H), 4.56 (d, J = 11.5 Hz, 1 H), 4.36–4.40 (m, 2 H), 4.18 (d, J = 11.5 Hz, 1 H), 4.10 (d, J = 5.5 Hz, 0.5 H), 3.91–3.94 (dd, J = 11.5, 3.5 Hz, 1 H), 3.34 (d, J = 11.0 Hz, 1 H), 2.95–2.97 (m, 1 H), 2.52–2.56 (m, 1 H), 2.16–2.35 (m, 5 H), 1.65–1.82 (m, 8 H), and 0.85–1.43 (m, 17 H). LRMS (ESI) *m/z* 780.4 [$(M+H)^+$; calcd for $C_{40}H_{53}N_5O_9S$: 780.9].

EXAMPLE 21

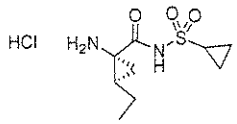
(5*R*,7*S*,10*S*)-10-Cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide (**III-226**)



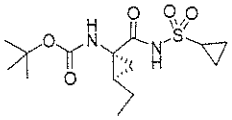
III-226

EXAMPLE 21 was prepared from EXAMPLE 20 using the procedure described for EXAMPLE 8. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.13 (s, 1 H), 7.22 (t, J = 7.5 Hz, 1 H), 7.10 (d, J = 7.5 Hz, 1 H), 7.05 (d, J = 7.5 Hz, 1 H), 6.73 (s, 1 H), 5.40 (d, J = 9.5 Hz, 1 H), 5.36 (m, 1 H), 4.67–4.76 (m, 2 H), 4.55 (d, J = 15.5 Hz, 1 H), 4.44 (d, J = 14.5 Hz, 1 H), 4.41 (d, J = 11.0 Hz, 1 H), 4.29–4.39 (m, 2 H), 4.16 (d, J = 11.0 Hz, 1 H), 3.82–3.85 (dd, J = 11.5, 3.5 Hz, 1 H), 3.25 (d, J = 11.0 Hz, 1 H), 2.95 (m, 1 H), 2.51–2.59 (m, 2 H), 2.36–2.44 (m, 2 H), 1.73–1.76 (m, 5 H), and 0.79 (br s, 2 H). LRMS (ESI) *m/z* 784.4 [$(M+H)^+$; calcd for $C_{40}H_{57}N_5O_9S$: 784.4].

Alternative preparation of (1*R*,2*R*)-1-amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride:



Step 1: *tert*-Butyl ((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)carbamate:

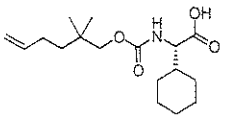


A hydrogenaton vessel was charged with a methanol (1000 mL) slurry of tert-butyl ((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)carbamate (164 g, 0.50 mol) (Wang et al, US 6,995,174) and 5% Ru/C (dry, 7.5 wt%, 12.4 g) and set stirring. The vessel was placed under nitrogen (20 psig) and vented to atmospheric pressure three times to remove residual oxygen. The vessel was then placed under hydrogen (50 psig). After 20 hours, the vessel was vented to atmospheric pressure. The reaction slurry was then transferred out of the reaction and filtered through solka flok (34 grams, wetted w/ 100 mL methanol) to yield a clear, light brown solution. The solka flok was rinsed with methanol (200 mL x 2). The combined methanol solutions were concentrated under reduced pressure to yield crude product as a white solid (153 g). The crude product was slurried in ethyl acetate (800 mL), warmed to 40 °C and aged 30 minutes. The solution was then seeded, aged 30 minutes, and heptane (500 mL) was added via addition funnel over 30 minutes. The partially crystallized solid was cooled to room temperature and aged overnight after which additional heptane (500 mL) was added. After one hour, additional heptane (250 mL) was added via addition funnel, and the white slurry aged for one hour. The solution was filtered and the solid was rinsed with heptane/EtOAc (500 mL, 4:1) and dried under reduced pressure to give tert-butyl ((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)carbamate (125.9 g).

Step 2: (1*R*,2*R*)-1-amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride:

A solution of the product from Step 1 above (92 g, 0.28 mol) in DCM (1200 mL) was cooled to 0°C and HCl bubbled through the solution for 10 min, the cooling bath removed and the recatio mixture stirred for 2 h. Nitrogen was bubbled through the reaction mixture for 5 min and the volatiles evaporated. The residue was azeotroped with DCM (x3) to give an off white powder (75 g).
LRMS $(M+H)^+$ Calcd. = 233; found 233.

Preparation of (2*S*)-cyclohexyl({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino)acetic acid:



(2*S*)-Cyclohexyl({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino)acetic acid was prepared according to the procedure for 3-methyl-*N*-[(pent-4-enyloxy)carbonyl]-L-valine using (2*S*)-amino(cyclohexyl)acetic acid and 2,2-dimethylhex-5-en-1-ol. LRMS (ESI) *m/z* 312.3 $[(M+H)^+$; calcd for $C_{17}H_{30}NO_4$: 312.2].

