TITLE OF THE INVENTION

MACROCYCLIC PEPTIDES AS HCV NS3 PROTEASE INHIBITORS

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

BACKGROUND OF THE INVENTION

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

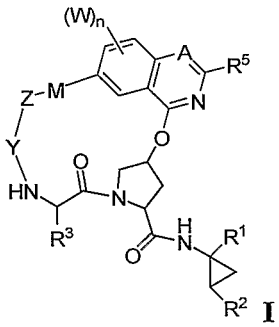
Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved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

Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3), a helicase (NS3), and an RNA-dependent

RNA polymerase (NS5B). The NS3 protease is located in the N-terminal domain of the NS3 protein, and is considered a prime drug target since it is responsible for an intramolecular cleavage at the NS3/4A site and for downstream intermolecular processing at the NS4A/4B, NS4B/5A and NS5A/5B junctions. Previous research has identified classes of peptides, such as hexapeptides as well as tripeptides discussed in U.S. patent applications US2005/0020503, US2004/0229818, and US2004/00229776, showing degrees of activity in inhibiting the NS3 protease. The aim of the present invention is to provide further compounds which exhibit activity against the HCV NS3 protease.

SUMMARY 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**) and/or a pharmaceutically acceptable salt and/or hydrate thereof:



I

wherein:

n is 1 or 2;

R^1 is CO_2R^{10}, $CONR^{10}SO_2R^6$, $CONR^{10}SO_2NR^8R^9$, or tetrazolyl;

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}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ 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 5-6 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}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ 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, $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_8$)alkyl, or aryl($C_1\text{-}C_8$)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}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ 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, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkyl, CN, CF_3, SR^{10}, $SO_2(C_1\text{-}C_6$ alkyl), $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkoxy, $C_1\text{-}C_6$ 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}, $N(R^7)_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), $C_3\text{-}C_6$ cycloalkyl, $C_3\text{-}C_6$ cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1\text{-}C_6$ 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

R^6 is $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_5$)alkyl, aryl, aryl($C_1\text{-}C_4$)alkyl, heteroaryl, heteroaryl($C_1\text{-}C_4$ alkyl), heterocyclyl, or heterocyclyl($C_1\text{-}C_8$ 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;

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

A is $C(R^{11})$ or N;

when R^5 is other than H, R^{11} is H, C_1-C_6 alkyl, halo, OR^{10}, SR^{10}, or $N(R^{10})_2$;

when R^5 is H, R^{11} 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^5 and R^{11} are optionally taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 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 0-2 heteroatoms selected from N, O and S;

each W' is independently 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 0-2 heteroatoms selected from N, O and S;

R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halo, OR^{10},

SR^{10}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl$)O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C(O)R^{10}$, $C_1\text{-}C_6$ haloalkyl, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

R^9 is $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkyl$(C_1\text{-}C_8$ alkyl), $C_1\text{-}C_8$ alkoxy, $C_3\text{-}C_8$ cycloalkoxy, aryl, aryl$(C_1\text{-}C_4$ alkyl), heteroaryl, heterocyclyl, heteroaryl$(C_1\text{-}C_4$ alkyl), or heterocyclyl$(C_1\text{-}C_8$ alkyl), wherein said alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, $C_3\text{-}C_8$ cycloalkyl, heteroaryl, heterocyclyl, $C_1\text{-}C_6$ alkyl, halo$(C_1\text{-}C_6$ alkoxy), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl$)O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C(O)R^{10}$, $C_1\text{-}C_6$ haloalkyl, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-8 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and

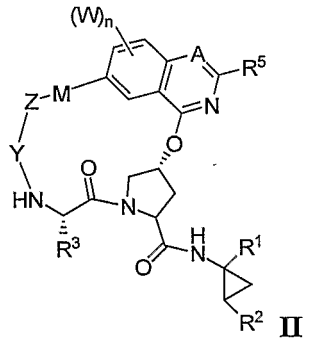
each R^{10} is independently H or $C_1\text{-}C_6$ alkyl.

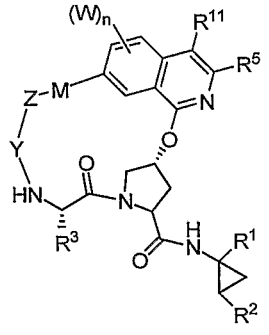
The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating or preventing one or more symptoms of HCV infection.

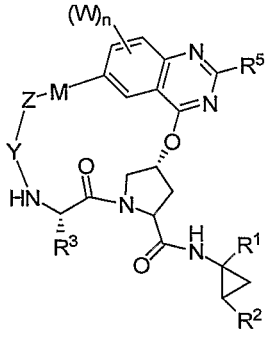
Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

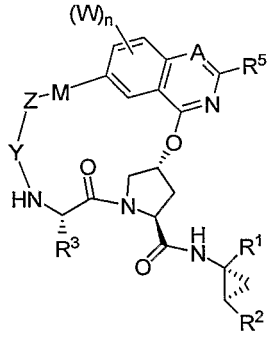
DETAILED DESCRIPTION OF THE INVENTION

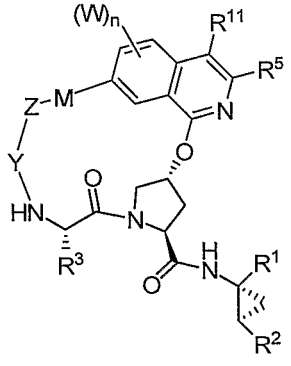
The present invention includes compounds of formula **I** above, and pharmaceutically acceptable salts and/or hydrates thereof. These compounds and their pharmaceutically acceptable salts and/or hydrates are HCV protease inhibitors (e.g., HCV NS3 protease inhibitors). The present invention also includes 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**.

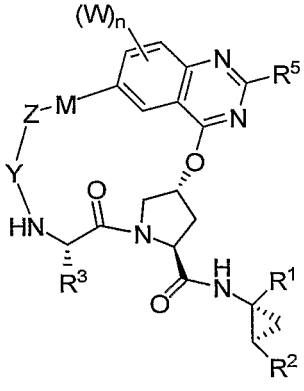

II


II-A


II-B


III


III-A


III-B

A first embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is CO_2R^{10} or $CONR^{10}SO_2R^6$, and all other variables are as originally defined (i.e., as defined in the Summary of the Invention). In a first aspect of the first embodiment, R^1 is $CONR^{10}SO_2R^6$; and all other variables are as defined in the first embodiment. In a feature of the first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is C_3-C_8 cycloalkyl, C_1-C_8 alkyl, aryl, aryl(C_1-C_4)alkyl, wherein said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 2 W' substituents; and all other variables are as defined in the first embodiment. In a second feature of the first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is cyclopropyl; and all other variables are as defined in the first embodiment. In a third feature of the first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is phenyl; and all other variables are as defined in the first embodiment. In a fourth feature of the first aspect of the first

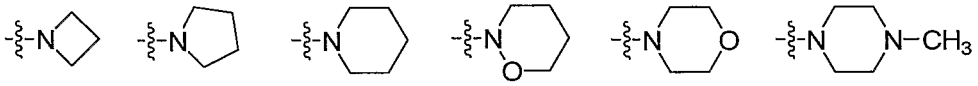
embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is benzyl; and all other variables are as defined in the first embodiment. In a fifth feature of the first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or t-butyl; and all other variables are as defined in the first embodiment. In a second aspect of the first embodiment, R^1 is CO_2R^{10}; and all other variables are as defined in the first embodiment. In a feature of the second aspect of the first embodiment, R^{10} is CO_2H; and all other variables are as defined in the first embodiment.

A second embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is $CONHSO_2NR^8R^9$; and all other variables are as originally defined. In a first aspect of the second embodiment, R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, or heteroaryl(C_1-C_4 alkyl); and R^9 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, aryl, aryl(C_1-C_4 alkyl), heteroaryl, or heteroaryl(C_1-C_4 alkyl), wherein said alkyl, cycloalkyl, alkoxy, aryl, or heteroaryl in both R^8 and R^9 is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, heteroaryl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), 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, $C(O)R^{10}$, C_1-C_6 haloalkyl, 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 and 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 wherein the 2 adjacent substituents of said cycloalkyl, aryl, or heteroaryl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S; or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-8 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and all other variables are as defined in the second embodiment.

In a second aspect of the second embodiment, R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, or heteroaryl(C_1-C_4 alkyl); and R^9 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, aryl, aryl(C_1-C_4 alkyl), heteroaryl, or heteroaryl(C_1-C_4 alkyl), wherein said alkyl, cycloalkyl, alkoxy, aryl, or heteroaryl in both R^8 and R^9 is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), 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, $C(O)R^{10}$, C_1-C_6 haloalkyl, 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 and 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 wherein the 2 adjacent substituents of said cycloalkyl, aryl, or heteroaryl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S; or R^8 and R^9 are optionally

taken together, with the nitrogen atom to which they are attached, to form a 4-6 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and all other variables are as defined in the second embodiment.

In a first feature of the second aspect of the second embodiment, R^8 is C_1-C_3 alkyl, wherein said alkyl 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, $C(O)R^{10}$, C_1-C_6 haloalkyl, 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 R^9 is C_1-C_3 alkyl, C_1-C_3 alkoxy, phenyl, or $-(CH_2)_{1\text{-}2}$-phenyl, wherein said alkyl or alkoxy 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, $C(O)R^{10}$, C_1-C_6 haloalkyl, 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 $C(O)N(R^{10})_2$; or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-6 membered monocyclic saturated ring containing 0-1 additional heteroatoms selected from N and O; and all other variables are as defined in the second embodiment. In a second feature of the second aspect of the second embodiment, R^8 is methyl; and all other variables are as defined in the second embodiment. In a third feature of the second aspect of the second embodiment, R^9 is methyl, methoxy, ethyl, i-propyl, phenyl, or benzyl; and all other variables are as defined in the second embodiment. In a fourth feature of the second aspect of the second embodiment, R^8 and R^9 are taken together to form a heteocyclic ring selected from the following:



; and all other variables are as defined in the second embodiment. In a fifth feature of the second aspect of the second embodiment, R^8 is methyl and R^9 is methoxy; and all other variables are as defined in the second embodiment.

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

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

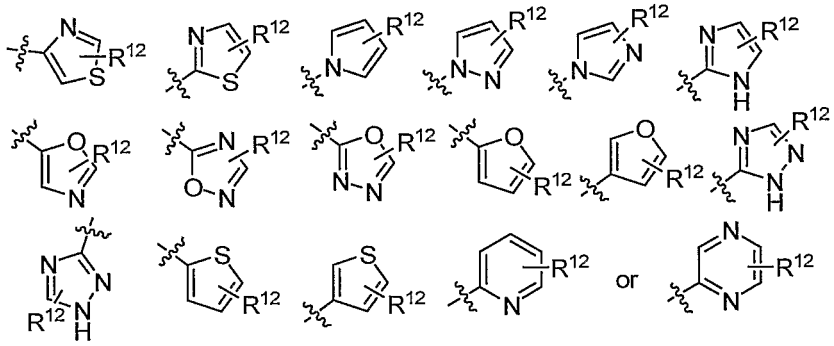
A fourth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^3 is C_3-C_8 cycloalkyl, Het, or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the fourth embodiment, R^3 is C_5-C_7 cycloalkyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the fourth embodiment, R^3 is C_5-C_6 cycloalkyl or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the fourth embodiment, R^3 is propyl or butyl; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a feature of the third aspect of the fourth embodiment, R^3 is i-propyl, n-butyl, i-butyl or t-butyl; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the fourth embodiment, R^3 is cyclopentyl or cyclohexyl; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a fifth aspect of the fourth embodiment, R^3 is CH_2CF_3 or CH_2CHF_2; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments.

A fifth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is H or halo; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the fifth embodiment, R^5 is H, F, or Cl; and all other variables are defined in the fifth embodiment or as defined in any one of the preceding embodiments. In another aspect of the fifth embodiment, R^5 is H; and all other variables are defined in the fifth embodiment or as defined in any one of the preceding embodiments.

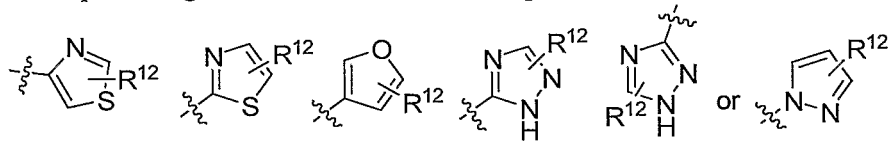
A sixth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is aryl or heteroaryl; wherein aryl is phenyl or naphthyl and heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl or heteroaryl 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), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$,

$S(O)(C_1\text{-}C_6$ alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

In a first aspect of the sixth embodiment, R^5 is aryl wherein aryl is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), $C_3\text{-}C_6$ cycloalkyl, $C_3\text{-}C_6$ cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1\text{-}C_6$ alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; and all other variables are as defined in the sixth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the sixth embodiment, R^5 is



; wherein R^{12} is H, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, $N(R^7)_2$, $NHCOR^{13}$, $NHCONHR^{13}$ or $NHCOOR^{13}$ and each R^{13} is independently $C_1\text{-}C_6$ alkyl or $C_3\text{-}C_6$ cycloalkyl; and all other variables are as defined in the sixth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the sixth embodiment, R^5 is



; wherein R^{12} is H, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, $N(R^7)_2$, $NHCOR^{13}$, $NHCONHR^{13}$ or $NHCOOR^{13}$ and each R^{13} is independently $C_1\text{-}C_6$ alkyl or $C_3\text{-}C_6$ cycloalkyl; and all other variables are as defined in the sixth embodiment or as defined in any one of the preceding embodiments.

In a fourth aspect of the sixth embodiment, R^5 is unsubstituted phenyl; and all other variables are as defined in the sixth embodiment or as defined in any one of the preceding embodiments.

A seventh embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is $C_1\text{-}C_6$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C_1\text{-}C_6$ haloalkyl, or heterocyclyl wherein 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 heterocyclyl, cycloalkyl, or alkyl is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), $C_3\text{-}C_6$ cycloalkyl, $C_3\text{-}C_6$ cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1\text{-}C_6$ 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 or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the seventh embodiment, R^5 is C_1-C_6 alkyl; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a feature of the first aspect of the seventh embodiment, R^5 is methyl; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a second aspect of the seventh embodiment, R^5 is heterocyclyl wherein 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 heterocyclyl, cycloalkyl, or alkyl 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 heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a feature of the second aspect of the seventh embodiment, R^5 is N-morpholinyl; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a third aspect of the seventh embodiment, R^5 is C_1-C_6 haloalkyl; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a feature of the third aspect of the seventh embodiment, R^5 is CF_3; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments.

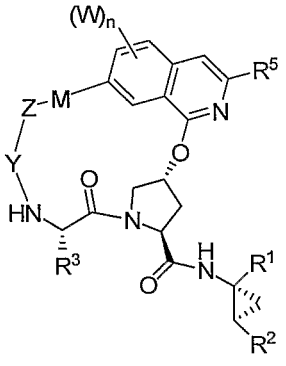
An eighth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is $N(R^7)_2$; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the eighth embodiment, R^5 is $N(R^7)_2$ wherein R^7 is H or C_1-C_6 alkyl; and all other variables are as defined in the eighth embodiment or as defined in any one of the preceding embodiments.

A ninth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **III**, or **III-A**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{11} is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy or halo; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the ninth embodiment, R^{11} is C_1-C_6 alkoxy; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a feature of the first aspect of the ninth embodiment, R^{11} is methoxy; and all other variables are as

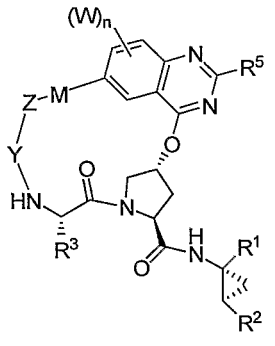
defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the ninth embodiment, R^{11} is C_1-C_6 alkyl; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a feature of the second aspect of the ninth embodiment, R^{11} is methyl; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the ninth embodiment, R^{11} is halo or hydroxy; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a feature of the third aspect of the ninth embodiment, R^{11} is OH, Cl, or Br; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the ninth embodiment, R^{11} is H; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments.

A tenth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **III**, or **III-A**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 and R^{11} are taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 1-2 oxygen atoms; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An eleventh embodiment of the present invention is a compound of formula **IV-A** or **IV-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is H, halo, aryl, heteroaryl, or $N(R^7)_2$; R^1 is CO_2R^{10} or $CONHSO_2R^6$ wherein R^6 is C_3-C_6 cycloalkyl, C_1-C_6 alkyl, phenyl or benzyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.



IV-A



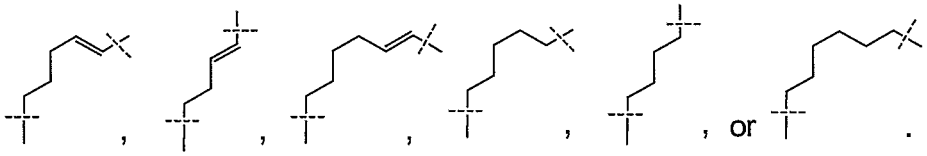
IV-B

A twelfth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein Y is C=O or SO_2; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the twelfth embodiment, Y is C=O; and all other variables are as defined in the twelfth embodiment or as defined in any one of the preceding embodiments.

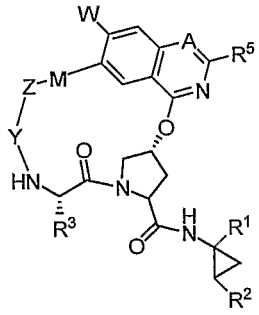
A thirteenth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is O, NH,

$N(C_1\text{-}C_8$ alkyl) or $C(R^{10})_2$; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the thirteenth embodiment, Z is O, NH, $N(CH_3)$, or CH_2; and all other variables are as defined in the thirteenth embodiment or as defined in any one of the preceding embodiments.

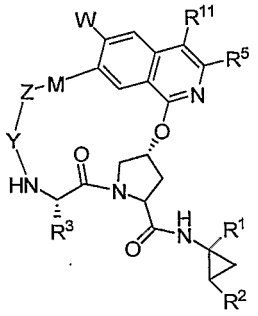
A fourteenth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein M is $C_1\text{-}C_8$ alkylene or $C_2\text{-}C_8$ alkenylene, wherein said alkylene or alkenylene is optionally substituted with 1 or 2 substituents selected from $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_8$ alkyl), or aryl($C_1\text{-}C_8$ alkyl); and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the fourteenth embodiment, M is unsubstituted $C_1\text{-}C_8$ alkylene or unsubstituted $C_2\text{-}C_8$ alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the fourteenth embodiment, M is unsubstituted C_4 alkylene or unsubstituted C_4 alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the fourteenth embodiment, M is unsubstituted C_5 alkylene or unsubstituted C_5 alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the fourteenth embodiment, M is unsubstituted C_6 alkylene or unsubstituted C_6 alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a fifth aspect of the fourteenth embodiment, M is unsubstituted C_7 alkylene or unsubstituted C_7 alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a feature of the first aspect of the fourteenth embodiment, M is:



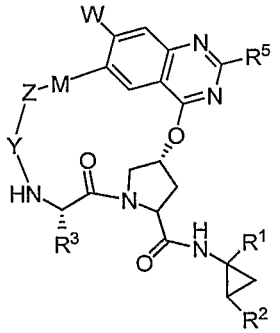
A fifteenth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein n is 1; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the fifteenth embodiment, W is ortho to the variable M as depicted in formulae **Ia**, **IIa**, **II-Aa**, **II-Ba**, **IIIa**, **III-Aa**, **III-Ba**, **IV-Aa** and **IV-Ba**.



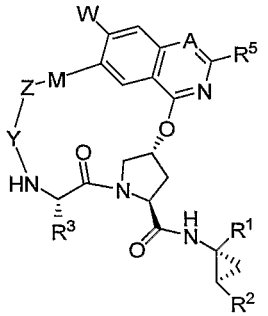
IIa



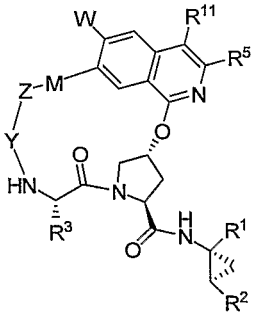
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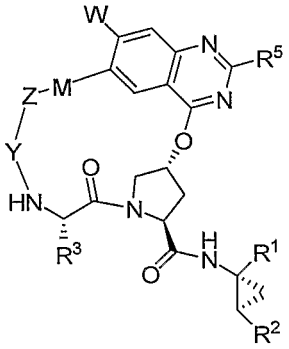
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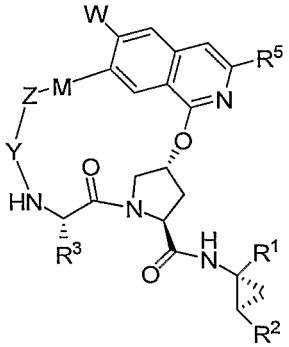
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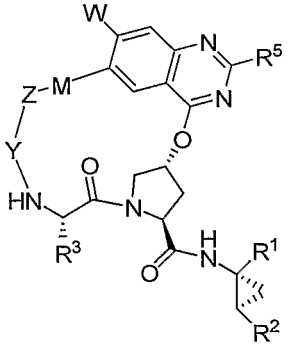
III-Aa



III-Ba



IV-Aa

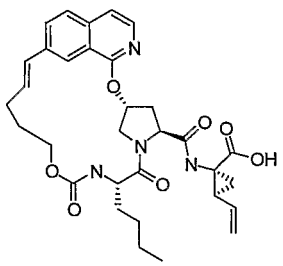


IV-Ba

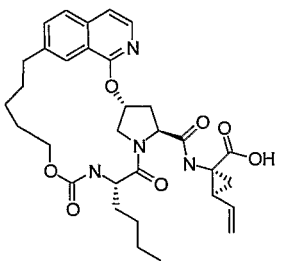
A sixteenth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein n is 2; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the sixteenth embodiment, the 2 adjacent W moieties are taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S. In another aspect of the sixteenth embodiment, the 2 adjacent W moieties are taken together to form a 5-membered saturated cyclic ring having 0-2 heteroatoms selected from N, O and S.

A seventeenth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein W is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, OH, halo, halo(C_1-C_6 alkoxy), $C(O)N(R^7)_2$, $C(O)R^7$, $N(R^7)_2$,or heterocyclyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the seventeenth embodiment, W is H; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the seventeenth embodiment, W is C_1-C_6 alkoxy; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a feature of the second aspect of the seventeenth embodiment, W is methoxy; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the seventeenth embodiment, W is C_1-C_6 alkyl, halo, OH, or $N(R^7)_2$ wherein R^7 is H or C_1-C_6 alkyl; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a feature of the third aspect of the seventeenth embodiment, W is methyl; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the seventeenth embodiment, W is halo(C_1-C_6 alkoxy); and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a feature of the fifth aspect of the seventeenth embodiment, W is OCF_3, $OCHF_2$, $OC(CH_3)_3$, or $OCH(CH_3)_2$; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a sixth aspect of the seventeenth embodiment, W is $C(O)N(R^7)_2$, $C(O)R^7$, or heterocyclyl; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a feature of the sixth aspect of the seventeenth embodiment, W is $C(O)N(R^7)_2$ wherein R^7 is H or C_1-C_6 alkyl; $C(O)R^7$ wherein R^7 is a 5-membered heteroaryl having 1 heteroatom O or S; or heterocyclyl wherein heterocyclyl is a 6-membered saturated ring having 1 or 2 heteroatoms selected from N, O and S; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments.

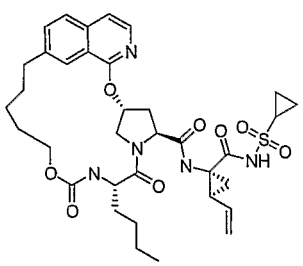
An eighteenth embodiment of the present invention is a compound, or a pharmaceutically acceptable salt or hydrate thereof, selected from the group consisting of the compounds **III-1** to **III-38**.



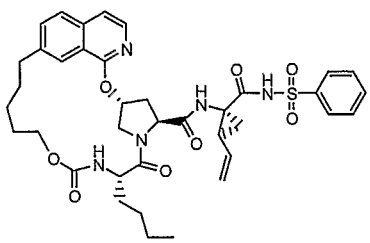
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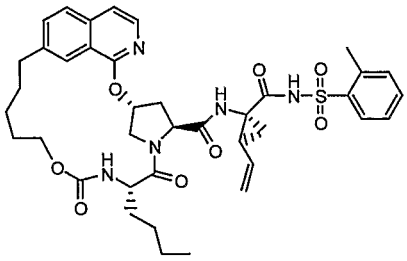
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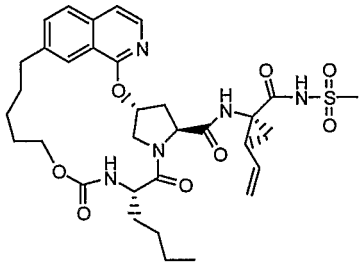
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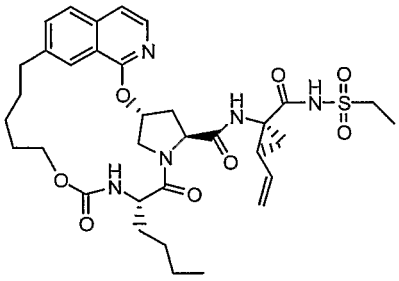
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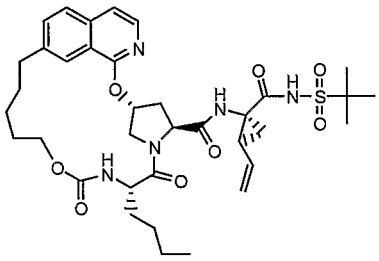
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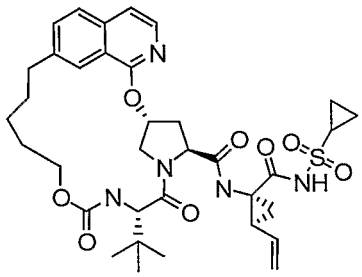
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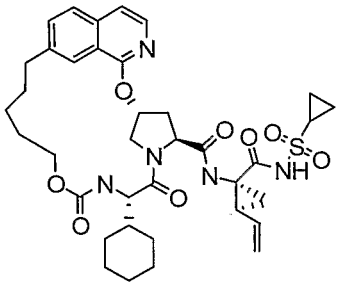
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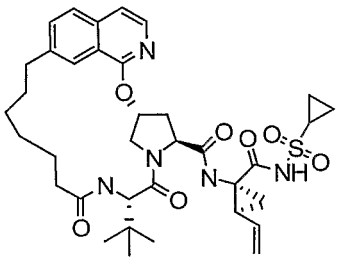
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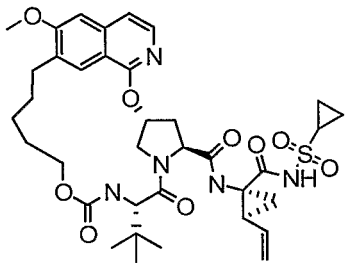
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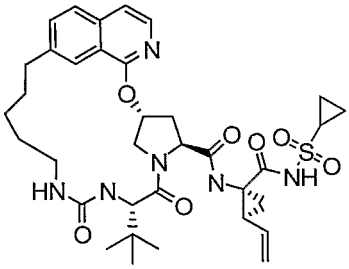
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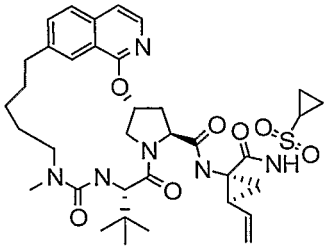
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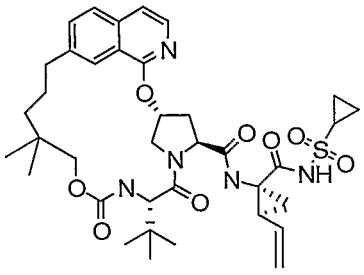
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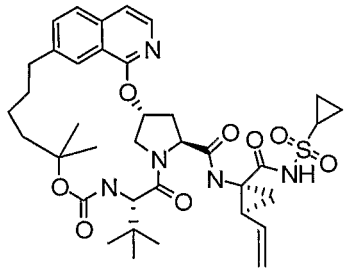
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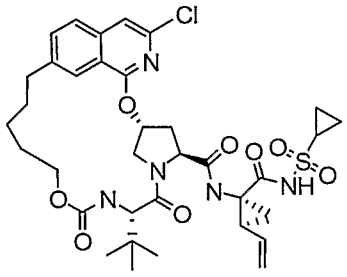
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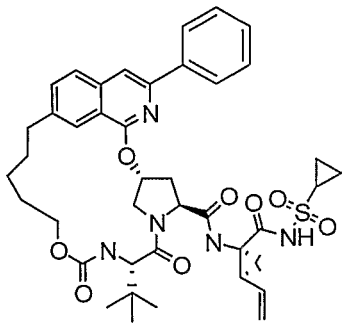
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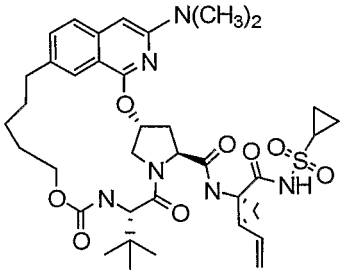
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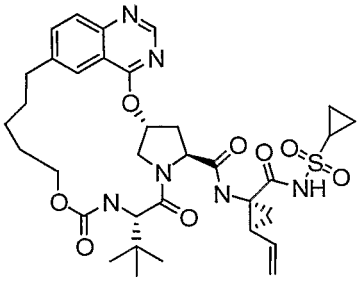
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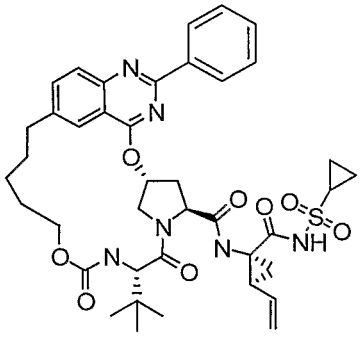
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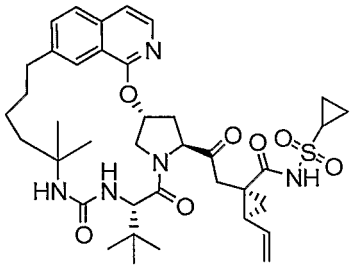
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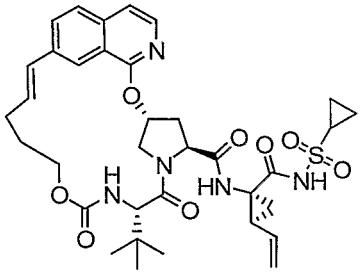
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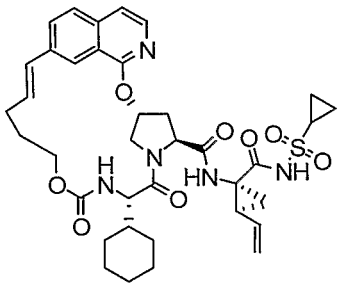
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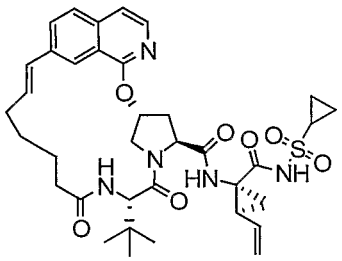
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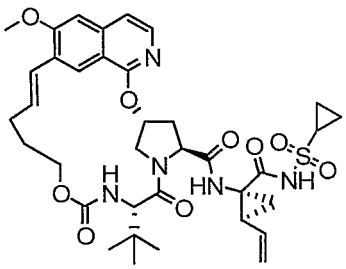
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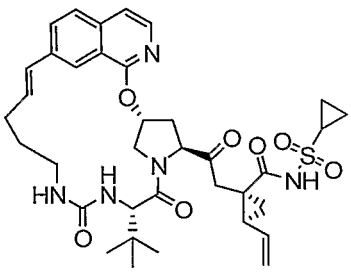
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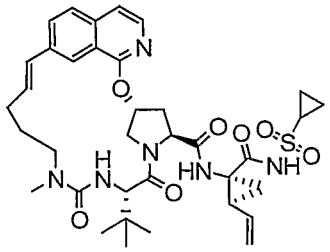
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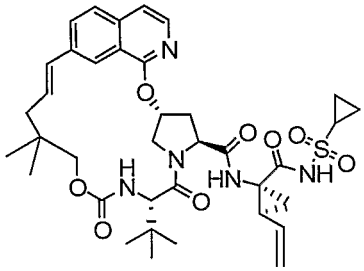
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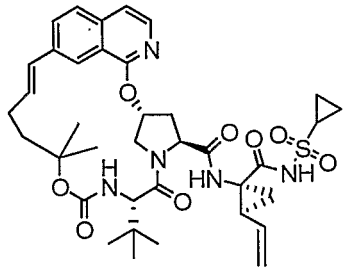
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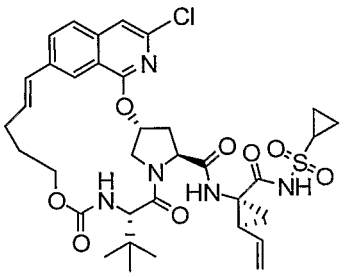
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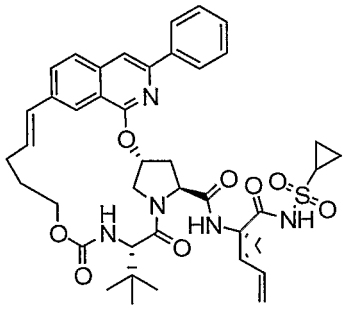
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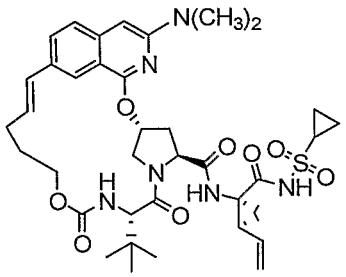
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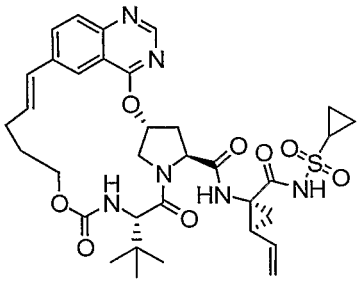
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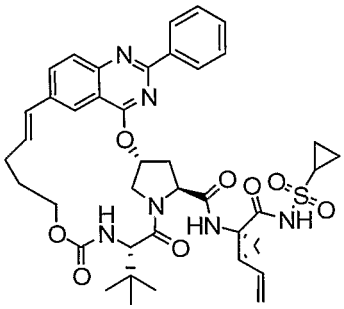
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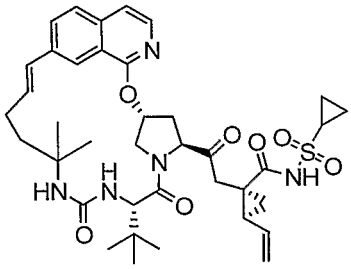
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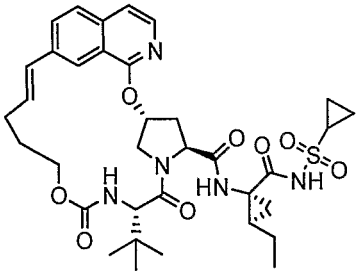
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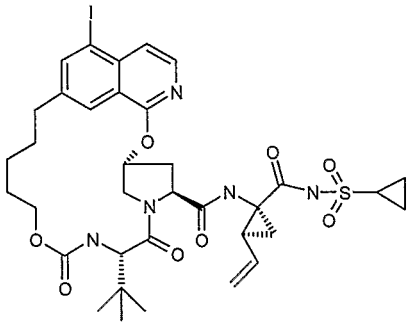
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III-36

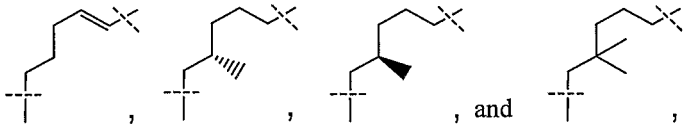


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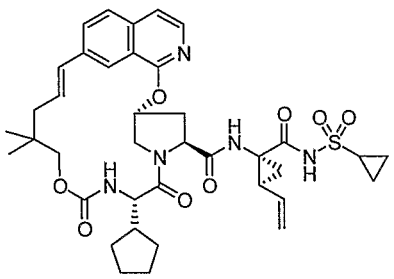
III-38

A nineteenth embodiment of the present invention is a compound of formula **III**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is $CONHSO_2R^6$, R^6 is C_3-C_8 cycloalkyl, C_1-C_8 alkyl, aryl, or aryl(C_1-C_4)alkyl, R^2 is C_1-C_4 alkyl or C_2-C_4 alkenyl, R^3 is C_5-C_6 cycloalkyl or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents, R^5 is H, halo, aryl, heteroaryl or $N(R^7)_2$, and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the nineteenth embodiment, R^5 is H, and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments. In a feature of the first aspect of the nineteenth embodiment, R3 is C5-C6 cycloalkyl or C3-C5-alkyl, and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments. In another feature of the first aspect of the nineteenth embodiment, R6 is C3-C5 cycloalkyl, and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the nineteenth embodiment, R^2 is C_2-C_4 alkenyl, R^5 is H, R^6 is C_3-C_8 cycloalkyl, W is R^7 or H, Y is C(=O), Z is O, and n is 1, and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the nineteenth embodinment, M is selected from the group consisting of:

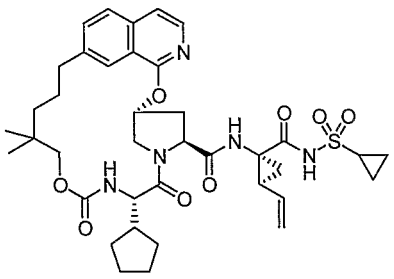


and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments.

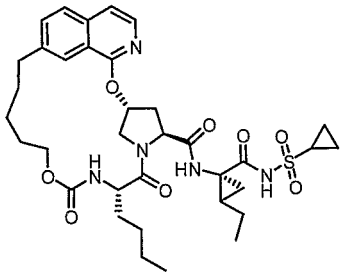
A twentieth embodiment of the present invention is a compound, or a pharmaceutically acceptable salt or hydrate thereof, selected from the group consisting of the compounds **III-39** to **III-187**.



