Abstract: The present application describes macrocyclic compounds of formula (I) with NS3 protease inhibitory activity for treating hepatitis C virus infection.
MACROCYCLIC COMPOUNDS AS HCV NS3 PROTEASE INHIBITORS

Background

Chronic hepatitis C virus (HCV) infection is a major global health burden, with an estimated 170 million people infected worldwide and an additional 3 to 4 million infected each year (See e.g. World Health Organization Fact Sheet No. 164. October 2000). Although 25% of new infections are symptomatic, 60-80% of patients will develop chronic liver disease, of whom an estimated 20% will progress to cirrhosis with a 1-4% annual risk of developing hepatocellular carcinoma (See e.g. World Health Organization Guide on Hepatitis C. 2002; Pawlotsky, J-M. (2006) Therapy of Hepatitis C: From Empiricism to Eradication. Hepatology 43:S207-S220). Overall, HCV is responsible for 50-76% of all liver cancer cases and two thirds of all liver transplants in the developed world (See e.g. World Health Organization Guide on Viral Cancers. 2006). And ultimately, 5-7% of infected patients will die from the consequences of HCV infection (See e.g. World Health Organization Guide on Hepatitis C. 2002).

The current standard therapy for HCV infection is pegylated interferon alpha (IFN-α) in combination with ribavirin. However, only up to 50% of patients with genotype 1 virus can be successfully treated with this interferon-based therapy. Moreover, both interferon and ribavirin can induce significant adverse effects, ranging from flu-like symptoms (fever and fatigue), hematologic complications (leukopenia, thrombocytopenia), neuropsychiatric issues (depression, insomnia, irritability), weight loss, and autoimmune dysfunctions (hypothyroidism, diabetes) from treatment with interferon to significant hemolytic anemia from treatment with ribavirin. Therefore, more effective and better tolerated drugs are still greatly needed.


NS3, an approximately 70 kDa protein, has two distinct domains: a N-terminal serine protease domain of 180 amino acids (AA) and a C-terminal helicase/NTPase domain (AA 181 to 631). The NS3 protease is considered a member of the chymotrypsin family because
of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. The HCV NS3 serine protease is responsible for proteolytic cleavage of the polyprotein at the NS3/NS4A, NS4A/NS4B, NS4B/NS5A and NS5A/NS5B junctions (See e.g. Bartenschlager, R., L. et al. (1993) J. Virol. 67:3835-3844; Grakoui, A. et al. (1993) J. Virol. 67:2832-2843; Tomei, L. et al. (1993) J. Virol. 67:4017-4026). NS4A, an approximately 6 kDa protein of 54 AA, is a co-factor for the serine protease activity of NS3 (See e.g. Failla, C. et al. (1994) J. Virol. 68:3753-3760; Tanji, Y. et al. (1995) J. Virol. 69:1575-1581). Autocleavage of the NS3/NS4A junction by the NS3/NS4A serine protease occurs intramolecularly (i.e., cis) while the other cleavage sites are processed intermolecularly (i.e., trans). It has been demonstrated that HCV NS3 protease is essential for viral replication and thus represents an attractive target for antiviral chemotherapy.

**Summary of the Invention**

There remains a need for new treatments and therapies for HCV infection, as well as HCV-associated disorders. There is also a need for compounds useful in the treatment or prevention or amelioration of one or more symptoms of HCV, as well as a need for methods of treatment or prevention or amelioration of one or more symptoms of HCV. Furthermore, there is a need for methods for modulating the activity of HCV-serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

In one aspect, the invention provides compounds of the Formula I:

![Chemical Structure](image)

and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof;

wherein the macrocycle:
comprises between 15 to 40 ring atoms; m, x and z are each independently selected from 0 or 1;
p is selected at each occurrence from the group consisting of 0, 1 and 2;
Ri and Rj are independently selected, at each occurrence, from hydrogen or cyano, or
from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, alkoxy, and
cycloalkyloxy, each of which is unsubstituted or substituted with 1-6 moieties which can be
the same or different and are independently selected from the group consisting of hydroxy,
oxo, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino,
alkylsulfonyl, arylsulfonyl, alkylsulphonamido, arylsulphonamido, heteroarylsulphonamido,
aryl sulfonamido, heteroarylaminosulfonyl, mono and dialkylaminosulfonyl, carboxy,
carbalkoxy, amido, carboxamido, alkoxy carbonylamino, aminocarbonyloxy,
alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each of said
alkyl, arkoxy, and aryl can be unsubstituted or optionally independently substituted with one
or more moieties which can be the same or different and are independently selected from
alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl,
alylaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and
heteroaralkyl;

R3 is selected from the group consisting of H and C1-4-alkyl;
E is a divalent residue selected from the group consisting OfC(O)NR23, NR23S(CO)p,
NR23S(CO)NR23;

L1 and L2 are divalent residues independently selected from the group consisting of
C0-4alkylene, (CH2)m-FG-(CH2)n, (CH2)m, C3-7cycloalkylene-(CH2)n, (CH2)m-C3.
γ-cycloheteroalkylene-(CH2)n, alkenylene, alkynylene, arylene, heteroarylene, cycloalkylene
and heterocycloalkylene, each of which is substituted with 0 to 4 independently selected Xi
or Xj groups;
i and k are independently selected integers of from 0 to 7;
L3 is a C0-4alkylene or a divalent ethylene or acetylene residue, wherein the C0-
4alkylene and divalent ethylene residues are substituted by 0-2 substituents selected from
alkyl, aryl, heteroaryl, mono- or di-alkylamino-Co-C$_6$alkyl, hydroxyl alkyl or alkoxyalkyl;

FG is absent or a divalent residue selected from the group consisting of O, S(O)$_p$, NR$_{23}$, C(O), C(O)NR$_{23}$, NR$_{23}$C(O), OC(O)NR$_{23}$, NR$_{23}$C(O)NR$_{23}$, S(O)$_p$NR$_{23}$, NR$_{23}$S(O)$_p$, and NR$_{23}$S(O)$_p$NR$_{23}$.

R$_{23}$ is independently selected at each occurrence from hydrogen or the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heteroaralkyl, aralkyl and heteroaralkyl, each of which is substituted with 0-2 substituents independently selected from halogen, alkyl, alkoxy, and mono- and di-alkylamino; or

Two R$_{23}$ residues, taken in combination, form a monocyclic, bicyclic or tricyclic heterocyclic ring system which is saturated, partially unsaturated, or aromatic, and which is substituted with Oto 3 substituents independently selected from C$_1$-alkyl, C$_1$-alkoxy, C$_1$-alkoxyC$_1$-alkoxy, mono- and di-C$_1$-alkylaminoC$_1$-alkoxy, C$_1$-haloalkyl, C$_1$-haloalkoxy, mono- and di-C$_1$-alkylamino, halogen, 4 to 7 member heterocycloalkyl, aryl, heteroaryl, and 3 to 6 member spirocycloalkyl or spiroheterocycloalkyl, each of which is substituted with O to 3 substituents independently selected from the group consisting of C$_1$-alkyl, Q$_1$-alkoxy, hydroxy, amino, and mono- and di-C$_1$-alkylamino;

R$_3$ is absent or selected from hydrogen, Q$_1$-alkyl, C$_3$-cycloalkyl-Co-C$_4$-alkyl, or hydroxy;

R$_7$, R$_{10}$, R$_n$, R$_{12}$, R$_{13}$, R$_{15}$, R$_{16}$, R$_{17}$, and R$_{22}$ are each, independently, hydrogen or selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, aralkyloxy and heterocyclylamino; each of which may be further substituted 0 to 5 times with substituents independently selected from X$_i$ and X$_2$;

X$_i$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein X$_i$ can be independently substituted with one or more of X$_2$ moieties which can be the same or different and are independently selected;

X$_2$ is hydroxy, oxo, alkyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, thio, alkythio, arythio, heteroarythio, amino, alkylamino, arylamino, heteroarylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfonamido, arylsulfonamido, heteroarylsulfonamido, arylaminosulfonyl, heteroarylaminosulfonyl, mono and dialkylaminosulfonyl, carboxy, carbalkoxy, amid, carboxamido, alkoxy carbonylamino,
aminocarbonyloxy, alkoxycarbonyloxy, carbamoyl, ureido, alkylureido, arylureido, halogen, 
cyano, or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or 
optionally independently substituted with one or more moieties which can be the same or 
different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, 
cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkyllaryl, aralkyl, arylheteroaryl, heteroaryl, 
heterocyclylamino, alkylheteroaryl and heteroaralkyl;

\[ Z_1 = C_{O_{2}} \text{alkylene, oxygen or NR}_{1_{0}}; \]
\[ Z_2 = CR_{p}, O \text{ or } N; \]
\[ R_{14} = C(O) \text{ or } S(O)_{p}; \]

10 \( V \) is selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, 
heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkylalkoxy, 
alkyl-aryloxy, arylxy, heteroarylxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, 
arylamino, alkyl-arylamino, arylamino, heteroarylaminino, cycloalkylamino, 
carboxyalkylamino, mono- and di-alkylcarboxamide, aralkyloxy and heterocyclylamino; each 
of which may be further independently substituted one or more times with \( X^{1} \) and \( X^{2}; \)

wherein \( X^{1} \) is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, 
 heterocyclylalkyl, aryl, alkyllaryl, aralkyl, arylxy, arylthio, arylheteroaryl, heteroaryl, 
heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein \( X^{1} \) can be independently 
substituted with one or more \( X^{2} \) moieties which can be the same or different and are 

independently selected; wherein \( X^{2} \) is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl, 
heterocycloalkyl, aryl, heteroaryl, alkoxy, arylxy, thio, alkylthio, amino, mono- and di- 
al-klylaminino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, 
carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyl, 
alcoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each \( X^{2} \)

residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently 
substituted with one or more moieties which can be the same or different and are 
independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, 
heterocyclyl, heterocyclylalkyl, aryl, alkyllaryl, aralkyl, arylheteroaryl, heteroaryl, 
heterocyclylamino, alkylheteroaryl and heteroaralkyl;

30 or \( V \) is selected from the group consisting of \( -Q^{1}Q^{2} \), wherein \( Q^{1} \) is absent, \( C(O), \) 
\( S(O)_{2}, N(H), N(C_{4}-4-alkyl), C=N(CN), C=N(SO_{2}CH_{2}), C=N-COH-C_{M}-alkyl, \) or \( C=N-COH, \) 
and \( Q^{2} \) is hydrogen or is selected from the group consisting of \( C{i}^{n}-alkyl, O-C{i}_{4}-alkyl, NH_{2}, \) 
\( N(H)-C_{14}-alkyl, N(C_{14}-alkyl)_{2}, SO_{2}-aryl, SO_{2}-heteroaryl, SO_{2}-C{i}_{4}-alkyl, C_{3-6}-cycloalkyl-C_{0-} \) 
\( 4-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one
or more times with a halogen atom, Ci-4-alkyl, Ci-4-alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl;

or R_2 and R_{16} may together form a 3, 4, 5, 6 or 7-membered ring and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or R_7 and R_{15} may together form a 3, 4, 5, 6 or 7-membered ring and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or R_{15} and R_{16} may together form a 4, 5, 6 or 7-membered ring and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or R_{15} and R_{16} may together form an arylene or heteroarylene ring and R_{8} and R_{22} are absent, wherein the ring may be further substituted one or more times;

or Ri and R_{2} may together form a 3, 4, 5, 6 or 7-membered ring that is saturated or partially unsaturated and may contain one or more heteroatoms, which ring is substituted with 0-3 residues independently selected from C^alkyl, Ci^alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, halogen, hydroxy, C_{3-6}cycloalkyl and C_{3-6}spirocycloalkyl;

or R_{17} and R_{16} may together form a 4, 5, 16, 7 or 8-membered ring of the formula:

![Ring Structure](image)

wherein

n and g are each, independently, 0, 1 or 2;

X is O, S, N, C or CR_{5a};

R_{4} is hydrogen or is selected from the group consisting of Ci_{6-}alkyl, C_{3-7}-cycloalkyl, aryl, heterocycle and heteroaryl, all of which may be independently substituted one or more times with a halogen atom or Ci_{4-}alkyl;

R_{5} is absent, hydrogen or oxo or is selected from the group consisting of hydroxyl, Ci_{8-}alkyl, Ci_{2-8}-alkenyl, Ci_{2-8}-alkynyl, C_{3-8}cycloalkyl-C_{5-4}-alkyl, aryl-C_{0-4}-alkyl, heterocycle-Co_{4-}alkyl, heteroaryl-Co_{4-}alkyl, C_{3-8}-cycloalkyloxy, arloxy, NR_{23}COR_{23}, CONR_{23}R_{23}, NR_{23}CONHR_{23}, OCONR_{23}R_{23}, NR_{23}COOR_{23}, OCOR_{23}, COOR_{23}, aryl-C(O)O, aryl-C(O)NR_{23}, heteroaryloxy, heteroaryl-C(O)O, heterocycle-C(O)O, heteroaryl-C(O)NR_{23}, heterocycle-C(O)NR_{23}, each of which may be independently substituted one or more times (or more preferably 0, 1, 2, 3, 4 or 5 times) with halogen, Ci_{1-4}-alkyl, Ci_{4-}alkoxy, 1 haloCi_{4-}
alkyl, haloCi-4-alkoxy, amino, mono- and di-C_{1,4}alkylaminoCo^alkyl, mono- and di-C_{1,4}alkylaminoCo^alkyl, C_{3,7}cycloalkyl, fused- or spiro-cyclic 3-7 membered ring, heterocycleC_{0,4}alkoxy, heterocycleCo^alkyl, aryl, or heteroaryl;

R_{5a} is selected from the group consisting of H, hydroxyl, Ci_{8}-alkyl, C_{2,8}-alkenyl, C_{2,8}-alkynyl, C_{3,8}-cycloalkylC_{0,4}-alkyl, aryl-C_{0,4}-alkyl and heteroaryl-Co^alkyl,

or R_{4} and R_{5} may together form a fused dimethyl cyclopentyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, heteroaryl, trihalomethyl, Ci_{4}-alkoxy or C_{1,4}-alkyl;

or R_{5} and R_{5a} may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, Ci_{8}-alkyl, C_{2,8}-alkenyl, C_{2,8}-alkynyl, Ci-s-alkoxy-Co^alkyl, Ci-g-haloalkyl, C_{2,8}-haloalkenyl, C_{2,8}-haloalkynyl, Ci_{8}-haloalkoxy, C_{1,8}-alkylthio, Q.g-alkylsulfonyl, Ci_{8}-alkylsulfoxyl, Ci_{8}-alkanoyl, C_{1,8}-alkoxy carbonyl, C_{3,7}-cycloalkylC_{0,4}-alkyl, aryl-Co_{4}-alkyl, heteroaryl-Co_{4}-alkyl, COOH, C(O)NH_{2}, mono- and di-C_{4}-alkyl-carboxamide, mono- and di-C_{1,4}-alkyl-amino-Co_{4}-alkyl, SO_{2}H, SO_{2}NH_{2}, and mono-and di-Ci_{4}-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, Ci_{8}-alkyl, C_{2,8}-alkenyl, C_{2,8}-alkynyl, Ci_{8}-alkoxy-Co_{4}-alkyl, Ci_{1,8}-haloalkyl, C_{2,8}-haloalkenyl, C_{2,8}-haloalkynyl, Ci_{8}-haloalkoxy, d-g-alkylthio, Ci_{8}-alkylsulfonyl, Ci_{8}-alkylsulfoxyl, Ci_{8}-alkanoyl, Ci-s-alkoxy carbonyl, C_{3,7}-cycloalkyl-Co^alkyl, aryl-C_{0,4}-alkyl, heteroaryl-C_{0,4}-alkyl, COOH, C(O)NH_{2}, mono- and di-C_{1,4}-alkyl-carboxamide, mono- and di-Ci_{1,4}-alkyl-amino-Co_{4}alkyl, SO_{2}H, SO_{2}NH_{2}, and mono-and di-Ci_{4}-alkylsulfonamide; and

R_{6} is independently selected at each occurrence from the group consisting of hydrogen, hydroxyl, amino, C_{1,4}alkyl, C_{1,4}alkoxy, and mono- and di-C_{1,4}alkylamino, and C_{3,6}cycloalkylCo_{4,alkyl};

or two R_{6} residues may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, Ci_{8}-alkyl, C_{2,8}-alkenyl, C_{2,8}-alkynyl, Ci_{8}-alkoxy-Co_{4,alkyl}, Ci-g-haloalkyl, C_{2,8}-haloalkenyl, C_{2,8}-haloalkynyl, Ci_{8}-haloalkoxy, Ci_{8}-alkylthio, Ci_{8}-alkylsulfonyl, Qi-g-alkylsulfoxyl, Ci_{8}-alkanoyl, C_{1,8}-alkoxy carbonyl, C_{3,7}-cycloalkyl-Co_{4}-alkyl, aryl-C_{0,4}-alkyl, heteroaryl-C_{0,4}-alkyl, COOH, C(O)NH_{2}, mono- and di-C_{4}-alkyl-amino-Co^alkyl, mono- and di-Ci_{4}-alkyl-amino-Co^alkyl,
SO₃H, SO₂NH₂, and mono-and di-C₁₋₄-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, mono- and di-C₁₋₄-alkylamino, mono- and di-C¹₋₄-alkyl-carboxamide, C₁⁻⁴-alkoxycarbonyl, and phenyl.

In one embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, such that the HCV-associated disorder is treated.

In another embodiment, the invention provides a method of treating an HIV infection comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention.

In still another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention. In one embodiment, the compounds of the invention inhibit the activity of the NS2 protease, the NS3 protease, the NS3 helicase, the NS5a protein, and/or the NS5b polymerase. In another embodiment, the interaction between the NS3 protease and NS4A cofactor is disrupted. In yet another embodiment, the compounds of the invention prevent or alter the severing of one or more of the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions of the HCV. In another embodiment, the invention provides a method of inhibiting the activity of a serine protease, comprising the step of contacting said serine protease with a compound of the invention. In another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention, wherein the compound interacts with any target in the HCV life cycle. In one embodiment, the target of the HCV life cycle is selected from the group consisting of NS2 protease, NS3 protease, NS3 helicase, NS5a protein and NS5b polymerase.

In another embodiment, the invention provides a method of decreasing the HCV RNA load in a subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In another embodiment, the compounds of the invention exhibit HCV protease activity. In one embodiment, the compounds are an HCV NS3-4A protease inhibitor.

In another embodiment, the invention provides a method of treating an HCV-associated disorder in a subject, comprising administering to a subject in need thereof a
pharmaceutically acceptable amount of a compound of the invention, and a pharmaceutically acceptable carrier, such that the HCV-associated disorder is treated.

In another embodiment, the invention provides a method of treating an HCV-associated disorder in a subject wherein the subject is suffering from or susceptible to a viral infection which is resistant to one or more anti-viral therapies, the method comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, and a pharmaceutically acceptable carrier, such that the drug-resistant HCV-associated disorder is treated.

In still another embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of a compound of the invention, in combination with a pharmaceutically effective amount of an additional HCV-modulating compound, such as interferon or derivatized interferon, or a cytochrome P450 monooxygenase inhibitor, such that the HCV-associated disorder is treated. In one embodiment, the additional HCV-modulating compound is selected from the group consisting of ITMN191, Sch 503034 and VX-950.

In another embodiment, the invention provides a method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell with a compound of the invention.

In yet another embodiment, the invention provides a packaged HCV-associated disorder treatment, comprising an HCV-modulating compound of the invention, packaged with instructions for using an effective amount of the HCV-modulating compound to treat an HCV-associated disorder.

In certain embodiments, the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

In another embodiment, the invention provides a method of treating HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and/or a suppressed innate intracellular immune response in subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In one embodiment, the HCV to be treated is selected of any HCV genotype. In another embodiment, the HCV is selected from HCV genotype 1, 2 and/or 3.

**Detailed Description of the Invention**

This invention is directed to compounds, e.g., peptide compounds, and intermediates
thereto, as well as pharmaceutical compositions containing the compounds for use in
treatment of HCV infection. This invention is also directed to the compounds of the
invention or compositions thereof as protease inhibitors, particularly as serine protease
inhibitors, and more particularly as HCV NS3 protease inhibitors. The compounds are
particularly useful in interfering with the life cycle of the hepatitis C virus and in treating or
preventing an HCV infection or physiological conditions associated therewith. The present
invention is also directed to methods of combination therapy for inhibiting HCV replication
in cells, or for treating or preventing an HCV infection in patients using the compounds of the
invention or pharmaceutical compositions, or kits thereof.

In one aspect, the compounds of the invention are compounds of Formula I, in which
R₁ and R₂ taken in combination form a 3, 4, 5, or 6-membered saturated carbocyclic ring
which is substituted with 0-2 substituents independently selected from halogen, alkyl,
alkenyl, alkoxy and C₃₋₄ cycloalkyl. In other aspects, compounds of the invention are
compounds of Formula I, in which R₁ and R₂ taken in combination form a cyclopropyl ring.

In certain compounds of Formula I include those compounds in which R₁ and R₂ are taken in
combination to form a cyclopropyl ring substituted with 0-2 substituents independently
selected from halogen, alkyl, alkenyl, and alkoxy or substituted with 0 to 2 Ci-C₄ alkyl
residues. Still other compounds of Formula I include those in which R₁ and R₂ are taken in
combination to form a cyclopropyl ring which is substituted with 0 or 1 substituents selected
Ci₃₋₄ alkyl, vinyl or cyclopropyl; and E is C(O)NH, NHS(O)₂, NH₂SO₂N(Me), NH₂SO₂N(Et) or
NH₂SO₂N(cyclopropyl).

In another aspect, the compounds of the invention are compounds of any one of
Formulae I, in which R₁ is H or Ci₄ alkyl; and R₂ is H, Ci-C₄ alkyl, Ci-C₄ fluoroalkyl, C₂₋₄
alkenyl, or C₃₋₄ cycloalkylCiₓ₋ₓ alkyl.

Certain other compounds of Formula I comprise a macrocycle having between 15 and
40 ring atoms, between 15 and 35, 15 and 30 or 15 and 25 ring atoms, or between 17 and 23
ring atoms. Certain compounds of Formula I comprise a macrocycle having 15, 16, 17, 18,
19, 20, 21, 22, 23, 24, or 25 ring atoms. In certain instances, compounds of Formula I
comprise a macrocycle having 16, 17, 18, 19, 20, 21, 22, or 23 ring atoms.

Certain other compounds of Formula I comprise a macrocycle selected from the group
consisting of macrocycles of the formulae:
In certain compounds of Formula I, L₁ is Ci-C₆alkylene, C₃-C₇cycloalkylene, arylene or heteroarylene, each of which is substituted by 0-4 residues independently selected from Ci-C₄alkyl, Ci-C₄alkoxy, hydroxyl, amino, mono- and di- Ci-C₄alkylamino, halogen, cyano, Ci-C₄fluoroalkyl, Ci-C₄fluoroalkoxy, COOH, carboxamide (CONH₂), mono- and di-Cr C₄alkylcarboxamide, aryl, heteroaryl and 5 or 6 membered saturated heterocycles;

L₂ is selected from Ci-C₆alkylene and C₂-C₆alkenylene, each of which is substituted by 0-4 residues independently selected from Ci-C₄alkyl, Ci-C₄alkoxy, hydroxyl, amino, mono- and di- Ci-C₄alkylamino, halogen, cyano, Ci-C₄fluoroalkyl, Ci-C₄fluoroalkoxy, Q^fluoroalkoxy, COOH, carboxamide (CONH₂), mono- and di-Q^alkylcarboxamide, aryl, heteroaryl and 5 or 6 membered saturated heterocycles; and

L₃ is absent or a divalent ethylene residue which is substituted by Oto 2 independently selected methyl or ethyl residues.

In yet other compounds of Formula I, Li is a divalent residue selected from C₂-C₄alkylene, 1,2-phenylene, 1,3-phenylene, 2,4-pyridylene, 2,3-pyridylene, 3,4-pyridylene or 1,7-indolylenne, 2,7-indolylenne, each of which is substituted with 0-3 residues selected from C₁-C₄alkyl, Ci-C₄alkoxy, hydroxyl, amino, mono- and di- Ci-C₄alkylamino, halogen, cyano, Ci-C₂fluoroalkyl, Ci-C₂fluoroalkoxy, COOH, carboxamide (CONH₂), and mono- and di-Ci-C₄alkylcarboxamide.

In certain compounds of Formula I, L₁ is C₃-C₇cycloalkylene, arylene or heteroarylene which is substituted by 0-4 residues independently selected from Ci-C₄alkyl, Ci-C₄alkoxy, hydroxyl, amino, mono- and di- Ci-C₄alkylamino, halogen, cyano, Ci-
C₄fluoroalkyl, Ci-Qfluoroalkoxy, COOH, carboxamide (CONH₂), mono- and di-Ci-
C₄alkylcarboxamide, aryl, heteroaryl and 5 or 6 membered saturated heterocycles;

L₂ is selected from Ci-C₆alkylene and C₂-C₆alkenylene, each of which is substituted by 0-4 residues independently selected from Ci-C₄alkyl, Ci-C₄alkoxy, hydroxyl, amino,
mono- and di- Ci-C₄alkylamino, halogen, cyano, Ci-C₄fluoroalkyl, Ci-C₂ fluoroalkoxy, COOH, carboxamide (CONH₂), mono- and di-Ci-C₄ alkylcarboxamide, aryl, heteroaryl and 5 or 6 membered saturated heterocycles; and

L₃ is absent or a divalent ethylene residue which is substituted by O to 2 independently selected methyl or ethyl residues.

In yet other compounds of Formula I, Li is a divalent residue selected from 1,2-
phenylene, 1,3-phenylene, 2,4-pyridylene, 2,3-pyridylene, 3,4-pyridylene or 1,7-indolylene, 2,7-indolylene, each of which is substituted with 0-3 residues selected from Ci-C₄alkyl, Ci-
C₄alkoxy, hydroxyl, amino, mono- and di- Ci-C₄alkylamino, halogen, cyano, Ci-
C₂fluoroalkyl, Ci-C₂fluoroalkoxy, COOH, carboxamide (CONH₂), and mono- and di-Ci-
C₄alkylcarboxamide.

Certain compounds of Formula I include compounds of Formula II:

and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof.

Yet other compounds of the invention according to Formula II include those
compounds in which:

x is O or 1;
n is O or 1;
R₁₄ is C(O) or S(O)₉;
Z₁ is absent or NH;
$Z_2$ is nitrogen or CH;

$R_1$ is selected from the group consisting of H and Ci-4-alkyl;

$R_2$ is selected from the group consisting of Ci^-alkyl, C(O)C_1-4-alkyl, C(O)OCi_4-alkyl, and (CH_2)_0-4-C_3-6-cycloalkyl;

or $R_1$ and $R_2$ together form a cyclopropane ring;

$R_3$ is selected from the group consisting of H and Ci^-alkyl;

$X$ is O, NR_5 or CR_5R_5a;

$R_4$ is hydrogen or is selected from the group consisting of C^-alkyl, C_3-6-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times with a halogen atom or C_1-4-alkyl;

$R_5$ is hydrogen or oxo or is selected from the group consisting of hydroxyl, Ci-8-alkyl, C_2-8-alkenyl, C_2-8-alkynyl, C_3-8-cycloalkyl-Co^-alkyl, aryl-Co^-alkyl, aryloxy, heteroaryloxy, heterocycle-Co^-alkyl and heteroaryl-Co^-aUcor, each of which may be independently substituted one or more times with a halogen atom, aryl, heteroaryl, trihalomethyl, C_1-4-alkoxy or C_1^-alkyl;

$R_5a$ is selected from the group consisting of H, hydroxyl, Ci-g-alkyl, C_2-g-alkenyl, C_2-8^-alkynyl, C_3-8-cycloalkyl-Co^-alkyl, aryl-Co^-alkyl and heteroaryl-Co^-alkyl,

or $R_4$ and $R_5$ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be

substituted with a halogen atom, aryl, heteroaryl, trihalomethyl, Ci^-alkoxy or Ci^-alkyl;

or $R_4$ and $R_5a$ may together form a spirocarbocyclic saturated ring having between 3 and 6 carbon ring atoms which is optionally substituted by 0-2 substituents selected from halogen, Ci^-alkyl, C_2^-alkenyl, C_2-6^-alkynyl, Ci^-alkoxide, C_3-7^-cycloalkyl-Co^-alkyl, phenyl-Co^-alkyl, naphthyl-Co^-alkyl, heteroaryl-Co^-alkyl, or two substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or Ci^-alkyl groups;

$R_{10}$ and $R_{11}$ are each, independently, selected from the group consisting of H and Ci^-alkyl;

$R_6$ and $R_{13}$ is H;

$R_{12}$ is selected from the group consisting of H, Ci-4-alkyl and C_3-6^-cycloalkyl; and

$V$ is selected from the group consisting of Q^-Q, wherein Q is absent, C(O), N(H), N(Ci^-alkyl), C-N(CN), C=N(SO_2CH_3), or C=N-COH, and Q is H, Ci-4-alkyl, C=N-COH-C_1-4^-alkyl, d^-alkoxy, C_3-7^-cycloalkyloxy, heterocycloalkyloxy, NH_2, N(H)-Ci^-alkyl, N(Ci^-alkyl)_2, SO_2-aryl, SO_2-Ci^-alkyl, C_3-6^-cycloalkyl-Co^-alkyl, aryl, heteroaryl and heterocycle,
each of which may be independently substituted one or more times with a halogen atom, C\textsubscript{i,4}-alkyl, C\textsuperscript{\^}{alkoxy}, C\textsubscript{2,4}-alkenyl, C\textsubscript{2,4}-alkynyl, C\textsuperscript{\^}{alkyl} substituted by one or more halogen atoms, or C\textsubscript{3,6}-cycloalkyl;

or when \(x\) is 0, \(R_i\) and \(V\) can form a cyclopropyl ring that may be further substituted by an amide group.

Still other compounds of the invention according to Formula II include those compounds in which \(X\) is \(C_{R_5}R_{5a}\), \(R_4\) is H, and \(R_5\) and \(R_{5a}\) taken in combination form a 3 to 6 member spirocyclic carbocycle substituted with 0-2 substituents selected from halogen, C\textsubscript{i,6}-alkyl, C\textsubscript{2,6}-alkenyl, C\textsubscript{2,6}-alkynyl, C\textsubscript{i,6}-alkoxide, C\textsubscript{3,7}-cycloalkyl-C\textsubscript{0,4}-alkyl, phenyl-C\textsubscript{0,4}-alkyl, naphthyl-C\textsubscript{0,4}-alkyl, heteroaryl-C\textsubscript{0,4}-alkyl, or two substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or C\textsuperscript{\^}{alkyl} groups.