EXAMPLE 22

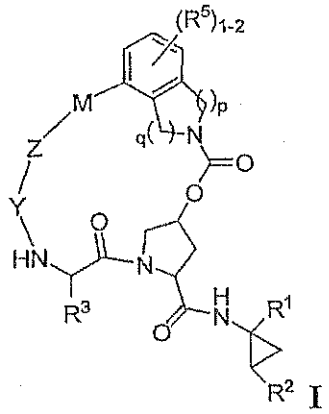
HCV NS3 protease time-resolved fluorescence (TRF) assay

The NS3 protease TRF assay was performed in a final volume of 100µl in assay buffer containing 50 mM HEPES, pH 7.5, 150 mM NaCl, 15 % glycerol, 0.15 % Triton X-100, 10 mM DTT, and 0.1 % PEG 8000. The NS3 protease was pre-incubated with various concentrations of inhibitors for 10-30 minutes. The peptide substrate for the assay is Ac-C(Eu)-DDMEE-Abu-[COO]-XSAK(QSY7)-NH2, where Eu is an europium-labeled group, Abu is 1-aminobutanoic acid which connects an ester linkage with 2-hydroxy propanoic acid (X). Hydrolysis of the peptide by NS3 protease activity causes in separation of the fluorophore from the quencher, resulting in an increase in fluorescence. Activity of the protease was initiated by adding the TRF peptide substrate (final concentration 50-100 nM). The reaction was quenched after 1 hour at room temperature with 100 µl of 500 mM MES, pH 5.5. Product fluorescence was detected using either a Victor V2 or Fusion fluorimeter (Perkin Elmer Life and Analytical Sciiences) with excitation at 340 nm and emission at 615 nm with 50-400 µs delay. Testing concentrations of different enzyme forms was selected with a signal to background ratio of 10-30. The inhibition constants were derived using a four-parameter fit.

Compounds in Examples 1-21 were tested to have a Ki value of less than 100 nM (e.g., less than 1 nM) in the NS3 protease TRF assay as described above.

Claims

1. A compound of formula (I)

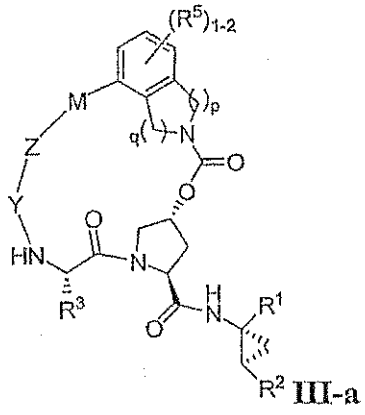


I

wherein:

p and q are both 1;
R^1 is $CONR^{10}SO_2R^6$,
R^2 is C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein said alkyl or alkenyl is optionally substituted with 1 to 3 halo;
R^3 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl;
R^5 is H;
R^6 is C_3-C_6 cycloalkyl;
Y is C(=O),
Z is O;
M is C_1-C_{12} alkylene or C_2-C_{12} alkenylene; and
each R^{10} is independently H or C_1-C_6 alkyl; or a pharmaceutically acceptable salt or hydrate thereof.

2. The compound of claim 1, wherein the compound is of formula **III-a**:



III-a

or a pharmaceutically acceptable salt or hydrate thereof.

3. The compound of claim 2, wherein R^1 is $CONHSO_2R^6$; or a pharmaceutically acceptable salt or hydrate thereof.

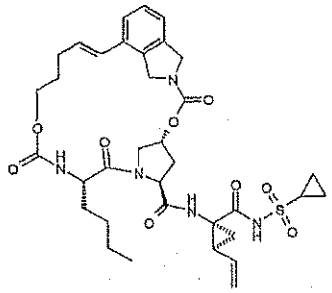
4. The compound of claim 3, wherein R^6 is cyclopropyl; or a pharmaceutically acceptable salt or hydrate thereof

5. The compound of claim 4, wherein R^2 is C_1-C_4 alkyl or C_2-C_4 alkenyl; or a pharmaceutically acceptable salt or hydrate thereof.

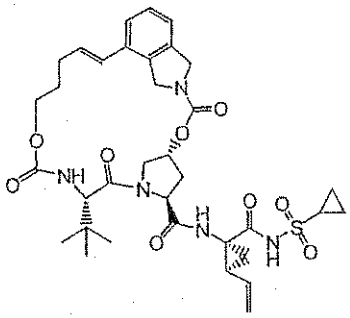
6. The compound of claim 5, wherein R^3 is C_3-C_6 cycloalkyl or C_1-C_4 alkyl; or a pharmaceutically acceptable salt or hydrate thereof.

7. The compound of claim 6, wherein M is C_4-C_{10} alkylene or C_4-C_{10} alkenylene, or a pharmaceutically acceptable salt or hydrate thereof.

