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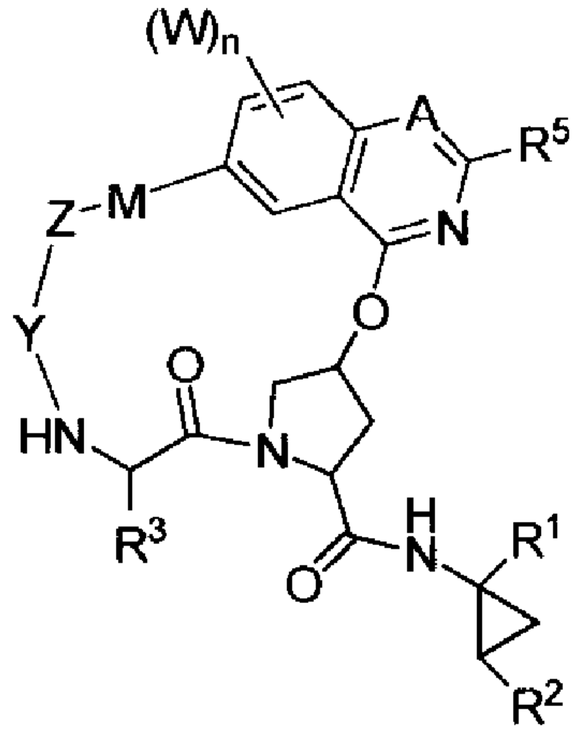
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(54) **Titre : INHIBITEURS DE LA PROTEASE NS3 DU VHC**
(54) **Title: HCV NS3 PROTEASE INHIBITORS**



(I)

(57) **Abrégé/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.

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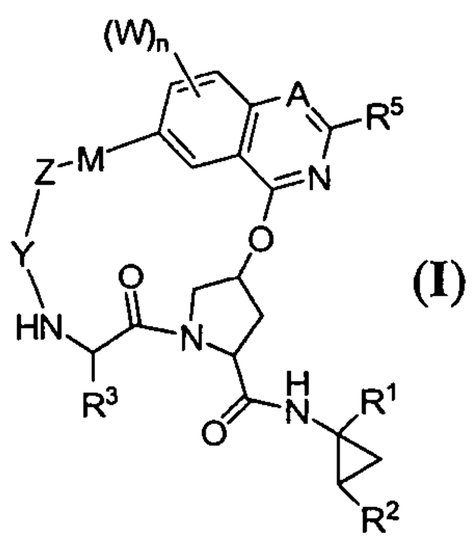
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(I)

(57) 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.

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TITLE OF THE APPLICATION

HCV NS3 PROTEASE INHIBITORS

FIELD OF THE INVENTION

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.

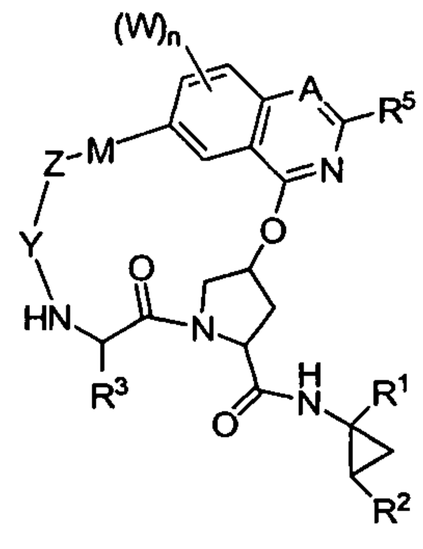
Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved 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 Application Publications US 2005/0020503, US 2004/0229818, and US 2004/00229776, 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 OF THE INVENTION

The present invention relates to novel macrocyclic compounds of formula (**I**) and/or pharmaceutically acceptable salts and/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 and/or hydrates (when appropriate), or as pharmaceutical composition ingredients, whether or not in combination with other HCV antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention relates to a compound of formula (**I**)



(**I**)

or a pharmaceutically acceptable salt and/or hydrate thereof, wherein:

n is 1 or 2;

R^1 is $-CONHR^6$, $-CONHP(O)R^{11}R^{12}$, or $-P(O)R^{11}R^{12}$;

R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl or C_3-C_8 cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

R^3 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, or Het, wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), $-NO_2$, -CN, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^{10}SO_2R^6$, $-SO_2N(R^6)_2$, $-NHCOOR^6$, $-NHCOR^6$, $-NHCONHR^6$, $-CO_2R^{10}$, $-C(O)R^{10}$, and $-CON(R^{10})_2$; Het is a 5- to 6-membered saturated cyclic ring having 1, 2 or 3 heteroatoms selected from N, O and S, wherein said ring is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), $-NO_2$, -CN, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^{10}SO_2R^6$, $-SO_2N(R^6)_2$, $-NHCOOR^6$, $-NHCOR^6$, $-NHCONHR^6$, $-CO_2R^{10}$, $-C(O)R^{10}$, and $-CON(R^{10})_2$;

R^4 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, or aryl(C_1-C_8)alkyl; wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), $-NO_2$, -CN, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^{10}SO_2R^6$, $-SO_2N(R^6)_2$, $-NHCOOR^6$, $-NHCOR^6$, $-NHCONHR^6$, $-CO_2R^{10}$, $-C(O)R^{10}$, and $-CON(R^{10})_2$;

R^5 is H, halo, -OH, C_1-C_6 alkoxy, C_1-C_6 alkyl, -CN, $-CF_3$, $-SR^{10}$, $-SO_2(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $-N(R^7)_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, $-OR^{10}$, $-SR^{10}$, $-N(R^7)_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, $-NO_2$, -CN, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-NR^{10}SO_2R^6$, $-SO_2N(R^6)_2$, $-S(O)(C_1$-C_6 alkyl), $-NHCOOR^6$, $-NHCOR^6$, $-NHCONHR^6$, $-CO_2R^{10}$,

-C(O)R^{10}, and -CON(R^{10})$_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S;

R^6 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_5)alkyl, aryl, aryl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents or aryl is substituted by -P(O)$R^{11}R^{12}$; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

Y is -C(=O)-, -SO_2-, or -C(=N-CN)-;

Z is -C(R^{10})$_2$-, -O-, or -N(R^4)-;

M is C_1-C_{12} alkylene or C_2-C_{12} alkenylene or C_2-C_{12} alkynylene, wherein said alkylene or alkenylene is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), and aryl(C_1-C_8 alkyl); wherein 2 substituents on adjacent carbon atoms of M are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S, or 2 substituents on the same carbon atom of M are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S;

A is -C(R^{16})- or -N-;

when R^5 is other than H, R^{16} is H, C_1-C_6 alkyl, halo, -OR^{10}, -SR^{10}, or-N(R^{10})$_2$;

when R^5 is H, R^{16} is H, C_1-C_6 alkyl, halo, -OH, C_1-C_6 alkoxy, -CN, -CF_3, -SR^{10}, -SO_2(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, -N(R^7)$_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, -OR^{10}, -SR^{10}, -N(R^7)$_2$, -N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl,

halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -$NR^{10}SO_2R^6$, -$SO_2N(R^6)_2$, -S(O)(C_1-C_6 alkyl), -$NHCOOR^6$, -$NHCOR^6$, -$NHCONHR^6$, -CO_2R^{10}, -$C(O)R^{10}$, and -$CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S;

or R^5 and R^{16} are optionally taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0 to2 heteroatoms selected from N, O and S;

each R^7 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_5)alkyl, aryl, aryl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

each W is independently H, halo, -OR^7, C_1-C_6 alkyl, -CN, -CF_3, -NO_2, -SR^7, -CO_2R^7, -$CON(R^7)_2$, -$C(O)R^7$, -$N(R^{10})C(O)R^7$, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, -$N(R^7)_2$, -N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), halo(C_1-C_6 alkoxy), -$NR^{10}SO_2R^7$, -$SO_2N(R^7)_2$, -$NHCOOR^7$, -$NHCONHR^7$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0 to 2 heteroatoms selected from N, O and S;

each W' is independently H, halo, -OR^{10}, C_1-C_6 alkyl, -CN, -CF_3, -NO_2, -SR^{10}, -CO_2R^{10}, -$CON(R^{10})_2$, -$C(O)R^{10}$, -$N(R^{10})C(O)R^{10}$, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, -$N(R^{10})_2$, -N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), halo(C_1-C_6 alkoxy), -$NR^{10}SO_2R^{10}$, -$SO_2N(R^{10})_2$, -$NHCOOR^{10}$, -$NHCONHR^{10}$, aryl, heteroaryl or

heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W' moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0 to 2 heteroatoms selected from N, O and S;

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

each R^{11} is independently C_1-C_6 alkyl, -OR^{13}, -$N(R^{10})$-V-CO_2R^{10}, -O-V-CO_2R^{10}, -S-V-CO_2R^{10}, -$N(R^{10})(R^{13})$, R^{14}, or -$N(R^{10})SO_2R^6$;

each R^{12} is independently -OR^{13}, -$N(R^{10})$-V-CO_2R^{10}, -O-V-CO_2R^{10}, -S-V-CO_2R^{10}, or -$N(R^{10})(R^{13})$;

or R^{11} and R^{12} are optionally taken together, with the phosphorus atom to which they are attached, to form a 5- to 7-membered monocyclic ring;

each V is independently -$CH(R^{15})$ or C_1-C_4 alkylene-$CH(R^{15})$;

each R^{13} is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, or heterocyclyl, wherein said alkyl, alkenyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 2 substituents selected from the group consisting of aryl, aryl(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, heterocyclyl(C_1-C_4 alkyl), C_1-C_6 alkyl, halo, -$OC(O)OR^6$, -$OC(O)R^6$, -OR^{10}, -SR^{10}, -$N(R^{10})_2$, -$C(O)R^{10}$, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^{10}SO_2R^6$, -$SO_2N(R^6)_2$, -NHCOOR^6, -NHCOR^6, -NHCONHR^6, -CO_2R^{10}, and -$C(O)N(R^{10})_2$; wherein each aryl is independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S;

R^{14} is C_1-C_6 alkyl, C_2-C_6 alkenyl, aryl or heteroaryl, wherein aryl is phenyl or naphthyl, and heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3

heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and wherein said aryl or heteroaryl is optionally substituted with 1 to 2 substituents selected from the group consisting of C_1-C_6 alkyl, halo, -OC(O)OR^6, -OC(O)R^6, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -C(O)R^{10}, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^{10}SO_2R^6$, -SO_2N(R^6)$_2$, -NHCOOR^6, -NHCOR^6, -NHCONHR^6, -CO_2R^{10}, and -C(O)N(R^{10})$_2$; and

each R_{15} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, or heterocyclyl, wherein said alkyl, alkenyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 2 substituents selected from the group consisting of C_1-C_6 alkyl, halo, -OC(O)OR^6, -OC(O)R^6, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -C(O)R^{10}, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^{10}SO_2R^6$, -SO_2N(R^6)$_2$, -NHCOOR^6, -NHCOR^6, -NHCONHR^6, -CO_2R^{10}, and -C(O)N(R^{10})$_2$; wherein each aryl is independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S.

In one embodiment of the invention, n is 1, and all other variables are as previously defined.

In another embodiment of the invention, R^1 is -P(O)$R^{11}R^{12}$, and all other variables are as previously defined. In a preferred group of this embodiment, R^{11} is independently C_1-C_6 alkyl, or -OR^{13}, and R^{12} is independently -OR^{13}, and all other variables are as previously defined. In a more preferred group of this embodiment, R^{13} is H or C_1-C_6 alkyl, and all other variables are as previously defined. In an even more preferred embodiment of the invention, R11 is selected from the group consisting of -OCH_2CH_3, -CH_3, and -OH, and R^{12} is -OH, and all other variables are as previously defined.

In another embodiment of the invention, R^2 is C_1-C_6 alkyl or C_2-C_6 alkenyl, and all other variables are as previously defined. In a more preferred group of this embodiment, R^2 is -CH=CH_2 or -CH_2CH_3, and all other variables are as previously defined.

In another embodiment of the invention, R^3 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl, and all other variables are as previously defined. In a preferred group of this embodiment, R^3 is -$C(CH_3)_3$, cyclohexyl or cyclopentyl, and all other variables are as previously defined.

In another embodiment of the invention, R^5 is H, and all other variables are as previously defined.

In another embodiment of the invention, Z is -O-, and all other variables are as previously defined.

In another embodiment of the invention, Y is -C(=O)-, and all other variables are as previously defined.

In another embodiment of the invention, W is H or -O-(C_1-C_6) alkyl, and all other variables are as previously defined. In a preferred group of this embodiment, W is H or -OCH_3.

In another embodiment of the invention, A is -$C(R^{16})$- and all other variables are as previously defined. In a preferred group of this embodiment, R^{16} is H.

In another embodiment of the invention, M is C_1-C_{12} alkylene wherein said alkylene is optionally substituted with 1 or 2 substituents selected from the group consisting of C_1-C_8 alkyl, and all other variables are as previously defined. In a preferred group of this embodiment, M is selected from the group consisting of -$(CH_2)_5$-, -$(CH_2)_3CH(CH_3)CH_2$-, and -$(CH_2)_3C(CH_3)_2CH_2$-, and all other variables are as previously defined.

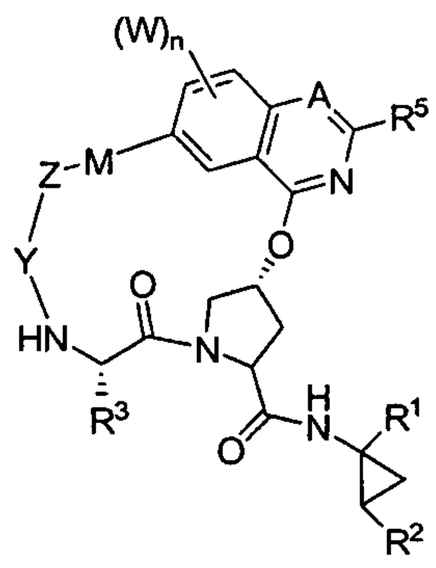
The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating or preventing one or more symptoms of HCV infection.

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

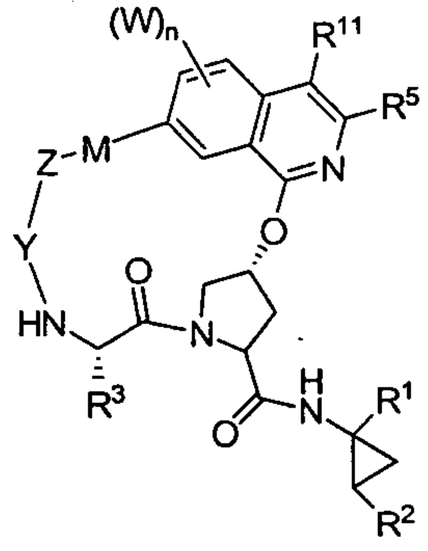
DETAILED DESCRIPTION OF THE INVENTION

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**, **II-A**, **II-B**,

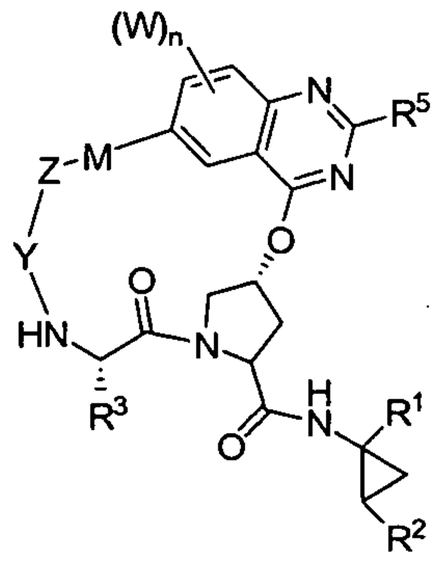
III, **III-A** and **III-B** wherein variables n, R^1, R^2, R^3, Y, Z, M, W, A, R^5 and R^{11} are as defined for formula **I**.



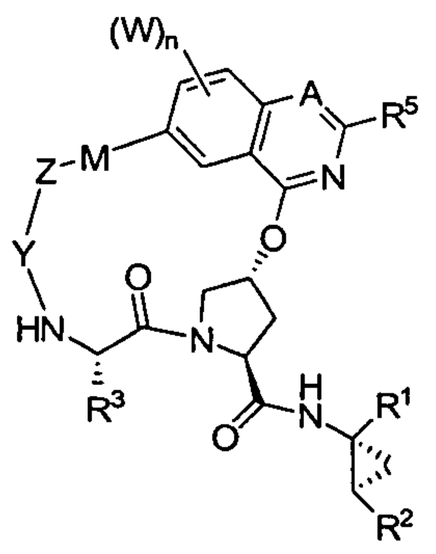
II



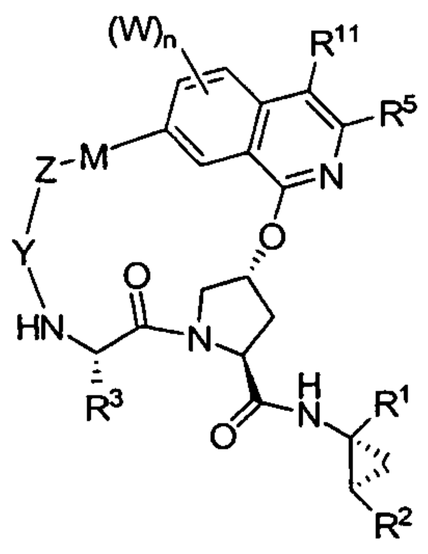
II-A



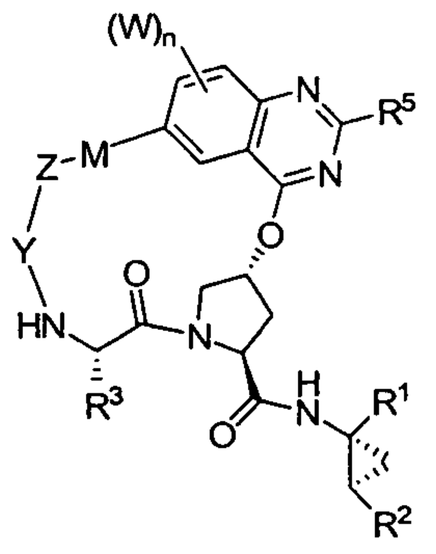
II-B



III



III-A



III-B

Other embodiments of the present invention include the following:

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

(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 I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**.

(h) The method of (g), wherein the compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B** 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).

In the embodiments of the compound provided above, it is to be understood that each embodiment may be combined with one or more other embodiments, to the extent that such a combination provides a stable compound and is consistent with the description of the embodiments. It is further to be understood that the embodiments of compositions and methods provided as (a) through (k) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

The present invention also includes a compound of the present invention for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) inhibiting HCV NS3 protease, or (b) treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection. 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 (or alternatively "alkanediyl") 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 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^7 and R^{10}) occurs more than one time in any constituent or in formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B** 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).

Terms referring to 2 substituents "on adjacent carbon atoms," which "optionally taken together" form specified cyclic rings, and 2 substituents "on the same carbon atom," which "optionally taken together" form specified cyclic rings, mean that the 2 substituents can form a ring that includes both of the adjacent carbon atoms, or can form a ring that includes the same carbon atom. For example, ring 1 shown below is formed by two single carbon substituents each attached to adjacent carbon atoms, and ring 2 shown below is formed by two single carbon substituents each attached to the same carbon atom:



ring 1 ring 2

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**, **II-A**, **II-B**, **III**, **III-A**, or **III-B** 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, 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), 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)].

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).

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, and WO 02/48165 (20 June 2002), 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), 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).

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.

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.; and HCV-796 (Viropharma Inc.).

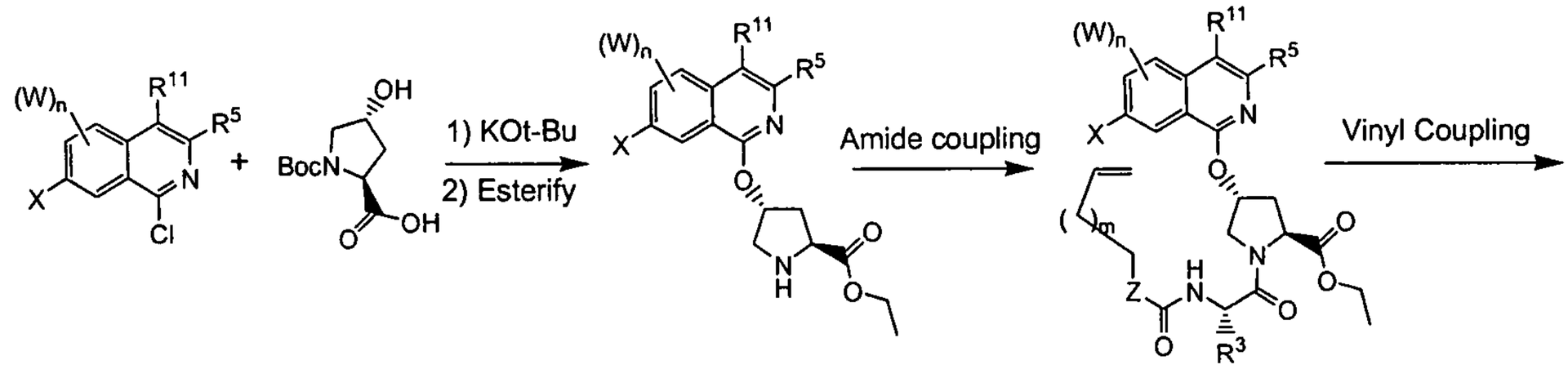
The HCV NS3 protease inhibitory activity of the present compounds may be tested using assays known in the art. One such assay is HCV NS3 protease time-resolved fluorescence (TRF) assay as described below and in WO 2006/102087. Other examples of such assays are described in e.g., International patent publication WO 2005/046712. Compounds useful as HCV NS3 protease inhibitors would have a K_i 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, II-A, II-B, III, III-A,** or **III-B**. 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 .

