Title: MACROCYCLIC PEPTIDES AS HCV NS3 PROTEASE InHIBITORS

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

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


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:

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\( (W) \)
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wherein:

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\( n \) is 1 or 2;

\( R^1 \) is \( \text{CO}_2R^{10}, \text{CONR}^{10}\text{SO}_2R^{6}, \text{CONR}^{10}\text{SO}_2\text{NR}^8R^9 \), or tetrazolyl;

\( R^2 \) is \( \text{C}_1-\text{C}_6 \) alkyl, \( \text{C}_2-\text{C}_6 \) alkenyl or \( \text{C}_3-\text{C}_8 \) cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

\( R^3 \) is \( \text{C}_1-\text{C}_4 \) alkyl, \( \text{C}_3-\text{C}_4 \) cycloalkyl, \( \text{C}_3-\text{C}_4 \) cycloalkyl(\( \text{C}_1-\text{C}_8 \))alkyl, aryl(\( \text{C}_1-\text{C}_8 \))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\(^{16}\))\(_2\), 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\(_2\)R\(^6\), SO\(_2\)N(R\(^6\))\(_2\), NHCOOR\(^6\), NHCOR\(^6\), NHCONHR\(^6\), CO\(_2\)R\(^{10}\), C(O)R\(^{10}\), and CON(R\(^{16}\))\(_2\);

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\(^{16}\))\(_2\), 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\(_2\)R\(^6\), SO\(_2\)N(R\(^6\))\(_2\), NHCOOR\(^6\), NHCOR\(^6\), NHCONHR\(^6\), CO\(_2\)R\(^{10}\), C(O)R\(^{10}\), and CON(R\(^{16}\))\(_2\);

R\(^4\) is H, C\(_1\)-C\(_6\) alkyl, C\(_3\)-C\(_6\) cycloalkyl(C\(_1\)-C\(_6\) alkyl), or aryl(C\(_1\)-C\(_6\) 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\(^{16}\))\(_2\), 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\(_2\)R\(^6\), SO\(_2\)N(R\(^6\))\(_2\), NHCOOR\(^6\), NHCOR\(^6\), NHCONHR\(^6\), CO\(_2\)R\(^{10}\), C(O)R\(^{10}\), and CON(R\(^{16}\))\(_2\);

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 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\(_1\)-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\(_2\)R\(^6\), SO\(_2\)N(R\(^6\))\(_2\), S(O)(C\(_1\)-C\(_6\) alkyl), NHCOOR\(^6\), NHCOR\(^6\), NHCONHR\(^6\), CO\(_2\)R\(^{10}\), C(O)R\(^{10}\), and CON(R\(^{16}\))\(_2\); 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\(_6\) alkyl, C\(_3\)-C\(_8\) cycloalkyl, C\(_3\)-C\(_8\) cycloalkyl(C\(_1\)-C\(_6\) alkyl), aryl, aryl(C\(_1\)-C\(_6\) alkyl), heteroaryl, heteroaryl(C\(_1\)-C\(_6\) 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 heterocycll 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), SO₂, or C(=N-CN);

Z is C(R¹⁰)₂, O, or N(R⁴);

M is C₁₋₇ alkylene or C₂₋₁₂ alkenylene or C₂₋₁₂ alkynylene, wherein said alkylene or alkenylene is
optionally substituted with 1, 2 or 3 substituents selected from the group consisting of C₁₋₇ alkyl, C₃₋₈
cycloalkyl(C₁₋₇ alkyl), and aryl(C₁₋₇ 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(R¹¹) or N;

when R⁵ is other than H, R¹¹ is H, C₁₋₇ alkyl, halo, OR¹⁰, SR¹⁰, or N(R¹⁰)₂;

when R⁵ is H, R¹¹ is H, C₁₋₇ alkyl, halo, OH, C₁₋₇ alkoxy, CN, CF₃, SR¹⁰, SO₂(C₁₋₇ alkyl), C₃₋₈
cycloalkyl, C₂₋₇ cycloalkoxy, C₁₋₇ haloalkyl, N(R¹⁰)₂, aryl, heteroaryl or heterocycll; 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 heterocycll 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,
attained through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocycll, cycloalkyl,
cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group
consisting of halo, OR¹⁰, SR¹⁰, N(R¹⁰)₂, N(C₁₋₇ alkyl)O(C₁₋₇ alkyl), C₁₋₇ alkyl, C₁₋₇ haloalkyl,
halo(C₁₋₇ alkoxy), C₂₋₇ cycloalkyl, C₃₋₇ cycloalkoxy, NO₂, CN, CF₃, SO₂(C₁₋₇ alkyl), NR¹⁰SO₂R⁶,
SO₂N(R⁵)₂, S(O)(C₁₋₇ alkyl), NHCOOR⁶, NHCOR⁶, NHCONHR⁶, CO₂R¹⁰, C(O)R¹⁰, and CON(R¹⁰)₂;
wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocycll are
optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from
N, O and S;

or R⁵ and R¹¹ 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 R² is independently H, C₁-C₆ alkyl, C₂-C₆ cycloalkyl, C₂-C₆ cycloalkyl(C₁-C₂)alkyl, aryl, aryl(C₁-C₄)alkyl, heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl, or heterocyclyl(C₁-C₄ alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W⁷ 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, OR², C₁-C₆ alkyl, CN, CF₃, NO₂, SR², CO₂R², CON(R⁷)₂, C(O)R², N(R⁰)C(O)R⁷, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), C₅-C₆ cycloalkyl, C₅-C₆ cycloalkoxy, C₁-C₆ haloalkyl, N(R⁰)₂, N(C₁-C₆ alkyl)(O(C₁-C₆ alkyl), halo(C₁-C₆ alkoxy), NR¹0SO₂R⁷, SO₂N(R⁰)₂, NHCOOR², NHCONHR², 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 W⁷ is independently halo, OR¹₀, C₁-C₆ alkyl, CN, CF₃, NO₂, SR¹₀, CO₂R¹₀, CON(R¹₀)₂, C(O)R¹₀, N(R¹₀)C(O)R¹₀, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), C₅-C₆ cycloalkyl, C₅-C₆ cycloalkoxy, C₁-C₆ haloalkyl, N(R¹₀)₂, N(C₁-C₆ alkyl)(O(C₁-C₆ alkyl), halo(C₁-C₆ alkoxy), NR¹₀SO₂R¹₀, SO₂N(R¹₀)₂, NHCOOR¹₀, NHCONHR¹₀, 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 W⁷ 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; R⁸ is C₁-C₆ alkyl, C₂-C₆ cycloalkyl, C₃-C₆ cycloalkyl(C₁-C₆ alkyl), aryl, aryl(C₁-C₄ alkyl), heteroaryl, heterocyclyl, heteroaryl(C₁-C₄ alkyl), or heterocyclyl(C₁-C₆ alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C₂-C₆ cycloalkyl, heteroaryl, heterocyclyl, C₁-C₆ alkyl, halo(C₁-C₆ alkoxy), halo, OR¹₀.
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_{2}R^{6}, SO_{2}N(R^{6})_{2}, NHCOOR^{5}, NHCOR^{5}, NHCONHR^{5}, CO_{2}R^{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_{6} alkyl, C_{2}-C_{6} cycloalkyl, C_{2}-C_{6} cycloalkyl(C_{1}-C_{6} alkyl), C_{1}-C_{6} alkoxy, C_{2}-C_{6} cycloalkoxy, aryl, aryl(C_{1}-C_{4} alkyl), heteroaryl, heterocyclyl, heteroaryl(C_{1}-C_{4} alkyl), or heterocyclyl(C_{1}-C_{6} 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_{2}-C_{6} 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_{2}R^{6}, SO_{2}N(R^{6})_{2}, NHCOOR^{5}, NHCOR^{5}, NHCONHR^{5}, CO_{2}R^{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.

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.

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 \( \text{CO}_2R^6 \) or \( \text{CONR}^{10}\text{SO}_2R^6 \), 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 \( \text{CONR}^{10}\text{SO}_2R^6 \); 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 \( \text{CONHSO}_2R^6 \) wherein \( R^6 \) is \( C_3-C_8 \) cycloalkyl, \( C_1-C_4 \) alkyl, aryl, or ary(aryl)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 \( \text{CONHSO}_2R^6 \) 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 \( \text{CONHSO}_2R^6 \) wherein \( R^5 \) 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, R¹ is CONHSO₂R⁶ wherein R⁶ 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, R¹ is CONHSO₂R⁶ wherein R⁶ 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, R¹ is CO₂R¹⁰; and all other variables are as defined in the first embodiment. In a feature of the second aspect of the first embodiment, R¹⁰ is CO₂H; 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 R¹ is CONHSO₂NR⁵R⁹; and all other variables are as originally defined. In a first aspect of the second embodiment, R⁸ is C₁₋₃ alkyl, C₅₋₇ cycloalkyl, C₅₋₇ cycloalkyl(C₁₋₃ alkyl), aryl, aryl(C₁₋₃ alkyl), heteroaryl, or heteroaryl(C₁₋₃ alkyl); and R⁵ is C₁₋₃ alkyl, C₅₋₇ cycloalkyl, C₅₋₇ cycloalkyl(C₁₋₃ alkyl), C₁₋₃ alkoxy, aryl, aryl(C₁₋₃ alkyl), heteroaryl, or heteroaryl(C₁₋₃ alkyl), wherein said alkyl, cycloalkyl, alkoxy, aryl, or heteroaryl in both R⁸ and R⁵ is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, heteroaryl, C₁₋₃ alkyl, halo(C₁₋₃ alkoxy), halo, OR¹⁰, SR¹⁰, N(R¹⁰)₂, N(C₁₋₃ alkyl)O(C₁₋₃ alkyl), C₁₋₃ alkoxy, C(O)R¹⁰, C₁₋₃ haloalkyl, NO₂, CN, CF₃, SO₂(C₁₋₃ alkyl), S(O)(C₁₋₃ alkyl), NR¹⁰SO₂R⁵, SO₂N(R⁵)₂, NHCOOR⁶, NHCONH₂, CO₂R¹⁰, and C(O)N(R¹⁰)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 R⁸ and R⁵ 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, R⁸ is C₁₋₃ alkyl, C₅₋₇ cycloalkyl(C₁₋₃ alkyl), aryl, aryl(C₁₋₃ alkyl), heteroaryl, or heteroaryl(C₁₋₃ alkyl); and R⁵ is C₁₋₃ alkyl, C₅₋₇ cycloalkyl(C₁₋₃ alkyl), C₁₋₃ alkoxy, aryl, aryl(C₁₋₃ alkyl), heteroaryl, or heteroaryl(C₁₋₃ alkyl), wherein said alkyl, cycloalkyl, alkoxy, aryl, or heteroaryl in both R⁸ and R⁵ is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C₅₋₇ cycloalkyl, heteroaryl, heterocyclyl, C₁₋₃ alkyl, halo(C₁₋₃ alkoxy), halo, OR¹⁰, SR¹⁰, N(R¹⁰)₂, N(C₁₋₃ alkyl)O(C₁₋₃ alkyl), S(O)(C₁₋₃ alkyl), NR¹⁰SO₂R⁵, SO₂N(R⁵)₂, NHCOOR⁶, NHCONH₂, CO₂R¹⁰, and C(O)N(R¹⁰)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 R⁸ and R⁵ 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 \( C_{1-3} \) alkyl, wherein said alkyl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, \( OR^{10} \), \( SR^{10} \), \( N(R^{10})_2 \), \( N(C_{1-6} \text{ alkyl})O(C_{1-6} \text{ alkyl}) \), \( C_{1-6} \text{ alkyl, C(O)R}^{10} \), \( C_{1-6} \text{ haloalkyl, NO}_{2x} \), \( CN \), \( CF_3 \), \( SO_2(C_{1-6} \text{ alkyl}) \), \( S(O)(C_{1-6} \text{ alkyl}) \), \( NR^{10}SO_2R^{6} \), \( SO_2N(R^{6})_2 \), \( NHCOOR^{6} \), \( NHCOR^{6} \), \( NHCONHR^{6} \), \( CO_2R^{10} \), and \( C(O)N(R^{10})_2 \); and \( R^8 \) is \( C_{1-3} \) alkyl, \( C_{1-3} \) alkoxy, phenyl, or -(CH_2)_2-phenyl, wherein said alkyl or alkoxy is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, \( OR^{10} \), \( SR^{10} \), \( N(R^{10})_2 \), \( N(C_{1-6} \text{ alkyl})O(C_{1-6} \text{ alkyl}) \), \( C_{1-6} \text{ alkyl, C(O)R}^{10} \), \( C_{1-6} \text{ haloalkyl, NO}_{2x} \), \( CN \), \( CF_3 \), \( SO_2(C_{1-6} \text{ alkyl}) \), \( S(O)(C_{1-6} \text{ alkyl}) \), \( NR^{10}SO_2R^{6} \), \( SO_2N(R^{6})_2 \), \( NHCOOR^{6} \), \( NHCOR^{6} \), \( NHCONHR^{6} \), \( CO_2R^{10} \), 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, \( R^3 \) 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 hetocyclic ring selected from the following:

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\begin{align*}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\end{array}
\end{align*}
```

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 \( C_{1-6} \) alkyl or \( C_{2-6} \) 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 \( C_{1-6} \) alkyl or \( C_{2-6} \) 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 \( C_{2-6} \) 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 \( C_{1-4} \) 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 \( R^3 \) 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, \( R^4 \) 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, \( R^4 \) 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 \( R^2 \) 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\(^3\))\(_2\), N(C\(_1-C_8\) alkyl)O(C\(_1-C_6\) alkyl), C\(_1-C_6\) alkyl, C\(_1-C_6\) haloalkyl, halo(C\(_1-C_6\) alkoxy), C\(_2-C_6\) cycloalkyl, C\(_2-C_6\) cycloalkoxy, NO\(_2\), CN, CF\(_3\), SO\(_2\)(C\(_1-C_6\) alkyl), NR\(^{10}\)SO\(_2\)R\(^6\), SO\(_2\)N(R\(^6\))\(_2\),
S(O)(C₁-C₆ alkyl), NHCOOR⁶, NHCOR⁶, NHCONHR⁶, CO₂R¹⁰, C(O)R¹⁰, and CON(R¹⁰)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, R⁵ is aryl wherein aryl is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR¹⁰, SR¹⁰, N(R³)₂, N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₁-C₆ haloalkyl, halo(C₁-C₆ alkox), C₃-C₆ cycloalkyl, C₃-C₆ cycloalkoxy, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), NR¹⁰SO₂R⁶, SO₂N(R⁶)₂, S(O)(C₁-C₆ alkyl), NHCOOR⁶, NHCOR⁶, NHCONHR⁶, CO₂R¹⁰, C(O)R¹⁰, and CON(R¹⁰)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, R⁵ is

; wherein R¹² is H, C₁-C₆ alkyl, C₁-C₆ alkox, N(R³)₂, NHCOR¹³, NHCONHR¹³ or NHCOOR¹³ and each R¹³ is independently C₁-C₆ alkyl or C₃-C₆ 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, R⁵ is

; wherein R¹² is H, C₁-C₆ alkyl, C₁-C₆ alkox, N(R³)₂, NHCOR¹³, NHCONHR¹³ or NHCOOR¹³ and each R¹³ is independently C₁-C₆ alkyl or C₃-C₆ 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, R⁵ 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 R⁵ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ 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, OR¹⁰, SR¹⁰, N(R³)₂, N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₁-C₆ haloalkyl, halo(C₁-C₆ alkox), C₃-C₆ cycloalkyl, C₃-C₆ cycloalkoxy, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), NR¹⁰SO₂R⁶, SO₂N(R⁶)₂, S(O)(C₁-C₆ alkyl),
NHCOOR, NHCOR, NHCONHR, CO₂R, CO₂R, O(C)R, and CON(R²)₂; wherein the 2 adjacent substitutions of said cycloalkyl or heterocycle 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, R² is C₁-C₆ 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, R² 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, R² 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, SR, N(R₁), N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₁-C₆ haloalkyl, halo(C₁-C₆ alkyl), C₅-C₆ cycloalkyl, C₅-C₆ cycloalkoxy, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), NR₃, SO₂R, SO₂N(R), S(O)(C₁-C₆ alkyl), NHCOOR, NHCOR, NHCONH₂, CO₂R, O(C)R, and CON(R²)₂; wherein the 2 adjacent substitutions 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, R² is N-morpholino; 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, R² is C₁-C₆ 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, R² is CF₃; 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, III, III-A, or III-B, or a pharmaceutically acceptable salt or hydrate thereof, wherein R² is N(R¹); 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, R² is N(R¹); wherein R² is H or C₁-C₆ 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 R¹₁ is H, C₁-C₆ alkyl, C₁-C₆ 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, R¹₁ is C₁-C₆ 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, R¹₁ 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 IV-A or IV-B, or a pharmaceutically acceptable salt or hydrate thereof, wherein \( R^2 \) 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 \( N(R')_2 \); \( R^1 \) is \( CO_2R^{10} \) or \( CONHSO_2R^{6} \) wherein \( R^5 \) is \( C_2-C_6 \) 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.

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\textsubscript{1}-C\textsubscript{8} alkyl) or C(R\textsuperscript{10})\textsubscript{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\textsubscript{3}), or CH\textsubscript{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\textsubscript{1}-C\textsubscript{8} alkylene or C\textsubscript{2}-C\textsubscript{8} alkenylene, wherein said alkylene or alkenylene is optionally substituted with 1 or 2 substituents selected from C\textsubscript{1}-C\textsubscript{8} alkyl, C\textsubscript{3}-C\textsubscript{4} cycloalkyl(C\textsubscript{1}-C\textsubscript{8} alkyl), or aryl(C\textsubscript{1}-C\textsubscript{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\textsubscript{1}-C\textsubscript{8} alkylene or unsubstituted C\textsubscript{2}-C\textsubscript{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\textsubscript{4} alkylene or unsubstituted C\textsubscript{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\textsubscript{5} alkylene or unsubstituted C\textsubscript{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\textsubscript{6} alkylene or unsubstituted C\textsubscript{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\textsubscript{7} alkylene or unsubstituted C\textsubscript{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:

\begin{align*}
\text{or } & \text{ or } \text{ or } \text{ or }
\end{align*}

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.
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, C₁-C₆ alkyl, C₁-C₆ alkoxy, OH, halo, halo(C₁-C₆ alkoxy), C(O)N(R₇)₂, C(O)R₇, N(R₇)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 C₁-C₆ 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 C₁-C₆ alkyl, halo, OH, or N(R₇)₂ wherein R₇ is H or C₁-C₆ 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(C₁-C₆ 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 OCF₃, OCHF₂, OC(CH₃)₃, or OCH(CH₃)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(R₇)₂, C(O)R₇, 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(R₇)₂ wherein R₇ is H or C₁-C₆ alkyl; C(O)R₇ wherein R₇ 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.
A nineteenth embodiment of the present invention is a compound of formula III, or a pharmaceutically acceptable salt or hydrate thereof, wherein R¹ is CONHSO₂R⁶, R⁶ is C₃-C₈ cycloalkyl, C₁-C₈ alkyl, aryl, or aryl(C₁-C₄)alkyl, R² is C₁-C₄ alkyl or C₂-C₄ alkenyl, R³ is C₃-C₆ cycloalkyl or C₁-C₈ alkyl optionally substituted with 1 to 3 halo substituents, R⁴ is H, halo, aryl, heteroaryl or N(R⁸)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, R⁵ 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, R² is C₂-C₄ alkenyl, R⁵ is H, R⁶ is C₃-C₈ cycloalkyl, W is R⁷ 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 embodiment, M is selected from the group consisting of:

\[
\text{\includegraphics{structure.png}}
\]

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

wherein:

n is 1 or 2;
R^1 is CO_2R^{10}, CONR^{10}SO_2R^4, CONR^{10}SO_2NR^{10}R^5, or tetrazolyl;

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

R^3 is C_1-C_6 alkyl, C_2-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_6)alkyl, aryl(C_1-C_6)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^5, 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^5, 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_6 alkyl, C_2-C_6 cycloalkyl(C_1-C_6)alkyl, or aryl(C_1-C_6)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^5, 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_2-C_6 cycloalkoxy, C_1-C_6 haloalkyl, N(R^7)_2, arey, heteroaryl or heterocyclic; 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 heterocyclic 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, heterocyclic, cycloalkoxy, alkyl 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_2-C_6 cycloalkoxy, NO_2, CN, CF_3, SO_2(C_1-C_6 alkyl), NR^{10}SO_2R^5, 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, arey, heteroaryl or heterocyclic 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_2-C_8 cycloalkyl, C_2-C_6 cycloalkyl(C_1-C_8)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl, heteroaryl(C_1-C_6 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^6);

M is C_1-C_{12} alkylenyl or C_2-C_{12} alkenylene, wherein said alkylenyl 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_2-C_6 cycloalkoxy, C_1-C_6 haloalkyl, N(R'^{10})_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'^{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), C_3-C_6 cycloalkyl, C_2-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-(\( C_1-C_3 \)alkyl), aryl, aryl-(\( C_1-C_6 \)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^9)(O)R^7, SO_2(C_1-C_6)alkyl, S(O)(C_1-C_6)alkyl, C_3-C_6 cycloalkyl, C_3-C_6 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 alkox), NR^10SO_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})(O)R^{10}, SO_2(C_1-C_6)alkyl, S(O)(C_1-C_6)alkyl, C_3-C_6 cycloalkyl, C_3-C_6 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 alkox), 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;
heteroaryl or heterocycl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C₃-C₅ cycloalkyl, heteroaryl, heterocyclyl, C₁-C₆ alkyl, halo(C₁-C₆ alkoxy), halo, OR¹⁰, SR¹⁰, N(R¹⁰)₂, N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C(O)R¹⁰, C₁-C₆ haloalkyl, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), NR¹⁰SO₂R⁶, SO₂N(R⁶)₂, NHCOOR⁶, NHCOR⁶, NHCONHR⁶, CO₂R¹⁰, and C(O)N(R¹⁰)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;

R² is C₁-C₅ alkyl, C₃-C₅ cycloalkyl, C₃-C₅ cycloalkyl(C₁-C₅ alkyl), C₁-C₅ alkoxy, C₃-C₅ cycloalkoxy, aryl, aryl(C₁-C₅ alkyl), heteroaryl, heterocyclyl, heteroaryl(C₁-C₅ alkyl), or heterocyclyl(C₁-C₅ 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, C₃-C₅ cycloalkyl, heteroaryl, heterocyclyl, C₁-C₅ alkyl, halo(C₁-C₅ alkoxy), halo, OR¹⁰, SR¹⁰, N(R¹⁰)₂, N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C(O)R¹⁰, C₁-C₆ haloalkyl, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), NR¹⁰SO₂R⁶, SO₂N(R⁶)₂, NHCOOR⁶, NHCOR⁶, NHCONHR⁶, CO₂R¹⁰, and C(O)N(R¹⁰)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 R⁸ and R⁹ 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 R¹⁰ is independently H or C₁-C₆ 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 ((1R,2S)-1-((((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]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, 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, "C1-6 alkyl" (or "C1-C6 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, "C1-4 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, "C1-6 alkylene." refers to any of the C1 to C6 linear or branched alkylene. A class of alkylene of particular interest with respect to the invention is -(CH2)1-6-, and sub-classes of particular interest include -(CH2)1-4-, -(CH2)1-3-, -(CH2)1-2-, and -(CH2)2-. Also of interest is the alkyne -CH(CH3)-.

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, "C3-8 cycloalkyl" (or "C3-C8 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., R⁷ and R¹⁰) 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:

\[
\begin{align*}
\text{ring 1} & & \text{ring 2} \\
\quad & & \\
\end{align*}
\]

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, intratrernal 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)].


Such 2'-C-branched ribonucleosides include, but are not limited to, 2'-C-methyl-cytidine, 2'-C-methyl-uridine, 2'-C-methyl-adenosine, 2'-C-methyl-guanosine, and 9-(2-C-methyl-β-D-ribofuranosyl)-2,6-diaminopurine, and the corresponding amino acid ester of the ribose C-2', C-3', and C-5' hydroxyls and the corresponding optionally substituted cyclic 1,3-propanediol esters of the 5'-phosphate derivatives.

The compounds of the present invention may also be combined for the treatment of HCV infection with other nucleosides having anti-HCV properties, such as those disclosed in WO 02/51425 (4 July 2002), assigned to Mitsubishi Pharma Corp.; WO 01/79246, WO 02/32920, and WO 02/48165 (20 June 2002), assigned to Pharmasset, Ltd.; WO 01/68663 (20 September 2001), assigned to ICN Pharmaceuticals; WO 99/43691 (2 Sept. 1999); WO 02/18404 (7 March 2002), assigned to Hoffmann-LaRoche; U.S. 2002/0019363 (14 Feb. 2002); WO 02/100415 (19 Dec. 2002); WO 03/026589 (3 Apr. 2003); WO 03/026675 (3 Apr. 2003); WO 03/093290 (13 Nov. 2003); US 2003/0236216 (25 Dec. 2003); US 2004/0006007 (8 Jan. 2004); WO 04/011478 (5 Feb. 2004); WO 04/013300 (12 Feb. 2004); US 2004/0063658 (1 Apr. 2004); and WO 04/028481 (8 Apr. 2004).

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS5B polymerase. Such HCV NS5B polymerase inhibitors that may be used as combination therapy include, but are not limited to, those disclosed in WO 02/057287, US 6,777,395, WO 02/057425, US 2004/0067901, WO 03/068244,
WO 2004/000858, WO 04/003138 and WO 2004/007512. Other such HCV polymerase inhibitors include, but are not limited to, valapicitabine (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; 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]pyrimidine-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-2C-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-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2,4-di-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-deoxy-3-fluoro-2-C-methylβ-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 Ricerca di Biologia Molecolare P. Angeletti S.P.A.; WO 02/20497 (3 March
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:

1. 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]benzodiazocine-11-carboxyl)amin] sulfonyl)acetate; ([(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxyl)amin] 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);

2. 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-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]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 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-(dimethylamino)ethyl]-7-oxo-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-cyclohexyl-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-5H-indolo[2,1-a][2,6]benzodiazonine-12-carboxylic acid; 15-cyclohexyl-8-oxo-6,7,8,9-tetrahydro-5H-indolo[2,1-a][2,5]benzodiazonine-12-carboxylic acid; 13-cyclohexyl-6-oxo-6,7-dihydro-5H-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 chloroisoquinoline. 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 R² group can be installed via displacement reactions or metal-mediated coupling reactions.

**SCHEME 3**

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$_3$CN  
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  
Diisopropylethylamine

DMF  
Dimethylformamide

DMSO  
Dimethyl Sulfoxide

EDC  
$N$-(3-Dimethylaminopropyl)-$N'$-ethylcarbodiimide

Et$_3$N  
Triethylamine

Et$_2$O  
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  
5  MeOH  Methanol  
MgSO₄  Magnesium Sulfate  
Na₂SO₄  Sodium sulfate  