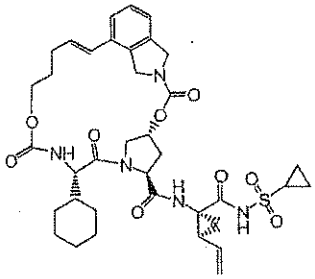
8. The compound of claim 1, wherein the compound is selected from the following:



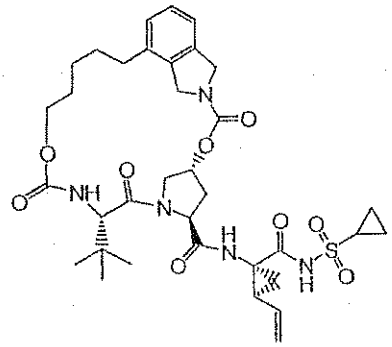
III-1



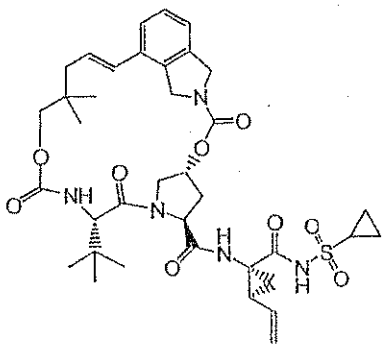
III-2



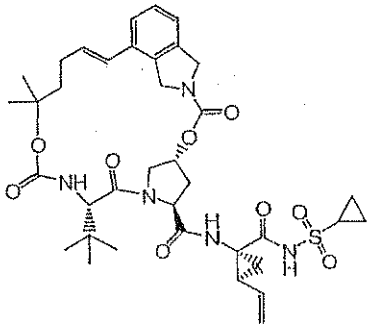
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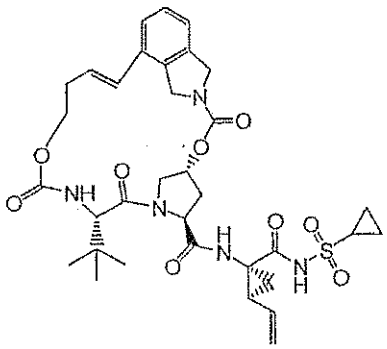
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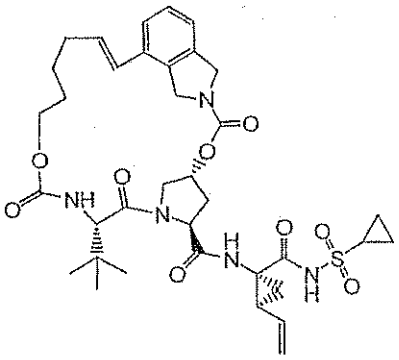
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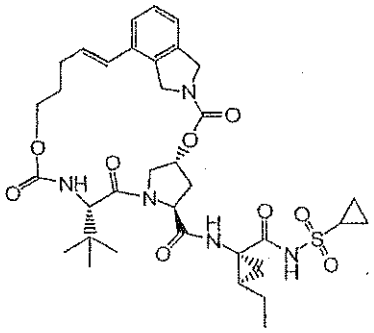
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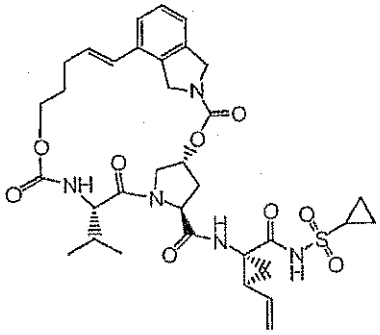
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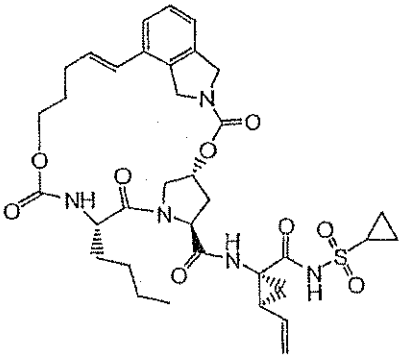
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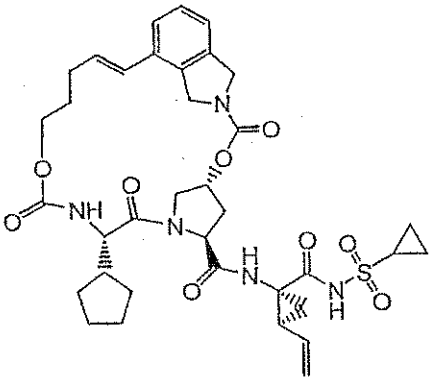
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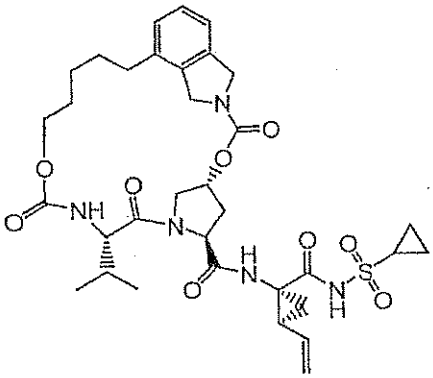
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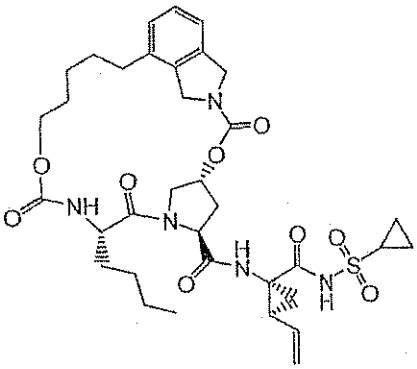
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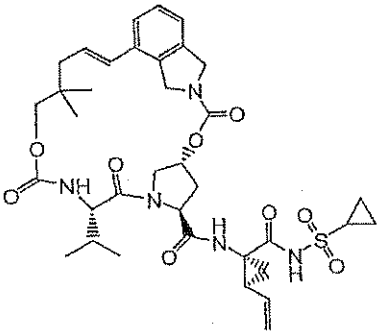
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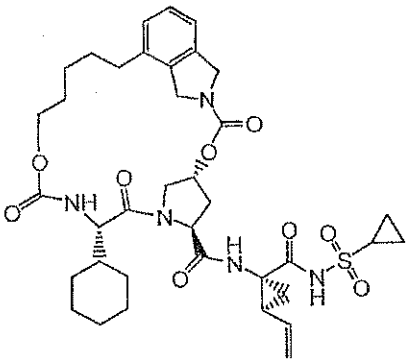
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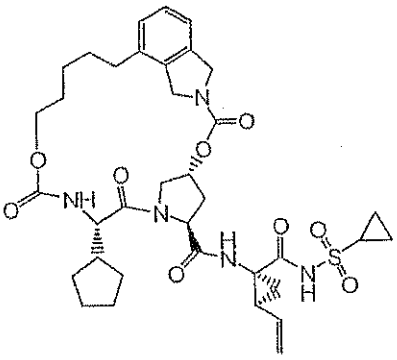
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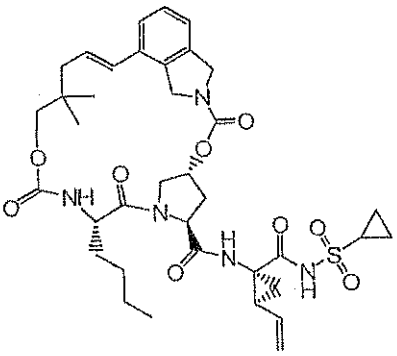
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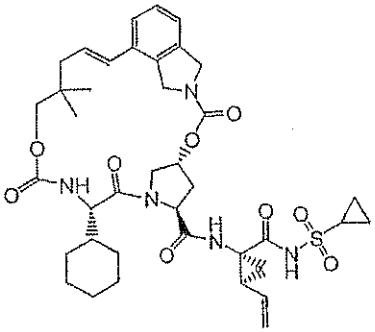
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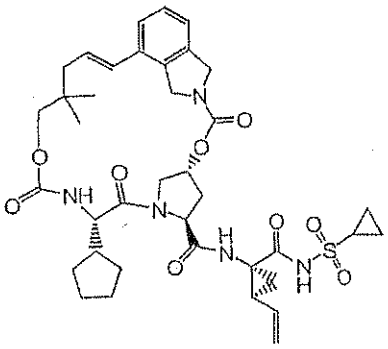
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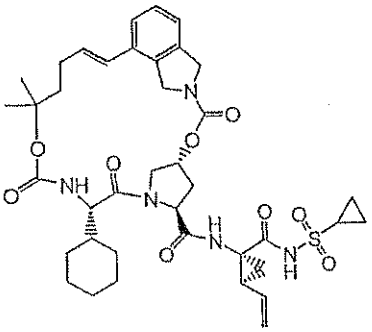
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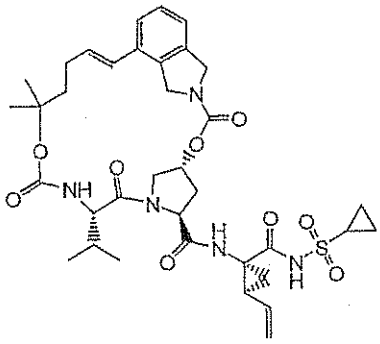
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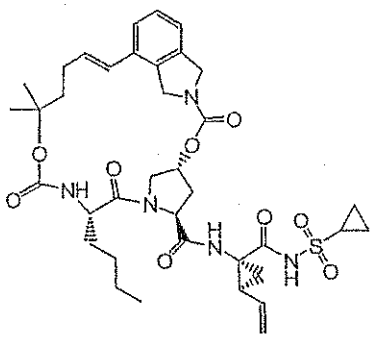
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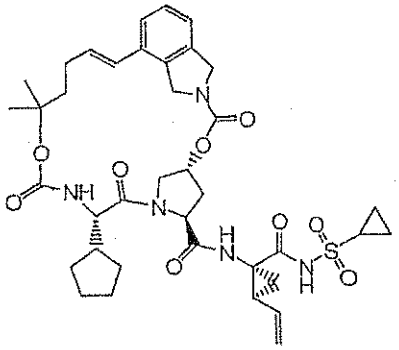