<u>General Description of Synthesis</u>

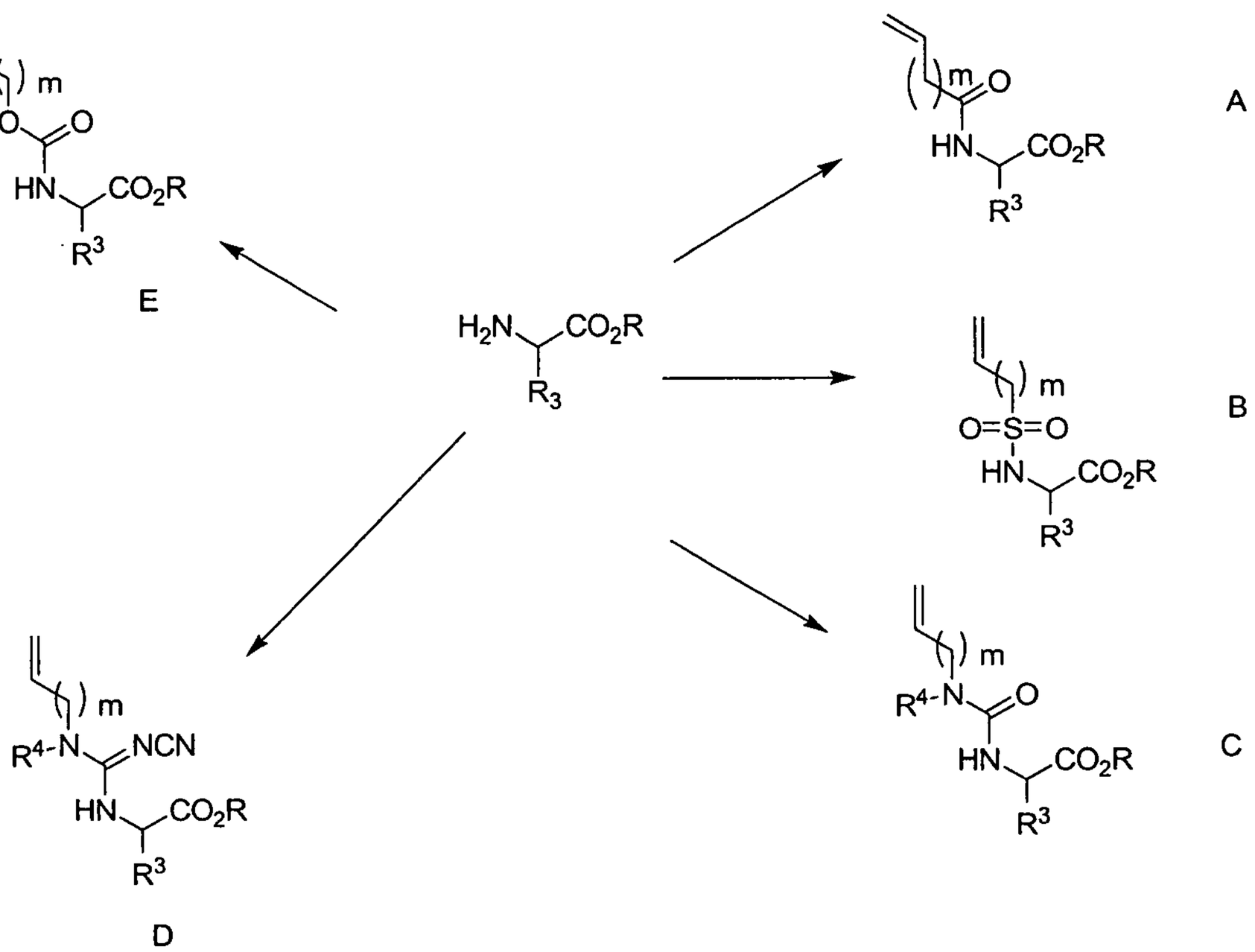
The compounds of the present invention may be synthesized as outlined in the general Schemes 1, 2 and 3.

Scheme 1



Scheme 1 (m=0-9) outlines the synthesis of a representative molecule. An appropriately protected 4-hydroxyproline derivative (for example, a carbamate protected nitrogen) can be reacted with potassium *t*-butoxide or equivalent reagent and then reacted with an appropriately substituted chloro-isoquinoline. The acid can then be esterified with acid in an appropriate alcohol solvent. These conditions also remove the BOC protecting group on the proline nitrogen.

Scheme 2



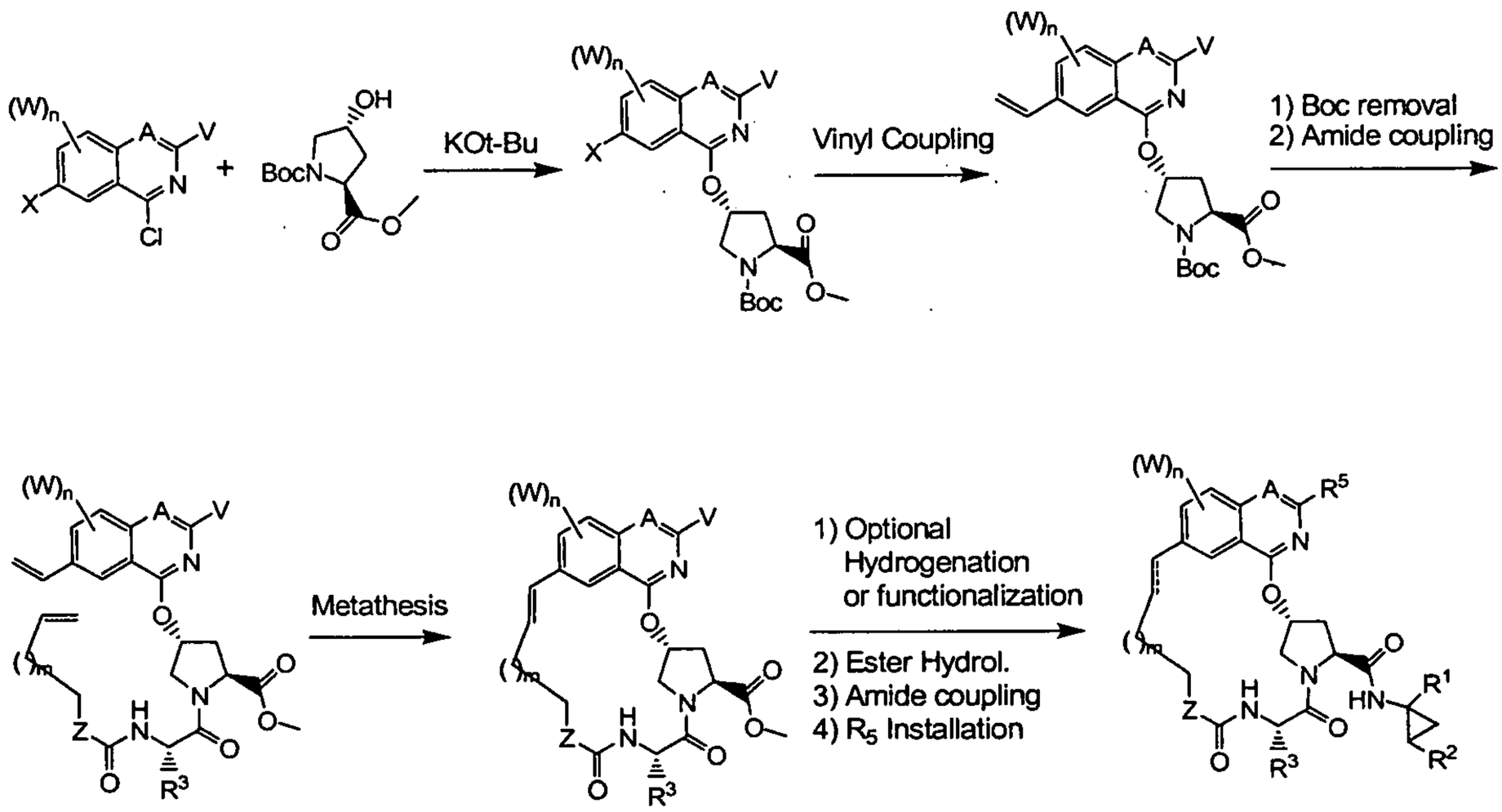
Scheme 2 describes the synthesis of the olefin-containing amino acid portion. An amino acid (either commercially available or may be prepared readily using known methods in the art) in which the acid functionality is protected as an ester (for example, R=methyl) can be converted to amides A by coupling 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.

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).

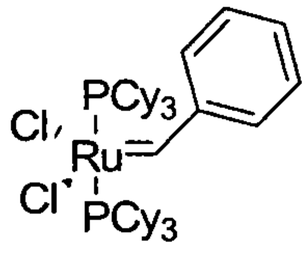
To complete the synthesis of the compounds of this invention, the amino acid derivative can be coupled to the proline derivative via a wide range of peptide coupling reagents such as DCC, EDC, BOP, TBTU etc (see Scheme 1). The alkenyl functionality may be introduced at this stage by palladium-catalyzed reaction of a halide substituent such as bromide or iodide, or other functionality such as a triflate with an organometallic reagent such as a vinyl or allyltrialkyltin. 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 an appropriate cyclopropyl containing P1 fragment, the syntheses of which have been described previously (Llinas-Brunet et al., US 6,323,180; Chaudhary, WO 2006/020276) and subjected to an additional hydrolysis step to provide the final compounds.

Scheme 3

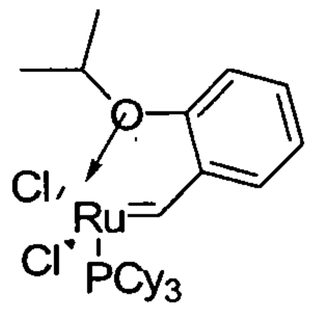


Molecules with 3-substituted isoquinolines or 2-substituted quinazolines may be prepared according to Scheme 3 (wherein V is, for example, halo such as chloro). An appropriately substituted 3-halo isoquinoline or 2-halo quinazoline can be employed in a sequence similar to the route shown in Scheme 1. In a final additional step, an R^5 group can be installed via displacement reactions or metal-mediated coupling reactions.

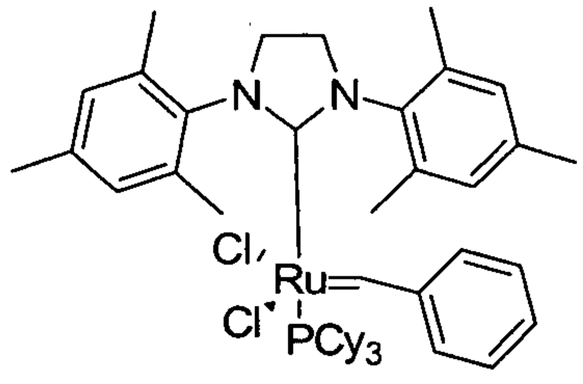
Olefin metathesis catalysts include the following Ruthenium-based species: F: Miller et al *J. Am. Chem. Soc* 1996, 118, 9606; G: Kingsbury et al *J. Am. Chem. Soc* 1999, 121, 791; H: Scholl et al Org. Lett. 1999, 1, 953; Hoveyda et al US2002/0107138; K: Furstner et al. J. Org. Chem 1999, 64, 8275. The 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).



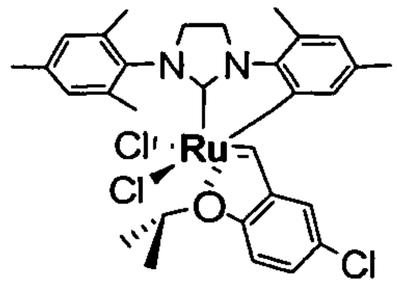
F



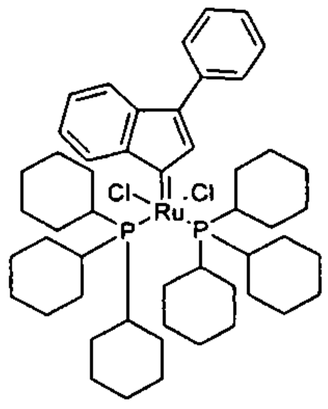
G



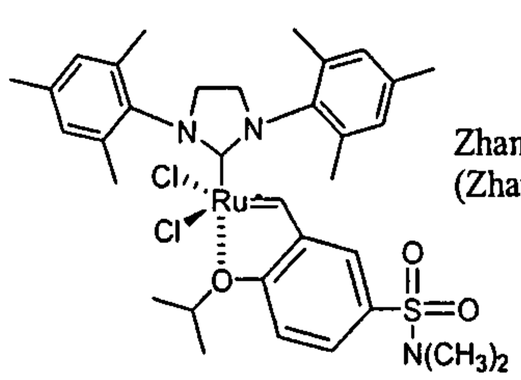
H



J



K



L

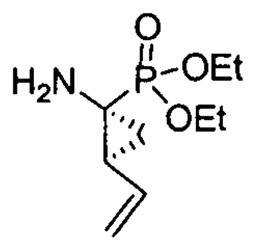
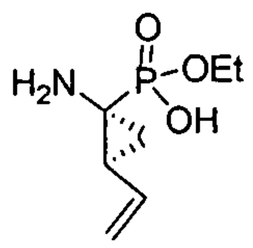
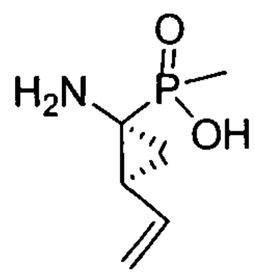
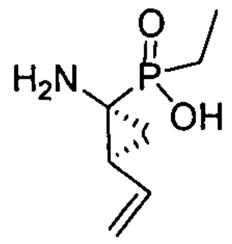
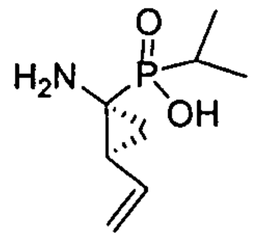
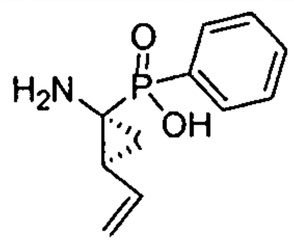
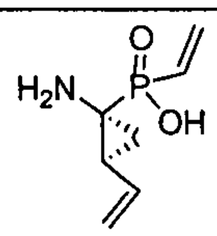
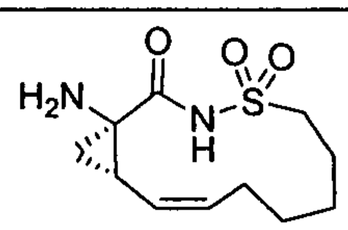
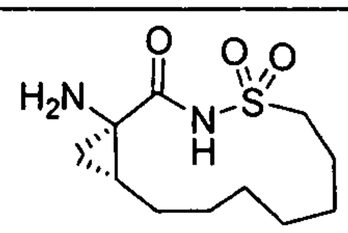
Zhan ruthenium metathesis catalyst RC-303
(Zhan catalyst 1B, RC-303, Zannan Pharma Ltd.)

List of Abbreviations

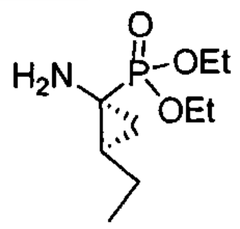
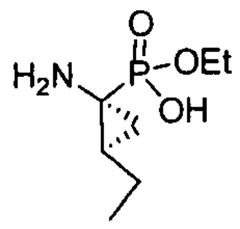
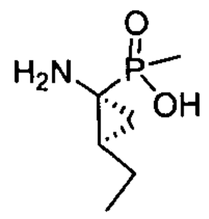
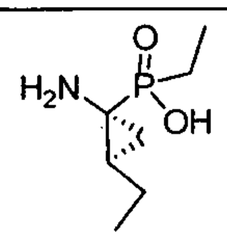
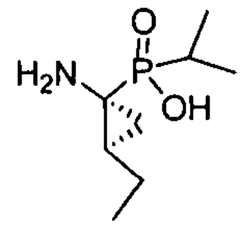
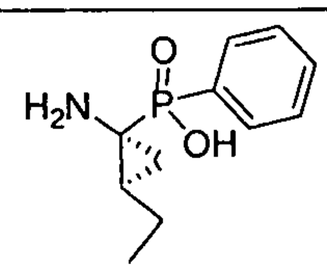
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
Brosyl chloride	4-Bromophenyl sulfonylchloride
CH_3CN	Acetonitrile
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane

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
Na_2SO_4	Sodium sulfate
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
Nle	Norleucine
Pd/C	Palladium on carbon
PhMe	Toluene
PPh_3	Triphenylphosphine
RT	Room temperature
TBAF	Tetrabutylammonium fluoride
TBTU	*O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate
THF	Tetrahydofuran

Synthesis of Intermediates:

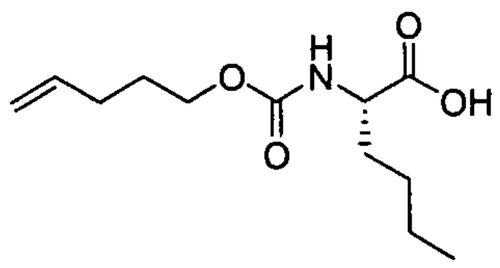
Intermediate #	Structure	Name	Lit. Reference
A1		diethyl [(1S,2R)-1-amino-2-vinylcyclopropyl]phosphonate	Chaudhary WO 2006/020276
A2		ethyl hydrogen [(1S,2R)-1-amino-2-vinylcyclopropyl]phosphonate	Chaudhary WO 2006/020276
A3		[(1S,2R)-1-amino-2-vinylcyclopropyl]methylphosphinic acid	Chaudhary WO 2006/020276
A4		[(1S,2R)-1-amino-2-vinylcyclopropyl]ethylphosphinic acid	Chaudhary WO 2006/020276
A5		[(1S,2R)-1-amino-2-vinylcyclopropyl]isopropylphosphinic acid	Chaudhary WO 2006/020276
A6		[(1S,2R)-1-amino-2-vinylcyclopropyl]phenylphosphinic acid	Chaudhary WO 2006/020276
A7		[(1S,2R)-1-amino-2-vinylcyclopropyl]vinylphosphinic acid	Chaudhary WO 2006/020276
A8		1-amino-4-thia-3-azabicyclo[10.1.0]tridec-10-en-2-one 4,4-dioxide	Chaudhary WO 2006/020276
A9		1-amino-4-thia-3-azabicyclo[10.1.0]tridecan-2-one 4,4-dioxide	Chaudhary WO 2006/020276

By hydrogenation of the intermediates above, or a suitable intermediate in their preparation, for example by treatment in an appropriate solvent or solvent mixture with a palladium, platinum or rhodium catalyst, the following intermediates can be prepared by a person skilled in the art.

Intermediate #	Structure	Name
A10		diethyl [(1S,2S)-1-amino-2-ethylcyclopropyl]phosphonate
A11		ethyl hydrogen [(1S,2S)-1-amino-2-ethylcyclopropyl]phosphonate
A12		[(1S,2S)-1-amino-2-ethylcyclopropyl]methylphosphinic acid
A13		[(1S,2S)-1-amino-2-ethylcyclopropyl]ethylphosphinic acid
A14		[(1S,2S)-1-amino-2-ethylcyclopropyl]isopropylphosphinic acid
A15		[(1S,2S)-1-amino-2-ethylcyclopropyl]phenylphosphinic acid

Intermediates B

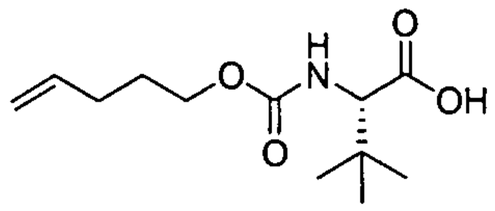
Intermediate B1: *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucine



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 RT and stirred for 30 minutes. 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 minutes. Upon cooling, the reaction mixture was diluted with ethyl ether and washed twice with water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography (gradient elution 10 to 90% EtOAc in hexanes) to afford 2.1 g (74%) methyl *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucinate as a clear oil.