Yet other compounds of the invention according to Formula II include compounds according to Formula Ia:

\[
\begin{align*}
\text{Z}_2 & \text{ is nitrogen or CH;} \\
\text{k}_i \text{ and } \text{k}_2 & \text{ are 0 or 1 such that a sum of } \text{k}_i \text{ and } \text{k}_2 \text{ equals 1 or 2;} \\
\text{R}_a & \text{ is hydrogen, C\textsuperscript{\^}{alkyl}, or phenyl;} \\
\text{R}_b & \text{ is hydrogen, C\textsubscript{1,4}-alkyl, C\textsubscript{1,4}-alkoxy-C\textsubscript{0,4}-alkyl, mono- and di-C\textsubscript{1,4}-alkylaminoC\textsubscript{0,4}-alkyl, mono- and di-C\textsubscript{1,4}-alkyl carbamamide, C\textsubscript{1,4}-alkanoyl, C\textsubscript{1,4}-alkoxy carbonyl, or phenyl} \\
\text{or } \text{R}_a \text{ and } \text{R}_b & \text{ taken together form a fused or spirocyclic 3 to 6 membered ring having 0, 1 or 2}
\end{align*}
\]
ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C𝑖-alkyl, C𝑖-alkoxy, Q,
alcanoyl, and phenyl; and

\( R_c \) represents 0 to 4 substituents which are independently selected at each occurrence of \( R_c \) from the group consisting of halogen, C1-4 alkyl, and phenyl, or two geminal \( R_c \) substituents, taken in combination form a 3 to 6 member spirocyclic ring.

Certain compounds of the invention according to Formula Ha include those compounds in which the divalent residue:

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R}_c \\
\text{k}_1 \text{k}_2 \\
\text{R}_a \text{R}_b \\
\end{array}
\]

is selected from the group consisting of:

\[
\begin{array}{c}
\text{O}, \\
\text{O}, \\
\text{O}, \\
\text{O}, \\
\text{O}, \\
\text{O}, \\
\text{O}, \\
\text{O}, \\
\text{O}, \\
\text{O}, \\
\end{array}
\]
Yet other compounds of the invention according to Formula II include those compounds in which: $X$ is $CRsR_{5a}$; and

$R_5$ and $R_{5a}$, taken in combination, form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which spirocyclic ring is substituted with a spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, and wherein each of the spirocyclic rings has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{i-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{i-8}$-alkoxy-$C_{i-4}$-alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, d-g-haloalkoxy, $C_{i-8}$-alkyl, $C_{2-8}$-alkenyl, and $C_{2-8}$-alkynyl, and wherein each of the spirocyclic rings has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{i-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{i-8}$-alkoxy-$C_{i-4}$-alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, d-g-haloalkoxy.
g'-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-
cycloalkyl-Co^g-alkyl, aryl-C_0-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, C(O)NH_2, mono- and di-
Ci-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-Co-alkyl, SO_3H, SO_2NH_2, and
mono-and di-Ci-alkylsulfonamide.

Certain other compounds according to Formula I or Formula II include those
compounds in which X is CR_5R_{5a} wherein R_{5a} is hydrogen, methyl or trifluoromethyl; and R_5
is a residue of the formula:

\[
\begin{align*}
Z_5 & \quad Z_4 & \quad Z_6 & \quad Z_7 \quad R_8 & \quad R_{8a} & \quad N & \quad CO
\end{align*}
\]

wherein

n and g are integers independently selected from 0, 1, or 2 (preferably n+g = 1, 2, 3 or
4; or more preferably n+g is 2 or 3);

Z_3 is NR_23 or O;

Z_4, Z_5, Z_6, and Z_7 are each independently selected from the group consisting of N, CH, and
CR_8; and

R_8 and R_{8a} each independently represent Oto 2 groups, each of which is independently
selected at each occurrence of R_8 and R_{8a} from the group consisting of hydrogen, halogen, C_1-
4-alkyl, C_{1-4}-alkoxy, haloC_{1-4}-alkyl, haloC_{1-4}-alkoxy, amino, mono- and di-C_{1-4}alkylaminoC_0-
4-alkyl, mono- and di-C_{1-4}alkylaminoC_0-alkoxy, heterocycleC_{0-4}alkoxy, heterocycleC_0-
4-alkylamino and heterocycleCo^alkyl; or
two R_{8a}, taken in combination, form a fused- or spiro-cyclic 3-7 membered ring.

Yet other compounds of Formula I or Formula II include those compounds in which
X is CR_{5a}, R_{5a} is hydrogen or methyl, and R_5 is a residue selected from the group consisting of:

\[
\begin{align*}
R_8 & \quad \text{O} & \quad \text{O} & \quad \text{N} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
R_8 & \quad \text{O} & \quad \text{O} & \quad \text{N} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
R_8 & \quad \text{O} & \quad \text{O} & \quad \text{N} & \quad \text{O} & \quad \text{O} & \quad \text{O}
\end{align*}
\]
wherein $R_8$ is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.
In still other compounds of Formula I or Formula II include those compounds in which the residue is a residue of the formula:

wherein $R_6$ is hydrogen, methyl, ethyl, and mono-, di-, and tri-fluoromethyl;

$R_8$ is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.

Still other compounds of Formula I or Formula II include those compounds in which $X$ is $CR_{5a}$, $R_{5a}$ is hydrogen or methyl, and $R_5$ is a residue selected from the group consisting of:
Still other compounds of the invention according to Formula II include compounds according to Formula lib:
$Z_2$ is nitrogen or CH;

$k_1$ and $k_2$ are 0 or 1 such that a sum of $k_1$ and $k_2$ equals 1 or 2;

$R_a$ and $R_b$ taken together form a spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring

heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2

independently selected substituents selected from halogen, $C_i^=alkyl$, $C^=alkoxy$, $C_i^=alkanoyl$, and phenyl;

$R_c$ represents 0 to 2 substituents which are independently selected at each occurrence of $R_0$

from the group consisting of halogen, $C_i^=alkyl$, and phenyl, or two geminal $R_c$ substituents,

taken in combination form a 3 to 6 member spirocyclic ring;

$R_4$ represents 0, 1, or 2 substituents each of which is independently selected from H and $C_{14}^-alkyl$; and

$R_6$ is hydrogen or $C_{14}^-alkyl$.

In certain compounds of the invention according to Formula lib, the divalent residue:
is selected from the group consisting of:

Certain compounds of Formula II, include those compounds, in which the ring is a divalent residue derived from a proline residue selected from the group consisting of:
Certain other compounds of Formula II, Formula Ha or Formula lib include compounds in which $X$ is $CR_{5}R_{5a}$. $R_{4}$ is $H$, and $R_{5}$ and $R_{5a}$ taken in combination form a 3 to 6 member spirocyclic carbocycle substituted with 0-2 substituents selected from halogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{1-6}$-alkoxide, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, phenyl-$Co_{4}$-alkyl, naphthyl-$Co_{4}$-alkyl, heteroaryl-$Co_{4}$-alkyl, or two substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or $Q_{1-6}$-alkyl groups.

Certain compounds of Formulae I include compounds of Formula III:

\[
\begin{align*}
\text{III} & \\
\end{align*}
\]

and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof.

Certain compounds of the invention according to Formula III include compounds in which:

$Z_{i}$ is absent or $NR_{4}$.
Z₂ is nitrogen or CH;
R₃ is selected from the group consisting of H, Ci-4-alkyl, and C₃-6-cycloalkylCo-C₄alkyl;
Rₙ, R₁₅ and R₁₄ are selected from the group consisting of H, alkyl-aryl, Ci^-alkyl, O-
Ci-4-alkyl, N(H)-C M^-alkyl, and C₃-6-cycloalkylCo-C₄alkyl;
R₉ and R₁₇ are each, independently, selected from the group consisting of H, Ci-4-
alkyl and (CH₂)₀-₄-C₃-6-cycloalkyl; or
R₁₅ and R₁₄ may together form a 3, 4, 5, 6 or 7-membered ring that may comprise
between 0 to 3 additional heteroatoms, wherein the ring may be further substituted with 0-5
substituents; or
R₆ and R₁₄ may together form a 3, 4, 5, 6 or 7-membered ring that may comprise
between 0 to 3 additional heteroatoms, wherein the ring may be further substituted with 0-5
substituents; and
V is selected from the group consisting of -Q¹-Q², wherein Q¹ is absent, C(O), N(H),
N(C₁-₄-alkyl), C=N(CN), C=N(SO₂₂CH₃), or C=N-COH, and Q² is H, C₁-₄-alkyl, C=N-COH-
Ci-4-alkyl, O-C₁-₄-alkyl, NH₂, N(H)-C₁-₄-alkyl, N(C₁-₄-alkyl)₂, SO₂-aryl, SO₂-C₁-₄-alkyl, C₃-6-
cycloalkyl-Co₄-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently
substituted one or more times with a halogen atom, Ci-4-alkyl, C₁-₄alkoxy, C₂-C₄alkenyloxy,
C₂-C₄alkynloxy, Ci-4-alkyl substituted by one or more halogen atoms, or C₃-6-cycloalkyl;
Certain other compounds of the invention according to Formula III include
compounds in which:
R₃ is selected from the group consisting of H and Ci-4-alkyl;
R₁₅ is H;
R₉, R₁₀ and Rₙ are each, independently, selected from the group consisting of H, Ci-4-
alkyl, and C₃-₇cycloalkylCo₄-alkyl;
R₁₄ is selected from the group consisting of H, Ci-4-alkyl and (CH₂)₀-₄-C₃-6-cycloalkyl; and
V is selected from the group consisting of-Q¹-Q², wherein Q¹ is absent, C(O), N(H),
N(Ci-₄-alkyl), C=N(CN), C=N(SO₂₂CH₃), or C=N-COH, and Q² is H, C M^-alkyl, C=N-COH-
d-4-alkyl, O-C₁-₄-alkyl, NH₂, N(H)-C^-alkyl, N(C₁-₄-alkyl)₂, SO₂-aryl, SO₂-C₁-₄-alkyl, C₃-6-
cycloalkyl-Co-₄-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently
substituted one or more times with a halogen atom, C₁-₄-alkyl, Ci^-alkyl substituted by one or
more halogen atoms, C^-alkoxy, C₂-C₄alkenyloxy, C₂-C₄alkynloxy, or C^-e-cycloalkyl.
Certain compounds of Formula III include compounds represented by Formula Ilia:
and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof;

wherein

$Z_2$ is nitrogen or CH;

$R_{25}$ and $R_{26}$ are each, independently, selected from the group consisting of H, C$_1$-$4$-alkyl, O-$Q$-$alkyl$, N($R_{24}$)$_2$, C$_3$-$6$-cycloalkylCo-C$_4$-alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, wherein each $R_{24}$ is independently selected from the group consisting of H, halogen, hydroxy, COOH, amino, carboxamide, substituted or unsubstituted-$d$-$4$-alkyl, substituted or unsubstituted C$_3$-$6$-cycloalkylCo-C$_4$-alkyl, substituted or unsubstituted-Ci-$d$-$4$-alkoxy, substituted or unsubstituted C-$^cycloalkylCo^alkyl$-oxy-, substituted or unsubstituted arylCo-C$_0$-$4$-alkyl, substituted or unsubstituted heterocycleCo-C$_4$-alkyl, substituted or unsubstituted arylCo-C$_4$alkyl-oxy and substituted or unsubstituted heterocycleCo-C$_4$-alkyl-oxy;

or $R_{22}$ or $R_{26}$ may together form a 3-membered ring that is substituted or unsubstituted.

In another embodiment of Formula IIia, $R_{25}$ is H and $R_{26}$ is amine, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl.

Certain other compounds of Formula III include compounds represented by Formula

$H_{lb}$:
and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof;

wherein

\[ Z_2 \text{ is nitrogen or CH; } \]

\[ R_{27} \text{ and } R_{28} \text{ are each, independently, selected from the group consisting of H, C}_{1-4}^{-}\text{alkyl, O-C}_{1-4}^{-}\text{alkyl, N(R}_{24})_2, C_{3-6}^{-}\text{cycloalkylCo-C}_{4}^{-}\text{alkyl, substituted or unsubstituted aryl, substituted or unsubstituted O-aryl and substituted or unsubstituted heterocycle, wherein } R_{24} \text{ is independently selected at each occurrence from the group consisting of H, halogen, hydroxy, COOH, amino, carboxamide, substituted or unsubstituted-C}_{1-4}^{-}\text{alkyl, substituted or unsubstituted C}_{3-6}^{-}\text{cycloalkylCo-C}_{4}^{-}\text{alkyl, substituted or unsubstituted-C}_{1-4}^{-}\text{alkoxy, substituted or unsubstituted C}_{3-6}^{-}\text{cycloalkylCo-C}_{4}^{-}\text{alkyl-oxo-, substituted or unsubstituted arylCo-C}_{4}^{-}\text{alkyl, substituted or unsubstituted heterocycleCo-C}_{4}^{-}\text{alkyl, substituted or unsubstituted arylCo-C}_{4}^{-}\text{alkyl-oxo and substituted or unsubstituted heterocycleC}_{0-4}^{-}\text{alkyl-oxo.} \]

In one embodiment of Formula IIIb, \( R_{28} \) is quinoline, \( C_{1-4}^{-}\text{alkyl, O-C}_{1-4}^{-}\text{alkyl, or O-quinoline, wherein the quinoline and O-quinoline substituents may be independently substituted one or more times (or preferably between one and five times) with halogen, amino, O-C}_{1-4}^{-}\text{-alkyl, substituted or unsubstituted-C}_{1-4}^{-}\text{-alkyl, substituted or unsubstituted-(CH}_{2})_{0-4}^{-}\text{-C}_{3-6}^{-}\text{-cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted O-aryl, and substituted or unsubstituted heterocycle.} \]

Yet other compounds of Formula III include compounds represented by Formula IIIc:
and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof;

wherein

5   $Z_2$ is nitrogen or CH;

   $R_{29}$ and $R_{30}$ are selected from the group consisting of H, Ci-4-alkyl, O-C^\-alkyl, N(R_{29})_2, C_{3-6}cycloalkylCo-C_{4}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aryl-ox and substituted or unsubstituted heterocycle, wherein each $R_{29}$ is independently selected at each occurrence from the group consisting of H, halogen, hydroxy, COOH, amino, carboxamide, substituted or unsubstituted-Ci-4-alkyl, substituted or unsubstituted C_{3-6}cycloalkylCo-C_{4}alkyl, substituted or unsubstituted-Ci-4-alkoxy, substituted or unsubstituted C_{3-6}cycloalkylCo-C_{4}alkyl-oxo-, substituted or unsubstituted arylCo-C_{4}alkyl, substituted or unsubstituted heterocycleCo-C_{4}alkyl, substituted or unsubstituted arylCo-C_{4}alkyl-oxo and substituted or unsubstituted heterocycleCo-C_{4}alkyl-oxo.

10  In one embodiment of Formula IIc, $R_{25}$ is selected from the group consisting of O-phenyl and O-benzyl.

Still other compounds of Formula III include compounds represented by Formula IIId:
and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof;

wherein

\[ Z_2 \text{ is nitrogen or CH;} \]

\( R_{31} \) represents one or two residues which are independently selected at each occurrence from the group consisting of H, Ci-4-alkyl, O-Ci-4-alkyl, N(R_{24})_2, (CH_2)_{0.4}^- C_{3.6}^-\text{cycloalkyl}, substituted or unsubstituted aryl, substituted or unsubstituted O-aryl and substituted or unsubstituted heterocycle, wherein each R_{24} is independently selected from the group consisting of H, halogen, hydroxy, COOH, amino, carboxamide, substituted or unsubstituted Ci^-alkyl, substituted or unsubstituted C_{3.6}^-\text{cycloalkylCo-C}_4^-\text{alkyl}, substituted or unsubstituted C_{1.4}^-\text{alkoxy}, substituted or unsubstituted C_{3.6}^-\text{cycloalkylCo-C}_4^-\text{alkyl-oxy-}, substituted or unsubstituted arylCo-C_4^-\text{alkyl}, substituted or unsubstituted heterocycleCo-C_4^-\text{alkyl-oxy};

or two R_{31} residues may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms selected from N, O or S, wherein the ring may be further substituted one or more times (or preferably between one and five times).

In another embodiment, Formula Hid is represented by a compound of the Formula IHe:

\[ \text{IIIe} \]
R$_3$ is $-Q'-Q_2$, wherein $Q^1$ is absent, C(O), S(O)$_p$, N(H), N(C$_{1-4}$-alkyl), C=N(CN), C=N(SO$_2$CH$_3$), or C=N-COH, and $Q^2$ is H, C$_{1-4}$-alkyl, C=N-COH-C$_{1-4}$-alkyl, O-C$_{1-4}$-alkyl, NH$_2$, N(H)-C$_{1-4}$-alkyl, N(C$_{1-4}$-alkyl)$_2$, SO$_2$-aryl, SO$_2$-C$_M$-alkyl, C$_{3-6}$-cycloalkyl-C$_{0-4}$-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, Ci$_{1-4}$-alkyl, Ci$_{1-4}$-alkyl substituted by one or more halogen atoms, or C$_3$-$^\wedge$-cycloalkyl.

In another embodiment, Formula IHd is represented by a compound of the Formula HIg:

and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof.

In another embodiment, Formula IHd is represented by a compound of the Formula IHg:

and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof.
Certain compounds of Formula III include compounds represented by Formula IIIh:

\[
\begin{align*}
&\text{and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers,} \\
&\text{diastereomers, or racemates thereof;}
\end{align*}
\]

wherein

\[R_{35}\] is H, halogen, hydroxy, COOH, amino, carboxamide, substituted or unsubstituted-Ci_4-alkyl, substituted or unsubstituted C_3-6-cycloalkylCo-C_4-alkyl, substituted or unsubstituted-Ci-4-alkoxy, substituted or unsubstituted C_3-6-cyclopalkylCo-C_4-alkyl-oxy-, substituted or unsubstituted arylCo-C_4-alkyl, substituted or unsubstituted heterocycleCo-C_4-alkyl-oxo and substituted or unsubstituted heterocycleCo-C_4-alkyl-oxy.

In one embodiment of Formula IIIh, \(R_{35}\) is phenyl, optionally substituted with chloro.

Certain compounds of Formula I include compounds of Formula IV:

\[
\begin{align*}
&\text{and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers,} \\
&tautomers, diastereomers, or racemates thereof.}
\end{align*}
\]

Certain compounds of Formula IV include those compounds in which:

\[y\] is 0 or 1;

\[Z_2\] is nitrogen or CH;
$R_3$ is selected from the group consisting of $H$ and $C_{i-4}$-alkyl;

$R_{i7}$ is hydrogen or is selected from the group consisting of $C_{i}$-alkyl, $C_{i-4}$-cycloalkyl, $(CH_2)_{o-4}$-C$_{3,6}$-cycloalkyl, aryl, alkyl-aryl and heterocycle, each of which may be independently substituted one or more times (or preferably between one and five times);

$R_{o}$ and $R_n$ are each, independently, selected from the group consisting of $H$ and $C_{i-4}$-alkyl;

$R_{i2}$ is selected from the group consisting of $H$, $C_{i-4}$-alkyl, $C_{i-6}$-cycloalkyl and aryl; and

$V$ is selected from the group consisting of $Q^1$-$Q^2$, wherein $Q^1$ is absent, $C$(O), $N$(H), $N$(Ci-4-alkyl), $C$=N(CN), $C$=N(SO$_2$CH$_3$), or $C$=N-COH, and $Q^2$ is $H$, $C$_{1,4}-alkyl, $C$=N-COH-CM-alkyl, O-Ci-4-alkyl, NH$_2$, N(H)-C$_{1,4}$-alkyl, N(C$_{1,4}$-alkyl)$_2$, SO$_2$-aryl, SO$_2$-C$_{1,4}$-alkyl, C$_{3,6}$-cycloalkyl-Co$_{1,4}$-alkyl, aryl, heteroaryl and heterocycle, each of which maybe independently substituted one or more times (or preferably between one and five times) with a halogen atom, $C$_{i-4}-alkyl, $C$_{1,4}alkoxy, $C$_{2,4}alkenyloxy, $C$_{2,4}alknyloxy, $C$_{1,4}-alkyl substituted by one or more halogen atoms, or $C$_{3,6}-cycloalkyl;

or $R_{i7}$ and $V$ form the following 5-membered ring which may be further substituted:

![Diagram](image)

Certain other compounds of Formula IV include those compounds in which $R_{17}$ is selected from the group consisting of $H$, cyclopropylCo-$C$_{2}alkyl, cyclopentylCo-$C$_{2}alkyl, phenylCi-$C$_{2}alkyl, and naphthylCi-$C$_{2}alkyl.

Certain other compounds of Formulae I, II (including Ha and lib), III (including IIIa through IIIc), and/or IV include those compounds in which $V$ is selected from the group consisting of $C$(O)$_{R_{24}}$, $C$(O)$_{C(O)OR_{24}}$, $C$(O)$_{N(H)R_{24}}$, $C$(O)$_{C(O)N(H)R_{24}}$ and $C$(O)OR$_{24}$, wherein each $R_{24}$ is independently selected from the group consisting of $H$, halogen, substituted or unsubstituted-$C$_{i-4}-alkyl, substituted or unsubstituted $C$_{3,6}-cycloalkylCo-$C$_{4}alkyl, substituted or unsubstituted arylCo-$C$_{4}alkyl and substituted or unsubstituted heterocycleCo-$C$_{4}alkyl, and any combination thereof.

Yet other compounds of Formulae I, II (including Ha and lib), III (including IIIa through IIIc), and/or IV include compounds in which $V$ is $C$(O)-$R_{20}$, wherein $R_{20}$ is selected from the group consisting of tert-butyl, $C$_{3,6}-cycloalkyl, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, thiazole, benzothiazole, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently
substituted with 0-5 substituents selected from a halogen atom, C_{1-4}-alkyl, Ci-4alkoxy, C_{2-}
Qalkenyloxy, C_{2-4}alkynyloxy, C_{1,4}-alkyl substituted by one or more halogen atoms, or C_{3-6} cycloalkyl.

Still other compounds of Formulae I, II (including Ha and lib), III (including Ila through IIIh), and/or IV include compounds in which V is R_{20} or C(O)-R_{20}, wherein R_{20} is a residue of the formula:

\[ \begin{align*}
&\text{R}_{34} \\
&\text{R}_{33} \\
&\text{N} \\
&\text{g} \\
&\text{Z}_8 \\
&\text{f} \\
&\text{j} \\
&\text{g} \\
&\text{f} \\
\end{align*} \]

wherein

Z_8 is absent or selected from NR_{33} or oxygen;

g and fare independently selected integers selected from the group consisting of 0, 1, 2, 3 and 4;

j is an integer selected from the group consisting of 1, 2, 3 and 4, wherein the sum of f + g + j is less than or equal to 5 and greater than or equal to 2 when Z_8 is absent and the sum of f + g + jk is less than or equal to 4 and greater than or equal to 1 when Z_8 is oxygen;

R_{33} is independently selected at each occurrence from the group consisting of hydrogen, C_{1,4}alkyl, haloC_{1,4}alkyl, C_{3,6}cycloalkyl, hydroxyC_{1,4}alkyl, and C_{1,4}alkoxyC_{1,4}alkyl; and

R_{34} represents zero to three residues each independently selected at each occurrence from the group consisting of halogen, hydroxy, amino, C_{1,4}alkyl, C_{3,6}cycloalkyl, C_{1,4}alkoxy, mono- and di-C_{1,4}alkylamino, hydroxyC_{1,4}alkyl, and C_{1,4}alkoxyC_{1,4}alkyl.

Yet other compounds of Formulae I, II (including Ila and lib), III (including Ila through IIIh), and/or IV include compounds in which V is C(O)-R_{20}, wherein R_{20} is a residue of the formula:

\[ \begin{align*}
&\text{R}_{34} \\
&\text{R}_{33} \\
&\text{N} \\
&\text{g} \\
&\text{Z}_8 \\
&\text{f} \\
&\text{j} \\
&\text{g} \\
&\text{f} \\
\end{align*} \]
wherein
g is an integer selected from the group consisting of 0, 1, 2, 3 and 4;
j is an integer selected from the group consisting of 1, 2, 3 and 4, wherein the sum of
\( g + j \) is less than or equal to 5 and greater than or equal to 2;
\( R^{33} \) is independently selected at each occurrence from the group consisting of
hydrogen, \( \text{Ci}^\text{alkyl}, \text{halo} \text{Ci}^\text{alkyl}, \text{C}_{3-6} \text{cycloalkyl}, \text{hydroxy} \text{Ci}^\text{alkyl}, \) and \( \text{Ci}^\text{alkoxy} \text{Ci}^\text{alkyl} \); and
\( R^{34} \) represents zero to three residues each independently selected at each occurrence from the group consisting of halogen, hydroxy, amino, \( \text{C}_1 \text{C}_4 \text{alkyl}, \text{C}_{3-6} \text{cycloalkyl}, \text{C}_1 \text{C}_4 \text{alkoxy}, \) mono-and \( \text{di} \text{\text{-C}_1 \text{\text{-alkylamino}}, \text{hydroxy} \text{C}_1 \text{C}_4 \text{alkyl}, \) and \( \text{C}_1 \text{C}_4 \text{alkoxy} \text{C}_1 \text{C}_4 \text{alkyl} \).

In another embodiment of Formula I, \( X \) is \( \text{CR}_5 \text{R}_{5a} \text{R}_4 \text{R}_5 \) and \( R_{5a} \) are \( \text{H} \) and \( R_5 \) is aryl-\( \text{C}_0 \text{C}_3 \)-alkyl, -O-heterocycle, or heterocycle-\( \text{CO}_5 \)-alkyl, wherein aryl and heterocycle may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyI, \( \text{C}_{5-6} \text{cycloalkyl} \) or \( \text{C}_1 \text{C}_4 \)-alkyl.

In yet another embodiment of Formula I, \( X \) is \( \text{CR}_3 \text{R}_5 \), \( R_4 \) and \( R_5 \) are \( \text{H} \) and \( R_5 \) is selected from the group consisting of piperidine, phenyl, -O-pyridinyl and \( \text{CH}_2 \text{pyridinyl}, \) wherein the phenyl and pyridinyl groups may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or \( \text{Ci}^\text{-alkyl} \).

In yet another embodiment of formula I, \( R_5 \) is 5-chloro-pyridin-2-yl.

In still another embodiment of formulae I or II (including Ha and lib), \( R_5 \) is selected from the group consisting of

\[
\begin{align*}
\text{CF}_3 & \quad \text{CF}_3 & \quad \text{Br} \\
\text{O} & \quad \text{Cl} & \quad \text{F}_3 \\
\text{HN} & \quad \text{HN} \\
\text{R}_{21} & \quad \text{R}_{21} \\
\end{align*}
\]

and
wherein $R_{2i}$ is independently selected from the group consisting of $C_{1-4}$-alkyl and aryl.

In still other embodiments, $CR_5R_{5a}$, taken in combination, form a spirocyclic 3 to 6 membered carbocyclic ring. Certain spirocyclic rings include groups of the formula:

\[
\begin{array}{c}
\text{R}_5c \\
\text{f} \\
\text{R}_{5d}
\end{array}
\]

wherein

- $f$ is 0, 1, 2, 3, or 4;
- $R_{5a}$ and $R_{5c}$ are independently selected from hydrogen halogen, $C_1$-$6$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_1$-$6$-alkoxide, $C_{3-7}$-cycloalkyl-$C_0$-$4$-alkyl, phenyl-$C_0$-$4$-alkyl, naphthyl-$C_0$-$4$-alkyl, heteroaryl-$C_0$-$4$-alkyl, or two substitutents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or $C_{1-4}$-alkyl groups.

In yet another embodiment of Formula I, $R_2$ is selected from the group consisting of propyl and $(CH_2)_2$-cyclobutyl.

In still another embodiment of Formula I, $R_n$ is H and $R_{12}$ is $C_{3-6}$-cycloalkyl.

In one embodiment of Formula I, $R_{12}$ is cyclohexyl.

In another embodiment of formula I, $V$ is selected from the group consisting of $C(O)$-$N(H)$-/-butyl.

Yet other compounds of any one of Formulae I, II (including Ha and lib), III (including IIIa through IIIc), and/or IV include compounds in which $V$ is $C(O)$-$N(H)$-/-butyl or $C(O)$-$R_{20}$, wherein $R_{20}$ is selected from the group consisting of $C_{3-6}$-cycloalkyl, phenyl, pyrazine, benzoxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, thiazole, benzothiazole, benzothiazole 1,1-dioxide and quinazoline, all of which may be further independently substituted with a halogen atom, $CF_3$, $Ct_4$-alkyl, $Q^\alpha$alkoxy, $C_2^\alpha$-$C_4$-alkenyl, or $C_{3-6}$-cycloalkyl.

In certain other compounds of any one of Formulae I, II (including Ha and lib), III (including IIIa through IIIc), and/or IV, $V$ is selected from the group consisting of $C_{3-6}$-cycloalkyl, phenyl, pyrazine, benzoxazole, 4,4-dimethyl-4,5-dihydro-oxazole,
benzoimidazole, pyrimidine, thiazole, benzothiazole, benzothiazole 1,1-dioxide and quinazoline, all of which may be further independently substituted with a halogen atom, CF₃, C_i-4-alkyl, C_i-4-alkoxy, C₂-C₄-alkenylfxy, C₂-C₄-alkynylfxy, or C₃-6-cycloalkyl.

In yet another embodiment of Formulae I, II (including Ha and lib), III (including Ilia through IIh), and/or IV, V is R₂₀ or C(O)-R₂₀, wherein R₂₀ is selected from the group consisting of C₃-6-cycloalkyl, phenyl, pyrazine, benzoazazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, all of which may be further independently substituted with a halogen atom, CF₃, C_i-4-alkyl or C₃-6-cycloalkyl.

In still another embodiment of Formulae I, II (including Ha and lib), III (including Ilia through IIh), and/or IV, V is R₂₀ or C(O)-R₂₀, wherein R₂₀ is selected from the group consisting of

![Chemical Structures](attachment:image.png)

wherein R₁₈ is selected from the group consisting of hydrogen, a halogen atom, aryl, C_i-4-alkyl, C_i-alkoxy, C₂-C₄-alkenylfxy, C₂-C₄-alkynylfxy, C⁸-alkyl substituted by one or more halogen atoms, or C₃-6-cycloalkyl.

In one embodiment of Formulae I, II (including Ha and lib), in (including Ilia through IIh), and/or IV, V is R₂⁰ or C(O)-R₂₀, wherein R₂₀ is selected from the group consisting of

![Chemical Structures](attachment:image.png)

wherein R₁₈ is selected from the group consisting of hydrogen, a halogen atom, aryl, C_i-4-alkyl.
alkyl, C_{1-4}alkoxy, C_2-C_4alkenyloxy, C_2-C_4alkynyloxy, d^-alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl.