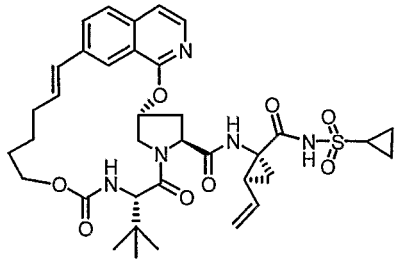
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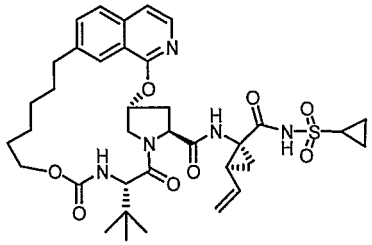
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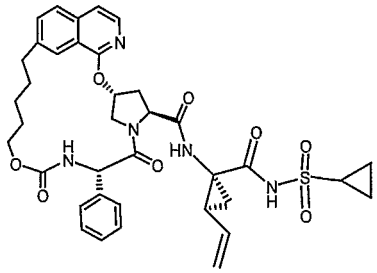
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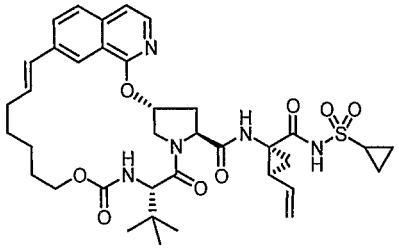
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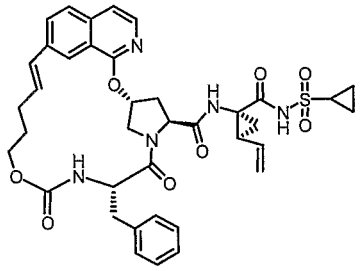
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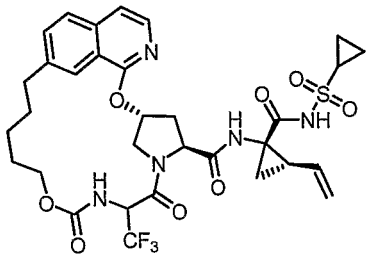
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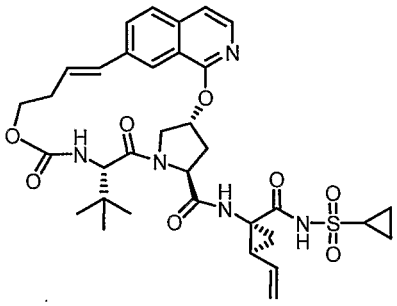
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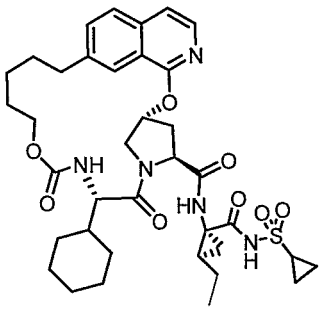
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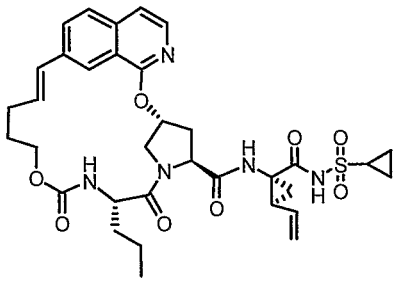
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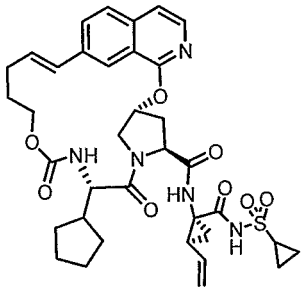
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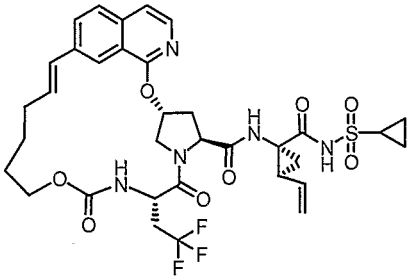
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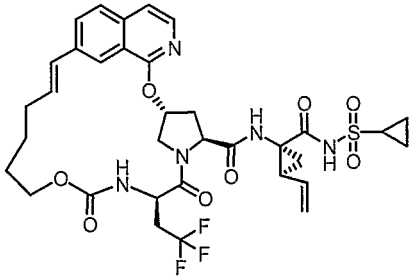
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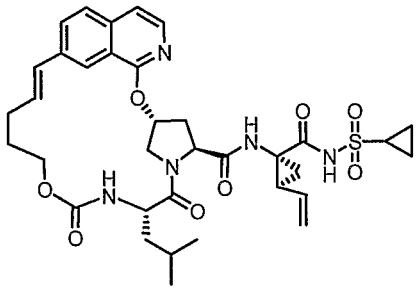
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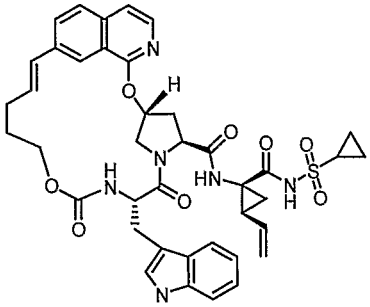
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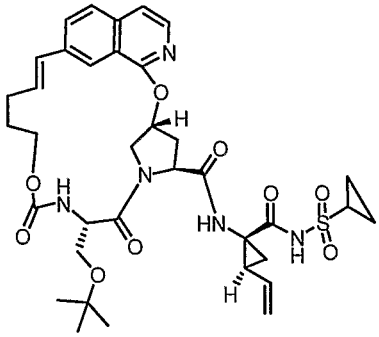
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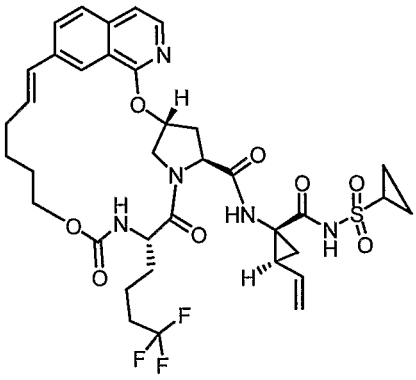
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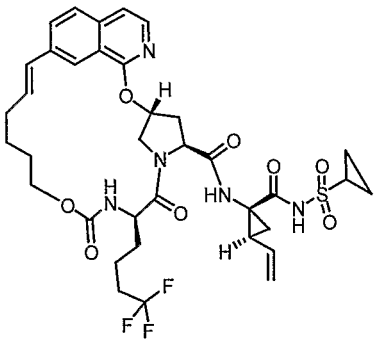
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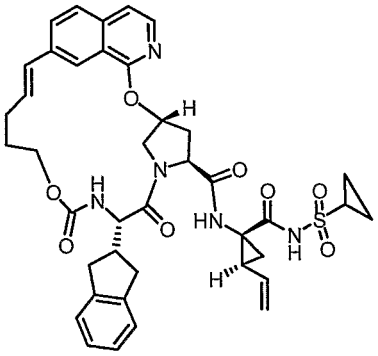
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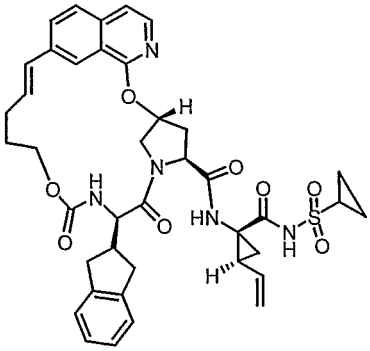
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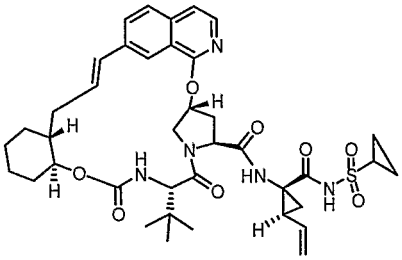
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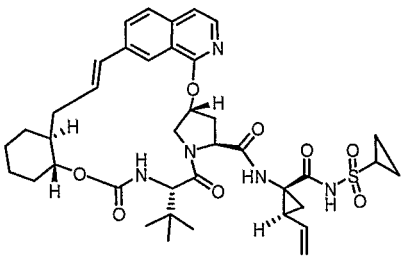
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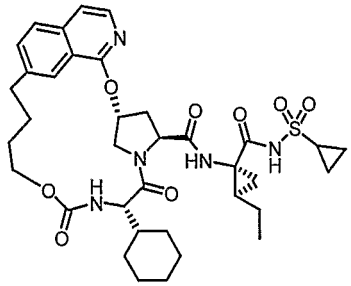
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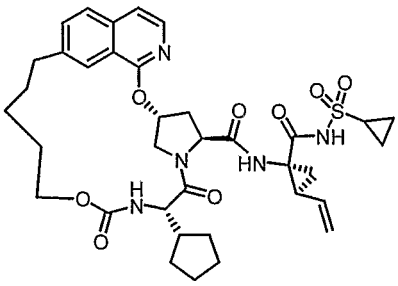
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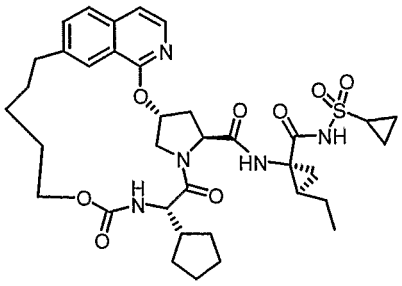
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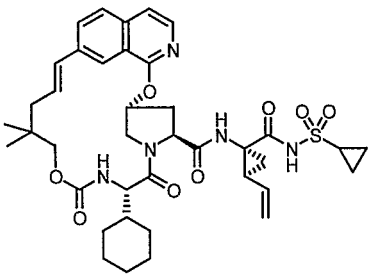
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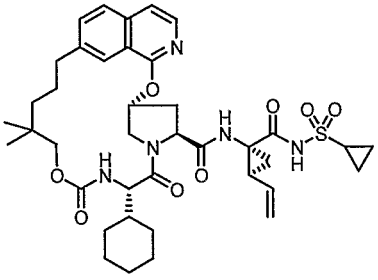
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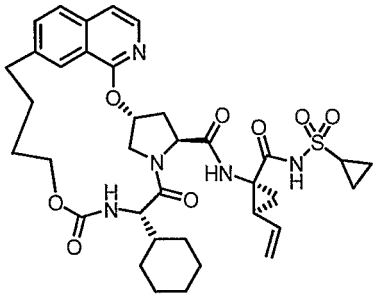
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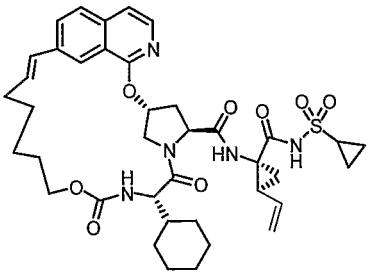
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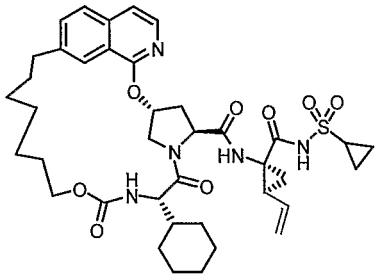
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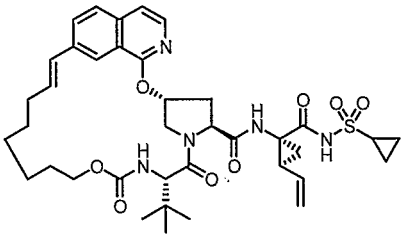
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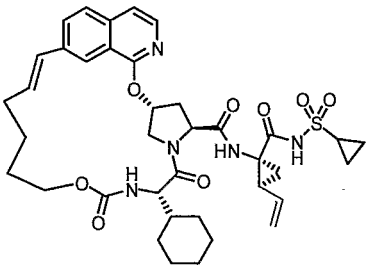
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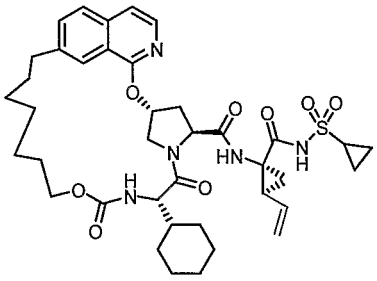
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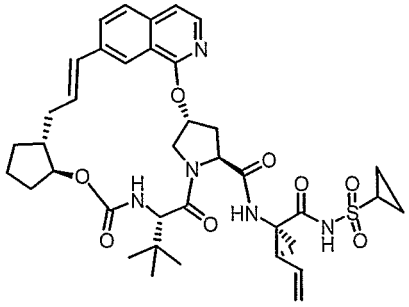
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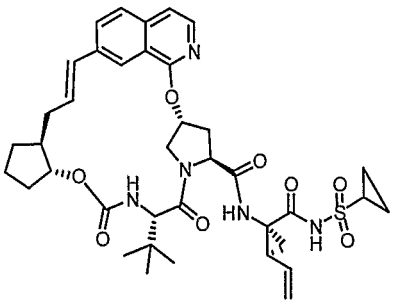
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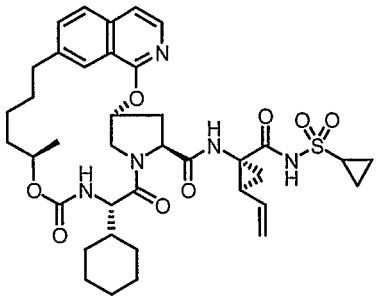
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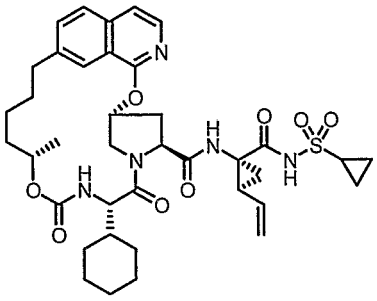
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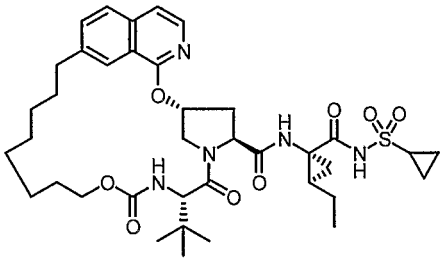
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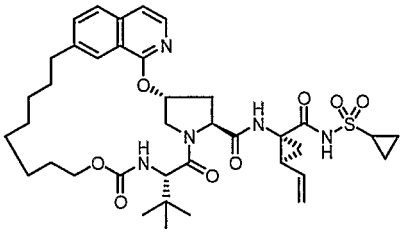
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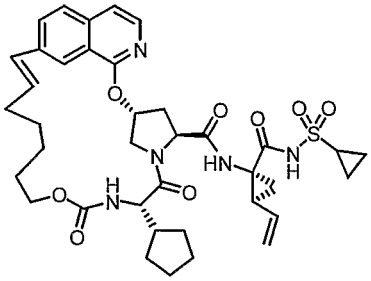
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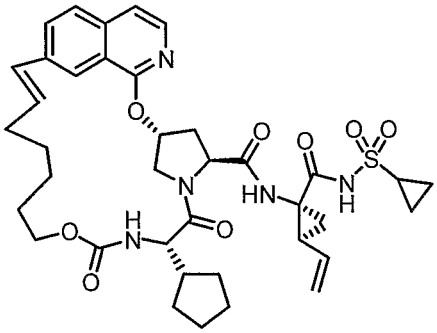
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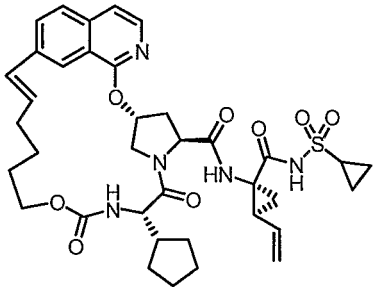
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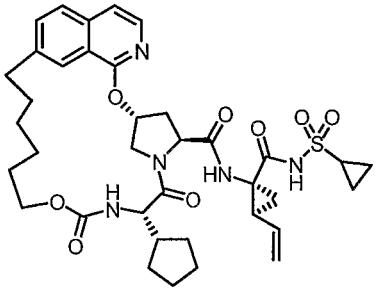
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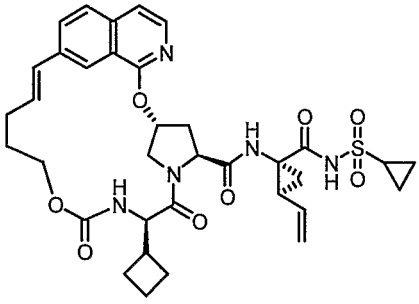
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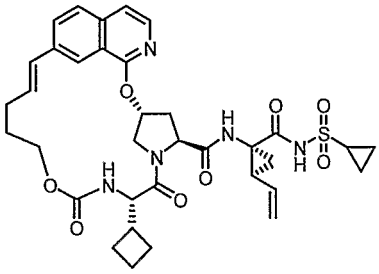
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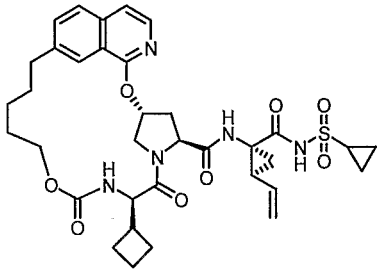
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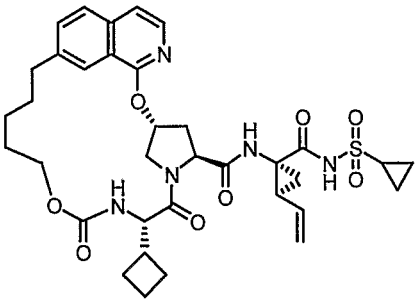
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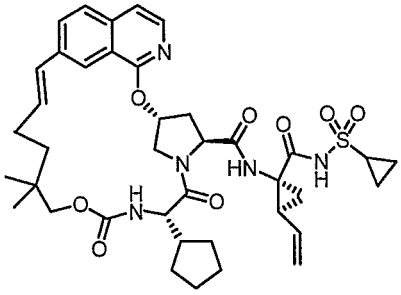
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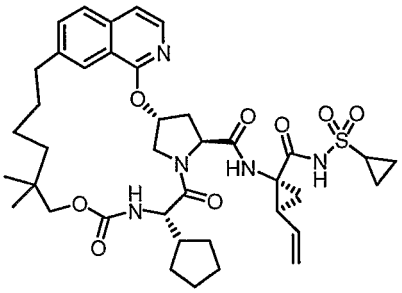
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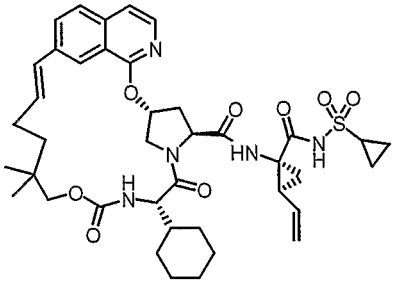
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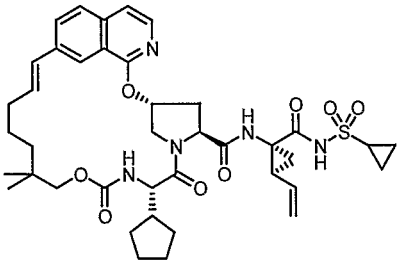
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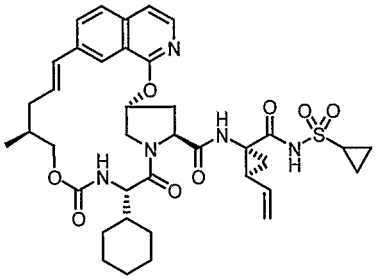
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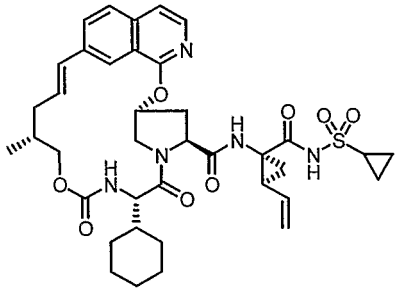
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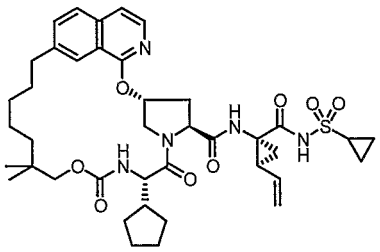
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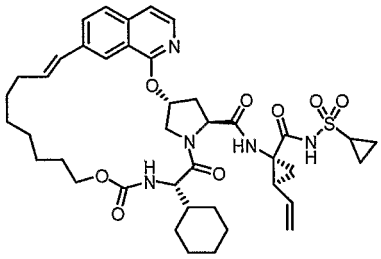
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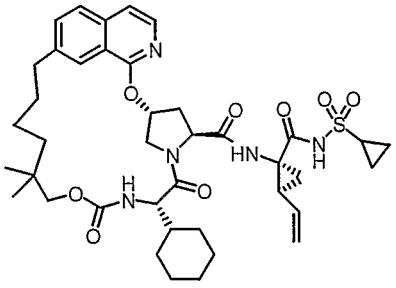
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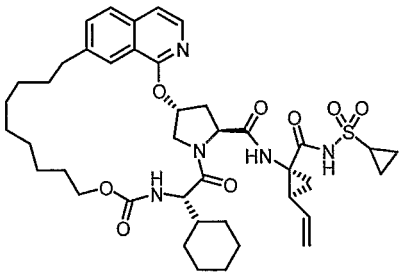
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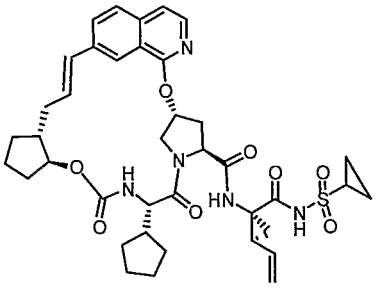
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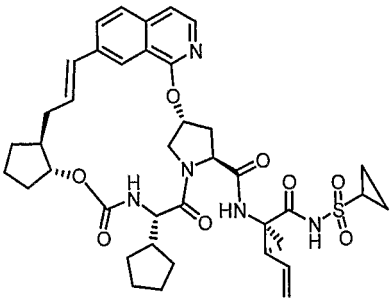
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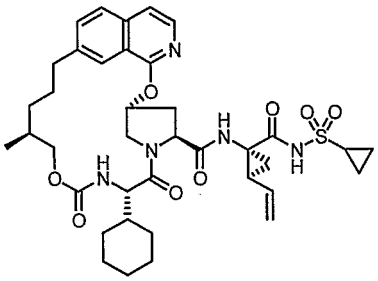
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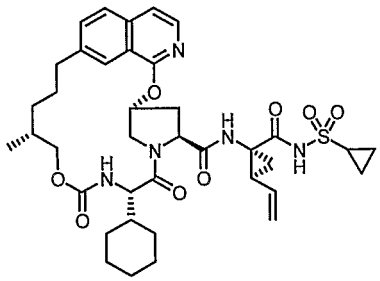
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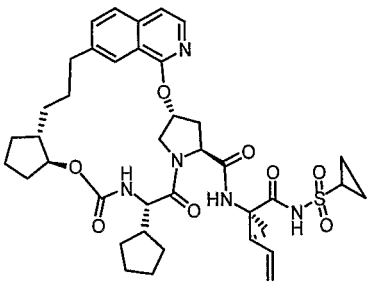
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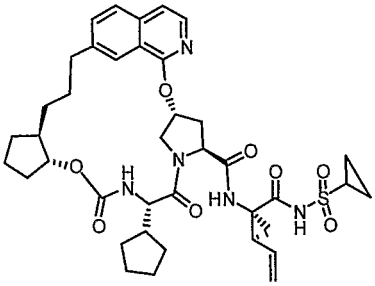
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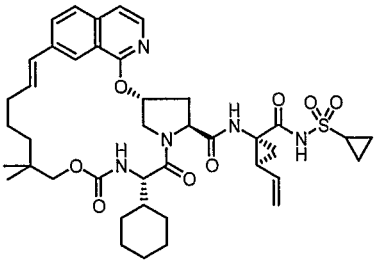
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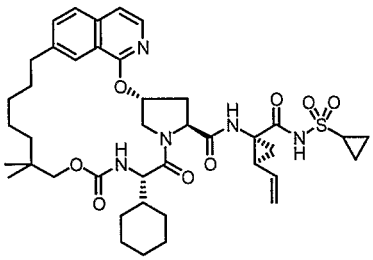
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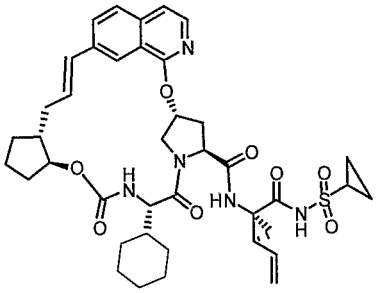
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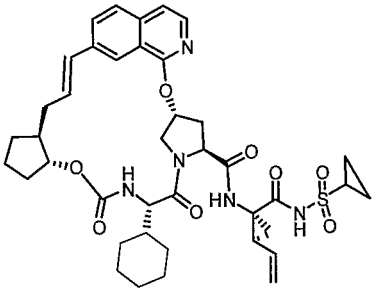
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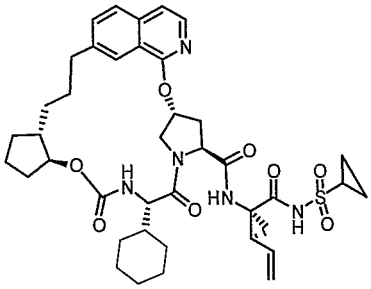
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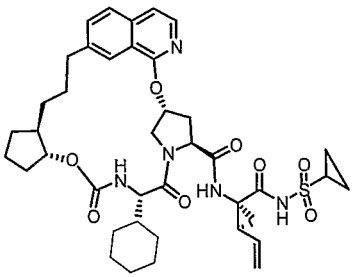
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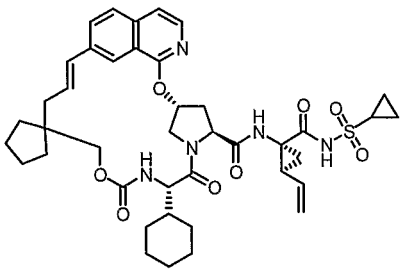
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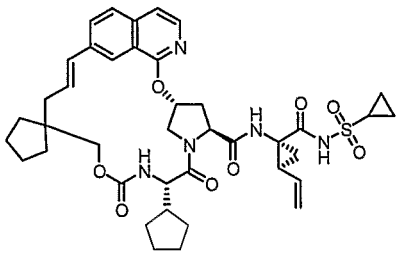
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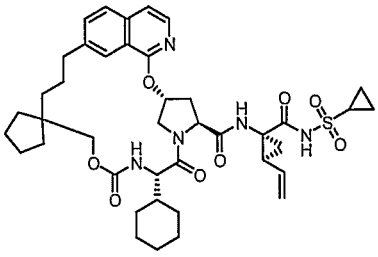
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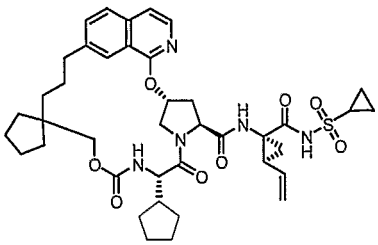
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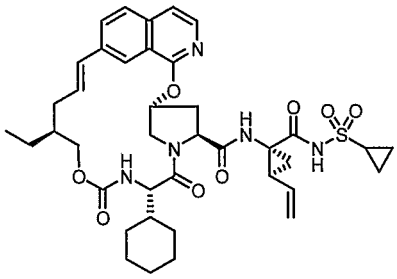
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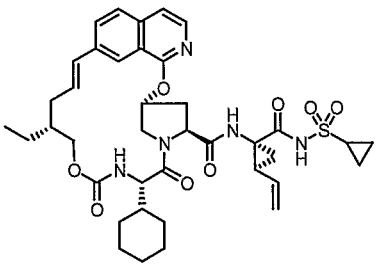
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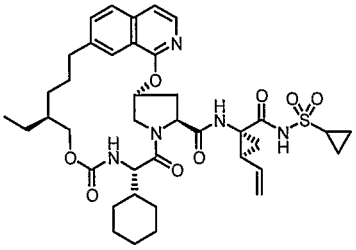
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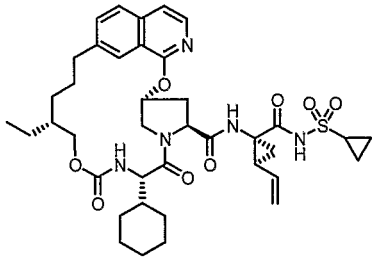
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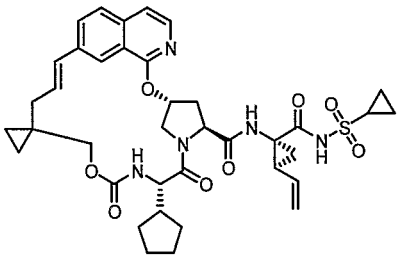
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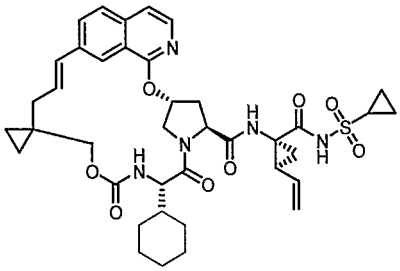
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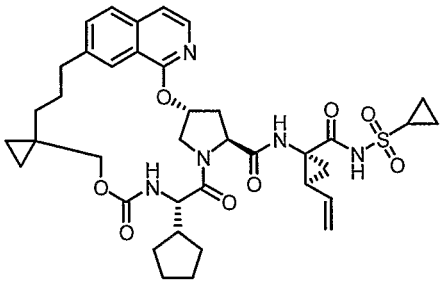
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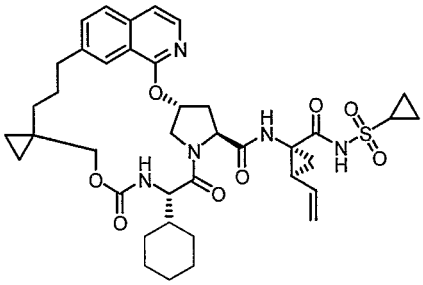
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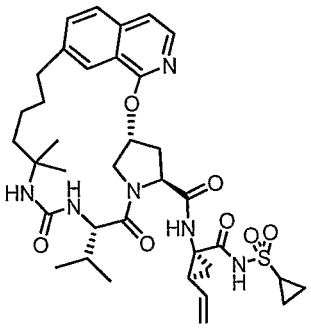
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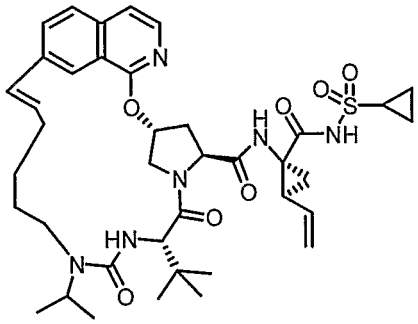
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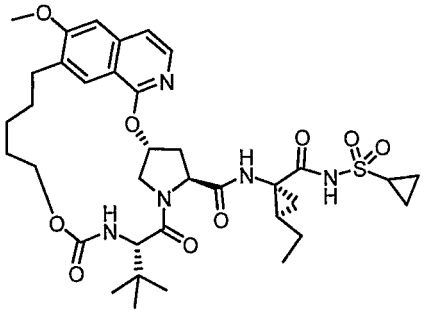
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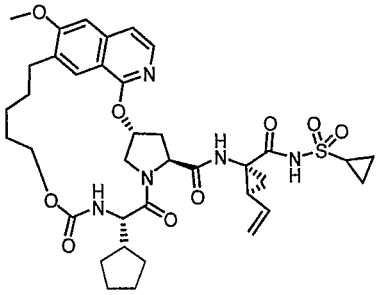
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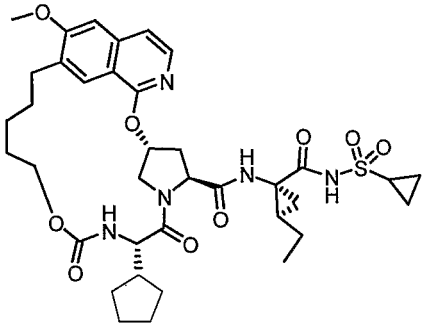
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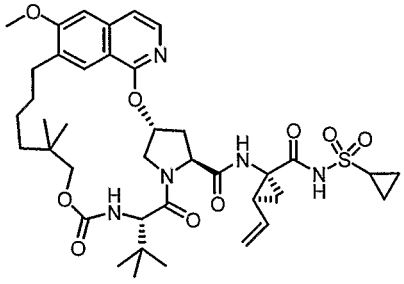
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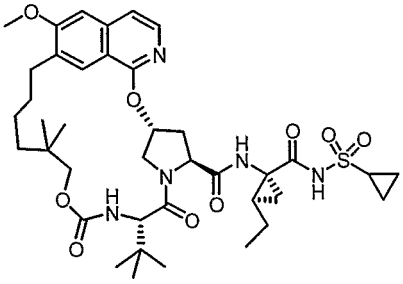
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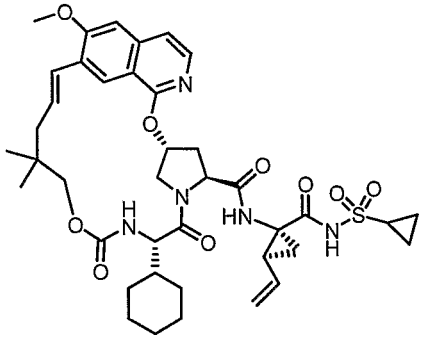
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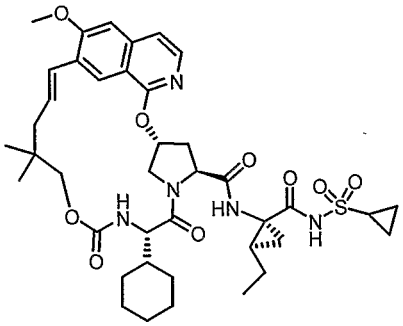
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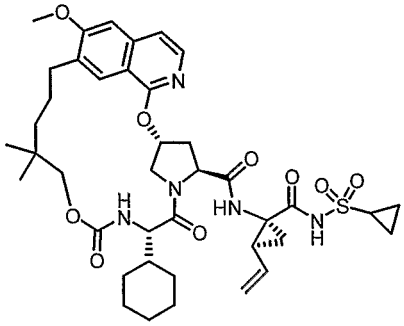
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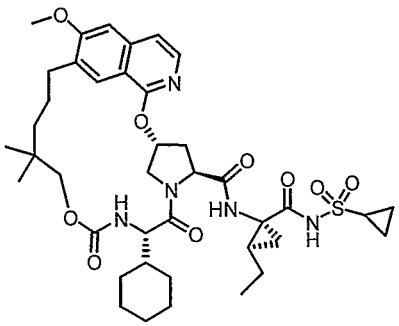
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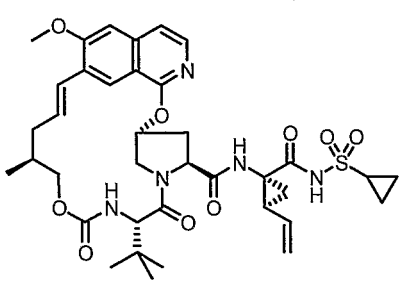
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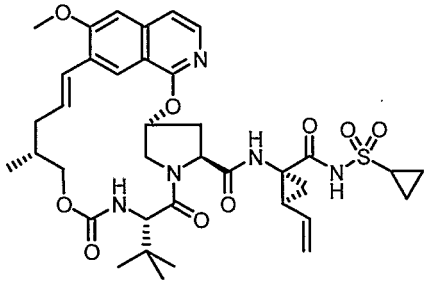
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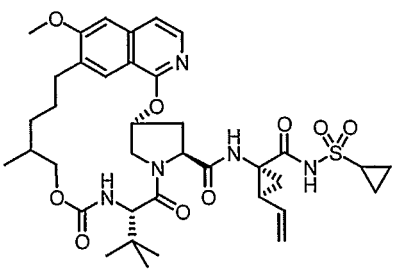
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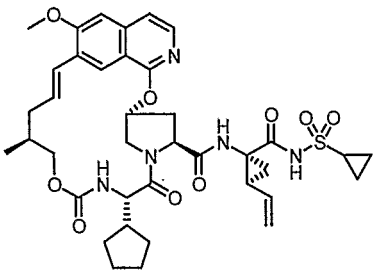
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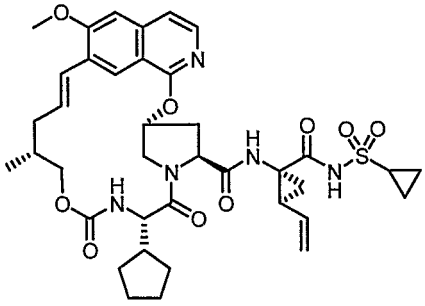
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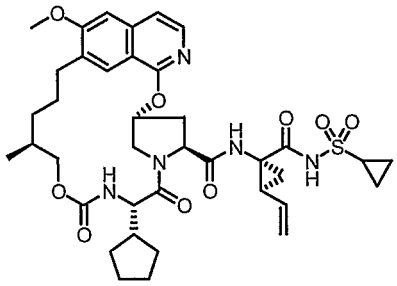
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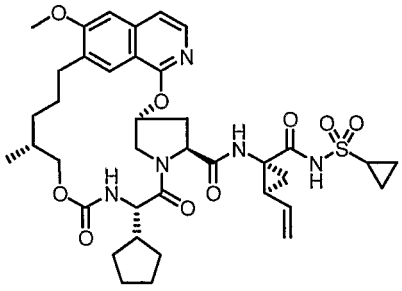
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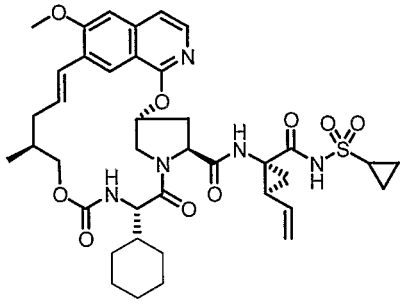
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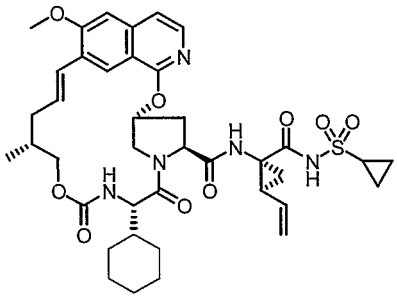
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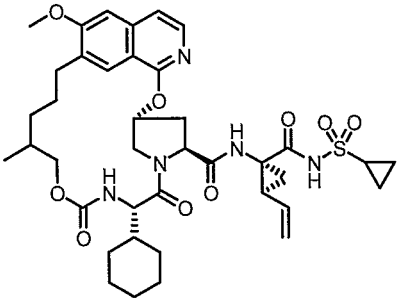
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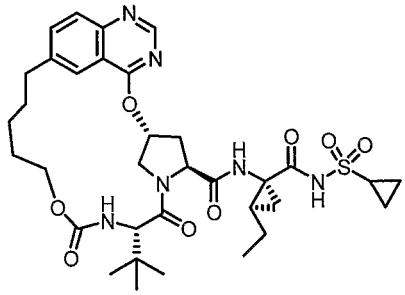
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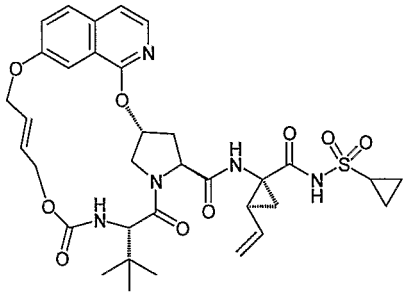
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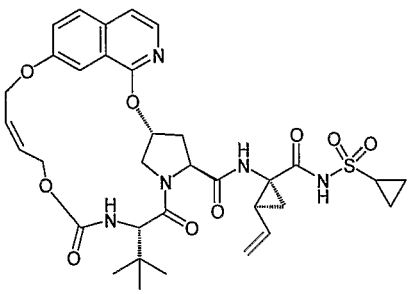
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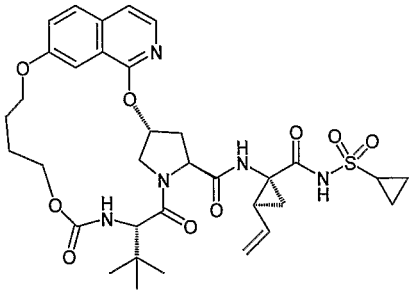
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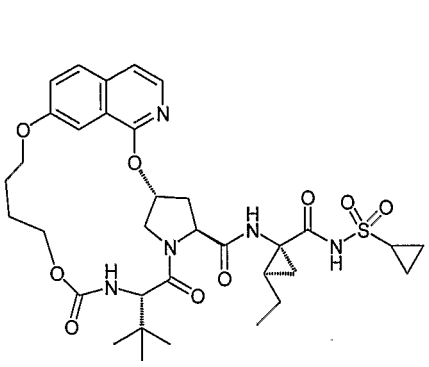
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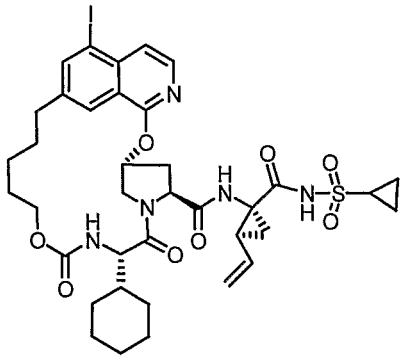
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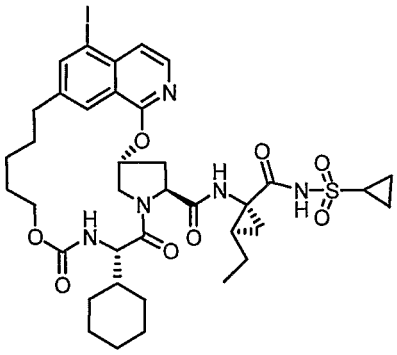
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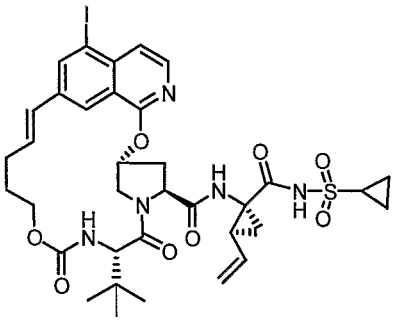
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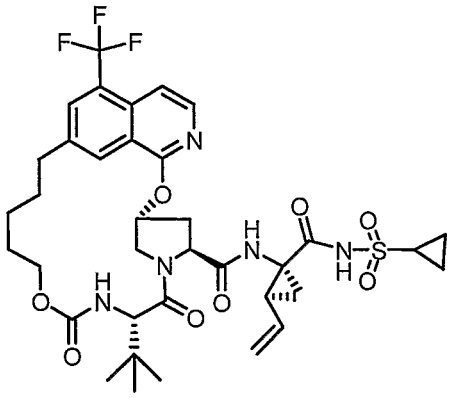
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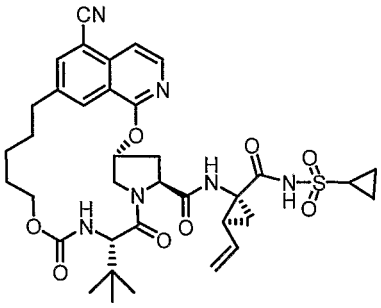
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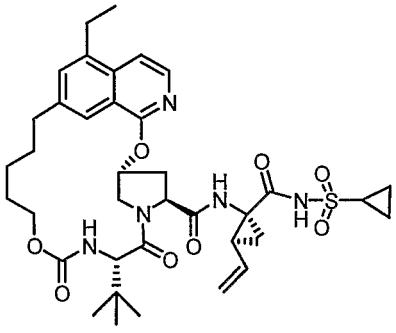
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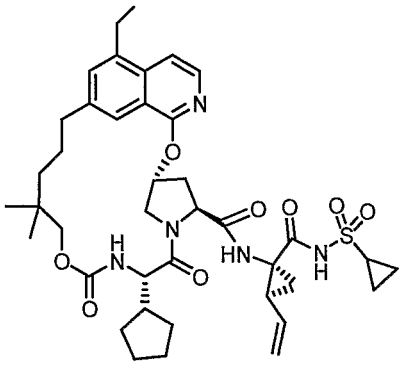
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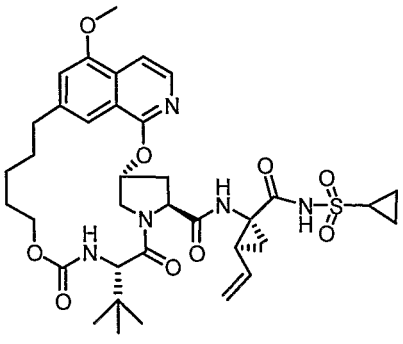
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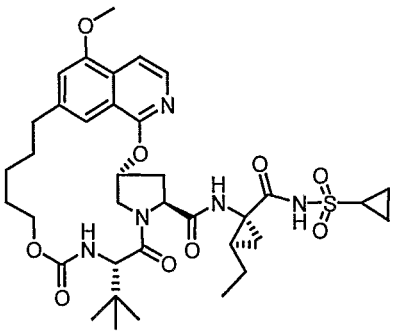
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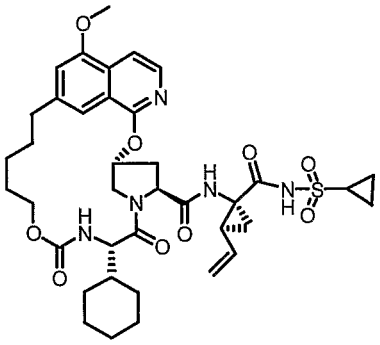
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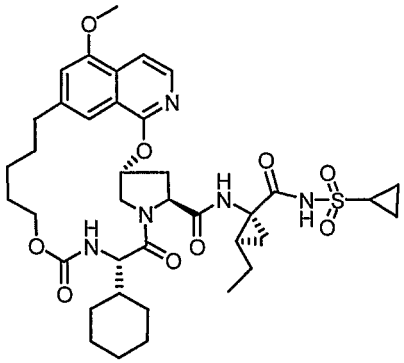
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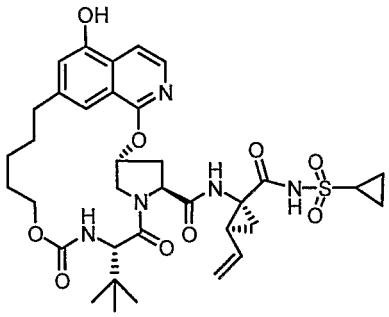
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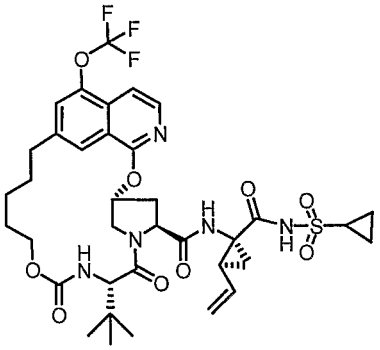
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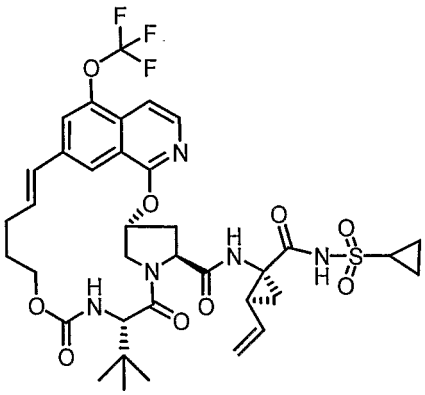
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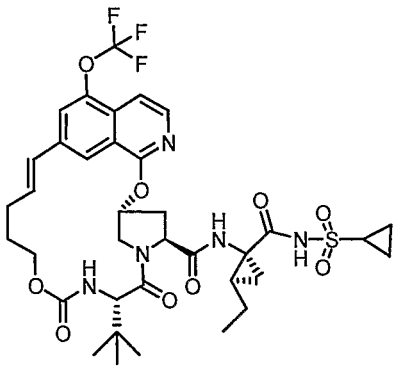
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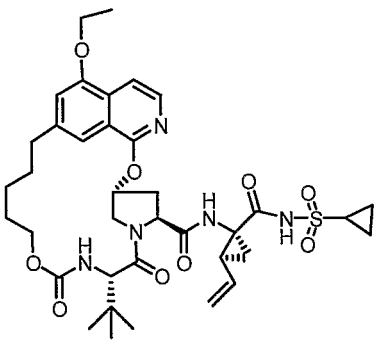
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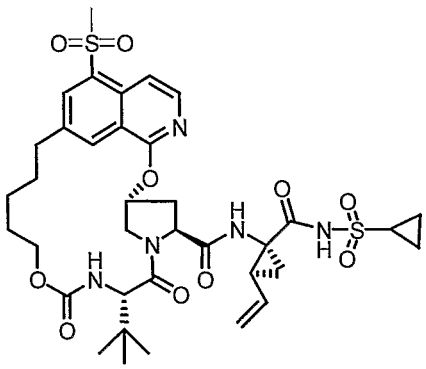
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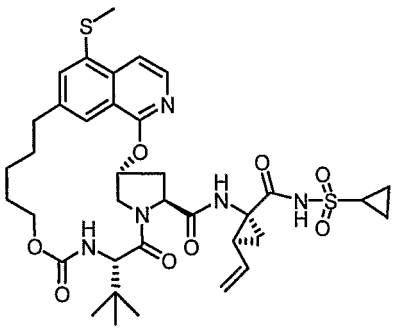
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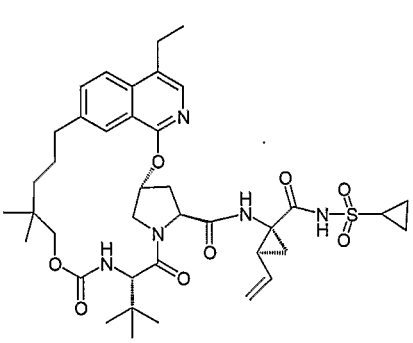
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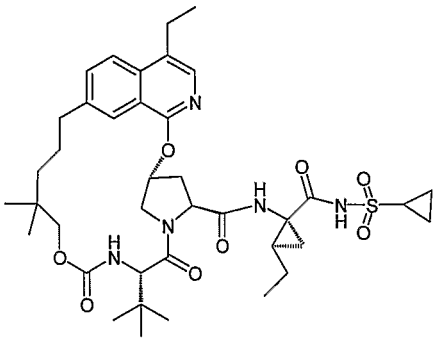
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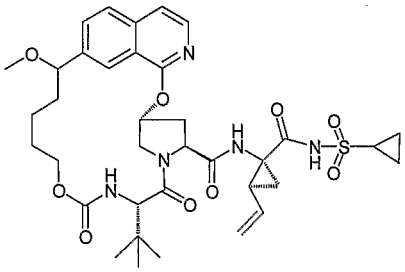
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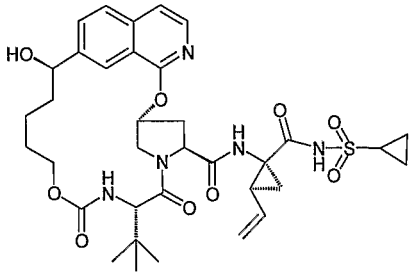
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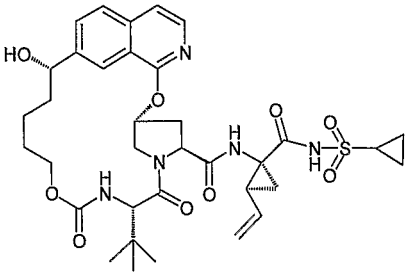
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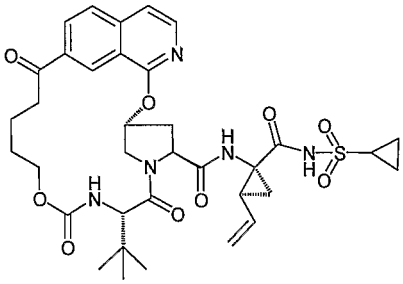
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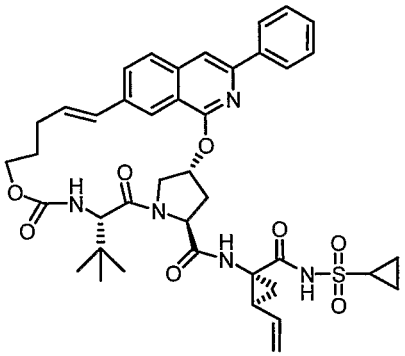
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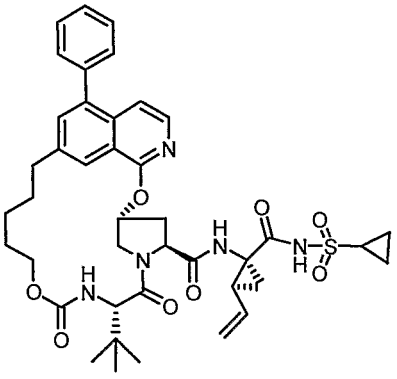
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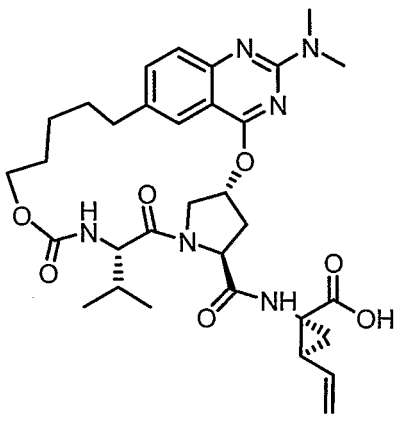