NaHCO₃  Sodium bicarbonate  
NaOH  Sodium hydroxide  
10  NH₄Cl  Ammonium chloride  
NH₄OH  Ammonium hydroxide  
Nle  Norleucine  
Pd/C  Palladium on carbon  
PhMe  Toluene  
15  PPh₃  Triphenylphosphine  
RT  Room temperature  
TBAF  Tetrabutylammonium fluoride  
TBTU  O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate  
THF  Tetrahydrofuran  

20  

**Synthesis of Intermediates:**  

**Synthesis of Intermediates A**

<table>
<thead>
<tr>
<th>Intermediate #</th>
<th>Structure</th>
<th>Name</th>
<th>Lit. Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td><img src="image" alt="" /></td>
<td>Ethyl (1R,2S)-1-amino-2-vinylcyclopropanecarboxylate hydrochloride</td>
<td>Llinas-Brunet et al, US 6,323,180</td>
</tr>
</tbody>
</table>

Intermediate A3: (1R,2R)-1-Amino-N-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride
Step 1: tert-Butyl (1R,2R)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-ethylcyclopropyl carbamate

A hydrogenation 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 floc (34 grams, wetted w/ 100 mL methanol) to yield a clear, light brown solution. The solka floc 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: (1R,2R)-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:**

![Chemical Structure](image)

A mixture of (1R,2S)-1-\{[(cyclopropylsulfonyl)amino]carbonyl\}-2-vinylcyclopropanaminium chloride (0.05 g, 0.187 mmol) and palladium on carbon (10% wt., 0.01 g) 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 (1R,2R)-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:**

![Chemical Structure](image)

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 (8.50 g, 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.

<table>
<thead>
<tr>
<th>Int</th>
<th>Amino Acid</th>
<th>Alcohol</th>
<th>Structure</th>
<th>Name</th>
<th>LRMS (M+H)^+</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>L-Norleucine</td>
<td>4-Penten-1-ol</td>
<td><img src="image" alt="Structure" /></td>
<td>N-{{(Pent-4-en-1-yloxy)carbonyl}L-norleucine (Intermediate 1)</td>
<td>244.3</td>
</tr>
<tr>
<td>B2</td>
<td>L-t-Butyl-glycine</td>
<td>4-Penten-1-ol</td>
<td><img src="image" alt="Structure" /></td>
<td>(2S)-3,3-Dimethyl-2-{{(pent-4-en-1-yloxy)carbonyl}amino}butanoic acid</td>
<td>244.2</td>
</tr>
<tr>
<td>B3</td>
<td>L-Valine</td>
<td>4-Penten-1-ol</td>
<td>( N)-([Pent-4-en-1-yloxy]carbonyl)-L-valine</td>
<td>230.3</td>
<td></td>
</tr>
<tr>
<td>----</td>
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<td>---------------------------------------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>B4</td>
<td>L-t-Butyl-glycine</td>
<td>3,3-Dimethyl-4-penten-1-ol</td>
<td>( N)-([2,2-Dimethylpent-4-en-1-yl]oxy]carbonyl)-3-methyl-L-valine</td>
<td>272.3</td>
<td></td>
</tr>
<tr>
<td>B5</td>
<td>L-t-Butyl-glycine</td>
<td>5-Hexen-1-ol</td>
<td>( N)-([Hex-5-en-1-yloxy]carbonyl]-3-methyl-L-valine</td>
<td>258.3</td>
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</tr>
<tr>
<td>B6</td>
<td>L-Phenyl-glycine</td>
<td>4-Penten-1-ol</td>
<td>(2S)-[([Pent-4-en-1-yloxy]carbonyl]amino )-(phenyl)acetic acid</td>
<td>264.3</td>
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<tr>
<td>B7</td>
<td>L-t-Butyl-glycine</td>
<td>6-Hepten-1-ol</td>
<td>( N)-([Hept-6-en-1-yloxy]carbonyl]-3-methyl-L-valine</td>
<td>272.3</td>
<td></td>
</tr>
<tr>
<td>B8</td>
<td>L-Cyclohexyl-glycine</td>
<td>4-Penten-1-ol</td>
<td>(2S)-Cyclohexyl{([pent-4-en-1-yloxy]carbonyl]amino }acetetic acid</td>
<td>270.3</td>
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</tr>
<tr>
<td>B9</td>
<td>L-Phenyl alanine</td>
<td>4-Penten-1-ol</td>
<td>( N)-([Pent-4-en-1-yloxy]carbonyl]-L-phenylalanine</td>
<td>278.2</td>
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<tr>
<td>B10</td>
<td>3,3,3-Trifluoroalanine</td>
<td>4-Penten-1-ol</td>
<td>3,3,3-trifluoro-( N)-([pent-4-en-1-yloxy]carbonyl]alanine</td>
<td>256.2</td>
<td></td>
</tr>
<tr>
<td>B11</td>
<td>L-t-Butyl-glycine</td>
<td>4-Pentyn-1-ol</td>
<td>3-Methyl-( N)-([pent-4-yyn-1-yloxy]carbonyl]-L-valine</td>
<td>242.2</td>
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</tr>
<tr>
<td></td>
<td>Formula</td>
<td>Molecular Weight</td>
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<td></td>
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<tr>
<td>B12</td>
<td>L-Norvaline</td>
<td>4-Penten-1-ol</td>
<td>N-[(Pent-4-en-1-yloxy)carbonyl]-L-norvaline</td>
<td>230.3</td>
<td></td>
</tr>
<tr>
<td>B13</td>
<td>L-Cyclopentyl-glycine</td>
<td>4-Penten-1-ol</td>
<td>(2S)-Cyclopentyl{[(pent-4-en-1-yloxy)carbonyl]amino}acetic acid</td>
<td>256.3</td>
<td></td>
</tr>
<tr>
<td>B14</td>
<td>2-Amino-4,4,4-trifluorobutanoic acid</td>
<td>5-Hexen-1-ol</td>
<td>4,4,4-Trifluoro-2-{[(hex-5-en-1-yloxy)carbonyl]amino}butanoic acid</td>
<td>305.2 (M+Na)^+</td>
<td></td>
</tr>
<tr>
<td>B15</td>
<td>L-Leucine</td>
<td>4-Penten-1-ol</td>
<td>N-[(Pent-4-en-1-yloxy)carbonyl]-L-leucine</td>
<td>244.3</td>
<td></td>
</tr>
<tr>
<td>B16</td>
<td>L-Tryptophan</td>
<td>4-Penten-1-ol</td>
<td>N-[(Pent-4-en-1-yloxy)carbonyl]-L-tryptophan</td>
<td>317.4</td>
<td></td>
</tr>
<tr>
<td>B17</td>
<td>O-(tert-Butyl)-L-serine</td>
<td>4-Penten-1-ol</td>
<td>O-(tert-Butyl)-N-[(pent-4-en-1-yloxy)carbonyl]-L-serine</td>
<td>218.3 (M-tBu)^+</td>
<td></td>
</tr>
<tr>
<td>B18</td>
<td>6,6,6-trifluoronorleucine</td>
<td>5-Hexen-1-ol</td>
<td>6,6,6-Trifluoro-N-[(hex-5-en-1-yloxy)carbonyl]norleucine</td>
<td>353.2 (M+MeCN)^+</td>
<td></td>
</tr>
<tr>
<td>B19</td>
<td>Amino(2,3-dihydro-1H-inden-2-yl)acetic acid</td>
<td>4-Penten-1-ol</td>
<td>2,3-Dihydro-1H-inden-2-yl{[(pent-4-en-1-yloxy)carbonyl]amino}acetic acid</td>
<td>304.3</td>
<td></td>
</tr>
</tbody>
</table>
| B20 | L-\text{-}t\text{-}Butyl-glycine | (trans)-2-allylcyclohexanol | \begin{align*} &N\text{-}([[(\text{trans})\text{-}2\text{-} \\
&\text{Allylcyclohexyl}\text{]}\text{oxy}}) \\
&\text{carbonyl})\text{-}3\text{-}methyl-L\text{-}valine \end{align*} | 298.4 |
|-----|-----------------------------|-----------------------------|-------------------------------------------------|------|
| B21 | L-Cyclohexyl-glycine        | 3-Buten-1-ol                | \begin{align*} &((2S)\text{-}[[\text{But}-3\text{-}en-1\text{-} \\
&\text{yloxy}\text{]}\text{carbonyl}]\text{amino}} \\
&\text{]}\text{(cyclohexyl)}\text{acetic acid} \end{align*} | 256.2 |
| B22 | L-\text{-}t\text{-}Butyl-glycine | 3-Buten-1-ol                | \begin{align*} &N\text{-}[\text{But}-3\text{-}en-1\text{-}yloxy\text{]}\text{carbonyl}]\text{-}3\text{-}methyl-L\text{-}valine \end{align*} | 230.3 |
| B23 | L-Cyclohexyl-glycine        | 2,2-Dimethyl-4-penten-1-ol  | \begin{align*} &((2S)\text{-} \text{Cyclohexyl}[[\text{2,2} \text{-} \\
&\text{dimethylpent-4-en-1-yloxy}]\text{carbonyl}]\text{amino}} \\
&\text{]}\text{acetic acid} \end{align*} | 298.3 |
| B24 | L-Cyclopentyl-glycine       | 2,2-Dimethyl-4-penten-1-ol  | \begin{align*} &((2S)\text{-} \text{Cyclopentyl}[[\text{2,2} \text{-} \\
&\text{dimethylpent-4-en-1-yloxy}]\text{carbonyl}]\text{amino}} \\
&\text{]}\text{acetic acid} \end{align*} | 284.3 |
| B25 | L-\text{-}t\text{-}Butyl-glycine | 2,2-Dimethylhex-5-en-1-ol   | \begin{align*} &N\text{-}[[2,2\text{-} \\
&\text{Dimethylhex-5-en-1-yloxy}]\text{carbonyl}]\text{-}3\text{-}methyl-L\text{-}valine \end{align*} | 286.3 |
| B26 | L-Cyclohexyl-glycine        | 6-Hepten-1-ol               | \begin{align*} &((2S)\text{-} \text{Cyclohexyl}[[\text{hept-6-en-1-yloxy}]\text{carbonyl}]\text{amino}} \\
&\text{]}\text{acetic acid} \end{align*} | 298.3 |
<p>| B27 | L-\text{-}t\text{-}Butyl-glycine | 7-Octen-1-ol               | \begin{align*} &amp;3\text{-}Methyl-N\text{-}[\text{oct-7-en-1-yloxy}]\text{carbonyl}]\text{-}L\text{-}valine \end{align*} | 286.3 |</p>
<table>
<thead>
<tr>
<th>B28</th>
<th>L-Cyclohexyl-glycine</th>
<th>5-Hexen-1-ol</th>
<th>(2S)-Cyclohexyl{[(hex-5-en-1-yloxy)carbonyl]amino}acetic acid</th>
<th>284.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>B29</td>
<td>L-t-Butyl-glycine</td>
<td>(trans)-2-Allylcyclopentanol</td>
<td>N-{{(trans)-2- Allylcyclopentyl}oxy}carbonyl]-3-methyl-L-valine</td>
<td>284.2</td>
</tr>
<tr>
<td>B30</td>
<td>L-Cyclohexyl-glycine</td>
<td>1-Methylpent-4-en-1-ol</td>
<td>(2S)-Cyclohexyl{[(1-methylpent-4-en-1-yloxy)carbonyl]amino}acetic acid</td>
<td>284.2</td>
</tr>
<tr>
<td>B31</td>
<td>L-Cyclopentyl-glycine</td>
<td>5-Hexen-1-ol</td>
<td>(2S)-Cyclopentyl{[(hex-5-en-1-yloxy)carbonyl]amino}acetic acid</td>
<td>270.3</td>
</tr>
<tr>
<td>B32</td>
<td>L-Cyclopentyl-glycine</td>
<td>6-Hepten-1-ol</td>
<td>(2S)-Cyclopentyl{[(hept-6-en-1-yloxy)carbonyl]amino}acetic acid</td>
<td>284.4</td>
</tr>
<tr>
<td>B33</td>
<td>L-Cyclobutyl-glycine</td>
<td>4-Penten-1-ol</td>
<td>Cyclobutyl{[(pent-4-en-1-yloxy)carbonyl]amino}acetic acid</td>
<td>242.3</td>
</tr>
<tr>
<td>B34</td>
<td>L-Cyclopentyl-glycine</td>
<td>2,2-Dimethylhex-5-en-1-ol</td>
<td>(2S)-Cyclopentyl{[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino}acetic acid</td>
<td>298.3</td>
</tr>
<tr>
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</tr>
<tr>
<td>B35</td>
<td>L-Cyclohexylglycine</td>
<td>2,2-Dimethylhex-5-en-1-ol</td>
<td>(2S)-Cyclohexyl([[2,2-dimethylhex-5-en-1-yl]oxy]carbonyl)aminocarboxylic acid</td>
<td>312.3</td>
</tr>
<tr>
<td>B36</td>
<td>L-Cyclopentylglycine</td>
<td>2,2-Dimethylhept-6-en-1-ol</td>
<td>(2S)-Cyclopentyl([[2,2-dimethylhept-6-en-1-yl]oxy]carbonyl)aminocarboxylic acid</td>
<td>312.2</td>
</tr>
<tr>
<td>B37</td>
<td>L-Cyclohexylglycine</td>
<td>8-Nonen-1-ol</td>
<td>(2S)-Cyclohexyl([[non-8-en-1-yloxy]carbonyl]amino)carboxylic acid</td>
<td>326.3</td>
</tr>
<tr>
<td>B38</td>
<td>L-Cyclopentylglycine</td>
<td>(trans)-2-Allylcyclopentanol</td>
<td>(2S)-[[trans]-2-Allylcyclopentanol]oxy]carbonyl]aminocarboxylic acid</td>
<td>296.4</td>
</tr>
<tr>
<td>B39</td>
<td>L-Cyclohexylglycine</td>
<td>2-Methylpent-4-en-1-ol</td>
<td>(2S)-Cyclohexyl([[2-methylpent-4-en-1-yl]oxy]carbonyl)aminocarboxylic acid</td>
<td>284.4</td>
</tr>
<tr>
<td>B40</td>
<td>L-Cyclohexylglycine</td>
<td>2,2-Dimethylhept-6-en-1-ol</td>
<td>(2S)-Cyclohexyl([[2,2-dimethylhept-6-en-1-yl]oxy]carbonyl)aminocarboxylic acid</td>
<td>326.4</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td><strong>B47</strong></td>
<td>L-Cyclopentyl-glycine</td>
<td>(1-Allyl cyclopentyl) methanol Ref: <em>J. Org. Chem.</em> (1992), 57, 1727.</td>
<td>(2S)-(((1-Allylcyclopentyl)methoxy) carbonyl)amino) (cyclopentyl)acetic acid</td>
<td>310.3</td>
</tr>
<tr>
<td><strong>B48</strong></td>
<td>L-Cyclopentyl-glycine</td>
<td>2-Methylpent-4-en-1-ol Ref: <em>Tetrahedron</em> (1993), 49, 947.</td>
<td>(2S)-Cyclopentyl(((2-methylpent-4-en-1-yl)oxy)carbonyl)amino)acetic acid</td>
<td>270.2</td>
</tr>
<tr>
<td><strong>B49</strong></td>
<td>L-(\tau)-Butyl-glycine</td>
<td>Allyl alcohol</td>
<td>(N)-(allyloxy)carbonyl]-3-methyl-L-valine</td>
<td>215.2</td>
</tr>
</tbody>
</table>

**Intermediate B50:** \(N\)-(((1,1-Dimethylpent-4-en-1-yl)amino)carbonyl)-L-valine

![Chemical Structure](image)

**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 \(\times\) 500mL). The combined organic phases were washed with brine, dried over anhydrous MgSO₄, 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 (CDCl₃ 500MHz) \(\delta\) 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, \(J=6.5\)Hz, 3 H) ppm.

**Step 2: Methyl \(N\)-(((1,1-dimethylpent-4-en-1-yl)amino)carbonyl)-L-valinate**

![Chemical Structure](image)
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 (2.71 g). 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 Na₂SO₄ 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.

<table>
<thead>
<tr>
<th>Int</th>
<th>Amino Acid</th>
<th>Amine</th>
<th>Structure</th>
<th>Name</th>
<th>LRMS (M+H)^+</th>
</tr>
</thead>
<tbody>
<tr>
<td>B51</td>
<td>L-γ-Butyl-glycine</td>
<td>N-Methylpent-4-en-1-amine</td>
<td><img src="image" alt="Structure" /></td>
<td>3-Methyl-N-[[methyl(pent-4-en-1-yl)amino]carbonyl]-L-valine</td>
<td>257.3</td>
</tr>
<tr>
<td>B52</td>
<td>L-γ-Butyl-glycine</td>
<td>N-Isopropylhex-5-en-1-amine</td>
<td><img src="image" alt="Structure" /></td>
<td>N-[[Hex-5-en-1-yl(isopropyl)amino]carbonyl]-3-methyl-L-valine</td>
<td>299.3</td>
</tr>
</tbody>
</table>

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 NaHCO₃ (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 Na₂SO₄, 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 C₁₄H₂₅NO₃: 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 Na₂SO₄, filtered and concentrated to give the title product (1.12 g, 84%). LRMS (ESI) m/z 242.3 [(M+H)⁺]; calcd for C₁₃H₂₄NO₃: 242.2.

Preparation of Intermediates C

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

Step 1: (E)-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.

5  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.

10  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$_2$SO$_4$, solvent evaporated and the solid triturated with Et$_2$O (20 mL) and filtered to give a solid (3.75 g). LRMS ESI$^+$ (M+H)$^+$ 274.0.

20  Step 4: Ethyl (4R)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-L-proline hydrochloride (Intermediate 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.

25  Intermediate C2: Methyl (4R)-4-[(6-bromoquinazolin-4-yl)oxy]-L-proline 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 Na₂CO₃ (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 Na₂SO₄, 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 (4R)-4-[(6-bromoquinazolin-4-yl)oxy]-L-proline hydrochloride (Intermediate 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 (4R)-4-[(7-bromo-3-chloroisoquinolin-1-yl)oxy]-l-proline 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 Na₂SO₄, 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 POCl₃ (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 MgSO₄, filtered and concentrated to give the title compound (1.40 g). LRMS (M+H)^+ = 276.0.
Step 3: Ethyl (4R)-4-[(7-bromo-3-chloroisouquinolin-1-yl)oxy]-L-proline hydrochloride (Intermediate C3)

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

Intermediate C4: Methyl (4R)-4-[(7-(allyloxy)isouquinolin-1-yl)oxy]-L-proline

Step 1: 1-Chloroisouquinolin-7-ol

7-Bromo-1-chloroisouquinoline (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$_2$SO$_4$, 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-chloroisouquinoline
1-Chloroisooquinolin-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 KHSO₄ (40 mL) and EtOAc (100 mL) and stirred. The organic extract was removed, dried over Na₂SO₄, 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 (4R)-4-{{7-(allyloxy)isoquinolin-1-yl}oxy}-L-proline (Intermediate C4)