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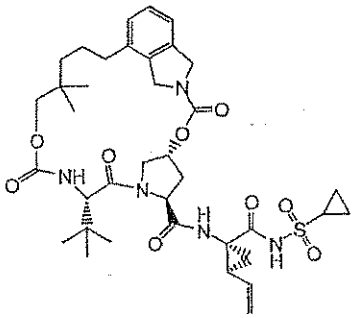
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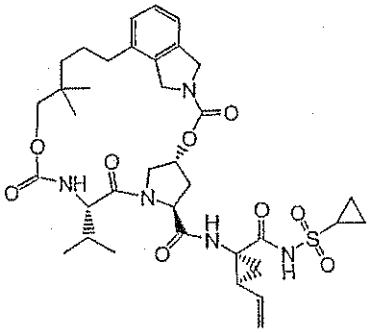
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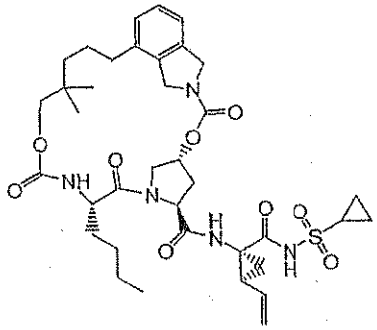
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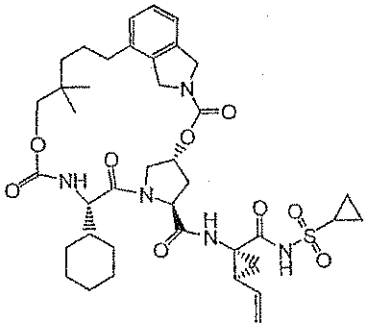
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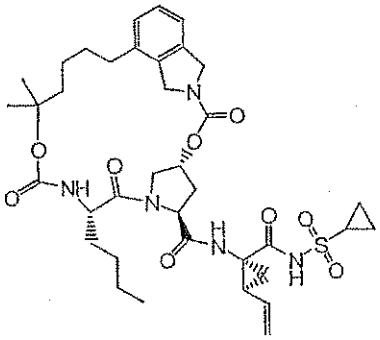
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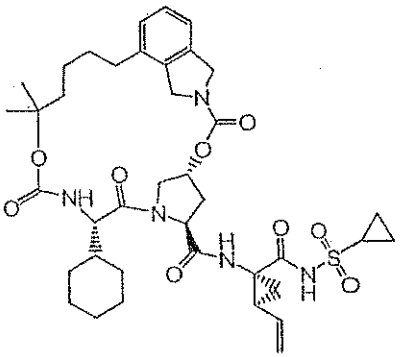
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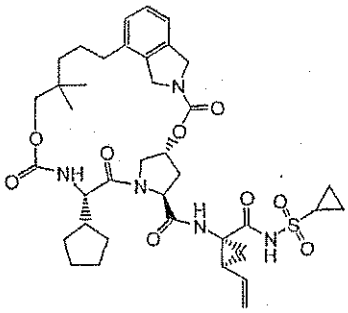
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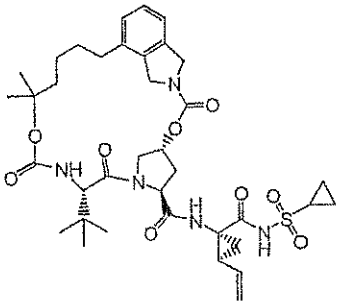
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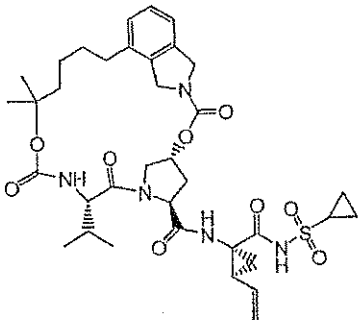
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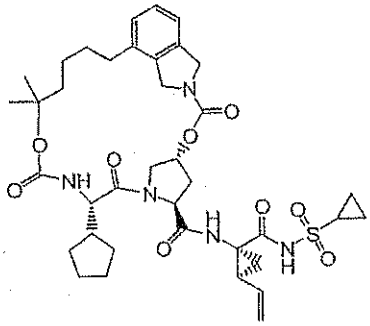
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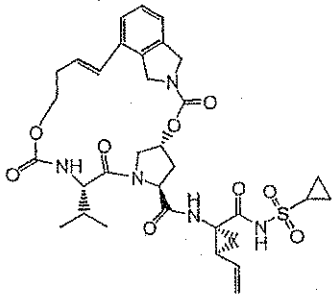
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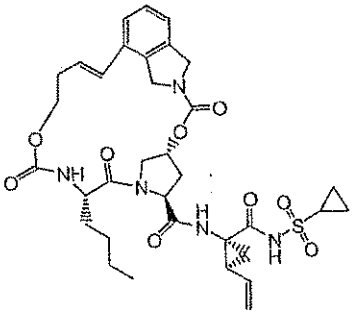
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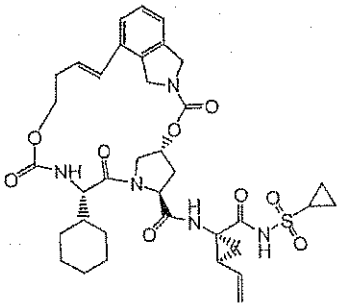
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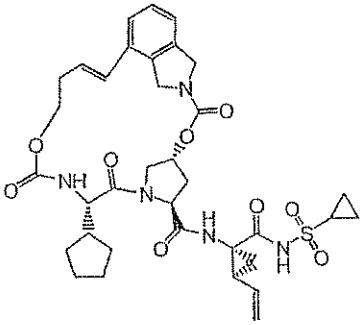
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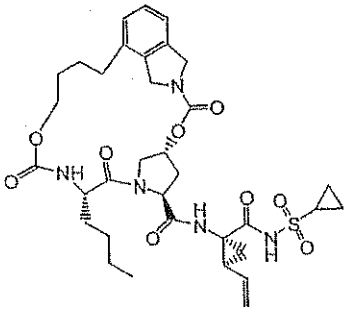
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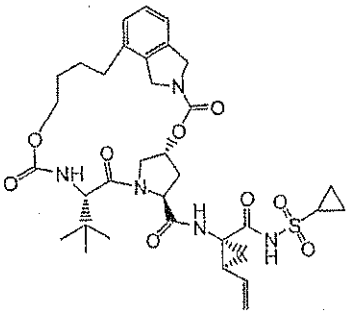
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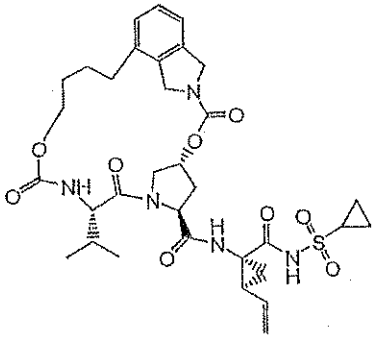
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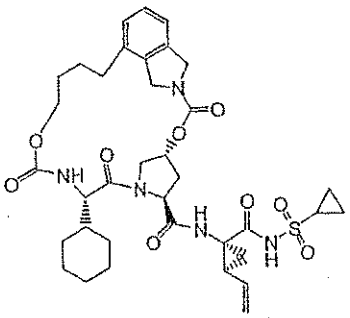
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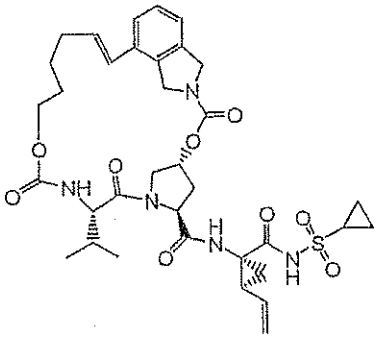
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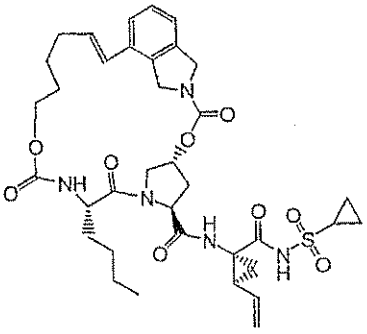