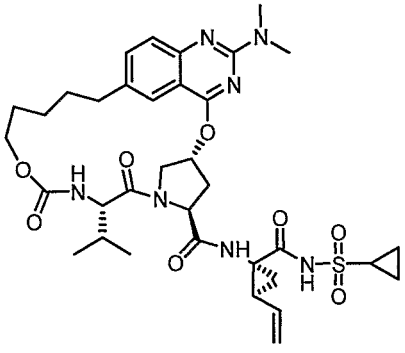
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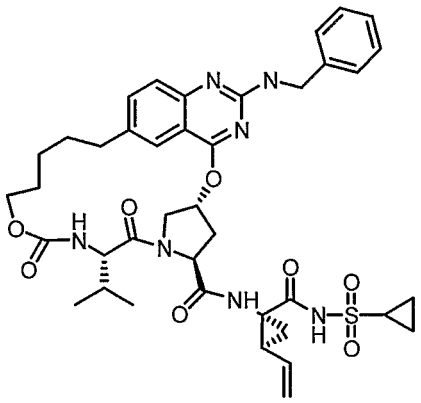
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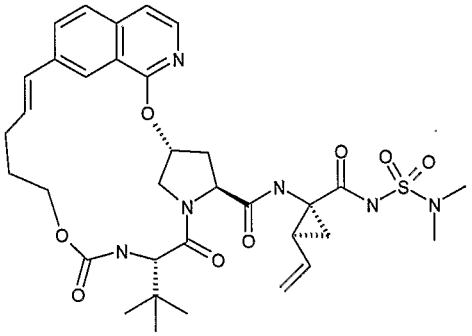




III-174



III-175

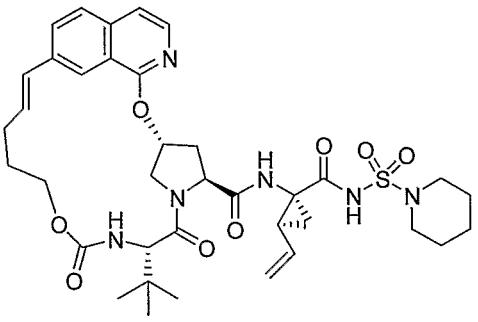


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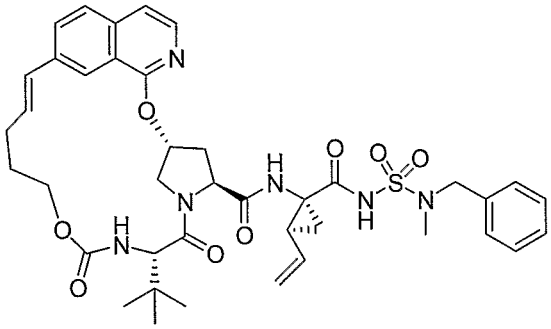
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III-178

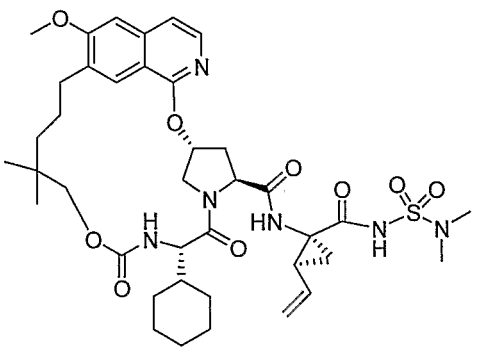
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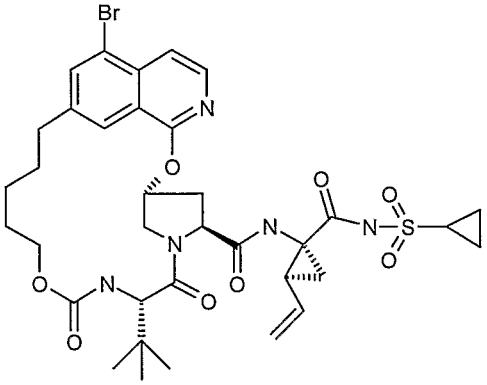
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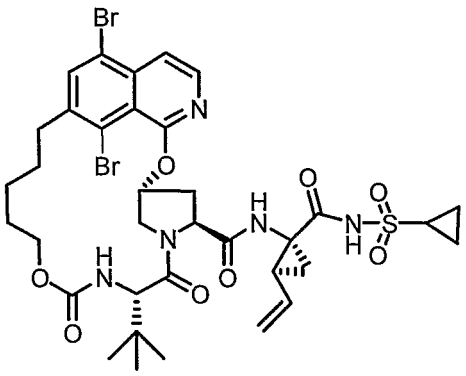


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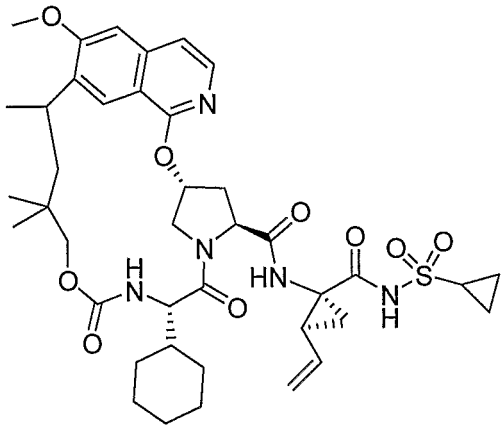


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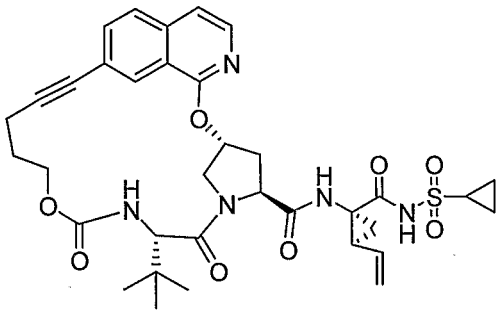




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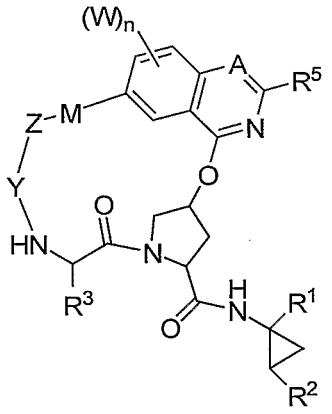


III-184



III-185

A twenty-first embodiment of the present invention is a compound of formula (**I**) and/or a pharmaceutically acceptable salt and/or hydrate thereof:



I

wherein:

n is 1 or 2;

R^1 is CO_2R^{10}, $CONR^{10}SO_2R^6$, $CONR^{10}SO_2NR^8R^9$, or tetrazolyl;

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 5-6 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 3-6 membered cyclic ring containing 0-3 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; 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, wherein said alkylene or alkenylene is optionally substituted with 1 or 2 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); and the 2 substituents on adjacent carbon atoms of M are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

A is $C(R^{11})$ or N;

when R^5 is other than H, R^{11} is H, C_1-C_6 alkyl, halo, OR^{10}, SR^{10}, or $N(R^{10})_2$;

when R^5 is H, R^{11} 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^5 and R^{11} are optionally taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 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 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 0-2 heteroatoms selected from N, O and S;

each W' is independently 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 0-2 heteroatoms selected from N, O and S;

R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl,

heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), 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, $C(O)R^{10}$, C_1-C_6 haloalkyl, 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

R^9 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), 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, $C(O)R^{10}$, C_1-C_6 haloalkyl, 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-8 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and

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

A twenty-second embodiment of the present invention is a compound, or a pharmaceutically acceptable salt or hydrate thereof, which is compound **III-23** ((1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid).

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).

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

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate.

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

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

The term "alkylene" refers to any linear or branched chain alkylene group (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); the contents of each of which are incorporated by reference in their entirety. Such 2'-*C*-branched ribonucleosides include, but are not limited to, 2'-*C*-methyl-cytidine, 2'-*C*-methyl-uridine, 2'-*C*-methyl-adenosine, 2'-*C*-methyl-guanosine, and 9-(2-*C*-methyl-β-D-ribofuranosyl)-2,6-diaminopurine, and the corresponding amino acid ester of the ribose C-2', C-3', and C-5' hydroxyls and the corresponding optionally substituted cyclic 1,3-propanediol esters of the 5'-phosphate derivatives.

The compounds of the present invention may also be combined for the treatment of HCV infection with other nucleosides having anti-HCV properties, such as those disclosed in WO 02/51425 (4 July 2002), assigned to Mitsubishi Pharma Corp.; WO 01/79246, WO 02/32920, 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); the content of each is incorporated herein by reference in its entirety.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS5B polymerase. Such HCV NS5B polymerase inhibitors that may be used as combination therapy include, but are not limited to, those disclosed in WO 02/057287, US 6,777,395, WO 02/057425, US 2004/0067901, WO 03/068244,

WO 2004/000858, WO 04/003138 and WO 2004/007512; the content of each is incorporated herein by reference in its entirety. Other such HCV polymerase inhibitors include, but are not limited to, valopicitabine (NM-283; Idenix) and 2'-F-2'-beta-methylcytidine (see also WO 2005/003147, assigned to Pharmasset, Ltd.).

In one embodiment, nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS3 protease inhibitors are selected from the following compounds: 4-amino-7-(2-C-methyl-β-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-methylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-dimethylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-vinyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-hydroxymethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-fluoromethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-methyl-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylic acid; 4-amino-5-bromo-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-chloro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2,4-diamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 4-amino-7-(2-C-ethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C,2-O-dimethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 2-amino-5-methyl-7-(2-C, 2-O-dimethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 4-amino-7-(3-deoxy-2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-deoxy-2-C-methyl-β-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-2-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-C-methyl-β-D-xylofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2,4-di-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-deoxy-3-fluoro-2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2 ,3-d]pyrimidine; and the corresponding 5'-triphosphates; or a pharmaceutically acceptable salt thereof.

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

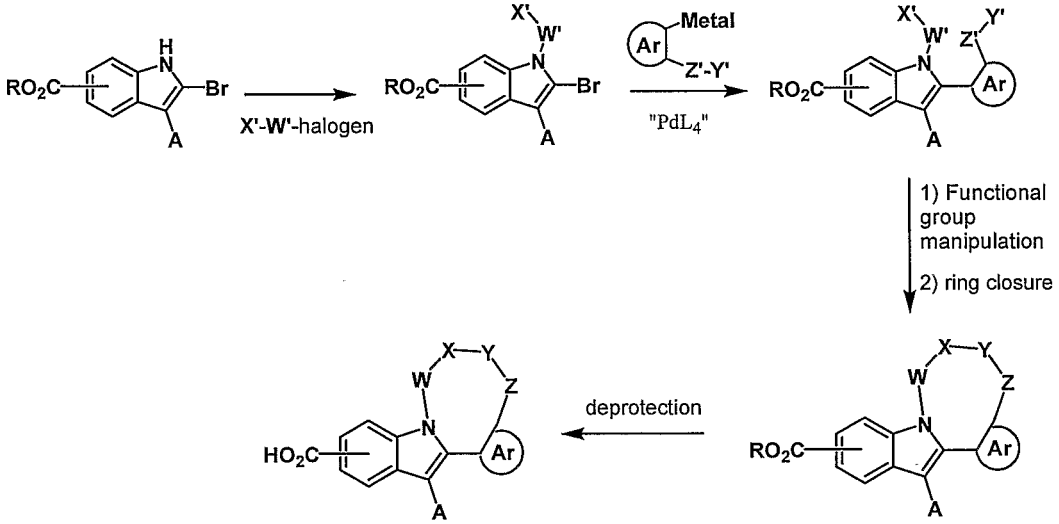
2002); WO 2005/016927 (in particular JTK003), assigned to Japan Tobacco, Inc.; the content of each is incorporated herein by reference in its entirety; and HCV-796 (Viropharma Inc.).

In one embodiment, non-nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS3 protease inhibitors are selected from the following compounds: 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; methyl ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetate; ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 3-chloro-14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine 11-carboxylic acid; *N*'-(11-carboxy-14-cyclohexyl-7,8-dihydro-*6H*-indolo[1,2-e][1,5]benzoxazocin-7-yl)-*N*,*N*-dimethylethane-1,2-diaminium bis(trifluoroacetate); 14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid; 14-cyclohexyl-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[3-(dimethylamino)propyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(diethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(1-methylpiperidin-4-yl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-N-[(dimethylamino)sulfonyl]-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-*N*-[(dimethylamino)sulfonyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 6-allyl-14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid;

14-cyclohexyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 13-cyclohexyl-5-methyl-4,5,6,7-tetrahydrofuro[3',2':6,7][1,4]diazocino[1,8-*a*]indole-10-carboxylic acid; 15-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,6]benzodiazonine-12-carboxylic acid; 15-cyclohexyl-8-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,5]benzodiazonine-12-carboxylic acid; 13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxylic acid; and pharmaceutically acceptable salts thereof.

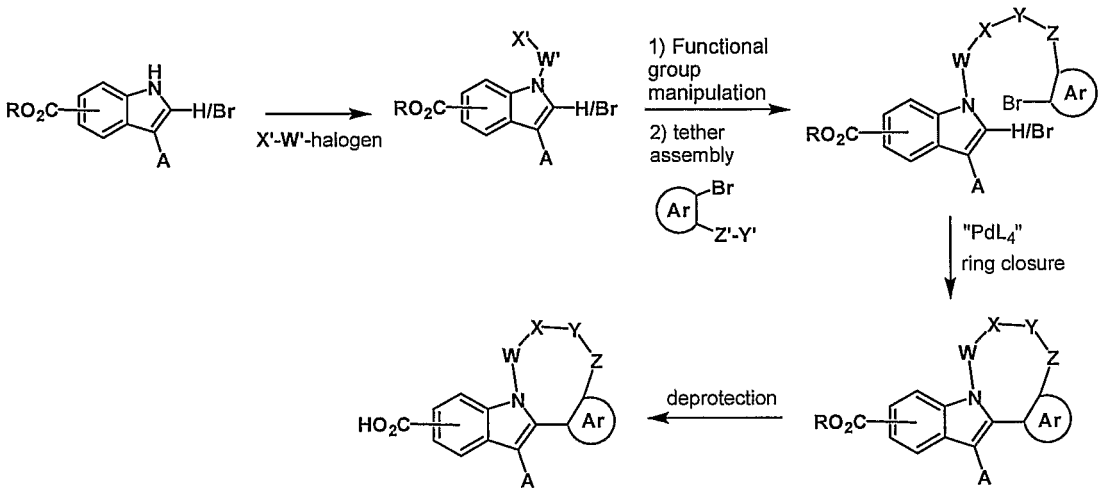
The above tetracyclic indole-based HCV NS5B polymerase inhibitors may be obtained following methods A-E as outlined below, wherein different variables may be selected in accordance with the specific tetracyclic indole compound to be prepared:

Method A



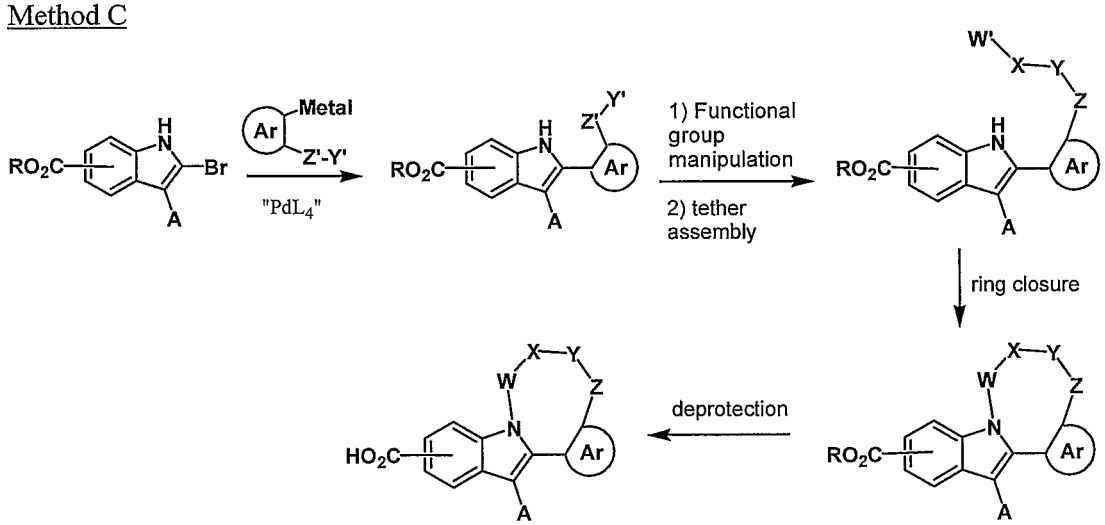
2-Bromoindole intermediate (prepared as described in published International patent application WO2004087714) was functionalized on the indole nitrogen to introduce pre-cursor functionality W'/X' to either or both of the elements W/X of the tether. Pd-mediated cross-coupling methodology (*eg*, Suzuki,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

Method B



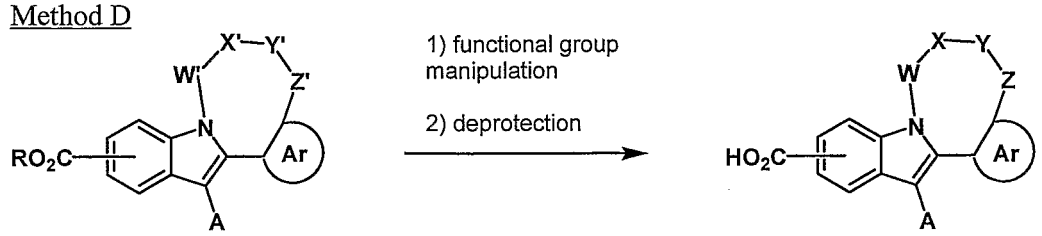
Following tether assembly out to the appropriate 2-haloaromatic, Pd-mediated ring closure afforded the fused tetracyclic system. Ester deprotection then yielded the target indole carboxylic acids, with the C2 aromatic tethered to the indole nitrogen.

Method C



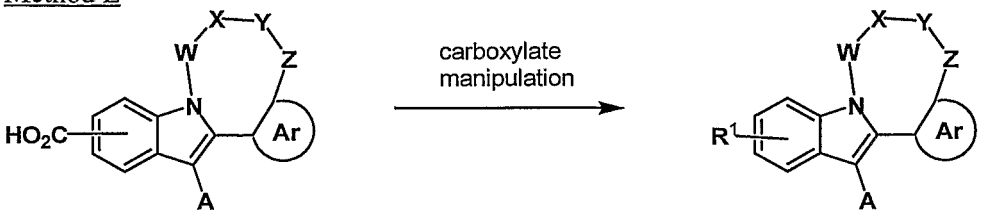
The C2 aromatic was introduced at the outset *via* Pd-mediated cross-coupling methodology (Suzuki, Stille *etc*). The tether was then built up, with cyclisation onto the indole nitrogen finally closing the ring. Ester deprotection then yielded the target indole carboxylic acids, with the C2 aromatic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

Method D



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

Method E



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

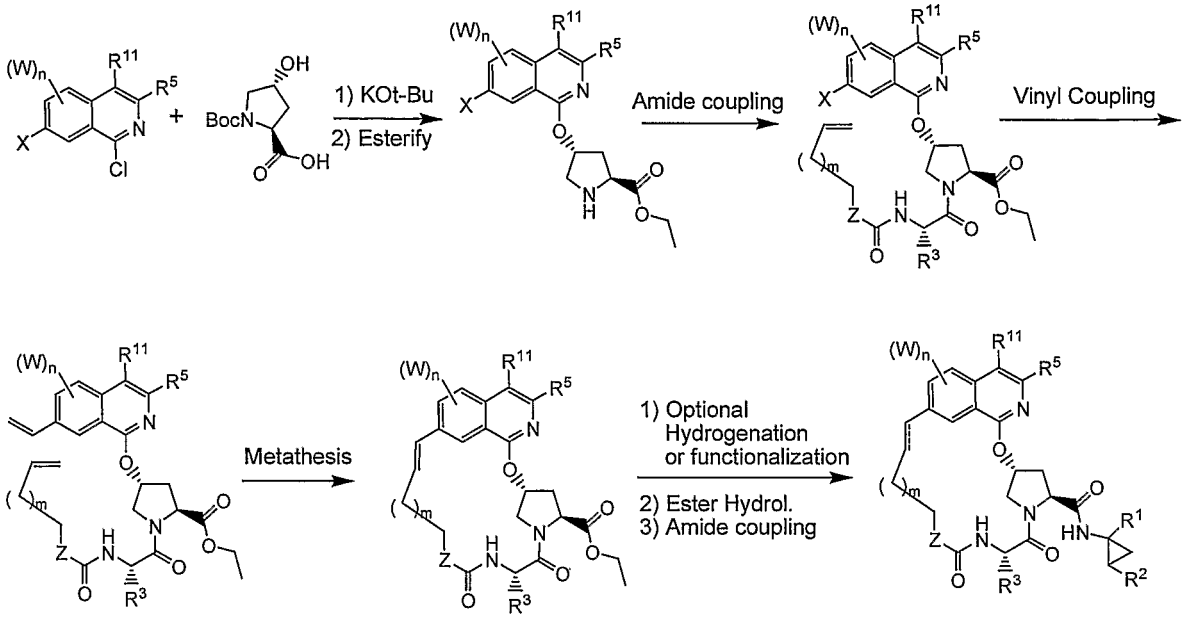
The HCV NS3 protease inhibitory activity of the present compounds may be tested using assays known in the art. One such assay is HCV NS3 protease time-resolved fluorescence (TRF) assay as described in Example 9. Other examples of such assays are described in e.g., International patent publication WO2005/046712. Compounds useful as HCV NS3 protease inhibitors would have a Ki less than 50 μM, more preferably less than 10 μM, and even more preferably less than 100 nM.

The present invention also includes processes for making compounds of formula **I**, **II**, **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 on the scope or spirit of the invention.

General Description of Synthesis:

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

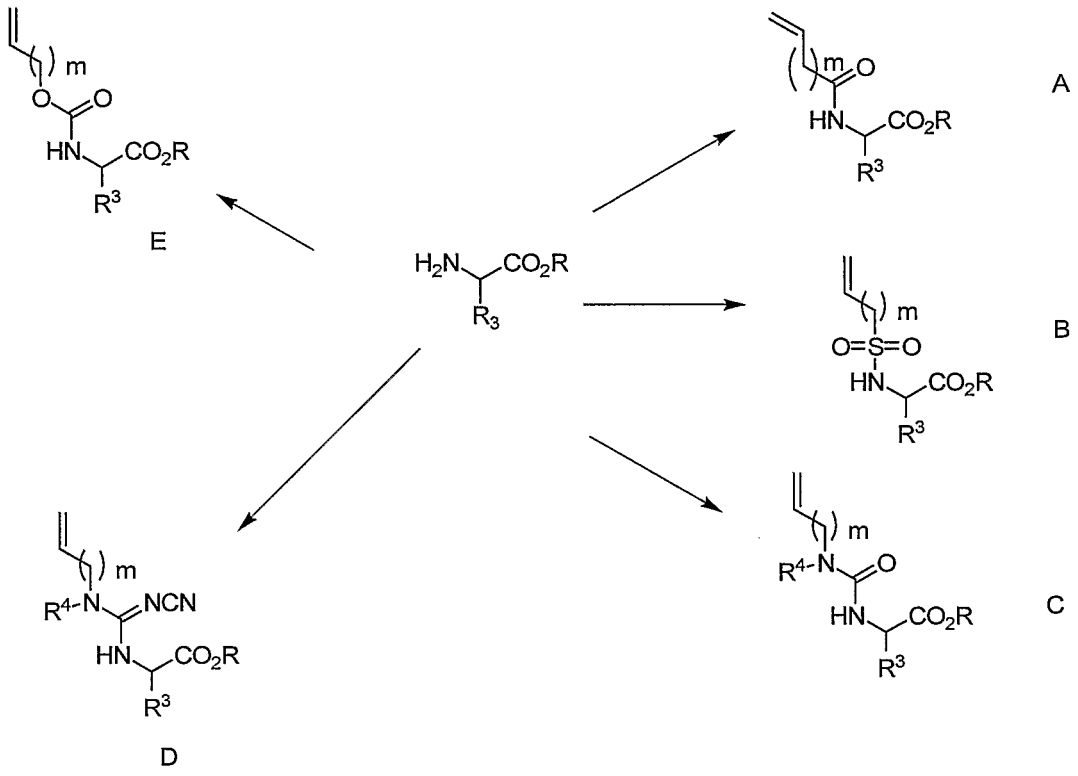
SCHEME 1



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

SCHEME 2



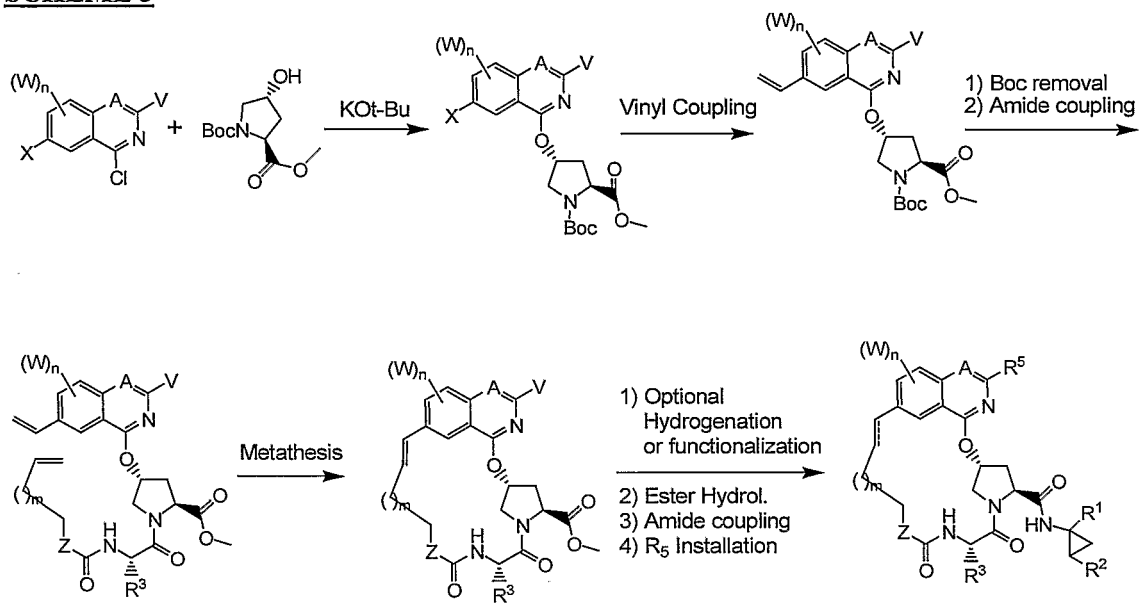
Following functionalization of the amine, the ester can be hydrolyzed under a range of basic conditions known to those skilled in the art (Theodora W. Greene, Protective Groups in Organic Synthesis, Third Edition, John Wiley and Sons, 1999).

Deprotection of the carbamate protecting group on the proline portion may be carried out by a variety of methods known to persons skilled in the art (Theodora W. Greene, Protective Groups in Organic Synthesis, Third Edition, John Wiley and Sons, 1999). To complete the synthesis of the compounds of this invention, the amino acid derivative can be coupled to the proline derivative via a wide range of peptide coupling reagents such as DCC, EDC, BOP, TBTU etc (see Scheme 1). 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 the cyclopropylamino acid ester (the appropriate alkenyl or alkylcyclopropane portion of the molecule can be prepared as described previously (Llinas-Brunet et al., US 6,323,180) and subjected to an additional basic hydrolysis step to provide the final compounds. The proline ester can also be hydrolyzed and directly coupled to an appropriately

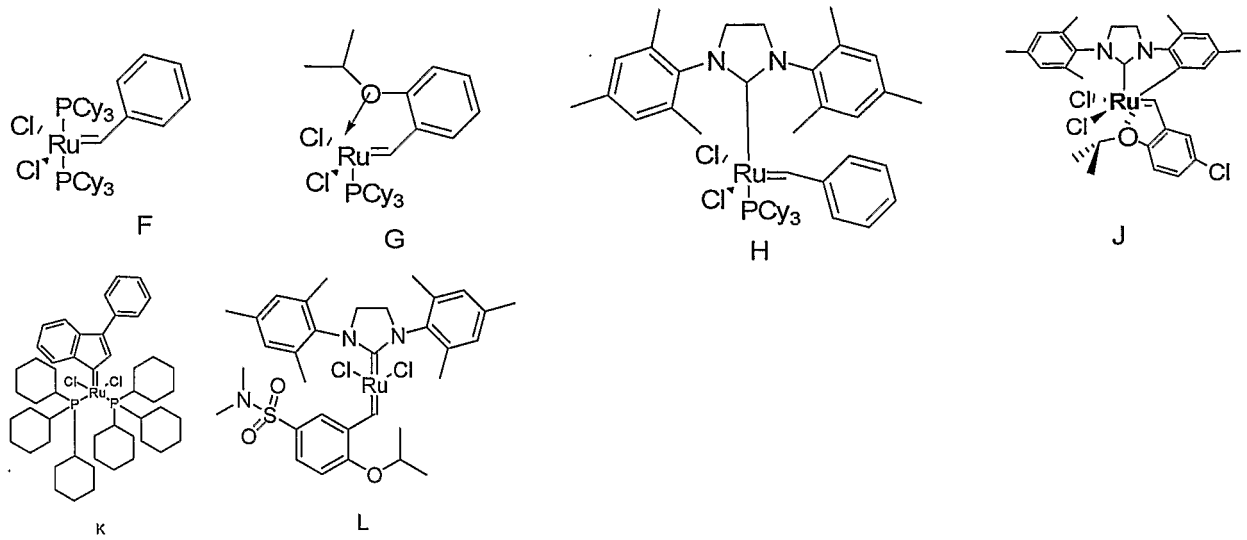
functionalized cyclopropylamino acid acyl sulfonamide (which can be prepared according to Wang X.A. et al. WO2003/099274) to provide the final compounds.

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.

SCHEME 3



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).



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

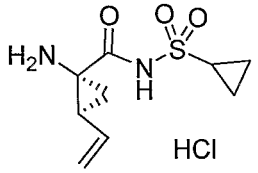
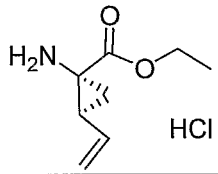
List of Abbreviations

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

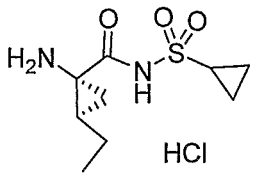
HCl	Hydrochloric acid
HOAc	Acetic acid
HOAt	1-Hydroxy-7-azabenzotriazole
LiOH	Lithium hydroxide
MeOH	Methanol
$MgSO_4$	Magnesium Sulfate
Na_2SO_4	Sodium sulfate
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
Nle	Norleucine
Pd/C	Palladium on carbon
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:

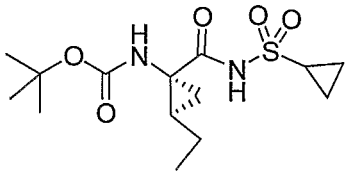
Synthesis of Intermediates A

Intermediate #	Structure	Name	Lit. Reference
A1		(1*R*,2*S*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride	Wang et al, US 6,995,174
A2		Ethyl (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylate hydrochloride	Llinas-Brunet et al, US 6,323,180

Intermediate A3: (1*R*,2*R*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride

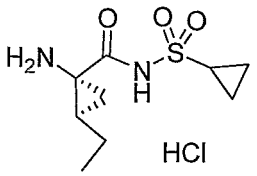


Step 1: tert-Butyl ((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)carbamate



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

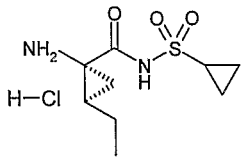
Step 2: (1*R*,2*R*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride (Intermediate A3)



A solution of the product from Step 1 above (92 g, 0.28 mol) in DCM (1200 mL) was cooled to 0 °C and HCl bubbled through the solution for 10 min, the cooling bath removed and the

reaction mixture stirred for 2 h. Nitrogen was bubbled through the reaction mixture for 5 min and the volatiles evaporated. The residue was azeotroped with DCM (x3) to give an off white powder (75 g). LRMS $(M+H)^+$ Calcd. = 233; found 233

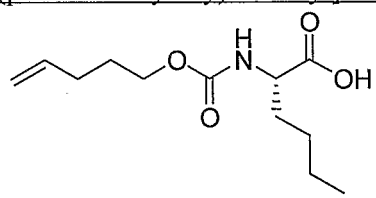
Alternative preparation of and name for Intermediate A3 (1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropanaminium chloride:



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

Preparation of Intermediates B

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

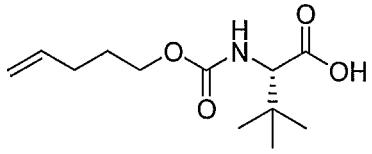


To a solution of 1-penten-4-ol (0.95 g, 11.0 mmol) in DMF (15 mL) at 0 °C was added carbonyldiimidazole (1.79 g, 11.0 mmol). The reaction mixture was warmed to room temperature and stirred for 30 min. L-norleucine methyl ester hydrochloride (2.0 g, 11.0 mmol) was then added, the reaction mixture was heated to 50 °C and stirred for 15 min. Upon cooling, the reaction mixture was diluted with ethyl ether and washed twice with water. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography (gradient elution 10 to 90% ethyl acetate in hexanes) to afford 2.1 g (74%) 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 r.t. for 3 h, then acidified to pH 3 with 1N HCl and extracted with (3 x 250 mL) EtOAc. The combined EtOAc layer was washed with 50 mL water, 50 mL brine, dried over sodium sulfate, filtered and concentrated to

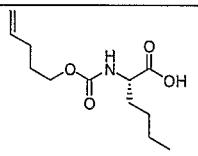
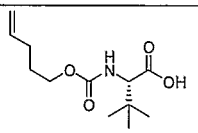
give 7.09 g (88%) of the title product as clear oil. LRMS (ESI) *m/z* 244 $[(M+H)^+$; calcd for $C_{12}H_{22}NO_4$: 244].

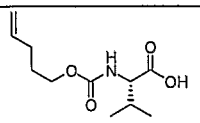
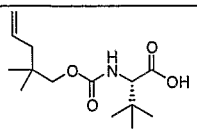
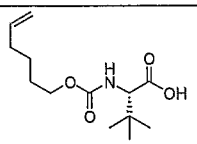
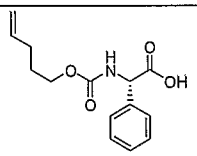
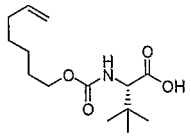
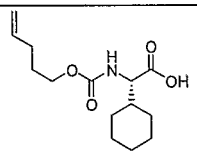
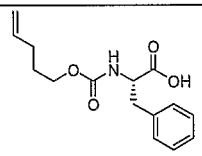
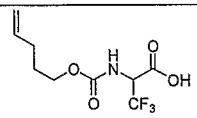
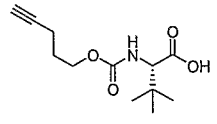
Preparation of Intermediate B2 (2S)-3,3-dimethyl-2-{[(pent-4-en-1-yloxy)carbonyl]amino}butanoic acid

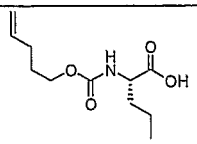
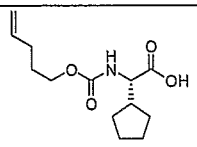
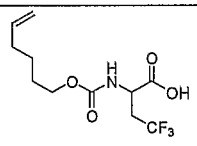
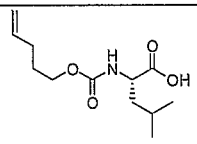
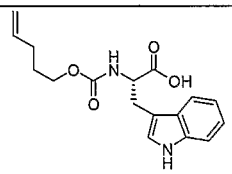
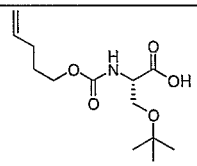
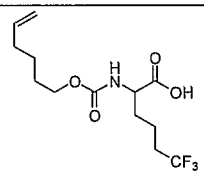
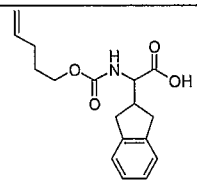


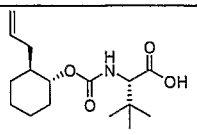
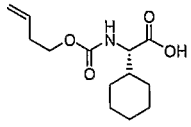
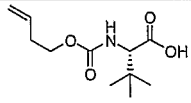
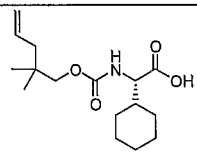
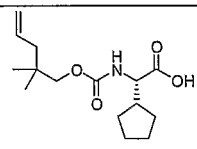
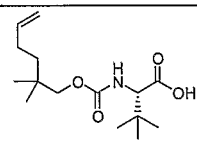
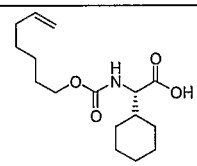
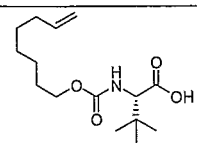
Diisopropylethyl amine (9.85 g, 76.2 mmol) was added dropwise to a 0 °C solution of 4-penten-1-ol (7.22 g, 83.9 mmol) and triphosgene (11.3 g, 38.1 mmol) in 160 mL dioxane. The resulting white suspension was stirred for 5 min at 0 °C, then allowed to warm to 25 °C over 1 h. The suspension was cooled to 0 °C with an ice bath and 1 N NaOH (76.2 mL) and *L-tert*-butylglycine (10.0 g, 76.2 mmol) were added. The reaction mixture was warmed to 25 °C and stirred for 18 h. The dioxane was removed *in vacuo* and the reaction mixture was basified to pH 12 with 1 N NaOH. The aqueous layer was extracted with dichloromethane (3x 150 mL), then acidified to pH~1 with 6 N HCl. The aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give 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].

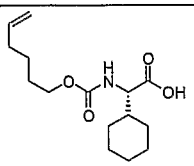
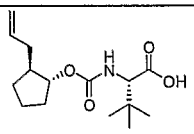
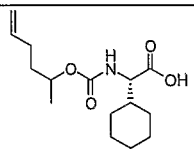
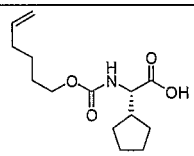
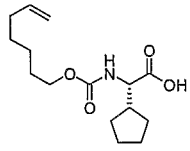
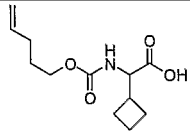
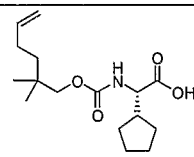
The following carbamate intermediates (B3-B49) were prepared using the chemistry described for the preparation of (2S)-3,3-dimethyl-2-{[(pent-4-en-1-yloxy)carbonyl]amino}butanoic acid (B2), by utilizing the appropriate amino acid and alcohol or the preparation of *N*-[(Pent-4-en-1-yloxy)carbonyl]-L-norleucine (B1) by utilizing the appropriate alcohol and amino ester.

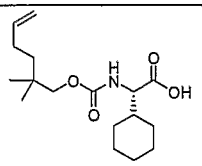
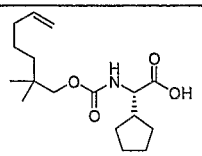
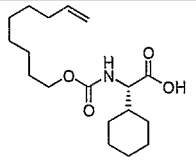
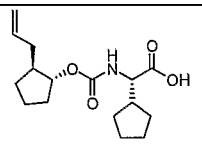
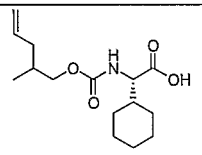
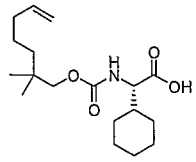
Int	Amino Acid	Alcohol	Structure	Name	LRMS $(M+H)^+$
B1	L-Norleucine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-norleucine (Intermediate 1)	244.3
B2	L-*t*-Butyl-glycine	4-Penten-1-ol		(2S)-3,3-Dimethyl-2-{[(pent-4-en-1-yloxy)carbonyl]amino}butanoic acid	244.2

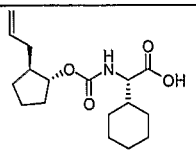
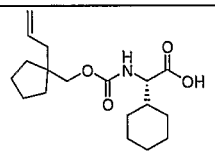
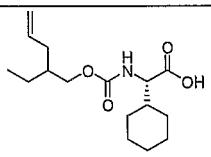
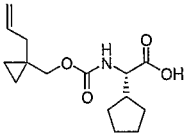
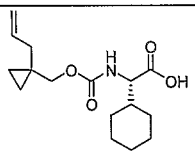
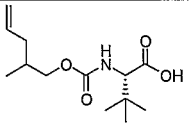
B3	L-Valine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-valine	230.3
B4	L-*t*-Butyl-glycine	3,3-Dimethyl-4-penten-1-ol Ref: *Tetrahedron Lett.* (**2004**), *45*, 2939.		*N*-{[(2,2-Dimethylpent-4-en-1-yl)oxy]carbonyl}-3-methyl-L-valine	272.3
B5	L-*t*-Butyl-glycine	5-Hexen-1-ol		*N*-[(Hex-5-en-1-yloxy)carbonyl]-3-methyl-L-valine	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

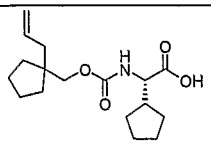
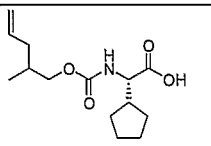
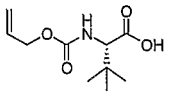
B12	L-Norvaline	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-norvaline	230.3
B13	L-Cyclopentyl-glycine	4-Penten-1-ol		(2*S*)-Cyclopentyl{[(pent-4-en-1-yloxy)carbonyl]amino}acetic acid	256.3
B14	2-Amino-4,4,4-trifluorobutanoic acid	5-Hexen-1-ol		4,4,4-Trifluoro-2-{[(hex-5-en-1-yloxy)carbonyl]amino}butanoic 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*-(*tert*-Butyl)- L-serine	4-Penten-1-ol		*O*-(*tert*-Butyl)-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-serine	218.3 $(M-tBu)^+$
B18	6,6,6-trifluoronorleucine	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)carbonyl]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
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: *Tetrahedron Lett.* (**2004**), *45*, 2939.		(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: *Tetrahedron Lett.* (**2004**), *45*, 2939.		(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

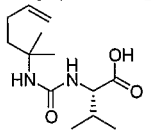
B28	L-Cyclohexyl-glycine	5-Hexen-1-ol		(2*S*)-Cyclohexyl{[(hex-5-en-1-yloxy)carbonyl]amino}acetic acid	284.4
B29	L-*t*-Butyl-glycine	(trans)-2-Allyl cyclopentanol Ref: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		*N*-({[(trans)-2-Allylcyclopentyl]oxy}carbonyl)-3-methyl-L-valine	284.2
B30	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
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
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

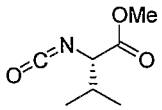
B41	L-Cyclohexyl-glycine	(trans)-2-Allyl cyclopentanol Ref: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		(2*S*)-[({[(trans)-2-Allylcyclopentyl]oxy} carbonyl)amino](cyclohexyl) acetic acid	310.5
B42	L-Cyclohexyl-glycine	(1-Allyl cyclopentyl) methanol Ref: *J. Org. Chem.* (**1992**), *57*, 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
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

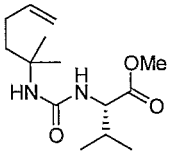


Step 1: Methyl *N*-(oxomethylene)-L-valinate



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 toluene (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 h, the reaction mixture was poured into ice cold 1M hydrochloric acid 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 hexane / 5 ethyl acetate) 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

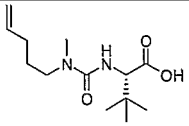
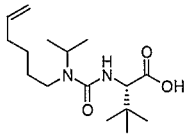


Methyl *N*-(oxomethylene)-L-valinate (2.80 g, 17.7 mmol) was added to 2-methylhex-5-en-2-amine [*J. Org. Chem.* (**1976**) *41*(5) 855-863.] (2.00 g, 17.7 mmol) in THF (15 mL). After 5 minutes, the reaction mixture was evaporated to give the title compound as a solid which was triturated with hexane and isolated by filtration (2.71g). LRMS $(M+H)^+ = 271.4$.