In another embodiment of Formulae I, II (including IIa and lib), III (including IIIa through IIIh), and/or IV, V is selected from the group consisting of C_3-C_5-cycloalkyl, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, thiazole, benothiazole, benothiazole 1,1-dioxide and quinazoline, all of which may be further independently substituted with a halogen atom, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, C_{1-4}alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl.

In yet another embodiment of Formula I, II (including IIa and lib), III (including IIIa through IIId), and/or IV, variable V is selected from the group consisting of R_{20} and C(O)-R_{20}, wherein R_{20} is selected from the group consisting of C_{3-6}-cycloalkyl, mono- and di-C_{1-4}alkylamino, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, CF_3, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, or C_{3-6}-cycloalkyl.

In still another embodiment of Formula I, II (including IIa and lib), III (including IIIa through IIIh), and/or IV, variable V is selected from the group consisting of R_{20} and C(O)-R_{20}, wherein R_{20} is selected from the group consisting of
wherein \( b \) is 0, 1, or 2; and \( R_{18} \) is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and \( C_{1-4} \)-alkyl.

In one embodiment, any of the \( C_{3-6} \)-cycloalkyl groups of Formula I, or any subformula thereof, may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, heteroaryl, trihalomethyl, \( C^\alpha \)-alkoxy or \( C_{1-4} \)-alkyl.

In one embodiment of Formula I, or any subformulae thereof, any of the heterocycle groups are independently selected from the group consisting of acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothiienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline, benzoimidazolyl, benzofuranyl, benzofurazanyl, pyrazinyl, pyridazinyl, pyridopyridinyl, tetrazolopyridyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-
onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, 
dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, 
dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, 
dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, 
dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, 
dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydroazetidinyl, 
methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof, all 
of which may be independently further substituted one or more times (or preferably between 
one and five times) with a halogen atom, C\textsubscript{i-4}-alkyl, C\textsuperscript{v-alkyl} substituted by one or more 
halogen atoms, or C\textsubscript{3-6}-cycloalkyl.

Preferred embodiments of the compounds of the invention (including 
pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, 
tautomers, diastereomers, or racemates thereof) are shown below in Table A and Table B, 
and are also considered to be "compounds of the invention."

\textbf{TABLE A}

<table>
<thead>
<tr>
<th>Structure</th>
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<tbody>
<tr>
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Certain additional compounds of Formula I (or subformulae thereof) which are contemplated in the present invention include compounds depicted in Table B.
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<th>Structure</th>
<th>Compound No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure B-1" /></td>
<td>B-1</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure B-2" /></td>
<td>B-2</td>
</tr>
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<td><img src="image3.png" alt="Structure B-3" /></td>
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</tr>
<tr>
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</tr>
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<td>-------------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>B-4</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>B-5</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>B-6</td>
</tr>
</tbody>
</table>

94
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure A" /></td>
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</tr>
<tr>
<td><img src="image" alt="Structure B" /></td>
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<tr>
<td><img src="image" alt="Structure C" /></td>
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<tr>
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</tr>
<tr>
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<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>B-10</td>
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<tr>
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<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>B-13</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>B-14</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
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</tr>
<tr>
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<tr>
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<tr>
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<td>-------------</td>
</tr>
<tr>
<td><img src="image" alt="Structure B-17" /></td>
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<tr>
<td><img src="image" alt="Structure B-18" /></td>
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<td><img src="image" alt="Structure B-19" /></td>
<td>B-19</td>
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<td><img src="image" alt="Structure B-20" /></td>
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</tr>
<tr>
<td>Structure</td>
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</tr>
<tr>
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</tr>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
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<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>B-22</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>B-23</td>
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<tr>
<td><img src="image4" alt="Structure 4" /></td>
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</tr>
<tr>
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</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td><img src="image" alt="Structure B-25" /></td>
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<td>B-26</td>
</tr>
<tr>
<td><img src="image" alt="Structure B-27" /></td>
<td>B-27</td>
</tr>
<tr>
<td><img src="image" alt="Structure B-28" /></td>
<td>B-28</td>
</tr>
</tbody>
</table>
Certain other compounds of Formula I, and subformulae thereof, include those compounds which contain a fragment selected from the residues of each of Tables C, D, E, F, and G. Thus, compounds of the invention include all P1-P2 compounds formed by combining all possible permutations of the fragments of Tables C, D, E, F, and G wherein the bond ending in an asterisk is the point of attachment P1 and P2 fragments are coupled by condensation of the amino residue on the P1 fragment with the carboxylic acid residue on the P2 fragment. For example, the compound C(1)-D(3)-E(10)-F(4)-G(15) is the compound in
which the residue of entry 1 of Table C, the residue of entry 3 of Table D, the residue of entry 10 of Table E, the residue of entry 4 of Table F (where \( n \) is 1) and the residue of entry 15 of Table G are combined to form a compound of formula I which has the structure:

![Chemical structure](image)

**TABLE C**
The fragment of Formula 1 has a residue of the formula selected from the group consisting of:

<table>
<thead>
<tr>
<th>C1</th>
<th>C2</th>
<th>C3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure C1" /></td>
<td><img src="image" alt="Structure C2" /></td>
<td><img src="image" alt="Structure C3" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<td><img src="image" alt="Structure C5" /></td>
<td><img src="image" alt="Structure C6" /></td>
</tr>
</tbody>
</table>

**TABLE D**
The variable, E, of Formula 1 is a residue selected from the group consisting of:
TABLE E
The fragment of Formula 1 has a residue of the formula

![Chemical Structures]

selected from the group consisting of:
The fragment of Formula 1 has a residue of the formula $L_3^L_2^{FG}L_1^{\text{@}}$ selected from the group consisting of:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F1</strong></td>
<td>$n = 0, 1, 2$</td>
<td>$\text{N}$</td>
</tr>
<tr>
<td><strong>F2</strong></td>
<td>$n = 0-5$</td>
<td>$\text{Me}$</td>
</tr>
<tr>
<td><strong>F3</strong></td>
<td>$n = 0-5$</td>
<td>$\text{O}$</td>
</tr>
<tr>
<td><strong>F4</strong></td>
<td>$n = 0-5$</td>
<td>$\text{Me}$</td>
</tr>
<tr>
<td><strong>F5</strong></td>
<td>$n = 0-5$</td>
<td>$\text{O}$</td>
</tr>
<tr>
<td><strong>F6</strong></td>
<td>$n = 0-5$</td>
<td>$\text{Me}$</td>
</tr>
<tr>
<td><strong>F7</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
<tr>
<td><strong>F8</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
<tr>
<td><strong>F9</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
<tr>
<td><strong>F10</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
<tr>
<td><strong>F11</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
<tr>
<td><strong>F12</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
<tr>
<td><strong>F13</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
<tr>
<td><strong>F14</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
<tr>
<td><strong>F15</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
<tr>
<td><strong>F16</strong></td>
<td>$\text{O}$</td>
<td></td>
</tr>
</tbody>
</table>
The fragment of Formula 1 has a residue of the formula selected from the group consisting of:

TABLE G

selected from the group consisting of:
<table>
<thead>
<tr>
<th>G13</th>
<th>G14</th>
<th>G15</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>G16</td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>G19</td>
<td>G20</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G22</td>
<td>G23</td>
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<td>G45</td>
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</tr>
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<td><img src="image" alt="Structure G50" /></td>
<td><img src="image" alt="Structure G51" /></td>
</tr>
<tr>
<td><img src="image" alt="Structure G52" /></td>
<td><img src="image" alt="Structure G53" /></td>
<td><img src="image" alt="Structure G54" /></td>
</tr>
</tbody>
</table>
Using the HCV NS3-4A protease and Luciferase-HCV replicon assays described in the exemplification section below, certain compounds of the invention (including compounds of Table A depicted above) are found to show IC$_{50}$ values for HCV inhibition in the range from 10 to more than 100 µM, or 0.5 to 30 µM, or show IC$_{50}$ values for HCV inhibition of less than 10 µM.

In certain embodiments, a compound of the present invention is further characterized as a modulator of HCV, including a mammalian HCV, and especially including a human HCV. In a preferred embodiment, the compound of the invention is an HCV inhibitor.

The terms "HCV-associated state" or "HCV-associated disorder" include disorders and states (e.g., a disease state) that are associated with the activity of HCV, e.g., infection of HCV in a subject. HCV-associated states include HCV-infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

HCV-associated states are often associated with the NS3 serine protease of HCV, which is responsible for several steps in the processing of the HCV polyprotein into smaller functional proteins. NS3 protease forms a heterodimeric complex with the NS4A protein, an essential cofactor that enhances enzymatic activity, and is believed to help anchor HCV to the endoplasmic reticulum. NS3 first autocatalyzes hydrolysis of the NS3-NS4A juncture, and then cleaves the HCV polyprotein intermolecularly at the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B intersections. This process is associated with replication of HCV in a subject. Inhibiting or modulating the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins will inhibit or modulate replication of HCV in a subject, thereby preventing or treating the HCV-associated state. In a particular embodiment, the HCV-associated state is associated with the activity of the NS3 protease. In another particular embodiment, the HCV-associated state is associated with the activity of NS3-NS4A heterodimeric complex.

In one embodiment, the compounds of the invention are NS3/NS4A protease inhibitors. In another embodiment, the compounds of the invention are NS2/NS3 protease inhibitors.

Without being bound by theory, it is believed that the disruption of the above protein-protein interactions by the compounds of the invention will interfere with viral polyprotein processing by the NS3 protease and thus viral replication.

HCV-associated disorders also include HCV-dependent diseases. HVC-dependent diseases include, e.g., any disease or disorder that depend on or related to activity or
misregulation of at least one strain of HCV.

The present invention includes treatment of HCV-associated disorders as described above, but the invention is not intended to be limited to the manner by which the compound performs its intended function of treatment of a disease. The present invention includes treatment of diseases described herein in any manner that allows treatment to occur, e.g., HCV infection.

In a related embodiment, the compounds of the invention can be useful for treating diseases related to HFV, as well as HIV infection and AIDS (Acquired Immune Deficiency Syndrome).

In certain embodiments, the invention provides a pharmaceutical composition of any of the compounds of the present invention. In a related embodiment, the invention provides a pharmaceutical composition of any of the compounds of the present invention and a pharmaceutically acceptable carrier or excipient of any of these compounds. In certain embodiments, the invention includes the compounds as novel chemical entities.

In one embodiment, the invention includes a packaged HCV-associated disorder treatment. The packaged treatment includes a compound of the invention packaged with instructions for using an effective amount of the compound of the invention for an intended use.

The compounds of the present invention are suitable as active agents in pharmaceutical compositions that are efficacious particularly for treating HCV-associated disorders. The pharmaceutical composition in various embodiments has a pharmaceutically effective amount of the present active agent along with other pharmaceutically acceptable excipients, carriers, fillers, diluents and the like. The phrase, "pharmaceutically effective amount" as used herein indicates an amount necessary to administer to a host, or to a cell, issue, or organ of a host, to achieve a therapeutic result, especially an anti-HCV effect, e.g., inhibition of proliferation of the HCV virus, or of any other HCV-associated disease.

In one embodiment, the diseases to be treated by compounds of the invention include, for example, HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

In other embodiments, the present invention provides a method for inhibiting the activity of HCV. The method includes contacting a cell with any of the compounds of the present invention. In a related embodiment, the method further provides that the compound is present in an amount effective to selectively inhibit the activity of one or more of the NS3,
NS4A, NS4B, NS5A and NS5B proteins. In another related embodiment, the method provides that the compound is present in an amount effective to diminish the HCV RNA load in a subject.

In other embodiments, the present invention provides a use of any of the compounds of the invention for manufacture of a medicament to treat HCV infection in a subject.

In other embodiments, the invention provides a method of manufacture of a medicament, including formulating any of the compounds of the present invention for treatment of a subject.

Definitions

The term "treat," "treated," "treating" or "treatment" includes the diminishment or alleviation of at least one symptom associated or caused by the state, disorder or disease being treated. In certain embodiments, the treatment comprises the induction of an HCV-inhibited state, followed by the activation of the HCV-modulating compound, which would in turn diminish or alleviate at least one symptom associated or caused by the HCV-associated state, disorder or disease being treated. For example, treatment can be diminishment of one or several symptoms of a disorder or complete eradication of a disorder.

The term "subject" is intended to include organisms, e.g., prokaryotes and eukaryotes, which are capable of suffering from or afflicted with an HCV-associated disorder. Examples of subjects include mammals, e.g., humans, dogs, cows, horses, pigs, sheep, goats, cats, mice, rabbits, rats, and transgenic non-human animals. In certain embodiments, the subject is a human, e.g., a human suffering from, at risk of suffering from, or potentially capable of suffering from an HCV-associated disorder, and for diseases or conditions described herein, e.g., HCV infection. In another embodiment, the subject is a cell.

The language "HCV-modulating compound," "modulator of HCV" or "HCV inhibitor" refers to compounds that modulate, e.g., inhibit, or otherwise alter, the activity of HCV. Similarly, an "NS3/NS4A protease inhibitor," or an "NS2/NS3 protease inhibitor" refers to a compound that modulates, e.g., inhibits, or otherwise alters, the interaction of these proteases with one another. Examples of HCV-modulating compounds include compounds of Formula I, as well as Table A and Table B (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof).

Additionally, the method includes administering to a subject an effective amount of an HCV-modulating compound of the invention, e.g., HCV-modulating compounds of Formula I, as well as Table A and Table B (including pharmaceutically acceptable salts
thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof).

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term "alkyl" also includes alkenyl groups and alkynyl groups. Furthermore, the expression "C<sub>x</sub>-C<sub>y</sub>-alkyl", wherein x is 1-5 and y is 2-10 indicates a particular alkyl group (straight- or branched-chain) of a particular range of carbons. For example, the expression Ci-C<sub>4</sub>-alkyl includes, but is not limited to, methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, isobutyl and sec-butyl.

Moreover, the term C<sub>3-5</sub>-cycloalkyl includes, but is not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. As discussed below, these alkyl groups, as well as cycloalkyl groups, may be further substituted. "Co-C<sub>n</sub>-alkyl" refers to a single covalent bond (Co) or an alkyl group having from 1 to n carbon atoms; for example "Co-C<sub>4</sub>-alkyl" refers to a single covalent bond or a C<sub>1</sub>-C<sub>4</sub>-alkyl group; "Co-C<sub>8</sub>-alkyl" refers to a single covalent bond or a C<sub>1</sub>-C<sub>8</sub>-alkyl group.

In some instances, a substituent of an alkyl group is specifically indicated. For example, "Ci-C<sub>4</sub>hydroxyalkyl" refers to a Ci-C<sub>4</sub>-alkyl group that has at least one hydroxy substituent.

"Alkylene" refers to a divalent alkyl group, as defined above. Co-C<sub>4</sub>alkylene is a single covalent bond or an alkylene group having from 1 to 4 carbon atoms; and C<sub>0</sub>-C<sub>8</sub>alkylene is a single covalent bond or an alkylene group having from 1 to 6 carbon atoms. "Alkenylene" and "Alkynylene" refer to divalent alkenyl and alkynyl groups respectively, as defined above.

The term alkyl further includes alkyl groups which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In an embodiment, a straight chain or branched chain alkyl has 10 or fewer carbon atoms in its backbone (e.g., Ci-Qo for straight chain, C<sub>3</sub>-C<sub>10</sub> for branched chain), and more preferably 6 or fewer carbons.

A "cycloalkyl" is a group that comprises one or more saturated and/or partially saturated rings in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of the foregoing, such as cyclohexenyl. Cycloalkyl groups do not comprise an aromatic ring or a heterocyclic ring. Certain cycloalkyl groups are C<sub>3</sub>-C<sub>8</sub>cycloalkyl, in which the group contains a single ring with from 3
to 8 ring members. A "(C₃-C₈ cycloalkyl)Co-C₄ alkyl" is a C₃-C₈ cycloalkyl group linked via a single covalent bond or a C₁-C₄ alkylene group. In certain aspects, C₃-₆-cycloalkyl groups are substituted one or more times (or preferably between one and five times) with substituents independently selected from a halogen atom, aryl, heteroaryl, trihalomethyl, Cᵣ⁻-alkoxy or C₄-alkyl.

Moreover, alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, etc.) include both "unsubstituted alkyl" and "substituted alkyl", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, which allow the molecule to perform its intended function.

The term "substituted" is intended to describe moieties having substituents replacing a hydrogen on one or more atoms, e.g. C, O or N, of a molecule. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carboxyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, m-phenolino, phenol, benzyl, phenyl, piperazine, cyclopentane, cyclohexane, pyridine, 5H-tetrazole, triazole, piperidine, or an aromatic or heteroaromatic moiety.

Further examples of substituents of the invention, which are not intended to be limiting, include moieties selected from straight or branched alkyl (preferably C₁-C₅), cycloalkyl (preferably C₃-C₅), alkoxy (preferably C₁-C₆), thioalkyl (preferably C₁-C₆), alkenyl (preferably C₂-C₆), alkylnyl (preferably C₂-C₆), heterocyclic, carbocyclic, aryl (e.g., phenyl), aryloxy (e.g., phenoxy), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenyoxyalkyl), arylepoxyl, alkylaryl, heteroarylalkyl, alkylcarbonyl and arylecarbonyl or other such acyl group, heteroarylecarbonyl, or heteroaryl group,

(CR'R")ₐ₁₋₃NR'R" (e.g., -NH₂, -(CR'R")ₐ₁₋₃CN (e.g., -CN), -NO₂, halogen (e.g., -F, -Cl, -Br or I), (CR'R")ₐ₁₋₃C(halogen)ₐ₁₋₃(e.g., -CF₃, (CR'R")ₐ₁₋₃CH(halogen)ₐ₁₋₃, (CR'R")ₐ₁₋₃CH₂(halogen), (CR'R")ₐ₁₋₃CONR'R", (CR'R")ₐ₁₋₃(CNH)NR'R", (CR'R")ₐ₁₋₃S(0)₁₋₂NR'R", (CR'R")ₐ₁₋₃CHO, (CR'R")ₐ₁₋₃O(OH)(CR'R")ₐ₁₋₃S(0)ₐ₁₋₃R" (e.g., -SO₃H, -OSO₃H), (CR'R")ₐ₁₋₃O(OH)(CR'R")ₐ₁₋₃(TH₂OCH₃ and -OCH₃), (CR'R")ₐ₁₋₃GS(SR")₁₋₃H (e.g., -SH and -SCH₃), (CR'R")ₐ₁₋₃OH (e.g., -OH), (CR'R"ₐ₁₋₃COR\ (CR'R")ₐ₁₋₃(substituted or
unsubstituted phenyl), (CR'R")o-3(C3-C8 cycloalkyl), (CR'R")0-3C02R' (e.g., -CO2H), or (CR'R")o-3OR' group, or the side chain of any naturally occurring amino acid; wherein R' and R" are each independently hydrogen, a Ci-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, or aryl group. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphorous, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, dialkylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, oxime, sulf hyd ryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamide, nitro, trifluoromethyl, cyano, azido, heterocycyl, or an aromatic or heteroaromatic moiety. In certain embodiments, a carbonyl moiety (C=O) may be further derivatized with an oxime moiety, e.g., an aldehyde moiety may be derivatized as its oxime (-C=NOH) analog. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "aralkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl, (i.e., benzyl)).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one double bond.

For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or aralkyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups that include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (e.g., C2-C6 for straight chain, C3-C6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C2-C6 includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can
include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkyl carbonyl, aryl carbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino (including alkyl carbonylamino, aryl carbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

For example, the term "alkynyl" includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkynyl or cycloalkenynyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups that include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C2-C6 for straight chain, C3-C6 for branched chain). The term C2-C6 includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkyl carbonyl, aryl carbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino (including alkyl carbonylamino, aryl carbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "amine" or "amino" should be understood as being broadly applied to both a molecule, or a moiety or functional group, as generally understood in the art, and may be primary, secondary, or tertiary. The term "amine" or "amino" includes compounds where a
nitrogen atom is covalently bonded to at least one carbon, hydrogen or heteroatom. The terms include, for example, but are not limited to, "alkylamino," "arylamino," "diarylmino," "alkylarylmino," "alkylaminoaryl," "arylaminoalkyl," "alkaminoalkyl," "amide," "amido," and "aminocarbonyl." The term "alkyl amino" comprises groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups.

The term "arylamino" and "diarylmino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylmino," "alklaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

The term "amide," "amido" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl and arylcarbonylamino groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl," "arylaminocarbonyl," "alkylcarbonylamino," "alkynylcarbonylamino," "alkylaminocarbonylaminocarbonyl," and "arylaminoalkylaminocarbonyl" are included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino).

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, phenyl, pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylene dioxyphenyl, quinoline, isoquinoline, anthryl, phenanthryl, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles," "heterocycles," "heteroaryls" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, alkyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate,
alkylcarbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diaryl amino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, car bamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, ary lthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamyl, sul fonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

Certain aryl groups recited herein are C₆-C₉-C₉-Cgalkyl groups (i.e., groups in which a 6- to 10-membered carbocyclic group comprising at least one aromatic ring is linked via a single covalent bond or a CrCgalkylene group). Such groups include, for example, phenyl and indanyl, as well as groups in which either of the foregoing is linked via Ci-C₉alkylene, preferably via Ci-C₄alkylene. Phenyl groups linked via a single covalent bond or Ci-C₉alkylene group are designated phenylCᵪ-Cᵪ-C₉alkyl (e.g., benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl).

"Arylene" refers to a divalent aryl group, as defined above. Arylene is intended to encompass divalent residues of phenyl, naphthyl and biphenyl. "Heteroarylene" refers to divalent heteroaryl groups as defined infra.

The term "heteroaryl", as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnoliny l, quinoxalinyl, pyrazolyl, indolyl, isoindoline, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinoliny l, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrol yl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

The term "heterocycle" or "heterocyclic" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups.
"Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and
tetrahydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited
to the following: benzoimidazolyl, benzofuranyl, benzofurazanpyrryldi, benzopyrazolyl,
benzotriazolyl, benzothiophenyl, benzoazolyl, carbazolyl, carbolinyl, cinnolynyl, furanyl,
imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl,
isoquinolyl, isotheazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline,
isoxazoline, oxetanyl, pyraninyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl,
pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyld, quinolynyl, quinoxalinyl,
tetrahydropyrryld, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiaphenyl, thienyl, triazolyl,
azetidinyl, 1,4-dioxanyld, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyld,
pyrrolidinyl, morpholinyl, thiomopholynyl, dihydrobenzoimidazolyl, dihydrobenzofuranyld,
dihydrobenzotheazolyl, dihydrobenzoazolyl, dihydrofuranyld, dihydroimidazolyl,
dihydroindolyl, dihydrosisoxazolyl, dihydroxadiazolyl,
dihydrooxazolyl, dihydropyrryld, dihydroquinolinyld, dihydroterazolyl, dihydrothiazolyl,
dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzolyl,
tetrahydrofuranyld, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl
substituent can occur via a carbon atom or via a heteroatom.

A "heterocyclylCo-Cgalkyl" is a heterocyclic group linked via a single covalent bond or
Ci-Qalkylene group. A (4- to 7-membered heterocycle)C0-C8alkyl is a heterocyclic group
(e.g., monocyclic or bicyclic) having from 4 to 7 ring members linked via a single covalent
bond or an alkylene group having from 1 to 8 carbon atoms. A "(6-membered heteroaryl)Co-
C8alkyl" refers to a heteroaryl group linked via a direct bond or Ci-Cgalkyl group.

The term "acyl" includes compounds and moieties which contain the acyl radical
(CH3CO-) or a carbonyl group. The term "substituted acyl" includes acyl groups where one
or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups,
halogens, hydroxyl, alkyloxycarboxyl, arylcarboxyl, alkoxyxycarboxyl, arlyloxycarboxyl,
aryloxycarboxyl, carboxylate, alkyloxycarbonyl, arylcarboxyl, aryloxycarbonyl, aminocarbonyl,
alkylaminocarbonyl, dialkylaminocarbonyl, alkythiocarbonyl, alkoxyl,
phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino,
arylamino, diarylamino, and alkyllamino), acylamino (including alkylcarboxylamino,
arylacarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkythio, arythio,
thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro,
trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic

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moiety.

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropoxy, propoxy, butoxy, and pentoxy groups and may include cyclic groups such as cyclopentoxy. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkylnyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl phosphate, phoshphonato, phoshpinato, cyano, amino (including alkyl amino, dialkyl amino, aminylamo, diarylamino, and alkylaminylamo), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkysulfanyl, sulfonat, sulfamoyl, sulfonamide, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom, and tautomeric forms thereof. Examples of moieties that contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc. The term "carboxy moiety" or "carbonyl moiety" refers to groups such as "alkylcarbonyl" groups wherein an alkyl group is covalently bound to a carbonyl group, "alkenylcarbonyl" groups wherein an alkenyl group is covalently bound to a carbonyl group, "alkynylcarbonyl" groups wherein an alkynyl group is covalently bound to a carbonyl group, "arylcarbonyl" groups wherein an aryl group is covalently attached to the carbonyl group. Furthermore, the term also refers to groups wherein one or more heteroatoms are covalently bonded to the carbonyl moiety. For example, the term includes moieties such as, for example, aminocarbonyl moieties, (wherein a nitrogen atom is bound to the carbon of the carbonyl group, e.g., an amide), aminocarbobnyloxy moieties, wherein an oxygen and a nitrogen atom are both bond to the carbon of the carbonyl group (e.g., also referred to as a "carbamate"). Furthermore, aminocarbonylamino groups (e.g., ureas) are also
include as well as other combinations of carbonyl groups bound to heteroatoms (e.g., nitrogen, oxygen, sulfur, etc. as well as carbon atoms). Furthermore, the heteroatom can be further substituted with one or more alkyl, alkenyl, alkynyl, aryl, aralkyl, acyl, etc. moieties.

The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom. The term "thiocarbonyl moiety" includes moieties that are analogous to carbonyl moieties. For example, "thiocarbonyl" moieties include aminothiocarbonyl, wherein an amino group is bound to the carbon atom of the thiocarbonyl group, furthermore other thiocarbonyl moieties include, oxythiocarboxyls (oxygen bound to the carbon atom), aminothiocarbonylamino groups, etc.

The term "ether" includes compounds or moieties that contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom that is covalently bonded to another alkyl group.

The term "ester" includes compounds and moieties that contain a carbon or a heteroatom bound to an oxygen atom that is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarboxyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxy carbonyl, etc. The alkyl, alkenyl, or alkynyl groups are as defined above.

The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom that is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

The term "hydroxy" or "hydroxyl" includes groups with an -OH or -O-.

The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The terms "polycyclyl" or "polycyclic radical" include moieties with two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for
example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkyl carbonyl, alkoxy carbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxycarbonyloxy, arylloxycarbonyloxy, carboxylate, ... diastereomers, or racemates) are included within the scope of this invention. Such isomers can be obtained in racemates) as asymmetric with number from more than nitrogen: following satisfy create further substituent. (i.e., architecture. Preferred listed azido, carbamoyl phosphinato, sulfates, alkenylcarbonyl, aralkylaminocarbonyl, aralkylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxycarbonyloxy, arylloxycarbonyloxy, carboxylate, ... diastereomers, or racemates) are included within the scope of this invention. Such isomers can be obtained in asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates) are included within the scope of this invention. Such isomers can be obtained in
substantially pure form by classical separation techniques and by stereochemical controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof. Compounds described herein may be obtained through art recognized synthesis strategies.

It will also be noted that the substituents of some of the compounds of this invention include isomeric cyclic structures. It is to be understood accordingly that constitutional isomers of particular substituents are included within the scope of this invention, unless indicated otherwise. For example, the term "tetrazole" includes tetrazole, 2H-tetrazole, 3H-tetrazole, 4H-tetrazole and 5H-tetrazole.

Use in HCV-associated disorders

The compounds of the present invention have valuable pharmacological properties and are useful in the treatment of diseases. In certain embodiments, compounds of the invention are useful in the treatment of HCV-associated disorders, e.g., as drugs to treat HCV infection.

The term "use" includes any one or more of the following embodiments of the invention, respectively: the use in the treatment of HCV-associated disorders; the use for the manufacture of pharmaceutical compositions for use in the treatment of these diseases, e.g., in the manufacture of a medicament; methods of use of compounds of the invention in the treatment of these diseases; pharmaceutical preparations having compounds of the invention for the treatment of these diseases; and compounds of the invention for use in the treatment of these diseases; as appropriate and expedient, if not stated otherwise. In particular, diseases to be treated and are thus preferred for use of a compound of the present invention are selected from HCV-associated disorders, including those corresponding to HCV-infection, as well as those diseases that depend on the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins, or a NS3-NS4A, NS4A-NS4B, NS4B-NS5A or NS5A-NS5B complex. The term "use" further includes embodiments of compositions herein which bind to an HCV protein sufficiently to serve as tracers or labels, so that when coupled to a fluor or tag, or made radioactive, can be used as a research reagent or as a diagnostic or an imaging agent.

In certain embodiments, a compound of the present invention is used for treating HCV-associated diseases, and use of the compound of the present invention as an inhibitor of any one or more HCVs. It is envisioned that a use can be a treatment of inhibiting one or more strains of HCV.

Assays
The inhibition of HCV activity may be measured as using a number of assays available in the art. An example of such an assay can be found in Anal Biochem. 1996 240(1): 60-7; which is incorporated by reference in its entirety. Assays for measurement of HCV activity are also described in the experimental section below.

5 **Pharmaceutical Compositions**

The language "effective amount" of the compound is that amount necessary or sufficient to treat or prevent an HCV-associated disorder, e.g. prevent the various morphological and somatic symptoms of an HCV-associated disorder, and/or a disease or condition described herein. In an example, an effective amount of the HCV-modulating compound is the amount sufficient to treat HCV infection in a subject. In another example, an effective amount of the HCV-modulating compound is the amount sufficient to treat HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response in a subject. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound of the invention. For example, the choice of the compound of the invention can affect what constitutes an "effective amount." One of ordinary skill in the art would be able to study the factors contained herein and make the determination regarding the effective amount of the compounds of the invention without undue experimentation.

The regimen of administration can affect what constitutes an effective amount. The compound of the invention can be administered to the subject either prior to or after the onset of an HCV-associated state. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compound(s) of the invention can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

Compounds of the invention may be used in the treatment of states, disorders or diseases as described herein, or for the manufacture of pharmaceutical compositions for use in the treatment of these diseases. Methods of use of compounds of the present invention in the treatment of these diseases, or pharmaceutical preparations having compounds of the present invention for the treatment of these diseases.