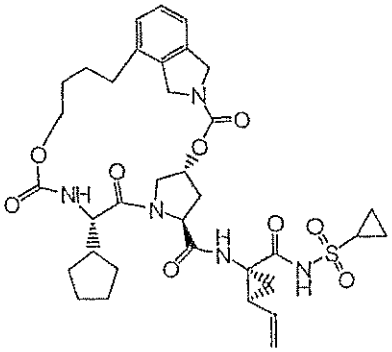
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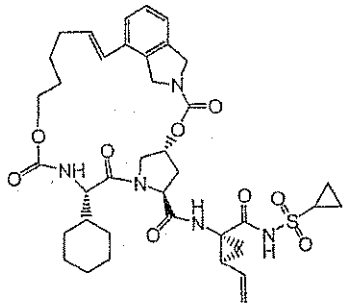
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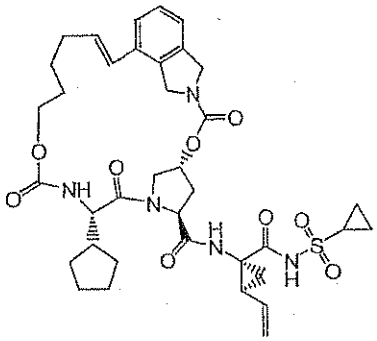