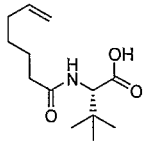
Step 3: *N*-{[(1,1-Dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine (Intermediate B50)

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, cooled to room temperature and THF removed by evaporation. Water was then added and the mixture extracted with DCM (4×). The aqueous layer was made acidic with 1M hydrochloric acid 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 $(M+H)^+ = 257.3$.

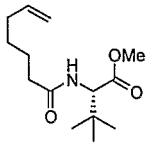
The following urea intermediates (B51-B52) were prepared using the chemistry described for the preparation of *N*-{[(1,1-dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine (as described in Intermediate B50), by utilizing the appropriate amino acid and amine.

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



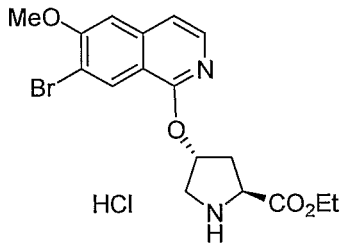
A solution of L-tert-leucine methyl ester (1.00 g, 6.89 mmol), 6-heptenoic acid (1.06 g, 8.26 mmol), EDC (1.58 g, 8.26 mmol) and HOAt (1.23 g, 8.26 mmol) in DMF (10 mL) was stirred at 22 °C for 2 h. The reaction mixture was diluted with aqueous saturated $NaHCO_3$ (30 mL), and extracted with EtOAc (3 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 (Intermediate B53)

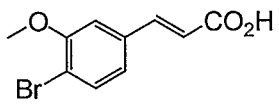
A solution of methyl *N*-hept-6-enoyl-3-methyl-L-valinate (1.40 g, 5.48 mmol) in THF (10 mL) and 1N NaOH (10 mL) was stirred at 22 °C for 2 h. The reaction mixture was acidified to pH 3 with 1 N HCl and extracted with EtOAc (3 x 150 mL). The combined EtOAc layers were washed with water (50 mL), brine (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].

Preparation of Intermediates C

Intermediate C1: Ethyl (4*R*)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-L-prolinate hydrochloride



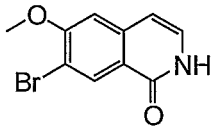
Step 1: (2E)-3-(4-Bromo-3-methoxyphenyl)acrylic acid



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), triethylamine (37.2 mL, 267 mmol) and palladium acetate (719 mg, 3.2 mmol). The reaction mixture was heated to 90 °C for 40 min, cooled to RT and poured into 2.4 L 1M HCl. After

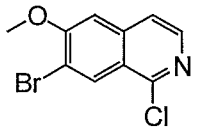
stirring for 30 min, the solid was filtered, heated to reflux in EtOH (230 mL), allowed to cool to RT and stirred overnight. The solid was filtered and washed with 1:1 EtOH hexane (50 mL) to give desired product. LRMS ESI$^+$ $(M+H)^+$ 257.0.

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



A portion of the product from Step 1 [(2E)-3-(4-bromo-3-methoxyphenyl)acrylic acid] (12.5 g, 48.6 mmol) was azeotroped with benzene and suspended in benzene (94 mL). Triethylamine (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 h. The mixture was filtered through a pad of silica and eluted with ~1 L of toluene, the volatiles evaporated, the residue resuspended in diphenylmethane (94 mL) and the mixture heated to reflux for three 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

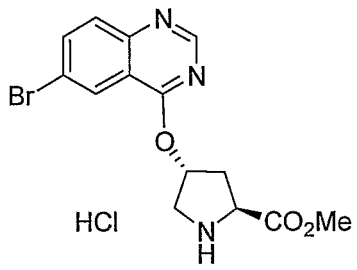


A mixture of the product from Step 2 (7-bromo-6-methoxyisoquinolin-1(2H)-one) (4.7 g, 18.5 mmol) in phosphorus oxychloride (30 mL) was heated to reflux for 2 h, cooled to RT, the volatiles evaporated and the residue partitioned between 3M NaOH and DCM. The organic phase was dried over Na_2SO_4, solvent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

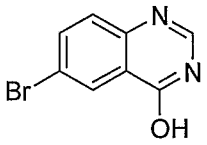
Step 4: Ethyl (4*R*)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (Intermedate C1)

The title compound was prepared from the product of Step 3 (7-bromo-1-chloro-6-methoxyisoquinoline), utilizing the procedure described in EXAMPLE 10, Step 1. LRMS ESI$^+$ $(M+H)^+$ 395.0.

Intermediate C2: Methyl (4*R*)-4-[(6-bromoquinazolin-4-yl)oxy]-L-prolinate hydrochloride

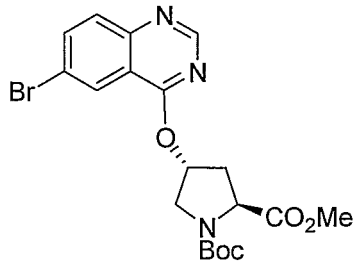


Step 1: 4-Hydroxy-6-bromoquinazoline



Bromoanthranilic acid (12.0 g, 55.5 mmol) and formamidine acetate (29.2 g, 281 mmol) were combined in acetic acid (96 mL) and heated to reflux for 2 h. The reaction mixture was cooled, concentrated to remove acetic acid and poured into water (500 mL). The reaction mixture was stirred for 0.5 h and resulting solids filtered. The solids were air dried to give a tan solid (12.0 g). LRMS $(M+H)^+ = 225.0$.

Step 2: 1-tert-Butyl 2-methyl (2S,4R)-4-[(6-bromoquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate

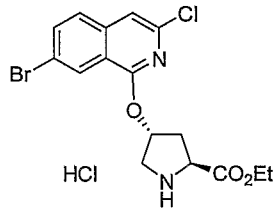


To a solution of N-boc-cis-hydroxyproline methyl ester (2.0 g, 8.15 mmol), 4-hydroxy-6-bromoquinazoline (1.84 g, 8.15 mmol) and triphenylphosphine (2.57 g, 9.79 mmol) at 0 °C in THF (80 mL) was added diisopropylazodicarboxylate (1.98 g, 9.79 mmol) dropwise. The mixture was stirred at 25 °C for 18 h. The reaction was diluted with EtOAc (100 mL), washed with 10% aqueous Na_2CO_3 (2 x 50 mL) and water (2 x 50 mL). The combined aqueous layers were backextracted with EtOAc (50 mL) and the combined EtOAc extracts dried over Na_2SO_4, filtered and concentrated to an oil. The oil was chromatographed on silica using 25 to 60% EtOAc/hexane to give the title compound (3.46 g). LRMS $(M+H)^+ = 452.2$.

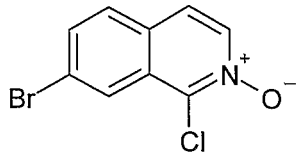
Step 3: Methyl (4*R*)-4-[(6-bromoquinazolin-4-yl)oxy]-L-prolinate hydrochloride (Intermedate C2)

To a solution of 1-tert-butyl 2-methyl (2S,4R)-4-[(6-bromoquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate (3.46 g, 6.65 mmol) in dioxane (80 mL) at 0 °C was introduced anhydrous HCl (g) over 30 min. The reaction was complete by HPLC/MS. The reaction mixture was concentrated and the resulting solids were azeotroped with diethyl ether (50 mL) to give the title compound (3.0 g). LRMS $(M+H)^+ = 352.2$.

Intermediate C3: Ethyl (4*R*)-4-[(7-bromo-3-chloroisoquinolin-1-yl)oxy]-L-prolinate hydrochloride

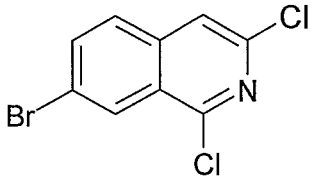


Step 1: 7-Bromo-1-chloroisoquinoline 2-oxide



To a solution of 7-bromo-1-chloroisoquinoline (4.0 g, 15.8 mmol) in DCM (100 mL) at 0 °C was added mCPBA (~77%, 7.46 g, 33.3 mmol). The reaction was allowed to stir at room temperature for 24 hours, diluted with DCM (100 mL) and washed with 1N NaOH and brine. The DCM extracts were dried over Na_2SO_4, filtered, concentrated and chromatographed on silica eluting with 5 to 15% acetone/DCM to give the title compound (1.43 g). LRMS $(M+H)^+ = 258.0$.

Step 2: 7-Bromo-1,3-dichloroisoquinoline

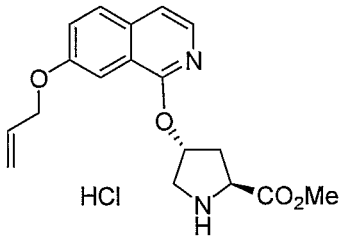


7-Bromo-1-chloroisoquinoline 2-oxide (1.43 g, 5.56 mmol) and $POCl_3$ (20 mL) were heated at reflux for 2 h. The reaction mixture was cooled and carefully poured onto a mixture of ice/water (500 g), stirred for 1 h and the pH adjusted to 10.0 with 10M NaOH. The mixture was extracted with chloroform (2x100 mL) and the chloroform extracts washed with brine, dried over $MgSO_4$, filtered and concentrated to give the title compound (1.40 g). LRMS $(M+H)^+ = 276.0$.

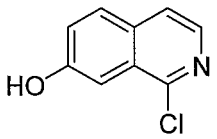
Step 3: Ethyl (4*R*)-4-[(7-bromo-3-chloroisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (Intermediate C3)

Ethyl (4*R*)-4-[(7-bromo-3-chloroisoquinolin-1-yl)oxy]-L-prolinate hydrochloride was prepared from 7-bromo-1,3-dichloroisoquinoline according to the procedure for EXAMPLE 10, Step 1. LRMS $(M+H)^+ = 399.1$.

Intermediate C4: Methyl (4*R*)-4-{[7-(allyloxy)isoquinolin-1-yl]oxy}-L-prolinate

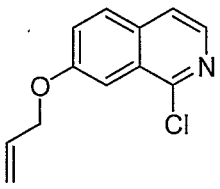


Step 1: 1-Chloroisoquinolin-7-ol



7-Bromo-1-chloroisoquinoline (2.0 g, 8.25 mmol), bis(pinacolato)diboron (2.20 g, 8.66 mmol), potassium acetate (2.43 g, 24.7 mmol) and $PdCl_2$(dppf)DCM adduct (0.337 g, 0.412 mmol) were combined under nitrogen in dioxane (40 mL) and heated in an oil bath at 100 °C for 24 h. The reaction mixture was cooled, diluted with EtOAc (100 mL) and washed with 10% aqueous $KHSO_4$. The organic phase was dried over Na_2SO_4, filtered and concentrated to an oil. The oil was dissolved in acetone (100 mL) and a solution of Oxone (5.07 g, 8.25 mmol) in water (20 mL) added over 2 min. The reaction mixture was stirred for 10 min, diluted with aqueous sodium bisulfate solution and stirred for an additional 20 min. and then concentrated to remove acetone. The resulting mixture was filtered to give the title compound (1.4 g) which was used without further purification. LRMS $(M+H)^+ = 180.1$.

Step 2: 7-(Allyloxy)-1-chloroisoquinoline



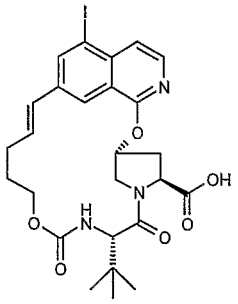
1-Chloroisoquinolin-7-ol (4.87 gm, 20,34 mmol) and cesium carbonate (6.63 g, 20.34 mmol) were combined in acetonitrile (100 mL) and stirred for 2 min. Allyl bromide (1.76 mL, 20.34 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was diluted with aqueous $KHSO_4$ (40 mL) and EtOAc (100mL) and stirred. The organic extract was removed, dried over Na_2SO_4, concentrated and chromatographed on silica gel using 20-50% EtOAc/hexanes to give 0.85 g of an oil which solidified upon storing in the freezer. LRMS $(M+H)^+ = 220.1$.

Step 3: Methyl (4*R*)-4-{[7-(allyloxy)isoquinolin-1-yl]oxy}-L-prolinate (Intermedate C4)

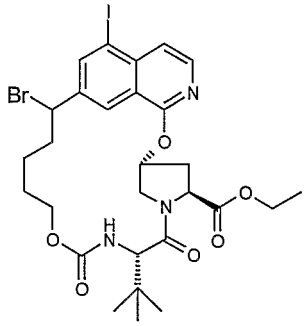
Intermediate C4 was prepared according to the procedure described in Example 10 Step 1, using 7-(allyloxy)-1-chloroisoquinoline. LRMS $(M+H)^+ = 329.3$.

Preparation of Intermediates D

Intermediate D1: (2R,4S,7S)-7-tert-Butyl-22-iodo-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-carboxylic acid



Step 1: Ethyl (2R,4S,7S)-15-bromo-7-tert-butyl-22-iodo-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



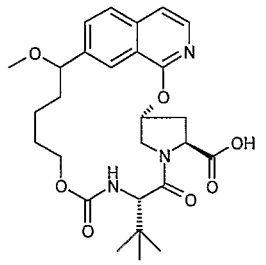
Ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (120 mg, 0.188 mmol) was dissolved in carbon tetrachloride (3 mL),

followed by the addition of N-bromosuccinimide (37 mg, 0.207 mmol) and catalytic benzoyl peroxide (4 mg). The reaction mixture was heated to reflux under N_2 for 3 h, cooled and concentrated and the resulting residue was purified on silica gel (10-60% EtOAc in hexanes) to yield the title compound as a white foam (113 mg). LRMS $(M+H)^+ = 716.4$.

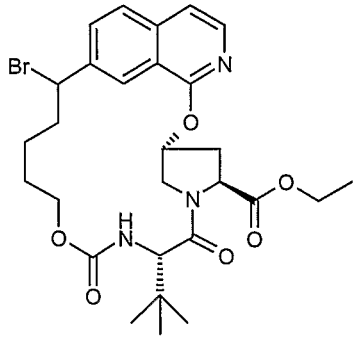
Step 2: (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid (Intermedate D1)

To a solution of the product from Step 1 (43 mg, 0.06 mmol) in THF (2 mL), under nitrogen, was added 1M potassium t-butoxide in THF (0.09 mL, 0.09 mmol), the reaction mixture stirred for 30 min and then a second portion of potassium t-butoxide (0.03 mL, 0.03 mmol) added. The reaction mixture was stirred for 45 min, diluted with water, acidified with 1N HCl and extracted with EtOAc (x2). The combined organics were washed with brine, dried over Na_2SO_4, filtered, concentrated, and azeotroped from Et_2O to yield the crude title compound as a dark yellow solid (36 mg). LRMS $(M+H)^+ = 608.4$.

Intermediate D2: (2R,4S,7S)-7-tert-Butyl-15-methoxy-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-carboxylic acid



Step 1: Ethyl (2R,4S,7S)-15-bromo-7-tert-butyl-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

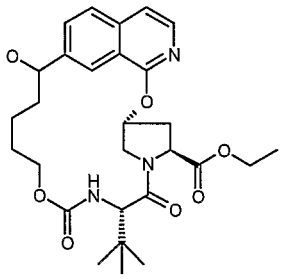


Ethyl (2R,4S,7S)-15-bromo-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared according to the procedure described for Intermediate D1, Step 1, starting with ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 11, Step 1). LRMS $(M+H)^+ = 590.5$.

Step 2: (2R,4S,7S)-7-tert-Butyl-15-methoxy-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-carboxylic acid (Intermedate D2)

A solution of the product from Step 1 (78 mg, 0.132 mmol) in MeOH (4 mL) was heated at 60 C for 6 h. Sodium hydroxide (1N, 0.528 mL, 0.528 mmol) was added and the reaction mixture was stirred for 4 h. The reaction mixture was concentrated and the resulting residue was partitioned between EtOAc and 1N HCl (x2). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield the title compound as a white foam (68 mg). LRMS $(M+H)^+ = 514.3$.

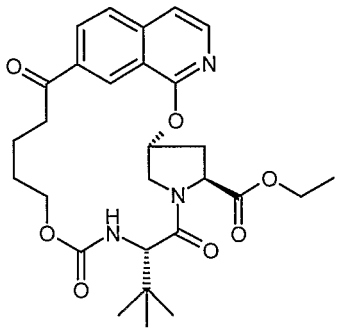
Intermediate D3: Ethyl (2R,4S,7S)-7-tert-butyl-15-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



To a solution of ethyl (2R,4S,7S)-15-bromo-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-

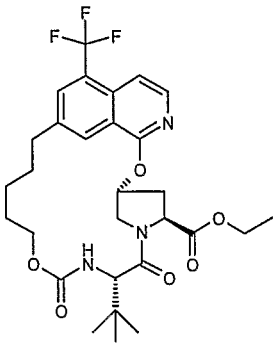
k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermediate D2, Step 1) (89 mg, 0.151 mmol) in acetone (1 mL) was added a solution of silver nitrate (38 mg, 0.226 mmol) in H_2O (1mL). The reaction mixture was stirred in the dark for 16 h filtered, concentrated, and the resulting residue partitioned between DCM and H_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified on silica gel (15% to 60% EtOAc in hexanes) to yield the title compound as a white foam (37 mg). LRMS $(M+H)^+ = 528.8$.

Intermediate D4: Ethyl (2R,4S,7S)-7-tert-butyl-6,9,15-trioxo-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



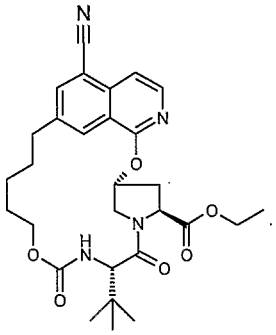
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-15-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermediate D3) (70 mg, 0.133 mmol) in DCM (3 mL) was added PCC (41 mg, 0.191 mmol) and the reaction mixture stirred for 4 h, filtered, concentrated, and the resulting residue purified on silica gel (0% to 5% acetone in DCM) to yield the title compound as a white solid (59 mg). LRMS $(M+H)^+ = 526.5$.

Intermediate D5: Ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-22-(trifluoromethyl)-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



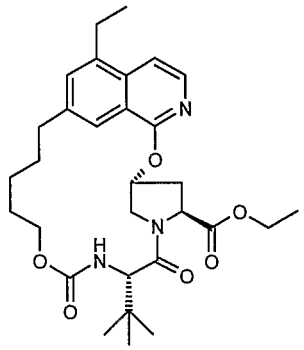
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (25 mg, 0.039 mmol) in DMF (1.5 mL) was added methyl fluorosulphonyldifluoroacetate (0.015 mL, 0.118 mmol) and copper (I) iodide (22 mg, 0.118 mmol). The mixture was heated to 150 °C in a microwave for 10 min, cooled, filtered, concentrated, and the resulting residue purified on silica gel (10% to 50% EtOAc in hexanes) to yield the title compound as a white solid (20 mg). LRMS $(M+H)^+ = 580.5$.

Intermediate D6: Ethyl (2R,4S,7S)-7-tert-butyl-22-cyano-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

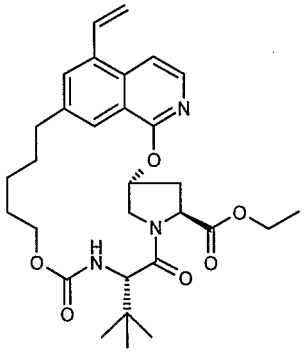


To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (75 mg, 0.118 mmol) in DMF (1.5 mL) was added copper (I) cyanide (32 mg, 0.353 mmol) and the mixture heated to 150 °C in a sealed tube for 4 h. The reaction mixture was partitioned between EtOAc and saturated $NaHCO_3$ (x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude material was purified on silica gel (10% to 50% EtOAc in hexanes) to yield the title compound as a white foam (40 mg). LRMS $(M+H)^+ = 537.4$.

Intermediate D7: Ethyl (2R,4S,7S)-7-tert-butyl-22-ethyl-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



Step 1: Ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-22-vinyl-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



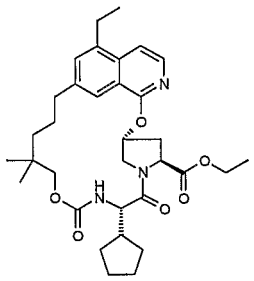
Nitrogen was bubbled through a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (90 mg, 0.141 mmol) in toluene (2 mL) for 30 min. Tributyl(vinyl)tin (0.049 mL, 0.169 mmol) and tetrakis(triphenylphosphine) palladium (0) (16 mg, 0.014 mmol) were added and the reaction mixture heated to reflux for 2 h. The cooled reaction mixture was concentrated and the residue purified by chromatography on silica gel (10% to 60% EtOAc in hexanes) to yield the title compound as a clear oil (58 mg). LRMS $(M+H)^+ = 538.5$.

Step 2: Ethyl (2R,4S,7S)-7-tert-butyl-22-ethyl-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 (Intermedate D7)

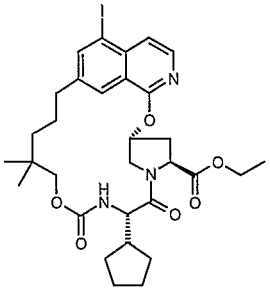
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-22-vinyl-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (58 mg, 0.108 mmol) in ethanol (5 mL) was added

10% palladium on carbon catalyst (20 mg). The reaction mixture was placed under a hydrogen balloon and stirred for 16 h. The reaction mixture was filtered, concentrated, and the title compound was obtained as white foam (46 mg). LRMS $(M+H)^+ = 540.5$.

Intermediate D8: Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



Step 1: Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-iodo-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



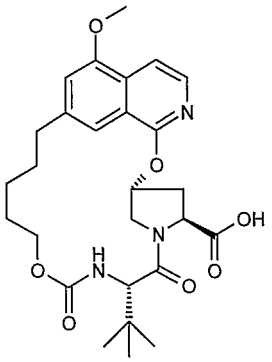
Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-iodo-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared according to the procedure described for EXAMPLE 13, Step 1 using ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 15, Step 1). LRMS $(M+H)^+ = 678.3$.

Step 2: Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermedate D8)

Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-

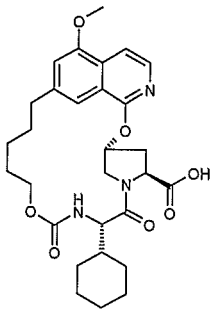
k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermediate D8) was prepared according to the procedure described for Intermediate D7 using ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-iodo-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate. LRMS $(M+H)^+$ = 580.3.

Intermediate D9: (2R,4S,7S)-7-tert-butyl-22-methoxy-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-carboxylic acid

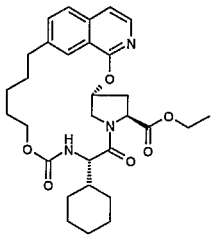


To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (195 mg, 0.306 mmol) in MeOH (4 mL) was added sodium methoxide (30% in MeOH, 0.17 mL, 0.918 mmol) and copper (I) iodide (9 mg, 0.046 mmol). The reaction mixture was heated to 100 °C in the microwave for 20 min, cooled, sodium hydroxide (1N, 1.0 mL, 1.0 mmol) added and the reaction mixture was stirred for 4 h. The mixture was filtered, concentrated, and the residue partitioned between EtOAc and 1N HCl (x3). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude title compound as a yellow oil. LRMS $(M+H)^+$ = 514.4.

Intermediate D10: (2*R*,4*S*,7*S*)-7-Cyclohexyl-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid

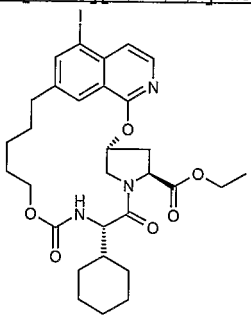


Step 1: Ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



Ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared using the procedures described in EXAMPLE 14, Steps 1-3 using Intermediate B8 in Step 1, followed by hydrogenation according to the procedure given in EXAMPLE 15, Step 1. LRMS $(M+H)^+ = 538.4$.

Step 2: Ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



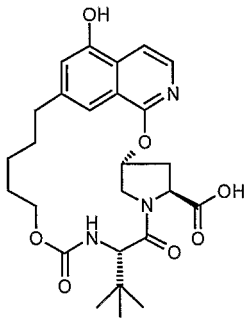
Ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared according to the procedure described for EXAMPLE 13, Step 1 using ethyl

(2*R*,4*S*,7*S*)-7-cyclohexyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate. LRMS $(M+H)^+$ = 664.4.

Step 3: (2*R*,4*S*,7*S*)-7-Cyclohexyl-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid (Intermediate D10)

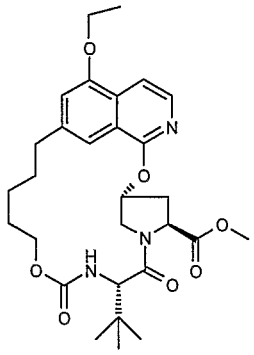
Intermediate D10 was prepared according to the procedure described for Intermediate D9 using ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate. LRMS $(M+H)^+$ = 540.4.

Intermediate D11: (2R,4S,7S)-7-tert-butyl-22-hydroxy-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-carboxylic acid

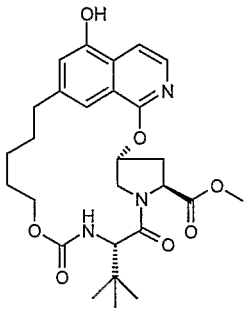


To a solution of (2R,4S,7S)-7-tert-butyl-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid (Intermediate D9) (53 mg, 0.103 mmol) in DCM (2 mL) was added boron tribromide (1M in DCM, 0.31 mL, 0.31 mmol) at -78 °C and the reaction mixture stirred for 1 h, then slowly warmed to RT and stirred for 1h. The reaction mixture was quenched with several drops of MeOH and H_2O and then concentrated. The residue was partitioned between EtOAc and 1N HCl (x3). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude title compound as a gray solid (33 mg). LRMS $(M+H)^+$ = 500.3.

Intermediate D12: Methyl (2R,4S,7S)-7-tert-butyl-22-ethoxy-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



Step 1: Methyl (2R,4S,7S)-7-tert-butyl-22-hydroxy-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



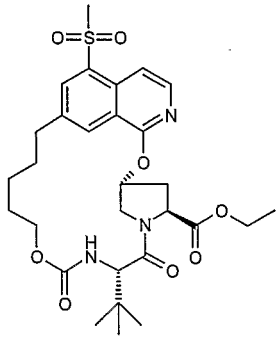
To a solution of (2R,4S,7S)-7-tert-butyl-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid (Intermediate D9) (53 mg, 0.103 mmol) in DCM (2 mL) was added boron tribromide (1M in DCM, 0.31 mL, 0.31 mmol) at -78 C and the reaction mixture was stirred for 1 h. Slowly warmed to RT and stirred for 1 h. The reaction was quenched with excess MeOH and then concentrated. The resulting residue was partitioned between EtOAc and 1N HCl. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude title compound as a gray solid (33 mg). LRMS $(M+H)^+ = 514.3$.

Step 2: Methyl (2R,4S,7S)-7-tert-butyl-22-ethoxy-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 (Intermedate D12)

To a solution of methyl (2R,4S,7S)-7-tert-butyl-22-hydroxy-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 (254 mg, 0.495 mmol) in DMF (5 mL) was added

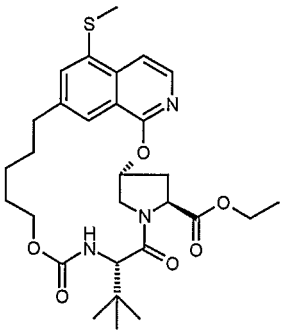
iodoethane (0.079 mL, 0.989 mmol) and DBU (0.185 mL, 1.24 mmol) and the reaction mixture stirred for 16 h. The reaction mixture was partitioned between EtOAc and 1N HCl. The layers were separated and the organic layer was washed with 1N HCl (2x), brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude compound was purified on silica gel (gradient elution 15% to 35% EtOAc in hexanes) to yield the title compound as a white foam (82 mg). LRMS $(M+H)^+ = 542.3$.

Intermediate D13: Ethyl (2R,4S,7S)-7-tert-butyl-22-(methylsulfonyl)-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



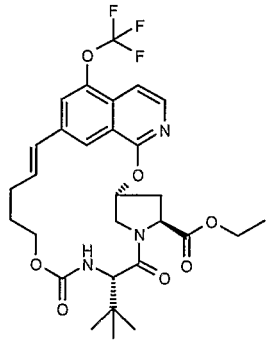
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (50 mg, 0.078 mmol) in DMSO (1 mL) was added sodium methanesulfinate (10 mg, 0.094 mmol), copper (I) trifluoromethanesulfonate toluene complex (1 mg, 0.004 mmol) and N,N'-dimethylethylendiamine (1 mg, 0.008 mmol). The reaction mixture was heated in a sealed tube at 110 °C for 16 h, cooled and partitioned between EtOAc and H_2O. The organic layer was washed with H_2O (2x), brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified on silica gel (25% to 60% EtOAc in hexanes) to yield the title compound as a white solid (23 mg). LRMS $(M+H)^+ = 590.3$.

Intermediate D14: Ethyl (2R,4S,7S)-7-tert-butyl-22-(methylthio)-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



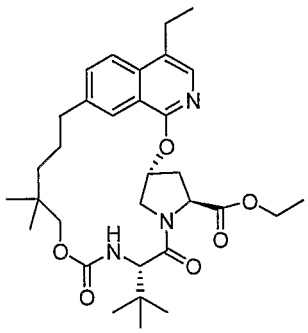
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (50 mg, 0.078 mmol) in pyridine (1 mL) was added dimethyldisulfide (0.004 mL, 0.039 mmol), and copper dust (1 mg, 0.016 mmol) and the mixture heated in a sealed tube at 100 °C for 16 h. The cooled reaction mixture was partitioned between EtOAc and 1N HCl and the layers were separated. The organic layer was washed with 1N HCl (2x), brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude title compound as a yellow oil. LRMS $(M+H)^+ = 558.4$.

Intermediate D15: Ethyl (2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate

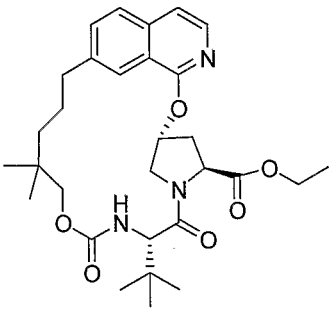


Ethyl (2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared according to the procedures described for Intermediate C1 using 4-bromo-2-(trifluoromethoxy)iodobenzene in Step 1, followed by the procedures described in EXAMPLE 14, Steps 1-3 using Intermediate B2 in Step 1. LRMS $(M+H)^+ =$ 596.3.

Intermediate D16: Ethyl (2R,4S,7S)-7-tert-butyl-19-ethyl-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

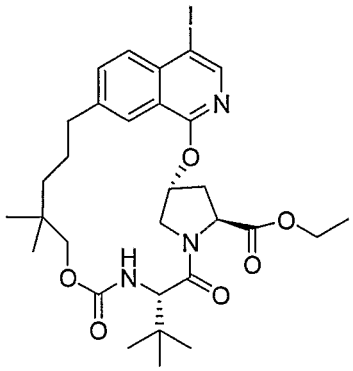


Step 1: Ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



Ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared using the procedure described for EXAMPLE 14, Steps 1-3 using Intermediate B4 in Step 1, followed by the hydrogenation procedure described in EXAMPLE 15, Step 1. LRMS $(M+H)^+ = 540.3$.

Step 2: Ethyl (2R,4S,7S)-7-tert-butyl-19-iodo-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



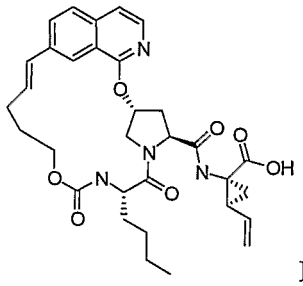
To a solution of ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (0.5 g, 0.93 mmol) in DCM (5 mL) was added triflic acid (0.165 ml, 1.853 mmol) and N-iodosuccinimide (208 mg, 0.93 mmol) and the mixture stirred under N_2 for 16 h. An additional portion of NIS (208 mg, 0.93 mmol) was added and the reaction mixture was stirred for an additional 24 h. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with DCM (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude compound was purified on silica gel (20% to 40% EtOAc in hexanes) to yield the title compound as a white foam (170 mg). LRMS $(M+H)^+ = 666.4$.

Step 3: Ethyl (2R,4S,7S)-7-tert-butyl-19-ethyl-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 (Intermedate D16)

Ethyl (2R,4S,7S)-7-tert-butyl-19-ethyl-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 was prepared using the procedure described for Intermediate D7, Steps 1 and 2 using ethyl (2R,4S,7S)-7-tert-butyl-19-iodo-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. LRMS $(M+H)^+ = 568.4$.

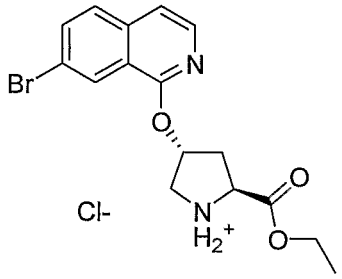
EXAMPLE 1

(1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (**III-1**)



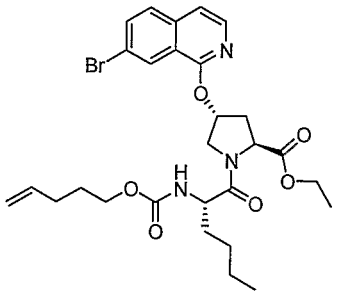
III-1

Step 1: Ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride



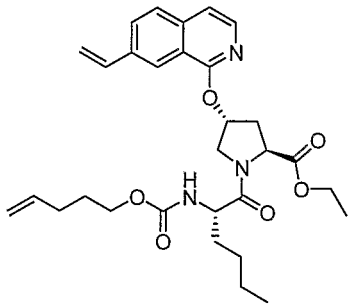
To a solution of trans 4-hydroxy L-BOC-proline (4.83 g, 20.9 mmol) in 100 mL DMSO at room temperature was added potassium t-butoxide (7.03 g, 62.66 mmol) in a single portion. The reaction mixture was stirred at r.t. for 30 min, cooled to 17 °C and 7-bromo-1-chloroisoquinoline (5.06 g, 20.9 mmol) added, the reaction allowed to warm to r.t. and stirred overnight. The reaction mixture was quenched with ice-cold 10% citric acid solution and partitioned with ethyl acetate. The organic layer was washed with aqueous citric acid solution, water and brine and the aqueous phases back extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate and the solvent evaporated to dark solid. The solid was dissolved in ethanol (120 mL), cooled to 0 °C and HCl bubbled through until the solution was saturated. The reaction mixture was then stirred at room temperature for 48 h and the volatiles evaporated under reduced pressure. The remaining solid was azeotroped with ethanol (4 x 100 mL) to give 11.95 g (>100% crude) of a gray solid used directly in the next step. LRMS (ESI) *m/z* 365 [$(M+H)^+$; calcd for $C_{16}H_{18}BrN_2O_3$: 365].

Step 2: Ethyl *N*-[(pent-4-en-1-yloxy)carbonyl]-l-norleucyl-(4R)-4-[(7-bromoisoquinolin-1-yl)oxy]-L-prolinate



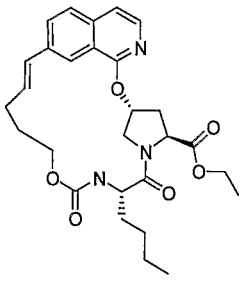
To a solution of crude ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (4 g, ~11 mmol) in DMF (30 mL) was added *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucine (Intermediate B1) (4.0 g, 16.4 mmol), diisopropylethylamine (4.9 mL, 27 mmol) and TBTU (5.13 g, 16 mmol). The reaction mixture was stirred at room temperature overnight and partitioned between water and ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate and the solvent was then evaporated. The crude product was purified by chromatography on silica (10-100% EtOAc hexane) to give desired product (3.3 g). LRMS (ESI) *m/z* 590 [$(M+H)^+$; calcd for $C_{28}H_{37}BrN_3O_6$: 590].

Step 3: Ethyl N-[(pent-4-en-1-yloxy)carbonyl]-L-norleucyl-(4R)-4-[(7-vinylisoquinolin-1-yl)oxy]-L-prolinate



The bromide from step 2 (62 mg, 0.105 mmol) was dissolved in 5 mL toluene and nitrogen bubbled through for 15 min. Tributylvinyltin (0.037 mL, 0.126 mmol) and tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol) were added and the reaction mixture heated to 100 °C under nitrogen. After 5h, the reaction was complete, the volatiles were evaporated and the residue purified by silica gel chromatography (10-75% EtOAc / hexane) to give a clear oil. LRMS (ESI) *m/z* 538 [$(M+H)^+$; calcd for $C_{30}H_{40}N_3O_6$: 538].

Step 4: Ethyl (2R,4S,7S)-7-butyl-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]dioxodiazacyclononadecine-4-carboxylate



The olefin from Step 3 (40 mg, 0.074 mmol) was dissolved in dichloroethane (10 mL) and nitrogen bubbled through the solution for 15 min. Dichloro(5-chloro-2-isopropoxybenzylidene)(1,3-

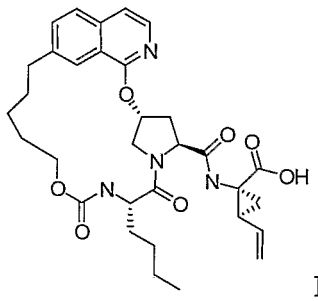
dimesitylimidazolidin-2-ylidene)ruthenium (Zhan ruthenium metathesis catalyst RC-301, Zhan Catalyst I (as depicted as J on page 35), RC-301, Zannan Pharma Ltd.) (5 mg, 0.007 mmol) was added and the reaction mixture heated in an 80 °C oil bath for 2 h, after which reaction was complete. Volatiles were evaporated and the residue purified by silica gel chromatography (10-75% EtOAc / hexane) to give the title compound (24 mg). LRMS (ESI) *m/z* 510 [$(M+H)^+$; calcd for $C_{28}H_{36}N_3O_6$: 510].

Step 5: (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid

The ester from Step 4 (24 mg, 0.047 mmol) was dissolved in THF (0.5 mL) and EtOH (0.5 mL) and a solution of LiOH in water (5 mg in 0.5 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h after which HPLC analysis indicated complete reaction and 1M HCl (0.2 mL) was added and the mixture was evaporated to a solid. The solid was dissolved in DMF (2 mL) and (1R,2S)-1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester hydrochloride (Intermediate A2)(Llinas-Brunet et al US6,323,180 and Wang et al WO 03/099274) ((4 mg, 0.019 mmol), diisopropylethylamine (0.017 mL, 0.095 mmol), and TBTU (6 mg, 0.019 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was purified directly by reverse phase HPLC to yield a white foam which was dissolved in THF (0.25 mL) and ethanol (0.25 mL) and a solution of LiOH in water (4.5 mg in 0.25 mL) was added. The reaction mixture was heated to 40 °C for 2 h, cooled to room temperature, 3M HCl (0.06 mL) and DMF (0.5 mL) were added and the reaction mixture was purified by reverse phase HPLC to give the desired product as solid. LRMS (ESI) *m/z* 591 [$(M+H)^+$; calcd for $C_{32}H_{39}N_4O_7$: 591].

EXAMPLE 2

(1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (**III-2**)



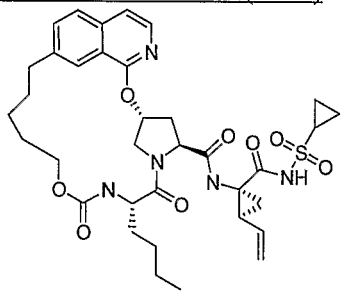
III-2

A solution of the olefin prepared as described in Example 1, Step 4 (180 mg, 0.353 mmol) in ethyl acetate (10 mL) was treated with 10% Pd/C and hydrogenated under a balloon of

hydrogen for 18 h. The catalyst was removed by filtration and the filtrate was evaporated to give an oil. The oil was treated as described in Example 1, Step 5 to afford the title compound. LRMS (ESI) *m/z* 593 $[(M+H)^+$; calcd for $C_{32}H_{40}N_4O_7$: 593].

EXAMPLE 3

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,15,16-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-3**)

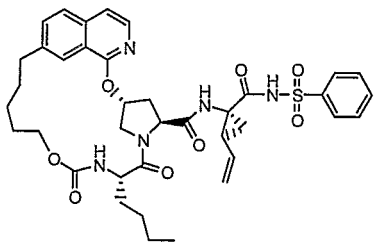


III-3

The title compound was prepared as described for Example 2, by using (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (Intermediate A1)(Wang *et al* WO 03/099274) in place of (1R,2S)-1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester hydrochloride in the coupling step. LRMS (ESI) *m/z* 696 $[(M+H)^+$; calcd for $C_{35}H_{45}N_5O_8S$: 696]. ^1H NMR (500 MHz, CD_3OD, ppm) δ 9.28 (s, 1 H), 7.97 (s, 1 H), 7.88 (d, J = 5.9 Hz, 1 H), 7.72 (d, J = 8.3 Hz, 1 H), 7.56 (dd, J = 8.3 and 1.7 Hz, 1 H), 7.28 (d, J = 5.9 Hz, 1 H), 6.13 (m, 1 H), 5.74 (m, 1 H), 5.27 (dd, J = 17.1 and 1.2 Hz, 1 H), 5.10 (dd, J = 10.3 and 1.5 Hz, 1 H), 4.65 (d, J = 11.2 Hz, 1 H), 4.53 (m, 1 H), 4.44 (t, J = 7.6 Hz, 1 H), 4.32 (m, 1 H), 3.99 (dd, J = 11.7 and 3.2 Hz, 1 H), 3.73 (m, 1 H), 2.96 (m, 1 H), 2.87 (m, 1 H), 2.71 (m, 1 H), 2.54 (m, 1 H), 2.28 (m, 1 H), 2.20 (m, 1 H), 1.60-1.90 (m, 6 H), 1.51 (m, 1 H), 1.12-1.40 (m, 10 H), 0.94 (t, J = 6.8 Hz, 3 H).

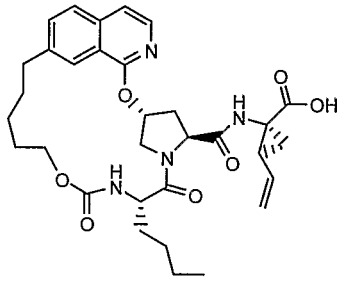
EXAMPLE 4

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{[(phenylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-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-carboxamide (**III-4**)



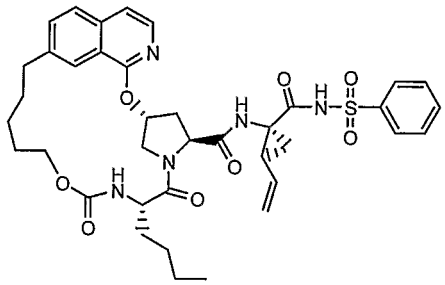
III-4

Step 1: (1R,2S)-1-({[(2R,4S,7S)-7-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyridine[2,3-k][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid



To a solution of the ethyl ester (initial hydrogenation product from Example 2) (400mg, 0.65 mmol) in tetrahydrofuran (10 mL), ethanol (5 mL) and water (5 mL) were added lithium hydroxide (155 mg, 6.45 mmol) and the mixture let stir at 40 °C for 24 h. The reaction was cooled, concentrated in vacuo to remove tetrahydrofuran and ethanol and diluted with 3N HCL (2.5 mL). The reaction was allowed to stir for 30 min and the resulting solids filtered and washed with water (1 mL). The solid was air dried to give the title compound as a white solid (0.44 g). LRMS (ESI) *m/z* 593 [$(M+H)^+$; calcd for $C_{32}H_{41}N_4O_7$: 593].

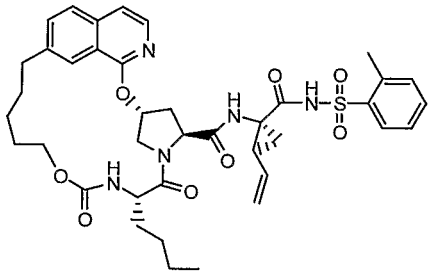
Step 2: (2R,4S,7S)-7-Butyl-6,9-dioxo-N-((1R,2S)-1-{[(phenylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyridine[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide



To a solution of the acid from Step 1 (30 mg, 0.05 mmol) in DMF (0.34 mL), under nitrogen, was added carbonyldiimidazole (13 mg, 0.078 mmol) and the mixture stirred at 40 °C for 2 hr. Benzenesulfonamide (12 mg, 0.078 mmol) was added and the reaction stirred overnight at 40 °C. The reaction was directly purified by reverse phase chromatography and the resulting product was concentrated in vacuo to give the title compound as a white solid (18 mg). LRMS (ESI) *m/z* 732 [$(M+H)^+$; calcd for $C_{38}H_{46}N_5O_8S$: 732].