The language "pharmaceutical composition" includes preparations suitable for administration to mammals, e.g., humans. When the compounds of the present invention are
administered as pharmaceuticals to mammals, e.g., humans, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The phrase "pharmaceutically acceptable carrier" is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present invention to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions. Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, \( \alpha \)-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical, transdermal, buccal, sublingual, rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient that can be
combined with a carrier material to produce a single dosage form will generally be that amount of the compound that produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients, high generally, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.
A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluent commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as,
for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.
Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.
The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc., administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administration is preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intrarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and
like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 1.0 to about 100 mg per kg per day. An effective amount is that amount treats an HCV-associated disorder.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical composition.

**Synthetic Procedure**

Compounds of the present invention are prepared from commonly available compounds using procedures known to those skilled in the art, including any one or more of the following conditions without limitation:

1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/1, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Amino acids, Peptides, Proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e., without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (e.g., by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g., the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, e.g., by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, e.g., a free carboxy group and a free amino group, may be formed, e.g., by the neutralisation of salts, such as acid addition salts, to the isoelectric point, e.g., with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by, e.g., medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation,
or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, e.g., using chromatographic methods, distribution methods, (re-)crystallization, and the like.

5 General process conditions

The following applies in general to all processes mentioned throughout this disclosure.

The process steps to synthesize the compounds of the invention can be carried out under reaction conditions that are known per se, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, e.g., in the H⁺ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100°C to about 190°C, including, for example, from approximately -80°C to approximately 150°C, for example at from -80 to -60°C, at room temperature, at from -20 to 40°C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described in Science of Synthesis: Houben-Weyl Methods of Molecular Transformation. Georg Thieme Verlag, Stuttgart, Germany. 2005.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofurane or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or
isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

Pro-drugs

The present invention also relates to pro-drugs of a compound of the present invention that are converted in vivo to the compounds of the present invention as described herein. Any reference to a compound of the present invention is therefore to be understood as referring also to the corresponding pro-drugs of the compound of the present invention, as appropriate and expedient.

Combinations

A compound of the present invention may also be used in combination with other agents, *e.g.*, an additional HCV-modulating compound that is or is not of the formula I, for treatment of and HCV-associated disorder in a subject.

By the term "combination", is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the present invention and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, *e.g.*, synergistic, effect, or any combination thereof.

For example, WO 2005/042020, incorporated herein by reference in its entirety, describes the combination of various HCV inhibitors with a cytochrome P450 (*"CYP"*) inhibitor. Any CYP inhibitor that improves the pharmacokinetics of the relevant NS3/4A protease may be used in combination with the compounds of this invention. These CYP inhibitors include, but are not limited to, ritonavir (WO 94/14436, incorporated herein by reference in its entirety), ketoconazole, ^oleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, fluoroxyzone, fluoxetine, fluvoxamine, miconazole, fluvoxamine, fluoxetin, fluoroxyzone, fluvoxamine, miconazole,
nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

Methods for measuring the ability of a compound to inhibit CYP activity are known (see, e.g., US 6,037,157 and Yun, et al. Drug Metabolism & Disposition, vol. 21, pp. 403-407 (1993); incorporated herein by reference). For example, a compound to be evaluated may be incubated with 0.1, 0.5, and 1.0 mg protein/ml, or other appropriate concentration of human hepatic microsomes (e.g., commercially available, pooled characterized hepatic microsomes) for 0, 5, 10, 20, and 30 minutes, or other appropriate times, in the presence of an NADPH-generating system. Control incubations may be performed in the absence of hepatic microsomes for 0 and 30 minutes (triplicate). The samples may be analyzed for the presence of the compound. Incubation conditions that produce a linear rate of compound metabolism will be used a guide for further studies. Experiments known in the art can be used to determine the kinetics of the compound metabolism \( (K_m, V_{max}) \). The rate of disappearance of compound may be determined and the data analyzed according to Michaelis-Menten kinetics by using Lineweaver-Burk, Eadie-Hofstee, or nonlinear regression analysis.

Inhibition of metabolism experiments may then be performed. For example, a compound (one concentration, \( \leq K_m \)) may be incubated with pooled human hepatic microsomes in the absence or presence of a CYP inhibitor (such as ritonavir) under the conditions determined above. As would be recognized, control incubations should contain the same concentration of organic solvent as the incubations with the CYP inhibitor. The concentrations of the compound in the samples may be quantitated, and the rate of disappearance of parent compound may be determined, with rates being expressed as a percentage of control activity.

Methods for evaluating the influence of co-administration of a compound of the invention and a CYP inhibitor in a subject are also known (see, e.g., US2004/0028755; incorporated herein by reference). Any such methods could be used in connection with this invention to determine the pharmacokinetic impact of a combination. Subjects that would benefit from treatment according to this invention could then be selected.

Accordingly, one embodiment of this invention provides a method for administering an inhibitor of CYP3A4 and a compound of the invention. Another embodiment of this invention provides a method for administering an inhibitor of isozyme 3A4 ("CYP3A4"),
isozyme 2C19 ("CYP2C19"), isozyme 2D6 ("CYP2D6"), isozyme 1A2 ("CYP 1A2"), isozyme 2C9 ("CYP2C9"), or isozyme 2E1 ("CYP2E1"). In embodiments where the protease inhibitor is VX-950 (or a stereoisomer thereof), the CYP inhibitor preferably inhibits CYP3A4.

As would be appreciated, CYP3A4 activity is broadly observed in humans. Accordingly, embodiments of this invention involving inhibition of isozyme 3A4 would be expected to be applicable to a broad range of patients.

Accordingly, this invention provides methods wherein the CYP inhibitor is administered together with the compound of the invention in the same dosage form or in separate dosage forms.

The compounds of the invention (e.g., compound of Formula I or subformulae thereof) may be administered as the sole ingredient or in combination or alteration with other antiviral agents, especially agents active against HCV. In combination therapy, effective dosages of two or more agents are administered together, whereas in alternation or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus. The dosages given will depend on absorption, inactivation and excretion rate of the drug as well as other factors. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. The efficacy of a drug against the viral infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third antiviral compound that induces a different gene mutation than that caused by the principle drug in a drug resistant virus. Alternatively, the pharmacokinetic, biodistribution or other parameters of the drug can be altered by such combination or alternation therapy.

Daily dosages required in practicing the method of the present invention will vary depending upon, for example, the compound of the invention employed, the host, the mode of administration, the severity of the condition to be treated. A preferred daily dosage range is about from 1 to 50 mg/kg per day as a single dose or in divided doses. Suitable daily dosages for patients are on the order of from e.g. 1 to 20 mg/kg p.o. or i.v. Suitable unit dosage forms for oral administration comprise from ca. 0.25 to 10 mg/kg active ingredient, e.g. compound of Formula I or any subformulae thereof, together with one or more
pharmaceutically acceptable diluents or carriers therefor. The amount of co-agent in the
dosage form can vary greatly, e.g., 0.00001 to 1000mg/kg active ingredient.

Daily dosages with respect to the co-agent used will vary depending upon, for
example, the compound employed, the host, the mode of administration and the severity of
the condition to be treated. For example, lamivudine may be administered at a daily dosage
of 100mg. The pegylated interferon may be administered parenterally one to three times per
week, preferably once a week, at a total weekly dose ranging from 2 to 10 million IU, more
preferable 5 to 10 million IU, most preferable 8 to 10 million IU. Because of the diverse
types of co-agent that may be used, the amounts can vary greatly, e.g., .0001 to 5,000 mg/kg
day.

The current standard of care for treating hepatitis C is the combination of pegylated
interferon alpha with ribavirin, of which the recommended doses are 1.5 μg/kg/wk
peginterferon alfa-2b or 180 μg/wk peginterferon alfa-2a, plus 1,000 to 1,200 mg daily of
ribavirin for 48 weeks for genotype I patients, or 800 mg daily of ribavirin for 24 weeks for
genotype 2/3 patients.

The compound of the invention (e.g., compound of Formula I or subformulae
thereof) and co-agents of the invention may be administered by any conventional route, in
particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets
or capsules or parenterally, for example in the form of injectable solutions or suspensions.

Certain preferred pharmaceutical compositions may be e.g. those based on
microemulsions as described in UK 2,222,770 A.

The compound of the invention (e.g., compound of Formula I or subformulae thereof)
are administered together with other drugs (co-agents) e.g. a drug which has anti-viral
activity, especially anti-Flaviviridae activity, most especially anti-HCV activity, e.g. an
interferon, e.g. interferon-α-2a or interferon-α-2b, e.g. IntronR A, RoferonR, AvonexR, RebifR,
or BetaferonR, or an interferon conjugated to a water soluble polymer or to human albumin,
e.g. albuferon, an anti-viral agent, e.g. ribavirin, lamivudine, the compounds disclosed in US
patent no. 6,812,219 and WO 2004/002422 A2 (the disclosures of which are incorporated
herein by reference in their entirieties), an inhibitor of the HCV or other Flaviviridae virus
encoded factors like the NS3/4A protease, helicase or RNA polymerase or a prodrug of such
an inhibitor, an anti-fibrotic agent, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g.
imatinib, an immune modulating agent, e.g. mycophenolic acid, a salt or a prodrug thereof,
e.g. sodium mycophenolate or mycophenolate mofetil, or a SlP receptor agonist, e.g.
FTY720 or an analogue thereof optionally phosphorylated, e.g. as disclosed in EP627406A1,
Conjugates of interferon to a water-soluble polymer are meant to include especially conjugates to polyalkylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols, polyoxylethenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinyl pyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon-polymer conjugates are described in U.S. Pat. Nos. 4,766,106, 4,917,888, European Patent Application No. 0 236 987, European Patent Application No. 0 510 356 and International Application Publication No. WO 95/13090, the disclosures of which are incorporated herein by reference in their entireties. Since the polymeric modification sufficiently reduces antigenic responses, the foreign interferon need not be completely autologous. Interferon used to prepare polymer conjugates may be prepared from a mammalian extract, such as human, ruminant or bovine interferon, or recombinantly produced. Preferred are conjugates of interferon to polyethylene glycol, also known as pegylated interferons.

Especially preferred conjugates of interferon are pegylated alfa-interferons, for example pegylated interferon-α-2a, pegylated interferon-α-2b; pegylated consensus interferon or pegylated purified interferon-α-product. Pegylated interferon-α-2a is described e.g. in European Patent 593,868 (incorporated herein by reference in its entirety) and commercially available e.g. under the tradename PEGASYS® (Hoffmann-La Roche). Pegylated interferon-α-2b is described, e.g. in European Patent 975,369 (incorporated herein by reference in its entirety) and commercially available e.g. under the tradename PEG-INTRON A® (Schering Plough). Pegylated consensus interferon is described in WO 96/1 1953 (incorporated herein by reference in its entirety). The preferred pegylated α-interferons are pegylated interferon-α-2a and pegylated interferon-α-2b. Also preferred is pegylated consensus interferon.

Other preferred co-agents are fusion proteins of an interferon, for example fusion proteins of interferon-α-2a, interferon-Q/-2b; consensus interferon or purified interferon-α product, each of which is fused with another protein. Certain preferred fusion proteins comprise an interferon (e.g., interferon-α-2b) and an albumin as described in U.S. Patent 6,973,322 and international publications WO02/60071, WO05/003296 and WO05/077042
(Human Genome Sciences). A preferred interferon conjugated to a human albumin is Albuferon (Human Genome Sciences).

Cyclosporins which bind strongly to cyclophilin but are not immunosuppressive include those cyclosporins recited in U.S. Patents 5,767,069 and 5,981,479 and are incorporated herein by reference. Melle\textsuperscript{4}.Cyclosporin is a preferred non-immunosuppressive cyclosporin. Certain other cyclosporin derivatives are described in WO2006039668 (Scynexis) and WO2006038088 (Debiopharm SA) and are incorporated herein by reference. A cyclosporin is considered to be non-immunosuppressive when it has an activity in the Mixed Lymphocyte Reaction (MLR) of no more than 5%, preferably no more than 2%, that of cyclosporin A. The Mixed Lymphocyte Reaction is described by T. Meo in "Immunological Methods", L. Lefkovits and B. Peris, Eds., Academic Press, N.Y. pp. 227 - 239 (1979). Spleen cells (0.5 x 10\textsuperscript{6}) from Balb/c mice (female, 8 - 10 weeks) are co-incubated for 5 days with 0.5 x 10\textsuperscript{6} irradiated (2000 rads) or mitomycin C treated spleen cells from CBA mice (female, 8 - 10 weeks). The irradiated allogeneic cells induce a proliferative response in the Balb c spleen cells which can be measured by labeled precursor incorporation into the DNA. Since the stimulator cells are irradiated (or mitomycin C treated) they do not respond to the Balb/c cells with proliferation but do retain their antigenicity. The IC\textsubscript{50} found for the test compound in the MLR is compared with that found for cyclosporin A in a parallel experiment. In addition, non-immunosuppressive cyclosporins lack the capacity of inhibiting CN and the downstream NF-AT pathway. [Melle]\textsuperscript{4}-ciclosporin is a preferred non-immunosuppressive cyclophilin-binding cyclosporin for use according to the invention.

Ribavirin (1-/3-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog sold under the trade name, Virazole (The Merk Index, 11\textsuperscript{th} edition, Editor: Budavar, S, Merck & Co., Inc., Rahway, NJ, pl304,1989). United States Patent No. 3,798,209 and RE29,835 (incorporated herein by reference in their entirety) disclose and claim ribavirin. Ribavirin is structurally similar to guanosine, and has in vitro activity against several DNA and RNA viruses including \textit{Flaviviridae} (Gary L. Davis, Gastroenterology 118:S104-S1 14, 2000).

Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis, Gastroenterology 118:S104-S1 14, 2000). Thus, ribavirin alone is not effective in reducing viral RNA levels. Additionally, ribavirin has significant toxicity and is known to induce anemia. Ribavirin is not approved for monotherapy against HCV; it is approved in combination with interferon alpha-2a or interferon alpha-2b for the treatment of HCV.
A further preferred combination is a combination of a compound of the invention (e.g., a compound of Formula I or any subformulae thereof) with a non-immunosuppressive cyclophilin-binding cyclosporine, with mycophenolic acid, a salt or a prodrug thereof, and/or with a SIP receptor agonist, e.g. FTY720.

Additional examples of compounds that can be used in combination or alternation treatments include:

1. Interferons, including interferon alpha 2a or 2b and pegylated (PEG) interferon alpha 2a or 2b, for example:
   - (a) Intron-A®, interferon alfa-2b (Schering Corporation, Kenilworth, NJ);
   - (b) PEG-Intron®, peginterferon alfa-2b (Schering Corporation, Kenilworth, NJ);
   - (c) Roferon®, recombinant interferon alfa-2a (Hoffmann-La Roche, Nutley, NJ);
   - (d) Pegasys®, peginterferon alfa-2a (Hoffmann-La Roche, Nutley, NJ);
   - (e) Berefor®, interferon alfa 2 available (Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT);
   - (f) Sumiferon®, a purified blend of natural alpha interferons (Sumitomo, Japan)
   - (g) Wellferon®, lymphoblastoid interferon alpha n1 (GlaxoSmithKline);
   - (h) Infergen®, consensus alpha interferon (InterMune Pharmaceuticals, Inc., Brisbane, CA);
   - (i) Alferon®, a mixture of natural alpha interferons (Interferon Sciences, and Purdue Frederick Co., CT);
   - (j) Viraferon®;
   - (k) Consensus alpha interferon from Amgen, Inc., Newbury Park, CA,

Other forms of interferon include: interferon beta, gamma, tau and omega, such as Rebif (Interferon beta 1a) by Serono, Omniferon (natural interferon) by Viragen, REBIF (interferon beta-1a) by Ares-Serono, Omega Interferon by BioMedicines; oral Interferon Alpha by Amarillo Biosciences; an interferon conjugated to a water soluble polymer or to a human albumin, e.g., Albuferon (Human Genome Sciences), an antiviral agent, a consensus interferon, ovine or bovine interferon-tau

Conjugates of interferon to a water-soluble polymer are meant to include especially conjugates to polyalkylene oxide homopolymers such as polyethylene glocol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxid-based polymers, effectively non-antigenic materials such as dextran, polyvinyl pyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Since the polymeric
modification sufficiently reduces antigenic response, the foreign interferon need not be completely autologous. Interferon used to prepare polymer conjugates may be prepared from a mammalian extract, such as human, ruminant or bovine interferon, or recombinantly produced. Preferred are conjugates of interferon to polyethylene glycol, also known as pegylated interferons.

(2) Ribavirin, such as ribavirin (l-beta-D-ribofuranosyl-lH-l,2,4-triazole-3-carboxamide) from Valeant Pharmaceuticals, Inc., Costa Mesa, CA; Rebetol® from Schering Corporation, Kenilworth, NJ, and Copegus® from Hoffmann-La Roche, Nutley, NJ; and new ribavirin analogues in development such as Levovirin and Viramidine by Valeant,

(3) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo K. et al., Antiviral Research, 1996, 32, 9-18), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;


(5) A phenan-threnequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of Streptomyces sp., Sch 68631 (Chu M. et al., Tetrahedron Letters, 1996, 37, 7229-7232), and Sch 351633, isolated from the fungus Penicillium griseofulvum, which demonstrates activity in a scintillation proximity assay (Chu M. et al, Bioorganic and Medicinal Chemistry Letters 9, 1949-1952);

(6) Protease inhibitors. Examples include substrate-based NS3 protease inhibitors (Attwood et al., Antiviral peptide derivatives, PCT WO 98/22496, 1998; Attwood et al., Antiviral Chemistry and Chemotherapy 1999, 10, 259-273; Attwood et al, Preparation and use of amino acid derivatives as anti-viral agents, German Patent Pub. DE 19914474; Tung et al. Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease; PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate (Llinas-Brunet et al. Hepatitis C inhibitor peptide analogues, PCT WO 99/07734) are being investigated.

Non-substrate-based NS3 protease inhibitors such as 2,4,6-trihydroxy-3-nitrobenzamide derivatives (Sudo K. et al., Biochemical and Biophysical Research Communications, 1997, 238 643-647; Sudo K. et al. Antiviral Chemistry and Chemotherapy, 1998, 9, 186), including RD3-4082 and RD3-4078, the former substituted on the amide with
a 14 carbon chain and the latter processing α/ω-PhenoxoPhenyl group are also being investigated.

Sch 68631, a phenanthrenequinone, is an HCV protease inhibitor (Chu M et al., *Tetrahedron Letters* 37:7229-7232, 1996). In another example by the same authors, Sch 351633, isolated from the fungus *Penicillium griesofulvum*, was identified as a protease inhibitor (Chu M. et al., *Bioorganic and Medicinal Chemistry Letters* 9:1949-1952).

Nanomolar potency against the HCV NS3 protease enzyme has been achieved by the design of selective inhibitors based on the macromolecule eglin c. Eglin c, isolated from leech, is a potent inhibitor of several serine proteases such as S. griseus proteases A and B, V-chymotrypsin, chymase and subtilisin. Qasim M.A. et al., *Biochemistry* 36:1598-1607, 1997.

U.S. patents disclosing protease inhibitors for the treatment of HCV include, for example, U.S. Patent No. 6,004,933 to Spruce et al (incorporated herein by reference in its entirety) which discloses a class of cysteine protease inhibitors for inhibiting HCV endopeptidase 2; U.S. Patent No. 5,990,276 to Zhang et al. (incorporated herein by reference in its entirety) which discloses synthetic inhibitors of hepatitis C virus NS3 protease; U.S. Patent No. 5,538,865 to Reyes et al. (incorporated herein by reference in its entirety).

Peptides as NS3 serine protease inhibitors of HCV are disclosed in WO 02/008251 to Corvas International, Inc., and WO 02/08187 and WO 02/008256 to Schering Corporation (incorporated herein by reference in their entireties). HCV inhibitor tripeptides are disclosed in U.S. Patent Nos. 6,534,523, 6,410,531 and 6,420,380 to Boehringer Ingelheim and WO 02/060926 to Bristol Myers Squibb (incorporated herein by reference in their entireties).

Diaryl peptides as NS3 serine protease inhibitors of HCV are disclosed in WO 02/48172 to Schering Corporation (incorporated herein by reference). Imidazoleidenones as NS3 serine protease inhibitors of HCV are disclosed in WO 02/18198 to Schering Corporation and WO 02/48157 to Bristol Myers Squibb (incorporated herein by reference in their entireties). WO 98/17679 to Vertex Pharmaceuticals and WO 02/481 16 to Bristol Myers Squibb also disclose HCV protease inhibitors (incorporated herein by reference in their entireties).

HCV NS3-4A serine protease inhibitors including BILN 2061 by Boehringer Ingelheim, VX-950 by Vertex, SCH 6/7 by Schering-Plough, and other compounds currently in preclinical development;

Substrate-based NS3 protease inhibitors, including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an elecrophile such as a boronic acid or phosphonate; Non-substrate-based NS3 protease inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives including RD3-4082 and RD3-4078, the former substituted on the
amide with a 14 carbon chain and the latter processing a para-phenoxyphenyl group; and Sch6863 1, a phenanthrenequinone, an HCV protease inhibitor.

Sch 351633, isolated from the fungus Penicillium griseofulvum was identified as a protease inhibitor. EgHn c, isolated from leech is a potent inhibitor of several serine proteases such as S. griseus proteases A and B, a-chymotrypsin, chymase and subtilisin.

US patent no. 6004933 (incorporated herein by reference in its entirety) discloses a class of cysteine protease inhibitors from inhibiting HCV endopeptidase 2; synthetic inhibitors of HCV NS3 protease (pat), HCV inhibitor tripeptides (pat), diaryl peptides such as NS3 serine protease inhibitors of HCV (pat), Imidazolidindiones as NS3 serine protease inhibitors of HCV (pat).

Thiazolidines and benzanilides (ref). Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate especially compound RD-16250 possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193

Phenan-thenequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of Streptomyces sp, Sch68631 and Sch351633, isolated from the fungus Penicillium griseofulvum, which demonstrates activity in a scintillation proximity assay.

(7) Nucleoside or non-nucleoside inhibitors of HCV NS5B RNA-dependent RNA polymerase, such as 2'-C-methyl-3'-O-L-valine ester ribofuranosyl cytidine (Idenix) as disclosed in WO 2004/002422 A2 (incorporated herein by reference in its entirety), R803 (Rigel), JTK-003 (Japan Tabacco), HCV-086 (ViroPharma/Wyeth) and other compounds currently in preclinical development;

gliotoxin (ref) and the natural product cerulenin;

2'-fluoronucleosides;

other nucleoside analogues as disclosed in WO 02/057287 A2, WO 02/057425 A2, WO 01/90121, WO 01/92282, and US patent no. 6,812,219, the disclosures of which are incorporated herein by reference in their entirety.

Idenix Pharmaceuticals discloses the use of branched nucleosides in the treatment of flaviviruses (including HCV) and pestiviruses in International Publication Nos. WO 01/90121 and WO 01/92282 (incorporated herein by reference in their entireties).

Specifically, a method for the treatment of hepatitis C infection (and flaviviruses and pestiviruses) in humans and other host animals is disclosed in the Idenix publications that includes administering an effective amount of a biologically active 1', 2', 3' or 4'-branced B-
D or B-L nucleosides or a pharmaceutically acceptable salt or prodrug thereof, administered either alone or in combination with another antiviral agent, optionally in a pharmaceutically acceptable carrier. Certain preferred biologically active 1', 2', 3', or 4' branched B-D or B-L nucleosides, including Telbivudine, are described in U.S. Patents 6,395,716 and 6,875,751, each of which are incorporated herein by reference.

Other patent applications disclosing the use of certain nucleoside analogs to treat hepatitis C virus include: PCTCAOO/01316 (WO 01/32153; filed November 3, 2000) and PCT/CA01/00197 (WO 01/60315; filed February 19, 2001) filed by BioChem Pharma, Inc., (now Shire Biochem, Inc.); PCT/US02/01531 (WO 02/057425; filed January 18, 2002) and PCT/US02/03086 (WO 02/057287; filed January 18, 2002) filed by Merck & Co., Inc., PCT/EP 1/09633 (WO 02/18404; published August 21, 2001) filed by Roche, and PCT Publication Nos. WO 01/79246 (filed April 13, 2001), WO 02/32920 (filed October 18, 2001) and WO 02/48165 by Pharmasset, Ltd. (the disclosures of which are incorporated herein by reference in their entireties).

PCT Publication No. WO 99/43691 to Emory University (incorporated herein by reference in its entirety), entitled "2'-Fluoronucleosides" discloses the use of certain 2'-fluoronucleosides to treat HCV.

Eldrup et al. (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (April 27, 2003, Savannah, GA)) described the structure activity relationship of 2'-modified nucleosides for inhibition of HCV.

Bhat et al. (Oral Session V, Hepatitis C Virus, Flaviviridae, 2003 (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International conference on Antiviral Research (April 27, 2003, Savannah, Ga); p A75) describes the synthesis and pharmacokinetic properties of nucleoside analogs as possible inhibitors of HCV RNA replication. The authors report that 2'-modified nucleosides demonstrate potent inhibitory activity in cell-based replicon assays.

Olsen et al. (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (April 27, 2003, Savannah, Ga)p A76) also described the effects of the 2'-modified nucleosides on HCV RNA replication.


(9) HCV NS3 helicase inhibitors, such as VP_50406 by ViroPhama and compounds from Vertex. Other helicase inhibitors (Diana G.D. et al., Compounds, compositions and methods for treatment of hepatitis C, U.S. Patent No. 5,633,358 (incorporated herein by

(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5′ non-coding region (NCR) of the virus (Alt M. et al., *Hepatology*, 1995, 22, 707-717), or nucleotides 326-348 comprising the 3′end of the NCR and nucleotides 371-388 located in the core coding region of the HCV RNA (Alt M. et al., *Archives of Virology*, 1997, 142, 589-599; Galderisi U. et al., *Journal of Cellular Physiology*, 199, 181, 251-257); such as ISIS 14803 by Isis Pharm/Elan, antisense by Hybridon, antisense by AVI bioPharma,


(12) Ribozymes, such as nuclease-resistant ribozymes (Maccjak, D.J. et al., *Hepatology* 1999, 30, abstract 995) and those directed in U.S. Patent No. 6,043,077 to Barber et al., and U.S. Patent Nos. 5,869,253 and 5,610,054 to Draper et al. (incorporated herein by reference in their entireties) for example, HEPTAZYME by RPI

(13) siRNA directed against HCV genome

(14) HCV replication inhibitor of any other mechanisms such as by VP50406ViroPharma/Wyeth, inhibitors from Achillion, Arrow

(15) An inhibitor of other targets in the HCV life cycle including viral entry, assembly and maturation

(16) An immune modulating agent such as an IMPDH inhibitor, mycophenolic acid, a salt or a prodrug thereof sodium mycophenolate or mycophenolate mofetil, or Merimebodib (VX-497); thymosin alpha-1 (Zadaxin, by SciClone); or a SIP receptor agonist, e.g. FTY720 or analogue thereof optionally phosphorylated.

(17) An anti-fibrotic agent, such as a N-phenyl-2-pyrimidine-amine derivative, imatinib (Gleevac), IP-501 by Indevus, and Interferon gamma 1b from InterMune

(18) Therapeutic vaccine by Intercell, Epimmune/Genecor, Merix, Triep (Chron-VacC), immunotherapy (Therapore) by Avant, T cell therapy by CellExSys, monoclonal antibody XTL-002 by STL, ANA 246 and ANA 246 BY Anadys,

(19) Other miscellaneous compounds including 1-amino-alkylecyclohexanes (U.S. Patent No. 6,034,134 to Gold et al.), alkyl lipids (U.S. Pat. No. 5,922,757 to Chojkier et al.),
vitamin E and other antioxidants (U.S. Patent. No. 5,922,757 to Chojkier et al.), amantadine, bile acids (U.S. Pat. No. 5,846,99964 to Ozeki et al.), N-(phosphonoacetyl)-L-aspartic acid, (U.S. Pat. No. 5,830,905 to Diana et al.), benzenedicarboxamides (U.S. Pat. No. 5,633,388 to Diane et al.), polyadenylic acid derivatives (U.S. Pat. No. 5,496,546 to Wang et al.), 2’3’-dideoxyinosine (U.S. Pat. No. 5,026,687 to Yarchao et al.), benzimidazoles (U.S. Pat. No. 5,891,874 to Colacino et al.), plant extracts (U.S. Pat. No. 5,837,257 to Tsai et al., U.S. Pat. No. 5,725,859 to Omer et al., and U.S. Pat. No. 6,056,961) and piperidines (U.S. Pat. No. 5,830,905 to Diana et al.); the disclosures of which are incorporated herein by reference in their entireties. Also, squalene, telbivudine, N-(phosphonoacetyl)-L-aspartic acid, benzenedicarboxamides, polyadenylic acid derivatives, glycosylation inhibitors, and nonspecific cytoprotective agents that block cell injury caused by the virus infection.

(20) Any other compound currently in preclinical or clinical development for the treatment of HCV, including Interleukin-10 (Schering-Plough), AMANTADINE (Symmetrel) by Endo Labs Solvay, caspase inhibitor EDN-6556 by Idun Pharma, HCV/MF59 by Chiron, CIVACIR (Hepatitis C Immune Globulin) by NABI, CEPLENE (histamine dichloride) by Maxim, IDN-6556 by Idun PHARM, T67, a beta-tubulin inhibitor, by Tularik. a therapeutic vaccine directed to E2 by Innogenetics, FK788 by Fujisawa Helathcare, IdB 1016 (Siliphos, oral silybin-phosphatidyl choline phytosome), fusion inhibitor by Trimeris, Dication by Immtech, hemopurifier by Aethlon Medical, UT 231B by United Therapeutics.

(21) Purine nucleoside analog antagonists of T1R7 (toll-like receptors) developed by Anadys, e.g., Isotorabine (ANA245) and its prodrug (ANA975), which are described in European applications EP348446 and EP636372, International Publications WO03/045968, WO05/121162 and WO05/25583, and U.S. Patent 6/973322, each of which is incorporated by reference.


(22) Other co-agents (e.g., non-immunomodulatory or immunomodulatory compounds) that may be used in combination with a compound of this invention include, but are not limited to, those specified in WO 02/18369, which is incorporated herein by reference.

Methods of this invention may also involve administration of another component comprising an additional agent selected from an immunomodulatory agent; an antiviral agent;
an inhibitor of HCV protease; an inhibitor of another target in the HCV life cycle; a CYP inhibitor; or combinations thereof.

Accordingly, in another embodiment, this invention provides a method comprising administering a compound of the invention and another anti-viral agent, preferably an anti-HCV agent. Such anti-viral agents include, but are not limited to, immunomodulatory agents, such as α, β, and δ interferons, pegylated derivatized interferon-a compounds, and thymosin; other anti-viral agents, such as ribavirin, amantadine, and telbivudine; other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors); inhibitors of other targets in the HCV life cycle, including helicase, polymerase, and metalloprotease inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., compounds of United States Patent 5,807, 876,6, 498,178, 6,344, 465,6, 054,472, WO 97/40028, WO 98/40381, WO 00/56331, and mycophenolic acid and derivatives thereof, and including, but not limited to VX-497, VX-148, and/or VX-944); or combinations of any of the above.