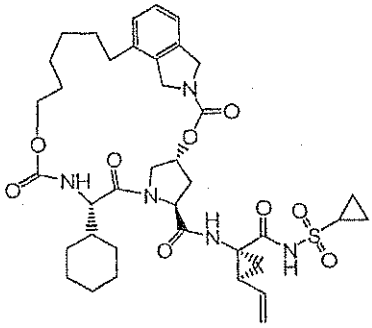
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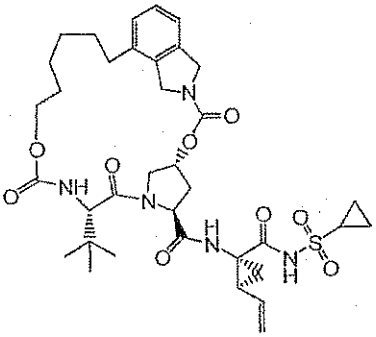
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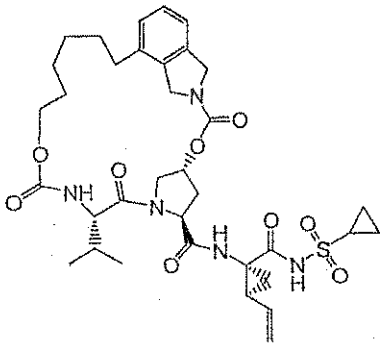
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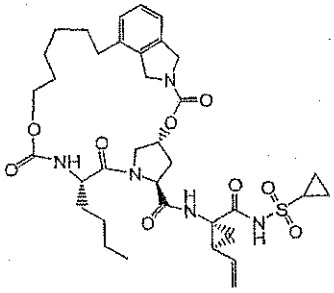
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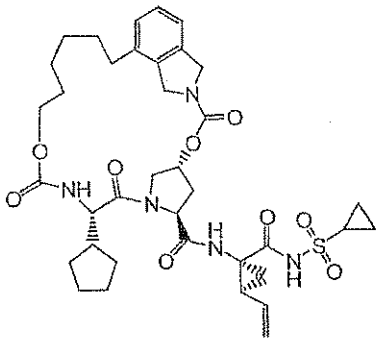
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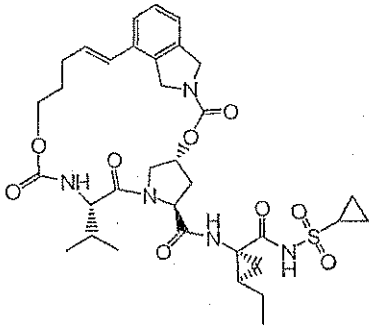
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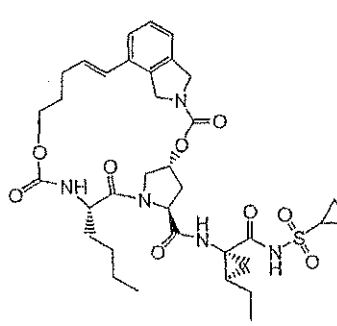
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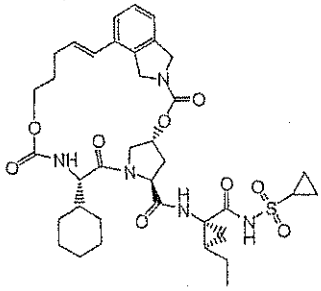