EXAMPLE 5

(2R,4S,7S)- N-((1R,2S)-1-{[(2-methylphenylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyridine[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-5**)

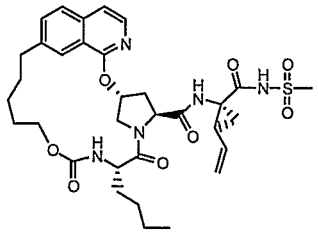


III-5

The title compound was prepared in a similar manner to that described in Example 4, replacing benzenesulfonamide with 2-methylphenylsulfonamide. LRMS (ESI) *m/z* 746 [$(M+H)^+$; calcd for $C_{39}H_{48}N_5O_8S$: 746].

EXAMPLE 6

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{[(methylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-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-carboxamide (**III-6**)

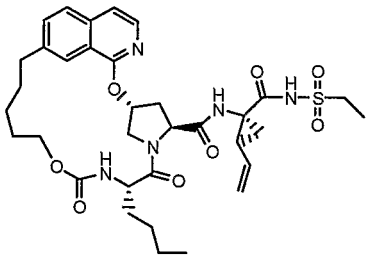


III-6

The title compound was prepared in a similar manner to that described in Example 4, replacing benzenesulfonamide with methanesulfonamide. LRMS (ESI) *m/z* 670 [(M+H)$^+$; calcd for $C_{33}H_{43}N_5O_8S$: 670].

EXAMPLE 7

(2R,4S,7S)-7-butyl-N-((1R,2S)-1-{[(ethylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-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-carboxamide (**III-7**)

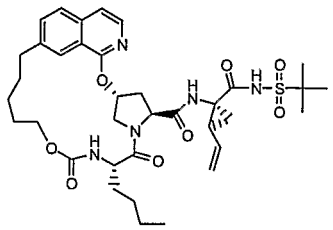


III-7

The title compound was prepared in a similar manner to that described in Example 4, replacing benzenesulfonamide with ethanesulfonamide. LRMS (ESI) *m/z* 684 [(M+H)$^+$; calcd for $C_{34}H_{46}N_5O_8S$: 684].

EXAMPLE 8

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{[(t-butylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-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-carboxamide (**III-8**)



III-8

The title compound was prepared in a similar manner to that described in Example 4, replacing benzenesulfonamide with t-butylsulfonamide. LRMS (ESI) *m/z* 712 [$(M+H)^+$; calcd for $C_{36}H_{50}N_5O_8S$: 712].

EXAMPLE 9

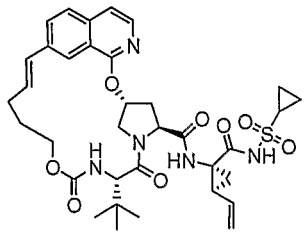
HCV NS3 protease time-resolved fluorescence (TRF) assay

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

Compounds **III-1** and **III-3** to **III-9, III-10, III-12, III-14, III-15, III-20, III-23, III-24, III-25, III-28, III-29, III-31, III-32, III-34, III-37, III-38, III-39 to III-46 and III-48 to III-185** were tested to have a Ki value of less than 100 nM in the NS3 protease TRF assay as described above.

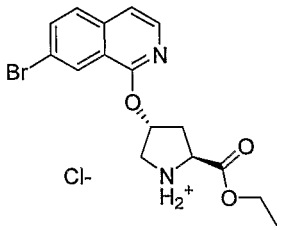
EXAMPLE 10

(1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (**III-23**)



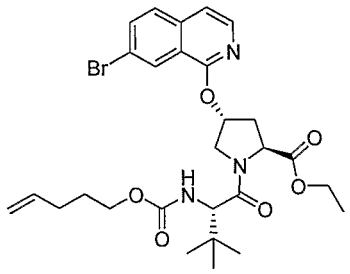
III-23

Step 1: Ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride



To a solution of trans 4-hydroxy L-BOC-proline (4.83 g, 20.9 mmol) in 100 mL DMSO at room temperature was added potassium t-butoxide (7.03 g, 62.66 mmol) in a single portion. The reaction mixture was stirred at r.t. for 30 min, cooled to 17 °C and 7-bromo-1-chloroisoquinoline (5.06 g, 20.9 mmol) added, the reaction allowed to warm to r.t. and stirred overnight. The reaction mixture was quenched with ice-cold 10% citric acid solution and partitioned with ethyl acetate. The organic layer was washed with aqueous citric acid solution, water and brine and the aqueous phases back extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate and the solvent evaporated to dark solid. The solid was dissolved in ethanol (120 mL), cooled to 0°C and HCl bubbled through until the solution was saturated. The reaction mixture was then stirred at room temperature for 48 h and the volatiles evaporated under reduced pressure. The remaining solid was azeotroped with ethanol (4 x 100 mL) to give 11.95 g (>100% crude) of a gray solid used directly in the next step. LRMS (ESI) *m/z* 365 $[(M+H)^+$; calcd for $C_{16}H_{18}BrN_2O_3$: 365].

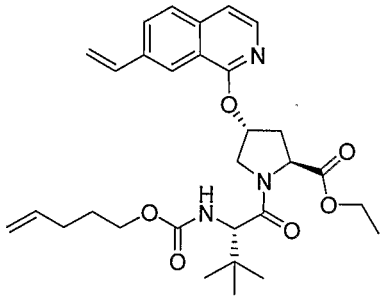
Step 2: Ethyl *N*-[(pent-4-en-1-yloxy)carbonyl]-l-tert-butyl-(4R)-4-[(7-bromoisoquinolin-1-yl)oxy]-L-prolinate



To a solution of crude ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (1.03 g, ~2.6 mmol) in DMF (10 mL) was added *N*-[(pent-4-en-1-yloxy)carbonyl]-L-tert-

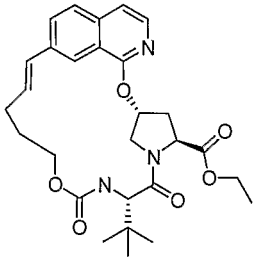
butylglycine (Intermediate B2) (0.44 g, 1.81 mmol), diisopropylethylamine (1.8 mL, 10.4 mmol) and TBTU (1.25 g, 3.9 mmol). The reaction mixture was stirred at room temperature overnight and partitioned between water and ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate and the solvent was then evaporated. The crude product was purified by chromatography on silica (20-60% EtOAc hexane) to give desired product (0.9 g). LRMS (ESI) *m/z* 590 [$(M+H)^+$; calcd for $C_{28}H_{37}BrN_3O_6$: 590].

Step 3: Ethyl N-[(pent-4-en-1-yloxy)carbonyl]-L-tert-butylglycine-(4R)-4-[(7-vinylisoquinolin-1-yl)oxy]-L-prolinate



The bromide from step 2 (0.90 gm, 1.53 mmol) was dissolved in toluene (20 mL) and nitrogen bubbled through for 15 min. Tributylvinyltin (0.54 mL, 1.83 mmol) and tetrakis(triphenylphosphine)palladium(0) (178.0 mg, 0.153 mmol) were added and the reaction mixture heated to 100 °C under nitrogen. After 3h, the reaction was complete, the volatiles were evaporated and the residue purified by silica gel chromatography (20-50% EtOAc / hexane) to give a clear oil. LRMS (ESI) *m/z* 538 [$(M+H)^+$; calcd for $C_{30}H_{40}N_3O_6$: 538].

Step 4: Ethyl (2R,4S,7S)-7-tert-butyl-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]dioxodiazacyclononadecine-4-carboxylate



The olefin from Step 3 (1.0 gm, 1.86 mmol) was dissolved in dichloromethane (200 mL) and nitrogen bubbled through the solution for 30 min. Bis(tricyclohexylphosphine)-3-phenyl-1H-indene-1ylideneruthenium dichloride (Neolyst M1 catalyst, Strem Chemicals, CAS#250220-36-1) (300 mg, 0.30 mmol) dissolved in degassed dichloromethane was added over 30 minutes and the reaction let stir 24hrs or until complete. Volatiles were evaporated and the residue purified by silica gel chromatography (20-

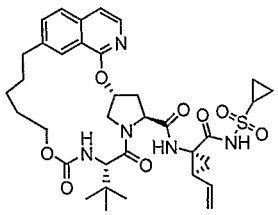
60% EtOAc / hexane) to give the title compound (0.73 gm). LRMS (ESI) *m/z* 510 [(M+H)$^+$; calcd for $C_{28}H_{36}N_3O_6$: 510].

Step 5: (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid

The ester from Step 4 (0.73 gm, 0.1.43 mmol) was dissolved in THF (20 mL) and EtOH (10 mL) and a solution of LiOH in water (257 mg in 10 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h after which HPLC analysis indicated complete reaction and 3M HCl (5.0 mL) was added and the mixture was evaporated to a solid. The solid was dissolved in ethyl acetate (20 mL) and water (20 mL) (pH~2.0) and ethyl acetate layer separated, dried over sodium sulfate, filtered and concentrated to a foam. The foam was dissolved in dichloromethane (40 mL) and cyclopropanesulfonic acid (1-(R)-amino-2-(S)-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt (A1)(0.419 mg, 1.58 mmol) (Llinas-Brunet et al US03/15755 and Wang et al WO 03/099274), diisopropylethylamine (0.75 mL, 4.30 mmol), dimethylaminopyridine (0.087 gm, 0.72 mmol) and HATU (0.65 gm, 1.72 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was purified directly by reverse phase HPLC to yield the desired product as a solid. LRMS (ESI) *m/z* 694 [(M+H)$^+$; calcd for $C_{35}H_{44}N_5O_8S$: 694]. ^{1}H NMR (500 MHz, ppm) (d_6-DMSO) δ 10.40 (s, 1 H), 8.70 (s, 1 H), 8.45 (s, 1 H), 7.95 (d, *J* = 5.9 Hz, 1 H), 7.81 (d, *J* = 8.3 Hz, 1 H), 7.61 (dd, *J* = 8.6 and 1.7 Hz, 1 H), 7.35 (d, J = 5.9 Hz, 1 H), 7.25 (d, *J* = 7.32 Hz, 1 H), 6.62 (d, *J* = 15.9 Hz, 1 H), 6.39 (m, 1 H), 5.68 (s, 1 H), 5.56 (m, 1 H), 5.17 (d, *J* = 18.1 Hz, 1 H), 5.06 (d, *J* = 11.5 Hz, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 4.31 (m, 3 H), 3.95 (m, 1 H), 3.86 (dd, 1 H, J = 11.5 and 2.9 Hz), 2.92 (m, 1 H), 2.61 (m, 1 H), 2.95 (m, 2 H), 2.10 (m, 2 H), 1.85 (m, 1 H), 1.75 (m, 1 H), 1.66 (m, 1 H), 1.28 (m, 1 H), 1.00-1.15 (m, 4 H), 1.04 (s, 9 H).

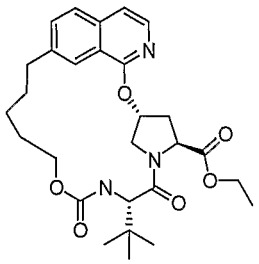
EXAMPLE 11

(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-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-carboxamide (**III-9**)



III-9

Step 1: Ethyl (2R,4S,7S)-7-tert-butyl-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



The ester from Example 10, Step 4 (512 mg, 1.00 mmol) was dissolved in ethyl acetate (40 mL) degassed with nitrogen and 10% palladium on carbon added (50 mg). The mixture was then purged with hydrogen 3 times and let stir under a hydrogen balloon for 24h. The reaction was filtered, concentrated in vacuo to give the compound (493 mg) as a foam. LRMS (ESI) *m/z* 512 [$(M+H)^+$; calcd for $C_{28}H_{38}N_3O_6$: 512].

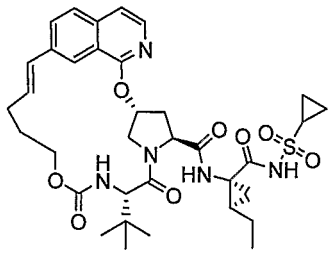
Step 2: (2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide

The title compound was prepared in a similar manner as described for the preparation of Example 10 Step 5 utilizing the ester from Step 1. LRMS (ESI) *m/z* 696 [$(M+H)^+$; calcd for $C_{35}H_{46}N_5O_8S$: 696].

^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 9.88 (s, 1 H), 7.92 (d, J = 7.1 Hz, 1 H), 7.78 (s, 1 H), 7.65 (d, J = 10.6 Hz, 1 H), 7.49 (dd, J = 10.7 and 1.6 Hz, 1 H), 7.30 (d, J = 7.1 Hz, 1 H), 7.19 (s, 1 H), 6.22 (m, 1 H), 5.76 (m, 1 H), 5.65 (d, J = 11.7, 1 H), 5.26 (d, J = 18.8 Hz, 1 H), 5.15 (d, J = 11.2 Hz, 1 H), 4.62 (m, 1 H), 4.46 (m, 3 H), 3.92 (dd, 1 H, J = 11.2 and 2.9 Hz), 3.73 (m, 1 H), 2.90 (m, 2 H), 2.70 (m, 1 H), 2.62 (m, 1 H), 2.51 (m, 1 H), 2.10 (m, 1 H), 1.96 (m, 1 H), 1.72 (m, 3 H), 1.48 (m, 2 H), 1.20-1.35 (m, 4 H), 1.07 (s, 9 H), 1.01 (m, 2 H).

EXAMPLE 12

(2R,4S,7S)-7-tert-butyl-N-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-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-carboxamide (**III-37**)

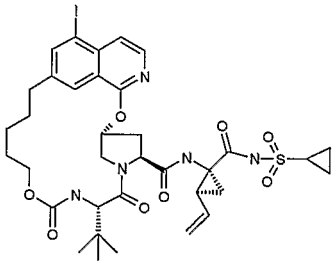


III-37

The title compound was prepared in a similar manner as described for the preparation of Example 10 Step 5 utilizing (1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropanaminium chloride (Intermediate A3). LRMS (ESI) *m/z* 696 $[(M+H)^+$; calcd for $C_{35}H_{46}N_5O_8S$: 696]. ^{1}H NMR (500 MHz, ppm) (d_6-DMSO) δ 10.28 (s, 1 H), 8.66 (s, 1 H), 8.45 (s, 1 H), 7.94 (d, *J* = 5.9 Hz, 1 H), 7.81 (d, *J* = 8.3 Hz, 1 H), 7.62 (dd, *J* = 8.3 and 1.7 Hz, 1 H), 7.35 (d, *J* = 5.9 Hz, 1 H), 7.23 (d, *J* = 7.32 Hz, 1 H), 6.62 (d, *J* = 15.6 Hz, 1 H), 6.39 (m, 1 H), 5.68 (m, 1 H), 4.52 (d, *J* = 11.0 Hz, 1 H), 4.31 (m, 3 H), 3.95 (m, 1 H), 3.86 (dd, *J* = 11.7 and 3.2 Hz, 1 H), 2.93 (m, 1 H), 2.55 (m, 1 H), 2.28 (m, 2 H), 2.08 (m, 1 H), 1.84 (m, 1 H), 1.75 (m, 1 H), 1.46 (m, 1 H), 1.24-1.38 (m, 3 H), 1.00-1.15 (m, 5 H), 1.04 (s, 9 H), 0.85 (t, *J* = 7.3 Hz, 3 H).

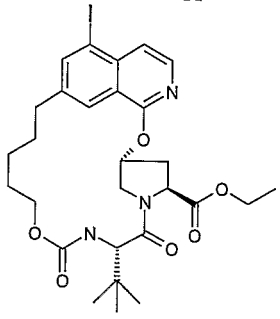
EXAMPLE 13

(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-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-carboxamide (**III-38**)



III-38

Step 1: Ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-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



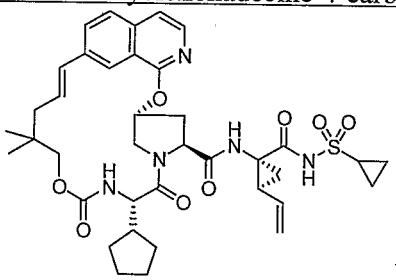
The ester from Example 11, Step 1 (0.79 gm, 1.55 mmol) was dissolved in triflic acid (5 mL) and added N-iodosuccinimide (0.90 gm, 4.0 mmol) in 4 portions over 4 h. Reaction was poured into a cold mixture of ethyl acetate and saturated sodium bicarbonate solution. Layers were separated and the organic layer was washed with saturated sodium bicarbonate solution and brine. Organics were dried over anhydrous sodium sulfate and the solvent was then evaporated to yield a crude oil. The crude product was purified by chromatography on silica (10-50% EtOAc hexane) to give the title compound (0.76 gm). LRMS (ESI) *m/z* 638 [(M+H)$^+$; calcd for $C_{28}H_{37}IN_3O_6$: 638].

Step 2: (2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-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-carboxamide

The title compound was prepared in a similar manner as described for the preparation of Example 10 Step 5 utilizing the ester from step 1. LRMS (ESI) *m/z* 822 [(M+H)$^+$; calcd for $C_{35}H_{45}IN_5O_8S$: 822]: ^{1}H NMR (400 MHz, ppm) (CD_3OD) δ 9.17 (s, 1 H), 8.17 (s, 1 H), 8.01 (d, *J* = 6.1 Hz, 1 H), 7.95 (s, 1 H), 7.43 (d, *J* = 6.04 Hz, 1 H), 6.2 (s, 1 H), 5.73 (m, 1 H), 5.28 (d, *J* = 18.7 Hz, 1 H), 5.12 (dd, *J* = 10.2 and 1.6 Hz, 1 H), 4.57 (m, 1 H), 4.41 (m, 3 H), 3.99 (dd, *J* = 11.7 and 3.1 Hz, 1 H), 3.74 (m, 1 H), 2.93 (m, 2 H), 2.64 (m, 1 H), 2.55 (m, 1 H), 2.24 (m, 2 H), 1.88 (m, 1 H), 1.73 (m, 3 H), 1.49 (m, 1 H), 1.43 (m, 1 H), 1.25 (m, 4 H), 1.09 (m, 2 H), and 1.06 (s, 9 H).

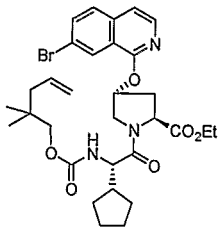
EXAMPLE 14

(2*R*,4*S*,7*S*,14*E*)-7-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-39**)



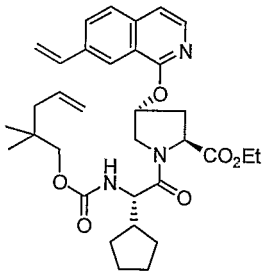
III-39

Step 1: Ethyl (4*R*)-4-[(7-bromoisoquinolin-1-yl)oxy]-1-[(2*S*)-2-cyclopentyl-2-({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetyl]-L-prolinate



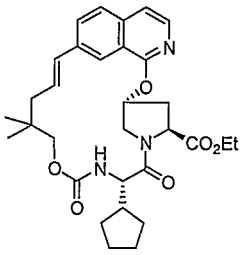
To a solution of ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (EXAMPLE 1, Step 1) (500 mg, 1.25 mmol) and (2*S*)-cyclopentyl({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetic acid (Intermediate B24) (353 mg, 1.25 mmol) in DMF (7 mL) at RT was added HATU (710 mg, 1.87 mmol) and DIPEA (0.87 mL, 5.00 mmol). After 2 h, the reaction mixture was poured into EtOAc, and extracted with 1 N HCl. The organic layer was washed with water and brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified on silica (gradient elution, 5% to 75% EtOAc in hexanes) to yield 526 mg (67%) of the title compound. LRMS (ESI) *m/z* 630.3 $[(M+H)^+$; calcd for $C_{31}H_{41}BrN_3O_6$: 630.2].

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



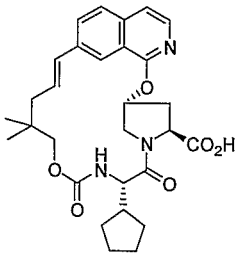
Ethyl (4*R*)-4-[(7-bromoisoquinolin-1-yl)oxy]-1-[(2*S*)-2-cyclopentyl-2-({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetyl]-L-prolinate (526 mg, 0.83 mmol) was dissolved in ethanol (10 mL) and nitrogen was bubbled through for 15 min. Potassium vinyltrifluoroborate (168 mg, 1.25 mmol) and dichloro [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) DCM adduct (34 mg, 0.04 mmol) were added and the reaction mixture heated to reflux under nitrogen. After 15 h, the reaction was complete and the volatiles were evaporated and the residue purified by silica gel chromatography (gradient elution, 10-75% EtOAc/hexane) to give a clear oil. LRMS (ESI) *m/z* 578.4 $[(M+H)^+$; calcd for $C_{33}H_{44}N_3O_6$: 578.3].

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



To a solution of the product from Step 2 (413 mg, 0.72 mmol) in degassed (nitrogen bubbling for 30 min) DCE (250 mL) was added Zhan 1B catalyst (Zhan catalyst 1B, RC-303, Zannan Pharma Ltd.) (52 mg, 0.07 mmol). The mixture was then stirred at 70 °C under an N_2 atmosphere. After 3 h, the reaction was complete and was concentrated in vacuo. The crude product was then directly purified on silica (gradient elution, 5% to 75% EtOAc in hexanes) to yield 325 mg (83%) of the title compound. LRMS (ESI) *m/z* 550.4 $[(M+H)^+$; calcd for $C_{31}H_{40}N_3O_6$: 550.3].

Step 4: (2*R*,4*S*,7*S*,14*E*)-7-Cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid



To a solution of the product from Step 3 (160 mg, 0.29 mmol) in THF (5 mL) and EtOH (0.5 mL) at RT was added LiOH (1 M, 2.9 mL, 2.9 mmol). After 1 h, the reaction mixture was partitioned between EtOAc and 1N HCl (x4). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo to yield 144 mg (95%) of the title compound which was used without further purification. LRMS (ESI) *m/z* 522.3 $[(M+H)^+$; calcd for $C_{29}H_{36}N_3O_6$: 522.3].

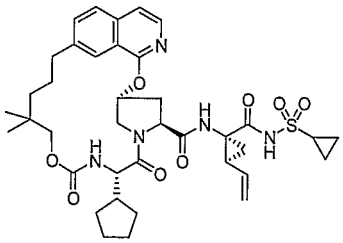
Step 5: (2*R*,4*S*,7*S*,14*E*)-7-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-39**)

To a solution of the product from Step 4 (147 mg, 0.28 mmol) and (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (Intermediate A1) (90 mg, 0.34 mmol) in DMF (2 mL) was added DIPEA (0.25 mL, 1.41 mmol), DMAP (3 mg, 0.03 mmol) and HATU (107 mg, 0.28 mmol). After full conversion (15 h), the reaction mixture was purified by reverse-phase

HPLC (gradient elution, 30% to 100% CH_3CN in 0.15% TFA/water) to yield 122 mg (59%) of the title compound as a white powder. ^1H NMR (500 MHz, CD_3OD) δ 9.16 (s, 1 H), 8.44 (s, 1 H), 7.87 (d, *J* = 5.9 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 1 H), 7.56 (d, *J* = 8.3 Hz, 1 H), 7.27 (d, *J* = 6.1 Hz, 1 H), 6.47 (s, 2 H), 5.77 (s, 1 H), 5.70 (m, 1 H), 5.24 (d, *J* = 17.1 Hz, 1 H), 5.07 (d, *J* = 10.3 Hz, 1 H), 4.79 (d, *J* = 11.7 Hz, 1 H), 4.43 (d, *J* = 11.0 Hz, 1 H), 4.34 (m, 2 H), 4.03 (dd, *J* = 11.5 & 2.7 Hz, 1 H), 2.95 (m, 1 H), 2.65 (m, 1 H), 2.42 (m, 2 H), 2.22 (m, 1 H), 2.13 (q, *J* = 8.8 Hz, 1 H), 2.01 (m, 1 H), 1.92 (m, 1 H), 1.86 (m, 1 H), 1.80 - 1.60 (m, 5 H), 1.43 - 1.20 (m, 5 H), 1.15 (s, 3 H), 1.10 (m, 2 H), 0.89 (s, 3 H) ppm. LRMS (ESI) *m/z* 734.4 $[(M+H)^+$; calcd for $C_{38}H_{48}N_5O_8S$: 734.3].

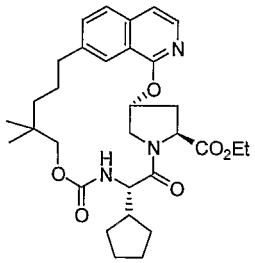
EXAMPLE 15

(2*R*,4*S*,7*S*)-7-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-40**)



III-40

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



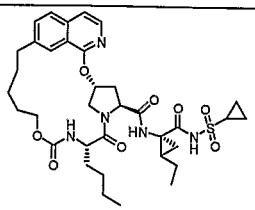
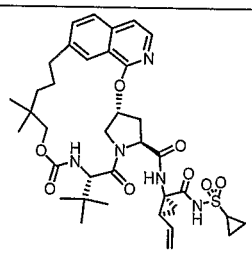
To a solution of ethyl (2*R*,4*S*,7*S*,14*E*)-7-cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 14, Step 3) (160 mg, 0.29 mmol) in EtOAc (7 mL) at RT was added Pd/C (100 mg). An H_2 balloon was then placed on the reaction flask, the flask was evacuated quickly and filled with H_2. After 7 h, the reaction mixture was filtered through celite and washed with EtOAc. Concentration of the filtrate gave 147 mg (92%) of the title compound which was used without further purification. LRMS (ESI) *m/z* 552.4 $[(M+H)^+$; calcd for $C_{31}H_{42}N_3O_6S$: 552.3].

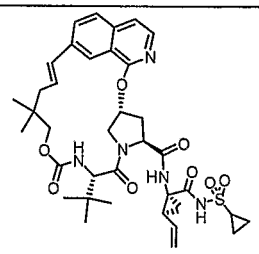
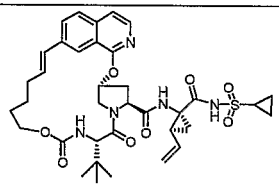
Step 2: (2*R*,4*S*,7*S*)-7-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-40**)

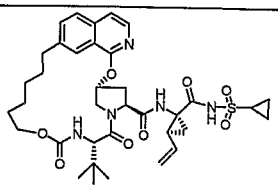
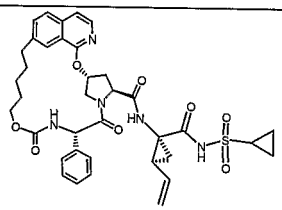
The title compound was prepared from ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate using the procedures described in EXAMPLE 14, Steps 4 and 5. ^{1}H NMR (500 MHz, CD_3OD) δ 9.26 (s, 1 H), 7.89 (s, 1 H), 7.87 (d, *J* = 5.9 Hz, 1 H), 7.71 (d, *J* = 8.3 Hz, 1 H), 7.55 (d, *J* = 8.3 Hz, 1 H), 7.29 (d, *J* = 5.9 Hz, 1 H), 6.03 (s, 1 H), 5.76 (m, 1 H), 5.28 (d, *J* = 15.6 Hz, 1 H), 5.10 (d, *J* = 8.5 Hz, 1 H), 4.58 (d, *J* = 11.5 Hz, 1 H), 4.46 (m, 1 H), 4.33 (d, *J* = 10.7 Hz, 2 H), 4.01 (dd, *J* = 11.5 & 2.7 Hz, 1 H), 3.28 (d, *J* = 10.7 Hz, 1 H), 2.97 (sep, *J* = 4.6 Hz, 1 H), 2.81 (m, 1 H), 2.64 (m, 1 H), 2.55 (q, *J* = 6.7 Hz, 1 H), 2.44 (m, 1 H), 2.26 (m, 1 H), 2.18 (q, *J* = 9.0 Hz, 1 H), 1.88 (m, 2 H), 1.70 (m, 4 H), 1.56 (m, 3 H), 1.40 (m, 3 H), 1.27 (m, 4 H), 1.07 (m, 4 H), 0.77 (s, 3 H) ppm. LRMS (ESI) *m/z* 736.4 $[(M+H)^+$; calcd for $C_{38}H_{50}N_5O_8S$: 736.3].

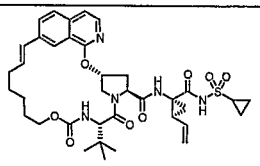
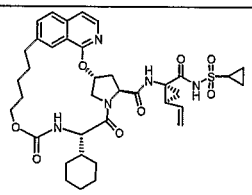
By using the appropriate procedures and the appropriate A and B intermediates in place of (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (Intermediate A1) and (2*S*)-cyclopentyl({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetic acid (Intermediate B24), the following compounds were prepared.

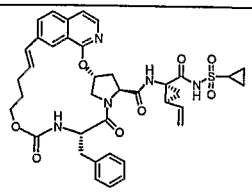
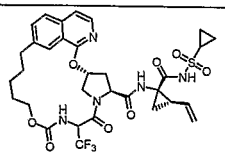
Ex.	Structure	Name	LRMS (M+H)$^+$	Prepared using the appropriate Intermediates according to the procedure below.	Int.

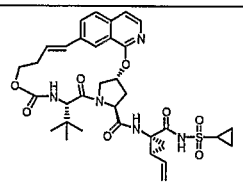
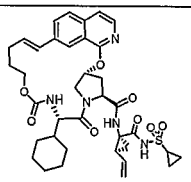
16, **III-41**		(2*R*,4*S*,7*S*)-7-butyl-*N*-((1*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	698.5	See Example 15	A3, B1
17, **III-15**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	724.4	See Example 15	A1, B4

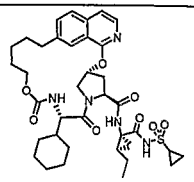
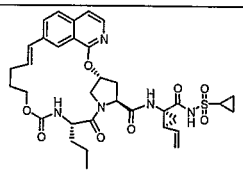
18, **III-29**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	722.3	See Example 14	A1, B4
19, **III-42**		(2*R*,4*S*,7*S*,15*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	708.6	See Example 14	A1, B5

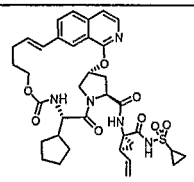
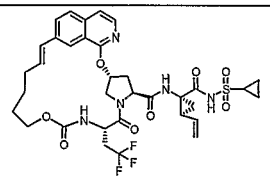
20, **III-43**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	710.6	See Example 15	A1, B5
21, **III-44**		(2*R*,4*S*,7*S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-phenyl-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	716.3	See Example 15	A1, B6

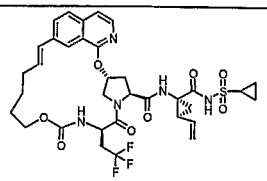
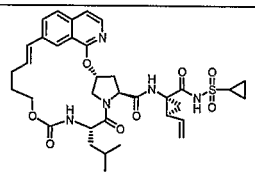
22, **III-45**		(2*R*,4*S*,7*S*,16*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	722.5	See Example 14	A1, B7
23, **III-10**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	708.3	See Example 15	A1, B8

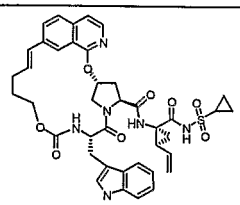
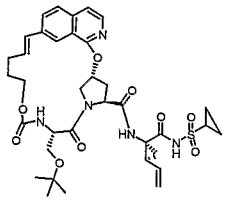
24, **III-46**		(2*R*,4*S*,7*S*,14*E*)-7-benzyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	728.4	See Example 14	A1, B9
25, **III-47**		(2*R*,4*S*)-*N*-((1*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(trifluoromethyl)-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	708.2	See Example 15	A1, B10

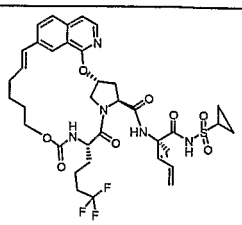
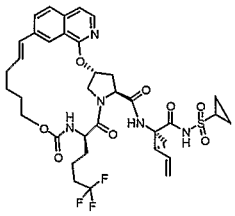
26, **III-48**		(2*R*,4*S*,7*S*,13*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12-octahydro-2*H*-15,17-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide	680.6	See Example 14	A1, B22
27, **III-24**		(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	720.6	See Example 14	A1, B8

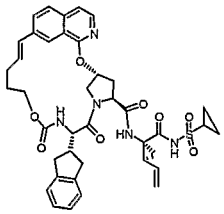
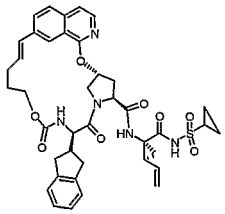
28, **III-49**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	724.5	See Example 15	A3, B8
29, **III-50**		(2*R*,4*S*,7*S*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-propyl-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	680.5	See Example 14	A1, B12

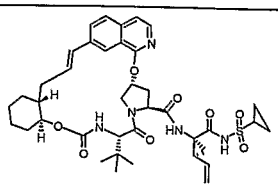
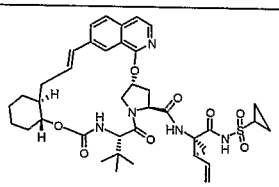
30, **III-51**		(2*R*,4*S*,7*S*,14*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	706.5	See Example 14	A1, B13
31, **III-52**		(2*R*,4*S*,7*S*,15*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(2,2,2-trifluoroethyl)-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	734.4	See Example 14, separated diastereomers	A1, B14

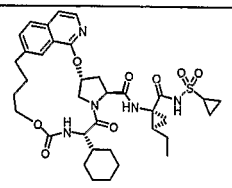
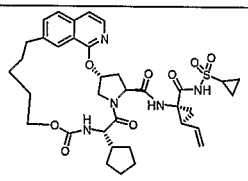
32, **III-53**		(2*R*,4*S*,7*R*,15*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(2,2,2-trifluoroethyl)-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	734.4	See Example 14, separated diastereomers	A1, B14
33, **III-54**		(2*R*,4*S*,7*S*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-isobutyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	694.5	See Example 14	A1, B15

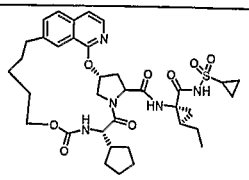
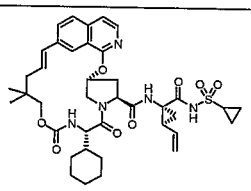
34, **III-55**		(2*R*,4*S*,7*S*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-(1*H*-indol-3-ylmethyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	767.3	See Example 14	A1, B16
35, **III-56**		(2*R*,4*S*,7*S*,14*E*)-7-(*tert*-butoxymethyl)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	724.4	See Example 14	A1, B17

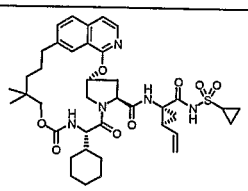
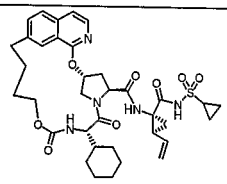
36, **III-57**		(2*R*,4*S*,7*S*,15*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(4,4,4-trifluorobutyl)-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	762.3	See Example 14, separated diastereomers	A1, B18
37, **III-58**		(2*R*,4*S*,7*R*,15*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(4,4,4-trifluorobutyl)-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	762.3	See Example 14, separated diastereomers	A1, B18

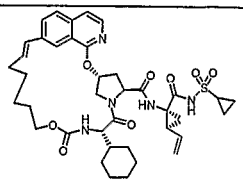
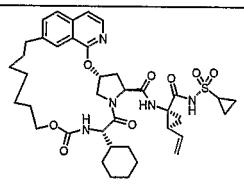
38, **III-59**		(2*R*,4*S*,7*S*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-(2,3-dihydro-1*H*-inden-2-yl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	754.3	See Example 14, separated diastereomers	A1, B19
39, **III-60**		(2*R*,4*S*,7*R*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-(2,3-dihydro-1*H*-inden-2-yl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	754.3	See Example 14, separated diastereomers	A1, B19

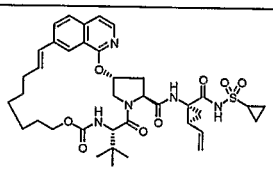
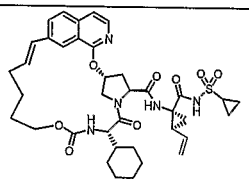
40, **III-61**		(6*R*,8*S*,11*S*,14a*S*,18a*R*,20*E*)-11-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,15,16,17,18,18a,19-dodecahydro-6*H*,14a*H*-1,22-etheno-6,9-methanopyrido[2,3-*k*][1,10,3,6]benzodioxadiazacyclononadecine-8-carboxamide	748.3	See Example 14, separated diastereomers	A1, B20
41, **III-62**		(6*R*,8*S*,11*S*,14a*R*,18a*S*,20*E*)-11-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,15,16,17,18,18a,19-dodecahydro-6*H*,14a*H*-1,22-etheno-6,9-methanopyrido[2,3-*k*][1,10,3,6]benzodioxadiazacyclononadecine-8-carboxamide	748.3	See Example 14, separated diastereomers	A1, B20

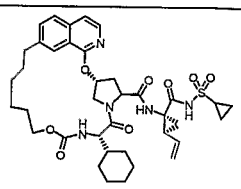
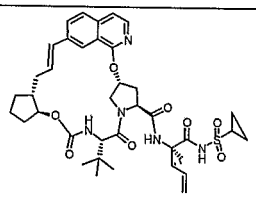
42, **III-63**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide	710.5	See Example 15	A3, B21
43, **III-64**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	708.4	See Example 15	A1, B13

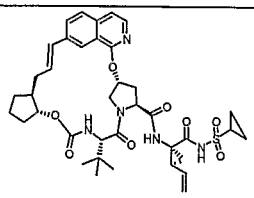
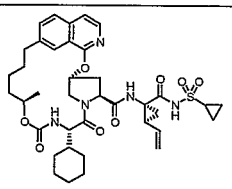
44, **III-65**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	710.5	See Example 15	A3, B13
45, **III-66**		(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	748.5	See Example 14	A1, B23

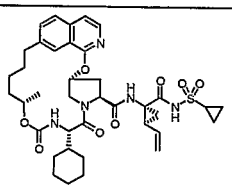
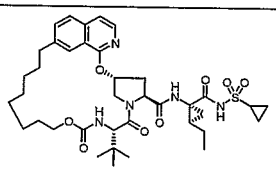
46, **III-67**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.5	See Example 15	A1, B23
47, **III-68**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide	708.3	See Example 15	A1, B21

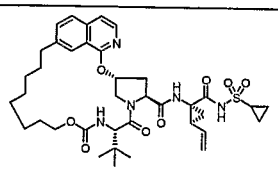
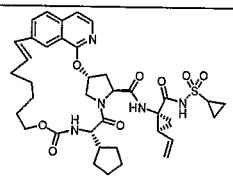
48, **III-69**		(2*R*,4*S*,7*S*,16*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	748.3	See Example 14	A1, B26
49, **III-70**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-18,20-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	750.5	See Example 15	A1, B26

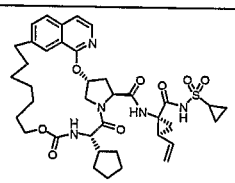
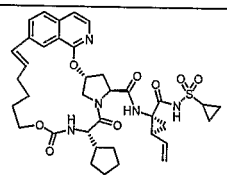
50, **III-71**		(2*R*,4*S*,7*S*,17*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-19,21-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide	736.5	See Example 14	A1, B27
51, **III-72**		(2*R*,4*S*,7*S*,15*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	734.4	See Example 14	A1, B28

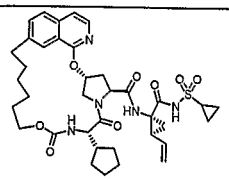
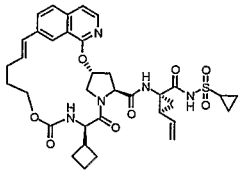
52, **III-73**		(2R,4S,7S)-7-cyclohexyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2H-17,19-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	736.5	See Example 15	A1, B28
53, **III-74**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	734.3	See Example 14, separated diastereomers	A1, B29

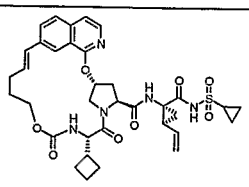
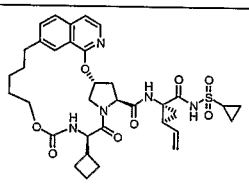
54, **III-75**		(6*R*,8*S*,11*S*,14a*R*,17a*S*,19*E*)-11-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	734.3	See Example 14, separated diastereomers	A1, B29
55, **III-76**		(2*R*,4*S*,7*S*,11*R*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	736.5	See Example 15, separated diastereomers	A1, B30

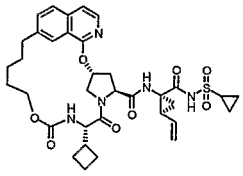
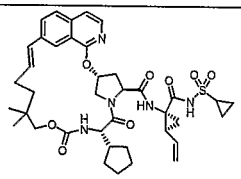
56, **III-77**		(2*R*,4*S*,7*S*,11*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	736.4	See Example 15, separated diastereomers	A1, B30
57, **III-78**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16,17,18-tetradecahydro-2*H*-19,21-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide	740.6	See Example 15	A3, B27

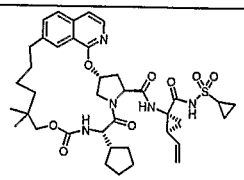
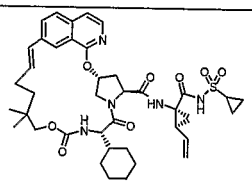
58, **III-79**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16,17,18-tetradecahydro-2*H*-19,21-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide	738.5	See Example 15	A1, B27
59, **III-80**		(2*R*,4*S*,7*S*,15*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	720.4	See Example 14	A1, B32

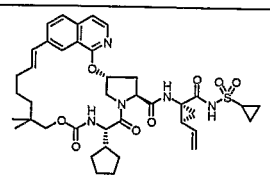
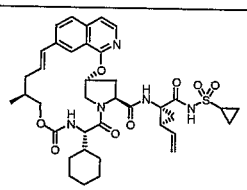
60, **III-81**		(2R,4S,7S)-7-cyclopentyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2H,11H-18,20-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	722.4	See Example 15	A1, B32
61, **III-82**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	734.4	See Example 14	A1, B31

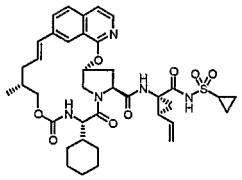
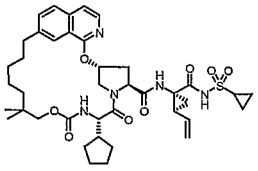
62, **III-83**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-18,20-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	736.4	See Example 15	A1, B31
63, **III-84**		(2*R*,4*S*,7*R*,14*E*)-7-cyclobutyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	692.3	See Example 14, separated diastereomers	A1, B33

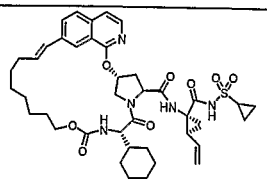
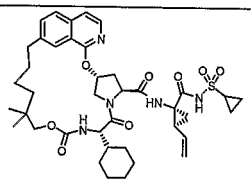
64, **III-85**		(2*R*,4*S*,7*S*,14*E*)-7-cyclobutyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	692.4	See Example 14, separated diastereomers	A1, B33
65, **III-86**		(2*R*,4*S*,7*R*)-7-cyclobutyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	694.3	See Example 15, separated diastereomers	A1, B33

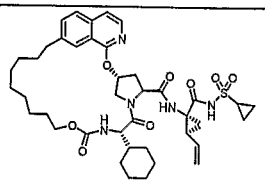
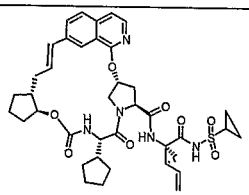
66, **III-87**		(2*R*,4*S*,7*S*)-7-cyclobutyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	694.3	See Example 15, separated diastereomers	A1, B33
67, **III-88**		(2*R*,4*S*,7*S*,15*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	748.4	See Example 14	A1, B34

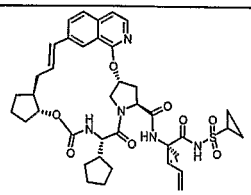
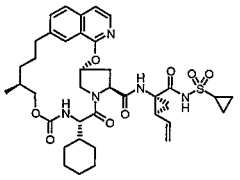
68, **III-89**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	750.4	See Example 15	A1, B34
69, **III-90**		(2*R*,4*S*,7*S*,15*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	762.4	See Example 14	A1, B35

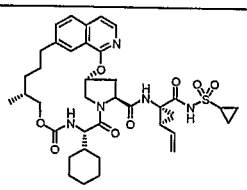
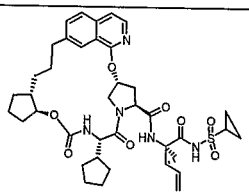
70, **III-91**		(2*R*,4*S*,7*S*,16*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	762.5	See Example 14	A1, B36
71, **III-92**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	734.4	See Example 14, separated diastereomers	A1, B39