In accordance with the foregoing the present invention provides in a yet further aspect:

- A pharmaceutical combination comprising a) a first agent which is a compound of the invention, e.g. a compound of formula I or any subformulae thereof, and b) a co-agent, e.g. a second drug agent as defined above.

- A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention, e.g. a compound of formula I or any subformulae thereof, and a co-agent, e.g. a second drug agent as defined above.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. Fixed combinations are also within the scope of the present invention. The administration of a pharmaceutical combination of the invention results in a beneficial effect, e.g. a synergistic therapeutic effect, compared to a monotherapy applying only one of its pharmaceutically active ingredients.

Each component of a combination according to this invention may be administered separately, together, or in any combination thereof. As recognized by skilled practitioners, dosages of interferon are typically measured in IU (e.g., about 4 million IU to about 12
If an additional agent is selected from another CYP inhibitor, the method would, therefore, employ two or more CYP inhibitors. Each component may be administered in one or more dosage forms. Each dosage form may be administered to the patient in any order.

The compound of the invention and any additional agent may be formulated in separate dosage forms. Alternatively, to decrease the number of dosage forms administered to a patient, the compound of the invention and any additional agent may be formulated together in any combination. For example, the compound of the invention inhibitor may be formulated in one dosage form and the additional agent may be formulated together in another dosage form. Any separate dosage forms may be administered at the same time or different times.

Alternatively, a composition of this invention comprises an additional agent as described herein. Each component may be present in individual compositions, combination compositions, or in a single composition.

**Exemplification of the Invention**

The invention is further illustrated by the following examples, which should not be construed as further limiting. The assays used throughout the Examples are accepted. Demonstration of efficacy in these assays is predictive of efficacy in subjects.

The following abbreviations are used throughout the examples and the specification.

**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
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<tbody>
<tr>
<td>abs.</td>
<td>Absolute</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>AcOEt / EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl (nBu = n-butyl, tBu = tert-butyl)</td>
</tr>
<tr>
<td>CDI</td>
<td>Carbonyldiimidazole</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]-undec-7-ene</td>
</tr>
</tbody>
</table>
DCE  1,2-Dichloroethane
DCM  Dichloromethane
DIPEA N-Ethyl_d_iisopropylamine
DMAP  Dimethylaminopyridine
DMF  N,N'-Dimethylformamide
DMSO  Dimethylsulfoxide
EI  Electronspray ionisation
Et₂O  Diethylether
Et₃N  Triethylamine
10 Ether  Diethylether
EtOH  Ethanol
FC  Flash Chromatography
h  hour(s)
HATU  O-(7-Azabenzotriazole-1-yl)-N,N,N',N'-
tetramethyluronium
tetramethyluronium hexafluorophosphate
HBTU  O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl  Hydrochloric acid
20 HOBt  1-Hydroxybenzotriazole
HPLC  High Performance Liquid Chromatography
H₂O  Water
L  liter(s)
LC-MS  Liquid Chromatography Mass Spectrometry
Me  methyl
MeI  Iodomethane
MeOH  Methanol
mg  milligram
min  minute(s)
30 mL  milliliter
MS  Mass Spectrometry
Pd/C  palladium on charcoal
PG  protecting group
Ph  phenyl
Prep  Preparative
Rf  ratio of fronts
RP  reverse phase
rt  Room temperature
SiO₂  Silica gel
TBAF  Tetrabutylammonium fluoride
TEA  Triethylamine
TFA  Trifluoroacetic acid
THF  Tetrahydrofuran
TLC  Thin Layer Chromatography

Trademarks
Hyflo = Celite® (The Celite Corporation) = filtering aid based on diatomaceous earth
Nucleosil = Nucleosil®, trademark of Machery & Nagel, Duren, FRG for HPLC materials.

Temperatures are measured in degrees Celsius. Unless otherwise indicated, the reactions take place at room temperature.

TLC conditions: Rf values for TLC are measured on 5 x 10 cm TLC plates, silica gel F254, Merck, Darmstadt, Germany.

HPLC (method A):
Instrument: Agilent system
column: Macherey-Nagel Nucleosil 100-3 C18 HD, particle size 3.5 Dm, pore size 100Å, length 70 mm, internal diameter 4 mm, flow 1.0 ml/min
solvent: CH₃CN (0.1% CF₃CO₂H); H₂O (0.1% CF₃CO₂H)
gradient: 0-6 min: 20-100% CH₃CN, 1.5 min: 100% CH₃CN, 0.5 min 100-20% CH₃CN

HPLC (method B):
Instrument: Kontron, Kroma-System
Column: Macherey-Nagel, Lichrosphere 100-5 RP 18
Solvent: CH$_3$CN (0.1% CF$_3$CO$_2$H); H$_2$O (0.1% CF$_3$CO$_2$H)
Gradient: 0-5 min: 10-100% CH$_3$CN; 5-7.5 min: 100% CH$_3$CN (Flow 1.5mL/min)

5 HPLC (method C):
Instrument: Agilent system
column: waters symmetry C18, 3.5 microm, 2.1 x 50mm, flow 0.6 ml/min
solvent: CH$_3$CN (0.1% CF$_3$CO$_2$H); H$_2$O (0.1% CF$_3$CO$_2$H)
gradient: 0-3.5 min: 20-95% CH$_3$CN, 3.5-5 min: 95% CH$_3$CN, 5.5-5.55 min 95% to 20% CH$_3$CN

10 MS (method D):
Instrument: Agilent 1100 Series
Detection: API-ES, positive/negative

15 LC-MS (method E):
Instrument: Agilent system
Column: Waters symmetry, 3.5 microm, 50 x 2.1 mm, 5 min, 20% to 95% CH$_3$CN
solvent: CH$_3$CN (0.1% HCO$_2$H); H$_2$O (0.1% HCO$_2$H)
gradient: 0-3.5 min: 20-95% CH$_3$CN, 3.5-5 min: 95% CH$_3$CN, 5.5-5.55 min 95% to 20% CH$_3$CN

Preparative HPLC (method F):
Instrument: Gilson system
column: waters C18 ODB, 5 microm, 50 x 19 mm
solvent: CH$_3$CN (0.1% HCO$_2$H); H$_2$O (0.1% HCO$_2$H)

Preparative HPLC (method G):
Instrument: Gilson
Column: Sun-Fire prep C18 OBD 5 microm, Column 19 x 50 mm (flow 20mL/min) or
30 Column: 30 x 100 mm (flow 40mL/min)
Solvent: CH$_3$CN (0.1% CF$_3$CO$_2$H) and H$_2$O (0.1% CF$_3$CO$_2$H)
Gradient: 0-20 min: 5-100% CH$_3$CN
Scheme 1: Keto-Sulfonamide macrocycles

In Scheme 1, the term "linker" refers to the L₁FG-L₂-L₃ residue of Formula I, the term "Pi" refers to the Ri residue of Formula I, and the term "P₂subst" refers to the R₂ residue of...
Scheme 2: Keto-Amide macrocycles (Synthesis of compounds in which $L_1$-FG-$L_2$-$L_3$ is an alkylene-amide-alkylene residue)

in Scheme 2, the term "linker" refers to the $L_i$-FG-$L_2$-$L_3$ residue of Formula I, the term "Pi" refers to the $R_1$ residue of Formula I, and the term "$P_2 subst$" refers to the $R_5$ residue of Formula I.
Example 1
(8S,1 OR)-10-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-5-[(lR,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-2,2-dioxo-2 λ*6*-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0*8,12*]heptacosa-l(27),23,25-triene-4,7,13,21-tetraone

To an ice-cold solution of 250 mg (0.25 mmol) (8-{2-[[((lR,2S)-l-[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenyl-carbamoyl]-}octanoic acid in 50 mL DCM/DMF (50:1) and 0.43 mL (2.5 mmol) of DIPEA is added 475 mg (1.3 mmol) HATU and the ice bath is removed. After stirring for 2 h the solvent is removed in vacuo and the residue is purified by preparative reverse phase HPLC (method G) to give the title compound as a colorless solid.

HPLC (method A) t_R = 4.78 min
TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0.5
MS (method D): 780 [M+]

Preparation of (8-{2-[[((lR,2S)-l-[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenyl-carbamoyl]-}octanoic acid

Step 1
[(lR,2S)-l-(2-Amino-benzenesulfonylamino)carbonyl]-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester

To a solution of 6.3 g (28 mmol) (IR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropane-
carboxylic acid (prepared according to WO 2000009558 Al) in 90 mL abs. THF is added 6.95 g (42 mmol) CDI and the mixture is refluxed for 2 h. After cooling to rt 5.1 g (29 mmol) 2-Aminobenzencesulfonamide and 6.5 g (42 mmol) DBU is added and stirring is continued for 45 min. The reaction mixture is diluted with 250 mL EtOAc and washed with 100 mL 0.5 N HCl and brine. The organic phase is dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is purified by FC on silica (eluent: CH₂Cl₂/MeOH 98:2) to give the title compound as a colorless solid.

HPLC (method A) tₚ = 3.99 min
TLC, Rf (CH₂Cl₂/MeOH 19:1) = 0.35
MS (method D): 382 [M+H]

Step 2

8-{2-[(lR,2S)-l-(2-tert-Butoxycarbonylamino-2-vinyl-cyclopropyl)carbamoyl]sulfamoyl]-phenylcarbamoyl}-octanoic acid methyl ester

To a solution of 2.65 g (13 mmol) Monomethyl azelate in 20 mL DCM is added at rt a solution of 1.87 g (16 mmol) Benzotriazole and 1.87 g (16 mmol) Thionylchloride in 10 mL DCM. The suspension is stirred for 1 h, filtered, washed with 20 mL DCM and the solvent is removed in vacuo. The residue is dissolved in 10 mL DCM and added at 0°C to a solution of 2.0 g (5.2 mmol) [(lR,2S)-l-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester, 5.1 g (50 mmol) NEt₃ and 100 mg DMAP in 50 mL DCM. After stirring for 15 h at rt the reaction is quenched by addition of aq. bicarbonate, extracted with DCM, dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is purified by FC on silica (eluent: CH₂Cl₂/MeOH 98:2 -> 95:5) to give the title compound as a red oil.

HPLC (method A) tₚ = 5.19 min
TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.46
MS (method D): 566 [M+]

Step 3
8-{2-[(IR,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyll-phenylcarbamoyl}-
acetic acid methyl ester

To a solution of 2.48 g (4.4 mmol) 8-{2-[(IR,2S)-1-tert-Butyloxycarbonylamino-2-vinyl-
cyclopropane-carbonyl]-sulfamoyl]-phenylcarbamoyl}-octanoic acid methyl ester in 4 mL
Dioxane is added 6 mL 4N HCl in Dioxane at rt and the mixture is stirred for 15 h. The
solvent is removed in vacuo to give the title compound as a hydrochloride salt which is used
without further purification.

HPLC (method A) \( t_R = 3.36 \) min

MS (method D): 466 [M+]

Step 4

(2S,4R)-2-[(IR,2S)-1-[2-(8-Methoxycarbonyl-octanoylamino)-
benzenesulfonylamino]carbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-
quinolin-4-yloxy)-pyrroHdine-l-carboxylic acid tert-butyl ester

To an ice-cold solution of 0.39 g (0.78 mmol) 8-{2-[(IR,2S)-1-Amino-2-vinyl-
cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl}-octanoic acid methyl ester (HCl-salt)
in 25 mL DCM is added 0.44 g (0.94 mmol) (2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l,2-dicarboxylic acid tert-butyl ester (prepared according to WO
2000009543), 0.46 g (1.2 mmol) HBTU and 0.51 g (3.9 mmol) DEPEA and the ice bath is
removed. After stirring for 15 h at rt the reaction is quenched by addition of aq. bicarbonate,
extracted with DCM, dried with \( \text{Na}_2\text{SO}_4 \), filtered and the solvent is removed in vacuo. The
residue is purified by FC on silica (eluent: CH$_2$Cl$_2$/MeOH 99:1 -> 95:5) to give the title compound as a colorless oil.

HPLC (method A) $t_R = 5.43$ min

MS (method D): 912 [M+]  

Step 5

8-{2-[(lR,2S)-l-[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yl oxy)-pyrrolidine-2-carbonyl]-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl}–octanoic acid

To a solution of 0.45 g (0.39 mmol) (2S,4R)-2-{(IR,2S)-l-[2-(8-Methoxycarbonyloctanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropyl carbamoyl}–4-(7-methoxy-2-phenyl-quinolin-4-yl oxy)-pyrrolidine-l-carboxylic acid tert-butyl ester is added 2 mL TFA at rt. After stirring for 1 h the solvent is removed in vacuo, the residue is dissolved in 10 mL THF/MeOH/H$_2$O (2:1:1) and 50 mg (2.1 mmol) LiOH is added at rt. After stirring for 15 h, pH 5 is adjusted by addition of IN HCl, the solvent is removed in vacuo, the residue is taken up in water and extracted with DCM. The combined organic phases are dried with Na$_2$SO$_4$, filtered and the solvent is removed in vacuo to give the title compound as a colorless oil, which is used without further purification.

HPLC (method A) $t_R = 4.49$ min

MS (method D): 798 [M+]

Example 2

(8S,10R)-10-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yl oxy]-5-[(lR,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-2,2-dioxo-2 $\lambda^6$-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0*8,12*]heptacosa-l(27),23,25-triene-4,7,13,21-tetraone
To an ice-cold solution of 90 mg (0.10 mmol) 8-\{2-\{(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl\}-amino\}-2-methyl-propionylsulfamoyl\}-phenylcarbamoyl\}-octanoic acid in 26 mL DCM/DMF (25:1) is added 135 mg (1.04 mmol) DIPEA followed by 59 mg (0.16 mmol) HATU. After 15 min the ice bath is removed and stirring is continued at rt for 1 h. The solvent is removed in vacuo and the residue is purified by preparative reverse phase HPLC (Method G) to give the title compound as a yellow solid.

HPLC (method A) \( t_R = 5.1 \) \text{ min} \\
TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH/H}_2\text{O/AcOH 75:27:5:0.5}) = 0.13 \)

MS (method D): 844 [M+]

**Preparation of** 8-\{2-\{(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl\}-amino\}-2-methyl-propionylsulfamoyl\}-phenylcarbamoyl\}-octanoic acid

**Step 1**

\[(2S,4R)-4-\{2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy\}-2-\{(\text{IR,2S})-1\-[2-(8-methoxycarbonyl-octanoylamino)\text{-benzenesulfonoylaminocarbonyl\}}-2-vinyl-cyclopropylcarbamoyl\}-pyrrolidine-1-carboxylic acid tert-butyl ester\]
The title compound is prepared analogously as described for the title compound in Example 1 (step 4) using 91 mg (0.18 mmol) 8-{2-\{[(lR,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl\}-phenyl-carbamoyl\}-octanoic acid methyl ester (HCl-salt), 95 mg (0.18 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (prepared according to WO 2005073216), 89 mg (0.23 mmol) HATU and 116 mg (0.90 mmol) DIPEA in 5 mL DMF.

HPLC (method A) $t_R = 5.71$ min

TLC, Rf (CH$_2$Cl$_2$/MeOH 9:1) = 0.42

**Step 2**

(2S,4R)-2-\{[(lR,2S)-1-\{2-(8-Carboxy-octanoylamino)-benzenesulfonylanilinocarbonyl\}-2-vinyl-cyclopropylcarbamoyl\}-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolitio-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of 103 mg (0.10 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2-\{[(1R,2S)-1-\{2-(methoxycarbonyl-octanoylamino)-benzenesulfonylanilinocarbonyl\}-2-vinyl-cyclopropylcarbamoyl\}-pyrrolidine-1-carboxylic
acid tert-butyl ester in 8 mL THF/MeOH/H₂O (2:1:1) is added 26 mg (1.1 mmol) LiOH at rt and the mixture is stirred for 2 h at 40°C. The solvent is removed in vacuo, pH 3 is adjusted by addition of IN HCl followed by extraction with DCM. The combined organic phase is washed with brine, dried with Na₂SO₄, filtered and the solvent is removed in vacuo to give the title compound as a yellow oil, which is used without further purification.

HPLC (method A) tᵣ = 5.23 min
TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.20
MS (method D): 962 [M+]

**Step 3**

8-(2-[(lR,2S)-l-[2-(8-Carboxy-octanoylamino)-benzenesulfonylamidocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carboxylic acid tert-butyl ester in 5 mL DCM is added 0.5 mL TFA at rt. After stirring for 2 h the solvent is removed in vacuo. To remove excess of TFA the residue is taken up in DCM and the solvent is removed in vacuo. This procedure is repeated three times. The title compound is obtained as a brown oil, which is used without further purification.

HPLC (method A) tᵣ = 4.55 min
TLC, Rf (CH₂Cl₂/MeOH/H₂O/AcOH 90:10:1:0.5) = 0.49
MS (method D): 862 [M+]

**Example 3**

4-Fluoro-1,3-dihydro-isooindole-2-carboxylic acid (8S,10R)-5-[(lR,2S)-l-carbonylamino-

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Example 3

4-Fluoro-1,3-dihydro-isooindole-2-carboxylic acid (8S,10R)-5-[(lR,2S)-l-carbonylamino-
2-vinyl-cyclopropyl]-2,2,4,7,13,21-hexaoxo-2 \(\lambda^6\)-thia-3,6,12,22-tetraazatriacyclo[21.4.0.0\(8,12^*\)]heptacosa-l(27),23,25-trien-10-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 using 119 mg (0.14 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-\{(lR,2S)-l-[2-(8-carboxy-octanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl\}-pyrrolidin-3-yl ester (TFA-salt), 182 mg (1.4 mmol) DIPEA and 268 mg (0.71 mmol) HATU.

HPLC (method A) \(t_R = 5.00\) min

TLC, \(R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 19:1) = 0.41\)

MS (method D): 710 [M+]+ 727 [M+H\_2O]

Preparation of (2S,4R)-4-(4-Fluoro-13-dihydro-isoindole-2-carbonyloxy)-pyrrolidine-1,2-dicarboxylic acid l-tert-butyl ester

Step 1

\((2S,4R)-4-(4-\text{Fluoro-1,3-dihydro-isoindole-2-carbonyloxy})\)-pyrrolidine-1,2-dicarboxylic acid l-tert-butyl ester 2-methyl ester

To a solution of 1.79 g (7.1 mmol) 2S,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid l-tert-butyl ester 2-methyl ester in 65 mL DCM is added 1.57 (9.2 mmol) CDI at it and the mixture is stirred for 1 h. A solution of 2.91 g (21.2 mmol) 4-Fluoro-2,3-dihydro-IH-
isoindole (prepared according to WO 2005037214) in 5 mL DCM is added and the reaction mixture is stirred at rt overnight. The mixture is diluted with DCM and washed three times with IN HCl, sat. NaHCO₃ and brine. The organic phase is dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is purified by FC (CH₂Cl₂/ZMeOH 98:2) to give the title compound as an oil.

LC-MS (method E) tᵣ = 3.76 min, [M-BOC] = 308
TLC, Rf(CH₂Cl₂/MeOH 9:1) = 0.85

Step 2

(ZS^[R^-]-Fluoro-l^-dihydro-isoiindole-l^-carbonyloxy^pyrrolidine-l^-dicarboxylic acid l-tert-butyl ester

To a mixture of 500 mg (1.2 mmol) (2S,4R)-4-(4-Fluoro-l,3-dihydro-isoiindole-2-carbonyloxy)-pyrrolidine-1,2-dicarboxylic acid l-tert-butyl ester 2-methyl ester in 10 mL THF/methanol/water (3:1:1) is added 62 mg (1.5 mmol) lithiumhydroxid-hydrate and the mixture is stirred at rt for 6 h. pH is adjusted to 3 and the mixture is extracted four times with DCM. The combined organic layers are washed with NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated in vacuo to yield the title compound which was used without further purification.

HPLC (method B) tᵣ = 3.15 min
LC-MS (method E) tᵣ = 3.49 min, [M-H] = 394
TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.48

Preparation of 4-Fluoro-l,3-dihydro-isoiindole-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-{((IR,2S)-l-[2-(8-carboxy-octanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester

Step 1
4-Fluoro-1,3-dihydro-isindo-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-{(lR,2S)-l-[2-(8-carboxy-octanoylaniino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 1 (step 4) using 200 mg (0.14 mmol) 8-{2-[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenyl carbamoyl-octanoic acid methyl ester (HCl-salt), 113 mg (0.29 mmol) (2S,4R)-4-(4-Fluoro-1,3-dihydro-isindo-2-carbonyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 136 mg (0.36 mmol) HATU and 93 mg (0.71 mmol) DIPEA in 5 mL DCM. HPLC (method A) = 5.72 min TLC, Rf(CH₂Cl₂:MeOH 9:1) = 0.50 MS (method D): 859 [M+H₂O]

Step 2
4-Fluoro-1,3-dihydro-isindo-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-{(lR,2S)-l-[2-(8-carboxy-octanoylaniino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}pyrrolidin-3-yl ester

To a solution of 118 mg (0.14 mmol) 4-Fluoro-1,3-dihydro-isindo-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-{(lR,2S)-l-[2-(8-carboxy-octanoylamiino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}pyrrolidin-3-yl ester...
benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester in 16 mL THF/MeOH/H$_2$O (2:1:1) is added 34 mg (1.4 mmol) LiOH at rt and the mixture is stirred for 2 h at 40°C. The solvent is removed in vacuo, pH 3 is adjusted by addition of IN HCl followed by extraction with DCM. The combined organic phase is washed with brine, dried with Na$_2$SO$_4$, filtered and the solvent is removed in vacuo to give the title compound as a yellow oil, which is used without further purification.

t$_R$ HPLC (method A) t$_R$ = 5.17 min
TLC, Rf (CH$_2$Cl$_2$/MeOH 85:15) = 0.54
MS (method D): 845 [M+H$_2$O]

Step 3
4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-{[(IR,2S)-1-[2-(8-carboxy-octanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester

To a solution of 116 mg (0.14 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-{[(IR,2S)-1-[2-(8-carboxy-octanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester in 25 mL DCM is added 1 mL TFA at rt. After stirring overnight the solvent is removed in vacuo. To remove excess of TFA the residue is taken up in DCM and the solvent is removed in vacuo, which is repeated three times. The title compound is obtained as a brown oil, which is used without further purification.

HPLC (method A) t$_R$ = 4.22 min
TLC, Rf (CH$_2$Cl$_2$/MeOH 85:15) = 0.56
MS (method D): 728 [M+]

Example 4
Il-[2-(l,2,3,4-tetrahydronaphthalene)]-8-[(lR,2S)-l-carbonylamino-2-vinyl-
The title compound is prepared analogously as described for the title compound in Example 2 using 65 mg (0.09 mmol) 8-[2-((1R,2S)-1-[(2-Amino-1,2,3,4-tetrahydro-naphthalene-2-carbonyl)-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid (TFA-salt), 114 mg (0.88 mmol) DIPEA and 167 g (0.44 mmol) HATU.

HPLC (method A) = 5.07 min
TLC, Rf (CH$_2$Cl$_2$/MeOH 85:15) = 0.23

MS (method D): 607 [M+]

**Preparation of** 8-[2-((1R,2S)-1-[(2-Amino-1,2,3,4-tetrahydro-naphthalene-2-carbonyl)-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid methyl ester

**Step 1**

8-[2-((1R,2S)-1-[(2-tert-Butoxycarbonylamino-1,2,3,4-tetrahydro-naphthalene-2-carbonyl)-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (step 4) using 150 mg (0.19 mmol) 8-[2-[[((1R,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-octanoic acid methyl ester (HCl-salt), 66 mg (0.22 mmol) 2-tert-Butoxycarbonylamino-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid, 84 mg (0.22
mmol) HBTU and 120 mg (0.93 mmol) DIPEA in 2 mL DMF.

HPLC (method A) $t_R = 5.77$ min

TLC, $R_f$ (CH$_2$Cl$_2$/MeOH 19:1) = 0.53

MS (method D): 739 [M+]

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**Step 2**

8-[2-(((lR,2S)-1-[2-Amino-1,2,3,4-tetrahydro-naphthalene-2-carbonyl]-amino]-2-vinyl-
cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid

The title compound is prepared analogously as described for the title compound in Example 1 (step 5) using 102 mg (0.14 mmol) 8-[2-(((lR,2S)-1-[2-tert-Butoxycarbonylamino-1,2,3,4-
tetrahydro-naphthalene-2-carbonyl]-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-
phenylcarbamoylj-octanoic acid methyl ester and 1 mL TFA in 10 mL DCM and 33 mg (1.4
mmol) LiOH in 12 mL THF/MeOH/H$_2$O (2:1:1).

HPLC (method A) $t_R = 3.93$ min

TLC, $R_f$ (CH$_2$Cl$_2$/MeOH 19:1) = 0.44

MS (method D): 625 [M+]

**Example 5**

ll-[2-indanyl]-8-[(lR,2S)-l-carbonyIainino-2-vinyl-cyclopropyl]-5,5-dioxo-
5,8,9,ll,12,15,16,17,18,19,20,22-dodecahydro-6H,14H-5λ*6*-thia-6,9,12,22-tetraaza-
benzocycloicosene-7,10,13^1-tetraone

Example 5
The title compound is prepared analogously as described for the title compound in Example 2 using 83 mg (0.012 mmol) 8-[(2-([IR,2S]-1-[(2-Amino-indane-2-carbonyl)-amino]-2-vinyl-cyclopropane-carbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid (TFA-salt), 149 mg (1.15 mmol) DEPEA and 219 g (0.58 mmol) HATU.

HPLC (method A) \( t_R = 4.91 \text{ min} \)
TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH 9:1}) = 0.25 \)
MS (method D): 593 [M+]

**Preparation of 8-[(2-([IR,2S]-1-[(2-Amino-indane-2-carbonyl)-amino]-2-vinyl-cyclopropane-carbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid**

**Step 1**

8-[(2-([IR,2S]-1-[(2-tert-Butoxycarbonylamino-indane-2-carbonyl)-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (step 4) using 163 mg (0.20 mmol) 8-[(2-([IR,2S]-1-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid methyl ester (HCl-salt), 67 mg (0.24 mmol) 2-tert-Butoxycarbonylamino-indane-2-carboxylic acid, 91 mg (0.24 mmol) HBTU and 130 mg (1.00 mmol) DIPEA in 2 mL DMF.

HPLC (method A) \( t_R = 5.61 \text{ min} \)
TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH 19:1}) = 0.41 \)
MS (method D): 725 [M+]

**Step 2**

8-[(2-([IR,2S]-1-[(2-tert-Butoxycarbonylamino-indane-2-carbonyl)-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid
The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 84 mg (0.12 mmol) 8-[2-((lR,2S)-[(2-tert-Butoxycarbonylamino-indane-2-carbonyl)-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid methyl ester and 28 mg (1.16 mmol) LiOH in 10 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) t_R = 5.02 min
TLC, Rf(CH₂Cl₂:MeOH 9:1) = 0.35
MS (method D): 711 [M+]

### Step 3

8-[2-((lR,2S)-[(2-tert-Butoxycarbonylamino-indane-2-carbonyl)-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid

The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 82 mg (0.12 mmol) 8-[2-((lR,2S)-[(2-tert-Butoxycarbonylamino-indane-2-carbonyl)-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid and 1 mL TFA in 25 mL DCM.

HPLC (method A) t_R = 2.85 min
MS (method D): 611 [M+]

### Example 6

12-Cyclopentylmethyl-8-[(lR,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-5,5-dioxo-5,8,9,ll,12,15,16,17,18,19,20,22-dodecahydro-6H,14H-5λ*6*-thia-6,9,12,22-tetraaza-
benzocycloicosene-?,! 0,1,3,21-tetraone

The title compound is prepared analogously as described for the title compound in Example 2 using 58 mg (0.08 mmol) 8-[2-([(IR,2S)-1-[(2-(Cyclopentylmethyl-amino)-acetylamino]-2-vinyl-cyclopropane-carbonyl]-sulfamoyl)-phenylcarbamoyl]-octanoic acid (TFA-salt), 106 mg (0.82 mmol) DIPEA and 156 mg (0.41 mmol) HATU in 5 mL DCM/MeOH (50:1).

HPLC (method A) \( t_R = 5.23 \) min
TLC, \( R_f \) (CH\(_2\)Cl\(_2\)/MeOH 85:15) = 0.23
MS (method D): 573 [M+H] + 590 [M+H\(_2\)O]

**Preparation of** (tert-Butoxycarbonyl-cyclopentylmethyl-amino)-acetic acid

**Step 1**
(Cyclopentylmethyl-amino)-acetic acid methyl ester

To a solution of 9.0 g (89 mmol) Cyclopentanecarboxaldehyde, 11.3 g (89 mmol) Glycine methylester hydrochloride and 13.1 g (116 mmol) NEt\(_3\) in 250 mL MeOH is added 2 g molecular sieves 4A. After stirring for 30 min at rt, 4.5 g (116 mmol) NaBH\(_4\) is added at 0\(^\circ\)C in 5 portions. The ice-bath is removed and stirring is continued for 2 h at rt. The reaction is quenched by addition of aq. bicarbonate, MeOH is evaporated and the residue is diluted with water. After extraction with DCM, the organic phase is washed with brine, dried with Na\(_2\)SO\(_4\), filtered and the solvent is removed in vacuo. The residue is purified by FC on silica (eluent: hexane/EtOAc 3:1) to give the title compound as a yellow oil.

TLC, \( R_f \) (hexane/EtOAc 1:1) = 0.55
MS (method D): 172 [M+H]

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Step 2
(tert-Butoxycarbonyl-cyclopentylmethyl-amino)-acetic acid methyl ester

A solution of 1.1 g (6.2 mmol) (Cyclopentylmethyl-amino)-acetic acid methyl ester and 1.25 g (12.4 mmol) NEt₃ in 60 mL DCM is cooled to 0°C and 2.03 g (9.3 mmol) (BOC)₂O is added. The ice-bath is removed after 15 min and stirring is continued for 2 h at rt. The reaction is quenched by addition of aq. bicarbonate and extracted with DCM. The organic phase is washed with brine, dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is purified by FC on silica (eluent: CH₂Cl₂/MeOH 99:1) to give the title compound as a yellow oil.