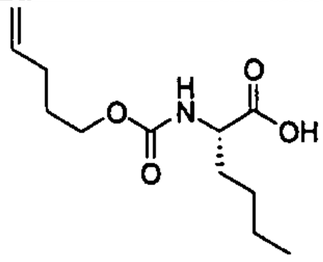
To a stirred solution of methyl *N*-[(pent-4-enyloxy)carbonyl]-L-norleucinate (8.50g, 33.03 mmol) in THF (20 mL) was added 1N NaOH (20 mL). This reaction solution was stirred at RT for 3 hours, then acidified to pH 3 with 1N HCl and extracted with (3 x 250 mL) EtOAc. The combined EtOAc layer was washed with 50 mL water, 50 mL brine, dried over Na_2SO_4, filtered and concentrated to give 7.09 g (88%) of the title product as clear oil. LRMS (ESI) *m/z* 244 $[(M+H)^+$; calcd for $C_{12}H_{22}NO_4$: 244].

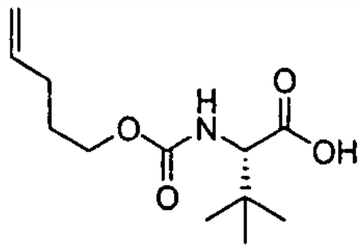
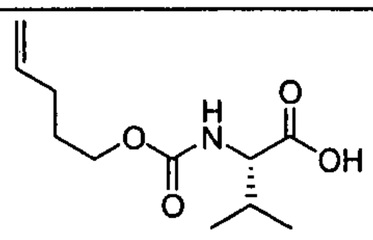
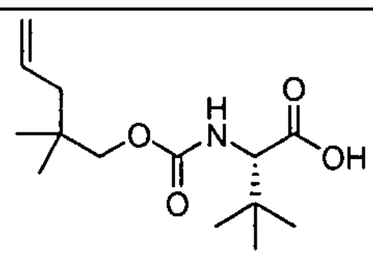
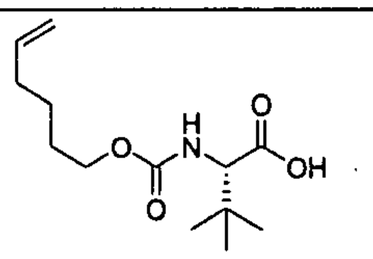
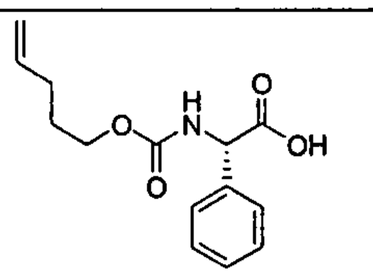
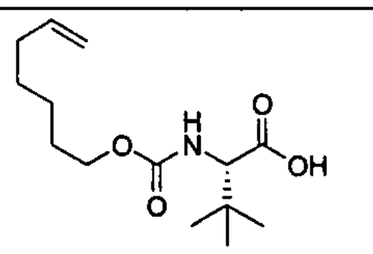
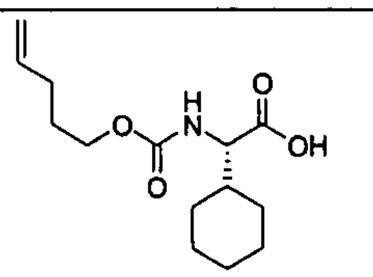
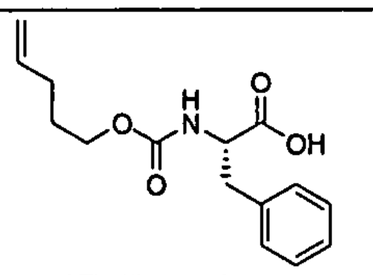
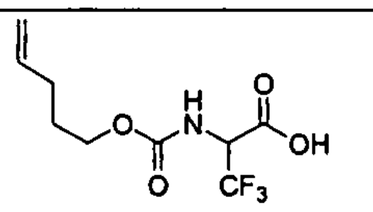
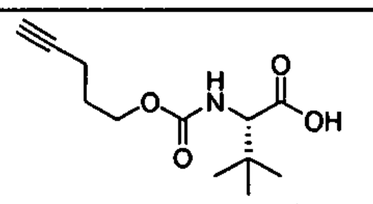
Intermediate B2: (2S)-3,3-dimethyl-2-{[(pent-4-en-1-yloxy)carbonyl]amino}butanoic acid

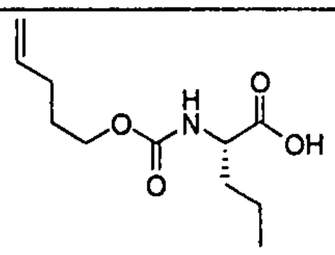
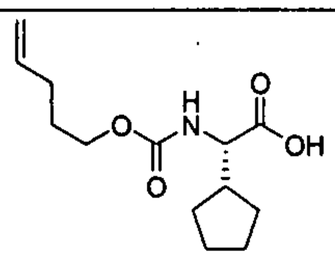
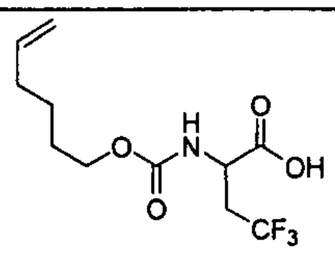
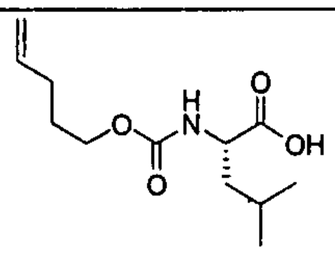
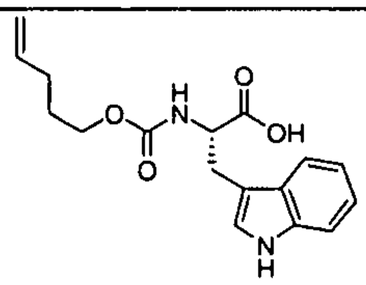
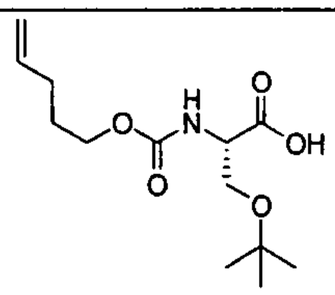
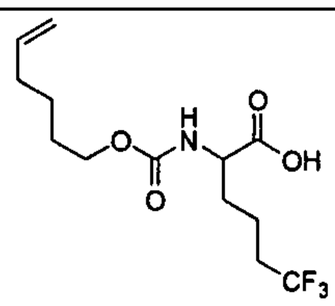
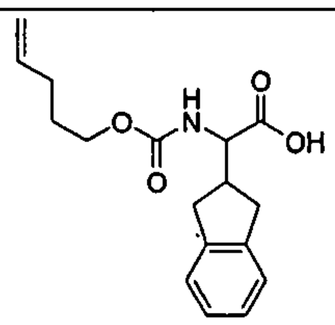
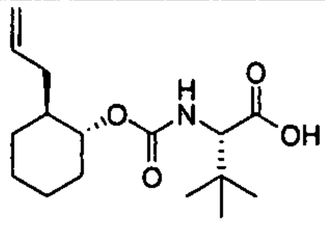
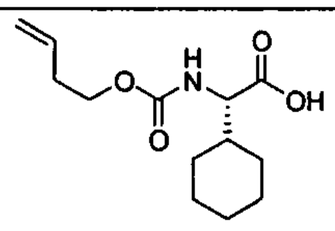


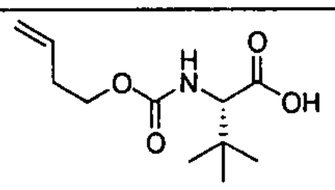
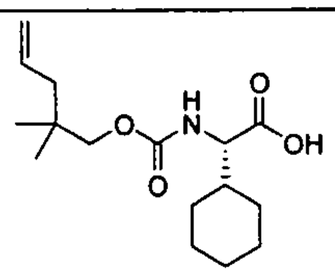
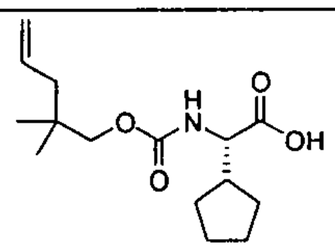
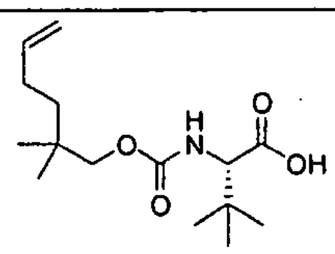
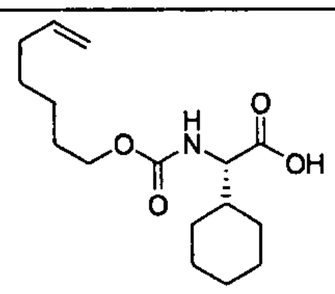
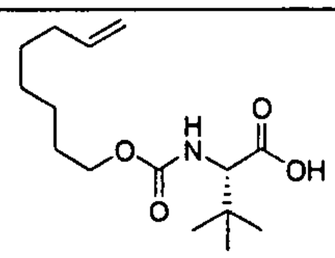
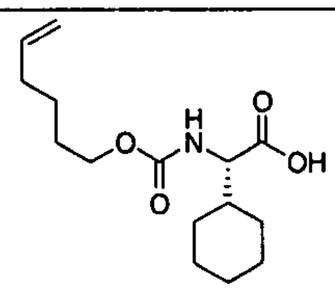
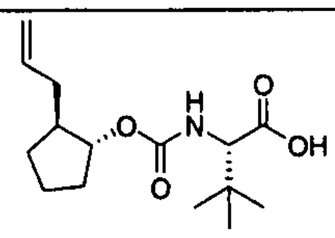
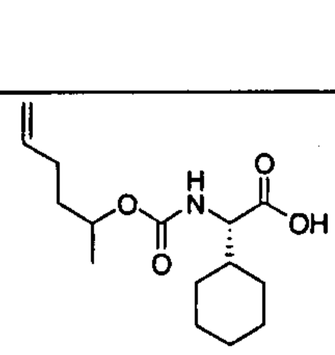
DIPEA (9.85 g, 76.2 mmol) was added dropwise to a 0°C solution of 4-penten-1-ol (7.22 g, 83.9 mmol) and triphosgene (11.3 g, 38.1 mmol) in 160 mL dioxane. The resulting white suspension was stirred for 5 minutes at 0°C, then allowed to warm to 25°C over 1 hour. The suspension was cooled to 0 °C with an ice bath and 1 N NaOH (76.2 mL) and *L-t*-butylglycine (10.0 g, 76.2 mmol) were added. The reaction mixture was warmed to 25°C and stirred for 18 hours. 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 DCM (3x 150 mL), then acidified to pH~1 with 6 N HCl. The aqueous layer was extracted with DCM (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give the compound as a tan oil (13.7 g, 73.9% yield). LRMS (ESI) *m/z* 244 $[(M+H)^+$; calcd for $C_{12}H_{22}NO_4$ 244].

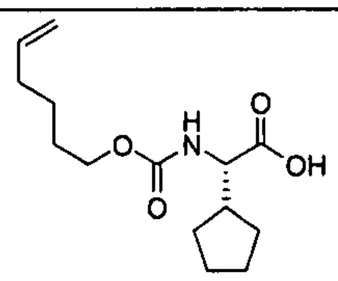
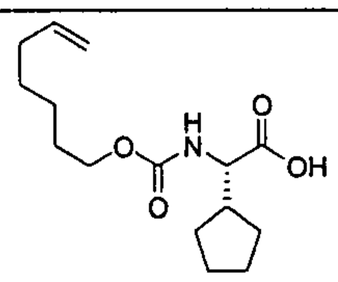
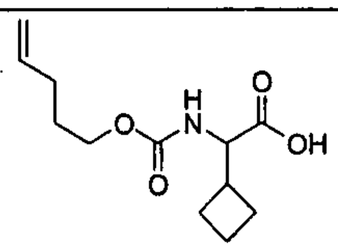
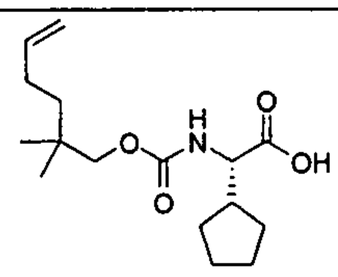
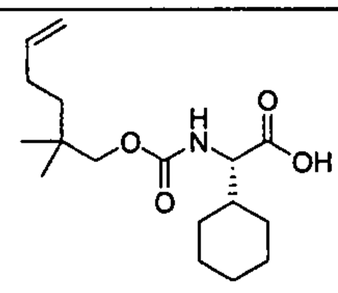
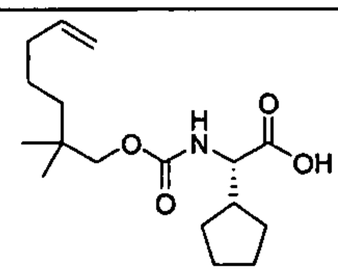
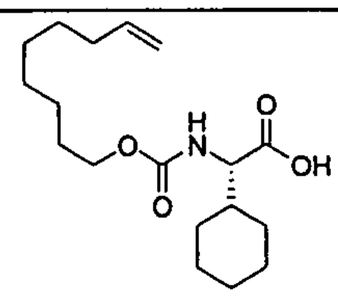
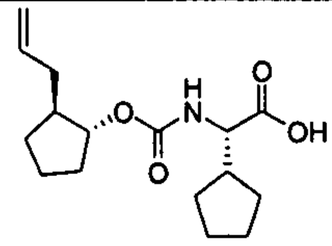
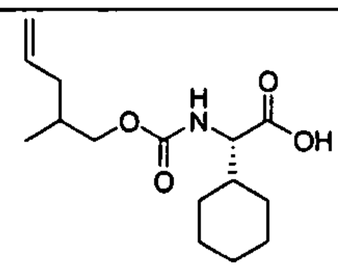
The following carbamate intermediates (B3-B49) were prepared using the chemistry described for the preparation Intermediate B2, by utilizing the appropriate amino acid and alcohol or the preparation of Intermediate B1 by utilizing the appropriate alcohol and amino ester.

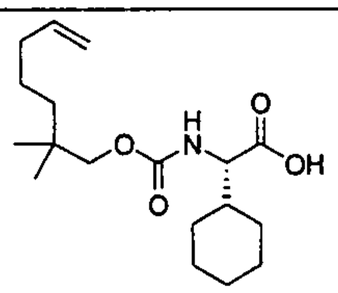
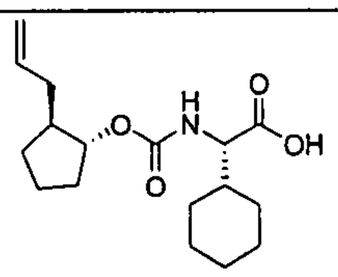
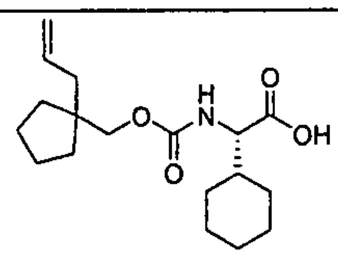
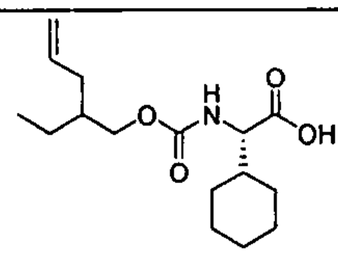
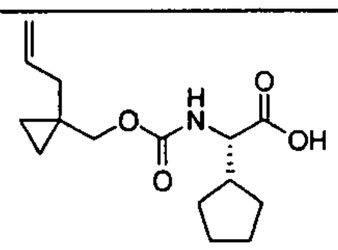
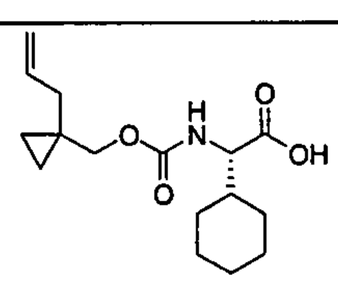
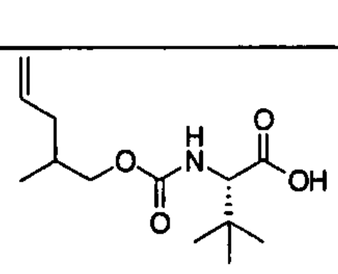
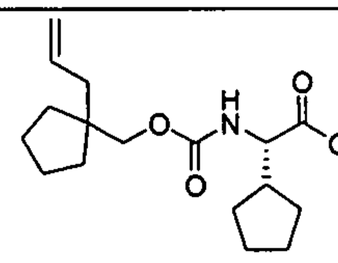
Int.	Amino Acid	Alcohol	Structure	Name	LRMS $(M+H)^+$
B1	L-Norleucine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-norleucine (Intermediate 1)	244.3

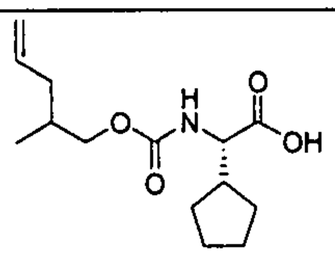
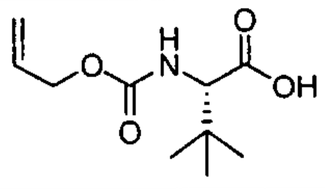
Int.	Amino Acid	Alcohol	Structure	Name	LRMS $(M+H)^+$
B2	L-*t*-Butyl-glycine	4-Penten-1-ol		(2S)-3,3-Dimethyl-2-{[(pent-4-en-1-yloxy)carbonyl] amino}butanoic acid	244.2
B3	L-Valine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-valine	230.3
B4	L-*t*-Butyl-glycine	2,2-Dimethyl-4-penten-1-ol Ref: *J. Org. Chem* (**1981**), *46*, 1177-1182.		*N*-{[(2,2-Dimethylpent-4-en-1-yl)oxy]carbonyl}-3-methyl-L-valine	272.3
B5	L-*t*-Butyl-glycine	5-Hexen-1-ol		*N*-[(Hex-5-en-1-yloxy)carbonyl]-3-methyl-L-valine	258.3
B6	L-Phenyl-glycine	4-Penten-1-ol		(2*S*)-{[(Pent-4-en-1-yloxy)carbonyl] amino}(phenyl) acetic acid	264.3
B7	L-*t*-Butyl-glycine	6-Hepten-1-ol		*N*-[(Hept-6-en-1-yloxy)carbonyl]-3-methyl-L-valine	272.3
B8	L-Cyclohexyl-glycine	4-Penten-1-ol		(2S)-Cyclohexyl{[(pent-4-en-1-yloxy) carbonyl]amino} acetic acid	270.3
B9	L-Phenyl alanine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-phenylalanine	278.2
B10	3,3,3-Trifluoroalanine	4-Penten-1-ol		3,3,3-trifluoro-*N*-[(pent-4-en-1-yloxy)carbonyl] alanine	256.2
B11	L-*t*-Butyl-glycine	4-Pentyn-1-ol		3-Methyl-*N*-[(pent-4-yn-1-yloxy) carbonyl]-L-valine	242.2

Int.	Amino Acid	Alcohol	Structure	Name	LRMS $(M+H)^+$
B12	L-Norvaline	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-norvaline	230.3
B13	L-Cyclopentyl-glycine	4-Penten-1-ol		(2*S*)-Cyclopentyl {[(pent-4-en-1-yloxy)carbonyl] amino}acetic acid	256.3
B14	2-Amino-4,4,4-trifluorobutanoic acid	5-Hexen-1-ol		4,4,4-Trifluoro-2-{[(hex-5-en-1-yloxy)carbonyl]amino}butanoic acid	305.2 $(M+Na)^+$
B15	L-Leucine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-leucine	244.3
B16	L-Tryptophan	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-tryptophan	317.4
B17	*O*-(*t*-Butyl)- L-serine	4-Penten-1-ol		*O*-(*t*-Butyl)-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-serine	218.3 $(M-tBu)^+$
B18	6,6,6-trifluoronorleu-cine	5-Hexen-1-ol		6,6,6-Trifluoro-*N*-[(hex-5-en-1-yloxy)carbonyl] norleucine	353.2 $(M+MeCN)^+$
B19	Amino(2,3-dihydro-1*H*-inden-2-yl)acetic acid	4-Penten-1-ol		2,3-Dihydro-1*H*-inden-2-yl{[(pent-4-en-1-yloxy)arbonyl] amino}acetic acid	304.3
B20	L-*t*-Butyl-glycine	(trans)-2-allylcyclohexanol Ref: *Tetrahedron* (**2004**), *60*, 4837.		*N*-({[(trans)-2-Allylcyclohexyl] oxy}carbonyl)-3-methyl-L-valine	298.4
B21	L-Cyclohexyl-glycine	3-Buten-1-ol		(2*S*)-{[(But-3-en-1-yloxy)carbonyl] amino}(cyclohexyl) acetic acid	256.2