Intermediate C4 was prepared according to the procedure described in Example 10 Step 1, using 7-(allyloxy)-1-chloroisooquinoline. 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-ethenediylidene-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-ethenediylidene-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-ethenediylidene-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 N₂ 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 (Intermediate 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 Na₂SO₄, filtered, concentrated, and azeotroped from Et₂O 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]dioxadiaicyclononadecine-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]dioxadiaicyclononadecine-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]dioxadiaicyclononadecine-4-carboxylic acid (Intermediate 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 Na₂SO₄, 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]dioxadiaicyclononadecine-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 H₂O (1 mL). The reaction mixture was stirred in the dark for 16 h filtered, concentrated, and the resulting residue partitioned between DCM and H₂O (x3). The combined organic phases were washed with brine, dried over Na₂SO₄, 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

![](image)

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]dioxadiazacyclonadecine-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]dioxadiazacyclonadecine-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]dioxadiazacyclonadecine-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 NaHCO₃ (x3). The combined organic layers were washed with brine, dried over Na₂SO₄, 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

5

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 (Intermediate 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.

5 Intermediate D8: Ethyl (2R,4S,7S)-7-cyclopentyl-22-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-κ][1,10,3,6]dioxadiazaclononadecine-4-carboxylate

Step 1: Ethyl (2R,4S,7S)-7-cyclopentyl-22-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-κ][1,10,3,6]dioxadiazaclononadecine-4-carboxylate

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

20 Step 2: Ethyl (2R,4S,7S)-7-cyclopentyl-22-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-κ][1,10,3,6]dioxadiazaclononadecine-4-carboxylate (Intermediate D8)

Ethyl (2R,4S,7S)-7-cyclopentyl-22-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-κ][1,10,3,6]dioxadiazaclononadecine-4-carboxylate (Intermediate D8)
15 Intermediate D10: \((2R,4S,7S)-7\text{-cyclohexyl}-22\text{-methoxy}-6,9\text{-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene}-2,5\text{-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid}\)
Step 1: Ethyl (2R,4S,7S)-7-cyclohexyl-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]dioxadiazacyclonadecine-4-carboxylate

Ethyl (2R,4S,7S)-7-cyclohexyl-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]dioxadiazacyclonadecine-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 (2R,4S,7S)-7-cyclohexyl-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]dioxadiazacyclonadecine-4-carboxylate

Ethyl (2R,4S,7S)-7-cyclohexyl-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]dioxadiazacyclonadecine-4-carboxylate was prepared according to the procedure described for EXAMPLE 13, Step 1 using ethyl
(2R,4S,7S)-7-cyclohexyl-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)^+ = 664.4.

Step 3: (2R,4S,7S)-7-Cyclohexyl-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 D10)

Intermediate D10 was prepared according to the procedure described for Intermediate D9 using ethyl (2R,4S,7S)-7-cyclohexyl-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. 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 H2O and then concentrated. The residue was partitioned between EtOAc and 1N HCl (x3). The combined organics were washed with brine, dried over Na2SO4, 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 Na₂SO₄, 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 (Intermediate 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 Na₂SO₄, 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

[Chemical structure diagram]

To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-ido-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'-dimethylthelylendiamine (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 H₂O. The organic layer was washed with H₂O (2x), brine, dried over Na₂SO₄, 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

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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 dimethyl disulfide (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 Na₂SO₄, filtered, and concentrated to yield the crude title compound as a yellow oil. LRMS (M+H)⁺ = 558.4.

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

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

Step 1: Ethyl (2R,4S,7S)-7-tert-butyl-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]dioxadiazyclononadecine-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]dioxadiazyclononadecine-4-carboxylate
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-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 (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 N₂ 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 NaHCO₃ and extracted with DCM (2x). The combined organic layers were washed with brine, dried over Na₂SO₄, 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 (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 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**

(1R,2S)-1-([(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]dioxadiazacyclononadecin-4-yl]carbonyl)amino)-2-vinylcyclopropane carboxylic acid (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_{16}BrN_{2}O_{3}: 365].

Step 2: Ethyl N-[(pent-4-en-1-yl)oxy]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-proline 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_{29}H_{37}BrN_{3}O_{6}: 590.

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

The bromide from step 2 (62 mg, 0.105 mmol) was dissolved in 5 mL toluene and nitrogen bubbled through for 15 min. Tributylinyltin (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_{29}H_{36}N_{3}O_{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-isopropoxybenzyldiene)(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_{39}N_{3}O_{6}: 510].

Step 5: (1R,2S)-1-(((2R,4S,7S)-7-buty1-6,9-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]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 at 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, 3 M 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_{4}O_{7}: 591].

EXAMPLE 2

(1R,2S)-1-(((2R,4S,7S)-7-buty1-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahyd ro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl) amino)-2-vinylcyclopropanecarboxylic acid (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)+]; calc'd for C_{32}H_{40}N_{4}O_{7}: 593.

EXAMPLE 3

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{{(cyclopropylsulfonfyl)amino}carbonyl}-2-vinylecyclopropyl}-6,9-dioxo-3,4,6,7,8,9,12,13,15,16-decahydro-2H,11H-16,18-ethanoquinolinonane-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-(cyclopropylsulfonfyl)-2-vinylecyclopropanecarboxamide hydrochloride (Intermediate A1) (Wang et al WO 03/099274) in place of (1R,2S)-1-amino-2-vinylecyclopropanecarboxylic acid ethyl ester hydrochloride in the coupling step. LRMS (ESI) m/z 696 [(M+H)+]; calc'd for C_{33}H_{43}N_{5}O_{8}S: 696. 1H NMR (500 MHz, CD_{3}OD, 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-{{(phenylsulfonfyl)amino}carbonyl}-2-vinylecyclopropyl}-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanoquinolinonane-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-vinylecyclopropanecarboxylic 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 C₃₂H₄₁N₄O₇: 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 carbonyldimidazole (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_{5}O_{8}S: 732].

**EXAMPLE 5**

(2R,4S,7S)-N-((1R,2S)-1-(((2-methylphenyl)sulfonfyl)amino)carbonyl)-2-vinylcyclopropyl)-7-buty1-6,9-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)

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_{5}O_{8}S: 746].

**EXAMPLE 6**

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-(((methylsulfonfyl)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)+; caled for C_{33}H_{48}N_{5}O_{8}S: 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]dioxadiazacyclonadecine-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)+; caled for C_{34}H_{46}N_{5}O_{8}S: 684].

EXAMPLE 8

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{{(t-butyrsulfonyl)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]dioxadiazacyclonadecine-4-carboxamide (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)^+]; calc'd for C_{36}H_{56}N_{5}O_{8}S: 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-aminothiobutyric 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 Sciences) 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

(1R,2S)-1-[[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]dioxadiazacyclononadecin-4-yl]carbonyl]amino)-2-vinylecyclopropanecarboxylic acid (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-chloroisooquinoline (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_{2}O_{5}: 365.

Step 2: Ethyl N-[(pent-4-en-1-yl)oxy]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-yl)oxy]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_{5}O_{6}: 590].

**Step 3: Ethyl N-[(pent-4-en-1-yloxy)carbonyl]-L-tert-butylyglycine-(4R)-4-([7-vinylisoquinolin-1-yloxy]-L-prolinylate**

![Chemical Structure Image]

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_{33}H_{46}N_{5}O_{6}: 538].

**Step 4: Ethyl (2R,4S,7S)-7-tert-buty1-6,9-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**

![Chemical Structure Image]

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-indenylideneruthenium dichloride (Neolyst M1 catalyst, Strem Chemicals, CAS#250220-38-1) (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-

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60% EtOAc / hexane) to give the title compound (0.73 gm). LRMS (ESI) m/z 510 [(M+H)^+; calcd for C_{38}H_{56}N_{3}O_{6}: 510].

Step 5: (1R,2S)-1-(((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]dioxadiazacyclononadecin-4-yl[carbonyl]amino)-2-vinylcyclopropanecarboxylic acid

The ester from Step 4 (0.73 gm, 0.143 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_{2}O_{6}S: 694]. ^1H 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, J = 11.5 and 2.9 Hz, 2.92 (m, 1 H), 2.61 (s, 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]dioxadiazacyclononadecin-4-carboxamide (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 24 h. 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_{26}H_{38}N_{2}O_{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_{39}H_{46}N_{2}O_{6}S: 696].

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-ethylecyclopropyl}-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)
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_{2}O_{5}S: 696. ^1H 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-vinyleclopropyl}-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]dioxadiazenonadecine-4-carboxamide (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]dioxadiazenonadecine-4-carboxylate
The ester from Example 11, Step 1 (0.79 gm, 1.55 mmol) was dissolved in trifluoroacetic 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_{3}O_{6}: 638].


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_{48}IN_{3}O_{8}S: 822]: 1H NMR (400 MHz, ppm) (CD_{3}OD) 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

![Diagram](III-39)

Step 1: Ethyl (4R)-4-[(7-bromoisoquinolin-1-yl)oxy]-1-[(2S)-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-proline hydrochloride (EXAMPLE 1, Step 1) (500 mg, 1.25 mmol) and (2S)-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 Na₂SO₄ 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 C₃₁H₄₁BrN₅O₆: 630.2.

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

Ethyl (4R)-4-[(7-bromoisoquinolin-1-yl)oxy]-1-[(2S)-2-cyclopentyl-2-([(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl]amino)acetyl]-L-proline (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 C₃₅H₄₄N₅O₆: 578.3.

Step 3: Ethyl (2R,4S,7S,14E)-7-cyclopentyl-12,12-dimethyl-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]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 N₂ 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 C₃₁H₄₀N₃O₆: 550.3].

Step 4: (2R,4S,7S,14E)-7-Cyclopentyl-12,12-dimethyl-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]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 Na₂SO₄ 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 C₂₉H₃₅N₅O₆: 522.3].

Step 5: (2R,4S,7S,14E)-7-Cyclopentyl-N-((1R,2S)-1-[[((cyclopropylsulfonyl)amino)carbonyl]-2-vinylecyclopropyl]-12,12-dimethyl-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]dioxadiazacyclononadecine-4-carboxamide (III-39)

To a solution of the product from Step 4 (147 mg, 0.28 mmol) and (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylecyclopropanecarboxamide 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% CH3CN in 0.15% TFA/water) to yield 122 mg (59%) of the title compound as a white powder. 1H NMR (500 MHz, CD3OD) 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 C39H48N5O8S: 734.3.

EXAMPLE 15

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

![III-40](image)

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

To a solution of ethyl (2R,4S,7S,14E)-7-cyclopentyl-12,12-dimethyl-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]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 H2 balloon was then placed on the reaction flask, the flask was evacuated quickly and filled with H2. 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 C31H42N3O8S: 552.3.
Step 2: (2R,4S,7S)-7-Cyclopentyl-N-((1R,2S)-1-(((cyclopropylsulfon)amino)carbonyl)-2-vinylecyclopentyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decacydro-2H,11H-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 (2R,4S,7S)-7-cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decacydro-2H,11H-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$_3$OD) δ 9.26 (s, 1 H), 7.89 (s, 1 H), 7.47 (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), 7.09 (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, $J$ = 15.1 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$_{36}$H$_{50}$N$_{10}$O$_8$S: 736.3.

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

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Name</th>
<th>LRMS (M$^+$ H)$^+$</th>
<th>Prepared using the appropriate Intermediates according to the procedure below.</th>
<th>Int.</th>
</tr>
</thead>
</table>

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<p>| | | | | | | |</p>
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</thead>
<tbody>
<tr>
<td>16, III-41</td>
<td>(2R,4S,7S)-7-butyln-N-(1R)-1-{(cyclopropylsulfonylamino)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]dioxidiazacyclononadecine-4-carboxamide</td>
<td>698.5</td>
<td>See Example 15</td>
<td>A3, B1</td>
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<tr>
<td>17, III-15</td>
<td>(2R,4S,7S)-7-tert-butyln-N-(1R,2S)-1-{(cyclopropylsulfonylamino)carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxidiazacyclononadecine-4-carboxamide</td>