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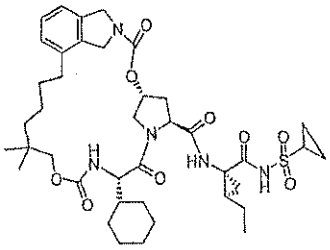
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III-193

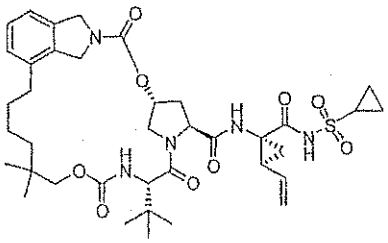
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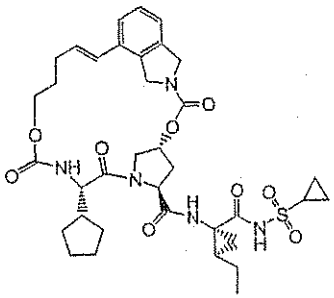


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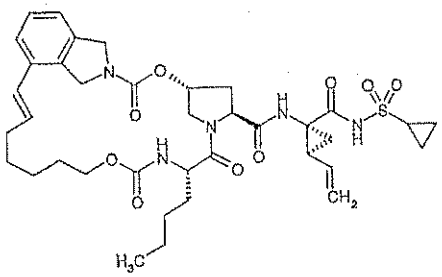


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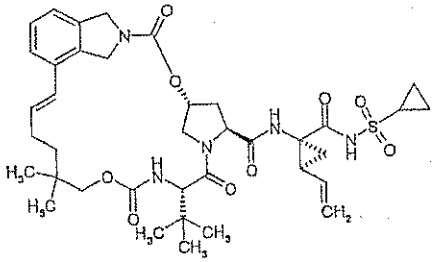