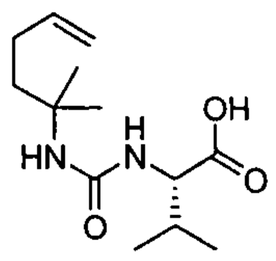
Int.	Amino Acid	Alcohol	Structure	Name	LRMS $(M+H)^+$
B22	L-*t*-Butyl-glycine	3-Buten-1-ol		*N*-[(But-3-en-1-yloxy)carbonyl]-3-methyl-L-valine	230.3
B23	L-Cyclohexyl-glycine	2,2-Dimethyl-4-penten-1-ol Ref: *J. Org. Chem* (**1981**), *46*, 1177-1182.		(2*S*)-Cyclohexyl({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl} amino)acetic acid	298.3
B24	L-Cyclopentyl-glycine	2,2-Dimethyl-4-penten-1-ol Ref: *J. Org. Chem* (**1981**), *46*, 1177-1182..		(2*S*)-Cyclopentyl({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl} amino)acetic acid	284.3
B25	L-*t*-Butyl-glycine	2,2-Dimethylhex-5-en-1-ol Ref: *J. Org. Chem.* (**1991**), *56*, 1623.		*N*-{[(2,2-Dimethylhex-5-en-1-yl)oxy]carbonyl}-3-methyl-L-valine	286.3
B26	L-Cyclohexyl-glycine	6-Hepten-1-ol		(2*S*)-Cyclohexyl{[(hept-6-en-1-yloxy)carbonyl] amino}acetic acid	298.3
B27	L-*t*-Butyl-glycine	7-Octen-1-ol		3-Methyl-*N*-[(oct-7-en-1-yloxy) carbonyl]-L-valine	286.3
B28	L-Cyclohexyl-glycine	5-Hexen-1-ol		(2*S*)-Cyclohexyl{[(hex-5-en-1-yloxy)carbonyl] amino}acetic acid	284.4
B29	L-*t*-Butyl-glycine	(trans)-2-Allyl cyclopentanol Ref: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		*N*-({[(trans)-2-Allylcyclopentyl]oxy}carbonyl)-3-methyl-L-valine	284.2
B30	L-Cyclohexyl-glycine	1-Methylpent-4-en-1-ol Ref: *Tetrahedron Assym.* (**1998**), *9*, 657.		(2*S*)-Cyclohexyl({[(1-methylpent-4-en-1-yl)oxy]carbonyl} amino)acetic acid	284.2

Int.	Amino Acid	Alcohol	Structure	Name	LRMS $(M+H)^+$
B31	L-Cyclopentyl-glycine	5-Hexen-1-ol		(2*S*)-Cyclopentyl{[(hex-5-en-1-yloxy)carbonyl] amino}acetic acid	270.3
B32	L-Cyclopentyl-glycine	6-Hepten-1-ol		(2*S*)-Cyclopentyl{[(hept-6-en-1-yloxy)carbonyl] amino}acetic acid	284.4
B33	L-Cyclobutyl-glycine	4-Penten-1-ol		Cyclobutyl{[(pent-4-en-1-yloxy)carbonyl] amino}acetic acid	242.3
B34	L-Cyclopentyl-glycine	2,2-Dimethylhex-5-en-1-ol Ref: *J. Org. Chem.* (**1991**), *56*, 1623.		(2*S*)-Cyclopentyl({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl} amino)acetic acid	298.3
B35	L-Cyclohexyl-glycine	2,2-Dimethylhex-5-en-1-ol Ref: *J. Org. Chem.* (**1991**), *56*, 1623.		(2*S*)-Cyclohexyl({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl} amino)acetic acid	312.3
B36	L-Cyclopentyl-glycine	2,2-Dimethylhept-6-en-1-ol Ref: *J. Org. Chem.* (**1980**), *45*, 2685.		(2*S*)-Cyclopentyl({[(2,2-dimethylhept-6-en-1-yl)oxy]carbonyl} amino)acetic acid	312.2
B37	L-Cyclohexyl-glycine	8-Nonen-1-ol		(2*S*)-Cyclohexyl{[(non-8-en-1-yloxy)carbonyl] amino}acetic acid	326.3
B38	L-Cyclopentyl-glycine	(trans)-2-Allyl cyclopentanol Ref: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		(2*S*)-[({[(trans)-2-Allylcyclopentyl]oxy}carbonyl)amino](cyclopentyl)acetic acid	296.4
B39	L-Cyclohexyl-glycine	2-Methylpent-4-en-1-ol Ref: *Tetrahedron* (**1993**), *49*, 947.		(2*S*)-Cyclohexyl({[(2-methylpent-4-en-1-yl)oxy]carbonyl} amino)acetic acid	284.4

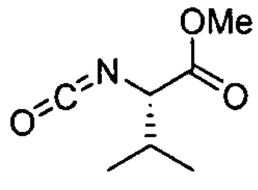
Int.	Amino Acid	Alcohol	Structure	Name	LRMS $(M+H)^+$
B40	L-Cyclohexyl-glycine	2,2-Dimethylhept-6-en-1-ol Ref: *J. Org. Chem.* (**1980**), *45*, 2685.		(2*S*)-Cyclohexyl({[(2,2-dimethylhept-6-en-1-yl)oxy]carbonyl} amino)acetic acid	326.4
B41	L-Cyclohexyl-glycine	(trans)-2-Allyl cyclopentanol Ref: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		(2*S*)-[({[(trans)-2-Allylcyclopentyl]oxy}carbonyl)amino] (cyclohexyl) acetic acid	310.5
B42	L-Cyclohexyl-glycine	(1-Allyl cyclopentyl) methanol Ref: *J. Org. Chem.* (**1992**), *57*, 1727.		(2*S*)-({[(1-Allylcyclopentyl) methoxy] carbonyl}amino) (cyclohexyl)acetic acid	324.3
B43	L-Cyclohexyl-glycine	2-Ethylpent-4-en-1-ol Ref: *Tetrahedron Lett.* (**1985**), *26*, 6085.		(2*S*)-Cyclohexyl({[(2-ethylpent-4-en-1-yl)oxy]carbonyl} amino) acetic acid	298.2
B44	L-Cyclopentyl-glycine	(1-Allyl cyclopropyl) methanol Ref: *Helv. Chim. Acta* (**1986**), *69*, 1655.		(2*S*)-({[(1-Allylcyclopropyl) methoxy]carbonyl} amino)(cyclopentyl) acetic acid	282.3
B45	L-Cyclohexyl-glycine	(1-Allyl cyclopropyl) methanol Ref: *Helv. Chim. Acta* (**1986**), *69*, 1655.		(2*S*)-({[(1-Allylcyclopropyl) methoxy]carbonyl} amino)(cyclohexyl) acetic acid	296.3
B46	L-*t*-Butyl-glycine	2-Methylpent-4-en-1-ol Ref: *Tetrahedron* (**1993**), *49*, 947.		3-Methyl-*N*-{[(2-methylpent-4-en-1-yl)oxy]carbonyl}-L-valine	258.3
B47	L-Cyclopentyl-glycine	(1-Allyl cyclopentyl) methanol Ref: *J. Org. Chem.* (**1992**), *57*, 1727.		(2*S*)-({[(1-Allylcyclopentyl) methoxy] carbonyl}amino) (cyclopentyl)acetic acid	310.3

Int.	Amino Acid	Alcohol	Structure	Name	LRMS $(M+H)^+$
B48	L-Cyclopentyl-glycine	2-Methylpent-4-en-1-ol Ref: *Tetrahedron* (**1993**), *49*, 947.		(2*S*)-Cyclopentyl({[(2-methylpent-4-en-1-yl)oxy]carbonyl} amino)acetic acid	270.2
B49	L-*t*-Butyl-glycine	Allyl alcohol		*N*-[(allyloxy)carbonyl] -3-methyl-L-valine	215.2

Intermediate B50: *N*-{[(1,1-Dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine

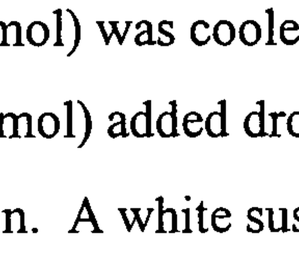


Step 1: Methyl *N*-(oxomethylene)-L-valinate



A mixture of L-valine methyl ester hydrochloride (10.0 g, 59.9 mmol), DCM (300 mL), and pyridine (19.3 mL, 240 mmol) was cooled in an ice/salt bath and a solution of 20% phosgene in PhMe (35.6 mL, 719 mmol) added dropwise, maintaining the reaction temperature below 5°C during the addition. A white suspension resulted and after 1.5 hours, the reaction mixture was poured into ice-cold 1M HCl and extracted with DCM (2 × 500mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Flash column chromatography on silica (95 hexanes / 5 EtOAc) gave the title compound as a colorless oil (6.43g). ^{1}H NMR ($CDCl_3$ 500MHz) δ 3.94 (d, J = 4.0 Hz, 1 H), 3.82 (s, 3 H), 2.24 (m, 1 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 6.5Hz, 3 H) ppm.

Step 2: Methyl *N*-{[(1,1-dimethylpent-4-en-1-yl)amino]carbonyl}-L-valinate



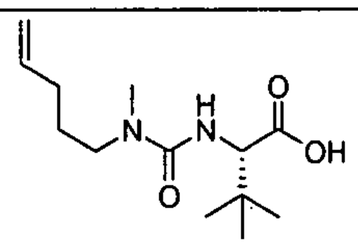
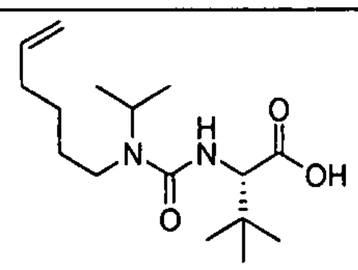
Methyl *N*-(oxomethylene)-L-valinate (2.80 g, 17.7 mmol) was added to 2-methylhex-5-en-2-amine [*J. Org. Chem.* (**1976**) *41*(5) 855-863.] (2.00 g, 17.7 mmol) in THF (15 mL). After 5 minutes, the reaction mixture was evaporated to give the title compound as a

solid, which was triturated with hexane and isolated by filtration (2.71g). LRMS $(M+H)^+$ = 271.4.

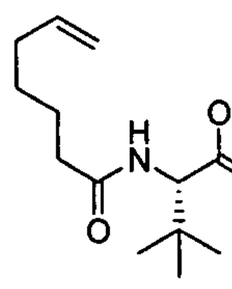
Step 3: *N*-{[(1,1-Dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine

1M lithium hydroxide (54 mL, 54 mmol) was added to *N*-{[(1,1-dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine (2.94 g, 10.9 mmol) in THF (20 mL). The reaction mixture was stirred at RT under nitrogen for 18 hours, then heated to reflux for 2 hours, and cooled to RT. The THF removed by evaporation. Water was then added, and the mixture extracted with DCM (4×). The aqueous layer was made acidic with 1M HCl and extracted with DCM (3 × 70 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent evaporated to give the title compound as a white foam (2.25 g). LRMS $(M+H)^+$ = 257.3.

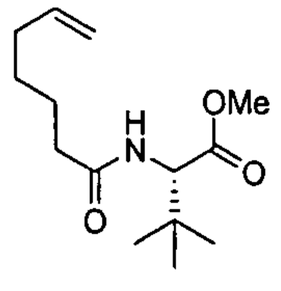
The following urea intermediates (B51-B52) were prepared using the chemistry described for the preparation of *N*-{[(1,1-dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine (as described in Intermediate B50), by utilizing the appropriate amino acid and amine.

Int	Amino Acid	Amine	Structure	Name	LRMS $(M+H)^+$
B51	L-*t*-Butyl-glycine	*N*-Methylpent-4-en-1-amine		3-Methyl-*N*-{[methyl(pent-4-en-1-yl)amino]carbonyl}-L-valine	257.3
B52	L-*t*-Butyl-glycine	*N*-Isopropylhex-5-en-1-amine		*N*-{[Hex-5-en-1-yl(isopropyl)amino]carbonyl}-3-methyl-L-valine	299.3

Intermediate B53: *N*-Hept-6-enoyl-3-methyl-L-valine



Step 1: Methyl *N*-Hept-6-enoyl-3-methyl-L-valinate



A solution of L-tert-leucine methyl ester (1.00 g, 6.89 mmol), 6-heptenoic acid (1.06 g, 8.26 mmol), EDC (1.58 g, 8.26 mmol) and HOAt (1.23 g, 8.26 mmol) in DMF (10 mL) was stirred at 22°C for 2 hours. The reaction mixture was diluted with aqueous saturated $NaHCO_3$ (30 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (3 x 30 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 5 - 50% EtOAc/hexane, to give the title product (1.42 g, 81%). LRMS (ESI) *m/z* 256.3 [$(M+H)^+$; calcd for $C_{14}H_{26}NO_3$: 256.2].

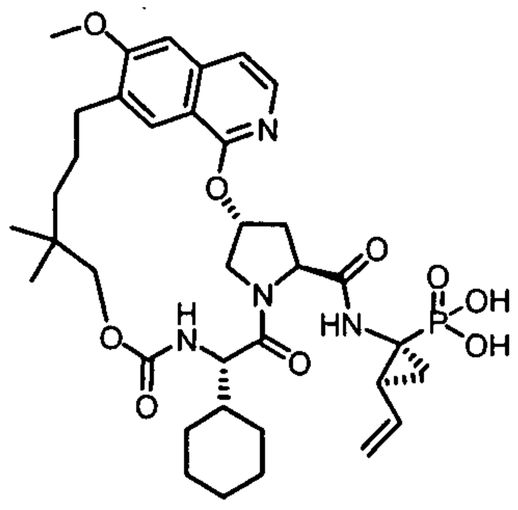
Step 2: N-Hept-6-enoyl-3-methyl-L-valine

A solution of methyl *N*-hept-6-enoyl-3-methyl-L-valinate (1.40 g, 5.48 mmol) in THF (10 mL) and 1N NaOH (10 mL) was stirred at 22°C for 2 hours. The reaction mixture was acidified to pH 3 with 1 N HCl and extracted with EtOAc (3 x 150 mL). The combined EtOAc layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the title product (1.12 g, 84%). LRMS (ESI) *m/z* 242.3 [$(M+H)^+$; calcd for $C_{13}H_{24}NO_3$: 242.2].

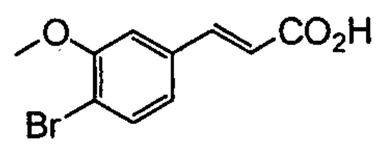
EXAMPLES

Example 1

[(1S,2S)-1-({[(2R,4S,7S)-7-cyclohexyl-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropyl]phosphonic acid

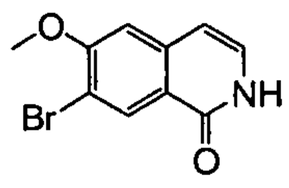


Step 1: (2E)-3-(4-Bromo-3-methoxyphenyl)acrylic acid



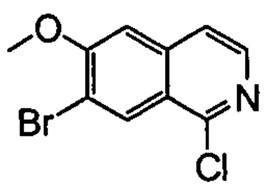
To a solution of 1-bromo-4-iodo-2-methoxybenzene (L. A. Hasvold et al, US 2004/0254159, EXAMPLE 57B) (33.45 g, 107 mmol) in MeCN (100 mL) was added acrylic acid (9.61 g,, 133 mmol), Et_3N (37.2 mL, 267 mmol) and palladium acetate (719 mg, 3.2 mmol). The reaction mixture was heated to 90°C for 40 minutes, cooled to RT and poured into 2.4 L 1M HCl. After stirring for 30 minutes, the solid was filtered, heated to reflux in EtOH (230 mL), allowed to cool to RT and stirred overnight. The solid was filtered and washed with 1:1 EtOH hexane (50 mL) to give desired product. LRMS ESI^+ $(M+H)^+$ 257.0.

Step 2: 7-Bromo-6-methoxyisoquinolin-1(2H)-one



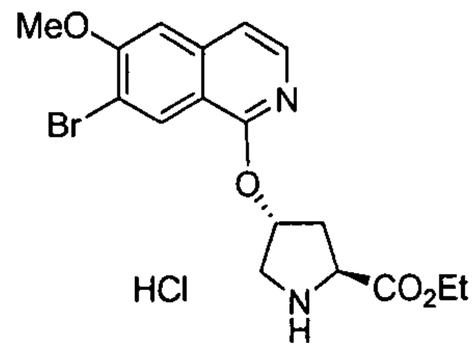
A portion of the product from Step 1 (12.5 g, 48.6 mmol) was azeotroped with benzene and suspended in benzene (94 mL). Et_3N (9.49 mL, 68.1 mmol) and diphenylphosphoryl azide (10.48 mL, 48.6 mmol) were added and the reaction mixture stirred at RT for 1 hour. The mixture was filtered through a pad of silica and eluted with ~1 L of PhMe, the volatiles evaporated, the residue resuspended in diphenylmethane (94 mL) and the mixture heated to reflux for 3 hours (internal temperature 250°C). The reaction mixture was allowed to cool to RT, stirred overnight, filtered and the solid washed with hexanes (100 mL) to give tan solid (7.4 g). LRMS ESI^+ $(M+H)^+$ 254.1.

Step 3: 7-Bromo-1-chloro-6-methoxyisoquinoline



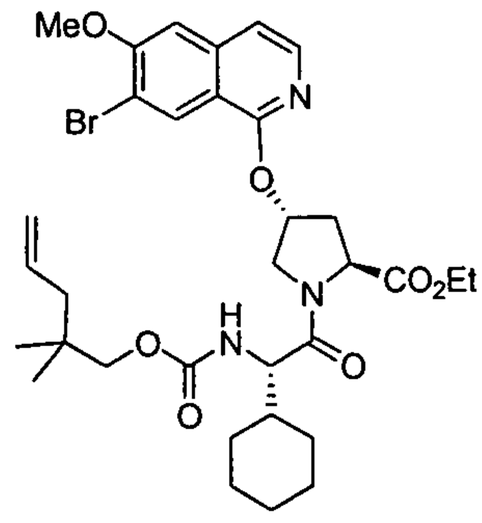
A mixture of the product from Step 2 (7-bromo-6-methoxyisoquinolin-1(2H)-one) (4.7 g, 18.5 mmol) in phosphorus oxychloride (30 mL) was heated to reflux for 2 hours and cooled to RT. The volatiles were then evaporated, and the residue was partitioned between 3 M NaOH and DCM. The organic phase was dried over Na_2SO_4; the solvent was evaporated; and the solid was triturated with Et_2O (20 mL) and filtered to give a solid (3.75 g). LRMS ESI^+ $(M+H)^+$ 274.0.

Step 4: Ethyl (4*R*)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-L-prolinate hydrochloride



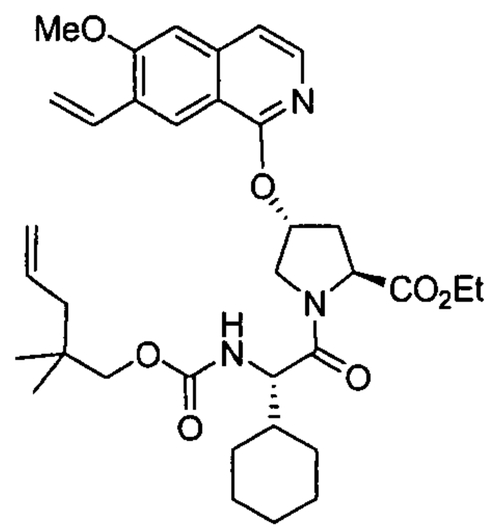
Potassium *t*-butoxide (618 mg, 5.5 mmol) was added to a stirred solution of BOC trans-4-hydroxyproline (424 mg, 1.83 mmol) in DMSO (10 mL) at RT. The reaction mixture was stirred for 30 minutes, cooled to 15°C and the product from Step 3 (500 mg, 1.83 mmol) added. The reaction mixture was stirred overnight and partitioned between ice-cold 10 % citric acid and EtOAc. The organic phase was washed with water and brine, dried over Na_2SO_4 and the solvent evaporated. The crude product was dissolved in EtOH (100 mL), cooled to 0°C, and HCl was bubbled through until saturated. The reaction mixture was allowed to warm to RT and stirred for 24 hours. The volatiles were evaporated and the residue azeotroped with EtOH (x4) to give the title compound as a tan solid (555 mg). LRMS ESI^+ $(M+H)^+$ 395.0.

Step 5: Ethyl (4R)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-1-[(2S)-2-cyclohexyl-2-({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetyl]-L-prolinate



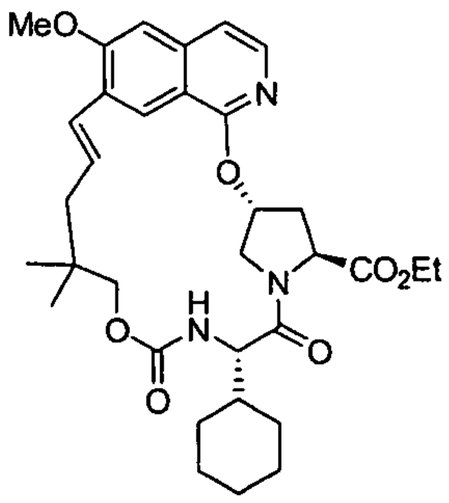
To a solution of the product from step 4 (900 mg, 2.09 mmol) in DMF (10 mL), was added Intermediate B23 (682 mg, 2.29 mmol), DIPEA (1.09 mL, 6.25 mmol) and HATU (1,190 mg, 3.13 mmol), and the reaction mixture stirred for 6 hours at RT. The mixture was then partitioned between EtOAc and 10% $KHSO_4$; the organic phase was washed with brine, dried over Na_2SO_4; and the solvent was evaporated. The crude product was purified by chromatography on silica (30-50% EtOAc/hexane) to afford the title compound (1.02 g) as a foam. LRMS ESI^+ $(M+H)^+$ 676.3.