<td>724.4</td>
<td>See Example 15</td>
<td>A1, B4</td>
<td></td>
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<tr>
<td>18, III-29</td>
<td>(2R,4S,7S,14E)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-(\alpha)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>722.3</td>
<td>See Example 14</td>
<td>A1, B4</td>
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<tr>
<td>19, III-42</td>
<td>(2R,4S,7S,15E)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2H-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-(\alpha)][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide</td>
<td>708.6</td>
<td>See Example 14</td>
<td>A1, B5</td>
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<tr>
<td></td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
<td>Number of Compounds</td>
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<td>20, III-43</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(2R,4S,7S)-7-tert-butyl-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-( \kappa )][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>710.6</td>
<td>See Example 15</td>
<td>A1, B5</td>
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<tr>
<td>21, III-44</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>(2R,4S,7S)-N-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-6,9-dioxo-7-phenyl-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-( \kappa )][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>716.3</td>
<td>See Example 15</td>
<td>A1, B6</td>
<td></td>
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<tr>
<td>22, III-45</td>
<td>(2R,4S,7S,16E)-7-tert-butyl-N-((1R,2S)-1-{(\text{cyclopropylsulfonyl)amino}\text{carbonyl}}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-18,20-etheno-2,5-methanopyrido[2,3-\alpha][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide</td>
<td>722.5</td>
<td>See Example 14</td>
<td>A1, B7</td>
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<td>23, III-10</td>
<td>(2R,4S,7S)-cyclohexyl-N-((1R,2S)-1-{(\text{cyclopropylsulfonyl)amino}\text{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-\alpha][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>708.3</td>
<td>See Example 15</td>
<td>A1, B8</td>
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<tr>
<td>24, III-46</td>
<td>(2R,4S,7S,14E)-7-benzyl-N-((1R,2S)-1-{(cyclopropylsulfonfonyl)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</td>
<td>728.4</td>
<td>See Example 14</td>
<td>A1, B9</td>
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<tr>
<td>25, III-47</td>
<td>(2R,4S)-N-((1S)-1-{(cyclopropylsulfonfonyl)amino}carbonyl)-2-vinylcyclopropyl)-6,9-dioxo-7-(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-carboxamide</td>
<td>708.2</td>
<td>See Example 15</td>
<td>A1, B10</td>
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<td>26, III-48</td>
<td>(2R,4S,7S,13E)-7-tert-butyl-N-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12-octahydro-2H-15,17-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide</td>
<td>680.6</td>
<td>See Example 14</td>
<td>A1, B2</td>
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<tr>
<td>27, III-24</td>
<td>(2R,4S,7S,14E)-7-cyclohexyl-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</td>
<td>720.6</td>
<td>See Example 14</td>
<td>A1, B8</td>
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<tr>
<td>28, III-49</td>
<td>(2R,4S,7S)-7-cyclohexyl-N-((1R,2R)-1-{(cyclopropylsulfonyl)amino}carbonyl)-2-ethylcyclopropyl)-6,9-dioxa-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-\kappa][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>724.5</td>
<td>See Example 15</td>
<td>A3, B8</td>
<td></td>
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<tr>
<td>29, III-50</td>
<td>(2R,4S,7S,14E)-N-((1R,2S)-1-{(cyclopropylsulfonyl)amino}carbonyl)-2-vinylcyclopropyl)-6,9-dioxa-7-propyl-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-\kappa][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>680.5</td>
<td>See Example 14</td>
<td>A1, B12</td>
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<tr>
<td>30, III-51</td>
<td>(2R,4S,7S,14E)-7-cyclopentyl-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-(h)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>706.5</td>
<td>See Example 14</td>
<td>A1, B13</td>
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<td></td>
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<tr>
<td>31, III-52</td>
<td>(2R,4S,7S,15E)-N-((1R,2S)-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-2H-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-(h)][1,10,3,6]dioxadiazacyclonicosine-4-carboxamide</td>
<td>734.4</td>
<td>See Example 14, separated diastereomers</td>
<td>A1, B14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32, III-53</td>
<td>((2R,4S,7R,15E)-N-({(1R,2S)-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-2H-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-(k]1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>734.4</td>
<td>See Example 14, separated diastereomers</td>
<td>A1, B14</td>
<td></td>
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<tr>
<td>33, III-54</td>
<td>((2R,4S,7S,14E)-N-({(1R,2S)-1-({(cyclopropylsulfonyl)amino}carbonyl}-2-vinylcyclopropyl}-7-isobutyl-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</td>
<td>694.5</td>
<td>See Example 14</td>
<td>A1, B15</td>
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</tbody>
</table>
| 34, III-55 | (2R,4S,7S,14E)-N-((1R,2S)-1-
\{[(cyclopropylsulfonyl)amino]carbonyl\}-2-
vinylcyclopropyl)-7-(1H-indol-3-ylmethyl)-6,9-
dioxo-3,4,6,7,8,9,12,13-
octahydro-2H,11H-16,18-
etheno-2,5-
methanopyrido[2,3-
\kappa][1,10,3,6]dioxadiazacycl
onadecine-4-
carboxamide | 767.3 | See Example 14 | A1, B16 |
| 35, III-56 | (2R,4S,7S,14E)-7-(tert-
butoxymethyl)-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-
etheno-2,5-
methanopyrido[2,3-
\kappa][1,10,3,6]dioxadiazacycl
onadecine-4-
carboxamide | 724.4 | See Example 14 | A1, B17 |
<p>| 36, III-57 | (2R,4S,7S,15E)-N-((1R,2S)-1-{([(cyclopropylsulfonyl)amino]carbonyl)-2-vinylcyclopropyl}-6,9-dioxo-7-(4,4,4-trifluorobuty)-3,4,6,7,8,9,11,12,13,14-decahydro-2H-17,19-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclonosine-4-carboxamide | 762.3 | See Example 14, separated diastereomers | A1, B18 |
| 37, III-58 | (2R,4S,7R,15E)-N-((1R,2S)-1-{([(cyclopropylsulfonyl)amino]carbonyl)-2-vinylcyclopropyl}-6,9-dioxo-7-(4,4,4-trifluorobuty)-3,4,6,7,8,9,11,12,13,14-decahydro-2H-17,19-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclonosine-4-carboxamide | 762.3 | See Example 14, separated diastereomers | A1, B18 |</p>
<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Formula</th>
<th>MW</th>
<th>Source</th>
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<tbody>
<tr>
<td>38, III-59</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(2R,4S,7S,14E)-N-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-7-(2,3-dihydro-1H-inden-2-yl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-(\lambda)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>754.3</td>
<td>See Example 14, separated diastereomers</td>
</tr>
<tr>
<td>39, III-60</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(2R,4S,7R,14E)-N-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-7-(2,3-dihydro-1H-inden-2-yl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-(\lambda)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>754.3</td>
<td>See Example 14, separated diastereomers</td>
</tr>
<tr>
<td>40, III-61</td>
<td>(6R,8S,11S,14aS,18aR,20E)-11-\textit{t}ert\textit{-}butyl-\textit{N}-(1(1R,2S)-1-{([\text{cyclopropylsulfon}y]l\textit{amino})\textit{carboxy}l})-2-vinylcyclopropyl}-10,13-dioxo-7,8,10,11,12,13,15,16,17,18,19-dodecahydro-6\textit{H},14\textit{a}H-1,22-etheno-6,9-methanopyrido[2,3-\textit{k}][1,10,3,6]benzodioxadiaza\textit{cyclononadec}ine-8-carboxamide</td>
<td>748.3</td>
<td>See Example 14, separated diastereomers</td>
<td>A1, B20</td>
</tr>
</tbody>
</table>

<p>| 41, III-62 | (6R,8S,11S,14aR,18aS,20E)-11-\textit{t}ert\textit{-}butyl-\textit{N}-(1(1R,2S)-1-{([\text{cyclopropylsulfon}y]l\textit{amino})\textit{carboxy}l})-2-vinylcyclopropyl}-10,13-dioxo-7,8,10,11,12,13,15,16,17,18,19-dodecahydro-6\textit{H},14\textit{a}H-1,22-etheno-6,9-methanopyrido[2,3-\textit{k}][1,10,3,6]benzodioxadiaza\textit{cyclononadec}ine-8-carboxamide | 748.3 | See Example 14, separated diastereomers | A1, B20 |
| 42, III-63 | (2R,4S,7S)-7-cyclohexyl-N-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2H,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 | (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-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-\k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide | 708.4 | See Example 15 | A1, B13 |</p>
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<td>44,</td>
<td>(2R,4S,7S)-7-cyclopentyl-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</td>
<td>710.5</td>
<td>See Example 15</td>
<td>A3, B13</td>
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<td>III-</td>
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<td>45,</td>
<td>(2R,4S,7S,14E)-7-cyclohexyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-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]dioxadiazacyclononadecine-4-carboxamide</td>
<td>748.5</td>
<td>See Example 14</td>
<td>A1, B23</td>
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| 46, III-67 | \((2R,4S,7S)-7\text{-cyclohexyl-}
N-\((1R,2S)-1\text{-}
\{[(cyclopropylsulfonil)amino]carbonyl\}-2-
vinylcyclopropyl\}-12,12-
dimethyl-6,9-dioxo-
3,4,6,7,8,9,12,13,14,15-
decahydro-2H,11H-16,18-
etheno-2,5-
methanopyrido[2,3-
\(k\)]\(1,10,3,6\)dioxadiazacyclo-
onadecine-4-
carboxamide | 750.5 | See Example 15 | A1, B23 |
| 47, III-68 | \((2R,4S,7S)-7\text{-cyclohexyl-}
N-\((1R,2S)-1\text{-}
\{[(cyclopropylsulfonil)amino]carbonyl\}-2-
vinylcyclopropyl\}-6,9-
dioxo-
3,4,6,7,8,9,11,12,13,14-
decahydro-2H-15,17-
(ethanediylidene)-2,5-
methanopyrido[2,3-
\(k\)]\(1,10,3,6\)dioxadiazacyclo-
octadecine-4-
carboxamide | 708.3 | See Example 15 | A1, B21 |
(2R,4S,7S,16E)-7-cyclohexyl-7-[(1R,2S)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-vinylcyclopropyl]-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-18,20-(ethanediylidene)-2,5-methanopyrido[2,3-\textbf{k}][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide

748.3 See Example 14 A1, B26

(2R,4S,7S)-7-cyclohexyl-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-\textbf{k}][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide

750.5 See Example 15 A1, B26
| 50, III-71 | (2R,4S,7S,17E)-7-tert-butyl-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-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 | (2R,4S,7S,15E)-7-cyclohexyl-N-((1R,2S)-1-\{[(cyclopropylsulfonyl)amino]carbonyl\}-2-vinylcyclopropyl\}-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2H-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide | 734.4 | See Example 14 | A1, B28 |
| 52, III-73 | (2R,4S,7S)-7-cyclohexyl-N-((1R,2S)-1-
(\{(cyclopropylsulfonyl)amino\})-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]dioxadiazacycl
ocicosine-4-carboxamide | 736.5 | See Example 15 | A1, B28 |
| 53, III-74 | (6R,8S,11S,14aS,17aR,19E)
-11-tert-butyl-N-((1R,2S)-
-1-
(\{(cyclopropylsulfonyl)amino\})-2-vinylcyclopropyl)-10,13-dioxo-
7,8,10,11,12,13,14a,15,16,
17,17a,18-dodecahydro-
6H-1,21-etheno-6,9-methanocyclopenta[r]pyrido
o[2,3-k][1,10,3,6]dioxadiazacycl
ononadecine-8-carboxamide | 734.3 | See Example 14, separated diastereomers | A1, B29 |
54, III-75

(6R,8S,11S,14aR,17aS,19E)-11-tert-butyl-N-((1R,2S)-1-
{(cyclopropylsulfonyl)amino}carbonyl)-2-vinylcyclopropyl)-10,13-
dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-
6H-1,21-etheno-6,9-methanocyclopenta[r]pyridine-[2,3-
κ][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide

734.3
See Example 14, separated diastereomers
A1, B29

55, III-76

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

736.5
See Example 15, separated diastereomers
A1, B30
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<td>56, III-77</td>
<td><img src="image" alt="Molecular Structure" /></td>
<td>(2R,4S,7S,11S)-7-cyclohexyl-7-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-11-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>736.4</td>
<td>See Example 15, separated diastereomers</td>
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<td>(2R,4S,7S)-7-tert-butyl-7-((1R,2R)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16,17,18-tetradecahydro-2H-19,21-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide</td>
<td>740.6</td>
<td>See Example 15</td>
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<td>(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16,17,18-tetradecahydro-2H-19,21-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide</td>
<td>738.5</td>
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<td>59, III-80</td>
<td>(2R,4S,7S,15E)-7-cyclopentyl-N-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2H-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide</td>
<td>720.4</td>
<td>See Example 14</td>
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<td>(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-ethanediyldiene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide</td>
<td>722.4</td>
<td>See Example 15</td>
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<td>See Example 14</td>
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<td>(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</td>
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<td>See Example 15</td>
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<td>(2R,4S,7R,14E)-7-cyclobutyl-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-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
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<td>See Example 14, separated diastereomers</td>
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<td>65, III-86</td>
<td>(2R,4S,7R)-7-cyclobutyl-N-((1R,2S)-1-(((\text{cyclopropylsulfonyl})\text{amino})\text{carbonyl})-2-\text{vinylcyclopropyl})-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
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<td>694.3</td>
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<td>(2R,4S,7S,15(E))-7-cyclopentyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2H-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-(k)][1,10,3,6]dioxadiazacyclicosine-4-carboxamide</td>
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<td>(2R,4S,7S)-7-cyclopentyl-N-((1R,2S)-1-{(cyclopropylsulfonyl)amino} carbonyl)-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,16-dodecahydro-2H-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclolicosine-4-carboxamide</td>
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<td>See Example 15</td>
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<td>762.4</td>
<td>See Example 14</td>