TLC, Rf (hexane/EtOAc 1:1) = 0.86
MS (method D): 216 [M⁺-55]

Step 3
(tert-Butoxycarbonyl-cyclopentylmethyl-ainino)-acetic acid

To a solution of 1.22 g (4.5 mmol) (tert-Butoxycarbonyl-cyclopentylmethyl-amino)-acetic acid methyl ester in 40 mL THF/MeOH/H₂O (2:1:1) is added 0.57 g (13.5 mmol) LiOH and the reaction stirred for 15 h at rt. The solvent is removed in vacuo, pH 3 is adjusted by addition of 4N HCl followed by extraction with EtOAc. The combined organic phase is washed with brine, dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is purified by FC on silica (eluent: CH₂Cl₂/MeOH 98:2) to give the title compound as a yellow oil.

TLC, Rf(CH₂Cl₂/ZMeOH 19:1) = 0.34
MS (method D): 202 [M⁺-55]

Preparation of 8-[2-((lR,2S)-1-[2-(Cyclopentylmethyl-amino)-acetylamino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-octanoic acid
Step 1

8-[2-(((R,2S)-L-L-2-(tert-Butoxycarbonyl-cyclopentylmethyl-amino)-acetylamino)-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-phenylcarbamoyl]-octanoic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (step 4) using 150 mg (0.19 mmol) 8-[2-(((R,2S)-L-L-Amino-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-phenylcarbamoyl]-octanoic acid methyl ester (HCl-salt), 57 mg (0.22 mmol) (tert-Butoxycarbonyl-cyclopentylmethyl-amino)-acetic acid, 84 mg (0.22 mmol) HBTU and 120 mg (0.93 mmol) DIPEA in 2 mL DMF.

HPLC (method A) t_R = 5.98 min

TLC, Rf (CH_2Cl_2/MeOH 19:1) = 0.30

MS (method D): 705 [M+]

Step 2

8-[2-(((R,2S)-L-L-(Cyclopentylmethyl-amino)-acetylamo)-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-phenylcarbamoyl]-octanoic acid

The title compound is prepared analogously as described for the title compound in Example 1 (step 5) using 102 mg (0.14 mmol) 8-[2-(((R,2S)-L-L-(Cyclopentylmethyl-amino)-acetylamo)-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-phenylcarbamoyl]-octanoic acid methyl ester and 1 mL TFA in 10 mL DCM and 33 mg (1.4 mmol) LiOH in 12 mL THF/MeOH/H_2O (2:1:1).
HPLC (method A) $t_R = 3.99$ min
TLC, $R_f(\text{CH}_2\text{Cl}_2/\text{MeOH 85:15}) = 0.57$
MS (method D): 591 [M+]

5 Example 7

(8S,10R)-10-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-5-[(lR,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-2,2-dioxo-$\lambda^6$-thia-3,6,12,23-tetraaza-tricyclo[22.4.0.(0*8,12*)]octacosa-l(28),24,26-triene-4,7,13,22-tetraone

The title compound is prepared analogously as described for the title compound in Example 2 using 150 mg (0.16 mmol) 9-{2-[[[(IR,2S)-l-[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropene-carbonyl]-sulfamoyl]-phenylcarbamoyl}-nonanoic acid (TFA-salt), 207 mg (1.6 mmol) DIPEA and 304 mg (0.80 mmol) HATU in 5 mL DCM/MeOH (50:1).

HPLC (method A) $t_R = 5.00$ min
TLC, $R_f(\text{CH}_2\text{Cl}_2/\text{MeOH 9:1}) = 0.5$
MS (method D): 794 [M+]

Preparation of (8-2-[[[(IR,2S)-l-[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-octanoic acid

Step 1

9-{2-[[[(IR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbo-$\pi$yl]-sulfamoyl]-phenylcarbamoyl]-nonanoic acid methyl ester
The title compound is prepared analogously as described for the title compound in Example 1 (Step 2) using 1.50 g (3.9 mmol) [(lR,2S)-l-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester, 2.12 g (9.8 mmol) Monomethyl sebacate, 1.41 g (11.8 mmol) Benzotriazole, 1.41 g (11.8 mmol) Thionylchloride, 1.84 g (20.0 mmol) NEt₃ and 100 mg DMAP in 50 mL DCM.

HPLC (method A) tᵣ = 5.42 min
TLC, Rf (CH₂Cl₂:MeOH 19:1) = 0.33
MS (method D): 580 [M+]

Step 2

9-{2-[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl}-nonanoic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (Step 3) using 1.10 g (1.9 mmol) 9-{2-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl}-nonanoic acid methyl ester and 3 mL 4 N HCl in Dioxane.

HPLC (method A) tᵣ = 3.65 min
MS (method D): 480 [M+]

Step 3

(2S,4R)-2-{(lR,2S)-l-[2-(9-Methoxycarbonyl-nonanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l-carboxylic acid tert-butyl ester
The title compound is prepared analogously as described for the title compound in Example 1 (Step 4) using 280 mg (0.43 mmol) 9-{2-[((IR,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-phenylcarbamoyl]-nonanoic acid methyl ester (HCl-salt), 218 mg (0.47 mmol) (2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 278 mg (2.15 mmol) DIPEA and 212 mg (0.56 mmol) HBTU in 2 mL DMF. HPLC (method A) t_R = 5.59 min
TLC, Rf (CH_2Cl_2/MeOH 19:1) = 0.23
MS (method D): 926 [M+]

**Step 4**

(2S,4R)-2-{((IR,2S)-1-[2-(9-Carboxy-nonanoylamino)-benzenesulfonfylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]^-T-methoxy-l-phenyl-quinolin^-yloxy^pyrrolidine-l-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (Step 2) using 152 mg (0.16 mmol) (2S,4R)-2-{((IR,2S)-1-[2-(9-Methoxycarbonyl-
nonanoylamino)-benzene-sulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-
 methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester and 38 mg
(1.6 mmol) LiOH in 8 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) \( t_R = 5.06 \) min

MS (method D): 912 [M+]

Step 5

9-{2-[((lR,2S)-l-[4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-
carbonyl]-amino)-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl}-
nonanoic acid

The title compound is prepared analogously as described for the title compound in Example 2
(Step 3) using 150 mg (0.16 mmol) (2S,4R)-2-((lR,2S)-l-2-(9-Carboxy-nonanoylamino)-
benze-sulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-
quinolin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester and 1 mL TFA in 5 mL
DCM.

HPLC (method A) \( t_R = 4.61 \) min

MS (method D): 812 [M+]

Example 8

(8S,10R)-10-2-(2-Isopropylamino-thiazol-4-yI)-7-methoxy-quinolin-4-yloxy]-5-[(lR,2S)-
l-carbonylamino-2-vinyl-cycIopropyl]-2,2-dioxo-2 \( \lambda^*6^*-\)thia-3,6,12,23-tetraaza-
tricyclo[22.4.0.0*8,12*]octacosa-l(28),24,26-triene-4,7,13,22-tetraone
The title compound is prepared analogously as described for the title compound in Example 2 using 57 mg (0.05 mmol) 9-(2-{{\((R,2S)-1-((2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarbonyl]-sulfamoyl}-phenylcarbamoyl)-nonanoic acid, 67 mg (0.52 mmol) DEPEA and 99 mg (0.26 mmol) HATU in 51 mL DCM/DMF (50:1).

HPLC (method A) \( t_R = 5.33 \) min

TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 9:1) = 0.30 \)

MS (method D): 858 [M+]

**Preparation of** 9-(2-{{\((R,2S)-1-((2S,4R)-4-[2-(2-Isopropyl-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarbonyl]-sulfamoyl}-phenylcarbamoyl)-nonanoic acid tert-butyl ester

**Step 1**

(2S,4R)-4-[2-(2-Isopropyl-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2-{{(R,2S)-1-[2-(8-methoxycarbonyl-octanoylamino]-benzenesulfonylaminocarbonyl]-Z-vinyl-cyclopropylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 150 mg (0.22 mmol) 9-\{2-[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl\}-phenylcarbamoyl\}-nonanoic acid methyl ester, 117 mg (0.22 mmol) (2S,4R)-4-\{2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-ylxy\}-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 101 mg (0.27 mmol) HATU and 143 mg (1.1 mmol) DIPEA in 5 mL DMF.

HPLC (method A) t_R = 5.80 min
TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0.30
MS (method D): 990 [M+]

**Step 2**

(2S,4R)-2-\{(lR,2S)-l-\{9-Carboxy-nonanoylamino\}-benzenesulfonfylaminocarbonyl\}-2-vinyl-cyclopropylcarbamoyl\}-4-\{2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinoliiii-4-ylxy\}-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 59 mg (0.053 mmol) (2S,4R)-4-\{2-(2-Isopropyl-thiazol-4-yl)-7-methoxy-quinolin-4-ylxy\}-2-\{(lR,2S)-l-\{8-methoxycarbonyl-octanoylamino\}-benzenesulfonfylaminocarbonyl\}-2-vinyl-cyclopropylcarbamoyl\} -pyrrolidine-1-carboxylic acid tert-butyl ester and 22 mg (0.53 mmol) LiOH in 8 mL THF/MeOH/H_2O (2:1:1).

HPLC (method A) t_R = 5.28 min
TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0.26
MS (method D): 976 [M+]

**Step 3**

9-\{(lR,2S)-l-\{(2S,4R)-4-\{2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-ylxy\}-pyrrolidine-1-carboxylic acid tert-butyl ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 50 mg (0.051 mmol) (2S,4R)-2-{(1R,2S)-1-[2-(9-Carboxy-nonanoylamino)-benzenesulfonyl-aminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester and 0.5 mL TFA in 5 mL DCM.

HPLC (method A) \( t_R = 4.74 \text{ min} \)

TLC, Rf \( (\text{CH}_2\text{Cl}_2/\text{MeOH/H}_2\text{O/AcOH} \ 90:10:1:0.5) = 0.16 \)

MS (method D): 876 [M+]

Example 9

\( (8S,10R)-10-(7\text{-Methoxy-2-phenyl-quinolin-4-yloxy})-5\{[(1R,2S)-1\text{-carbonylamino-2-vinyl-cyclopropyl}]\}-2,2\text{-dioxo-} \, \lambda^*6^*\text{-thia-3,6,12,21-tetraaza-tricyclo[20.4.0.0^{8,12}]hexacosa-l}(26),22,24\text{-triene-4,7,13,20-tetraone} \)
The title compound is prepared analogously as described for the title compound in Example 2 using 121 mg (0.14 mmol) 7-{2-[(R,2S)-1-[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-heptanoic acid (TFA-salt), 174 mg (1.4 mmol) DEPEA and 257 mg (0.66 mmol) HATU in 51 mL DCM/DMF (50:1).

HPLC (method A) $t_R = 4.68$ min
TLC, $R_f$ (CH$_2$Cl$_2$/MeOH 85:15) = 0.43
MS (method D): 766 [M+]

**Preparation of 7-{2-[(R,2S)-1-[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-heptanoic acid methyl ester**

**Step 1**

7-{2-[(R,2S)-1-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-heptanoic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (Step 2) using 0.76 g (1.99 mmol) [(R,2S)-1-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester, 0.94 g (4.97 mmol) Monomethyl suberate, 0.71 g (5.97 mmol) Benzotriazole, 0.71 g (5.97 mmol) Thionyl chloride, 0.92 g (10 mmol) NEt$_3$ and 70 mg DMAP in 40 mL DCM.

HPLC (method A) $t_R = 4.95$ min
TLC, $R_f$ (CH$_2$Cl$_2$/MeOH 19:1) = 0.23
MS (method D): 552 [M+]

**Step 2**

7-{2-[(R,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-heptanoic acid methyl ester
The title compound is prepared analogously as described for the title compound in Example 1 (Step 3) using 0.78 g (1.4 mmol) 7-{2-[((IR,2S)-1-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-phenylcarbamoyl}-heptanoic acid methyl ester and 1 mL 4N HCl in Dioxane.

HPLC (method A) t_R = 3.04 min
MS (method D): 452 [M+]

Step 3

(2S,4R)-2-{([R,2S]-1-[2-(7-Methoxycarbonyl-heptanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (Step 4) using 150 mg (0.22 mmol) 7-{2-[(IR,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl}-heptanoic acid methyl ester, 120 mg (0.26 mmol) (2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 98 mg (0.26 mmol) HBTU and 139 mg (1.1 mmol) DIPEA in 2 mL DMF.

HPLC (method A) t_R = 5.19 min

TLC, Rf (CH_2Cl_2/MeOH 19:1) = 0.43
MS (method D): 898 [M+]
Step 4

(2S,4R)-2-{(lR,2S)-l-[2-(7-Carboxy-heptanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (Step 2) using 179 mg (0.17 mmol) (2S,4R)-2-{(lR,2S)-l-[2-(7-Methoxycarbonyl-heptanoylamino)-benzenesulfonfylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l-carboxylic acid tert-butyl ester and 41 mg (1.7 mmol) LiOH in 10 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) t_R = 4.74 min
TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.32
MS (method D): 884 [M+]

Step 5

7-{2-[(lR,2S)-l-[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-ylxoy)-pyrrolidine-2-carbonyl]-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-heptanoic acid
The title compound is prepared analogously as described for the title compound in Example 2 (Step 3) using 134 mg (0.15 mmol) (2S,4R)-2-[(Lr,2S)-l-[2-(7-carboxy-heptanoylamino)benzenesulfonyl-aminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenylquinolin-4-yloxy)-pyrrolidine-l-carboxylic acid tert-butyl ester and 1 mL TFA in 25 mL DCM.

HPLC (method A) t<sub>R</sub> = 4.04 min
TLC, Rf (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 85:15) = 0.54
MS (method D): 784 [M+]

Example 10

(8S,10R)-10-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-5-[(Lr,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-2,2-dioxo-2*6*-thia-3,6,12,21-tetraaza-tricyclo[20.4.0.0*8,12*]hexacosa-l(26),22,24-triene-4,7,13,20-tetraone

The title compound is prepared analogously as described for the title compound in Example 2 using 121 mg (0.11 mmol) 7-(2-[(Lr,2S)-l-([(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)]:

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7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-
cyclopropanecarbonyl]-sulfamoyl]-phenyl-carbamoyl]-heptanoic acid (TFA-salt), 145 mg (1.1 mmol) DIPEA and 213 mg (0.56 mmol) HATU in 51 mL DCM/DMF (50:1).

HPLC (method A) \( t_R = 4.98 \) min

TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 85:15) = 0.46 \)

MS (method D): 830 [M+]

Preparation of 7-(2-{[(lR,2S)-1-({(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-
methoxy-quinolin-4-yloxyJ-pyrrolidine-2-carbonyl]-amino)-2-vinyl-
cyclopropanecarbonyl]-sulfamoyl]-phenyl-carbamoyl]-heptanoic acid

Step 1

(2S,4R)-4-2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2-{[(lR,2S)-1-
[2-(7-methoxycarbonyl-heptanoylamino]-benzenesulfonylaminocarbonyl]-2-vinyl-
cyclopropyl-carbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2
(step 1) using 170 mg (0.24 mmol) 7-[2-2-((lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-
sulfamoyl]-phenyl-carbamoyl]-heptanoic acid methyl ester (HCl-salt), 207 mg (0.29 mmol)

(2S,4R)-442-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1,2-
dicarboxylic acid 1-tert-butyl ester, 111 mg (0.29 mmol) HBTU and 158 mg (1.2 mmol)

DIPEA in 2 mL DMF.

HPLC (method A) \( t_R = 5.35 \) min

TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 19:1) = 0.27 \)

MS (method D): 962 [M+]
Step 2

(2S,4R)-2-{{(1R,2S)-1-[2-(7-Carboxy-heptanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yl]oxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 138 mg (0.14 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yl]oxy]-2-{{(1R,2S)-1-[2-(7-methoxycarbonyl-heptanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl} -pyrrolidine- 1-carboxylic acid tert-butyl ester and 35 mg (1.4 mmol) LiOH in 10 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) tₘₙ = 5.07 min
TLC, Rf (CH₂Cl₂/MeOH  85:15) = 0.55
MS (method D): 948 [M+]

Step 3

8-[[{(1R,2S)-1-[(2-Amino-indane-2-carbonyl)-amino]-2-vinyl-cyclopropenecarbonyl}]-sulfamoyl]-phenylcarbamoyl]-octanoic acid
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 135 mg (0.14 mmol) (2S,4R)-2-{[(lR,2S)-l-[2-(7-Carboxy-heptanoylamino)-benzenesulfonyl-aminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-{2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-l-carboxylic acid tert-butyl ester and 1 mL TFA in 25 mL DCM.

HPLC (method A) $t_R = 4.33$ min
TLC, Rf(CH$_2$Cl$_2$MeOH 85:15) = 0.46
MS (method D): 848 [M+]

Example 11

(8S,10R)-10-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-5-{[(IR,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-2,2-dioxo-6,-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0*8,12*Jheptacosa-l(27),23,25-triene-4,7,13-trione

The title compound is prepared analogously as described for the title compound in Example 2 using 80 mg (0.08 mmol) 9-{2-[(IR,2S)-l-[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-...
Preparation of 9-[(1R,2S)-1-{[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-nonanoic acid

Step 1

9-Hydroxy-nonanoic acid methyl ester

To an ice-cold solution of 10.0 g (45 mmol) Mono-methyl azelate in 250 mL THF is added 90 mL (90 mmol) BH₃*THF-Komplex (IM in THF), the ice-bath is removed and stirring is continued at rt for 90 min. The reaction is quenched by careful addition of Methanol, the main solvent is evaporated, the residue is diluted with water and extracted with EtOAc. The combined organic phase is dried with Na₂SO₄, filtered, and the solvent is removed in vacuo to give the title compound as a colorless oil, which is used without further purification.

MS (method D): 206 [M+H₂O]

Step 2

9-Oxo-nonanoic acid methyl ester

To a solution of 5.2 g (28 mmol) 9-Hydroxy-nonanoic acid methyl ester in 350 mL DCM is added 9.1 g (41 mmol) Pyridinium chlorochromate and the reaction is stirred for 15 h at rt. The reaction is diluted with DCM, silica is added, the mixture is filtered through a pad of Hyflo and thoroughly washed with DCM. The solvent is removed in vacuo to give the title compound as a green oil, which is used without further purification.

MS (method D): 204 [M+H₂O]
Step 3
9-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino]-nonanoic acid methyl ester

To a solution of 100 mg (0.26 mmol) [(lR,2S)-l-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester and 98 mg (0.52 mmol) 9-Oxo-nonanoic acid methyl ester in 15 mL 1,2-Dichloroethane is added at rt 0.045 mL (0.79 mmol) AcOH followed by 145 mg (0.67 mmol) NaBH(OAc)_3. After stirring for 15 h at rt the solvent is removed in vacuo and the residue is purified by preparative reverse phase HPLC (Method G) to give the title compound as a yellow oil.

HPLC (method A) t_R = 5.68 min
MS (method D): 552 [M+]

Step 4
9-[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino]-nonanoic acid methyl ester

To a solution of 2.10 g (1.56 mmol) 9-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropane-carbonyl]-sulfamoyl]-phenylamino]-nonanoic acid methyl ester in 50 mL Dioxane is added 25 mL 4N HCl in Dioxane and the reaction is stirred for 15 h at rt. The solvent is removed in vacuo and the residue is purified by preparative reverse phase HPLC (Method G) to give the title compound as an orange oil.

HPLC (method A) t_R = 4.00 min
TLC, R_f (CH_2Cl_2/MeOH 19:1) = 0.38
MS (method D): 452 [M+]
Step 5

(2S,4R)-2-{[(1R,2S)-l-[2-(8-Methoxycarbonyl-octylamino)-benzenesulfonylami πocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 105 mg (0.21 mmol) 9-{2-[[[(1R,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino]-nonanoic acid methyl ester, 95 mg (0.21 mmol) (2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l,2-dicarboxylic acid 1-tert-butyl ester, 102 mg (0.27 mmol) HATU and 133 mg (1.0 mmol) DIPEA in 5 mL DMF.

HPLC (method A) t_R = 5.83 min
MS (method D): 898 [M+]

Step 6

(2S,4R)-2-{[(1R,2S)-l-[2-(8-Carboxy-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l-carboxylic acid tert-butyl ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 73 mg (0.08 mmol) (2S,4R)-2-[(IR,2S)-1-[2-(8-Methoxycarbonyl-octylamino)-benzenesulfonyl-amino-carbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester and 20 mg LiOH in 8 mL THF/MeOH/H2O (2:1:1).

HPLC (method A) \( t_R = 5.29 \) min
TLC, \( R_f \) (CH\(_2\)Cl\(_2\)/MeOH/H\(_2\)O/AcOH 90:10:1:0.5) = 0.66
MS (method D): 884 [M+]

**Step 7**

9-{{(IR,2S)-1-[[2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino]-2-vinyl-cyclopanecarbonyl]-sulfamoyl]-phenylamino]-nonanoic acid

![Chemical structure](image)

The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 71 mg (0.08 mmol) (2S,4R)-2-[(IR,2S)-1-[2-(8-Carboxy-octylamino)-benzenesulfonyl-amino-carbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester and 0.3 mL TFA in 5 mL DCM.

HPLC (method A) \( t_R = 4.78 \) min
TLC, \( R_f \) (CH\(_2\)Cl\(_2\)/MeOH/H\(_2\)O/AcOH 90:10:1:0.5) = 0.41
MS (method D): 784 [M+]

**Example 12**

(8S,10R)-10-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-5-[(IR,2S)-1-carbonylamino-2-vinyl-cyclopropyl]-2,2-dioxo-2 \( \lambda^6 \)-thia-3,6,12,22-tetraaza-
tricyclo[21.4.0.0^8,12]heptacosa-l(27),23,25-triene-4,7,13-trione πe

The title compound is prepared analogously as described for the title compound in Example 2 using 168 mg (0.14 mmol) 9-[(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino)-nonanoic acid (TFA-salt), 182 mg (1.4 mmol) DIPEA and 268 mg (0.71 mmol) HATU in 75 mL DCM and 1 mL DMF.

HPLC (method A) \( t_R = 5.90 \) min
TLC, Rf (CH\(_2\)Cl\(_2\)/MeOH 19:1) = 0.37

MS (method D): 830 [M+]

**Preparation of** 9-[(2R,2S)-1-([(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino)-nonanoic acid tert-butyl ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 200 mg (0.44 mmol) 9-{2-[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenyl-amino}-nonanoic acid methyl ester, 234 mg (0.44 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yl]oxy]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 219 mg (0.58 mmol) HATU and 287 mg (2.2 mmol) DDPEA in 5 mL DMF. HPLC (method A) $t_R = 6.1$ min 
TLC, $R_f$ (CH$_2$Cl$_2$/MeOH 9:1) = 0.81
MS (method D): 962 [M+]

**Step 2**
(IS$^R$I-KIR-IS$^A$I-$^S$-Carboxy-octylamino$^b$benzenesulfonylaminocarbonyl]-$^l$-vinyl-cyclopropylcarbamoyl)-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yl]oxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 174 mg (0.18 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yl]oxy]-2-[(lR,2S)-l-[(8-methoxycarbonyl-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropyl-carbamoyl]-pyrrolidine-1-carboxylic
acid tert-butyl ester and 44 mg (1.81 mmol) LiOH in 14 mL THF/MeOH/H_2O (2:1:1).

HPLC (method A) t_R = 5.58 min
TLC, Rf (CH_2Cl_2/MeOH) = 0.27
MS (method D): 948 [M+]

Step 3

9-((2S,4R)-2-((lR,2S)-l-amino)-2-vinyl-cyclopropylcarbamoyl)-4-(2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carboxylic acid tert-butyl ester and 4 mg (1.81 mmol) LiOH in 14 mL THF/MeOH/H_2O (2:1:1).

HPLC (method A) t_R = 5.58 min
TLC, Rf (CH_2Cl_2/MeOH) = 0.27
MS (method D): 948 [M+]

Example 13

4-Fluoro-1,3-dihydro-isooindoIe-2-carboxylic acid (8S,10R)-5-((lR,2S)-1-carbonylamino-2-vinyl-cyclopropyl)-2,2,4,7,13-pentaaxo-2 λ*6*-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0^{8,12}]heptacosa-l(27),23,25-trien-10-yl ester
The title compound is prepared analogously as described for the title compound in Example 2 using 78 mg (0.08 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-{(1R,2S)-1-[2-(8-carboxy-octylamino)-benzenesulfonylamino carbonyl]-2-vinyl-cyclopropylcarbamoyl}-pyrrolidin-3-yl ester (TFA-salt), 107 mg (0.83 mmol) DIPEA and 158 mg (0.42 mmol) HATU in 50 mL DCM and 1 mL DMF.

HPLC (method A) t_R = 5.65 min
TLC, R_f (CH_2Cl_2/MeOH 19:1) = 0.27
MS (method D): 696 [M+] 

Preparation of 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-{(1R,2S)-1-[2-(8-carboxy-octylamino)-benzenesulfonylamino carbonyl]-2-vinyl-cyclopropylcarbamoyl}-pyrrolidin-3-yl ester

Step 1
4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-{(1R,2S)-1-[2-(8-methoxycarbonyl-octylamino)-benzenesulfonylamino carbonyl]-2-vinyl-cyclopropylcarbamoyl}-pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 150 mg (0.18 mmol) 9-{2-[(1R,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl]-
sulfamoyl]-phenyl-amino]-nonanoic acid methyl ester, 71 mg (0.18 mmol) (2S,4R)-4-(4-
Fluoro-1,3-dihydro-isoiindle-2-carboxyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl
ester, 103 mg (0.27 mmol) HATU and 70 mg (0.54 mmol) DIPEA in 5 mL DCM.

HPLC (method A) $t_R = 6.10$ min

TLC, $R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 9:1) = 0.69$

MS (method D): $828 [\text{M}+]$

Step 2

4-Fluoro-1,3-dihydro-isoiindle-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-
{(1R,2S)-1-[2-(8-carboxy-octylamino)-benzenesulfonylamino-carbonyl]-2-vinyl-
cyclopropylcarbamoyl}-pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 2
(step 2) using 80 mg (0.09 mmol) 4-Fluoro-1,3-dihydro-isoiindle-2-carboxylic acid (3R,5S)-
1-tert-butoxycarbonyl-5-{(1R,2S)-1-[2-(8-methoxycarbonyl-octylamino)-
benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl}-pyrrolidin-3-yl ester and 36
mg (0.85 mmol) LiOH in 12 mL THF/MeOH/H$_2$O (2:1:1).

HPLC (method A) $t_R = 5.53$ min

TLC, $R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 9:1) = 0.51$

MS (method D): $814 [\text{M}+]$

Step 3

4-Fluoro-1,3-dihydro-isoiindle-2-carboxylic acid (3R,5S)-5-{(1R,2S)-1-[2-(8-carboxy-
octylamino)-benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl}-pyrrolidin-
3-yl ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 68 mg (0.08 mmol) 4-Fluoro-1,3-dihydro-isooindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-\{(IR,2S)-1-[2-(8-carboxy-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl\}-pyrrolidin-3-yl ester and 1 mL TFA in 5 mL DCM.

HPLC (method A) \( t_R = 4.74 \text{ min} \)

TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} \ 9:1) = 0.35 \)

MS (method D): 714 [M+]

**Example 14**

The title compound is prepared analogously as described for the title compound in Example 2 using 23 mg (0.03 mmol) 3-\{-2-{\{(lR,2S)-1-\{[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino\}-2-vinyl-cyclopropanecarbonyl\}-sulfamoyl]-phenylcarbamoyl\}-methyl\}-phenyl\}-propionic acid (TFA-salt), 32 mg (0.25 mmol) DIPEA and 48 mg (0.71 mmol) HATU in 10 mL DCM and 0.2 mL DMF.

HPLC (method A) \(t_R = 4.58\) min
TLC, \(R_f\) (CH\(_2\)Cl\(_2\)/MeOH 9:1) = 0.44
MS (method D): 800 [M+]

**Preparation of** 3-\{-2-{\{(lR,2S)-1-\{[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino\}-2-vinyl-cyclopropanecarbonyl\}-sulfamoyl]-phenylcarbamoyl\}-methyl\}-phenyl\}-propionic acid

**Step 1**

(E)-3-(3-Carboxymethyl-phenyl)-acrylic acid methyl ester

A microwave-vial is charged with 2.2 g (10 mmol) 3-Bromophenylacetic acid, 2.62 g (30 mmol) Methyl acrylate, 0.31 g (1.0 mmol) P(o-tol)\(_3\), 90 mg (0.4 mmol) Pd(OAc)\(_2\), and 1.2 g (12 mmol) NEt\(_3\). The vial is purged with argon, sealed and heated in the microwave (Personal Chemistry, Emrys Optimizer) for 15 min at 150°C. After cooling to rt the mixture is diluted with water and EtOAc, filtered through a pad of Hyflo and washed thoroughly with EtOAc. The filtrate is separated, the aqueous phase is extracted with EtOAc and the combined organic phases are dried with Na\(_2\)SO\(_4\), filtered and the solvent is removed in vacuo. The residue is purified by FC on silica (eluent: CH\(_2\)Cl\(_2\)/MeOH 98:2 - 95:5) to give the title compound as a colorless solid.

HPLC (method A) \(t_R = 3.14\) min
TLC, \(R_f\) (CH\(_2\)Cl\(_2\)/MeOH 19:1) = 0.22
MS (method D): 221 [M+H]

**Step 2**
3-(3-Carboxymethyl-phenyl)-propionic acid methyl ester

A shaking flask charged with 3.9 g (16.0 mmol) (E)-3-(3-Carboxymethyl-phenyl)-acrylic acid methyl ester and 0.4 g 10% Pd/C (Engelhard 4505) in 80 mL EtOAc is purged with hydrogen and shaken for 10 h. The catalyst is removed by filtration, washed with EtOAc and the filtrate is concentrated in vacuo to give the title compound as a colorless solid which is used without further purification.

HPLC (method A) \( t_R = 2.96 \) min
TLC, Rf(CH\(_2\)Cl\(_2\)/MeOH 19:1) = 0.19

Step 3

3-[3-{[2-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl}-methyl]-phenyl]-propionic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (Step 2) using 1.0 g (2.6 mmol) [(lR,2S)-l-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester, 2.0 g (9.0 mmol) 3-(3-Carboxymethyl-phenyl)-propionic acid methyl ester, 1.30 g (10.8 mmol) Benzotriazole, 1.30 g (10.8 mmol) Thionylchlordie, 2.65 g (26 mmol) NEt\(_3\) and 100 mg DMAP in 40 mL DCM.

HPLC (method A) \( t_R = 4.90 \) min
TLC, Rf (CH\(_2\)Cl\(_2\)/MeOH 19:1) = 0.36
MS (method D): 613 [M+H\(_2\)O]

Step 4
3-[3-([(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfainoyl]-phenylcarbamoyl}-methyl)-phenyl]-propionic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (Step 3) using 0.38 g (0.59 mmol) 3-[3-([(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropane-carbonyl]-sulfamoyl]-phenylcarbamoyl]-methyl)-phenyl]-propionic acid methyl ester and 5 mL 4N HCl in Dioxane.