Step 6: Ethyl (4R)-1-[(2S)-2-cyclohexyl-2-({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetyl]-4-[(6-methoxy-7-vinylisoquinolin-1-yl)oxy]-L-prolinate



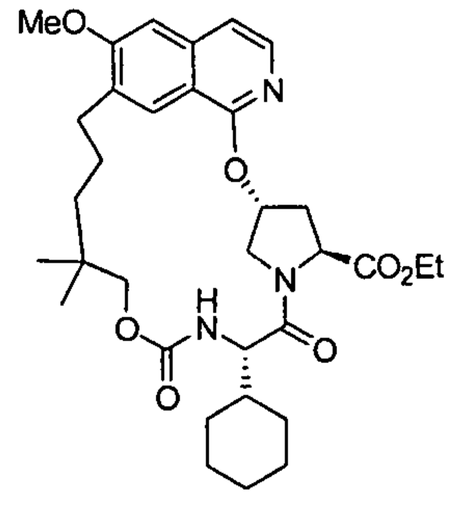
A solution of the product from Step 5 (1.02 g, 1.51 mmol) in PhMe (30 mL) was degassed for 30 minutes by bubbling nitrogen. Tri-*n*-butylvinyltin (533 μL, 1.81 mmol) and tetrakis(triphenylphosphine)palladium (175 mg, 0.151 mmol) were added, and the reaction mixture was heated to 105°C for 3 hours, then cooled to RT for 18 hours. The volatiles were evaporated, and the residue was purified by chromatography on silica (20-50% EtOAc/hexane) to afford the title compound (820 mg) as a foam. LRMS ESI$^+$ $(M+H)^+$ 622.5.

Step 7: Ethyl (2R,4S,7S,14E)-7-cyclohexyl-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



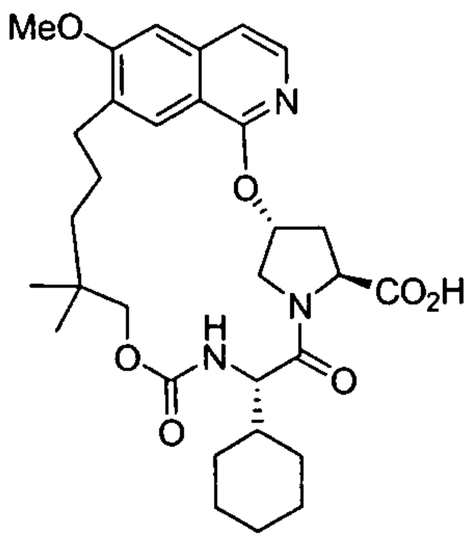
A solution of the product from Step 6 (800 mg, 1.29 mmol) in DCM (200 mL) was degassed for 30 minutes by bubbling nitrogen. Zhan 1B catalyst (189 mg, 0.26 mmol) in degassed DCM (20 mL) was added over 1 hour; the reaction mixture was stirred at RT for 18 hours, then concentrated; and the residue was purified by chromatography on silica (20-50% EtOAc/hexane) to afford the title compound (700 mg) as a foam. LRMS ESI$^+$ $(M+H)^+$ 594.5.

Step 8: Ethyl (2R,4S,7S)-7-cyclohexyl-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



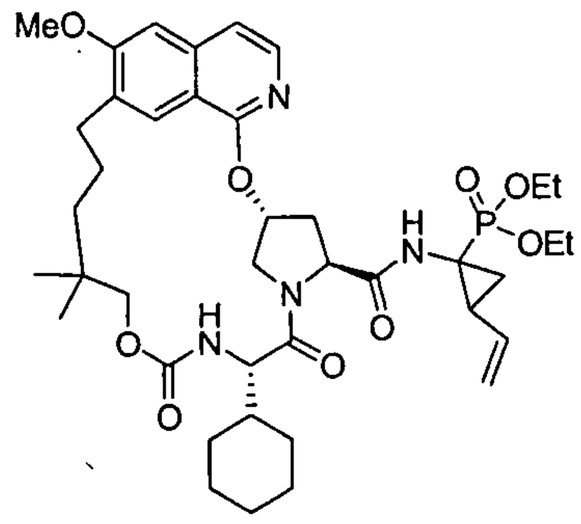
To a solution of the product from Step 7 (600 mg, 1.01 mmol) in EtOAc (50 mL) was added 10% Pd/C (100 mg), and the mixture was hydrogenated under 1 atmosphere of hydrogen for 18 hours. EtOH and additional 10% Pd/C (100 mg) were added, and hydrogenation was continued for 72 hours. The reaction mixture was filtered, and the filtrate was concentrated to afford the title compound (600 mg). LRMS ESI^+ $(M+H)^+$ 596.5.

Step 9: (3R,5S,8S)-8-cyclohexyl-18-methoxy-13,13-dimethyl-7,10-dioxo-2,11-dioxa-6,9,23-triazatetracyclo[15.6.2.1~3,6~.0~20,24~]hexacosa-1(23),17,19,21,24-pentaene-5-carboxylic acid



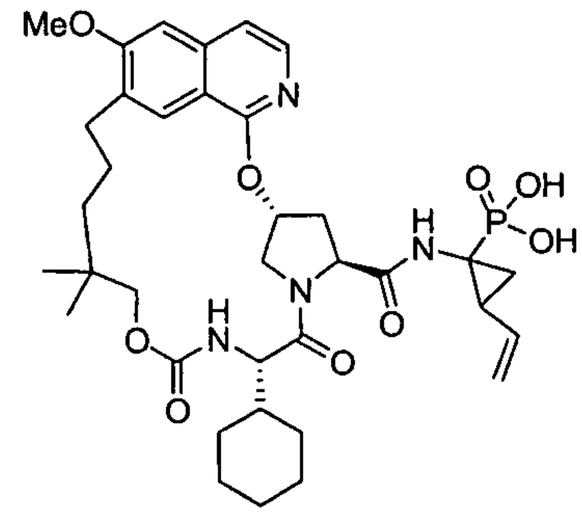
A solution of the product from Step 8 (600 mg, 1.01 mmol) was dissolved in THF (48 mL), water (12 mL) and EtOH (12 mL), and LiOH (169 mg, 7.05 mmol) was added. The reaction mixture was stirred at RT for 18 hours, diluted with 10% aqueous $KHSO_4$, concentrated to remove THF and EtOH and partitioned between water and EtOAc. The organic phase was dried over Na_2SO_4, and the solvent was evaporated to afford the title compound (543 mg) as a foam. LRMS ESI^+ $(M+H)^+$ 568.4.

Step 10: Diethyl [1-({[(3R,5S,8S)-8-cyclohexyl-18-methoxy-13,13-dimethyl-7,10-dioxo-2,11-dioxa-6,9,23-triazatetracyclo[15.6.2.1~3,6~.0~20,24~]hexacosa-1(23),17,19,21,24-pentaen-5-yl]carbonyl}amino)-2-vinylcyclopropyl]phosphonate



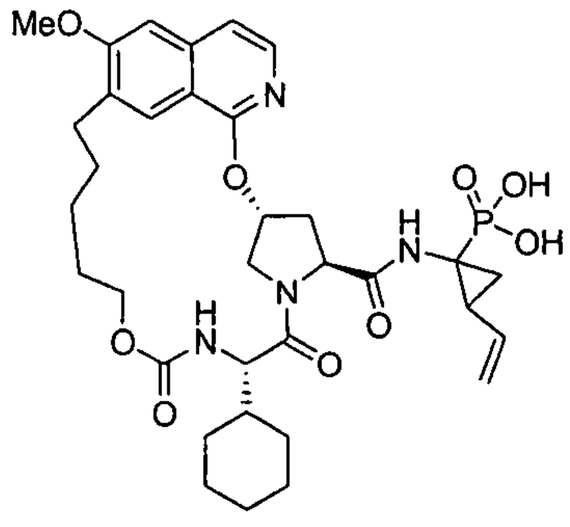
A solution of the product from Step 9 (180 mg, 0.317 mmol) in DMF (2 mL) was treated with Intermediate A1 (77 mg, 0.351 mmol), DIPEA (0.166 mL, 0.95 mmol), DMAP (19 mg, 0.16 mmol) and HATU (145 mg, 0.38 mmol). The reaction mixture was stirred at RT for 18 hours and then directly purified by reverse-phase chromatography (C18 5-100% CH_3CN/(water+0.1% TFA)) to give the product (200 mg) as a white foam. LRMS ESI^+ $(M+H)^+$ 769.2.

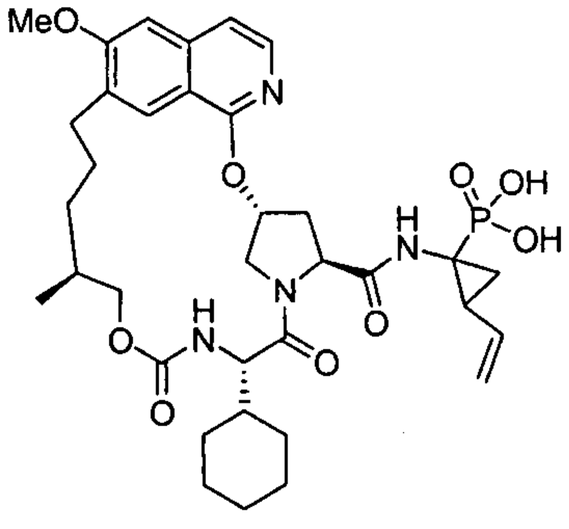
Step 11: [1-({[(3R,5S,8S)-8-cyclohexyl-18-methoxy-13,13-dimethyl-7,10-dioxo-2,11-dioxa-6,9,23-triazatetracyclo[15.6.2.1~3,6~.0~20,24~]hexacosa-1(23),17,19,21,24-pentaen-5-yl]carbonyl}amino)-2-vinylcyclopropyl]phosphonic acid

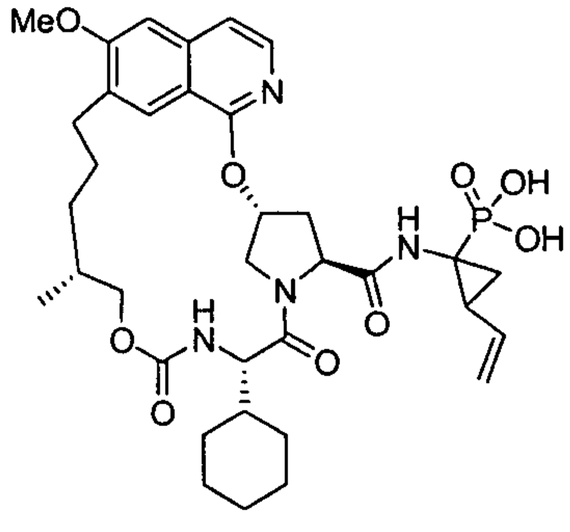


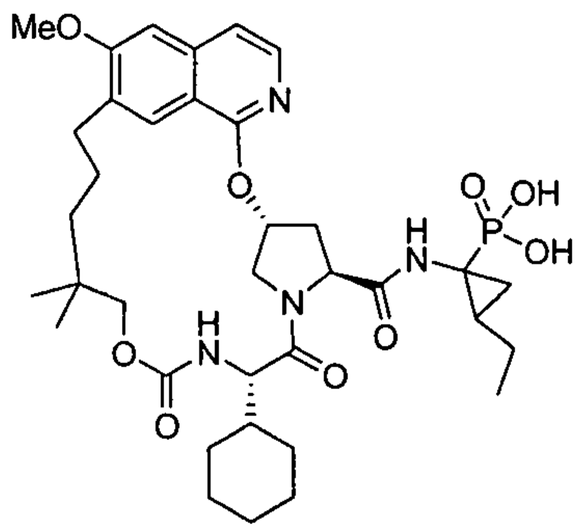
To a solution of the product from Step 10 (100 mg, 0.13 mmol) in CH_3CN (5 mL) at 0°C, was added 2,6-lutidine (0.042 mL, 0.36 mmol) followed by iodotrimethylsilane (0.05 mL, 0.36 mmol). Three additional portions of iodotrimethylsilane (0.05 mL, 0.36 mmol) were added at 1 hour intervals, and the reaction mixture then was stirred at RT for 18 hours. MeOH (0.5 mL) and Et_3N (0.2 mL) were added; the volatiles were evaporated; and the residue was dissolved in DMSO and purified by reverse-phase chromatography (C18 5-100% CH_3CN/(water+0.1% TFA)) to give the product (200 mg) as a white foam. LRMS ESI^+ $(M+H)^+$.

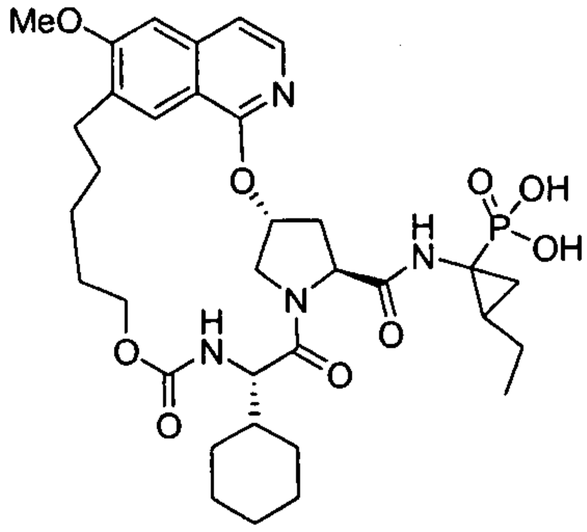
By utilizing the appropriate Intermediates A and B, the following compounds may be prepared in a similar fashion:

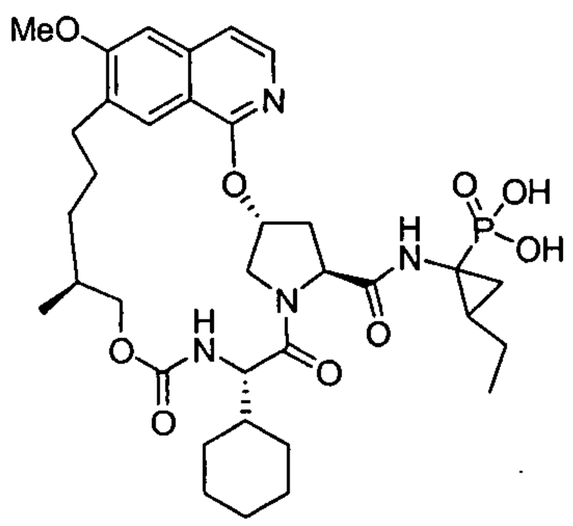


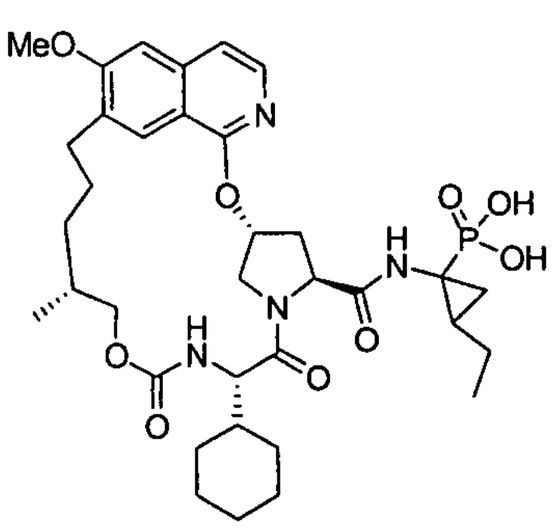


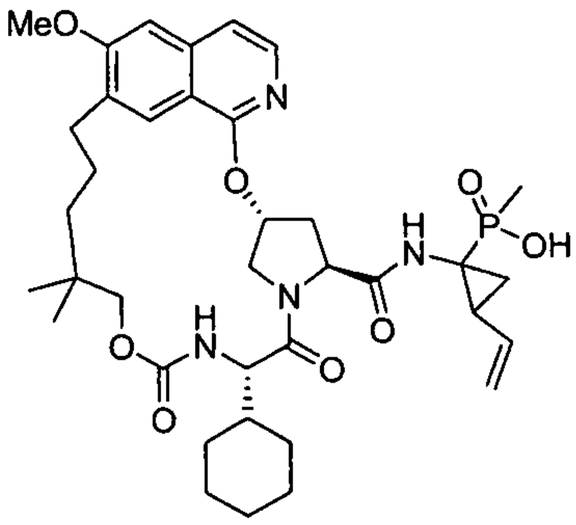


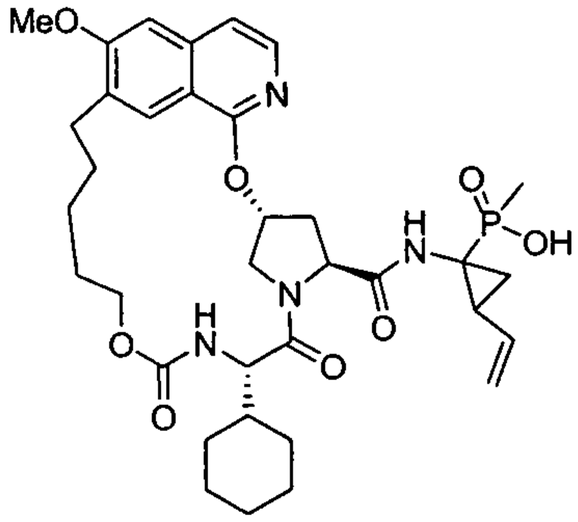


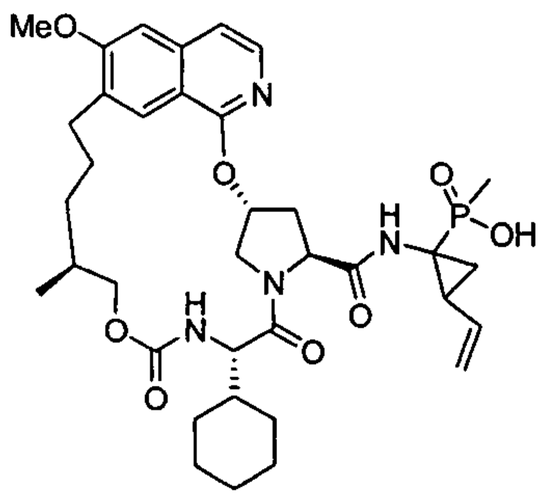


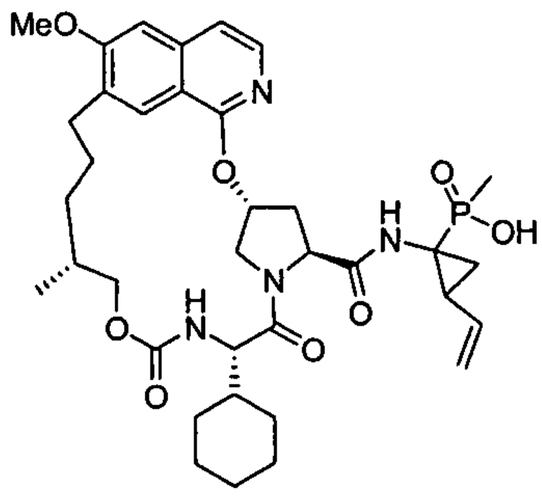


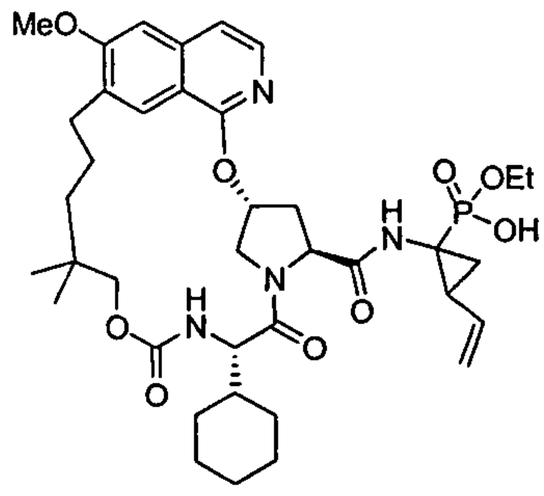


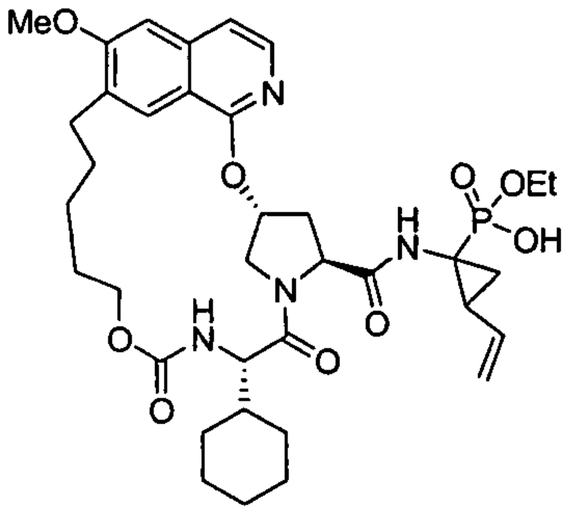


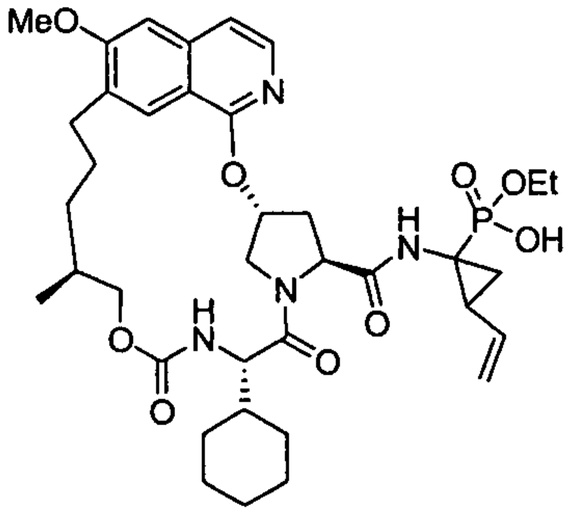


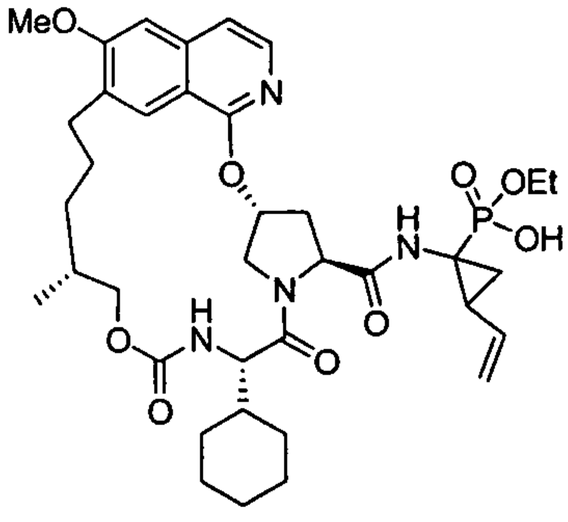




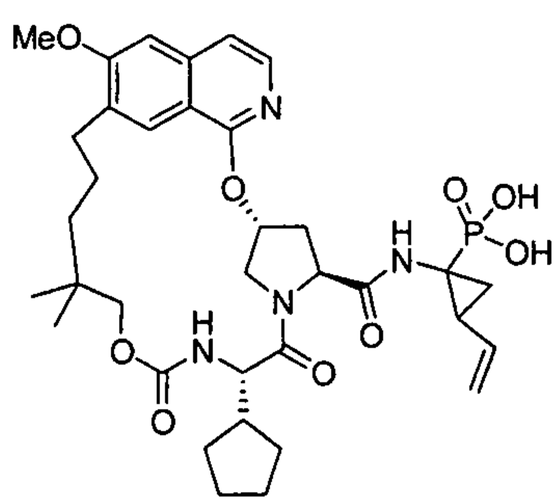
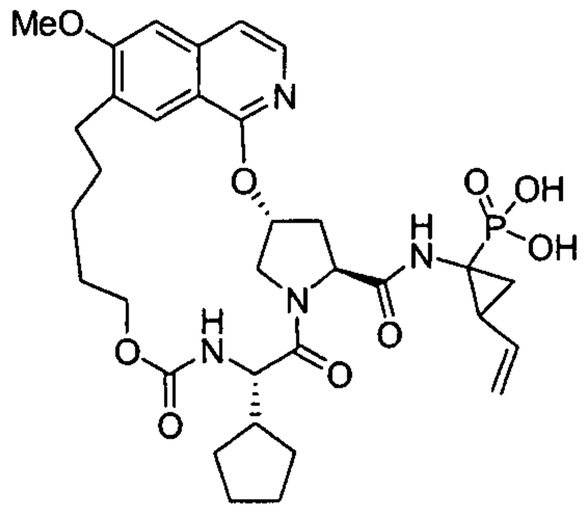
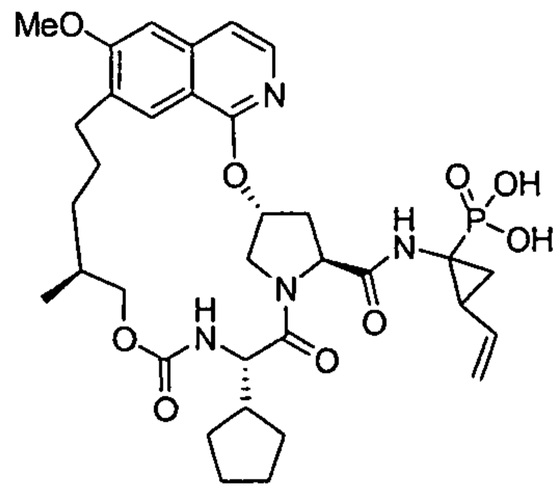
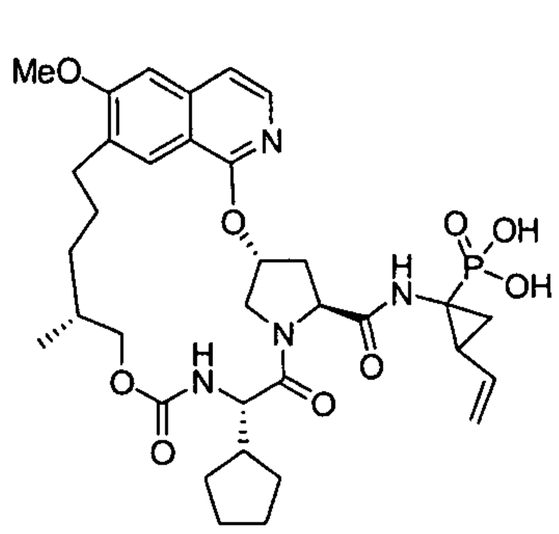
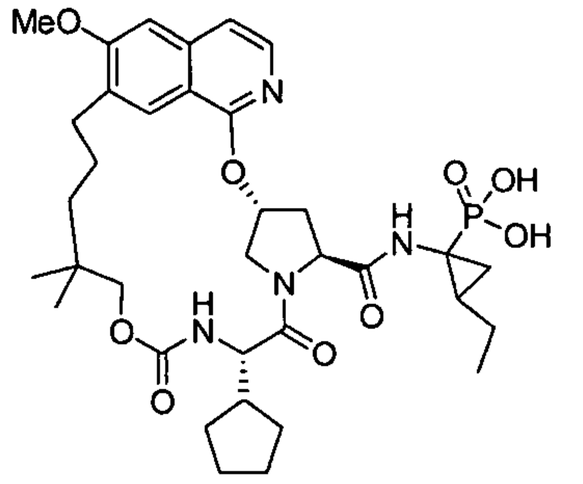
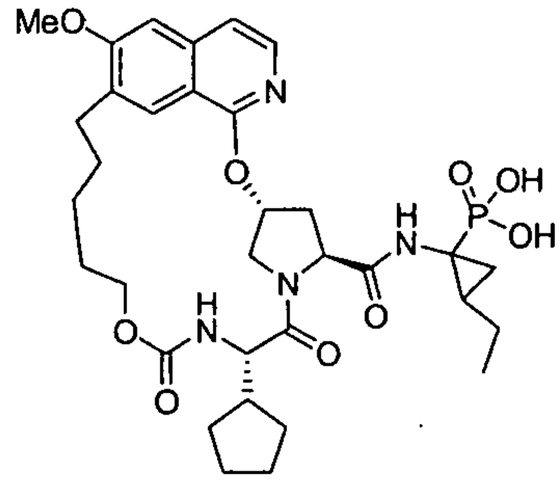
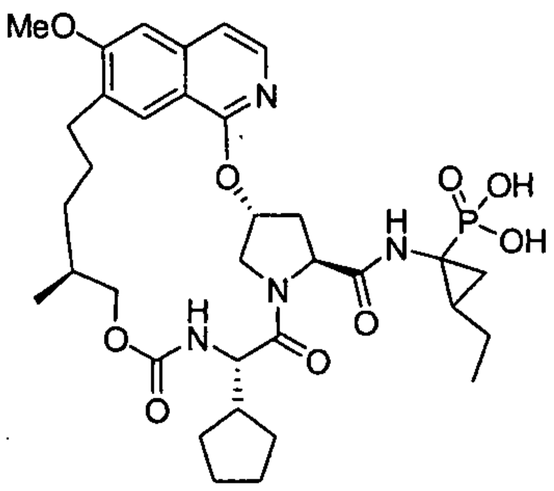
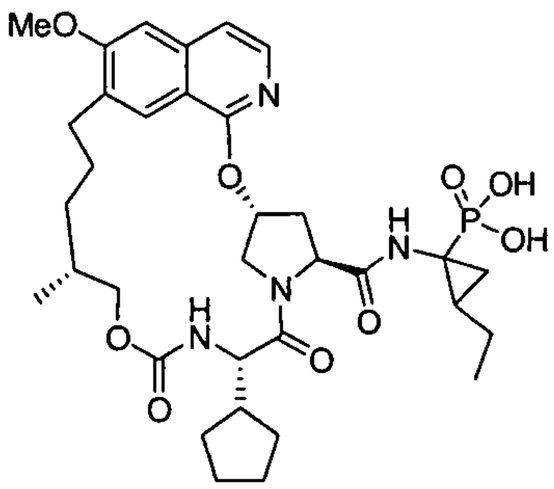
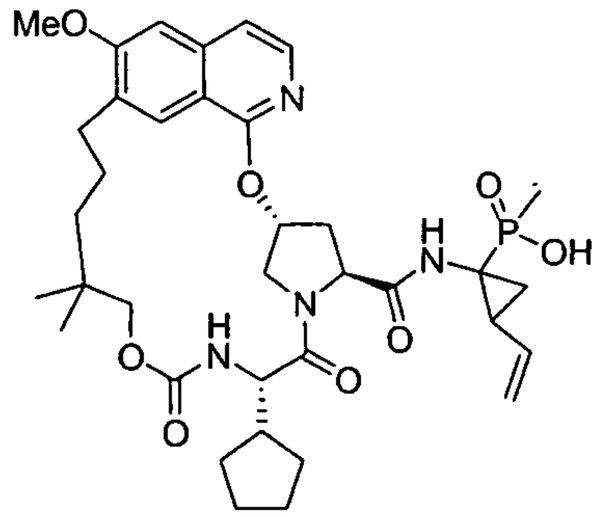
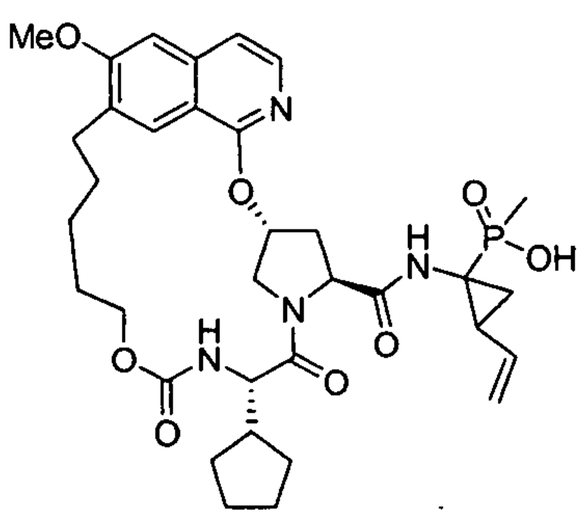
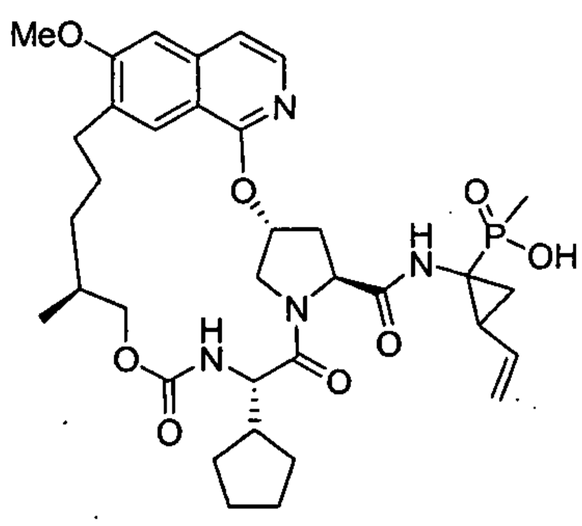
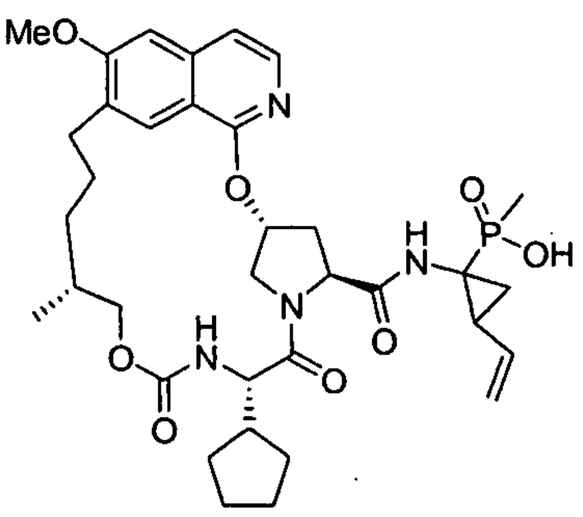
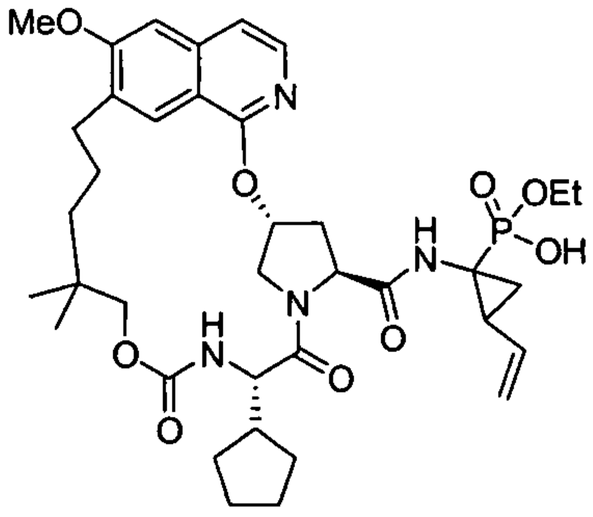
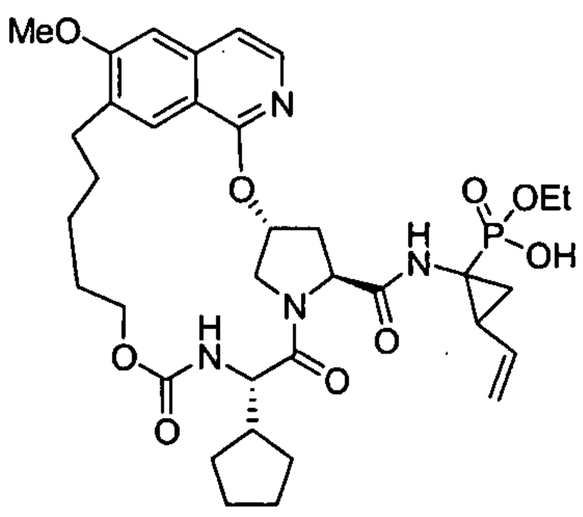
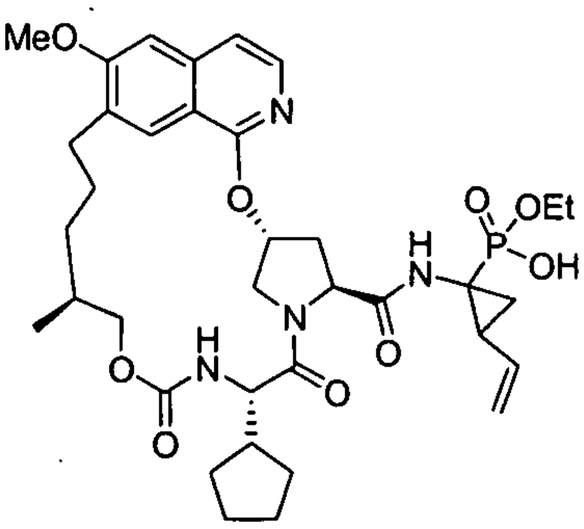




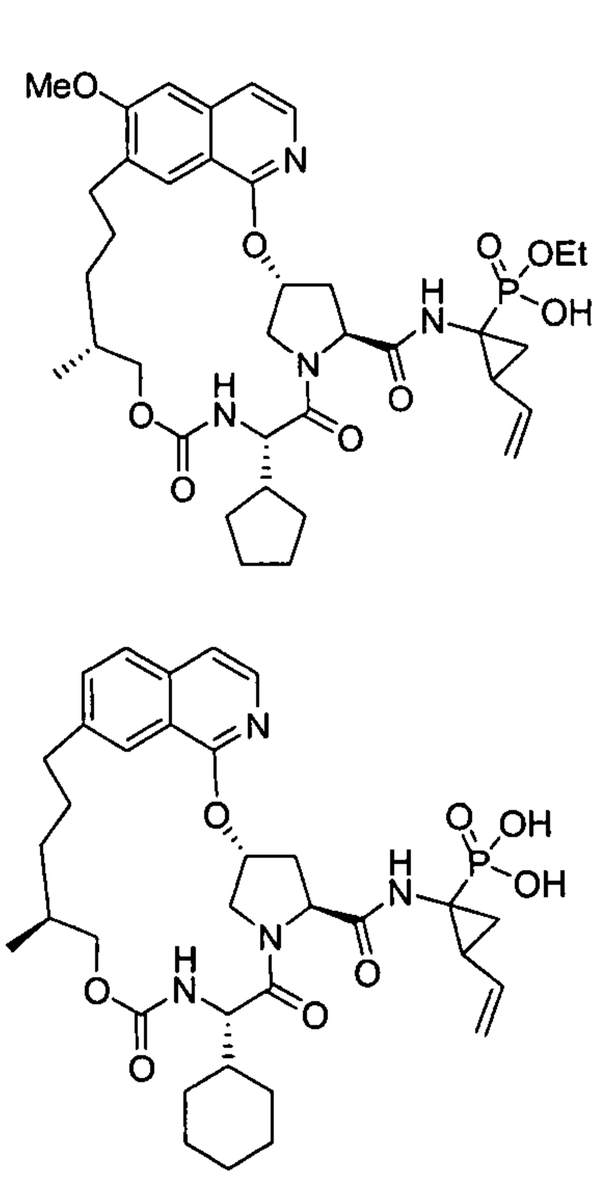
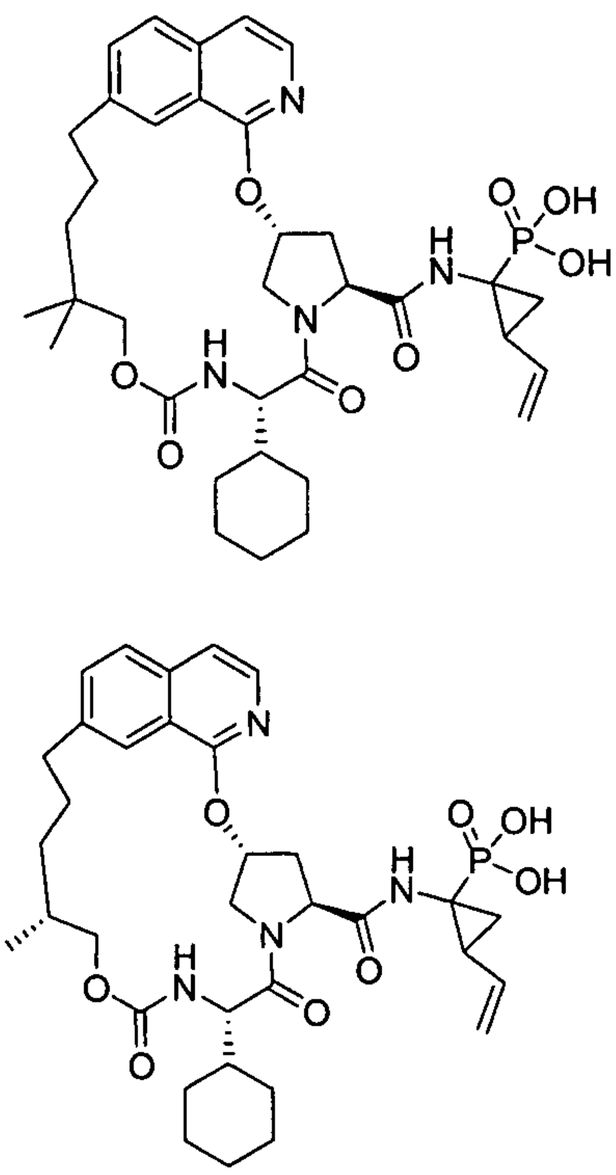
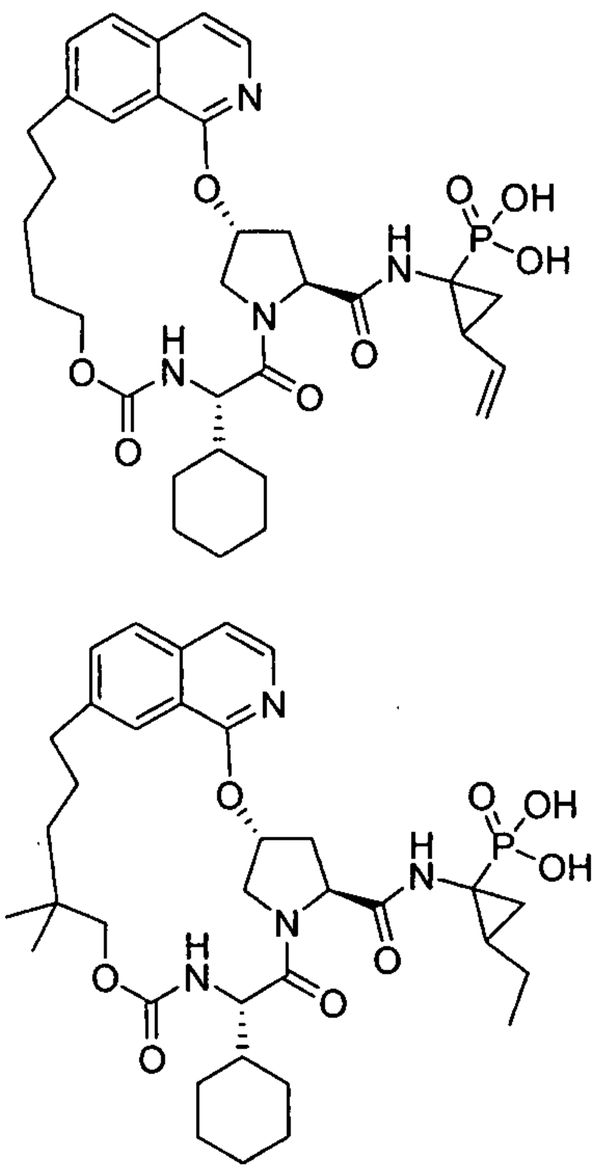