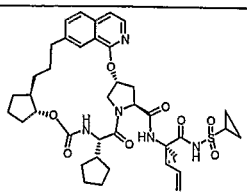
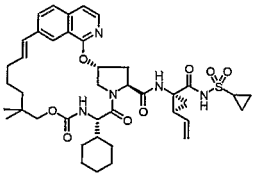
72, **III-93**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	734.4	See Example 14, separated diastereomers	A1, B39
73, **III-94**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	764.6	See Example 15	A1, B36

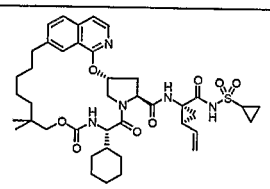
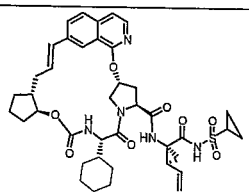
74, **III-95**		(2*R*,4*S*,7*S*,18*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-20,22-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclotricosine-4-carboxamide	776.5	See Example 14	A1, B37
75, **III-96**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	764.4	See Example 15	A1, B35

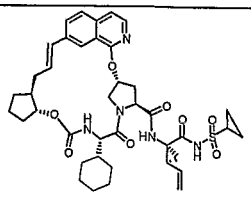
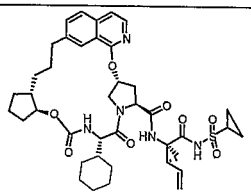
76, **III-97**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17,18,19-tetradecahydro-2*H*,11*H*-20,22-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclotricosine-4-carboxamide	778.5	See Example 15	A1, B37
77, **III-98**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	746.4	See Example 14, separated diastereomers	A1, B38

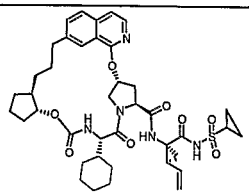
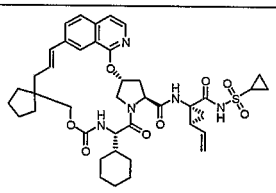
78, **III-99**		(6*R*,8*S*,11*S*,14a*R*,17a*S*,19*E*)-11-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	746.4	See Example 14, separated diastereomers	A1, B38
79, **III-100**		(2*R*,4*S*,7*S*,12*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	736.3	See Example 15, separated diastereomers	A1, B39

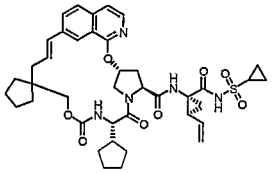
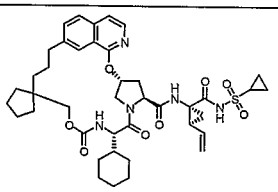
80, **III-101**		(2*R*,4*S*,7*S*,12*R*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	736.3	See Example 15, separated diastereomers	A1, B39
81, **III-102**		(6*R*,8*S*,11*S*,14a*S*,17a*S*)-11-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	748.3	See Example 15, separated diastereomers	A1, B38

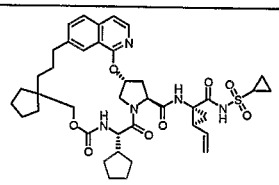
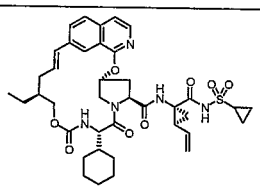
82, **III-103**		(6*R*,8*S*,11*S*,14a*R*,17a*R*)-11-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	748.3	See Example 15, separated diastereomers	A1, B38
83, **III-104**		(2*R*,4*S*,7*S*,16*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	776.3	See Example 14	A1, B40

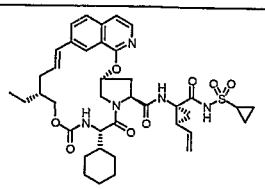
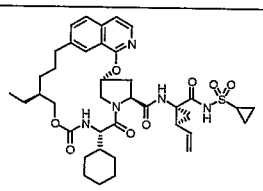
84, **III-105**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	778.4	See Example 15	A1, B40
85, **III-106**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	760.5	See Example 14, separated diastereomers	A1, B41

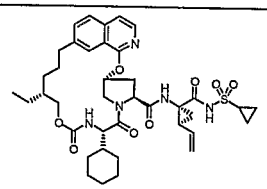
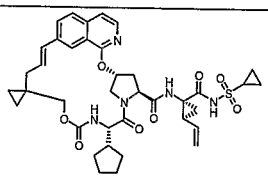
86, **III-107**		(6*R*,8*S*,11*S*,14a*R*,17a*S*,19*E*)-11-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	760.5	See Example 14, separated diastereomers	A1, B41
87, **III-108**		(6*R*,8*S*,11*S*,14a*S*,17a*S*)-11-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	762.6	See Example 15, separated diastereomers	A1, B41

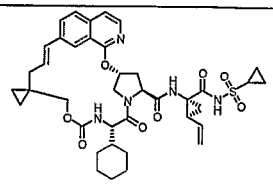
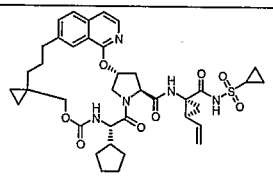
88, **III-109**		(6*R*,8*S*,11*S*,14a*R*,17a*R*)-11-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	762.6	See Example 15, separated diastereomers	A1, B41
89, **III-110**		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9'-hexahydro-2'*H*,13'*H*-spiro[cyclopentane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18]etheno[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	774.2	See Example 14	A1, B42

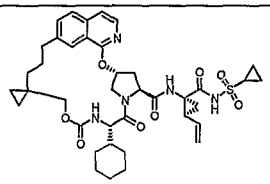
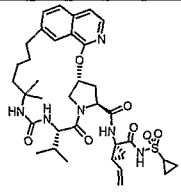
90, **III-111**		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9'-hexahydro-2'*H*,13'*H*-spiro[cyclopentane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18]etheno[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	760.3	See Example 14	A1, B47
91, **III-112**		(2'*R*,4'*S*,7'*S*)-7'-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahydro-2'*H*,13'*H*-spiro[cyclopentane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18]etheno[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	776.4	See Example 15	A1, B42

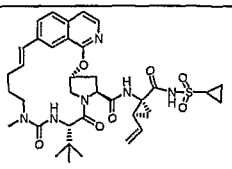
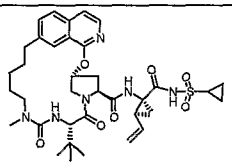
92, **III-113**		(2'*R*,4'*S*,7'*S*)-7'-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahydro-2'*H*,13'*H*-spiro[cyclopentane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18]etheno[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	762.3	See Example 15	A1, B47
93, **III-114**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	748.4	See Example 14, separated diastereomers	A1, B43

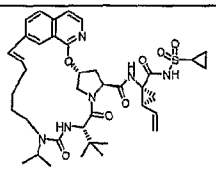
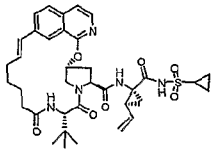
94, **III-115**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	748.4	See Example 14, separated diastereomers	A1, B43
95, **III-116**		(2*R*,4*S*,7*S*,12*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.4	See Example 15, separated diastereomers	A1, B43

96, **III-117**		(2*R*,4*S*,7*S*,12*R*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.5	See Example 15, separated diastereomers	A1, B43
97, **III-118**		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9'-hexahydro-2'*H*,13'*H*-spiro[cyclopropane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18](ethanediylidene)[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	732.3	See Example 14	A1, B44

98, **III-119**		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9'-hexahydro-2'*H*,13'*H*-spiro[cyclopropane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18](ethanediylidene)[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	746.3	See Example 14	A1, B45
99, **III-120**		(2'*R*,4'*S*,7'*S*)-7'-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahydro-2'*H*,13'*H*-spiro[cyclopropane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18](ethanediylidene)[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	734.3	See Example 15	A1, B44

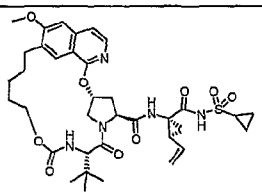
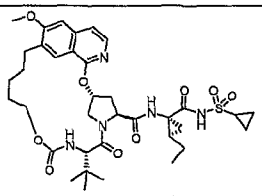
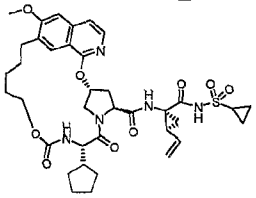
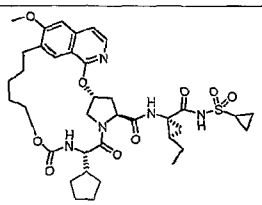
100, **III-121**		(2'*R*,4'*S*,7'*S*)-7'-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahydro-2'*H*,13'*H*-spiro[cyclopropane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18](ethanediylidene)[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	748.3	See Example 15	A1, B45
101, **III-122**		(2*R*,4*S*,7*S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-isopropyl-11,11-dimethyl-6,9-dioxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,2-*r*][1,5,8,10]oxatriazacyclononadecine-4-carboxamide	709.4	See Example 15	A1, B50

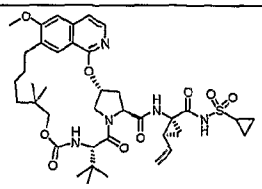
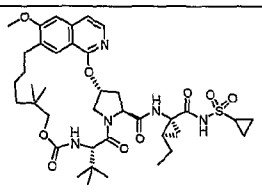
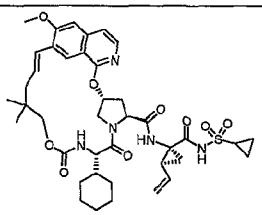
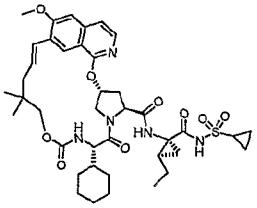
102, **III-28**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-methyl-6,9-dioxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8,10]oxatriazacyclononadecine-4-carboxamide	707.6	See Example 14	A1, B51
103, **III-14**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-methyl-6,9-dioxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8,10]oxatriazacyclononadecine-4-carboxamide	709.7	See Example 15	A1, B51

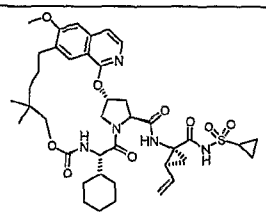
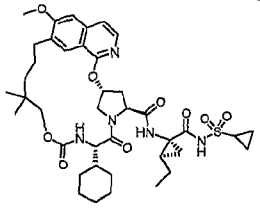
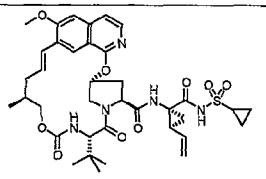
104, **III-123**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-6,9-dioxo-3,4,7,8,9,10,11,12,13,14-decahydro-2*H*,6*H*-17,19-etheno-2,5-methanopyrido[3,2-*s*][1,5,8,10]oxatriazacycloicosine-4-carboxamide	749.4	See Example 14	A1, B52
105, **III-25**		(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,10,11,12,13-decahydro-2H-16,18-ethanediylidene-2,5-methanopyrido[3,2-r][1,5,8]oxadiazacyclononadecine-4-carboxamide	692.6	See Example 14	A1, B53

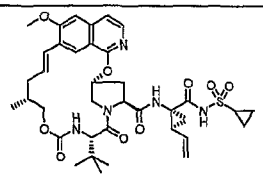
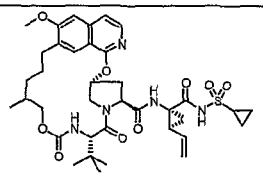
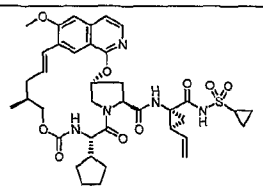
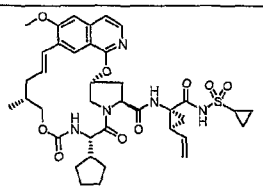
By using the appropriate procedures and the appropriate A, B and C intermediates the following compounds were prepared.

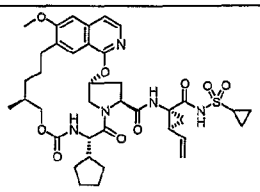
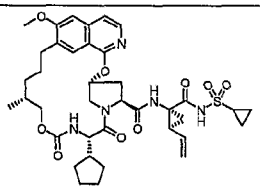
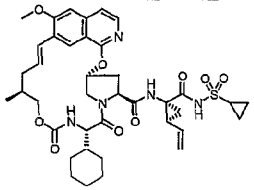
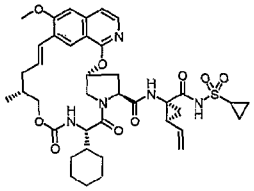
Ex.	Structure	Name	LRMS $(M+H)^+$	Prepared using the appropriate Intermediates according to the procedure below.	Int.

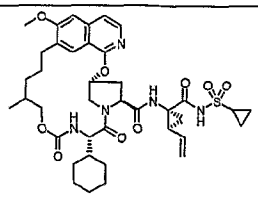
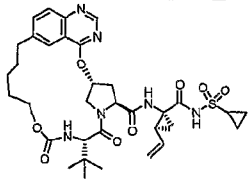
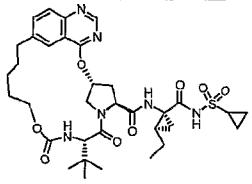
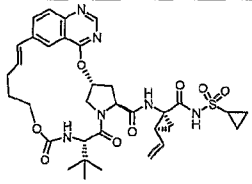
106, **III-12**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	726.5	See Example 15	A1, B2, C1
107, **III-124**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	728.6	See Example 15	A3, B2, C1
108, **III-125**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	738.5	See Example 15	A1, B13, C1
109, **III-126**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	740.6	See Example 15	A3, B13, C1

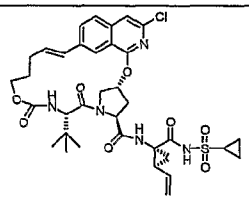
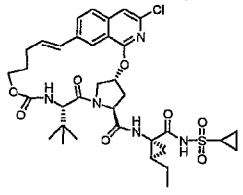
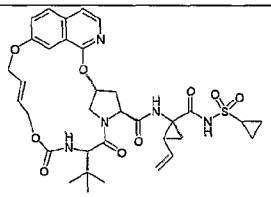
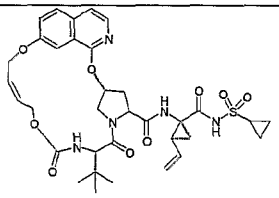
110, **III-127**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-24-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	768.6	See Example 15	A1, B25, C1
111, **III-128**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-24-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	770.7	See Example 15	A3, B25, C1
112, **III-129**		(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	778.6	See Example 14	A1, B23, C1
113, **III-130**		(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	780.6	See Example 14	A3, B23, C1

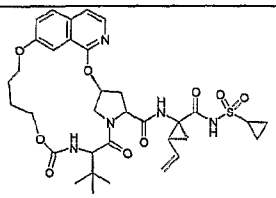
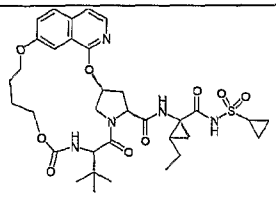
114, **III-131**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	780.5	See Example 15	A1, B23, C1
115, **III-132**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	782.6	See Example 15	A3, B23, C1
116, **III-133**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	738.3	See Example 14, separated diastereomers	A1, B46, C1

117, **III-134**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	738.3	See Example 14, separated diastereomers	A1, B46, C1
118, **III-135**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	740.2	See Example 15	A1, B46, C1
119, **III-136**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.4	See Example 14, separated diastereomers	A1, B48, C1
120, **III-137**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.4	See Example 14, separated diastereomers	A1, B48, C1

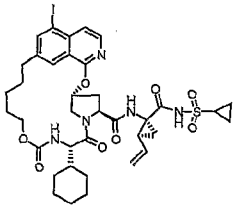
121, **III-138**		(2*R*,4*S*,7*S*,12*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	752.4	See Example 15, separated diastereomers	A1, B48, C1
122, **III-139**		(2*R*,4*S*,7*S*,12*R*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	752.5	See Example 15, separated diastereomers	A1, B48, C1
123, **III-140**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	764.3	See Example 14, separated diastereomers	A1, B39, C1
124, **III-141**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	764.3	See Example 14, separated diastereomers	A1, B39, C1

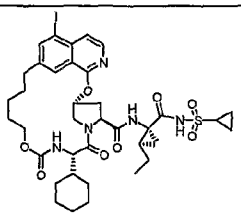
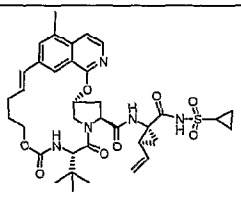
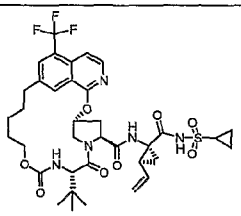
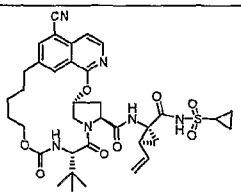
125, **III-142**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	766.4	See Example 15	A1, B39, C1
126, **III-20**		(15*S*,18*S*,20*R*)-15-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-etheno-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	697.5	See Example 15	A1, B2, C2
127, **III-143**		(15*S*,18*S*,20*R*)-15-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-etheno-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	699.5	See Example 15	A3, B2, C2
128, **III-34**		(7*E*,15*S*,18*S*,20*R*)-15-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13,16-dioxo-10,11,13,14,15,16,19,20-octahydro-9*H*,18*H*-4,6-etheno-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	695.4	See Example 14	A1, B2, C2

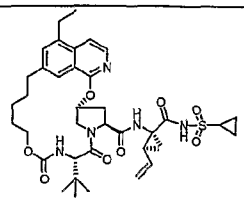
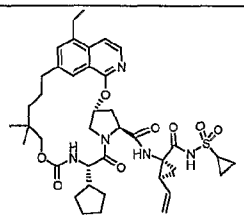
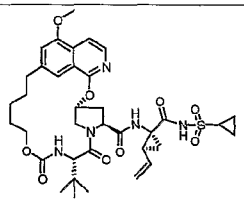
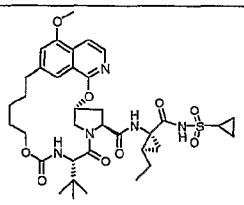
129, **III-31**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-20-chloro-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	728.5	See Example 14	A1, B2, C3
130, **III-32**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-20-chloro-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	730.5	See Example 14	A3, B2, C3
131, **III-144**		(2*R*,4*S*,7*S*,12*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,14-octahydro-2*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,15,3,6]trioxadiazacyclononadecine-4-carboxamide	696.5	See Example 14, separated olefin isomers	A1, B49, C4
132, **III-145**		(2*R*,4*S*,7*S*,12*Z*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,14-octahydro-2*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,15,3,6]trioxadiazacyclononadecine-4-carboxamide	696.5	See Example 14, separated olefin isomers	A1, B49, C4

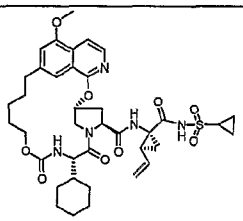
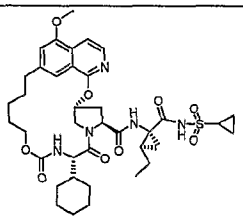
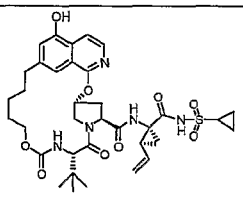
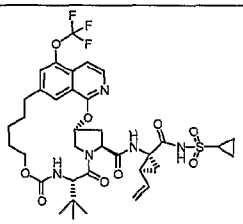
133, **III-146**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,15,3,6]trioxadiazacyclononadecine-4-carboxamide	698.4	See Example 15	A1, B49, C4
134, **III-147**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,15,3,6]trioxadiazacyclononadecine-4-carboxamide	700.5	See Example 15	A3, B49, C4

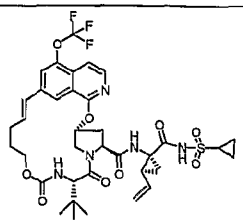
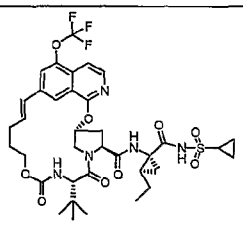
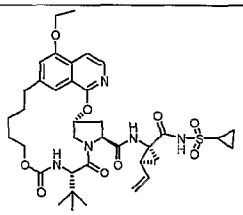
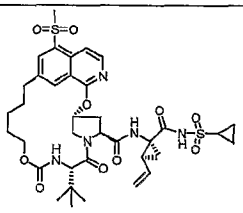
By using the appropriate procedures and the appropriate A, B and D intermediates, the following compounds were prepared.

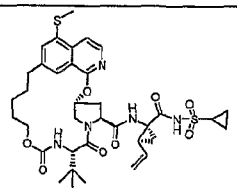
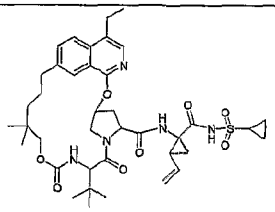
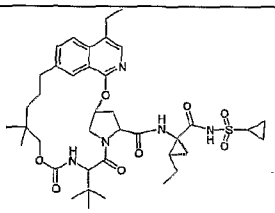
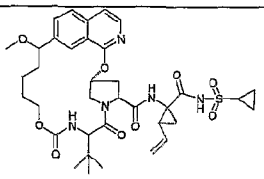
Ex.	Structure	Name	LRMS (M+H)$^+$	Prepared using the appropriate Intermediates according to the procedure below.	Int.
135, **III-148**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	848.4	See Example 13	A1, B8

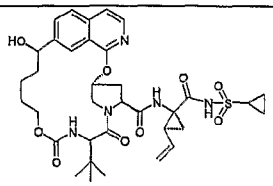
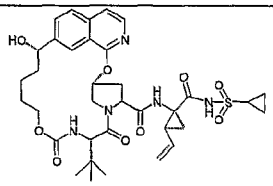
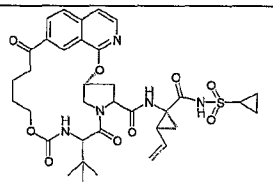
136, **III-149**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	850.5	See Example 13	A3, B8
137, **III-150**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	820.2	See Example 14, Step 5	A1, D1
138, **III-151**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-22-(trifluoromethyl)-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	764.3	See Example 14, Steps 4 and 5	A1, D5
139, **III-152**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-22-cyano-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	721.6	See Example 14, Steps 4 and 5	A1, D6

140, **III-153**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	724.7	See Example 14, Steps 4 and 5	A1, D7
141, **III-154**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	764.4	See Example 14, Steps 4 and 5	A1, D8
142, **III-155**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	726.7	See Example 14, Step 5	A1, D9
143, **III-156**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	728.5	See Example 14, Step 5	A3, D9

144, **III-157**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	752.5	See Example 14, Step 5	A1, D10
145, **III-158**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	754.5	See Example 14, Step 5	A3, D10
146, **III-159**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	712.5	See Example 14, Step 5	A1, D11
147, **III-160**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	780.5	See Example 15	A1, D15

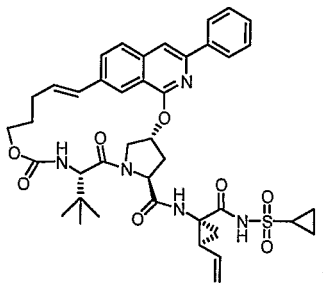
148, **III-161**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	778.4	See Example 14, Steps 4 and 5	A1, D15
149, **III-162**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	780.5	See Example 14, Steps 4 and 5	A3, D15
150, **III-163**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-ethoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	740.5	See Example 14, Steps 4 and 5	A1, D12
151, **III-164**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-(methylsulfonyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	774.5	See Example 14, Steps 4 and 5	A1, D13

152, **III-165**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-(methylthio)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	742.5	See Example 14, Steps 4 and 5	A1, D14
153, **III-166**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-19-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	752.6	See Example 14, Steps 4 and 5	A1, D16
154, **III-167**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-19-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	754.5	See Example 14, Steps 4 and 5	A3, D16
155, **III-168**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	726.3	See Example 14, Step 5	A1, D2

156, **III-169**		(2*R*,4*S*,7*S*,15*R*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	712.6	See Example 14, Steps 4 and 5, separated diastereomers	A1, D3
157, **III-170**		(2*R*,4*S*,7*S*,15*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	712.6	See Example 14, Steps 4 and 5, separated diastereomers	A1, D3
158, **III-171**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9,15-trioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	710.5	See Example 14, Steps 4 and 5	A1, D4

EXAMPLE 159

(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-20-phenyl-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-172**)

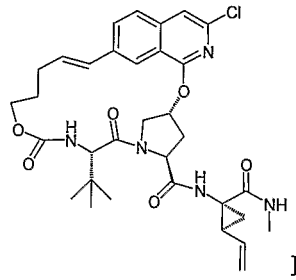


III-172

To a solution of (2R,4S,7S,14E)-7-tert-butyl-20-chloro-N-((1R,2S)-1-{[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)-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-carboxamide (EXAMPLE 129, **III-31**) (25 mg, 0.034 mmol) in THF (2 mL) was added phenylboronic acid (5.6 mg, 0.0447 mmol), cesium carbonate (56 mg, 0.16 mmol) and tricyclohexylphosphine (1.0 mg, 0.34 mmol). To this mixture was added $Pd_2(dba)_3$ (1.6 mg, 0.00172 mmol) and the mixture heated to 80°C for 2 hours. The reaction was concentrated and purified by reverse phase HPLC to give the title compound (20 mg) as a foam. LRMS (ESI) *m/z* 770.6 [$(M+H)^+$; calcd for $C_{41}H_{48}N_5O_8S$: 770.3].

EXAMPLE 160

(2*R*,4*S*,7*S*,14*E*)-7-*tert*-Butyl-20-chloro-*N*-{(1*R*,2*S*)-1-[(methylamino)carbonyl]-2-vinylcyclopropyl}-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-173**)

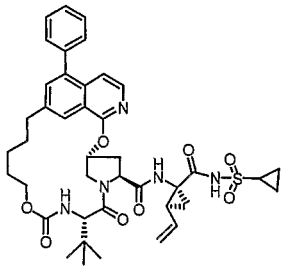


III-173

To a solution of (2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-20-chloro-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (EXAMPLE 129, **III-31**) (20 mg, 0.0275 mmol) in THF (1 mL) was added 40% aqueous methylamine and the mixture was heated in a microwave reactor at 180 °C for 30 min. The reaction mixture was concentrated and purified by reverse phase HPLC to give 2 mg product as foam. LRMS (ESI) m/z 638.5 [$(M+H)^+$; calcd for $C_{33}H_{41}ClN_5O_6$: 638.3].

EXAMPLE 161

(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-22-phenyl-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-174**)

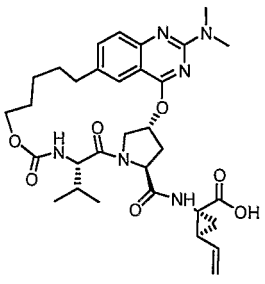


III-174

To a sealed tube containing (2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-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-carboxamide (**III-38**) (EXAMPLE 13) (17 mg, 0.021 mmol) in toluene (1 mL) was added phenylboronic acid (3 mg, 1.1 mmol), 2M sodium carbonate (0.021 mL, 0.041 mmol), and tetrakis(triphenylphosphine)palladium (1 mg, 0.001 mmol). The reaction mixture was heated at 80 C for 10 h. The reaction mixture was diluted with EtOAc, washed with 1N HCl, brine, dried the organics, and concentrated to a yellow oil. The resulting oil was purified by reverse phase HPLC to yield the title compound as a yellow solid. (5 mg). LRMS (ESI) m/z 772.7 $[(M+H)^+$; calcd for $C_{41}H_{50}N_5O_8S$: 772.3].

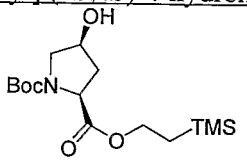
EXAMPLE 162

(1*R*,2*S*)-1-({[(15*S*,18*S*,20*R*)-2-(Dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecin-18-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (**III-175**)



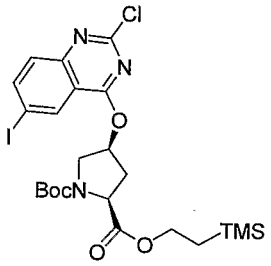
III-175

Step 1: 1-*tert*-Butyl 2-[2-(trimethylsilyl)ethyl] (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate



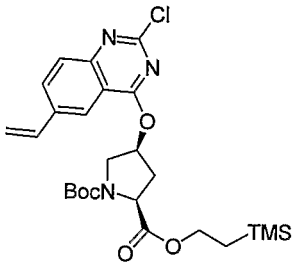
To a solution of 1-*tert*-butyl 2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (1.0 g, 4.08 mmol) in THF (30 mL) and water (6 mL) cooled to 0 °C was added a 1 M solution of NaOH (6.12 mL, 6.12 mmol). The mixture was stirred at this temperature for 2 h. At this time, TLC (100% Et_2O) indicated complete consumption of the starting material and formation of a more polar compound ($KMnO_4$ stain). The THF was then removed in vacuo, and the pH of the water layer was adjusted to 2-3 with 1 N HCl. The mixture was then extracted with EtOAc, dried over $MgSO_4$, and the solvent was removed in vacuo. LC-MS indicated that the major product had the desired mass. The crude compound was then taken up in PhMe (30 mL), O-2-trimethylsilyl-N,N'-diisopropylisourea (T. Eicher, M. Ott, A. Speicher *Synthesis*, 1996, 755-762)(1.99 g, 8.15 mmol) was added, and the mixture was refluxed for 2 h. At this time, 30% EtOAc/hexanes (10 mL) was added and the mixture was filtered. The solvent was then removed in vacuo, and the crude product was purified on silica (40% EtOAc/hex) to yield the title compound (1.23 g). LRMS $(M+H)^+ = 332.2$.

Step 2: 1-tert-Butyl 2-[2-(trimethylsilyl)ethyl] (2S,4S)-4-[(2-chloro-6-iodoquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate



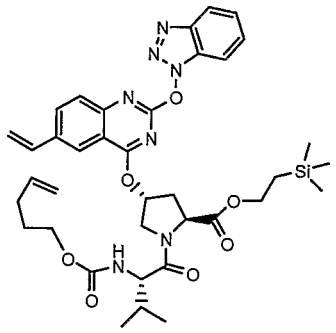
To a solution of the product from step 1 (1.02 g, 3.08 mmol) and 2,4-dichloro-6-iodoquinazoline (1.0 g, 3.08 mmol) (M. C. Venuti et al., *J. Med. Chem.* **1988**, *31*, 2136-2145) in toluene (25 mL) was added 60% sodium hydride (600 mg, excess) and the reaction mixture stirred at room temperature for 45 min. The reaction mixture was carefully partitioned between ice cold pH5.2 citrate buffer and EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and solvent evaporated. The crude product was purified by chromatography on silica (0-30% EtOAc hexane) to afford the title compound (1.61 g).

Step 3: 1-tert-Butyl 2-[2-(trimethylsilyl)ethyl] (2S,4S)-4-[(2-chloro-6-vinylquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate



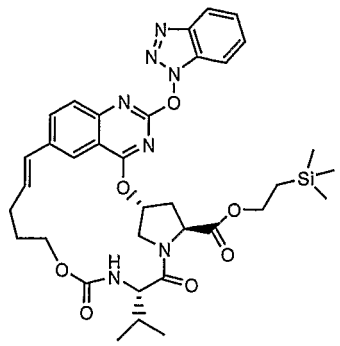
The title compound was prepared from 1-tert-butyl 2-[2-(trimethylsilyl)ethyl] (2S,4S)-4-[(2-chloro-6-iodoquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate as described in Example 1 Step 3.

Step 4: 2-(trimethylsilyl)ethyl N-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4R)-4-{[2-(1H-1,2,3-benzotriazol-1-yloxy)-6-vinylquinazolin-4-yl]oxy}-L-prolinate



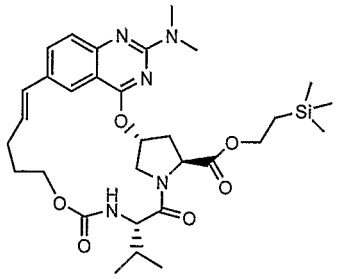
A solution of 1-tert-butyl 2-[2-(trimethylsilyl)ethyl] (2S,4S)-4-[(2-chloro-6-vinylquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate (495 mg, 0.95 mmol) in EtOAC (10 mL) was cooled to 0 C and hydrogen chloride bubbled through for 30 min. Nitrogen was then bubbled through for 5 min, the solvent evaporated and the residue azeotroped with EtOAc (x3). The residue was dissolved in DMF (5 mL) and DIPEA (479 µL, 2.67 mmol), Intermediate B3 (307 mg, 1.34 mmol) and TBTU (472 mg, 1.47 mmol) added. The reaction mixture was stirred at room temperature overnight and partitioned between pH 5.2 citrate buffer and EtOAc. The organic phase was washed with water, saturated $NaHCO_3$, brine, dried over Na_2SO_4 and the solvent evaporated. The crude product was purified by chromatography on silica (5-50% EtOAc hexane) to afford the title compound (479 mg). LRMS $(M+H)^+ = 702.3$.

Step 5: 2-(Trimethylsilyl)ethyl (7*E*,15*S*,18*S*,20*R*)-2-(1*H*-1,2,3-benzotriazol-1-yloxy)-15-isopropyl-13,16-dioxo-10,11,13,14,15,16,19,20-octahydro-9*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxylate



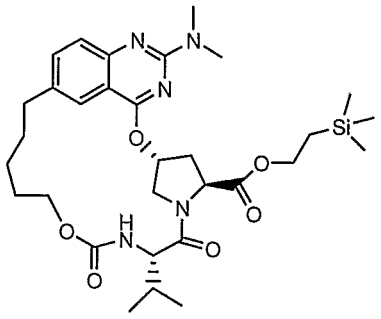
as the title compound was prepared from the product from Step 4 using the procedure described in Example 1 Step 4.

Step 6: 2-(Trimethylsilyl)ethyl (7*E*,15*S*,18*S*,20*R*)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-10,11,13,14,15,16,19,20-octahydro-9*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxylate:



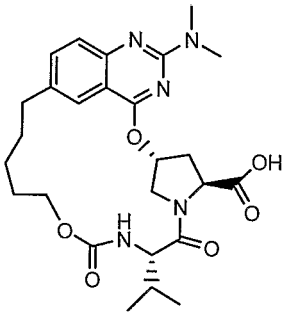
To a solution of the product from step 4 (130 mg, 0.185 mmol) in DCM (2 mL) was added a solution of 2.0M dimethylamine in THF (0.5 mL, 1.0 mmol) and the mixture was stirred at room temperature for 3 h. Additional 2.0M dimethylamine in THF (0.5 mL, 1.0 mmol) was added and the reaction was stirred for an additional 18 h. The reaction mixture was concentrated to an oil and chromatographed on silica using a gradient elution from dichloromethane to 5% acetone/dichloromethane to give the title compound as an oil (92 mg). LRMS $(M+H)^+ = 612.4$.

Step 7: 2-(Trimethylsilyl)ethyl (15*S*,18*S*,20*R*)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxylate



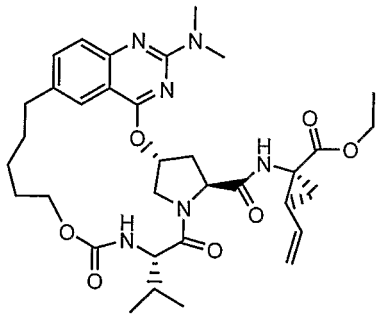
To a solution of the oil from step 5 (92 mg, 0.151 mmol) in ethyl acetate (20 mL) and under nitrogen was added 10 % palladium on carbon (20 mg) and the mixture stirred under hydrogen (1 atm) for 18 h. The reaction mixture was filtered and concentrated in vacuo to give the product as an oil (92 mg). LRMS $(M+H)^+ = 614.3$.

Step 8: (15*S*,18*S*,20*R*)-2-(Dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxylic acid



To a solution of the oil from step 6 (92 mg, 0.151 mmol) in THF (5 mL), under nitrogen, was added a solution of 1.0M tetrabutylammonium fluoride in THF (0.9 mL, 0.90 mmol). The reaction mixture was stirred for 0.5 hr and then concentrated in vacuo to give an oil. LRMS $(M+H)^+ = 514$.

Step 9: Ethyl (1*R*,2*S*)-1-({[(15*S*,18*S*,20*R*)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecin-18-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylate

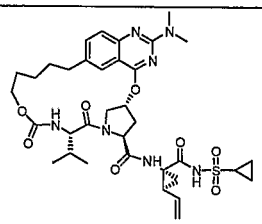
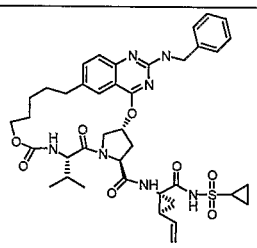


The oil from step 7 was dissolved in DMF (2 mL) and diisopropylamine (80 μL, 0.45 mmol), and (2R,3S)-3-vinyl-2-aminocyclopropyl carboxylic acid ethyl ester hydrochloride (Intermediate A2) (44 mg, 0.23 mmol) added, followed by TBTU (36 mg, 0.23 mmol) and the reaction mixture stirred at RT for 1 h. The mixture was diluted with EtOAc (20mL), washed with pH 5.2 citric acid (10 mL), 10% aqueous sodium bicarbonate (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give an oil, chromatographed on silica (30 to 100% ethyl acetate/hexanes) to give the title compound as an oil, (45 mg). LRMS $(M+H)^+ = 651.4$.

Step 10: (1*R*,2*S*)-1-({[(15*S*,18*S*,20*R*)-2-(Dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecin-18-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (**III-175**)

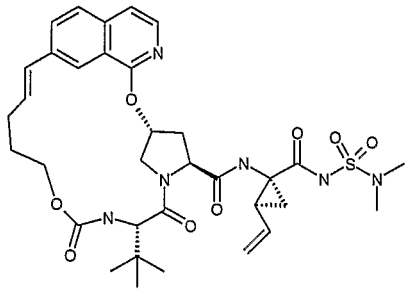
To a solution of the oil from step 8 (45 mg, 0.068 mmol) in THF (2 mL) was added a solution of lithium hydroxide (16 mg, 0.68 mmol) in water (0.4 mL) and the mixture stirred at 40 °C for 8 h. The reaction mixture was diluted with 1N hydrochloric acid (0.7 mL) and purified by reverse phase HPLC to give the title compound as a foam (45 mg) after concentration. ^{1}H NMR (500 Mhz, CD_3OD) δ 8.69 (s, 1H), 7.82 (d, 1H, J = 1.7 Hz), 7.79 (dd, 1H, J = 8.5 and 1.9 Hz), 7.68 (d, 1H, J = 8.5 Hz), 6.25 (m,1H), 5.84 (m, 1H), 5.27 (dd,1H, J = 16.8 and 1.5 Hz), 5.09 (dd, 1H, J = 10.3 and 1.7 Hz), 4.71 (d, 1H, J = 1.7 Hz), 4.66 (t, 1H, J = 10.0 Hz), 4.17 (m, 1H), 4.02 (m, 2H), 3.73 (m, 2H), 3.44 (brs, 6H), 2.86 (m, 1H), 2.69 (m, 1H), 2.19 (dd, 1H, J = 17.6 and 8.8 Hz), 2.02 (m, 1H), 1.80 (m,1H), 1.6 8(m, 2H), 1.40-1.55 (m, 3H), 1.10-1.30 (m, 2H), 1.02 (d, 6H) ppm; LRMS (ESI) *m/z* 623.3 $[(M+H)^+$; calcd for $C_{32}H_{43}N_6O_7$: 623.3].

By using the appropriate procedures and the appropriate A and B intermediates, the following compounds were prepared.

Ex.	Structure	Name	LRMS $(M+H)^+$	Prepared using the appropriate Intermediates according to the procedure below.	Int.
163, **III-176**		(15*S*,18*S*,20*R*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	726.6	Example 162	A1
164, **III-177**		(15*S*,18*S*,20*R*)-2-(benzylamino)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	788.6	Example 162	A1, benzylamine

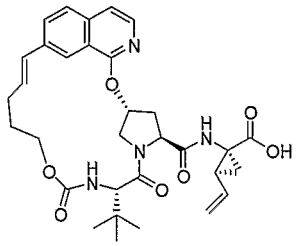
EXAMPLE 165

(2*R*,4*S*,7*S*,14*E*)-7-*tert*-Butyl-*N*-[(1*R*,2*S*)-1-({[(dimethylamino)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-178**)



III-178

Step 1: (1R,2S)-1-({[(2R,4S,7S,14E)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid



Ethyl (2R,4S,7S)-7-tert-butyl-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]dioxodiazacyclononadecine-4-carboxylate (EXAMPLE 10, Step 4) (0.73 g, 0.1.43 mmol) was dissolved in THF (20 mL) and EtOH (10 mL) and a solution of LiOH in water (257 mg in 10 mL) added. The reaction mixture was stirred at room temperature for 1.5 h after which HPLC analysis indicated complete reaction,3M HCl (5.0 mL) was added and the mixture was evaporated to a solid. The solid was partitioned between EtOAc (20 mL) and water (20 mL),the organic phase, dried over Na_2SO_4, filtered and concentrated to a foam which was used without further purification.

LRMS $(M+H)^+ = 591.5$.

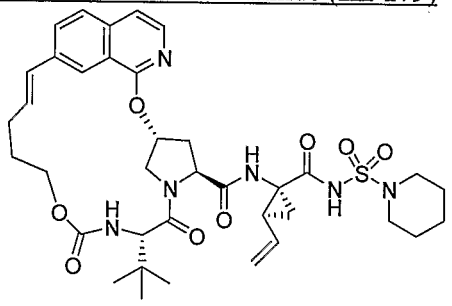
Step 2: (2*R*,4*S*,7*S*,14*E*)-7-*tert*-Butyl-*N*-[(1*R*,2*S*)-1-({[(dimethylamino)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-178**)

To the product from step 1 (100 mg, 0.169 mmol), N,N-dimethylsulfamide (84 mg, 0.677 mmol), DIPEA (0.148 mL, 0.847 mmol), and DMAP (83 mg, 0.677 mmol) in DMF (3 mL) was added DBU (0.115 mL, 0.762 mmol) and the mixture was stirred for 5 min. HATU (70.8 mg, 0.186 mmole) was added and mixture was stirred for 18 h. Additional HATU (15 mg) was added and the mixture stirred for an additional 3 h. The mixture was then purified by prep HPLC to give 65 mg of the title compound as a foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.26 (s, 1H), 7.89 (d, 1H, J = 6.1 Hz), 7.64 (d, 1H, J = 8.3 Hz), 7.50 (dd, 1H, J = 1.7 and 8.3 Hz), 7.20 (d, 1H, J = 5.8 Hz), 7.17 (s, 1H), 6.50 (d,

1H, J = 15.8 Hz), 6.36 (m, 1H), 5.82 (m, 1H), 5.66 (m, 2H), 5.17 (dd, 1H, J = 0.8 and 17.1 Hz), 5.09 (dd, 1H, J = 0.8 and 10.3 Hz), 4.61(d, 1H, J = 10.3 Hz), 4.48 (m, 3H), 3.94 (m, 2H), 2.8 3(s, 6H), 2.73 (m, 1H), 2.46 (m, 1H), 2.38 (m, 2H), 2.00 (m, 2H), 1.85 (m, 2H), 1.34 (m, 1H), 1.08 (s, 9H). LRMS (ESI) *m/z* 697.5 [(M+H)$^+$; calcd for $C_{34}H_{45}N_6O_8S$: 697.3].

EXAMPLE 166

(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-6,9-dioxo-*N*-((1*R*,2*S*)-1-{[(piperidin-1-ylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-179**)

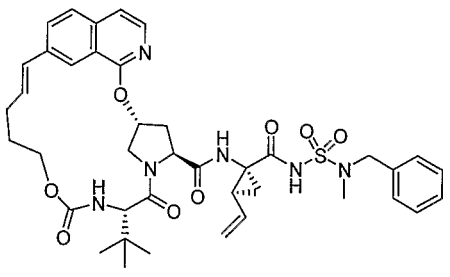


III-179

EXAMPLE 166 was prepared according to the procedure described for EXAMPLE 165 by using piperidine-1-sulfonamide in Step 2. LRMS (ESI) *m/z* 737.5 [(M+H)$^+$; calcd for $C_{37}H_{49}N_6O_8S$: 737.3].

EXAMPLE 167

(2*R*,4*S*,7*S*,14*E*)-*N*-{(1*R*,2*S*)-1-[({[benzyl(methyl)amino]sulfonyl}amino)carbonyl]-2-vinylcyclopropyl}-7-*tert*-butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-180**)

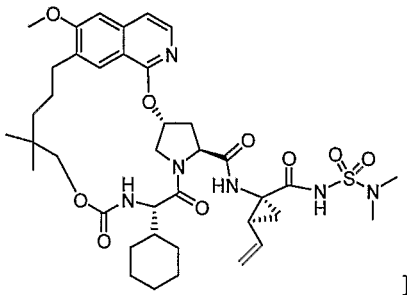


III-180

EXAMPLE 167 was prepared according to the procedure described for EXAMPLE 165 by using N-benzyl-N-methylsulfamide in Step 2. LRMS (ESI) *m/z* 773.6 [(M+H)$^+$; calcd for $C_{40}H_{49}N_6O_8S$: 773.3].