HPLC (method A) t_R = 3.09 min

MS (method D): 486 [M+]

Step 5

(2S,4R)-2-[(lR,2S)-l-(2-[3-(2-Methoxycarbonyl-ethyl)-phenyl]-acetylamino]-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (step 4) using 114 mg (0.59 mmol) 3-[3-([(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-methyl)-phenyl]-propionic acid methyl ester, 73 mg (0.16 mmol) (2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l,2-
dicarboxylic acid 1-tert-butyl ester, 90 mg (0.24 mmol) HATU and 102 mg (0.79 mmol)
DIPEA in 5 mL DMF.
HPLC (method A) \( t_R = 5.20 \) min
TLC, \( \text{Rf}(\text{CH}_2\text{Cl}_2/\text{MeOH} 9:1) = 0.38 \)

**Step 6**

\((2S,4R)-2-[(lR,2S)-1-(2-\{2-[3-(2-Methoxycarbonyl-ethyl)-phenyl]-acetyl-amino}\}
benzenesulfonamidocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-
quinolin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2
(step 2) using 28 mg (0.03 mmol) (2S,4R)-2-[(lR,2S)-1-(2-\{2-[3-(2-Methoxycarbonyl-ethyl)-
phenyl]-acetyl-amino}\}-benzenesulfonamidocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-4-(7-
methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester and 13 mg
(0.3 mmol) LiOH in 8 mL THF/MeOH/H\(_2\)O (2:1:1).

HPLC (method A) \( t_R = 4.77 \) min
TLC, \( \text{Rf}(\text{CH}_2\text{Cl}_2/\text{MeOH} 9:1) = 0.17 \)
MS (method D): 918 [M+]

**Step 7**

3-[3-\{2-[(lR,2S)-1-\{(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-
carbonyl]-amino\}-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl]-methyl)-phenyl]-propionic acid
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 26 mg (0.03 mmol) (2S,4R)-2-[(lR,2S)-l-(2-[2-[3-(2-Carboxy-ethyl)-phenyl]acetylamino]-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-l-carboxylic acid tert-butyl ester and 1 mL TFA in 5 mL DCM.

HPLC (method A) t_R = 3.82 min

TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0.35

MS (method D): 818 [M+]

Example 15

8S,10R)-10-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-5-[(lR,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-2,2-dioxo-16,19-dioxo-\lambda^6*-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0*8,12*]heptacosa-l(27),23,25-triene-4,7,13,21-tetraone

The title compound is prepared analogously as described for the title compound in Example 2
using 20 mg (0.02 mmol) 3-{2-[2-(2-{[(IR,2S)-1-((2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino)-ethoxy]-ethoxy} -propionic acid (TFA-salt), 22 mg (0.20 mmol) DIPEA and 32 mg (0.09 mmol) HATU in 10 mL DCM and 0.2 mL DMF.

HPLC (method A) \( t_R = 4.65 \) min
TLC, \( R_f(\text{CH}_2\text{Cl}_2\text{MeOH} \ 9:1) = 0.34 \)
MS (method D): 834 [M+]

Preparation of 3-{2-[2-(2-Oxo-ethoxy)-ethoxy]-propionic acid methyl ester

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To a solution of 20 g (0.19 mol) 2-Allyloxyethanol in 250 mL abs. THF is added 44 mg Sodium and the mixture is refluxed until the sodium disappears. After cooling to RT 28.3 g (0.33 mol) methyl acrylate is added and stirring is continued overnight. The solvent is removed in vacuo, 400 mL MeOH and 1 mL cone. \( \text{H}_2\text{SO}_4 \) is added and the mixture is refluxed overnight. The solvent is removed in vacuo and the residue is purified by FC on silica (eluent: hexane/EtOAc 3:1) to give the title compound as a colorless oil.

TLC, \( R_f(\text{hexane/EtOAc} \ 3:1) = 0.48 \)
MS (method D): 206 [M+18]

Step 2

3-[2-(2-Oxo-ethoxy)-ethoxy]-propionic acid methyl ester

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\end{array}} \]

A suspension of 1.5 g (8.0 mmol) 3-(2-Allyloxy-ethoxy)-propionic acid methyl ester and 134 mg (1.6 mmol) sodium bicarbonate in 160 mL DCM is cooled to \(-78^\circ\text{C}\). Ozone is bubbled through until a blue color appears (-15 min). Oxygen is bubbled through the mixture for 2
min to remove excess of ozone, 2.7 g (10 mmol) PPh₃ is added and stirring is continued for 1 h at -78°C. After warming to RT, the solvent is removed in vacuo and the residue is used without further purification.

5 Step 3
3-[2-(2-{2-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-ethoxy)-ethoxy]-propionic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 11 (step 3) using 200 mg (0.52 mmol) [(IR,2S)-l-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester, 500 mg crude 3-[2-(2-Oxo-ethoxy)-ethoxy]-propionic acid methyl ester (from the previous step), 292 mg (1.31 mmol) NaBH(OAc)₃ and 94 mg (1.6 mmol) AcOH in 20 mL 1,2 DCE HPLC (method A) tᵣ = 4.57 min
MS (method D): 556 [M+]

Step 4
3-[2-(2-{2-[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-ethoxy)-ethoxy]-propionic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 11 (step 4) using 485 mg (0.58 mmol) 3-[2-(2-[2-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-ethoxy)-ethoxy]-propionic acid methyl ester and 1.5 mL TFA in 20 mL DCM.
HPLC (method A) tᵣ = 2.64 min
MS (method D): 456 [M+]
Step 5

(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2-[2-{2-(2-methoxycarbonyl-ethoxy)-ethoxyl-ethylamino}]-benzenesulfonfylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 235 mg (0.34 mmol) 3-[2-(2-{2-[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-ethoxy)-ethoxy]-propionic acid methyl ester, 182 mg (0.34 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1,2-dicarboxylic acid l-tert-butyl ester, 196 mg (0.52 mmol) HATU and 134 mg (1.0 mmol) DIPEA in 20 mL DCM.

HPLC (method A) t_R = 5.08 min

TLC, Rf(CH_2Cl_2/Me0H 9:1) = 0.31

MS (method D): 966 [M+]

Step 6

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 170 mg (0.18 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2-[(1R,2S)-1-(2-2-[2-(2-methoxycarbonyl-ethoxy)-ethoxy]-ethylamino)-benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidine-l-carboxylic acid tert-butyl ester (TFA-salt) and 76 mg (1.8 mmol) LiOH in 20 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) tR = 4.79 min
TLC, Rf(CH₂Cl₂/MeOH 9:1) = 0.33

MS (method D): 952 [M+]

Step 7

(2S,4R)-2-[(1R,2S)-1-(2-[2-(2-Carboxy-ethoxy)-ethoxy]-ethylamino]-benzenesulfonylamino-carbonyl)-2-vinyl-cyclopropylcarbamoyl]-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-l-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 12 mg (0.01 mmol) (2S,4R)-2-[(1R,2S)-1-(2-[2-(2-Carboxy-ethoxy)-ethoxy]...
ethoxy]-ethylamino]-benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-[2-
(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1-carboxylic
acid
tert-butyl ester (TFA-salt) and 0.1 mL TFA in 3 mL DCM.

HPLC (method A) \( t_R = 4.27 \) min

TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} \text{H}_2\text{O}/\text{AcOH} \text{90:10:1:0.5}) = 0.26 \)

MS (method D): 852 [M+]

**Example 16**

\((8S,10R)-10-[2-(2-Isop^opylallino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-5-\[(lR,2S)-
1-carbonylamino-2-vinyl-cyclopropyl]-2,2-dioxo-16,19-dioxo- \lambda^*6*-thia-3,6,12,22-
tetraaza-tricyclo[21.4.0.0^8,12^*]heptacosa-l(27),23,25-triene-4,7,13,21-tetraone

The title compound is prepared analogously as described for the title compound in Example 2

using 108 mg (0.10 mmol) 3-{2-[(2-\{(IR,2S)-l-\{(2S,4R)-4-[2-(2-Isopropylamino-thiazoI-
4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-
cyclopropanecarbonylj-sulfamoyl}-phenylcarbamoyl)-methoxy]-ethoxy} -propionic acid
(TFA-salt), 128 mg (1.0 mmol) DEPEA and 188 mg (0.5 mmol) HATU in 100 mL DCM and
2 mL DMF.

HPLC (method A) \( t_R = 4.50 \) min

TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} \text{9:1}) = 0.18 \)

MS (method D): 848 [M+]

**Preparation of** 33-\{2-[(2-\{(IR,2S)-l-\{(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-
methoxy-quinolin-4-yloxyJ-pyrrolidine-2-carbonyl]-amino)-2-vinyl-
cyclopropanecarbonylj-sulfamoyl}-phenylcarbamoyl]-methoxy]-ethoxy\} -propionic acid
Step 1

3-(2-Carboxymethoxy-ethoxy)-propionic acid methyl ester

To a solution of 1.0 g (5.3 mmol) 3-(2-allyloxy-ethoxy)-propionic acid methyl ester (according to example 15 step 1) in 50 mL CCl₄:ZACNZH₂O (2:2:3) is added 5.68 g (27 mmol) Sodium(meta)periodate followed by 135 mg (0.27 mmol) RuCl₃ monohydrate at RT. After stirring overnight the reaction is diluted with water and extracted thoroughly with DCM and the organic phase is discarded. The aq. phase is adjusted to pH 1 by addition of 4N HCl, and extracted thoroughly (12 x) with DCM. The organic phase is dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is used without further purification.

TLC, Rf(CH₂Cl₂:ZMeOH 9:1) = 0.16
MS (method D): 224 [M+18]

Step 2

3-[2-[(2-[((lR,2S)-l-tert-Butoxycarbonylamino-2-vinyI-cyclopropanecarbonyl)-sulfamoyl]-phenylcarbamoyl]-methoxy-ethoxy]-propionic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (Step 2) using 100 mg (0.26 mmol) [(lR,2S)-l-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester, 200 mg (0.97 mmol) 3-(2-Carboxymethoxy-ethoxy)-propionic acid methyl ester, 140 mg (1.2 mmol) Benzotriazole, 140 mg (1.2 mmol) Thionylchloride, 265 mg (2.6 mmol) NEt₃ and 20 mg DMAP in 20 mL DCM.

HPLC (method A) tᵣ = 4.31 min

TLC, Rf(CH₂Cl₂:ZMeOH 19:1) = 0.56
MS (method D): 570 [M+]

Step 3
3-[2-\(((lR,2S)-l\text{-Amino-2-vinyl-cyclopropanecarbonyl})\text{-sulfamoyl}\text{-phenylcarbamoyl}\text{-methoxy})\text{-ethoxy}]\text{-propionic \ acid methyl ester}

The title compound is prepared analogously as described for the title compound in Example 11 (step 4) using 116 mg (0.20 mmol) 33-[2-\(((lR,2S)-l\text{-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl})\text{-sulfamoyl}\text{-phenylcarbamoyl}\text{-methoxy})\text{-ethoxy}]\text{-propionic \ acid methyl ester} and 0.5 mL TFA in 6 mL DCM.

HPLC (method A) \(t_R = 1.95\) min

TLC, Rf (CH\(_2\)Cl\(_2\)/MeOH 19:1) = 0.32

MS (method D): 470 [M+]

**Step 4**

(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2-[((lR,2S)-l\text{-}(2-\text{-[2-(2-methoxycarbonyl-ethoxy)-ethoxy}]\text{-acetylamino}\text{-benzenesulfonylaminocarbonyl})\text{-2-vinyl-cyclopropylcarbamoyl})\text{-pyrroloidine-1-carboxylic acid tert-butyl ester}

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 118 mg (0.20 mmol) 33-[2-\(((lR,2S)-l\text{-Amino-2-vinyl-cyclopropanecarbonyl})\text{-sulfamoyl}\text{-phenylcarbamoyl}\text{-methoxy})\text{-ethoxy}]\text{-propionic \ acid methyl ester}, 107 mg (0.20 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-
quinolin-4-yloxy]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 115 mg (0.30 mmol) HATU and 78 mg (0.61 mmol) DIPEA in 6 mL DCM.

HPLC (method A) $t_R = 5.05 \text{ min}$

TLC, $R_f(CH_2Cl_2MeOH \ 9:1) = 0.35$

MS (method D): 980 [M+]

**Step 5**

(2S,4R)-2-[(lR,2S)-l-(2-{2-(2-Carboxy-ethoxy)-ethoxy}-acetylamino)-benzenesulfonylamino-carbonyl)-2-vinyl-cyclopropylcarbamoyl]-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 110 mg (0.10 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2-[(1R,2S)-1-(2-{2-[2-(2-methoxycarbonyl-ethoxy)-ethoxy]-acetylamino}-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (TFA-salt) and 43 mg (1.0 mmol) LiOH in 16 mL THF/MeOH/H$_2$O (2:1:1).

HPLC (method A) $t_R = 4.73 \text{ min}$

TLC, $R_f(CHzCh/MeOH/HiO/AcOH \ 90:10:1:0.5) = 0.40$

MS (method D): 966 [M+]

**Step 6**

3-{2-{[(IR,2S)-l-[(2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclopropanecarbonyl]-sulfamoyl}-
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 96 mg (0.10 mmol) ((2S,4R)-2-[(lR,2S)-l-(2-[2-(2-Carboxy-ethoxy)ethoxy]-acetylamino)-benzenesulfonylamino-carbonyl)-2-vinyl-cyclopropylcarbamoyl]-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (TFA-salt) and 0.5 mL TFA in 6 mL DCM.

HPLC (method A) tₚ = 3.92 min
TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.42

Example 17

4-Fluoro-l,3-dihydro-isoindole-2-carboxylic acid (8S,10R)-5-[(lR,2S)-l-carbonylammo-2-vinyl-cycIoprophyl]-2,2,4,7,13-pentaomo-16,19-dioxa-2 λ*-6*-thia-3,6,12,22-tetraaza-tricyclo[2.1.4.0*8,12*]heptacosa-l(27),23,25-trien-10-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 using 56 mg (0.05 mmol) 4-Fluoro-l,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-[(lR,2S)-l-(2-[2-(2-carboxy-ethoxy)-ethoxy]-ethylamino)-phenylcarbamoyl)-methoxy]-ethoxy]-propionic acid.
benzenesulfonylamino-carbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester (TFA-salt), 70 mg (0.54 mmol) DIPEA and 103 mg (0.27 mmol) HATU in 50 mL DCM and 1 mL DMF.

HPLC (method A) \( t_R = 4.52 \) min

TLC, \( R_f(\text{CH}_2\text{Cl}_2\text{MeOH } 9:1) = 0.45 \)

MS (method D): 700 [M+]

**Preparation of 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-\[(lR,2S)-l-(2\{-[2\{-[2-(\text{2-methoxycarbonyl-ethoxy})-ethoxy\}J-ethylaminoJ-benzenesulfonylaminocarboiiyl\})^-\}

vinyl-cyclopropyl-carbamoyl-\text{pyrrolidiii-}3-yl ester**

**Step 1**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-((lR,2S)-l-(2\{-[2-(\text{2-methoxycarbonyl-ethoxy})-ethoxy\}J-ethylaminoJ-benzenesulfonylaminocarboiiyl\})^-\}
benzenesulfonylamino-carbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 235 mg (0.34 mmol) 3\{-[2\{-[2\{-[\text{(IR,2S)-l-Am ino-2-vinyl-cyclopropanecarbonyl)-sulfamoylJ-phenylaminoJ} -ethoxy\}J-ethoxy\}J-propionic acid methyl ester, 136 mg (0.34 mmol) (2S,4R)-4-(4-Fluoro-1,3-dihydro-isoindole-2-carboxyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 196 mg (0.52 mmol) HATU and 134 mg (1.0 mmol) DIPEA in 20 mL DCM.

HPLC (method A) \( t_R = 5.08 \) min

TLC, \( R_f(\text{CH}_2\text{Cl}_2\text{MeOH } 19:1) = 0.31 \)

MS (method D): 832 [M+]

**Step 2**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-
[(lR,2S)-1-(2-[2-(2-carboxy-ethoxy)-ethoxy]-ethylamino)-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 170 mg (0.18 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-[(lR,2S)-l-(2-{2-[2-(2-methoxycarbonyl-ethoxy)-ethoxy]-ethylamino}-benzene-sulfonylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester (TFA-salt) and 76 mg (1.8 mmol) LiOH in 20 mL THF/MeOH/H$_2$O (2:1:1). HPLC (method A) t$_R$ = 4.78 min

TLC, Rf (CH$_2$Cl$_2$/MeOH 9:1) = 0.33

MS (method D): 818 [M+]

Step 3

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-[(lR,2S)-l-(2-[2-(2-carboxy-ethoxy)-ethoxy]-ethylamino]-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 52 mg (0.06 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-[(lR,2S)-l-(2-[2-(2-carboxy-ethoxy)-ethoxy]-ethylamino]-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl-ester (TFA-
HPLC (method A) $t_R = 3.85$ min
TLC, $R_f (\text{CH}_2\text{Cl}_2/\text{MeOH 9:1}) = 0.25$
MS (method D): 718 [M+]

**Example 18**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (8S,10R)-5-[(1R,2S)-1-carbonylamino-2-vinyl-cyclopropyl]-2,2,4,7,13-pentaoxo-15,19-dioxo-2 $\lambda^6$-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0^8,12^*]heptacosa-1(27),23,25-trien-10-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 using 8 mg (0.008 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-[(1R,2S)-1-[2-[2-(3-carboxymethoxy-propoxy)-ethylamino]-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester (TFA-salt), 10 mg (0.08 mmol) DIPEA and 15 mg (0.04 mmol) HATU in 25 mL DCM and 0.5 mL DMF.

HPLC (method A) $t_R = 4.63$ min
TLC, $R_f (\text{CH}_2\text{Cl}_2/\text{MeOH 9:1}) = 0.54$
MS (method D): 700 [M+]

**Preparation of** 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R^5S)-5-[(1R,2S)-1-[2-[2-(3-carboxymethoxy-propoxy)-ethylamino]-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropyl-carbamoyl]-pyrrolidin-3-yl ester

**Step 1**

(3-AHyloxy-propoxy)-acetic acid
To an ice-cold solution of 7.8 g (67 mmol) 3-Allyloxy-propan-1-ol (prepared according to Synth. Comm. 1992, 22, 189-200) in 250 mL abs. THF is added 12.7 g (61 mmol) Sodium iodopropionate followed by 5.4 g (134 mmol) NaH (60% suspension in mineral oil). The ice-bath is removed and the reaction is refluxed for 5 h. After cooling to RT the reaction is quenched by addition of water and THF is removed in vacuo. The aq. phase is adjusted to pH 1 with 4 N HCl and extracted with DCM. The organic phase is washed with brine, dried with Na₂SO₄, filtered, the solvent is removed in vacuo and the residue is purified by FC on silica (eluent: CH₂Cl₂/MeOH 85:15) to give the title compound as a yellow oil.

TLC, Rf (CH₂Cl₂/MeOH 85:15) = 0.62

MS (method D): 175 [M+H]

Step 2
(3-Allyloxy-propoxy)-acetic acid methyl ester

To a solution of 7.5 g (43 mmol) (3-Allyloxy-propoxy)-acetic acid in 300 mL acetone is added 6.9 g (68 mmol) KHCO₃ followed by 6.7 mL (108 mmol) Iodomethane and the reaction is refluxed for 3 h. Additional 6.7 mL (108 mmol) Iodomethane is added and reflux is continued for 3 h. A third portion of 6.7 mL (108 mmol) Iodomethane is added and the mixture is refluxed overnight. After cooling to RT the reaction mixture is filtered and the solvent is removed in vacuo. The residue is taken up in EtOAc, washed with sat. NaHCO₃ solution and brine, dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is used without further purification.

TLC, Rf (CH₂Cl₂/MeOH 19:1) = 0.78

MS (method D): 206 [M+18]

Step 3
[3-(2-Oxo-ethoxy)-propoxy]-acetic acid methyl ester

A solution of 2.0 g (11.0 mmol) (3-Allyloxy-propoxy)-acetic acid methyl ester in 200 mL
DCM is cooled to -78°C. Ozone is bubbled through until a blue color appears (-30 min). Oxygen is bubbled through the mixture for 2 min to remove excess of ozone, 1.0 mL (14 mmol) Dimethylsulfide is added and stirring is continued for 1 h at -78°C. After warming to RT, the solvent is removed in vacuo and the residue is used without further purification.

**Step 4**

\[
[3-(2-{2-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl}]-phenylamino\}-ethoxy)-propoxy]-acetic acid methyl ester
\]

![Chemical structure of Step 4](image)

The title compound is prepared analogously as described for the title compound in Example 11 (step 3) using 1.9 g (5 mmol) [(IR,2S)-l-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester, 2.56 g crude [3-(2-Oxo-ethoxy)-propoxy]-acetic acid methyl ester (from the previous step), 3.3 g (15 mmol) NaBH(OAc)_3 and 0.90 g (15 mmol) AcOH in 150 mL 1,2 DCE.

MS (method D): 556 [M+]

**Step 5**

\[
[3-(2-{2-[(lR,2S)-l-Amino-2-vinyl-cydopropanecarbonyl]-sulfamoyl}]-phenylamino\}-ethoxy)-propoxy]-acetic acid methyl ester
\]

![Chemical structure of Step 5](image)

The title compound is prepared analogously as described for the title compound in Example 11 (step 4) using 1.78 g (3.2 mmol) [3-(2-{2-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropane-carbony]-sulfamoyl}]-phenylamino\}-ethoxy)-propoxy]-acetic acid methyl ester and 5 mL TFA in 25 mL DCM.
Step 6

^Fluoro-l-S-dihydro-isoindole^-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-
((lR,2S)-l-3-[2-(3-methoxycarbonylmethoxy-propoxy)-ethylamino]-
benzenesulfonyleminocarbony1]-2-vinyl-cyclopropylcarbamoyl)-pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 520 mg (0.38 mmol) [3-(2-{2-[(lR,2S)-l-Amino-2-vinyl-
cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-ethoxy)-propoxy]-acetic acid methyl ester (TFA-salt), 150 mg (0.38 mmol) (((2S,4R)-4-(4-Fluoro-l,3-dihydro-isoindole-2-
carbonyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 217 mg (0.57 mmol)
HATU and 295 mg (2.3 mmol) DIPEA in 10 mL DCM.
HPLC (method A) \( t_R = 5.23 \text{ min} \)
TLC, Rf (CH\(_2\)Cl\(_2\)/MeOH 9:1) = 0.63
MS (method D): 832 [M+]
The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 28 mg (0.015 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-{(1R,2S)-1-2-[2-(3-methoxycarbonylpropoxy)-ethylamino]-benzenesulfonylaminocarbonyl}-2-vinyl-cyclopropylcarbamoyl)-pyrrolidin-3-yl ester (TFA-salt) and 7 mg (0.3 mmol) LiOH in 20 mL THF/MeOH/H$_2$O (2:1:1).

HPLC (method A) $t_R = 4.82$ min

TLC, Rf(CH$_2$Cl$_2$/ZMeOH 9:1) = 0.29

MS (method D): 818 [M+]

Step 8

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-{(1R,2S)-1-[1-(3-carboxymethoxy-propoxy)-ethylamino]-benzenesulfonylaminocarbonyl}-2-vinyl-cyclopropylcarbamoyl)-pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 8 mg (0.01 mmol) (4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-{(1R,2S)-1-[2-(3-carboxymethoxy-propoxy)-ethylamino]-benzenesulfonylamino-carbonyl}-2-vinyl-cyclopropylcarbamoyl)-pyrrolidin-3-yl ester (TFA-salt) and 0.2 mL TFA in 1 mL DCM.

HPLC (method A) $t_R = 3.88$ min
Example 19

(8S,10R)-10-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-5-[(IR,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-17-methyl-2,2-dioxo-2 λ*6*-thia-3,6,12,17,22-pentaaza-tricyclo [21.4.0.0*8,12*]heptacosa-1(27),23,25-triene-4,7, 13-trione

The title compound is prepared analogously as described for the title compound in Example 2 using 330 mg (0.16 mmol) 4-[[4-(2-[(IR,2S)-l-((2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino]-butyl]-methyl-amino]-butyric acid (TFA-salt), 0.29 mL (1.64 mmol) DIPEA and 312 mg (0.82 mmol) HATU in 40 mL DCM and 1 mL DMF.

HPLC (method A) t_R = 4.24 min
MS (method D): 845 [M+]

Preparation of 4-[[4-(2-[(IR,2S)-l-((2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino]-butyl]-methyl-amino]-butyric acid

Step 1
4-Methylamino-butyric acid methyl ester

A solution of 2.3 g (15 mmol) 4-Methylamino-butyric acid hydrochloride and 25 mL (31
mmol) HCl (1.25 M in MeOH) in 150 mL MeOH is stirred overnight at RT. The solvent is removed in vacuo and the residue is used without further purification.

MS (method D): 132 [M+H]

5 Step 2

4-[[4-(tert-Butyl-dimethyl-silyl-oxy)-butyl]-methyl-amino]-butyric acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 11 (step 3) using 1.6 g (9.5 mmol) 4-Methylamino-butyrlic acid methyl ester hydrochloride, 1.93 g (9.5 mmol) 4-(tert-Butyl-dimethyl-silyl-oxy)-butyraldehyde (prepared according to J. Org. Chem. 2005, 70(6), 2097), 4.50 g (19 mmol) NaBH(OAc)_3 and 1.1 mL (19 mmol) AcOH in 100 mL 1,2 DCE.

MS (method D): 318 [M+]

15 Step 3

4-[(4-Hydroxy-butyl)-methyl-amino]-butyric acid methyl ester

To an ice-cold solution of 2.1 g (6.6 mmol) 4-[[4-(tert-Butyl-dimethyl-silyl-oxy)-butyl]-methyl-amino]-butyric acid methyl ester in 10 mL abs. THF is slowly added 7.9 mL (7.9 mmol) TBAF (1M in THF). After 2 h at RT additional 2 mL TBAF is added stirring is continued for 2 h, the solvent is removed in vacuo and the residue is purified by FC on silica (eluent: TBME/MeOH/NHUOH 90:10:1) to give the title compound as a brown oil.

MS (method D): 204 [M+]

25 Step 4

4-[Methyl-(4-oxo-butyl)-amino]-butyric acid methyl ester

To a solution of 100 mg (0.47 mmol) 4-[(4-Hydroxy-butyl)-methyl-amino]-butyric acid methyl ester in 2 mL DCM is added 220 mg (0.98 mmol) PCC. After stirring overnight at RT, the solvent is removed in vacuo and the residue is purified by FC on silica (eluent:
TBME/MeOH/NH$_4$OH 85:15:1) to give the title compound as a brown oil.

TLC, R$_f$ (TBME/MeOH/NH$_4$OH 90:10:1) = 0.30

**Step 5**

4-[(4-[[[(lR,2S)-l-tert-Butoxycarbonylainino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-butyl)-methyl-amino]-butyric acid methylester

![Chemical structure](image1)

The title compound is prepared analogously as described for the title compound in Example 11 (step 3) using 2.0 g (5.2 mmol) (IR,2S)-l-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester, 1.27 g (6.3 mmol) 4-[Methyl-(4-oxo-butyl)-amino]-butyric acid methyl ester, 3.1 g (13 mmol) NaBH(OAc)$_3$ and 0.90 mL (16 mmol) AcOH in 80 mL 1,2-Dichloroethane.

HPLC (method B) $t_R = 5.67$ min

MS (method D): 567 [M$^+$]

**Step 6**

4-[(4-2-[[[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-butyl)-methyl-amino]-butyric acid methyl ester

![Chemical structure](image2)

The title compound is prepared analogously as described for the title compound in Example 11 (step 4) using 210 mg (0.37 mmol) (4-[(4-2-[[[(IR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-butyl)-methyl-amino]-butyric acid methylester and 1.4 mL TFA in 15 mL DCM.

MS (method D): 467 [M$^+$]

**Step 7**
The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 244 mg (0.37 mmol) 4-[(4-{2-[((IR,2S)-L-Amino-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-phenylamino} -butyl)-methyl-amino]-butyric acid methyl ester, 210 mg (0.37 mmol) (2S,4R)-4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 212 mg (0.56 mmol) HATU and 0.39 mL (2.23 mmol) DIPEA in 5 mL DCM.

HPLC (method B) t_R = 5.95 min

MS (method D): 977.5 [M+]
The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 160 mg (0.16 mmol) (2S,4R)-2-[(lR,2S)-1-(2-[(3-Methoxycarbonylpropyl)-methyl-amino]-butylamino)-benzenesulfonfylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-4-[7-methoxy-2-(2-isopropylamino-thiazol-4-yl)-quinolin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (TFA-salt) and 35 mg (0.82 mmol) LiOH in 10 mL THF/MeOH/H₂O (2:1:1).

HPLC (method B) tᵣ = 6.06 min

MS (method D): 963 [M+]

Step 9

4-[(4-(2-[(lR,2S)-1-(2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl)-amino)-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino)-buryl]-methyl-amino}-butyric acid

The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 176 mg (0.16 mmol) (2S,4R)-2-[(lR,2S)-1-(2-[(3-Carboxy-propyl)-methyl-amino]-butylamino)-benzenesulfonfylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1-carboxylic acid
tert-butyl ester (TFA-salt) and 0.8 mL TFA in 10 mL DCM.
HPLC (method B) $t_R = 5.66$ min
MS (method D): 863 [M+]

### Example 20

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (8S,10R)-5-[(IR,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-17-methyI-2,2,4,7,13-pentaoxo-2-λ*6*-thia-3,6,12,17,22-pentaaza-tricyclo[2.4.0.0*8,12*]heptacosa-1(27),23,25-trien-1-0-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 using 300 mg (0.19 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-[(IR,2S)-l-2-[(4-[(3-carboxy-propyl)-methyl-amino]-butylamino)-benzenesulfonylamino]-carbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester (TFA-salt), 0.32 mL (1.9 mmol) DIPEA and 361 mg (0.95 mmol) HATU in 50 mL DCM and 1 mL DMF.
HPLC (method A) $t_R = 4.10$ min
MS (method D): 711 [M+]

### Preparation of 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-[(IR,2S)-l-2-[(4-[(3-carboxy-propyl)-methyl-amino]-butylamino)-benzenesulfonylamino]-carbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester

**Step 1**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-[(IR,2S)-l-2-[(4-[(3-methoxycarbonyl-propyl)-methyl-aminol-butyliamino)-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 250 mg (0.29 mmol) 4-[[4-{{1-(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl}-sulfamoyl}-phenylamino}-butyl]-methyl-amino]-butyric acid methyl ester, 110 mg (0.28 mmol) (2S,4R)-4-((4-Fluoro-l,3-dihydro-isoindole-2-carboxyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 159 mg (0.42 mmol) HATU and 0.29 mL (1.7 mmol) DIPEA in 5 mL DCM.