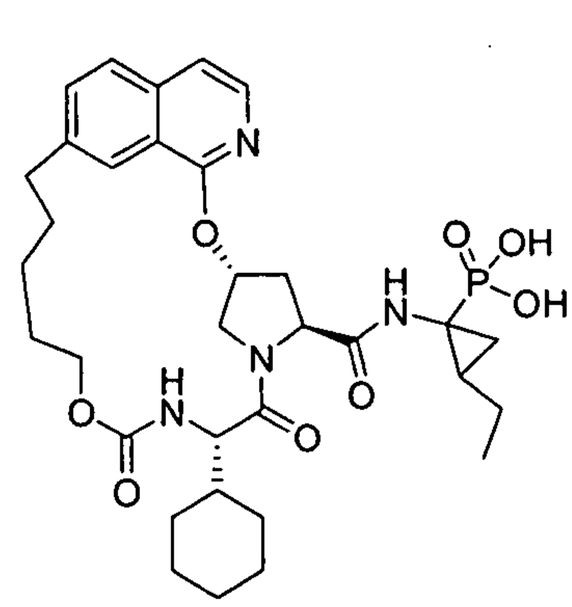
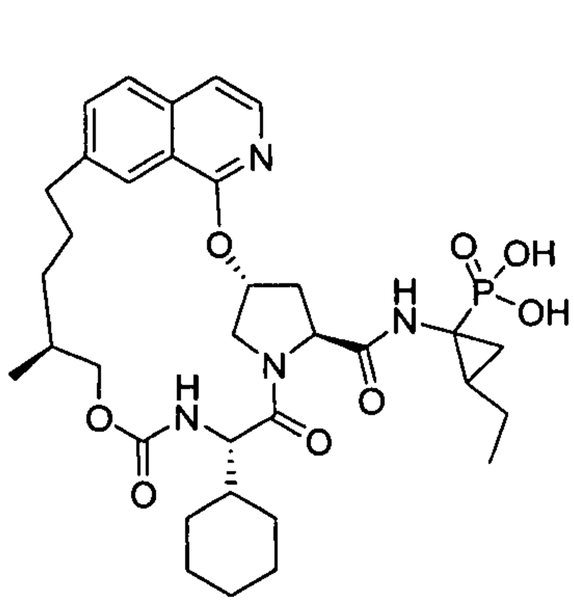
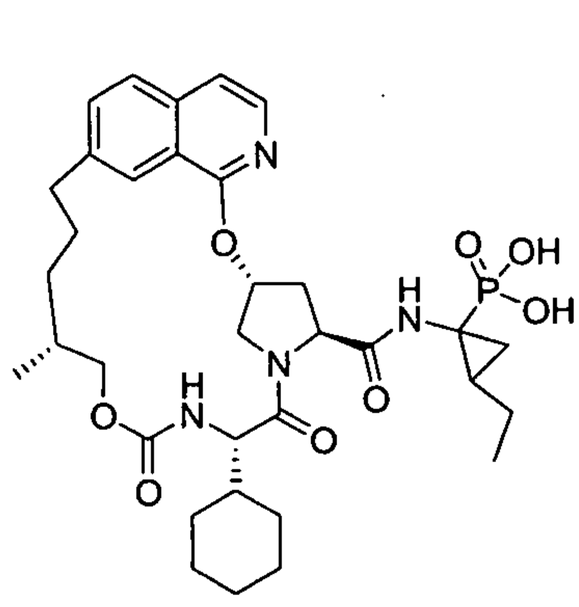
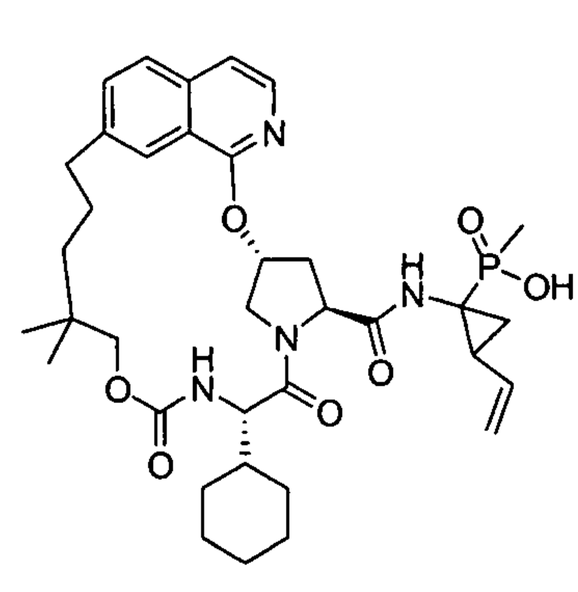
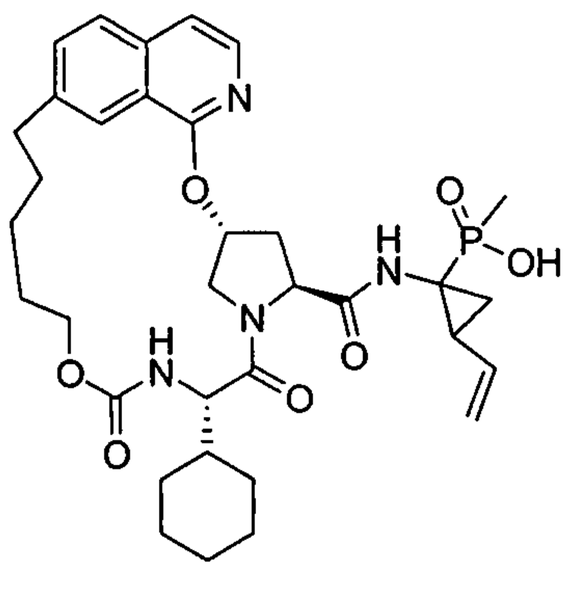
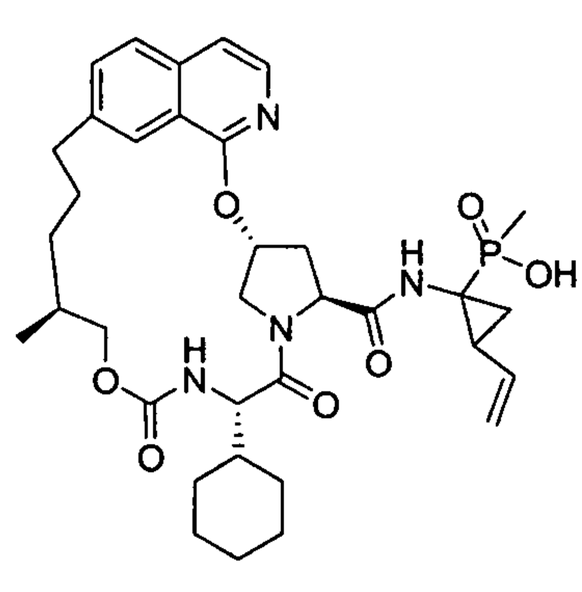


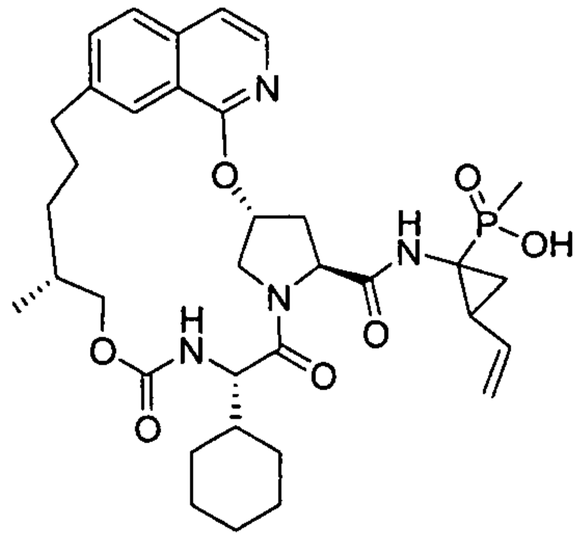
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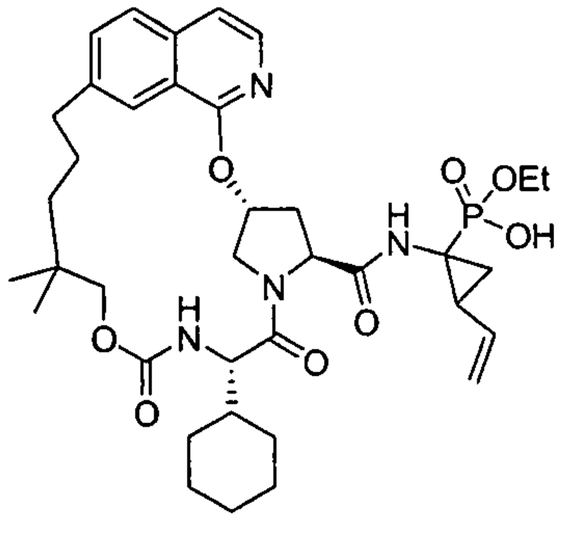
















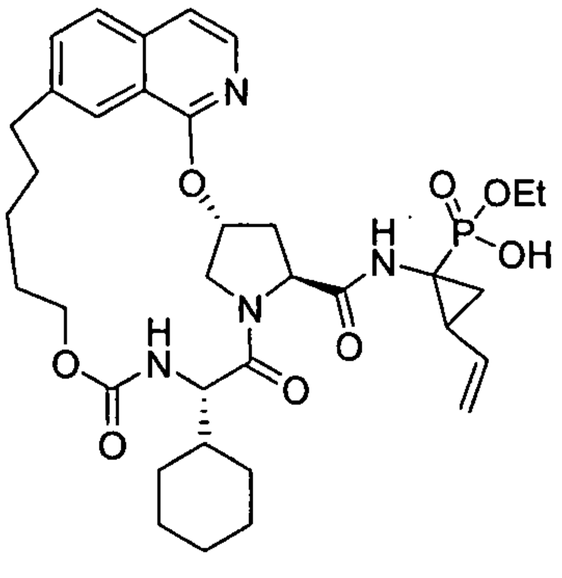
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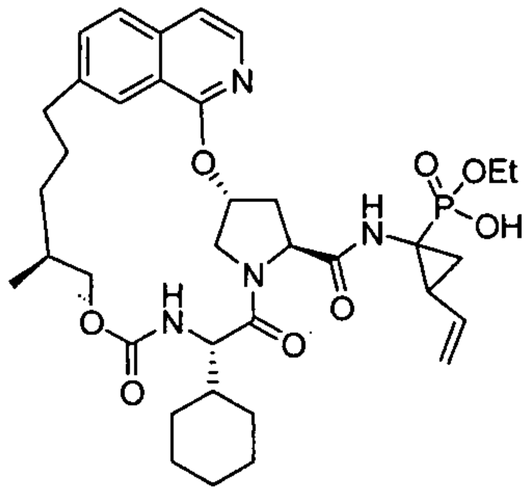