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<td>(2R,4S,7S,16E)-7-cyclopentyl-N-((1R,2S)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-18,20-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazaacyclohenicosine-4-carboxamide</td>
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<td>See Example 14</td>
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<td>(2R,4S,7S,12S,14D)-7-cyclohexyl-N-((1R,2S)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-vinylcyclopropyl)-12-methyl-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]dioxadiazaacyclononadecine-4-carboxamide</td>
<td>734.4</td>
<td>See Example 14, separated diastereomers</td>
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<td>(2R,4S,7S,12R,14E)-7-cyclohexyl-N-((1R,2S)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-vinylcyclopropyl)-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-\kappa][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
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<td>(2R,4S,7S)-7-cyclopentyl-N-((1R,2S)-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-2H,11H-18,20-etheno-2,5-methanopyrido[2,3-\kappa][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide</td>
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<td>(2R,4S,7S)-7-cyclohexyl-N-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinyl(cyclopropyl)-12,12-dimethyl-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]dioxadiazacyclotricosine-4-carboxamide</td>
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<td>(6R,8S,11S,14aS,17aR,19E)-11-cyclopentyl-N-((1R,2S)-1-{((cyclopropylsulfonyl)amino]carbonyl]-2-vinylcyclopropyl]-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6H-1,21-etheno-6,9-methanocyclopenta[\r]pyridine-6-carboxamide</td>
<td>746.4</td>
<td>See Example 14, separated diastereomers</td>
<td>A1, B38</td>
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78, III-99

(6R,8S,11S,14aR,17aS,19E)-11-cyclopentyl-N-((1R,2S)-1-
{(cyclopropylsulfonyl)amino}carbonyl)-2-
vinylcyclopropyl)-10,13-
dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-
dodecahydro-6H-1,21-etheno-6,9-
methanocyclopenta[r]pyrido-
[2,3-\kappa][1,10,3,6]dioxadiazacycl
ononadecine-8-
carboxamide

746.4 See Example 14, separated diastereomers A1, B38

79, III-100

(2R,4S,7S,12S)-7-
cyclohexyl-N-((1R,2S)-1-
{(cyclopropylsulfonyl)amino}carbonyl)-2-
vinylcyclopropyl)-12-
methyl-6,9-dioxo-
3,4,6,7,8,9,12,13,14,15-
decahydro-2H,11H-16,18-
etheno-2,5-
methanopyrido[2,3-
\kappa][1,10,3,6]dioxadiazacycl
ononadecine-4-
carboxamide

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

See Example 15, separated diastereomers

A1, B38

(2R,4S,7S,16E)-7-cyclohexyl-N-((1R,2S)-1-\{(cyclopropylsulfonamido)carbonyl\}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-18,20-etheno-2,5-methanopyrido[2,3-\kappa][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide

See Example 14

A1, B40
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<th>778.4</th>
<th>See Example 15</th>
<th>A1, B40</th>
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<td>85, III-106</td>
<td>(6R,8S,11S,14aS,17aR,19E)-11-cyclohexyl-N-&lt;br&gt;((1R,2S)-1-&lt;br&gt;[(cyclopropylsulfonyl)amino]carbonyl)-2-&lt;br&gt;vinylecyclopropyl)-10,13-&lt;br&gt;dioxo-&lt;br&gt;7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-&lt;br&gt;6H-1,21-etheno-6,9-&lt;br&gt;methanocyclopenta[r]pyrid&lt;br&gt;o[2,3-&lt;br&gt;k][1,10,3,6]dioxadiazacycl&lt;br&gt;ononadecine-8-&lt;br&gt;carboxamide&lt;br&gt;</td>
<td>760.5</td>
<td>See Example 14, separated diastereomers</td>
<td>A1, B41</td>
</tr>
</tbody>
</table>
| 86, III-107 | (6R,8S,11S,14aR,17aS,19E)-11-cyclohexyl-N-((1R,2S)-1-
{[(cyclopropylsulfonyl)amino]carbonyl}-2-
vinylcyclopropyl)-10,13-
dioxo-7,8,10,11,12,13,14a,15,16,
17,17a,18-dodecahydro-
6H-1,21-etheno-6,9-
methanocyclopenta[r]pyridin-
[2,3-\(k\)][1,10,3,6]dioxadiaza
cyclononadecine-8-
carboxamide | 760.5 | See Example 14, separated diastereomers | A1, B41 |

| 87, III-108 | (6R,8S,11S,14aS,17aS)-11-cyclohexyl-N-((1R,2S)-1-
{[(cyclopropylsulfonyl)amino]carbonyl}-2-
vinylcyclopropyl)-10,13-
dioxo-7,8,10,11,12,13,14a,15,16,
17,17a,18,19,20-
tetradecahydro-6H-1,21-
etheno-6,9-
methanocyclopenta[r]pyridin-
[2,3-\(k\)][1,10,3,6]dioxadiaza
cyclononadecine-8-
carboxamide | 762.6 | See Example 15, separated diastereomers | A1, B41 |
<p>| 88, III-109 | (6R,8S,11S,14aR,17aR)-11-cyclohexyl-N-((1R,2S)-1-{(cyclopropylsulfonyl)amino}carbonyl)-2-vinylicyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahydro-6H,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 |
| 93, III-114 | ( (2R,4'S,7'S,12S,14'E)-7')-cyclohexyl-N-((1R,2S)-1- {[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylecyclopropyl}-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 | (2R,4S,7S,12R,14E)-7-cyclohexyl-N-((1R,2S)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-vinylcyclopropyl}-12-ethyl-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]dioxadiazacyclononadecine-4-carboxamide | 748.4 | See Example 14, separated diastereomers | A1, B43 |
| 95, III-116 | (2R,4S,7S,12S)-7-cyclohexyl-N-((1R,2S)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-vinylcyclopropyl}-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide | 750.4 | See Example 15, separated diastereomers | A1, B43 |
| 96, III-117 | (2R,4S,7S,12R)-7-cyclohexyl-N-((1R,2S)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-vinylcyclopropyl}-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-\kappa][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide | 750.5 | See Example 15, separated diastereomers | A1, B43 |
| 101, III-122 | (2R,4S,7S)-N-((1R,2S)-1-{[(cyclopropyl)sulfonyl]amino}carbonyl)-2-vinylicyclopropyl)-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]oxatriazacyclononadecene-4-carboxamide | 709.4 | See Example 15 | A1, B50 |</p>
<table>
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<tr>
<th>Compound</th>
<th>Structure</th>
<th>Chemical Formula</th>
<th>Molecular Weight</th>
<th>Reference</th>
<th>Classification</th>
</tr>
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<tbody>
<tr>
<td>102, III-28</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(2R,4S,7S,14E)-7-tert-butyl-N-(((1R,2S)-1-{[(cyclopropylsulfanyl)amino]carbonyl}-2-vinylcyclopropyl)-10-methyl-6,9-dioxo-3,4,6,7,8,9,10,11,12,13-decahydro-2H-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-r][1,5,8,10]oxatriazacyclo nonadecine-4-carboxamide</td>
<td>707.6</td>
<td>See Example 14</td>
<td>A1, B51</td>
</tr>
<tr>
<td>103, III-14</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(2R,4S,7S)-7-tert-butyl-N-(((1R,2S)-1-{[(cyclopropylsulfanyl)amino]carbonyl}-2-vinylcyclopropyl)-10-methyl-6,9-dioxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2H-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-r][1,5,8,10]oxatriazacyclo nonadecine-4-carboxamide</td>
<td>709.7</td>
<td>See Example 15</td>
<td>A1, B51</td>
</tr>
<tr>
<td>Ex.</td>
<td>Structure</td>
<td>Name</td>
<td>LRMS (M+H)⁺</td>
<td>Prepared using the appropriate intermediates according to the procedure below.</td>
<td></td>
</tr>
<tr>
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<td>---------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td><img src="image" alt="Structure" /></td>
<td>(2R,4S,7S)-7-tert-butyl-N-(((1R,2S)-1-{{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl}-10-isopropyl-6,9-dioxo-3,4,7,8,9,10,11,12,13,14-decahydro-2H,6H-17,19-etheno-2,5-methanopyrido[3,2-s][1,5,8,10]oxatriazacyclononadecine-4-carboxamide</td>
<td>749.4</td>
<td>See Example 14 A1, B52</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td><img src="image" alt="Structure" /></td>
<td>(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</td>
<td>692.6</td>
<td>See Example 14 A1, B53</td>
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</tr>
</tbody>
</table>

By using the appropriate procedures and the appropriate A, B and C intermediates the following compounds were prepared.
<table>
<thead>
<tr>
<th>No.</th>
<th>Formula</th>
<th>Molecular Weight</th>
<th>Additional Info</th>
</tr>
</thead>
<tbody>
<tr>
<td>106, III-12</td>
<td>(2R,4S,7S)-7-tart-butyl-N-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-κ][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>726.5</td>
<td>See Example 15  A1, B2, C1</td>
</tr>
<tr>
<td>107, III-124</td>
<td>(2R,4S,7S)-7-tart-butyl-N-((1R,2R)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-ethylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-κ][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>728.6</td>
<td>See Example 15  A3, B2, C1</td>
</tr>
<tr>
<td>108, III-125</td>
<td>(2R,4S,7S)-7-cyclopentyl-N-((1R,2S)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-κ][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>738.5</td>
<td>See Example 15  A1, B13, C1</td>
</tr>
<tr>
<td>109, III-126</td>
<td>(2R,4S,7S)-7-cyclopentyl-N-((1R,2R)-1-(((cyclopropylsulfonyl)amino)carbonyl)-2-ethylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-κ][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>740.6</td>
<td>See Example 15  A3, B13, C1</td>
</tr>
<tr>
<td>No.</td>
<td>Image</td>
<td>Chemical Structure</td>
<td>Molecular Formula</td>
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<tr>
<td>110, III-127</td>
<td><img src="110_III-127.png" alt="Image" /></td>
<td>(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-(((cyclpropylsulfonyl)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-2H-17,19-etheno-2,5-methanopyrido[2,3-(\alpha)][1,10,3,6]dioxadiazacyclosine-4-carboxamide</td>
<td>768.6</td>
</tr>
<tr>
<td>111, III-128</td>
<td><img src="111_III-128.png" alt="Image" /></td>
<td>(2R,4S,7S)-7-tert-butyl-N-((1R,2R)-1-(((cyclpropylsulfonyl)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-2H-17,19-etheno-2,5-methanopyrido[2,3-(\alpha)][1,10,3,6]dioxadiazacyclosine-4-carboxamide</td>
<td>770.7</td>
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<tr>
<td>112, III-129</td>
<td><img src="112_III-129.png" alt="Image" /></td>
<td>(2R,4S,7S,14E)-7-cyclohexyl-N-((1R,2S)-1-(((cyclpropylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-(\alpha)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>778.6</td>
</tr>
<tr>
<td>113, III-130</td>
<td><img src="113_III-130.png" alt="Image" /></td>
<td>(2R,4S,7S,14E)-7-cyclohexyl-N-((1R,2R)-1-(((cyclpropylsulfonyl)amino)carbonyl)-2-ethylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-(\alpha)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>780.6</td>
</tr>
</tbody>
</table>
| 114, III-131 | \((2R,4S,7S)-7\text{-cyclohexyl-}\text{-N-}((1R,2S)\text{-1-}\
|{}\text{[cyclopropylsulfanyl]amino}\text{[carbonyl]}\text{-2-vinylcyclopropyl]-23-methoxy-12,12-}\
|{}\text{dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-}\
|{}\text{methanopyrido}[2,3-k][1,10,3,6]\text{dioxadiazacyclononadecine-4-carboxamide} | 780.5 | See Example 15 | A1, B23, C1 |

| 115, III-132 | \((2R,4S,7S)-7\text{-cyclohexyl-}\text{-N-}((1R,2R)\text{-1-}\
|{}\text{[cyclopropylsulfanyl]amino}\text{[carbonyl]}\text{-2-ethylcyclopropyl]-23-methoxy-12,12-}\
|{}\text{dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-}\
|{}\text{methanopyrido}[2,3-k][1,10,3,6]\text{dioxadiazacyclononadecine-4-carboxamide} | 782.6 | See Example 15 | A3, B23, C1 |

| 116, III-133 | \((2R,4S,7S,12S,14E)-7\text{-tert-butyl-}\text{-N-}((1R,2S)\text{-1-}\
|{}\text{[cyclopropylsulfanyl]amino}\text{[carbonyl]}\text{-2-vinylcyclopropyl]-23-methoxy-12-methyl-}\
|{}\text{6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-}\
<p>|{}\text{methanopyrido}[2,3-k][1,10,3,6]\text{dioxadiazacyclononadecine-4-carboxamide} | 738.3 | See Example 14, separated diastereomers | A1, B46, C1 |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Molecular Structure</th>
<th>Chemical Formula</th>
<th>Molecular Weight</th>
<th>See Example</th>
<th>Separation Method</th>
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<tr>
<td>117, III-134</td>
<td><img src="image" alt="Molecular Structure" /></td>
<td>(2R,4S,7S,12R,14E)-7-tert-butyl-N-((1R,2S)-1-(((cyclopropylsulfonfyl)amino)carbonyl)-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-κ][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>738.3</td>
<td>See Example 14, separated diastereomers</td>
<td>A1, B46, Cl</td>
</tr>
<tr>
<td>118, III-135</td>
<td><img src="image" alt="Molecular Structure" /></td>
<td>(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-(((cyclopropylsulfonfyl)amino)carbonyl)-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-κ][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>740.2</td>
<td>See Example 15</td>
<td>A1, B46, Cl</td>
</tr>
<tr>
<td>119, III-136</td>
<td><img src="image" alt="Molecular Structure" /></td>
<td>(2R,4S,7S,12S,14E)-7-cyclopentyl-N-((1R,2S)-1-(((cyclopropylsulfonfyl)amino)carbonyl)-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-κ][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>750.4</td>
<td>See Example 14, separated diastereomers</td>
<td>A1, B48, Cl</td>
</tr>
<tr>
<td>120, III-137</td>
<td><img src="image" alt="Molecular Structure" /></td>
<td>(2R,4S,7S,12R,14E)-7-cyclopentyl-N-((1R,2S)-1-(((cyclopropylsulfonfyl)amino)carbonyl)-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-κ][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>750.4</td>
<td>See Example 14, separated diastereomers</td>
<td>A1, B48, Cl</td>
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<tr>
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<td>Structure</td>
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<td>Molecular Weight</td>
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<tr>
<td>121, 138</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>$(2R,4S,7S,12S)-7$-cyclopentyl-$N$-$(1R,2S)$-1-[[[(cyclopropylsulfonyl)amino]carbonyl]-2-vinylcyclopropyl]-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-$\delta$][1,10,3,6]dioxaiazacyclononadecine-4-carboxamide</td>
<td>752.4</td>
<td>15</td>
<td>A1, B48, C1</td>
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<tr>
<td>122, 139</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>$(2R,4S,7S,12S)-7$-cyclopentyl-$N$-$(1R,2S)$-1-[[[(cyclopropylsulfonyl)amino]carbonyl]-2-vinylcyclopropyl]-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-$\delta$][1,10,3,6]dioxaiazacyclononadecine-4-carboxamide</td>
<td>752.5</td>
<td>15</td>
<td>A1, B48, C1</td>
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<tr>
<td>123, 140</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>$(2R,4S,7S,12S,14E)-7$-cyclohexyl-$N$-$(1R,2S)$-1-[[[(cyclopropylsulfonyl)amino]carbonyl]-2-vinylcyclopropyl]-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-$\delta$][1,10,3,6]dioxaiazacyclononadecine-4-carboxamide</td>
<td>764.3</td>
<td>14</td>
<td>A1, B39, C1</td>
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<tr>
<td>124, 141</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>$(2R,4S,7S,12S,14E)-7$-cyclohexyl-$N$-$(1R,2S)$-1-[[[(cyclopropylsulfonyl)amino]carbonyl]-2-vinylcyclopropyl]-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-$\delta$][1,10,3,6]dioxaiazacyclononadecine-4-carboxamide</td>