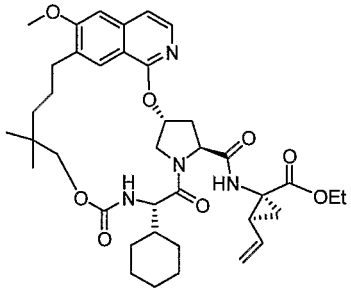
EXAMPLE 168

(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-[(1*R*,2*S*)-1-({[(dimethylamino)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-181**)



III-181

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



Ethyl (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-cyclohexyl-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylate was prepared using the procedure described for EXAMPLE 15 using Intermediates A2, B23 and C1. LRMS $(M+H)^+ = 705.6$.

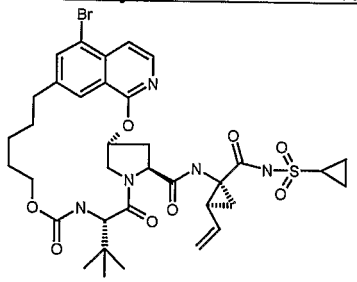
Step 2: (2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-[(1*R*,2*S*)-1-({[(dimethylamino)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide

EXAMPLE 168 was prepared according to the procedure described for EXAMPLE 165 by using ethyl (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-cyclohexyl-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-

k][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylate in Step 1. LRMS (ESI) *m/z* 783.6 [(M+H)$^+$; calcd for $C_{39}H_{55}N_6O_9S$: 783.4].

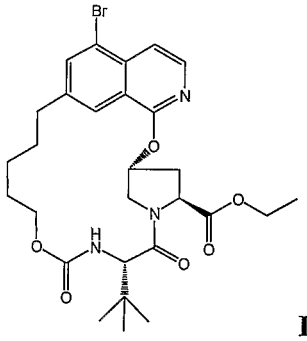
EXAMPLE 169

(2R,4S,7S)-22-bromo-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-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-carboxamide (**III-182**)

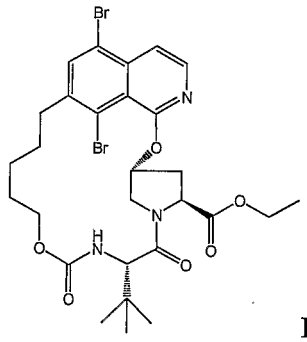


III-182

Step 1: Ethyl (2*R*,4*S*,7*S*)-22-bromo-7-*tert*-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (**III-186**) and Ethyl (2*R*,4*S*,7*S*)-17,22-dibromo-7-*tert*-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (**III-187**)



III-186



III-187

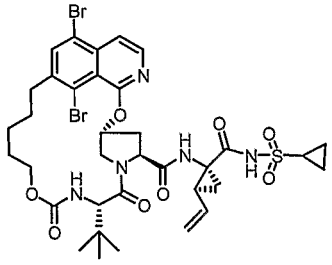
Compounds **III-186** and **III-187** were prepared according to the procedure given for EXAMPLE 13, Step 1 using N-bromosuccinimide. The mono- and di-brominated compounds were separated by reverse-phase HPLC. **III-186**: LRMS (M+H)$^+$ = 590.4. **III-187**: LRMS (M+H)$^+$ = 668.3.

Step 2: (2R,4S,7S)-22-bromo-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-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-carboxamide (**III-182**)

EXAMPLE 169 was prepared from **III-186** using the procedure described for EXAMPLE 14, Steps 4 and 5. LRMS (ESI) *m/z* 774.5 [(M+H)$^+$; calcd for $C_{35}H_{45}BrN_5O_8S$: 774.2].

EXAMPLE 170

(2R,4S,7S)-17,22-dibromo-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-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-carboxamide (**III-183**)

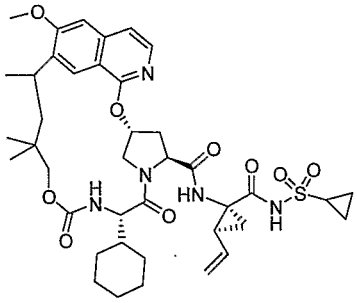


III-183

The title compound was prepared from **III-187** using the procedure described for EXAMPLE 14, Steps 4 and 5. LRMS (ESI) *m/z* 852.5 $[(M+H)^+$; calcd for $C_{35}H_{44}Br_2N_5O_8S$: 852.1].

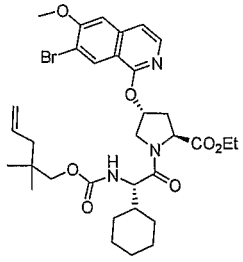
EXAMPLE 171

(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-12,12,14-trimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide (**III-184**)



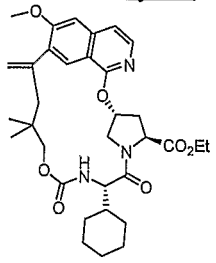
III-184

Step 1: 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



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 was prepared according to the procedure given for EXAMPLE 14, Step 1 using intermediates B23 and C1. LRMS $(M+H)^+$ = 674.3

Step 2: Ethyl (2R,4S,7S)-7-cyclohexyl-22-methoxy-12,12-dimethyl-14-methylene-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2H-15,17-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclooctadecine-4-carboxylate



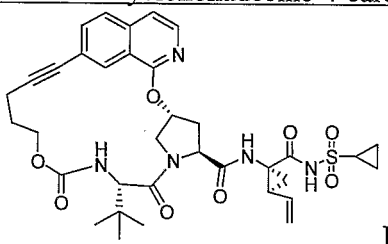
To a solution of the product from step 1 (448 mg, 0.664 mmol) dissolved in ethanol (10 mL) was added triethylamine (0.139 mL, 0.996 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (24.3 mg, 0.033 mmol) and the reaction mixture heated to 90 °C. After 1 hour, additional catalyst (5mg) was added and reaction mixture was stirred an additional 18 h at 90 °C. The reaction mixture was concentrated in vacuo and chromatographed on silica (20 to 50% EtOAc/hexane) to give impure product. Prep HPLC purification gave the title compound (140 mg) as a foam. LRMS $(M+H)^+$ = 594.5.

Step 3: (2*R*,4*S*,7*S*)-7-Cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-12,12,14-trimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide (**III-184**)

(2*R*,4*S*,7*S*)-7-Cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-12,12,14-trimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide (**III-184**) was prepared from the product from step 2 according to the procedure given for EXAMPLE 14, Steps 4 and 5 using intermediate A1 in Step 5. LRMS (ESI) *m/z* 780.6 [$(M+H)^+$; calcd for $C_{40}H_{53}N_5O_9S$: 780.4].

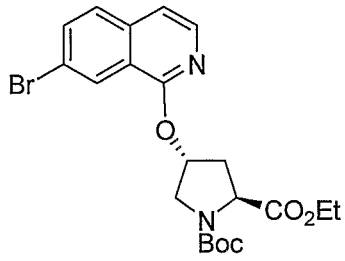
EXAMPLE 172

(2*R*,4*S*,7*S*)-7-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-185**)



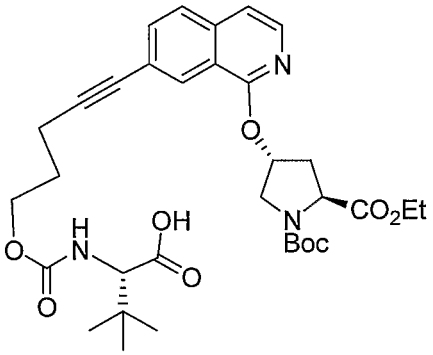
III-185

Step 1: 1,2-Pyrrolidinedicarboxylic acid, 4-[(7-bromo-1-isoquinolinyl)oxy]-, 1-(1,1-dimethylethyl) 2-ethyl ester, (2*S*,4*R*)-



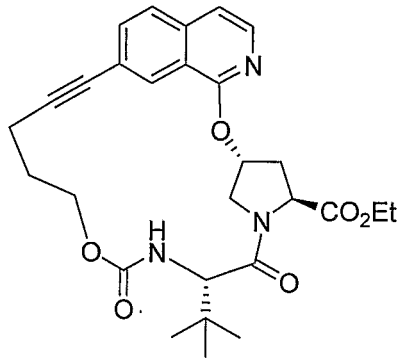
To a solution of di-*tert*-butyldicarbonate (1.14 g, 5.23 mmol) in CH_3CN (15 mL) was added Et_3N (2.08 mL, 14.9 mmol) and (4*R*)-4-[(7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (EXAMPLE 10, Step 1) (1.5 g, 3.73 mmol) at RT. After 15 min, DCM (150 mL) was added and the solution was extracted with 1 N HCl. The organic layer was dried over K_2CO_3 and the solvent was removed in vacuo. The crude material was purified on silica gel (gradient elution 0-30% EtOAc in hexanes) to yield the title compound as a foam (1.73 g). LRMS $(M+H)^+$ Calcd. = 465.1; found 465.2.

Step 2: *N*-({[5-(1-{[(3*R*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-(ethoxycarbonyl)pyrrolidin-3-yl]oxy}isoquinolin-7-yl)pent-4-yn-1-yl]oxy}carbonyl)-3-methyl-L-valine



To a portion of the product from Step 1 (0.94 g, 2.02 mmol), in degassed THF (10 mL) and pyrrolidine (10 ml) was added intermediate B11, 3-methyl-*N*-[(pent-4-yn-1-yloxy)carbonyl]-L-valine (0.8 g, 3.33 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), and CuI (19 mg, 0.1 mmol). The mixture was then heated to 70 °C for 2h. The mixture was then poured into a mixture of water and EtOAc and the pH adjusted to ~1 with 1 N HCl. The organic layer was then separated, dried over $MgSO_4$, and the solvent evaporated. The crude product was purified on silica gel (20-100% EtOAc in hexanes) to yield the title compound as a foam (1.2 g). LRMS $(M+H)^+$ Calcd. = 626.3; found 626.4.

Step 3: 7-Ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



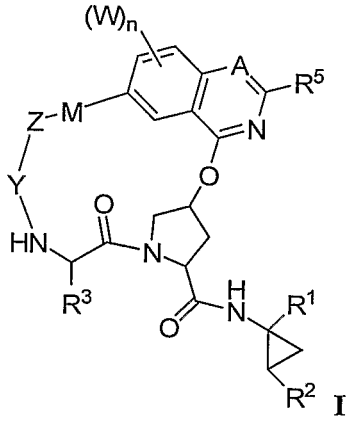
To a portion of the product from Step 2 (0.93 g, 1.49 mmol), was added HCl/dioxane (37 mL, 4M, 148 mmol). The mixture was stirred for 30 min and then the solvent was removed in vacuo. DCM (400 mL) was then added the mixture along with DIEA (1.3 mL, 7.4 mmol) and HATU (622 mg, 1.6 mmol). After 20 h, the solvent was removed in vacuo and the crude product was purified on silica gel (gradient elution 0-60% EtOAc in hexanes) to yield the title compound as a foam (0.11 g). LRMS $(M+H)^+$ Calcd. = 508.3; found 508.4.

Step 4: (2*R*,4*S*,7*S*)-7-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-185**)

The title compound was prepared from 7-ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate and Intermediate A1 using the procedure described in EXAMPLE 14, Steps 4 and 5. LRMS (ESI) *m/z* 692.3 $[(M+H)^+$; calcd for $C_{35}H_{42}N_5O_8S$: 692.3].

WHAT IS CLAIMED IS:

1. A compound of formula (I):



I

wherein:

n is 1 or 2;

R^1 is CO_2R^{10}, $CONR^{10}SO_2R^6$, $CONR^{10}SO_2NR^8R^9$, or tetrazolyl;

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 5-6 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}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ 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, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkyl, CN, CF_3, SR^{10}, $SO_2(C_1\text{-}C_6$ alkyl), $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkoxy, $C_1\text{-}C_6$ 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}, $N(R^7)_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), $C_3\text{-}C_6$ cycloalkyl, $C_3\text{-}C_6$ cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1\text{-}C_6$ 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

R^6 is $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_5$)alkyl, aryl, aryl($C_1\text{-}C_4$)alkyl, heteroaryl, heteroaryl($C_1\text{-}C_4$ alkyl), heterocyclyl, or heterocyclyl($C_1\text{-}C_8$ 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;

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

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

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

A is $C(R^{11})$ or N;

when R^5 is other than H, R^{11} is H, C_1-C_6 alkyl, halo, OR^{10}, SR^{10}, or $N(R^{10})_2$;

when R^5 is H, R^{11} 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^5 and R^{11} are optionally taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 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 0-2 heteroatoms selected from N, O and S;

each W' is independently 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 0-2 heteroatoms selected from N, O and S;

R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, $halo(C_1$-C_6 alkoxy), 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, $C(O)R^{10}$, C_1-C_6 haloalkyl, 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

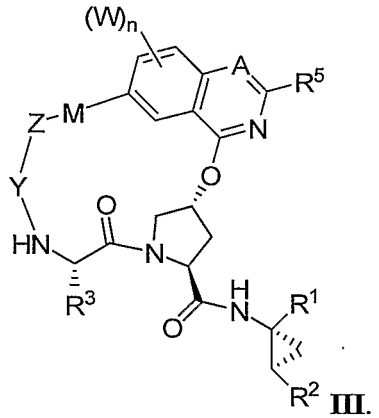
R^9 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl,

C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), 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, $C(O)R^{10}$, C_1-C_6 haloalkyl, 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 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-8 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and

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

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



III.

3. The compound of claim 2, wherein R^1 is CO_2R^{10} or $CONR^{10}SO_2R^6$.

4. The compound of claim 3, wherein R^1 is CO_2H.

5. The compound of claim 3, wherein R^1 is $CONHSO_2R^6$.

6. The compound of claim 5, wherein R^1 is $CONHSO_2R^6$ wherein R^6 is C_3-C_8 cycloalkyl, C_1-C_8 alkyl, aryl, or aryl(C_1-C_4)alkyl.

7. The compound of claim 3, wherein R^2 is C_1-C_4 alkyl or C_2-C_4 alkenyl.

8. The compound of claim 7, wherein R^3 is C_5-C_6 cycloalkyl or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents.

9. The compound of claim 8, wherein R^5 is H, halo, aryl, heteroaryl or $N(R^7)_2$.

10. The compound of claim 9, wherein R^5 is H or halo.

11. The compound of claim 9, wherein R^5 is aryl or heteroaryl.

12. The compound of claim 9, wherein Y is C=O.

13. The compound of claim 12, wherein Z is O, NH, $N(C_1$-C_8 alkyl) or $C(R^{10})_2$.

14. The compound of claim 13, wherein M is unsubstituted C_4-C_7 alkylene or unsubstituted C_4-C_7 alkenylene.

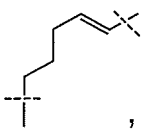
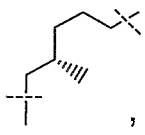
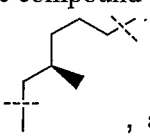
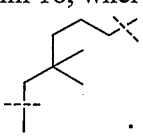
15. The compound of claim 14, wherein n is 1 and W is H, C_1-C_6 alkoxyl, C_1-C_6 alkyl, OH, halo, $N(R^7)_2$ wherein R^7 is H or C_1-C_6 alkyl.

16. The compound of claim 15, wherein A is N.

17. The compound of claim 15, wherein A is $C(R^{11})$ wherein R^{11} is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy or halo.

18. The compound of claim 10, wherein R^2 is C_2-C_4 alkenyl, R^5 is H, R^6 is C_3-C_8 cycloalkyl, W is R^7 or H, Y is C(=O), Z is O, and n is 1.

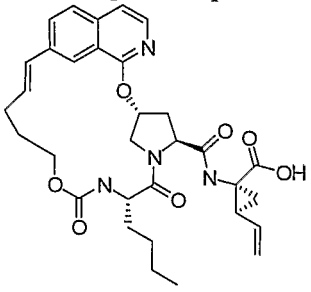
19. The compound of claim 18, wherein M is selected from the group consisting of:


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, and

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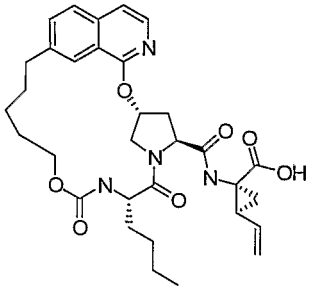
20. The compound of claim 19, wherein R^3 is C_5-C_6 cycloalkyl or C_3-C_5 alkyl.

21. The compound of claim 20, wherein R^6 is C_3-C_5 cycloalkyl.

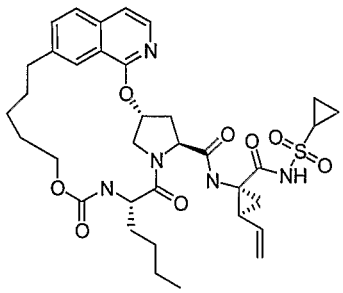
22. The compound of claim 1, wherein the compound is selected from the group consisting of compounds **III-1** to **III-38**:



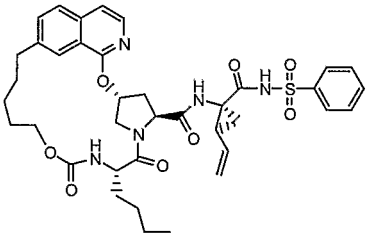
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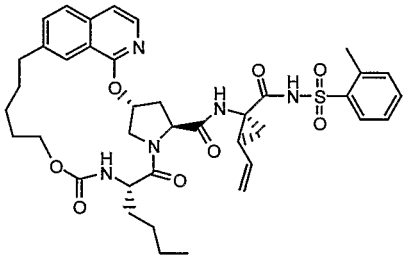
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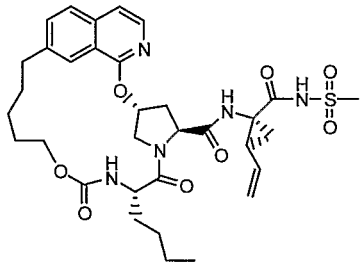
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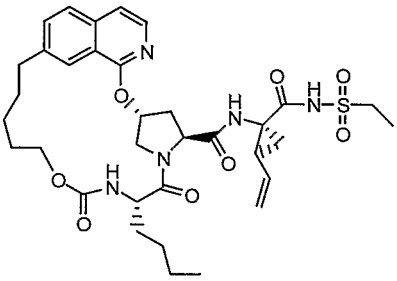
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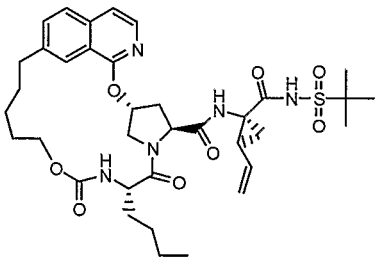
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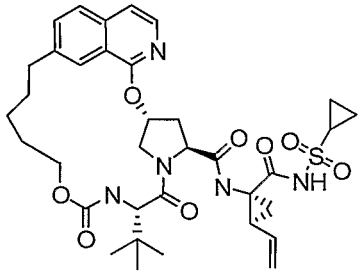
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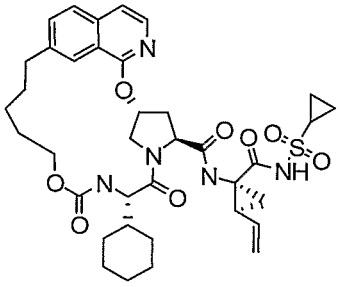
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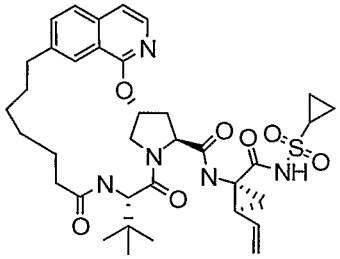
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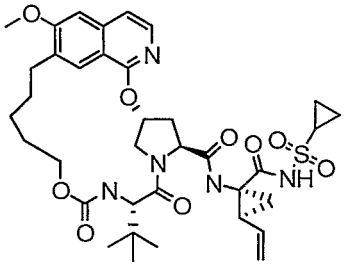
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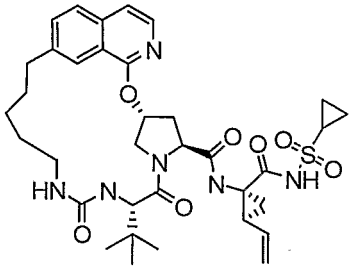
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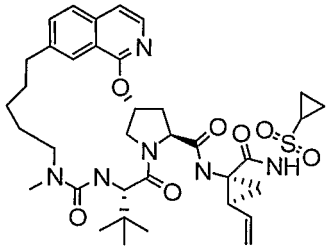
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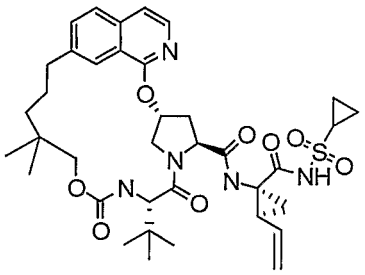
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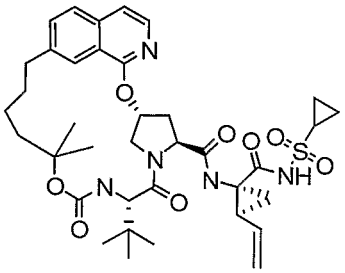
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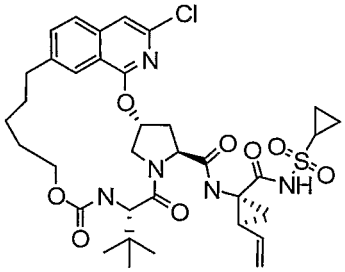
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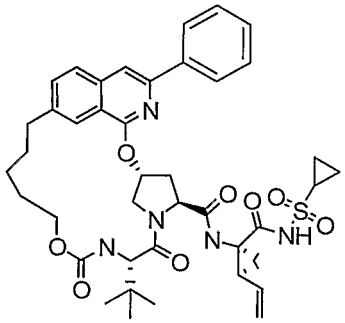
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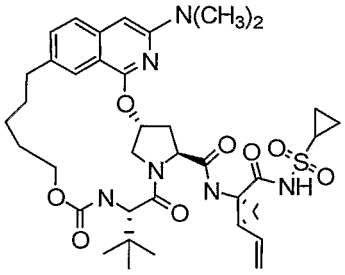
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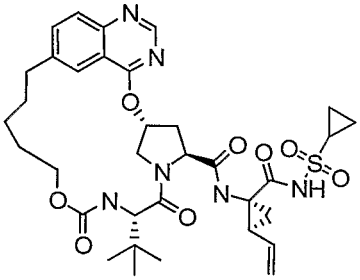
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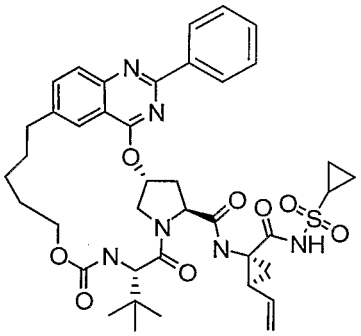
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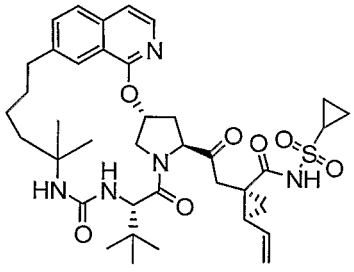
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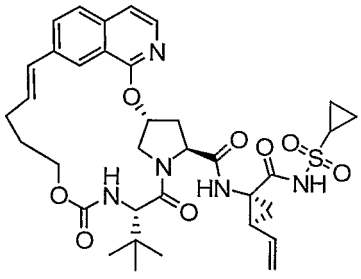
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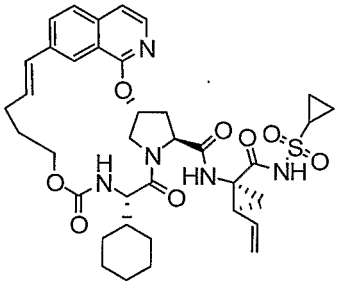
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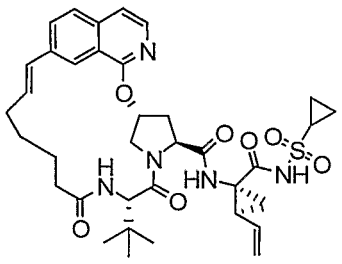
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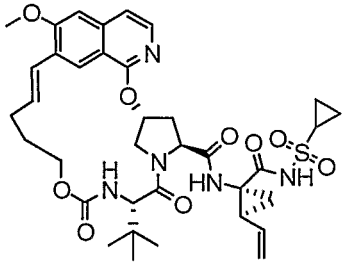
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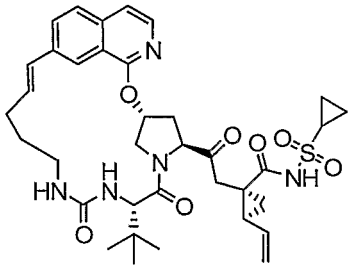
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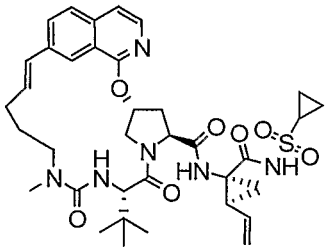
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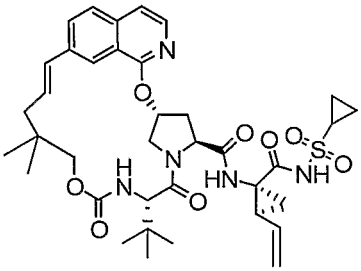
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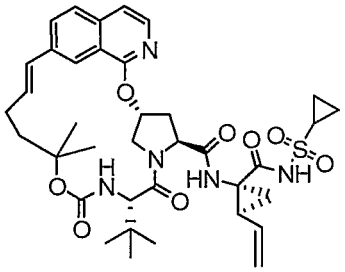
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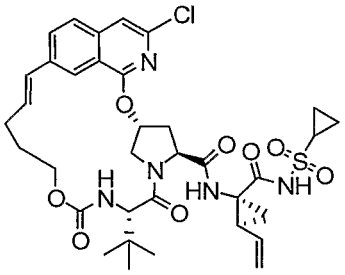
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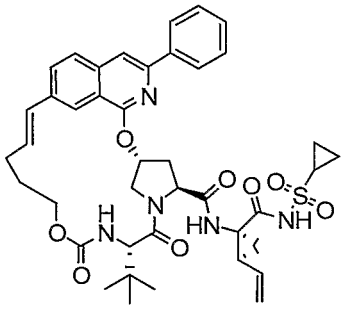
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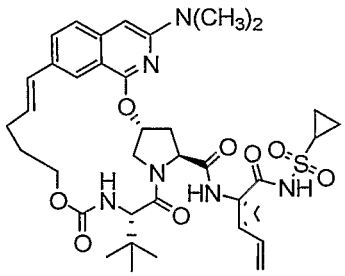
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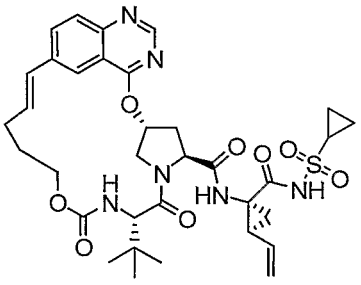
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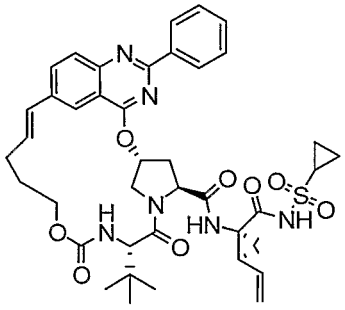
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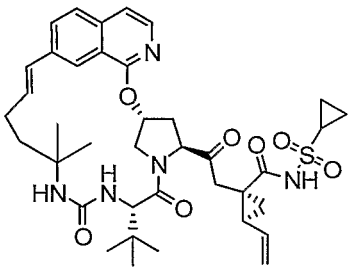
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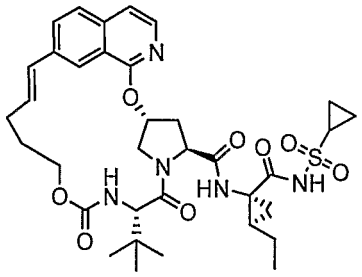
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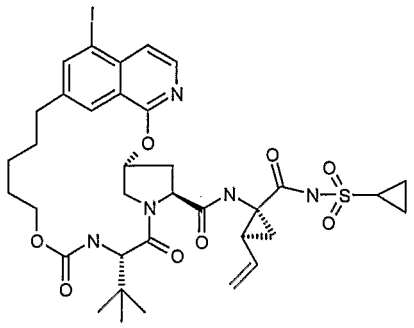
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III-36

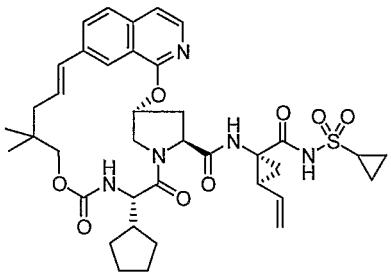


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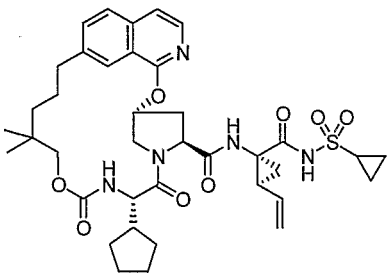


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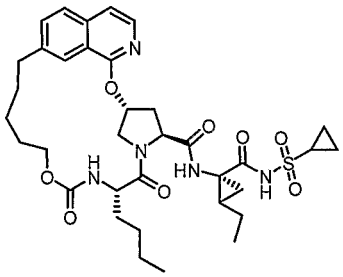
23. The compound of claim 1, wherein the compound is selected from the group consisting of compounds **III-39** to **III-187**:



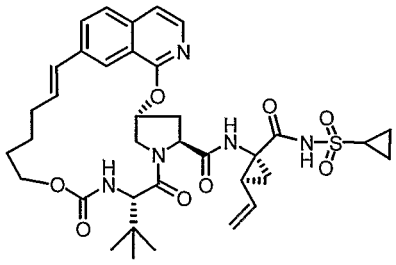
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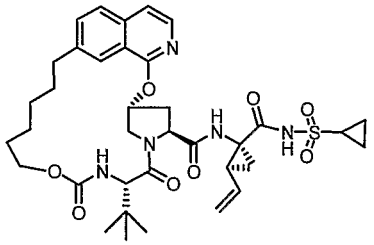
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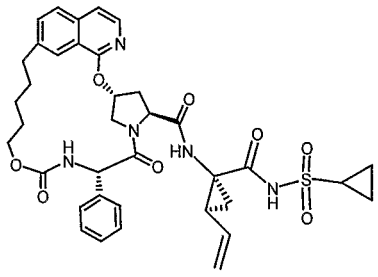
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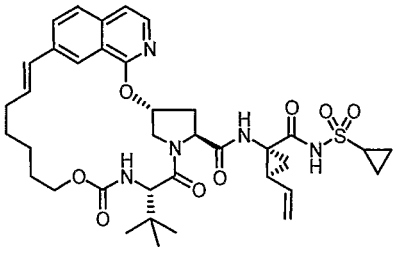
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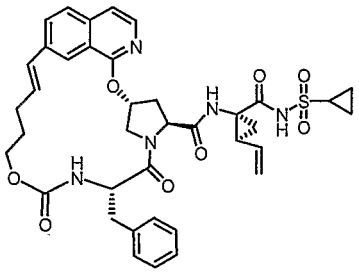
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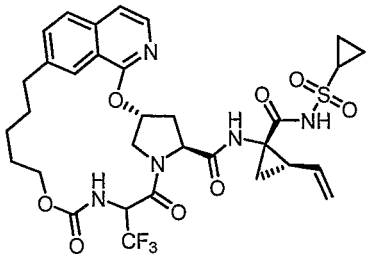
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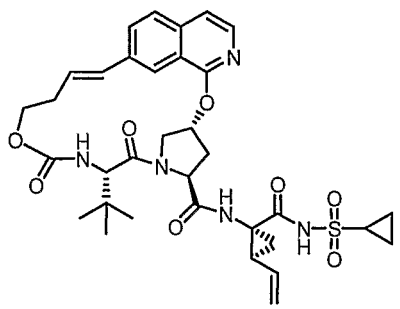
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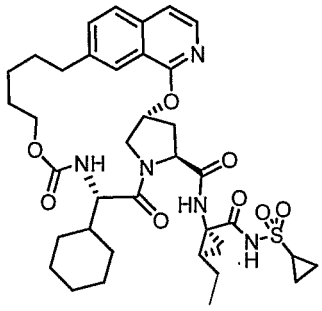
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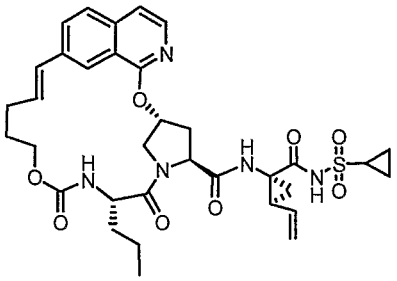
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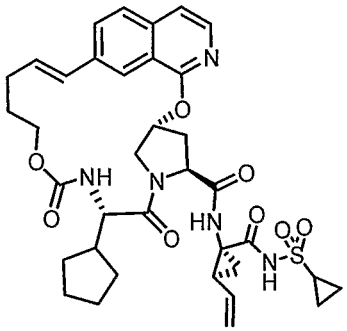
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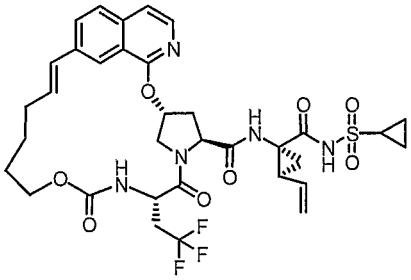
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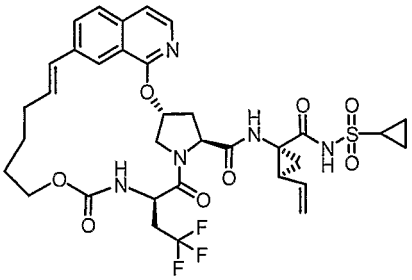
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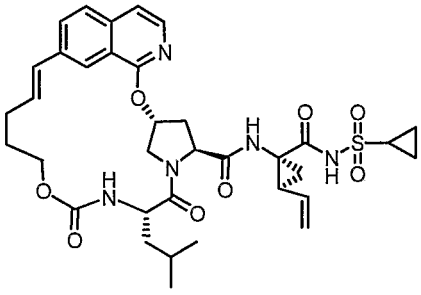
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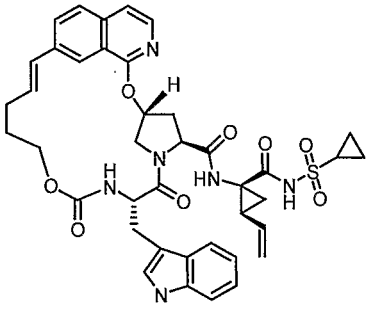
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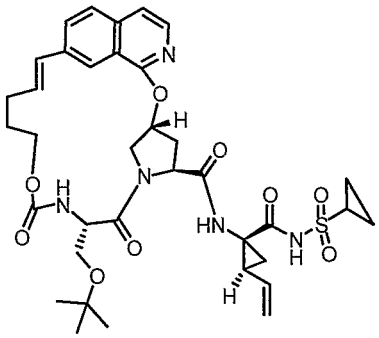
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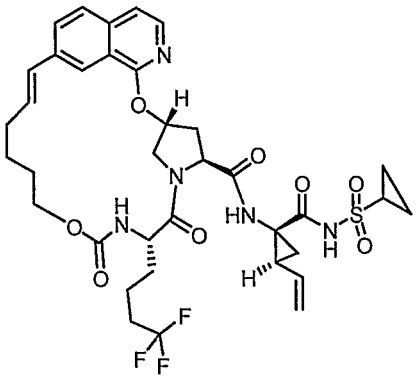
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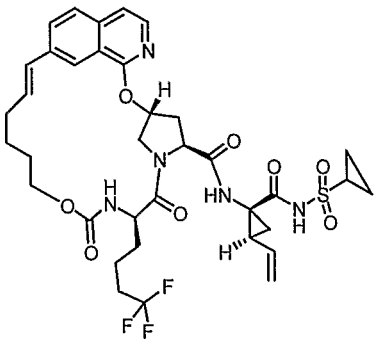
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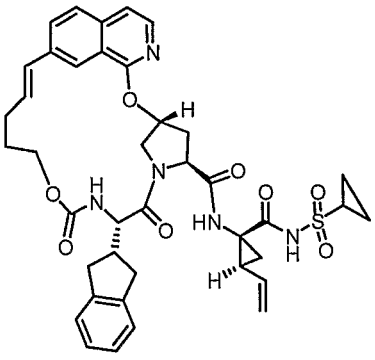
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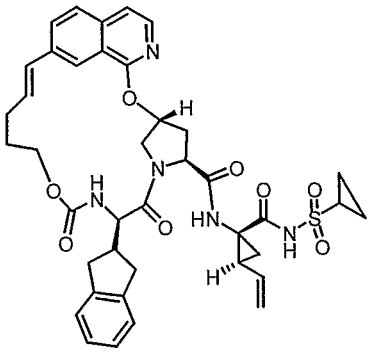
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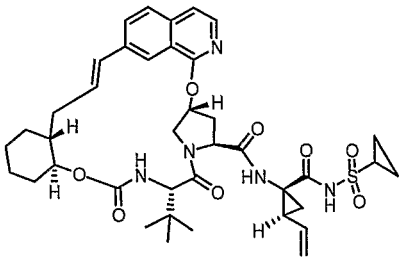
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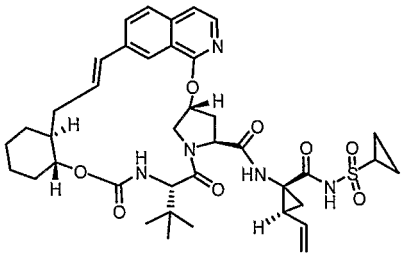
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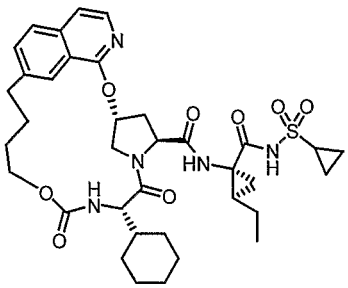
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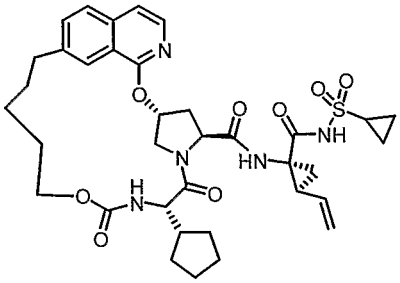
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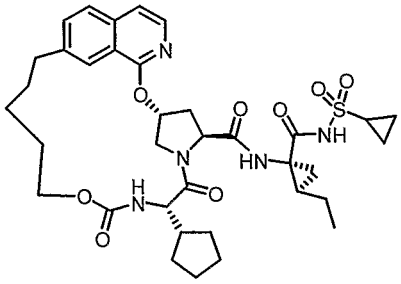
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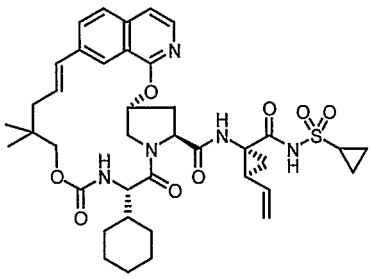
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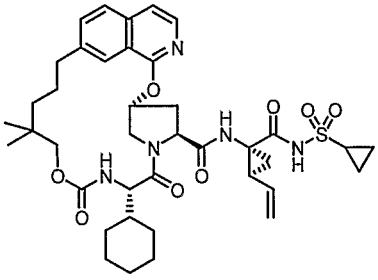
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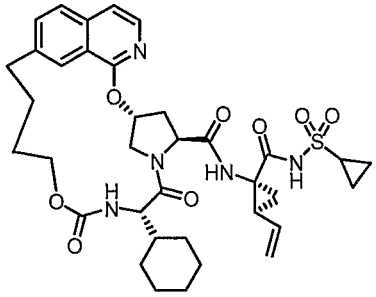
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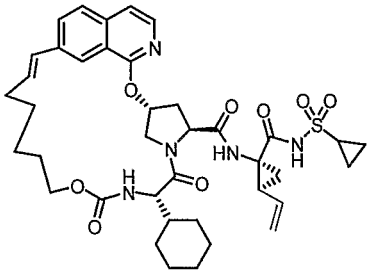
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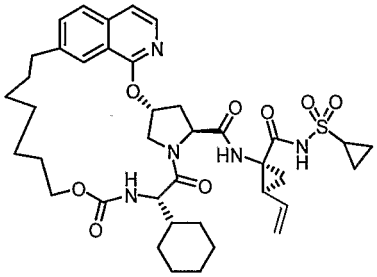
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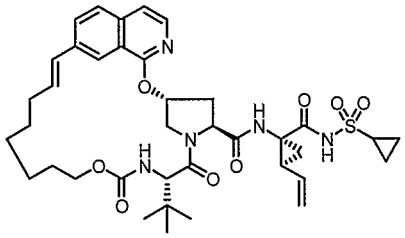
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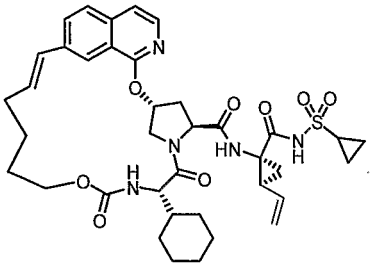
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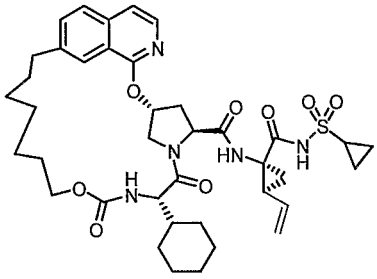
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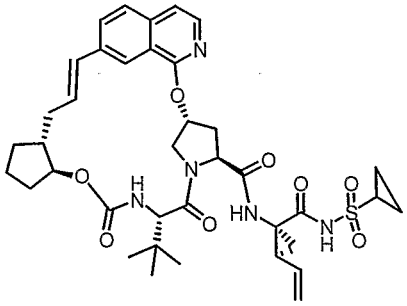
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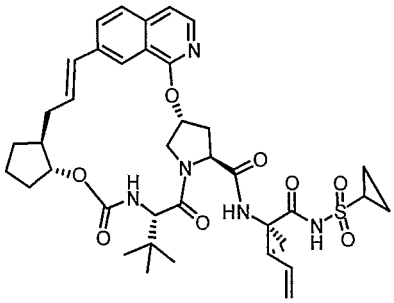
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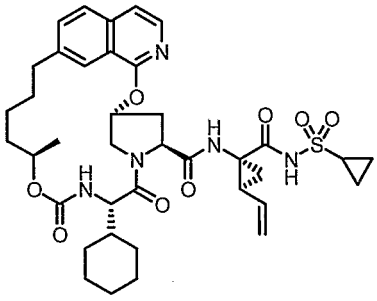
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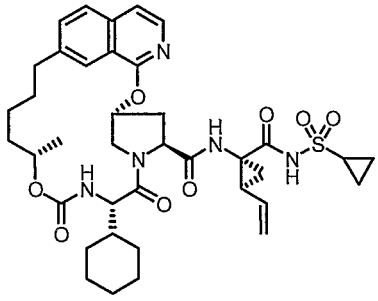
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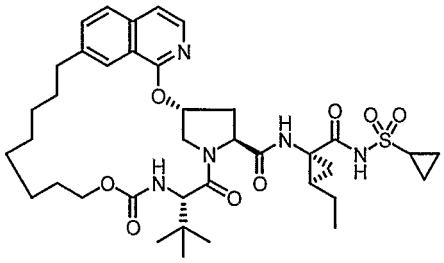
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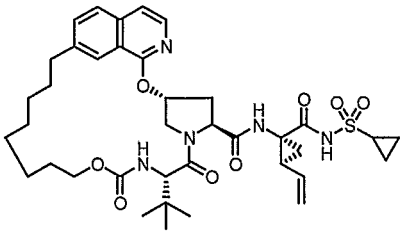
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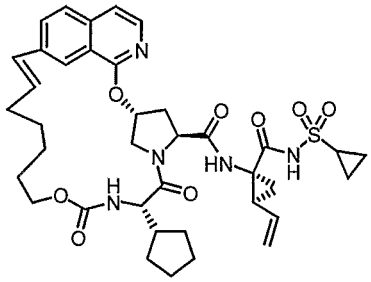
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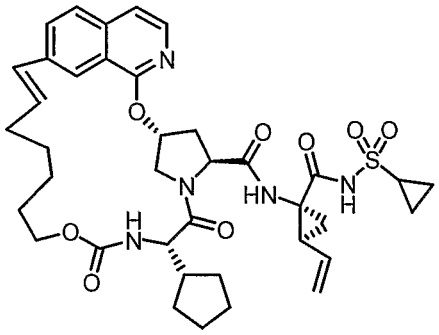
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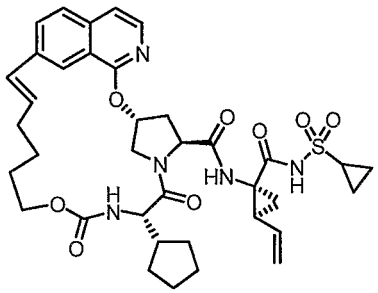
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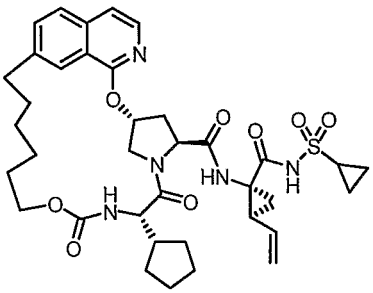
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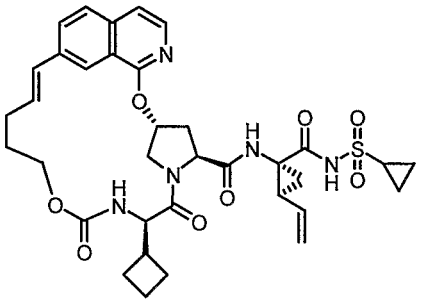
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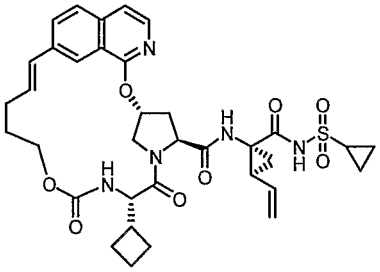
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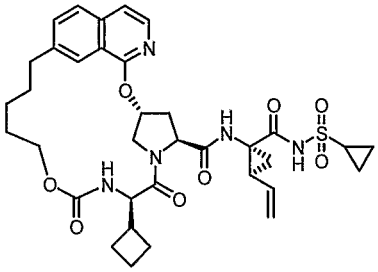
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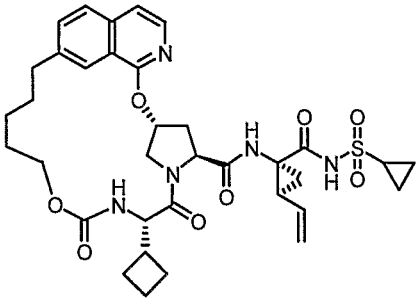
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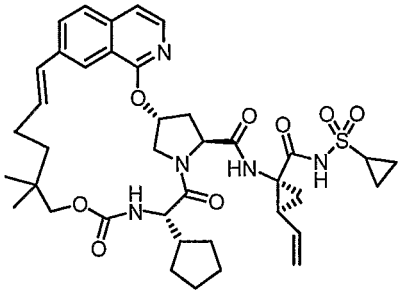
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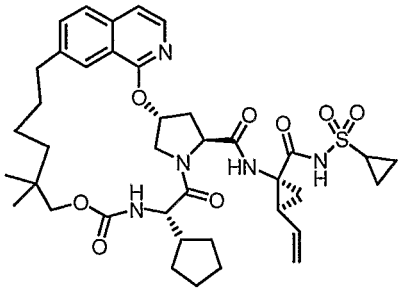
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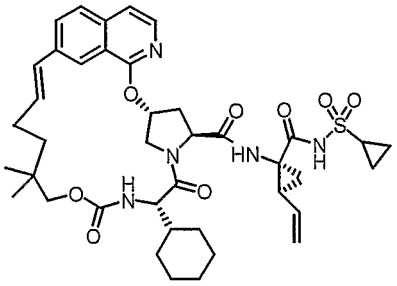
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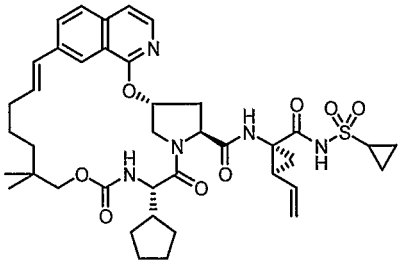
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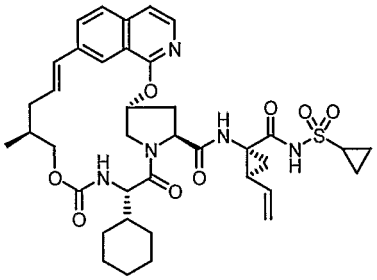
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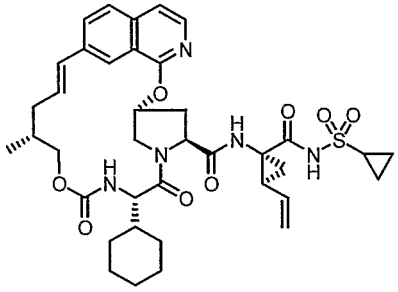
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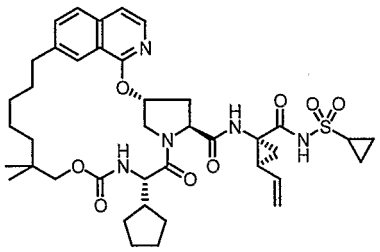
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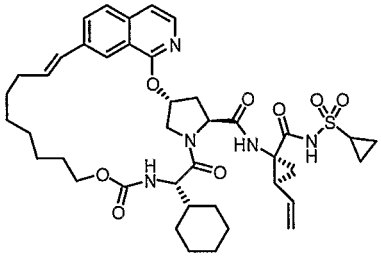
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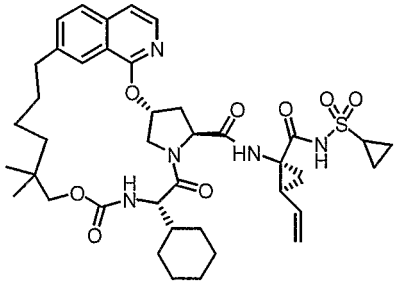
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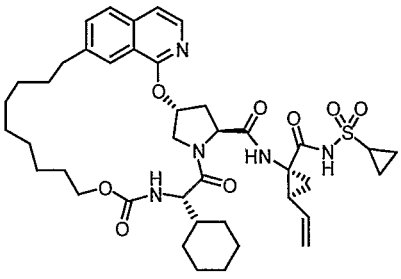
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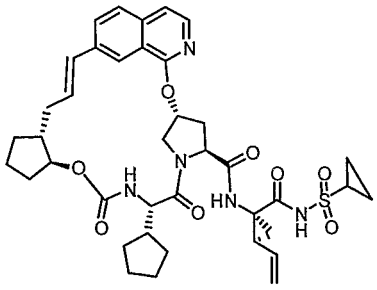
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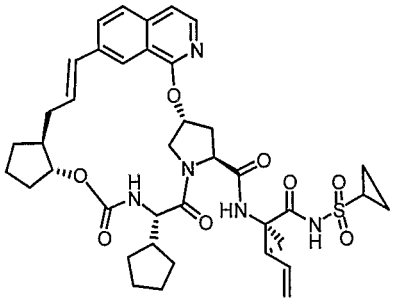
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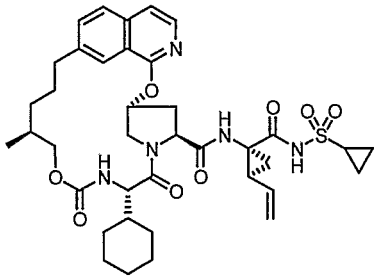
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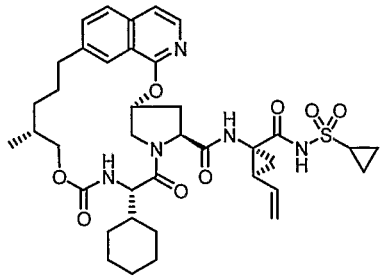
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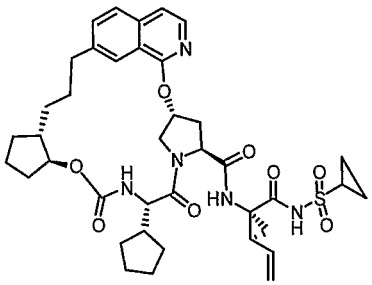
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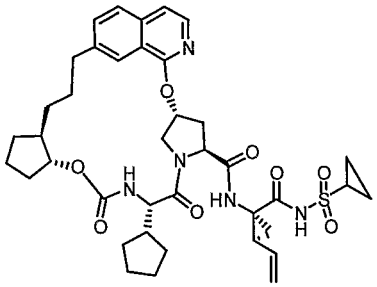
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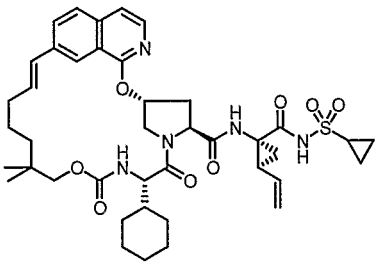
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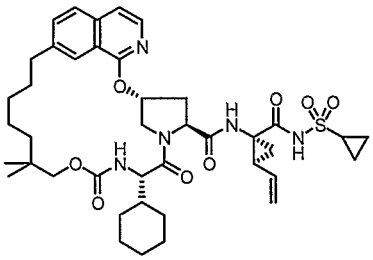
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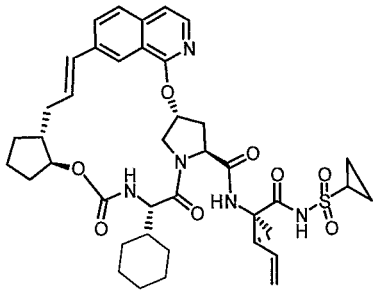
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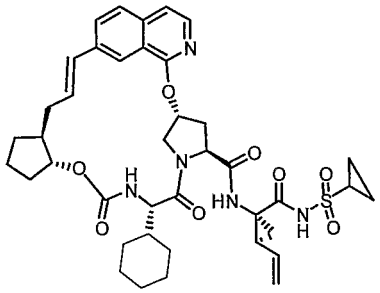
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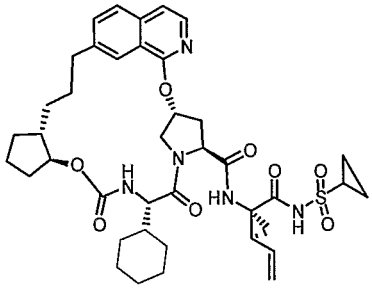
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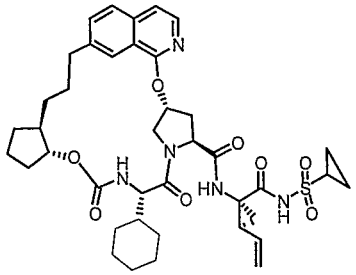
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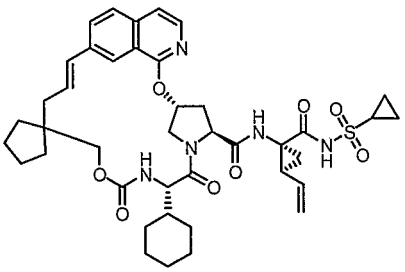
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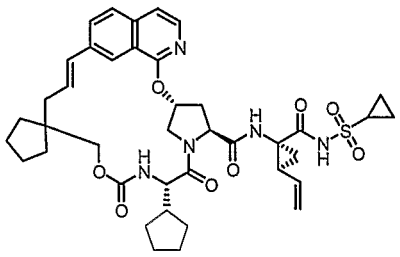
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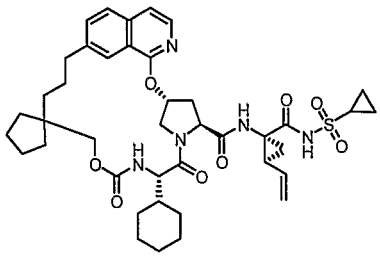
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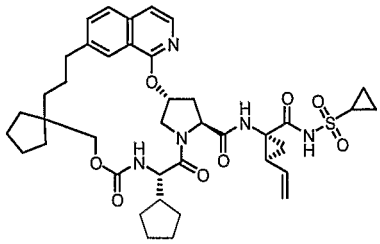
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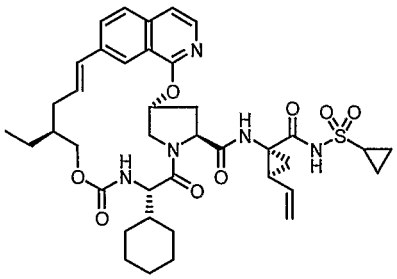
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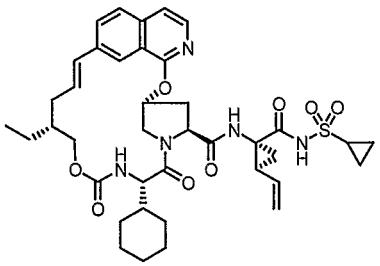
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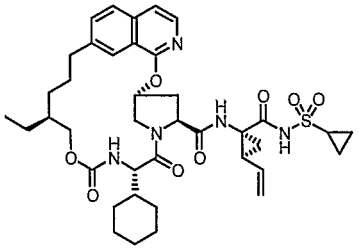
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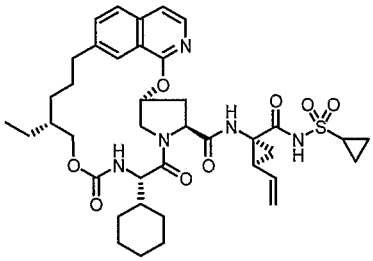
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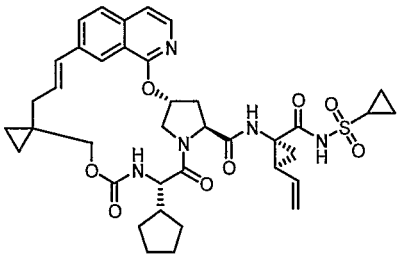
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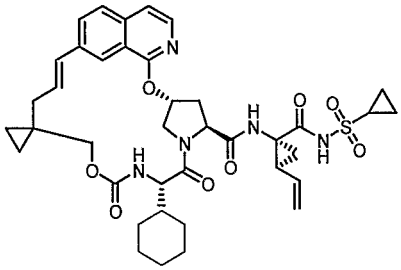
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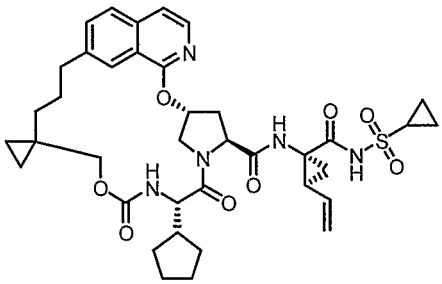
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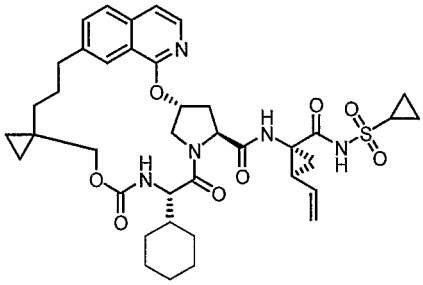
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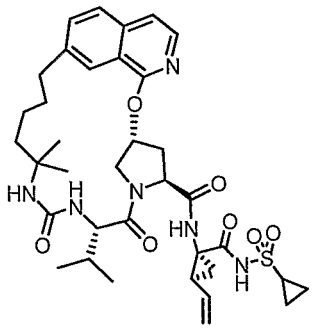
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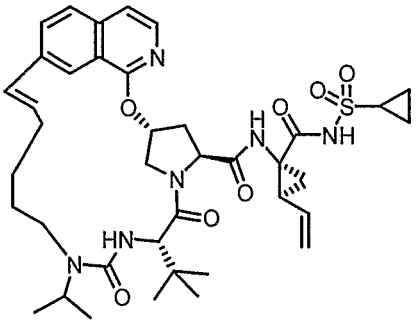
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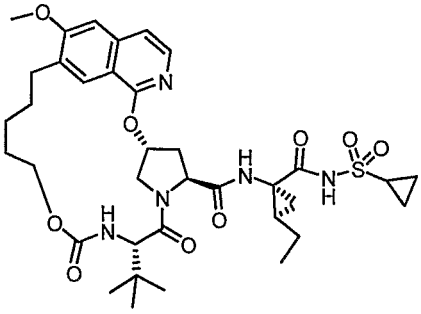
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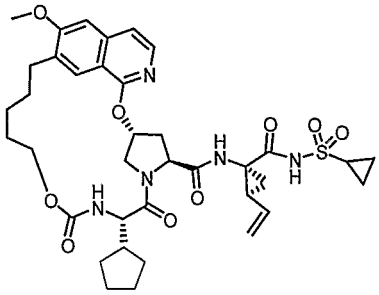
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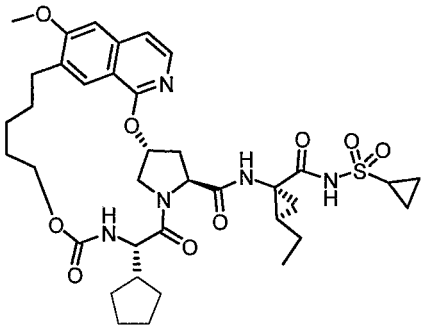
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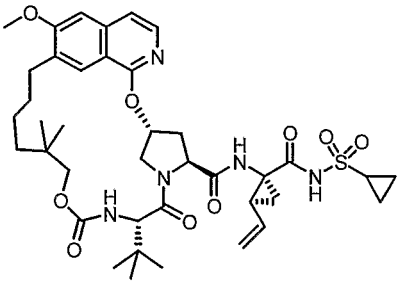
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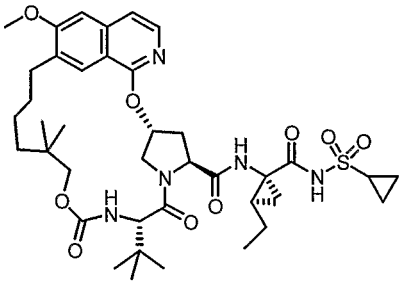
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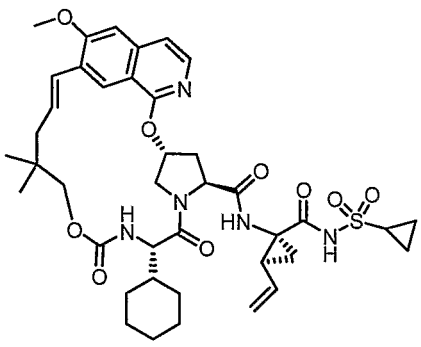
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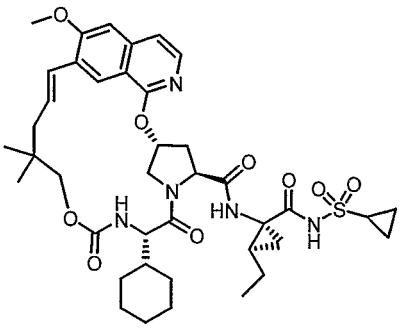
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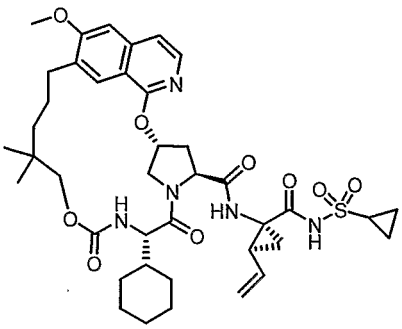
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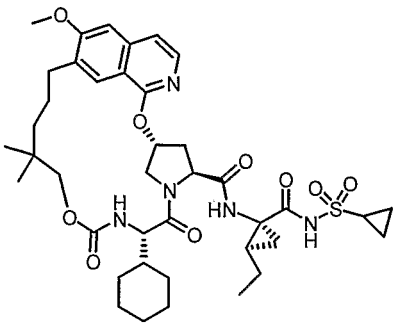
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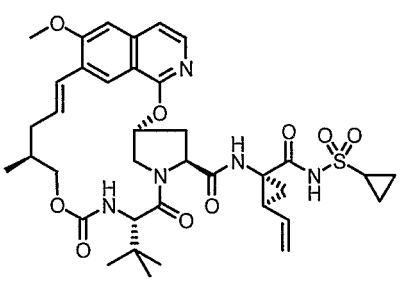
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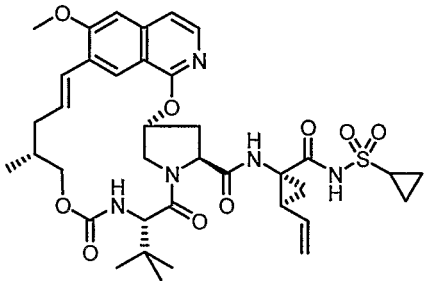
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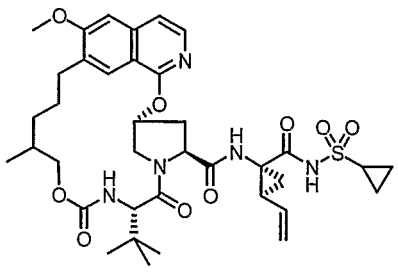
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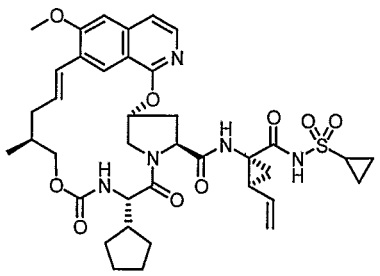
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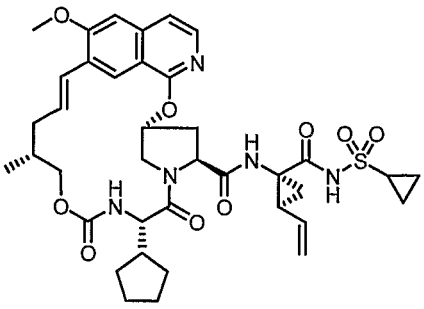
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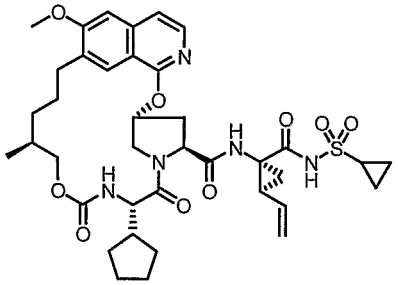
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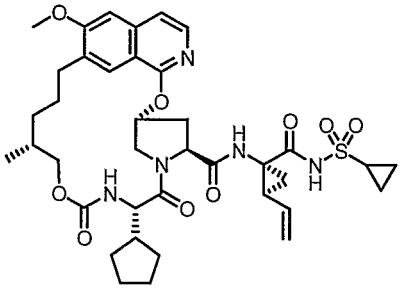
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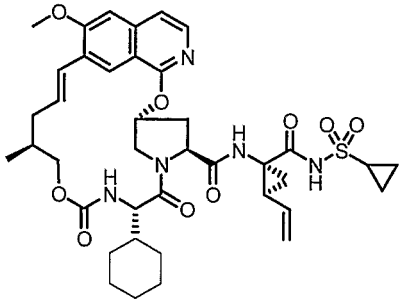
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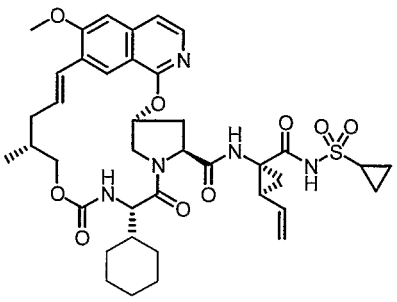
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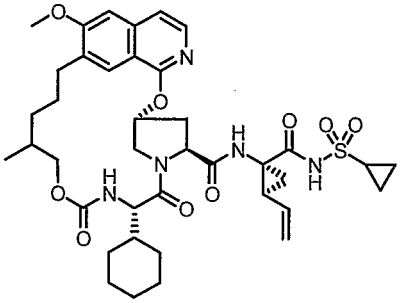
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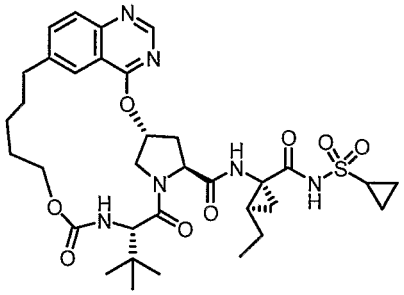
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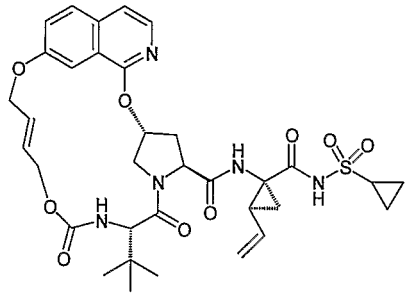
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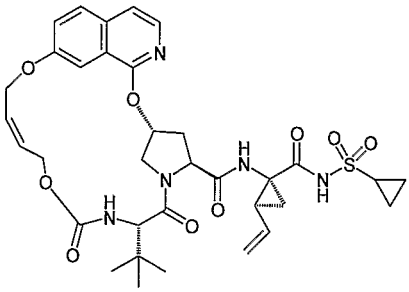
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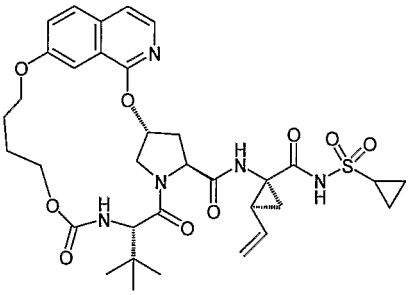
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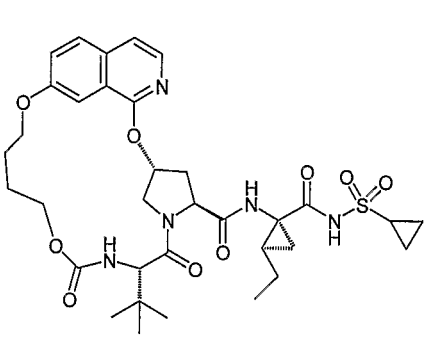
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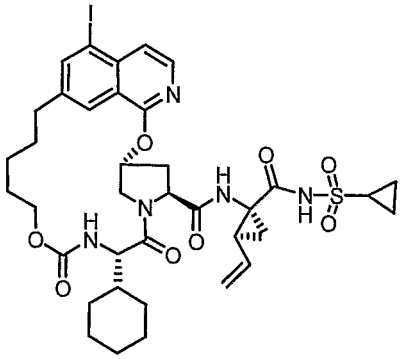
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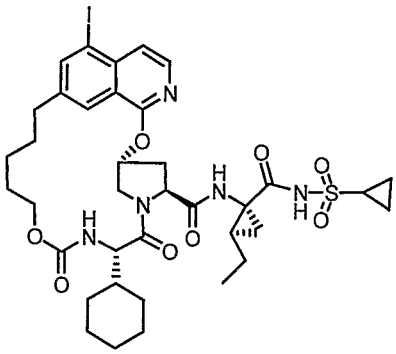
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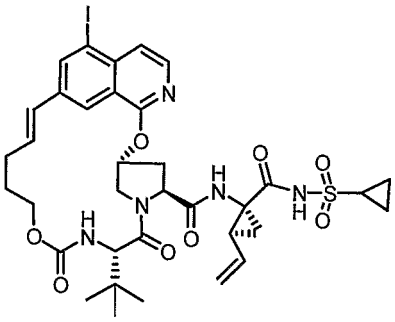
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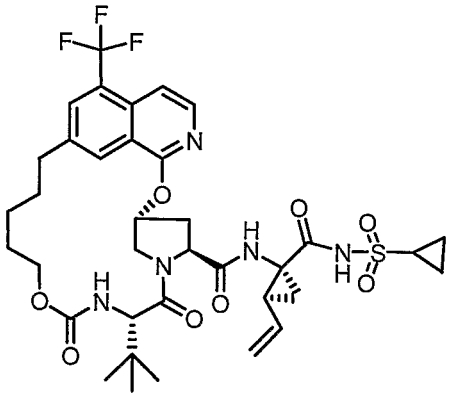
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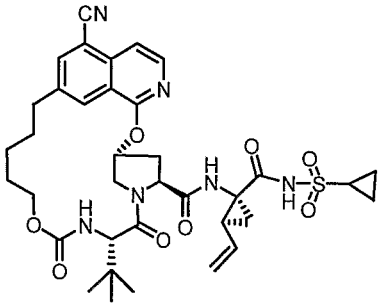
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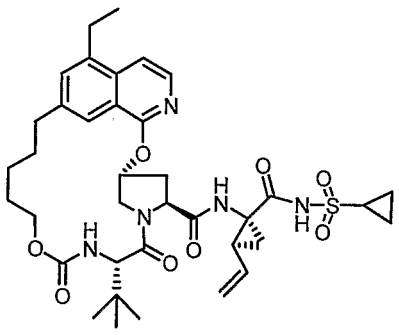
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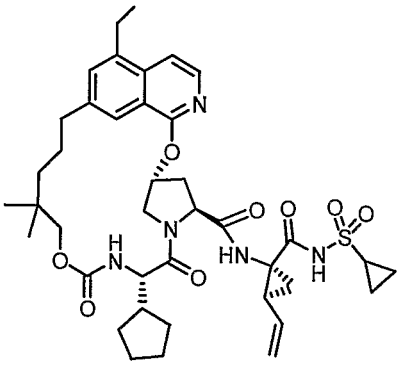
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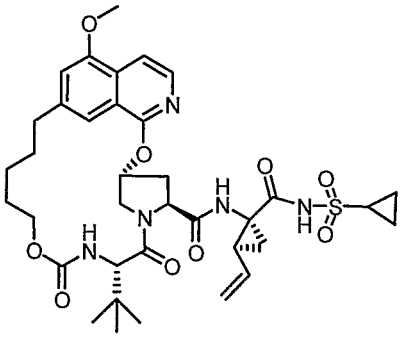
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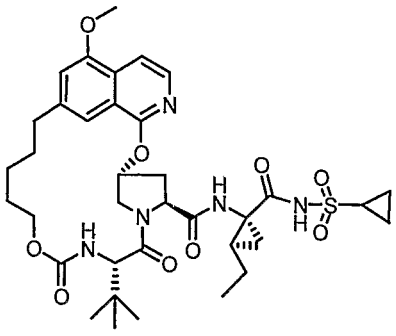
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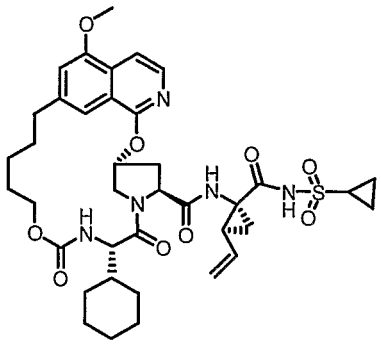
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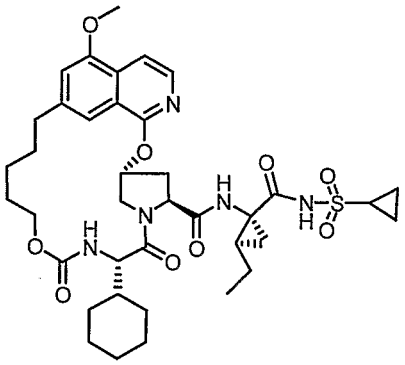
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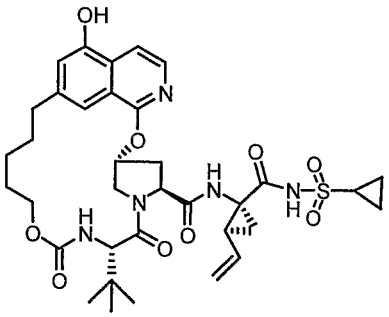
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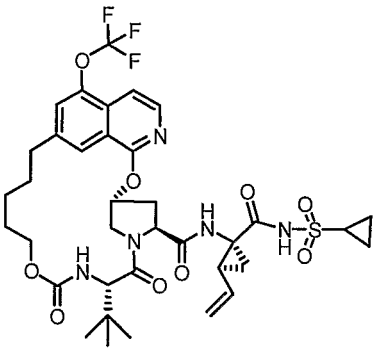
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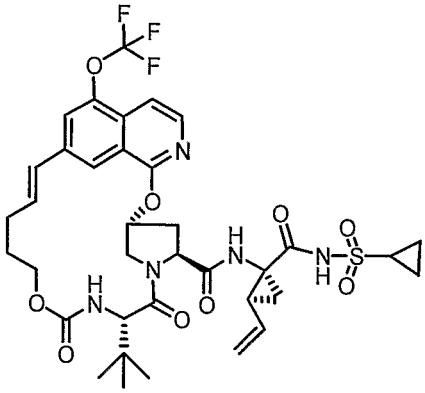
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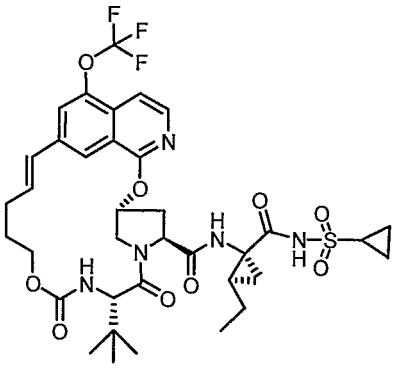
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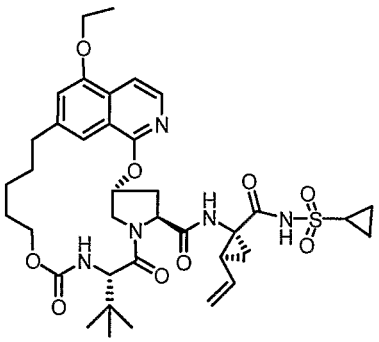
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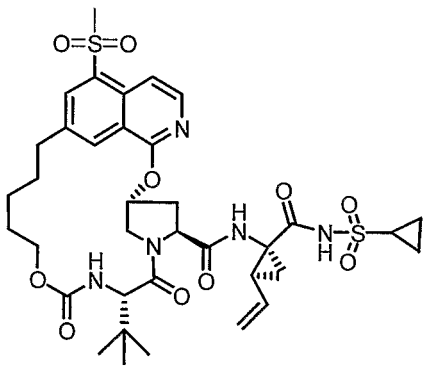
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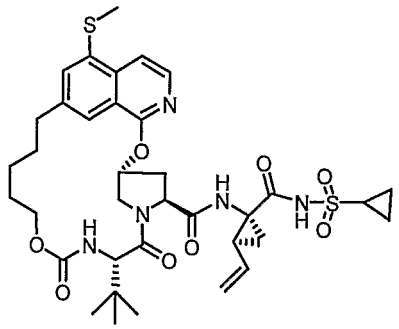
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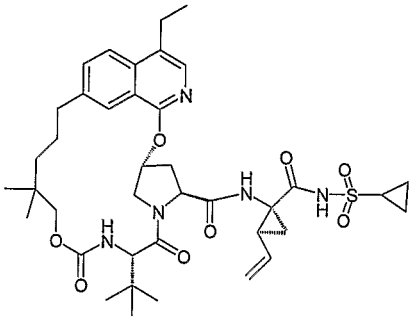
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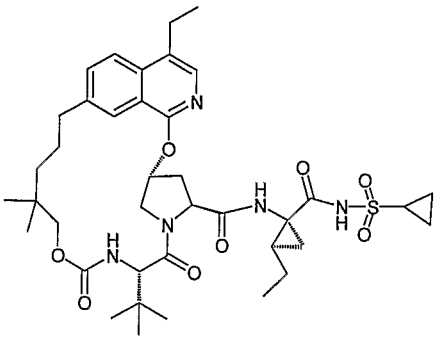
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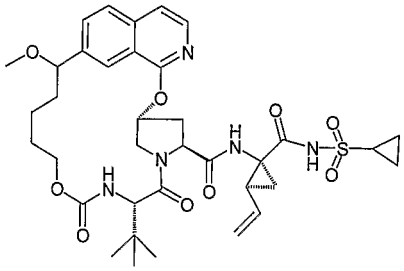
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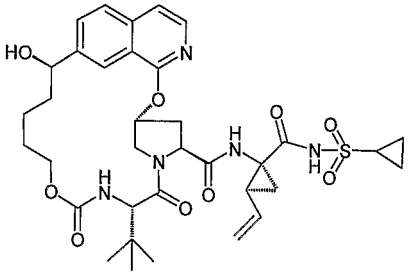
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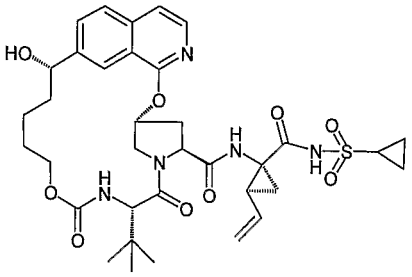
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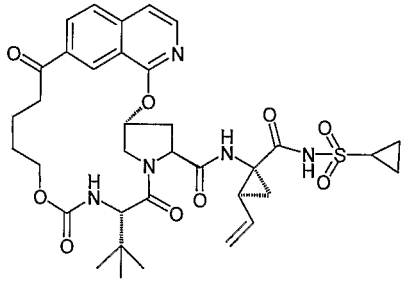
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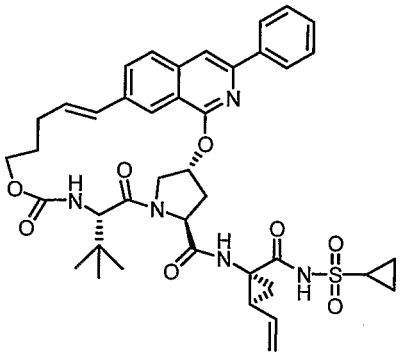
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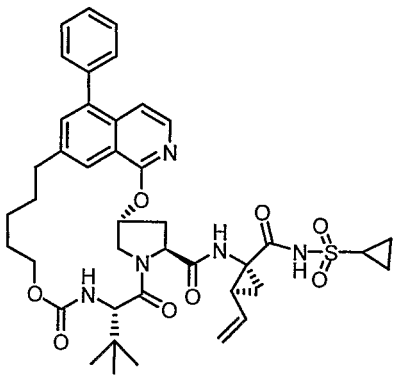
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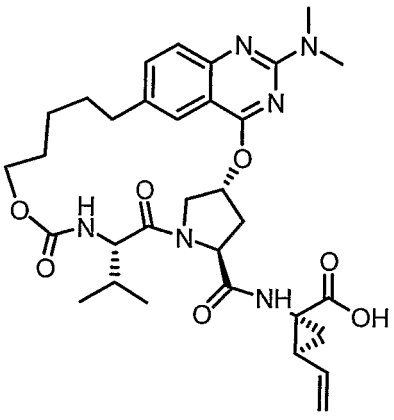


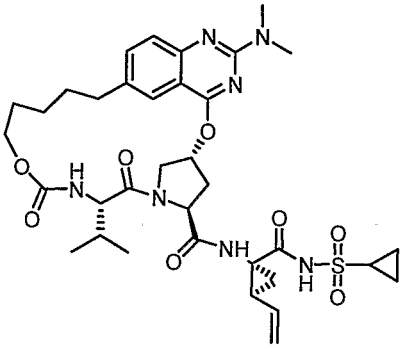
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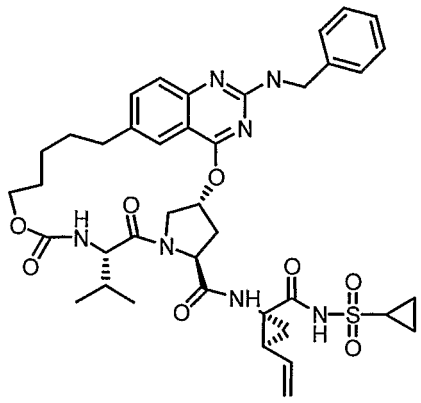
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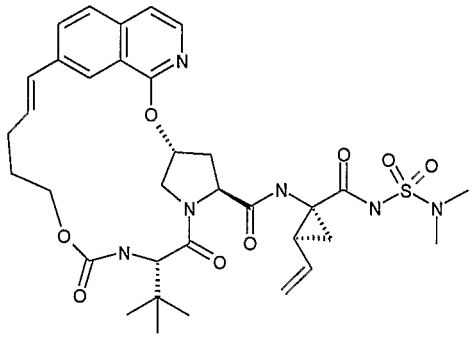




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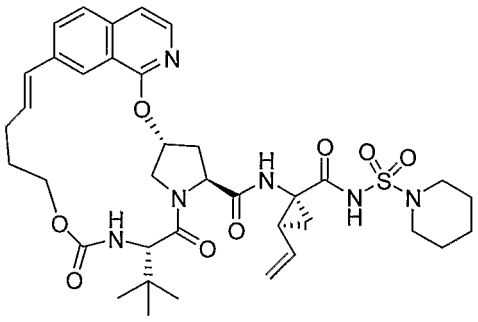


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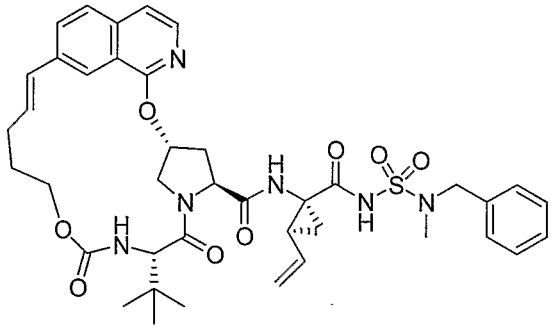


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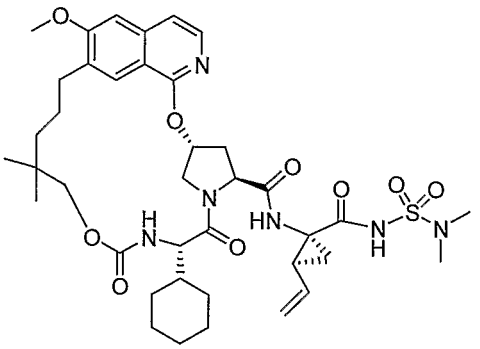
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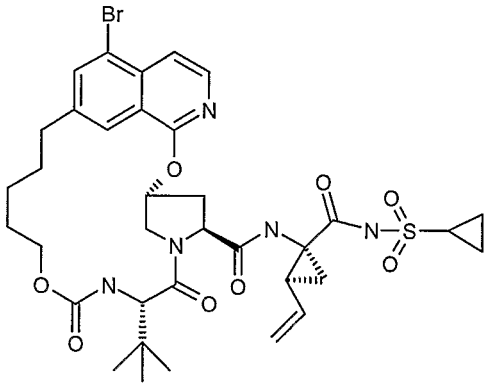
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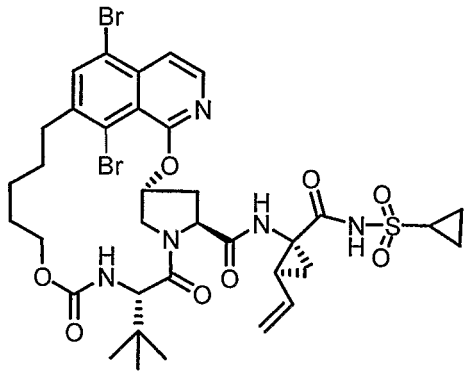


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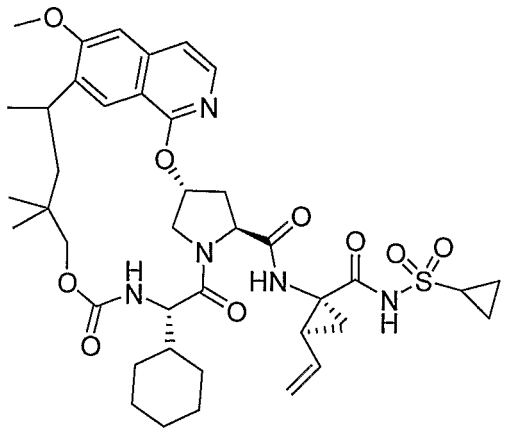
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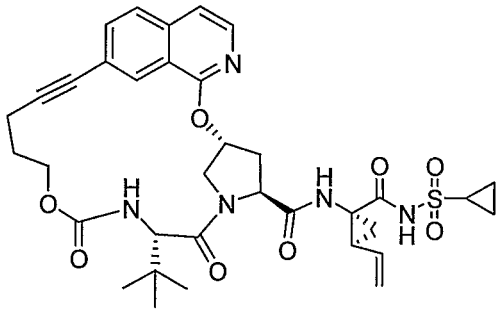




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24. The compound of claim 1, wherein the compound is (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid.

25. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1-24, and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, further comprising a second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

27. The pharmaceutical composition of claim 26, wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

28. A use of a compound of any one of claims 1-24 in the preparation of a medicament for inhibiting HCV NS3 protease activity in a subject in need thereof.

29. A use of a compound of any one of claims 1-24 in the preparation of a medicament for preventing or treating infection by HCV in a subject in need thereof.

30. The use of claim 29, wherein said medicament further comprises at least one second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

31. The use of claim 30, wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.