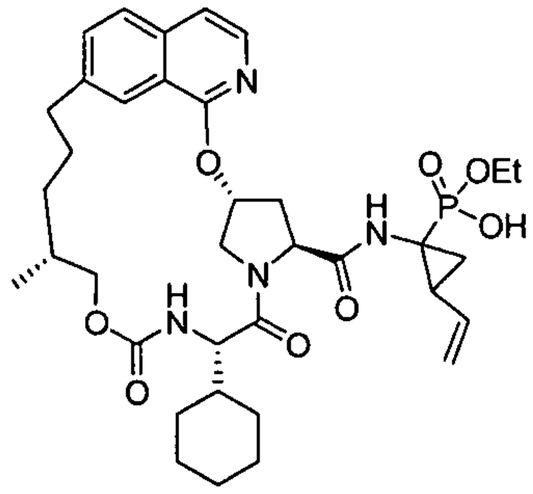







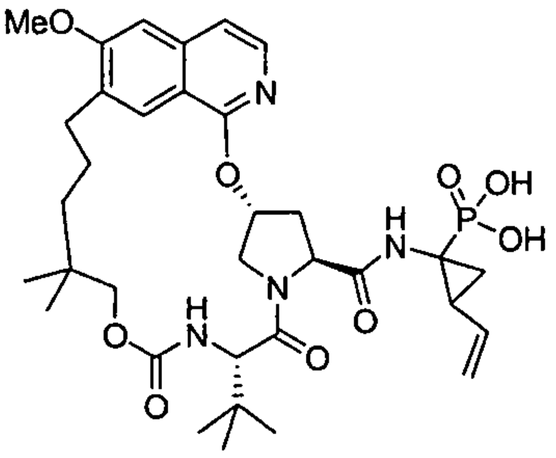


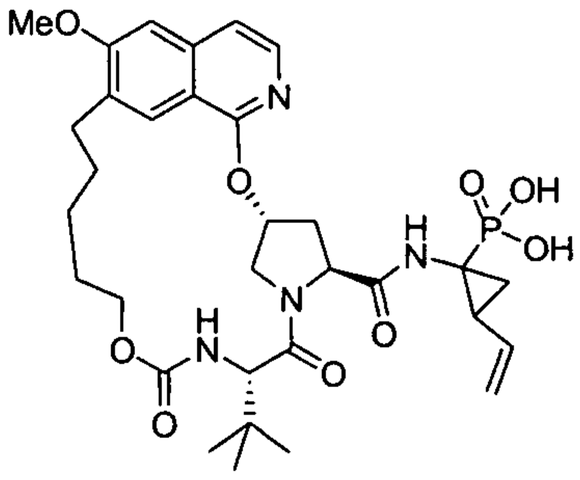


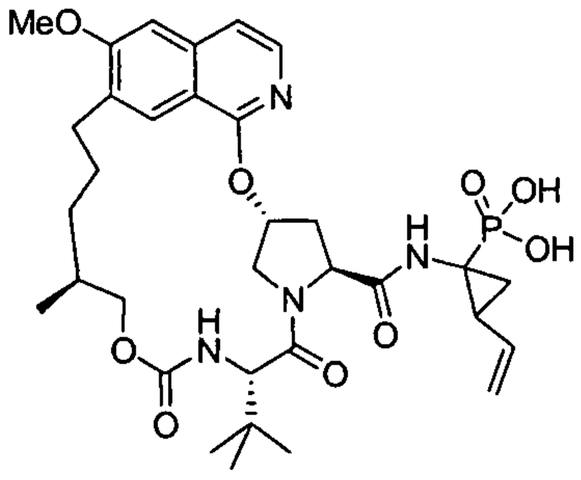


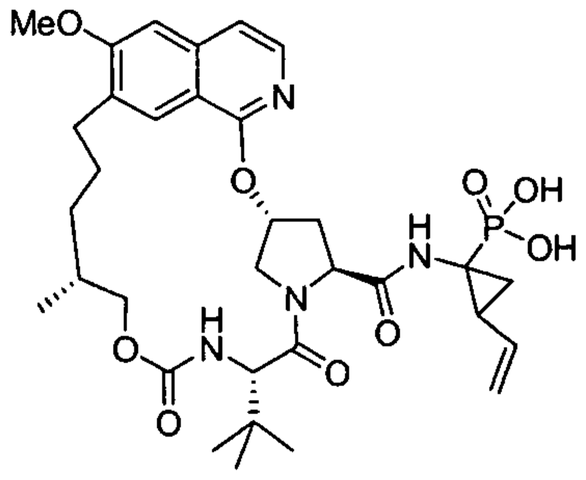


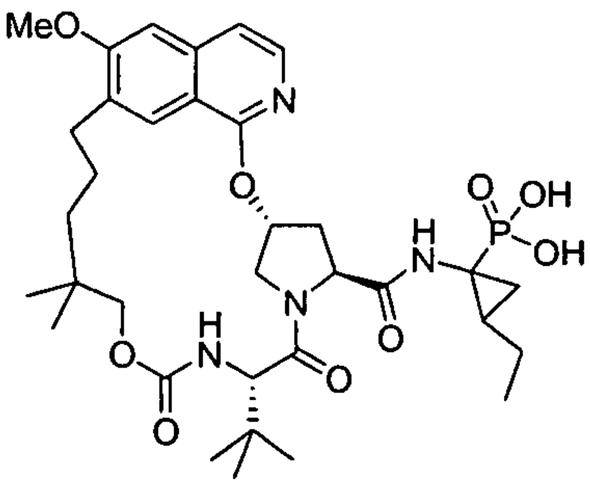


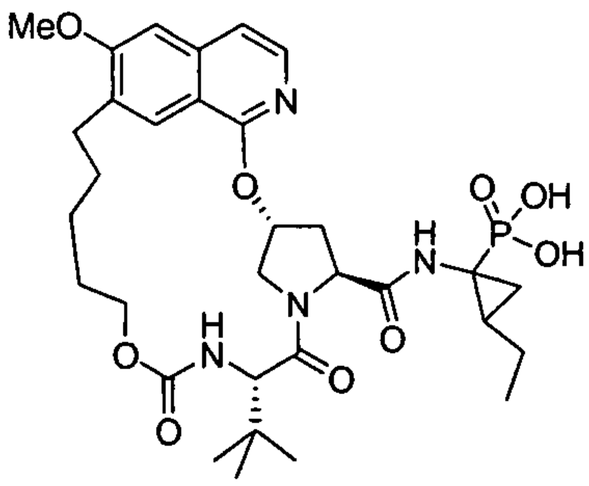


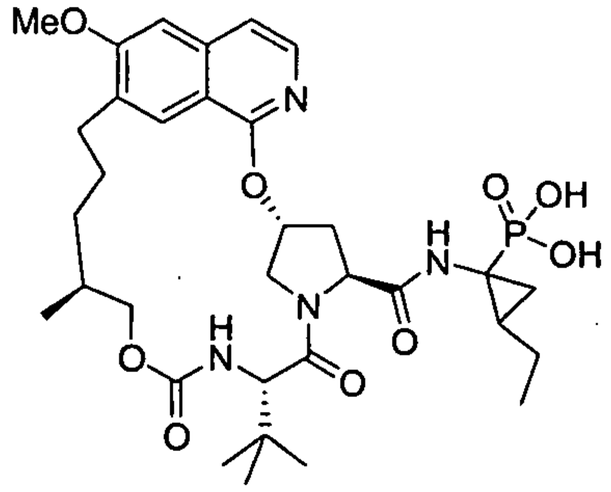


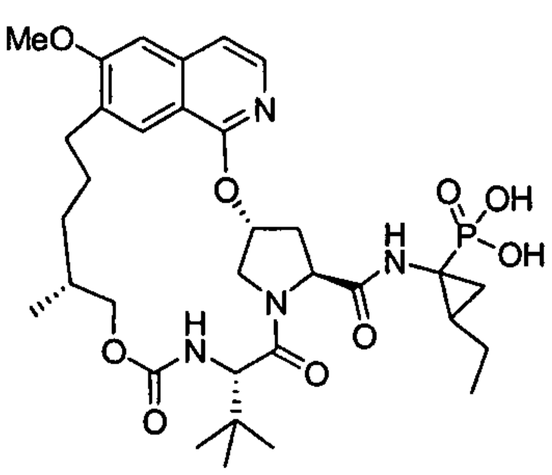


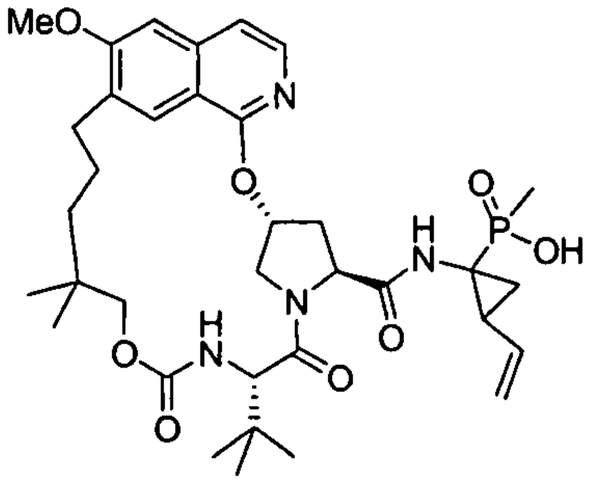


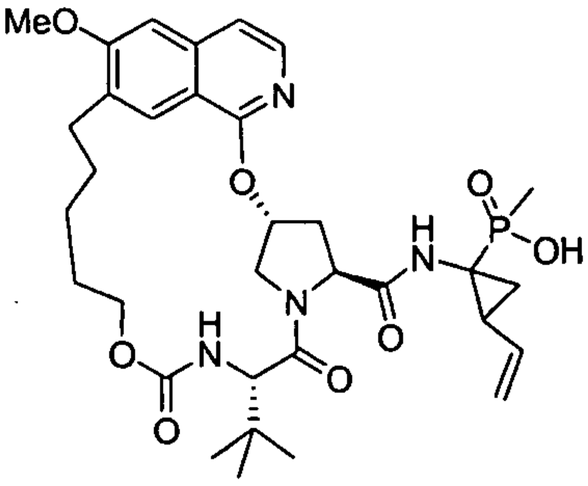




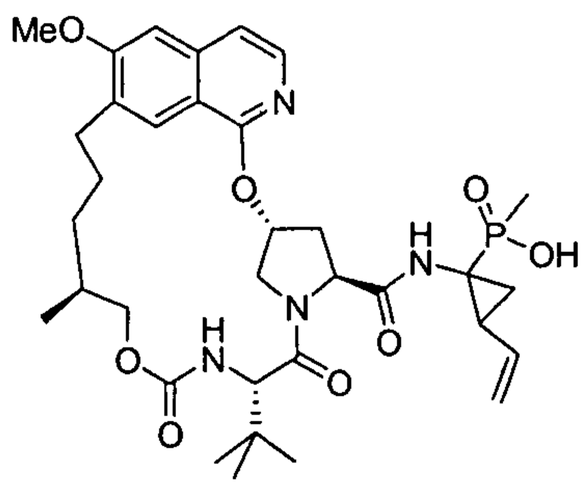
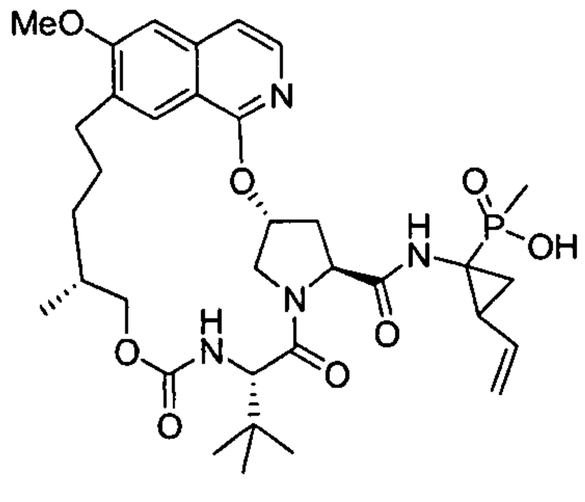
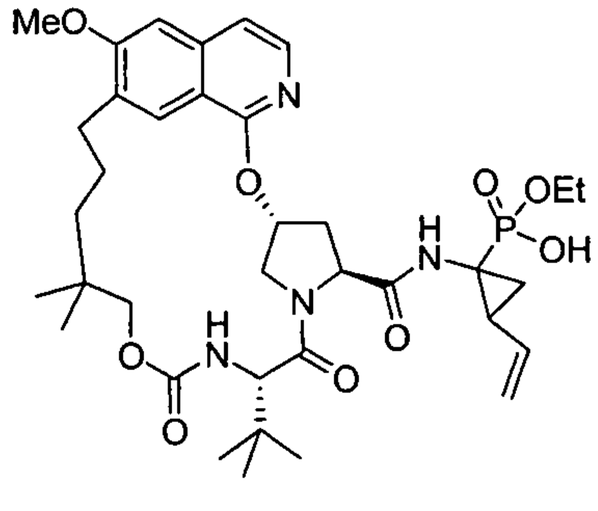
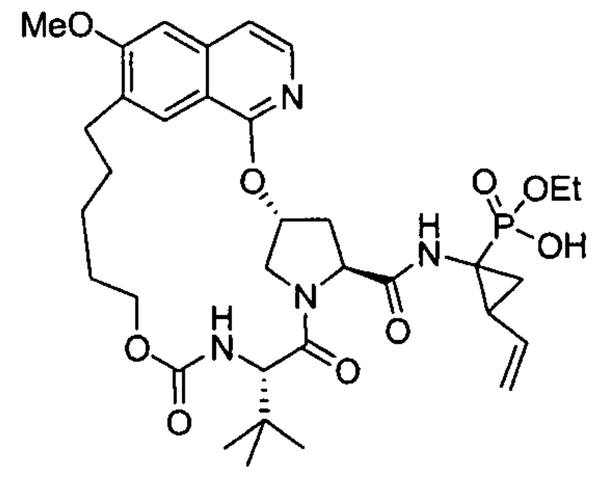
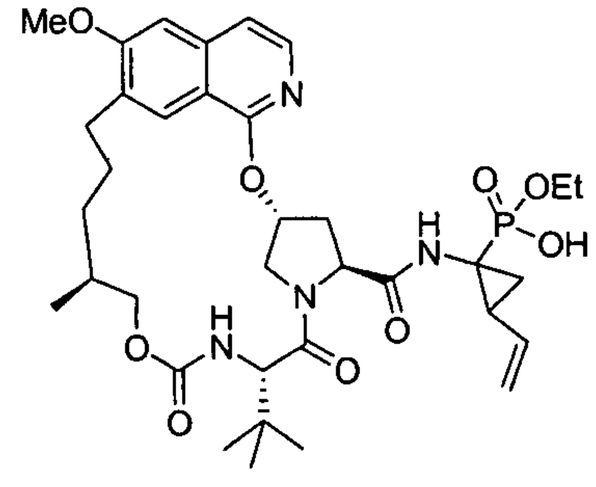
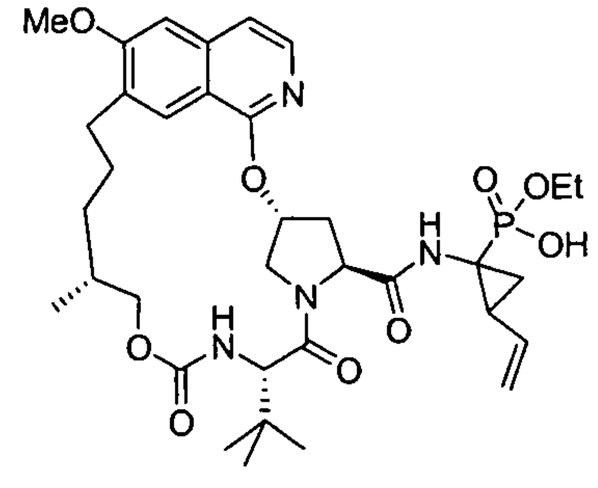






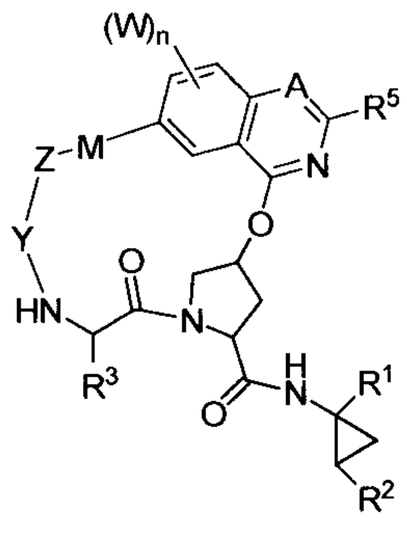


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We Claim:

1. A compound of formula (**I**):



(**I**)

or a pharmaceutically acceptable salt and/or hydrate thereof, wherein:

n is 1 or 2;

R^1 is $-CONHP(O)R^{11}R^{12}$ or $-P(O)R^{11}R^{12}$;

R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl or C_3-C_8 cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

R^3 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, or Het, wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), $-NO_2$, $-CN$, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^{10}SO_2R^6$, $-SO_2N(R^6)_2$, $-NHCOOR^6$, $-NHCOR^6$, $-NHCONHR^6$, $-CO_2R^{10}$, $-C(O)R^{10}$, and $-CON(R^{10})_2$; Het is a 5- to 6-membered saturated cyclic ring having 1, 2 or 3 heteroatoms selected from N, O and S, wherein said ring is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), $-NO_2$, $-CN$, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^{10}SO_2R^6$, $-SO_2N(R^6)_2$, $-NHCOOR^6$, $-NHCOR^6$, $-NHCONHR^6$, $-CO_2R^{10}$, $-C(O)R^{10}$, and $-CON(R^{10})_2$;

R^4 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, or aryl(C_1-C_8)alkyl; wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), $-NO_2$, $-CN$,

-CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^{10}SO_2R^6$, -$SO_2N(R^6)_2$, -$NHCOOR^6$, -$NHCOR^6$, -$NHCONHR^6$, -CO_2R^{10}, -$C(O)R^{10}$, and -$CON(R^{10})_2$;

R^5 is H, halo, -OH, C_1-C_6 alkoxy, C_1-C_6 alkyl, -CN, -CF_3, -SR^{10}, -SO_2(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, -$N(R^7)_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, -OR^{10}, -SR^{10}, -$N(R^7)_2$, -N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -$NR^{10}SO_2R^6$, -$SO_2N(R^6)_2$, -S(O)(C_1-C_6 alkyl), -$NHCOOR^6$, -$NHCOR^6$, -$NHCONHR^6$, -CO_2R^{10}, -$C(O)R^{10}$, and -$CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S;

R^6 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_5)alkyl, aryl, aryl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents or aryl is substituted by -$P(O)R^{11}R^{12}$; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

Y is -C(=O)-, -SO_2-, or -C(=N-CN)-;

Z is -$C(R^{10})_2$-, -O-, or -$N(R^4)$-;

M is C_1-C_{12} alkylene or C_2-C_{12} alkenylene or C_2-C_{12} alkynylene, wherein said alkylene or alkenylene is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), and aryl(C_1-C_8 alkyl); wherein 2 substituents on adjacent carbon atoms of M are optionally taken together to form a 3- to

6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S, or 2 substituents on the same carbon atom of M are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S;

A is $-C(R^{16})-$ or -N-;

when R^5 is other than H, R^{16} is H, C_1-C_6 alkyl, halo, $-OR^{10}$, $-SR^{10}$, or $-N(R^{10})_2$;

when R^5 is H, R^{16} is H, C_1-C_6 alkyl, halo, -OH, C_1-C_6 alkoxy, -CN, $-CF_3$, $-SR^{10}$, $-SO_2(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $-N(R^7)_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, $-OR^{10}$, $-SR^{10}$, $-N(R^7)_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, $-NO_2$, -CN, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-NR^{10}SO_2R^6$, $-SO_2N(R^6)_2$, $-S(O)(C_1$-C_6 alkyl), $-NHCOOR^6$, $-NHCOR^6$, $-NHCONHR^6$, $-CO_2R^{10}$, $-C(O)R^{10}$, and $-CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S;

or R^5 and R^{16} are optionally taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0 to 2 heteroatoms selected from N, O and S;

each R^7 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_5)alkyl, aryl, aryl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring

having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

each W is independently H, halo, $-OR^7$, C_1-C_6 alkyl, -CN, $-CF_3$, $-NO_2$, $-SR^7$, $-CO_2R^7$, $-CON(R^7)_2$, $-C(O)R^7$, $-N(R^{10})C(O)R^7$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $-N(R^7)_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), halo(C_1-C_6 alkoxy), $-NR^{10}SO_2R^7$, $-SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCONHR^7$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0 to 2 heteroatoms selected from N, O and S;

each W' is independently H, halo, $-OR^{10}$, C_1-C_6 alkyl, -CN, $-CF_3$, $-NO_2$, $-SR^{10}$, $-CO_2R^{10}$, $-CON(R^{10})_2$, $-C(O)R^{10}$, $-N(R^{10})C(O)R^{10}$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $-N(R^{10})_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), halo(C_1-C_6 alkoxy), $-NR^{10}SO_2R^{10}$, $-SO_2N(R^{10})_2$, $-NHCOOR^{10}$, $-NHCONHR^{10}$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W' moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0 to 2 heteroatoms selected from N, O and S;

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

each R^{11} is independently C_1-C_6 alkyl, $-OR^{13}$, $-N(R^{10})$-V-CO_2R^{10}, -O-V-CO_2R^{10}, -S-V-CO_2R^{10}, $-N(R^{10})(R^{13})$, R^{14}, or $-N(R^{10})SO_2R^6$;

each R^{12} is independently $-OR^{13}$, $-N(R^{10})$-V-CO_2R^{10}, -O-V-CO_2R^{10}, -S-V-CO_2R^{10}, or $-N(R^{10})(R^{13})$;

or R^{11} and R^{12} are optionally taken together, with the phosphorus atom to which they are attached, to form a 5- to 7-membered monocyclic ring;

each V is independently -CH(R^{15}) or C_1-C_4 alkylene-CH(R^{15});

each R^{13} is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, or heterocyclyl, wherein said alkyl, alkenyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 2 substituents selected from the group consisting of aryl, aryl(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, heterocyclyl(C_1-C_4 alkyl), C_1-C_6 alkyl, halo, -OC(O)OR^6, -OC(O)R^6, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -C(O)R^{10}, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^{10}SO_2R^6$, -SO_2N(R^6)$_2$, -NHCOOR^6, -NHCOR^6, -NHCONHR^6, -CO_2R^{10}, and -C(O)N(R^{10})$_2$; wherein each aryl is independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S;

R^{14} is C_1-C_6 alkyl, C_2-C_6 alkenyl, aryl or heteroaryl, wherein aryl is phenyl or naphthyl, and heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and wherein said aryl or heteroaryl is optionally substituted with 1 to 2 substituents selected from the group consisting of C_1-C_6 alkyl, halo, -OC(O)OR^6, -OC(O)R^6, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -C(O)R^{10}, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^{10}SO_2R^6$, -SO_2N(R^6)$_2$, -NHCOOR^6, -NHCOR^6, -NHCONHR^6, -CO_2R^{10}, and -C(O)N(R^{10})$_2$; and

each R^{15} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, or heterocyclyl, wherein said alkyl, alkenyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 2 substituents selected from the group consisting of C_1-C_6 alkyl, halo, -OC(O)OR^6, -OC(O)R^6, -OR^{10}, -SR^{10}, -N(R^{10})$_2$, -C(O)R^{10}, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^{10}SO_2R^6$, -SO_2N(R^6)$_2$, -NHCOOR^6, -NHCOR^6, -NHCONHR^6, -CO_2R^{10}, and -C(O)N(R^{10})$_2$; wherein each aryl is

independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms selected from N, O and S.

2. The compound of Claim 1, wherein n is 1.

3. The compound of Claim 1, wherein R^1 is $-P(O)R^{11}R^{12}$.

4. The compound of Claim 3, wherein R^{11} is independently C_1-C_6 alkyl, or $-OR^{13}$, and R^{12} is independently $-OR^{13}$.

5. The compound of Claim 4, wherein R^{13} is H or C_1-C_6 alkyl.

6. The compound of Claim 4, wherein R^{11} is selected from the group consisting of $-OCH_2CH_3$, $-CH_3$, and -OH, and R^{12} is -OH.

7. The compound of Claim 1, wherein R^2 is C_1-C_6 alkyl or C_2-C_6 alkenyl.

8. The compound of Claim 7, wherein R^2 is $-CH=CH_2$ or $-CH_2CH_3$.

9. The compound of Claim 1, wherein R^3 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl.

10. The compound of Claim 9, wherein R^3 is $-C(CH_3)_3$, cyclohexyl or cyclopentyl.

11. The compound of Claim 1, wherein R^5 is H, Z is -O-, and Y is -C(=O)-.

12. The compound of Claim 1, wherein W is H or -O-C_1-C_6 alkyl.

13. The compound of Claim 12, wherein W is H or -OCH_3.

14. The compound of Claim 1, wherein A is -$C(R^{16})$-.

15. The compound of Claim 14, wherein R^{16} is H.

16. The compound of Claim 1, wherein M is C_1-C_{12} alkylene wherein said alkylene is optionally substituted with 1 or 2 substituents selected from the group consisting of C_1-C_8 alkyl.

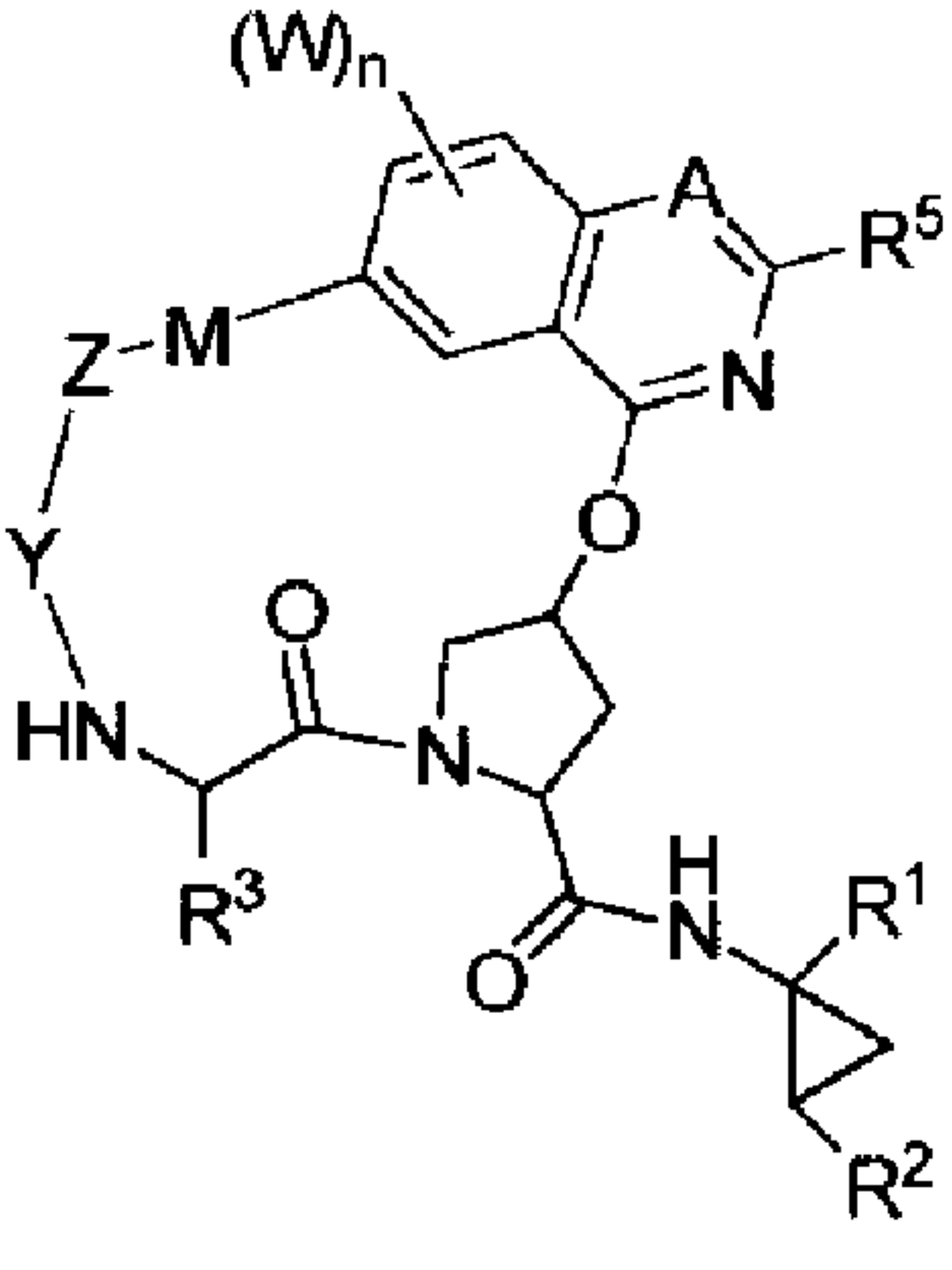
17. The compound of Claim 16, wherein M is selected from the group consisting of -$(CH_2)_5$-, -$(CH_2)_3CH(CH_3)CH_2$-, and -$(CH_2)_3C(CH_3)_2CH_2$-.

18. A pharmaceutical composition comprising a compound of Claim 1, and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition of Claim 18, further comprising a second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

20. The use of a compound of Claim 1 in the preparation of a medicament for preventing or treating infection by HCV in a subject in need thereof.

21. The use of a compound of Claim 1 for preventing or treating infection by HCV in a subject in need thereof.



(I)