<td>764.3</td>
<td>14</td>
<td>A1, B39, C1</td>
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<td>Chemical Structure</td>
<td>CAS Number</td>
<td>Example Reference</td>
<td>Literature References</td>
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<tr>
<td>125, 142</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(2R,4S,7S)-7-cyclohexyl-N-((1R,2S)-1-[[[[cyclopropylsulfonfyl]amino]carbonyl]-2-vinylicyclopropyl]-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decacyclohydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-(k)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>766.4</td>
<td>See Example 15</td>
<td>A1, B39, C1</td>
</tr>
<tr>
<td>129, III-31</td>
<td>(2R,4S,7S,14E)-7-tert-butyl-20-chloro-N-{(1R,2S)-1-[(cyclopropylsulfonfyl)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- ( \lambda )][1,10,3,6]dioxadiazaclonadecine-4-carboxamide</td>
<td>728.5</td>
<td>See Example 14</td>
<td>A1, B2, C3</td>
<td></td>
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<tr>
<td>130, III-32</td>
<td>(2R,4S,7S,14E)-7-tert-butyl-20-chloro-N-{(1R,2R)-1-[(cyclopropylsulfonfyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3- ( \lambda )][1,10,3,6]dioxadiazaclonadecine-4-carboxamide</td>
<td>730.5</td>
<td>See Example 14</td>
<td>A3, B2, C3</td>
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<tr>
<td>131, III-144</td>
<td>(2R,4S,7S,12E)-7-tert-butyl-N-{(1R,2S)-1-[(cyclopropylsulfonfyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,14-octahydro-2H-16,18-etheno-2,5-methanopyrido[2,3- ( \lambda )][1,10,15,3,6]trioxadiazaclonadecine-4-carboxamide</td>
<td>696.5</td>
<td>See Example 14, separated olefin isomers</td>
<td>A1, B49, C4</td>
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<tr>
<td>132, III-145</td>
<td>(2R,4S,7S,12Z)-7-tert-butyl-N-{(1R,2S)-1-[(cyclopropylsulfonfyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,14-octahydro-2H-16,18-etheno-2,5-methanopyrido[2,3- ( \lambda )][1,10,15,3,6]trioxadiazaclonadecine-4-carboxamide</td>
<td>696.5</td>
<td>See Example 14, separated olefin isomers</td>
<td>A1, B49, C4</td>
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</table>
By using the appropriate procedures and the appropriate A, B and D intermediates, the following compounds were prepared.

<table>
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<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Name</th>
<th>LRM S (M+ H)^+</th>
<th>Prepared using the appropriate Intermediates according to the procedure below.</th>
<th>Int.</th>
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<tr>
<td>135, III-148</td>
<td>(2R,4S,7S)-7-cyclohexyl-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-(ethanediyliidene)-2,5-methanopyrido[2,3-(\delta)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide</td>
<td>848.4</td>
<td>See Example 13</td>
<td>B8</td>
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(2R,4S,7S)-7-cyclohexyl-N-((1R,2R)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-ethylcyclopropyl)-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-\(\lambda\)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide

850. See Example 13
5 A3, B8

(2R,4S,7S,14E)-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-octahydropyrido[2,3-\(\lambda\)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide

820. See Example 14, Step 5
2 A1, D1

(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{{(cyclopropylsulfonyl)amino}carbonyl}-2-vinylcyclopropyl)-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-\(\lambda\)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide

764. See Example 14, Steps 4 and 5
3 A1, D5

(2R,4S,7S)-7-tert-butyl-22-cyano-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-\(\lambda\)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide

721. See Example 14, Steps 4 and 5
6 A1, D6
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<th>Chemical Structure</th>
<th>Chemical Formula</th>
<th>Page Number</th>
<th>Notes</th>
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</thead>
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<tr>
<td>140, III-153</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(2R,4S,7S)-7-tert-butyl-N-(((1R,2S)-1-(((cyclopropylsulfonfyl)amino)carbonyl)-2-vinylcyclopropyl)-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-carboxamide</td>
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<td>See Example 14, Steps 4 and 5</td>
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<td>141, III-154</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(2R,4S,7S)-7-cyclopentyl-N-(((1R,2S)-1-(((cyclopropylsulfonfyl)amino)carbonyl)-2-vinylcyclopropyl)-22-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-carboxamide</td>
<td>764</td>
<td>See Example 14, Steps 4 and 5</td>
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<td>142, III-155</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(2R,4S,7S)-7-tert-butyl-N-(((1R,2S)-1-(((cyclopropylsulfonfyl)amino)carbonyl)-2-vinylcyclopropyl)-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-carboxamide</td>
<td>726</td>
<td>See Example 14, Step 5</td>
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<tr>
<td>143, III-156</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>(2R,4S,7S)-7-tert-butyl-N-(((1R,2R)-1-(((cyclopropylsulfonfyl)amino)carbonyl)-2-ethylcyclopropyl)-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-carboxamide</td>
<td>728</td>
<td>See Example 14, Step 5</td>
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<td>Reaction Step</td>
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<tr>
<td>144, III-157</td>
<td><img src="image1.png" alt="Image" /></td>
<td>[(2R,4S,7S)-7-cyclohexyl-N-{{(1R,2S)-1-[({cyclopropylsulfonyl}amino)carbonyl}}-2-vinylcyclopropyl}-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-carboxamide]</td>
<td>752.5</td>
<td>See Example 14, Step 5</td>
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<tr>
<td>145, III-158</td>
<td><img src="image2.png" alt="Image" /></td>
<td>[(2R,4S,7S)-7-cyclohexyl-N-{{(1R,2S)-1-[({cyclopropylsulfonyl}amino)carbonyl}}-2-ethylcyclopropyl}-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-carboxamide]</td>
<td>754.5</td>
<td>See Example 14, Step 5</td>
</tr>
<tr>
<td>146, III-159</td>
<td><img src="image3.png" alt="Image" /></td>
<td>[(2R,4S,7S)-7-tert-buty1-N-{{(1R,2S)-1-[({cyclopropylsulfonyl}amino)carbonyl}}-2-vinylcyclopropyl}-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-carboxamide]</td>
<td>712.5</td>
<td>See Example 14, Step 5</td>
</tr>
<tr>
<td>147, III-160</td>
<td><img src="image4.png" alt="Image" /></td>
<td>[(2R,4S,7S)-7-tert-buty1-N-{{(1R,2S)-1-[({cyclopropylsulfonyl}amino)carbonyl}}-2-vinylcyclopropyl}-6,9-dioxo-22-(trifluoromethoxy)-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]</td>
<td>780.5</td>
<td>See Example 15</td>
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<td>148, III-161</td>
<td>(2R,4S,7S,14E)-7-tert-butyl-N-((1R,2S)-1-[(cyclopropyl)sulfonyl]amino)carbonyl)-2-vinylcyclopropyl)-6,9-dioxo-22-(trifluoromethoxy)-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</td>
<td>778</td>
<td>See Example 14, Steps 4 and 5</td>
<td>A1, D15</td>
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<tr>
<td>149, III-162</td>
<td>(2R,4S,7S,14E)-7-tert-butyl-N-((1R,2R)-1-[(cyclopropyl)sulfonyl]amino)carbonyl)-2-ethylycyclopropyl)-6,9-dioxo-22-(trifluoromethoxy)-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</td>
<td>780</td>
<td>See Example 14, Steps 4 and 5</td>
<td>A3, D15</td>
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<tr>
<td>150, III-163</td>
<td>(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-[(cyclopropyl)sulfonyl]amino)carbonyl)-2-vinylcyclopropyl)-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-carboxamide</td>
<td>740</td>
<td>See Example 14, Steps 4 and 5</td>
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<tr>
<td>151, III-164</td>
<td>(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-[(cyclopropyl)sulfonyl]amino)carbonyl)-2-vinylcyclopropyl)-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-carboxamide</td>
<td>774</td>
<td>See Example 14, Steps 4 and 5</td>
<td>A1, D13</td>
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(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-\{(cyclopropylsulfonyl)amino\}[carbonyl]-2-vinylcyclopentyl)-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-\lambda][1,10,3,6]dioxadiazacyclononacene-4-carboxamide

(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-\{(cyclopropylsulfonyl)amino\}[carbonyl]-2-vinylcyclopentyl)-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-\lambda][1,10,3,6]dioxadiazacyclononacene-4-carboxamide

(2R,4S,7S)-7-tert-butyl-N-((1R,2R)-1-\{(cyclopropylsulfonyl)amino\}[carbonyl]-2-ethylcyclopentyl)-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-\lambda][1,10,3,6]dioxadiazacyclononacene-4-carboxamide

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

**EXAMPLE 159**

\((2R,4S,7S,14\text{E})-7\text{-}\text{tert\text{-}butyl\text{-}}N\text{-}\((1R,2S)\text{-}1\text{-}\{(\text{cyclopropylsulfonyl})\text{amino\text{-}carbonyl\text{-}2\text{-}vinylcyclopropyl\text{-}15\text{-}hydroxy\text{-}6,9\text{-}dioxo\text{-}3,4,6,7,8,9,12,13\text{-octahydro\text{-}2\text{-}H\text{-}11\text{-}H\text{-}16,18\text{-}\text{(ethanediylidene\text{-}2,5\text{-}methanopyrido}[2,3-\kappa][1,10,3,6]\text{dioxadiazaclononadecine-4\text{-}carboxamide}}}\text{(III-172)}\)
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$_2$O$_8$S: 770.3].

EXAMPLE 160

(2R,4S,7S,14E)-7-tert-Butyl-20-chloro-N-((1R,2S)-1-\{[methylamino]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 (III-173)

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) (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$_{35}$H$_{41}$ClN$_2$O$_6$: 638.3].
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, 0.011 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 organic, 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 C₄₁H₅₀N₅O₇S: 772.3].

EXAMPLE 162

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

Step 1: 1-tert-Butyl 2-[2-(trimethylsilyl)ethyl] (2S,4S)-4-hydroxypyrrolidine-1,2-dicarboxylate
To a solution of 1-tert-butyl 2-methyl (2S,4S)-4-hydroxypyrrrolidine-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% Et₂O) indicated complete consumption of the starting material and formation of a more polar compound (KMnO₄ 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 MgSO₄, 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 Na₂SO₄ 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 TBUTU (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 NaHCO₃, brine, dried over Na₂SO₄ 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 [7E,15S,18S,20R]-2-(1H-1,2,3-benzotriazol-1-yloxy)-15-isopropyl-13,16-dioxo-10,11,13,14,15,16,19,20-octahydro-9H,18H-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-κ][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 (7E,15S,18S,20R)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-10,11,13,14,15,16,19,20-octahydro-9H,18H-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-\(\bar{k}\)][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 (15S,18S,20R)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7H,18H-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-\(\bar{k}\)][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:** (15S,18S,20R)-2-(Dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydroy-7H,18H-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 (1R,2S)-1-[[((15S,18S,20R)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydroy-7H,18H-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-$k$][1,10,3,6]dioxadiazacyclononadecine-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 (20 mL), washed with pH 5.2 citric acid (10 mL), 10% aqueous sodium bicarbonate (10 mL), dried over Na₂SO₄, 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: (1R,2S)-1-(((15S,18S,20R)-2-(Dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7H,18H-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-A][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. ¹H NMR (500 MHz, CD₃OD) 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), 4.65 (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), 1.68 (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 C₃₂H₄₅N₆O₇: 623.3.

By using the appropriate procedures and the appropriate A and B intermediates, the following compounds were prepared.
<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Name</th>
<th>LRMS (M+H)+</th>
<th>Prepared using the appropriate Intermediates according to the procedure below.</th>
<th>Int.</th>
</tr>
</thead>
<tbody>
<tr>
<td>163, III-176</td>
<td><img src="image" alt="Structure" /></td>
<td>(15S,18S,20R)-N-((1R,2S)-1- {(cyclopropylsulfonyl)amino}carbonyl)-2-vinylcyclopropyl)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7H,18H-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-(\alpha)][1,10,3,6]dioxadiazacyclonona decine-18-carboxamide</td>
<td>726.6</td>
<td>Example 162</td>
<td>A1</td>
</tr>
<tr>
<td>164, III-177</td>
<td><img src="image" alt="Structure" /></td>
<td>(15S,18S,20R)-2-(benzylamino)-N-((1R,2S)-1- {(cyclopropylsulfonyl)amino}carbonyl)-2-vinylcyclopropyl)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7H,18H-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-(\alpha)][1,10,3,6]dioxadiazacyclonona decine-18-carboxamide</td>
<td>788.6</td>
<td>Example 162</td>
<td>A1, benzylamine</td>
</tr>
</tbody>
</table>

**EXAMPLE 165**

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

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

(EXAMPLE 10, Step 4) (0.73 g, 0.143 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 Na₂SO₄, filtered and concentrated to a foam which was used without further purification. LRMS (M+H)⁺ = 591.5.

Step 2: (2R,4S,7S,14E)-7-tert-Butyl-N-(((dimethylamino)sulfonyl)amino)carbonyl)-2-vinylcyclopropyl]-6,9-dioxyo-3,4,6,7,8,9,12,13-octahydro-2H,11H-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. ¹H NMR (500 MHz, CDCl₃) 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_{6}O_{8}S: 697.3.

EXAMPLE 166

(2R,4S,7S,14E)-7-tert-buty1-6,9-dioxo-N-((1R,2S)-1-(((piperidin-1-ylsulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-\kappa][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (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_{27}H_{49}N_{6}O_{8}S: 737.3.

EXAMPLE 167

(2R,4S,7S,14E)-N-((1R,2S)-1-(((benzyl(methyl)amino)sulfonyl)amino)carbonyl)-2-vinylcyclopropyl)-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-\kappa][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (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_{6}O_{8}S: 773.3.
EXAMPLE 168

(2R,4S,7S)-7-cyclohexyl-N-[(1R,2S)-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-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-\(\alpha\)][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-181)

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