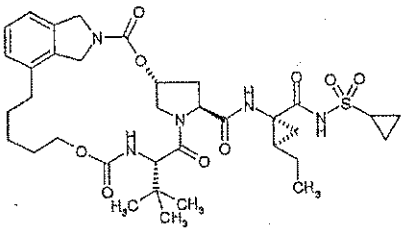
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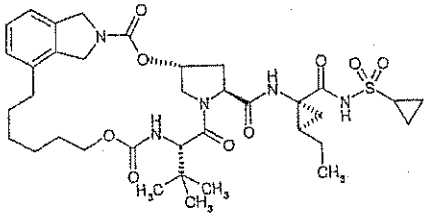
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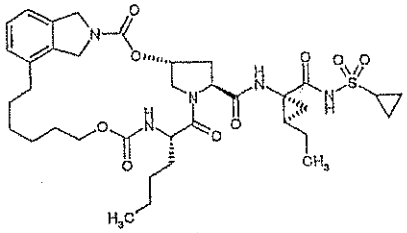
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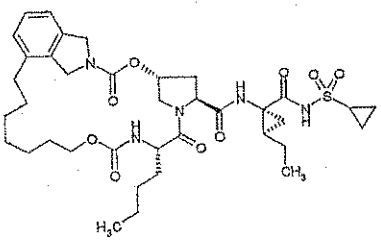
III-200



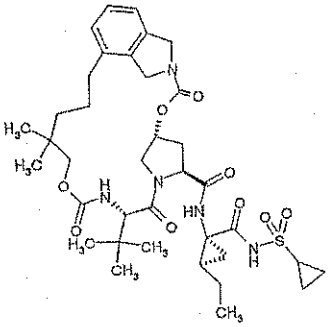
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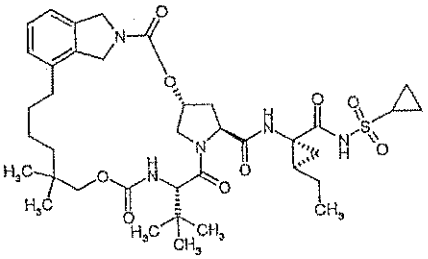
III-202



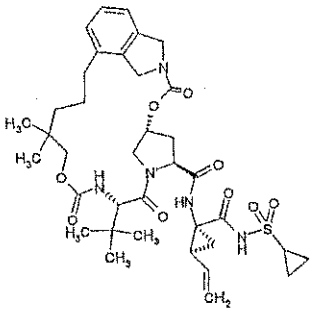
III-203



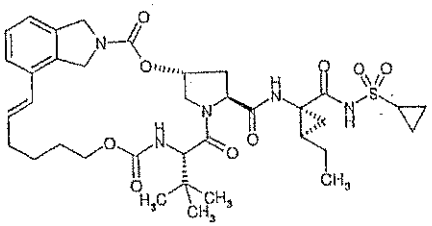
III-204



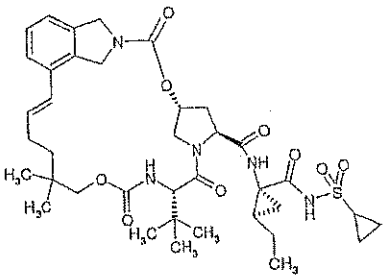
III-205



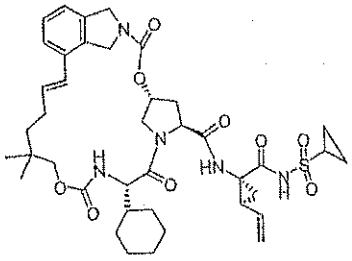
III-206



III-207



III-208



III-225

or a pharmaceutically acceptable salt or hydrate thereof.

9. Compound III-205 according to claim 8; or a pharmaceutically acceptable salt or hydrate thereof.

10. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1-9 or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, further comprising a second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

12. The pharmaceutical composition of claim 11, wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NSSB polymerase inhibitor.

13. A compound of any one of claims 1-9 or a pharmaceutically acceptable salt or hydrate thereof, for use in therapy.

14. A use of a compound of any one of claims 1-9 or a pharmaceutically acceptable salt or hydrate thereof, in the preparation of a medicament for preventing or treating infection by HCV in a subject in need thereof.

15. A compound according to claim 13 for use in a method of preventing or treating HCV.

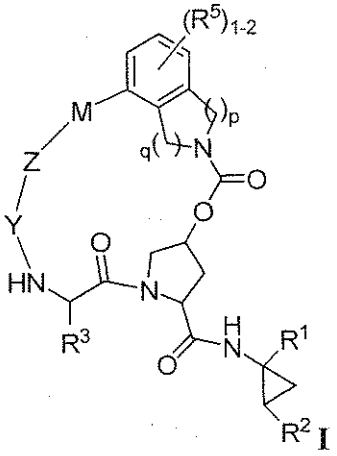
16. A combination of a compound of any one of claims 1 to 9 or a pharmaceutically acceptable salt or hydrate thereof and at least one second therapeutic agent selected from HCV antiviral agents, immunomodulators and anti-infective agents.

17. A combination according to claim 16 where the antiviral agent is an HCV protease inhibitor or an HCV NS5B polymerase inhibitor.

HCV NS3 PROTEASE INHIBITORS

ABSTRACT

The present invention relates to macrocyclic compounds of formula (I) that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, their synthesis, and their use for treating or preventing HCV infections.



I

(No Suitable Figure)