EXAMPLE 168 was prepared according to the procedure described for EXAMPLE 165 by using ethyl (1R,2S)-1-{{[(2R,4S,7S)-7-cyclohexyl-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-\(\alpha\)][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino}-2-vinylcyclopropanecarboxylate.
δ][1,10,3,6]dioxadiazyclononadecin-4-yl[carbonyl]amino)-2-vinylcyclopropanecarboxylate in Step 1. LRMS (ESI) m/z 783.6 [(M+H)^+; calcd for C_{39}H_{55}N_{6}O_{8}S: 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]dioxadiazyclononadecine-4-carboxamide (III-182)

![Chemical structure of III-182]

III-182

Step 1: Ethyl (2R,4S,7S)-22-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]dioxadiazyclononadecine-4-carboxylate (III-186) and Ethyl (2R,4S,7S)-17,22-dibromo-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]dioxadiazyclononadecine-4-carboxylate (III-187)

![Chemical structures of III-186 and III-187]

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]dioxadiazyclononadecine-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_{33}H_{43}BrN_{6}O_{8}S: 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_{46}Br_{2}N_{7}O_{8}S: 852.1.

EXAMPLE 171

(2R,4S,7S)-7-cyclohexyl-N-((1R,2S)-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-decacydro-2H-15,17-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacycloctadecine-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 (5 mg) 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: (2R,4S,7S)-7-Cyclohexyl-N-((1R,2S)-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-2H-15,17-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide (III-184)

(2R,4S,7S)-7-Cyclohexyl-N-((1R,2S)-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-2H-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_{33}N_{3}O_{8}S: 780.4.

EXAMPLE 172

(2R,4S,7S)-7-tert-Butyl-N-((1R,2S)-1-[[cyclopropylsulfonyl]amino]carbonyl]-2-vinylcyclopropyl)-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2H,11H-16-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-185)
Step 1: 1,2-Pyrrolidinedicarboxylic acid, 4-[[7-bromo-1-isoquinolinyl]oxy]-1-(1,1-dimethylethyl)2-ethyl ester, (2S,4R)-

![Chemical Structure](image)

To a solution of di-tert-butyldicarbonate (1.14 g, 5.23 mmol) in CH$_3$CN (15 mL) was added Et$_3$N (2.08 mL, 14.9 mmol) and (4R)-4-[[7-bromoisoquinolin-1-yl]oxy]-L-proline 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$_2$CO$_3$ 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-[[3R,5S]-1-(tert-Butyloxycarbonyl)-5-(ethoxycarbonyl)pyrrolidin-3-yl]oxy]isoquinolin-7-yl]pent-4-yn-1-yl]oxy]carbonyl]-3-methyl-L-valine

![Chemical Structure](image)

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

The title compound was prepared from 7-ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-f][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 C35H32N3O8S: 692.3].
WHAT IS CLAIMED IS:

1. A compound of formula (I):

   \[ \text{[Diagram]} \]

   \( n = 1 \text{ or } 2; \)

   \( R^1 \) is CO\(_2\)R\(_6^{10}\), CONR\(_{10}^{10}\)SO\(_2\)R\(_6\), CONR\(_{10}^{10}\)SO\(_2\)NR\(_5\)R\(_5\), or tetrazolyl;

   \( R^2 \) is C\(_1\)-C\(_6\) alkyl, C\(_2\)-C\(_6\) alkenyl or C\(_2\)-C\(_6\) cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

   \( R^3 \) is C\(_1\)-C\(_6\) alkyl, C\(_3\)-C\(_4\) cycloalkyl, C\(_3\)-C\(_4\) cycloalkyl(C\(_1\)-C\(_6\))alkyl, aryI(C\(_1\)-C\(_6\))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\(_{10}^{10}\), SR\(_{10}^{10}\), N(R\(_{10}^{10}\)), 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\(_{10}^{10}\)SO\(_2\)R\(_6\), SO\(_2\)N(R\(_{10}^{10}\)), NHCOR\(_6\), NHCO\(_6\), NHCNHR\(_6\), CO\(_2\)R\(_{10}^{10}\), C(O)R\(_{10}^{10}\), and CON(R\(_{10}^{10}\));

   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\(_{10}^{10}\), SR\(_{10}^{10}\), N(R\(_{10}^{10}\)), 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\(_{10}^{10}\)SO\(_2\)R\(_6\), SO\(_2\)N(R\(_{10}^{10}\)), NHCOR\(_6\), NHCO\(_6\), NHCNHR\(_6\), CO\(_2\)R\(_{10}^{10}\), C(O)R\(_{10}^{10}\), and CON(R\(_{10}^{10}\));

   \( R^4 \) is H, C\(_1\)-C\(_6\) alkyl, C\(_2\)-C\(_6\) cycloalkyl(C\(_1\)-C\(_6\))alkyl, or aryI(C\(_1\)-C\(_6\))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, SR, N(R)\textsuperscript{10}, N(C\textsubscript{1}-C\textsubscript{6} alkyl)O(C\textsubscript{1}-C\textsubscript{6} alkyl), C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{1}-C\textsubscript{6} haloalkyl, halo(C\textsubscript{1}-C\textsubscript{6} alkoxy), NO\textsubscript{2}, CN, CF\textsubscript{3}, SO\textsubscript{2}(C\textsubscript{1}-C\textsubscript{6} alkyl), S(O)(C\textsubscript{1}-C\textsubscript{6} alkyl), NR\textsubscript{10}SO\textsubscript{2}R\textsubscript{6}, SO\textsubscript{2}N(R\textsubscript{6})\textsubscript{2}, NHCOOR\textsuperscript{6}, NHCOR\textsuperscript{6}, NHCONHR\textsuperscript{6}, CO\textsubscript{2}R\textsuperscript{10}, C(O)R\textsuperscript{10}, and CON(R\textsubscript{10})\textsubscript{2i}.

5 R\textsuperscript{3} is H, halo, OH, C\textsubscript{1}-C\textsubscript{6} alkoxy, C\textsubscript{1}-C\textsubscript{6} alkyl, CN, CF\textsubscript{3}, SR, SO\textsubscript{2}(C\textsubscript{1}-C\textsubscript{6} alkyl), C\textsubscript{3}-C\textsubscript{8} cycloalkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkoxy, C\textsubscript{1}-C\textsubscript{6} haloalkyl, N(R\textsubscript{3})\textsubscript{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, SR, N(R\textsubscript{3})\textsubscript{2}, N(C\textsubscript{1}-C\textsubscript{6} alkyl)O(C\textsubscript{1}-C\textsubscript{6} alkyl), C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{1}-C\textsubscript{6} haloalkyl, halo(C\textsubscript{1}-C\textsubscript{6} alkoxy), C\textsubscript{3}-C\textsubscript{8} cycloalkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkoxy, NO\textsubscript{2}, CN, CF\textsubscript{3}, SO\textsubscript{2}(C\textsubscript{1}-C\textsubscript{6} alkyl), NR\textsubscript{10}SO\textsubscript{2}R\textsubscript{6}, SO\textsubscript{2}N(R\textsubscript{6})\textsubscript{2}, S(O)(C\textsubscript{1}-C\textsubscript{6} alkyl), NHCOOR\textsuperscript{6}, NHCOR\textsuperscript{6}, NHCONHR\textsuperscript{6}, CO\textsubscript{2}R\textsuperscript{10}, C(O)R\textsuperscript{10}, and CON(R\textsubscript{10})\textsubscript{2i}; 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\textsuperscript{5} is C\textsubscript{1}-C\textsubscript{8} alkyl, C\textsubscript{1}-C\textsubscript{8} cycloalkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl(C\textsubscript{1}-C\textsubscript{8} alkyl), aryl, aryl(C\textsubscript{1}-C\textsubscript{8} alkyl), heteroaryl, heteroaryl(C\textsubscript{1}-C\textsubscript{8} alkyl), heterocyclyl, or heterocyclyl(C\textsubscript{1}-C\textsubscript{8} alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W\textsuperscript{*} 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\textsubscript{2}, or C(=N-CN);

Z is C(R\textsubscript{10})\textsubscript{2}, O, or N(R\textsubscript{3});

M is C\textsubscript{1}-C\textsubscript{12} alkylene or C\textsubscript{2}-C\textsubscript{12} alkenylene or C\textsubscript{2}-C\textsubscript{12} alkyneylene, wherein said alkylene or alkenylene is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of C\textsubscript{1}-C\textsubscript{8} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl(C\textsubscript{1}-C\textsubscript{8} alkyl), and aryl(C\textsubscript{1}-C\textsubscript{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') or N; 

when R' is other than H, R' is H, C₁-C₄ alkyl, halo, OR', SR', or N(R')₂; 

when R' is H, R' is H, C₁-C₄ alkyl, halo, OH, C₁-C₆ alkoxy, CN, CF₃, SR', SO₂(C₁-C₆ alkyl), C₅-C₆ cycloalkyl, C₅-C₆ cycloalkoxy, C₁-C₆ haloalkyl, N(R')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, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR', SR', N(R')₂, N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), C₁-C₄ alkyl, C₁-C₆ haloalkyl, halo(C₁-C₆ alkoxy), C₅-C₆ cycloalkyl, C₁-C₆ cycloalkoxy, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), NR'₃SO₂R', SO₃N(R')₂, S(O)(C₁-C₆ alkyl), NHCOOR', NHCOR', NHCONHR', CO₂R', C(O)R', and CON(R')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' is H or R' is H, C₁-C₄ alkyl, C₁-C₆ cycloalkyl, C₅-C₆ cycloalkyl(C₁-C₆ alkyl), aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₆ alkyl), heterocyclyl, or heterocyclyl(C₁-C₆ 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', C₁-C₆ alkyl, CN, CF₃, NO₂, SR', CO₂R', CON(R')₂, C(O)R', N(R')₂C(O)R', SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), C₅-C₆ cycloalkyl, C₁-C₆ cycloalkoxy, C₁-C₆ haloalkyl, N(R')₂N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), halo(C₁-C₆ alkoxy), NR'₃SO₂R', SO₃N(R')₂, NHCOOR', NHCONHR', 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 heterocycle 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, C1-C8 alkyl, CN, CF3, NO2, SR, CO2R, CON(R)2, C(O)R, N(R)C(O)R, SO2(C1-C6 alkyl), S(O)(C1-C6 alkyl), C1-C8 cycloalkyl, C1-C6 haloalkyl, N(R)2, N(C1-C6 alkyl)O(C1-C6 alkyl), halo(C1-C8 alkoxy), NR10SO2R, SO2N(R)2, NHCOOR, NHCONHR, 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 is C1-C8 alkyl, C3-C8 cycloalkyl, C5-C8 cycloalkyl(C1-C8 alkyl), aryl, aryl(C1-C4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C1-C4 alkyl), or heterocyclyl(C1-C8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C3-C8 cycloalkyl, heteroaryl, heterocyclyl, C1-C8 alkyl, halo(C1-C8 alkoxy), halo, OR, SR, N(R)2, N(C1-C8 alkyl)O(C1-C8 alkyl), C1-C8 alkyl, C(O)R, C1-C8 haloalkyl, NO2, CN, CF3, SO2(C1-C8 alkyl), S(O)C1-C8 alkyl), NR10SO2R, SO2N(R)2, NHCOOR, NHCONHR, NHCOOR, NHCONHR, NHCOOR, NHCONHR, SO2R, and C(O)N(R)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 is C1-C8 alkyl, C3-C8 cycloalkyl, C5-C8 cycloalkyl(C1-C8 alkyl), C1-C8 alkoxy, C3-C8 cycloalkoxy, aryl, aryl(C1-C4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C1-C4 alkyl), or heterocyclyl(C1-C8 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, C3-C8 cycloalkyl, heteroaryl, heterocyclyl, C1-C8 alkyl, halo(C1-C8 alkoxy), halo, OR, SR, N(R)2, N(C1-C8 alkyl)O(C1-C8 alkyl), C1-C8 alkyl, C(O)R, C1-C8 haloalkyl, NO2, CN, CF3, SO2(C1-C8 alkyl), S(O)C1-C8 alkyl), NR10SO2R, SO2N(R)2, NHCOOR, NHCONHR, NHCOOR, NHCONHR, NHCOOR, NHCONHR, SO2R, and C(O)N(R)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;
C₁-C₆ alkyl, halo(C₁-C₆ alkoxy), halo, OR¹⁰, SR¹⁰, N(R¹⁰), N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C(O)R¹⁰, C₁-C₆ haloalkyl, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), NR¹⁰SO₂R⁶, SO₂N(R⁶), NHCOOR⁶, NHCOR⁶, NHCONHR⁶, CO₂R¹⁰, and C(O)N(R¹⁰); 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 heterocycyl 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 R¹ and R² 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 R¹⁰ is independently H or C₁-C₆ alkyl or a pharmaceutically acceptable salt thereof.

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

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, wherein R¹ is CO₂R¹⁰ or CONR¹⁰SO₂R⁶, or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3, wherein R¹ is CO₂H, or a pharmaceutically acceptable salt thereof.

5. The compound of claim 3, wherein R¹ is CONHSO₂R⁶, or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein R¹ is CONHSO₂R⁶ wherein R⁶ is C₃-C₄ cycloalkyl, C₁-C₆ alkyl, aryl, or aryl(C₁-C₆)alkyl, or a pharmaceutically acceptable salt thereof.

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7. The compound of claim 3, wherein R² is C₁−C₄ alkyl or C₂−C₄ alkenyl, or a pharmaceutically acceptable salt thereof.

8. The compound of claim 7, wherein R³ is C₅−C₆ cycloalkyl or C₁−C₅ alkyl optionally substituted with 1 to 3 halo substituents, or a pharmaceutically acceptable salt thereof.

9. The compound of claim 8, wherein R⁴ is H, halo, aryl, heteroaryl or N(R⁷)₂, or a pharmaceutically acceptable salt thereof.

10. The compound of claim 9, wherein R⁵ is H or halo, or a pharmaceutically acceptable salt thereof.

11. The compound of claim 9, wherein R⁶ is aryl or heteroaryl, or a pharmaceutically acceptable salt thereof.

12. The compound of claim 9, wherein Y is C=O, or a pharmaceutically acceptable salt thereof.

13. The compound of claim 12, wherein Z is O, NH, N(C₁−C₄ alkyl) or C(R¹⁵)₂, or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13, wherein M is unsubstituted C₄−C₇ alkenylene or unsubstituted C₄−C₇ alkenylene, or a pharmaceutically acceptable salt thereof.

15. The compound of claim 14, wherein n is 1 and W is H, C₁−C₆ alkoxy, C₁−C₆ alkyl, OH, halo or N(R⁷)₂ wherein R⁷ is H or C₁−C₆ alkyl, or a pharmaceutically acceptable salt thereof.

16. The compound of claim 15, wherein A is N, or a pharmaceutically acceptable salt thereof.

17. The compound of claim 15, wherein A is C(R¹¹) wherein R¹¹ is H, C₁−C₆ alkyl, C₁−C₆ alkoxy, hydroxy or halo, or a pharmaceutically acceptable salt thereof.

18. The compound of claim 10, wherein R² is C₂−C₄ alkenyl, R⁵ is H, R⁶ is C₃−C₈ cycloalkyl, W is OR⁷ or H, Y is C(=O), Z is O, and n is 1, or a pharmaceutically acceptable salt thereof.

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

![Chemical structures](image)

or a pharmaceutically acceptable salt thereof.

20. The compound of claim 19, wherein R³ is C₁−C₆ cycloalkyl or C₂−C₅ alkyl, or a pharmaceutically acceptable salt thereof.
21. The compound of claim 20, wherein R° is C₃-C₅ cycloalkyl, or a pharmaceutically acceptable salt thereof.

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

III-1

III-2

III-3

III-4

III-5

III-6

III-7

III-8

III-9

III-10

III-11

III-12
or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1, wherein the compound is selected from the group consisting of compounds III-39 to III-172 and compounds III-174 to III-185:
24. The compound of claim 1, wherein the compound is (1R,2S)-1-(((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-
\text{k}][1,10,3,6]dioxadiazacyclononadecin-4-yl)carbonyl)amino)-2-vinylcyclopropanecarboxylic acid, or a pharmaceutically acceptable salt thereof.

25. A compound of claim 1 wherein the compound is

or a pharmaceutical acceptable salt thereof.
26. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 – 24, and a pharmaceutically acceptable carrier.

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

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

29. 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.

30. A use of a compound of any one of claims 1 – 24 for inhibiting HCV NS3 protease activity in a subject in need thereof.

31. 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.

32. A use of a compound of any one of claims 1 – 24 for preventing or treating infection by HCV in a subject in need thereof.

33. The use of claim 31, wherein said medicament further comprises at least one second therapeutic agent selected from the group consisting of HCV antiviral agent, an immunomodulator, and an anti-infective agent.
34. The use of claim 32 further comprising a use of at least one second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

35. The use of claim 33 or 34, wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.