HPLC (method B) t\textsubscript{R} = 6.52 min

MS (method D): 843 [M+]

**Step 2**

4-Fluoro-l,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-[(lR,2S)-l-2-{4-[(3-methoxycarbonyl-propyl)-methyl-amino]-butylamino}-benzenesulfonfylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 160 mg (0.19 mmol) 4-Fluoro-l,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-[(lR,2S)-l-2-{4-[(3-methoxycarbonyl-propyl)-methyl-amino]-butylamino}-benzenesulfonfylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester (TFA-salt) and 32 mg (0.76 mmol) LiOH in 10 mL THF/MeOH/H\textsubscript{2}O
HPLC (method B) $t_R = 6.3 \text{ min}$  
MS (method D): 829 [M+] 

**Step 3**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-[(lR,2S)-l-(2-{4-[(3-carboxy-propyty-methyl-amino)-butylamino]-benzenesulfonaminocarboiiyl}^-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 190 mg (0.19 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-[(lR,2S)-l-(2-{4-{[3-methoxycarbonyl-propyl]-methyl-amino]}-butylamino}-benzenesulfonaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester (TFA-salt) and 0.8 mL TFA in 10 mL DCM.

HPLC (method B) $t_R = 5.94 \text{ min}$  
MS (method D): 729 [M+] 

**Example 21**

\{(8S,10R,14S)-10-[2-(2-IsopropyIamino-thiazol-4-yl]-7-methoxy-quinolin-4-yloxy]-5-\}

$\lambda^*6^*$-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0*8,12*]heptacosa-l(23),24,26-trien-14-yl]-carbamic acid cyclopentyl ester
The title compound is prepared analogously as described for the title compound in Example 2 using 120 mg (0.07 mmol) (S)-2-Cyclopentyloxycarbonylamino-9-{2-[(lR,2S)-1-((2S,4R)-4-[2-(2-isopropyl-amino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclopropane-carbonyl]-sulfamoyl}-phenylamino)-nonanoic acid (TFA-salt), 92 mg (0.71 mmol) DIPEA and 135 mg (0.36 mmol) HATU in 50 mL DCM and 1 mL DMF.

HPLC (method A) \( t_R = 6.03 \) min

TLC, \( R_f \left( \text{CH}_2\text{Cl}_2, \text{MeOH} \right) = 0.58 \)

MS (method D): 957 [M+]

**Preparation of** (S)-2-Cyclopentyloxycarbonylamino-9-{2-[(lR,2S)-1-((2S,4R)-4-[2-(2-isopropyl-amino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclopropane-carbonyl]-sulfamoyl}-phenylamino)-nonanoic acid

**Step 1**

(2S,5R)-3,6-Diethoxy-2-hept-6-enyl-5-isopropyl-2,5-dihydro-pyrazine
A solution of 26.2 g (123 mmol) of (R)-3,6-Diethoxy-2-isopropyl-2,5-dihydro-pyrazine in 450 ml of abs. THF under argon is cooled to -75°C and 77 ml (123 mmol) n-BuLi (1.6 M in Toluene) is added within 45 min while the temperature is maintained below -70°C. A solution of 15 g (85 mmol) of 7-bromo-1-heptene in 80 ml of THF abs is added at -70°C. The reaction mixture is stirred for 3h at -70°C, for 17h at -4°C and for 3h at RT. Ice-cold saturated NH₄Cl (70 ml) and H₂O (500 ml) are added and the resulting mixture is extracted with EtOAc (500 ml). The organic layer is washed with H₂O. The combined aqueous phases are extracted with EtOAc (500 ml). The combined organic phases are dried over Na₂SO₄, concentrated in vacuo and the residue purified by FC on silica gel. (eluent: Hexane/EtOAc 30:1) to give the title compound as a yellow oil.

TLC, Rf (Hexane/ EtOAc 30:1) = 0.46
MS (method D): 309 [M+H]

Step 2

(S)-2-Amino-non-8-enoic acid ethyl ester

To a solution of 19 g (62 mmol) (2S,5R)-3,6-Diethoxy-2-hept-6-enyl-5-isopropyl-2,5-dihydro-pyrazine in 400 mL ACN at RT, is added 250 mL of IN aq HCl. The reaction mixture is stirred for 2 h at RT. Saturated aq. NaHCO₃ (250 mL) is added to adjust pH 8. The reaction mixture is stirred overnight at RT and then concentrated in vacuo. The aq. phase is extracted with 500 mL of EtOAc. The organic phase is washed twice with 250 mL H₂O, dried over Na₂SO₄, concentrated in vacuo and the residue is purified on silica gel. (eluent: EtOAc).

The product is distilled under high vacuum to give the title compound (S)-2-Amino-non-8-enoic acid ethyl ester as a colorless oil.
TLC, Rf (Hexane/ EtOAc 1:2) = 0.21
MS (method D): 200 [M+H]

Step 3
(S)-2-Cyclopentyloxycarboxycarbonylamino-non-8-enoic acid ethyl ester

To a solution of 9.3 mL (100 mmol) of cyclopentanol in 200 mL of THF abs under nitrogen atmosphere at 10°C, is added over a 20-min period 89 mL (169 mmol) of a phosgen solution (20% in Toluene). The reaction mixture is warmed up to RT and stirred for 2h, while a nitrogen stream is passed through the solution, so that the reaction volume is concentrated to 150 mL. A solution of 8.0 g (41mmol) of (S)-2-amino-non-8-enoic acid ethyl ester in 20 mL abs. THF is added at RT, followed by triethylamine added at 0°C until pH 9.4 is adjusted. The reaction mixture is stirred for 1h at 0°C and concentrated in vacuo. EtOAc (500 mL) is added and the organic layer is washed 3x with H2O (100 mL), with NaHCO3 (100 mL) and with brine (100 mL). The organic layer is dried over Na2SO4, concentrated in vacuo, and the residue is purified by FC on silica gel. (Eluent: Hexane/EtOAc 7:1) to give the title compound as a yellow oil.

TLC, Rf (Hexane/ EtOAc 3:1) = 0.33

MS (method D): 312 [M+H]

Step 4

(S)-2-Cyclopentyloxycarbonylamino-non-8-enoic acid

To a solution of 460 g (1.5 mol) of (S)-2-Cyclopentyloxycarboxycarbonylamino-non-8-enoic acid ethyl ester in 4.0 L of THF 1.8 L of Methanol is added at RT. A solution of 137g (3.25 mol) of LiOH monohydrate in 1.8 L of water is added over a 40-min period. The reaction mixture is stirred at RT for 3 h, concentrated in vacuo, taken up in H2O (2L), washed with 10% aqueous citric acid (2.5 L) and extracted with EtOAc (2.5 L). The organic layer is washed with H2O (2x 2 L) and brine (2 L). The organic layer is dried over Na2SO4, concentrated in vacuo and the residue purified by FC on silica gel (eluent: Hexane/EtOAc 10:1 -> EtOAc) to give the title compound as a red amorphous solid.

TLC, Rf (CH2C12/MeOH 9:1) = 0.3
MS (method D): 282 [M-H]

Step 5
(S)-2-Cyclopentyloxycarbonylamino-non-8-enoic acid methyl ester

To a solution of 11.5 g (41 mmol) (S)-2-Cyclopentyloxycarbonylamino-non-8-enoic acid in 200 mL Acetone is added at it 6.5 g (65 mmol) KHCO₃ and 14.4 g (101 mmol) Iodomethane and the reaction is refluxed for 15 h. After cooling to rt the reaction mixture is filtered, washed with Acetone and the solvent removed in vacuo. The residue is dissolved in EtOAc, washed with aq. bicarbonate and brine, dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is purified by FC on silica (eluent: CH₂Cl₂/MeOH 99:1 - > 95:5) to give the title compound as a yellow oil.

HPLC (method A) t_R = 5.29 min
TLC, Rf (CH₂Cl₂/MeOH 99:1) = 0.50

Step 6
(S)-2-Cyclopentyloxycarbonylamino-9-hydroxy-nonanoic acid methyl ester

To an ice-cold solution of 8.1 g (27 mmol) (S)-2-Cyclopentyloxycarbonylamino-non-8-enoic acid methyl ester in 200 mL THF is added 82 mL (41 mmol) 9-BBN (0.5 M in THF) and the ice-bath is removed. After stirring for 2 h the reaction is cooled to 0°C and quenched by addition of 25 mL aq. bicarbonate and 5 mL aq. 35% H₂O₂. After extraction with EtOAc, the combined organic phase is dried with Na₂SO₄, filtered and the solvent is removed in vacuo.

The residue is purified by FC on silica (eluent: CH₂Cl₂/ZMeOH 98:2 - > 95:5) to give the title compound as a colorless oil.

HPLC (method A) t_R = 3.95 min
TLC, Rf (CH$_2$Cl$_2$/MeOH 19:1) = 0.34
MS (method D): 316 [M+H]

**Step 7**

(S)-2-Cyclopentyloxycarbonylamino-9-oxo-nonanoic acid methyl ester

To a solution of 2.2 g (7.0 mmol) (S)-2-Cyclopentyloxycarbonylamino-9-hydroxy-nonanoic acid methyl ester in 150 mL DCM is added 2.3 g (10.5 mmol) PCC. After stirring for 4 h at rt silica is added, the reaction is filtered through a pad of Hyflo and thoroughly washed with DCM. The solvent is removed in vacuo to give the title compound as a brown oil, which is used without further purification.

TLC, Rf (CH$_2$Cl$_2$/MeOH 19:1) = 0.54
MS (method D): 314 [M+H]

**Step 8**

(S)-9-{2-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyI-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-2-cyclopentyloxycarbonylarnino-nonanoic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 11 (step 3) using 0.95 g (2.5 mmol) IR,2S)-l-(2-Amino-benzenesulfonylamidocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester, 1.95 g (4.98 mmol) (S)-2-Cyclopentyloxycarbonylamino-9-oxo-nonanoic acid methyl ester, 1.58 g (7.5 mmol) NaBH(OAc)$_3$ and 0.43 mL (7.5 mmol) AcOH in 100 mL 1,2-Dichloroethane.

HPLC (method A) t$_R$ = 5.76 min

HPLC (method A) t$_R$ = 5.76 min
TLC, Rf(CH₂Cl₂:MeOH 19:1) = 0.33
MS (method D): 679 [M+]

Step 9

(S)-9-{2-[(lR,ZSVl-Amino-l-vinyl-cyclopropanecarbonylJ-sulfamoyll-phenylamino}-!-
cyclopentyloxy carbonylamino-nonanoic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 11 (step 4) using 310 mg (0.46 mmol) (S)-9-{2-[(lR,2S)-l-tert-Butoxycarbonylamino-2-
vinyl-cyclopropane-carbo nyty-sulfamoylj-phenylarnino} -2-cyclopentyloxy carbonylamino-
nonanoic acid methyl ester and 1 mL TFA in 10 mL DCM.
HPLC (method A) tR = 4.27 min
TLC, Rf (CH₂Cl₂:MeOH 9:1) = 0.59
MS (method D): 579 [M+]

Step 10

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 185 mg (0.32 mmol) (S)-9-{(LR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-phenylamino]-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester, 170 mg (0.32 mmol) (2S,4R)-4-{2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-l,2-dicarboxylic acid 1-tert-butyl ester, 183 mg (0.48 mmol) HATU and 124 mg (0.96 mmol) DIPEA in 10 mL DCM.

HPLC (method A) \( t_R = 6.12 \text{ min} \)
TLC, \( R_f \) (CH\(_2\)Cl\(_2\)/MeOH 19:1) = 0.20

MS (method D): 1089 [M+]

**Step 11**

\( (2S,4R)-2-[(LR,2S)-1-[(S)-8-Carboxy-8-cyclopentyloxycarbonylamino-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropyl carbamoyl]-4-[2-(2-isopropyl-amino-thiazoM-yO-T-methoxy-quinolin-^\wedge-yloxyJ-pyrrolidine-l-carboxylic \textbf{acid tert-butyl ester} \)
The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 205 mg (0.14 mmol) (2S,4R)-2-([(IR,2S)-1-[2-((S)-8-Cyclopentoxy carbonylamino-8-methoxy-carbonyl-octylamino)-benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbonyl]-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-l-carboxylic acid tert-butyl ester (TFA-salt) and 59 mg (1.4 mmol) LiOH in 16 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) tᵣ = 5.72 min
TLC, Rf(CH₂Cl₂:MeOH 9:1) = 0.34

MS (method D): 1075 [M+]

Step 12
(S)-2-Cyclopentoxy carbonylamino-9-2-([(IR,2S)-1-([(2S,4R)-4-2-(2-isopropylanino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-
cyclopropanecarbonyl]-sulfamoyl]-phenylamino)-nonanoic acid
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 119 mg (0.09 mmol) (2S,4R)-2-[(R,2S)-1-2-(S)-8-Carboxy-8-cyclopentyloxycarbonylamino-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-2-(2-isopropyl-amino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (TFA-salt) and 0.5 mL TFA in 5 mL DCM.

HPLC (method A) \( t_R = 5.33 \text{ min} \)

TLC, \( R_f \) (CH\(_2\)Cl\(_2\)/MeOH/H\(_2\)O/AcOH 90:10:1:0.5) = 0.46

\[ \text{MS (method D): 975 [M+] } \]

**Example 22**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (8S,10R,14S)-14-cyclopentyloxycarbonyl-amino-5-[(R,2S)-1-carbonylamino-2-vinyl-cyclopropyl]-2,2,4,7,13-pentaooxo-2\( ^\lambda \\*6\)*-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0\( ^*8,12\)*]heptacosa-l(23),24,26-trien-10-yl ester
The title compound is prepared analogously as described for the title compound in Example 2 using 217 mg (0.21 mmol) 4-Fluoro-1,3-dihydro-isooindole-2-carboxylic acid (3R,5S)-5-\{(IR,2S)-1-[2-((S)-8-carboxy-8-cyclopentylcarboxylamino-octylamino)-benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl\}-pyrrolidin-3-yl ester (TFA-salt), 262 mg (2.0 mmol) DIPEA and 386 mg (1.1 mmol) HATU in 50 mL DCM and 1 mL DMF.

HPLC (method A) t_R = 5.97 min

TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0.75

MS (method D): 823 [M+]

**Preparation of** ^4-Fluoro-1^-dihydro-isooindole^-carboxylic acid (3R,5S)-5-\{(IR,2S)-1-[2-((S)-8-carboxy-8-cyclopentylcarboxylamino-octylamino)-benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl\}-pyrrolidin-3-yl ester

**Step 1**

4-Fluoro-1,3-dihydro-isooindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-\{(IR,2S)-1-[2-((S)-8-cyclopentylcarboxylamino-8-methoxycarbonyl-octylamino)-benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl\}-pyrrolidin-3-yl ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 368 mg (0.46 mmol) (S)-9-{2-[(R,R,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester (TFA-salt), 216 mg (0.55 mmol) (2S,4R)-4-(4-Fluoro-1,3-dihydro-isoindole-2-carbonyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 260 mg (0.68 mmol) HATU and 354 mg (2.74 mmol) DEPEA in 8 mL DCM.

HPLC (method A) \( t_R = 6.15 \text{ min} \)

TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 19:1) = 0.50 \)

MS (method D): 955 [M+]

**Step 2**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-{(IR,2S)-1-[2-((S)-8-carboxy-8-cyclopentyloxycarbonylaminooctylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrroloidin-3-yl} ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 217 mg (0.20 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-{[(1R,2S)-1-[2-((S)-8-cyclopentylcarbonylamino-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl} ester (TFA-salt) and 49 mg (2.0 mmol) LiOH in 16 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) tᵣ = 5.59 min

TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.60

MS (method D): 941 [M+]

**Step 3**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-{[(1R,2S)-1-[2-((S)-8-carboxy-8-cyclopentylcarbonylamino-octylaminio)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl} ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 191 mg (0.20 mmol) 4-Fluoro-1,3-dihydro-isooindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-[(IR,2S)-1-[2-((S)-8-carboxy-8-cyclopentyloxycarbonylamino-octylamino)-benzene-sulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester and 1 mL TFA in 25 mL DCM.

HPLC (method A) \( t_R = 5.01 \) min

MS (method D): 841 [M+]

Example 23

\{(8S,10R,14S)-10-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yl]oxy]-5-[(IR,2S)-1-carbonylamino-2-vinyl-cyclopropyl]-2,2,4,7,13,21-hexaoxo-\( \lambda^6 * \)-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0^{8,12}]*]-heptacosa-l(23),24,26-trien-14-yl\}-carbamic acid cyclopentyl ester
The title compound is prepared analogously as described for the title compound in Example 2 using 118 mg (0.097 mmol) (S)-2-Cyclopentyloxycarbonylamino-8-(2-{[(IR,2S)-l-({(2S,4R)-4-[2-(2-isopropyl-amino-thiazol-4-yl)-7-methoxy-quinolin-4-yl-oxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclo-propanecarbonyl]-sulfamoyl}-phenylcarbamoyl)-octanoic acid (TFA-salt), 126 mg (0.97 mmol) DIPEA and 184 mg (0.49 mmol) HATU in 100 mL DCM and 2 mL DMF.

HPLC (method A) $t_R = 5.43$ min

TLC, $R_f$ (CH$_2$Cl$_2$/MeOH 9:1) = 0.45

MS (method D): 971 [M+]

**Preparation of** (S)-2-Cyclopentyloxycarbonylamino-8-(2-{[(IR,2S)-l-({(2S,4R)-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yl-oxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclo-propanecarbonyl]-sulfamoyl}-phenylcarbamoyl)-octanoic acid

**Step 1**
(S)-2-Cyclopentyloxycarbonylamino-nonanedioic acid 1-methyl ester

To a solution of 1.88 g (6.0 mmol) ((S)-2-Cyclopentyloxycarbonylamino-9-oxo-nonanoic
acid methyl ester in 20 mL tBuOH is added at rt 2.1 g (30 mmol) 2-Methyl-2-buten, 2.81 g (18 mmol) NaH$_2$PO$_4$ (in 15 mL H$_2$O) and 1.62 g (18 mmol) NaClO$_2$ (in 15 mL H$_2$O). After stirring for 1 h, the solvent is removed in vacuo, the residue is diluted with water, acidified with 0.5 N HCl and extracted with EtOAc. The combined organic phase is dried with Na$_2$SO$_4$, filtered and the solvent is removed in vacuo. The residue is purified by FC on silica (eluent: CH$_2$Cl$_2$/MeOH 98:2 -> 95:5) to give the title compound as a colorless oil.

**HPLC (method A)** $t_R = 3.83$ min
**TLC, Rf(CH$_2$Cl$_2$/MeOH 19:1) = 0.26**
**MS (method D):** 330 [M+H]

**Step 2**

(S)-8-{2-[((lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl)-
sulfamoyl]-phenylcarbamoyl]-2-cyclopentyl oxycarbonylamino-octanoic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (Step 2) using 0.85 g (2.23 mmol) [(lR,2S)-l-(2-Amino-benzenesulfonylamino carbonyl)-2-vinyl-cyclopropylj-carbamic acid tert-butyl ester, 0.96 g (2.9 mmol) (S)-2-Cyclopentyl oxycarbonylamino-nonanedioic acid 1-methyl ester, 0.40 g (3.3 mmol) Benzotriazole, 0.40 g (3.3 mmol) Thionylchloride, 0.92 g (10 mmol) NEt$_3$ and 100 mg DMAP in 50 mL DCM.

**HPLC (method A)** $t_R = 5.31$ min
**TLC, Rf(CH$_2$Cl$_2$/MeOH 19:1) = 0.31**
**MS (method D):** 693 [M+]
phenylcarbamoyl]-2-cyclopentyloxycarbonylamino-octanoic acid methyl ester

The title compound is prepared analogously as described for the title compound in Example 1 (Step 3) using 0.85 g (2.23 mmol) (S)-8-{2-[((lR,2S)-1-tert-Butoxycarbonylamino-2-vinyl-cyclopropane-carbonyl)-sulfamoyl]-phenylcarbamoyl]-2-cyclopentyloxycarbonylamino-octanoic acid methyl ester and 5 mL 4N HCl in Dioxane.

HPLC (method A) $t_R = 3.76$ min

MS (method D): 593 [M+]

**Step 4**

(2S,4R)-2-{{(IR,2S)-1-[2-((S)-8-Cyclopentyloxycarbonylamino-8-methoxycarbonyl-octanoyl-amino)-benzenesulfonylaminocarbonylI]2-vinyl-cyclopropylcarbamoylI]-4-{-2-(2-isopropyl-amino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 190 mg (0.27 mmol) (S)-8-{2-[[((IR,2S)-l-Amino-2-vinyl-phenylcarbamoyl]-2-cyclopentyloxycarbonylamino-octanoic acid methyl ester

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cyclopropanecarbonyl)-sulfamoyl]-phenylcarbamoyl}-2-cyclopentyloxy carbonylamino-
octanoic acid methyl ester (HCl-salt), 141 mg (0.27 mmol) (2S,4R)-4-[2-(2-Isopropylamino-
thiazol-4-yl)-7-methoxy-quinolin-4-yl oxy]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester, 152 mg (0.40 mmol) HATU and 103 mg (0.80 mmol) DIPEA in 10 mL DCM.

HPLC (method A) \( t_R = 5.63 \) min
TLC, Rf (CH\(_2\)Cl\(_2\)/MeOH 9:1) = 0.20
MS (method D): 1103 [M+]

**Step 5**

(2S,4R)-2-{(lR,2S)-l-[2-((S)-8-Carboxy-8-cyclopentyloxy carbonylamino-octanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}-4-[2-(2-isopropyl-amino-thiazol-4-yl)-7-methoxy-quinolin-4-yl oxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 120 mg (0.099 mmol) (2S,4R)-2-{(lR,2S)-l-[2-((S)-8-Cyclopentyloxy carbonylamino-8-methoxycarbonyl-octanoyl-amino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}-4-{[2-(2-isopropyl-amino-thiazol-4-yl)-7-methoxy-quinolin-4-yl oxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (TFA-salt) and 42 mg (0.99 mmol) LiOH in 16 mL THF/MeOH/H\(_2\)O (2:1:1).

HPLC (method A) \( t_R = 5.38 \) min
TLC, Rf (CH\(_2\)Cl\(_2\)/MeOH 9:1) = 0.1 1
MS (method D): 1089 [M+]
Step 6

(S)-2-Cyclopentyloxycarbonylamino-8-(2-[(lR,2S)-l-{(2S,4R)-4-[2-(2-isopropylaminothiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl)-octanoic acid

The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 106 mg (0.097 mmol) (2S,4R)-2-[(lR,2S)-l-2-((S)-8-Carboxy-8-cyclopentyloxycarbonylamino-octanoylamino)-benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-[-2-(2-isopropyl-amino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester and 1 mL TFA in 5 mL DCM.

HPLC (method A) \( t_R = 4.78 \) min

TLC, RF (CH\(_2\)Cl\(_2\)/MeOH/H\(_2\)O/AcOH 90:10:1:0.5) = 0.21

MS (method D): 989 [M+]

Example 24

\[ ((8S,10R,14S)-10-(5-Chloro-pyridin-2-yloxy)-5-[(lR,2S)-l-carbonylamino-2-vinyl-cyclopropyl]-2,2,4,7,13-pentaoxo-2 \lambda^{*}6*-thia-3,6,12,22-tetraaza-tricyclo [2.4.0.0^{*}8,12^{*}] heptacosa-1(23),24,26-trien-1 4-yI]-carbamic acid cyclopentyl ester \]
The title compound is prepared analogously as described for the title compound in Example 2 using 250 mg (0.25 mmol) (S)-9-{[[(R,2S)-1-[(2S,4R)-4-(5-Chloro-pyridin-2-yloxy)-pyrrolidine-2-carbonyl]-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-2-cyclopentyloxy-carbonyl-amino-nonanoic acid (TFA-salt), 318 mg (2.5 mmol) DIPEA and 468 mg (1.2 mmol) HATU in 50 mL DCM and 1 mL DMF.

HPLC (method A) \( t_R = 6.27 \text{ min} \)

TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} \, 19:1) = 0.37 \)

MS (method D): \( 771 \, [\text{M}+] \)

**Preparation of** (S)-9-{[[(R,2S)-1-[(2S,4R)-4-(5-Chloro-pyridin-2-yloxy)-pyrrolidine-2-carbonyl]-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-2-cyclopentyloxy-carbonyl-amino-nonanoic acid**

**Step 1**

(2S,4R)-4-(5-Chloro-pyridin-2-yloxy)-2-{[(R,2S)-1-2-((S)-8-cyclopentyloxy carbonylamino-8-methoxycarbonyl-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbainoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester
The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 380 mg (0.47 mmol) (S)-9-{2-[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-2-cyclopentoxycarbonylamino-nonanoic acid methyl ester (TFA-salt), 194 mg (0.57 mmol) ((2S,4R)-4-(5-Chloro-pyridin-2-ylxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (prepared according to WO 2005035525), 269 mg (0.70 mmol) HATU and 365 mg (2.82 mmol) DIPEA in 10 mL DCM.

HPLC (method A) \( t_R = 6.33 \) min

TLC, \( R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} 9:1) = 0.69 \)

MS (method D): 903 [M+]

**Step 2**

\( (2S,4R)-2-[(lR,2S)-l-[2-((S)-8-Carboxy-8-cyclopentoxycarbonylaminooctylamino)-benzene-sulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-4-(5-chloro-pyridin-2-ylxy)-pyrrolidine-1-carboxylic acid tert-butyl ester \)
The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 250 mg (0.25 mmol) (2S,4R)-4-(5-Chloro-pyridin-2-yloxy)-2-{{(IR,2S)-1-[2-((S)-8-cyclopentyloxy-carbonylamino-8-methoxycarbonyl-octylamino)-benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropyl-carbamoyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (TFA-salt) and 59 mg (2.5 mmol) LiOH in 16 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) tᵣ = 5.86 min
TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.48

Step 3

(S)-9-{{[IR,2S)-1-{{(2S,4R)-4-(5-Chloro-pyridii-2-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylamino}-2-
cyclopenryloxy carbamoylaminonoanoic acid
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 219 mg (0.25 mmol) (2S,4R)-2-((1R,2S)-1-[2-((S)-8-Carboxy-8-cyclopentyloxycarbonylamino-octylamino)-benzene-sulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl)-4-(5-chloro-pyridin-2-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester and 1 mL TFA in 10 mL DCM.

HPLC (method A) t_R = 4.99 min

TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0.51

MS (method D): 789 [M+]

Example 25

((8S,14S)-5-[(1R,2S)-1-carbonylamino-2-vinyl-cyclopropyl]-2,2,4,7,13-pentaoxo-2_\lambda^*6^*-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0^8,12^*]heptacosa-l(23),24,26-trien-14-yl)-carbamic acid cyclopentyl ester

The title compound is prepared analogously as described for the title compound in Example 2.
using 62 mg (0.07 mmol) ((S)-2-Cyclopentyl oxycarbonylamino-9-[2-((S)-pyrrolidine-2-carbonyl)-amino]-2-vinyl-cyclopropanecarbonyl]-sulfamoyl)-phenylamino]-nonanoic acid (TFA-salt), 90 mg (0.7 mmol) DIPEA and 133 mg (0.35 mmol) HATU in 25 mL DCM and 0.5 mL DMF.

HPLC (method A) t\textsubscript{R} = 5.68 min
TLC, Rf (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 19:1) = 0.41
MS (method D): 644 [M+]
(S)-2-[(1R,2S)-1-(2-((S)-8-Carboxy-8-cyclopentylcarbonylamino-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 79 mg (0.09 mmol) (S)-2-[(1R,2S)-1-[(2-((S)-8-Carboxy-8-cyclopentylcarbonylamino-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (TFA-salt) and 21 mg (0.89 mmol) LiOH in 16 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) tᵣ = 5.35 min
TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.37
MS (method D): 762 [M+]

Step 3

(S)-2-Cyclopentylcarbonylamino-9-[(2-[(1R,2S)-1-[(S)-pyrrolidine-2-carbonyl]amino]-2-vinyl-cyclopropylcarbonyl]-sulfamoyl]-phenylamino]-nonanoic acid

The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 59 mg (0.08 mmol) (S)-2-[(1R,2S)-1-[(2-((S)-8-Carboxy-8-cyclopentylcarbonylamino-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester and 1 mL TFA in 10
mL DCM.

HPLC (method A) $t_R = 4.44$ min

TLC, $R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} \ 9:1) = 0.40$

MS (method D): 662 [M+]

Example 26

cyclopentyl $[(\text{IR},2\text{S},1\text{y}	ext{S})\text{-2y,23'-dioxido-14',15'S,1 V-trioxo-2-viByl-}$$\text{5',6',7',8',9',10',11',12',13',14',16\text{a},17',17\text{a}M7\text{b},1,18',19',21,22'}\text{-octadecahydro-16'H-spiro[cyclopropane-1,20'-cyclopropane[3,4]pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-13'-yl}$$\text{carbamate}}$

The title compound is prepared analogously as described for the title compound in Example 2 using 176 mg (0.20 mmol) (S)-9-[2-(((\text{IR},2\text{S})-\text{1-[(3-Aza-bicyclo[3.1.0]hexane-2-carbonyl)-amino]-2-vinyl-cyclopropane-carbonyl}-sulfamoyl)-phenylamino]-2-cyclopentyloxycarbonylamino-nonanoic acid (TFA-salt), 252 mg (0.98 mmol) DLPEA and 371 mg (1.95 mmol) HATU in 50 mL DCM and 1 mL DMF.

HPLC (method A) $t_R = 5.68$ min

TLC, $R_f (\text{CH}_2\text{Cl}_2/\text{MeOH} \ 9:1) = 0.62$

MS (method D): 656 [M+]
To a solution of 0.70 g (5.5 mmol) trans-rac-3-Aza-bicyclo[3.1.0]hexane-2-carboxylic acid (Aldrich) in 20 mL DCM is added 1.11 g (11.0 mmol) NEt₃. 1.68 g (7.7 mmol) (BOC₂)O is added in three portions over 10 min and the mixture is stirred overnight at ambient temperature. The reaction is quenched by addition of water, acidified with IN HCl and extracted with DCM. The combined organic phase is washed with brine, dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is purified by FC on silica (eluent: CH₂Cl₂/MeOH 98:2) to give the title compound as a colorless solid.

TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.62

MS (method D): 172 [M-55]

Step 2

2-{(IR,2S)-1-[2-((S)-8-Cyclopentyloxycarbonylamino-8-methoxycarbonyl-octylamino)-benzene-sulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 244 mg (0.30 mmol) (S)-9-{2-{{(IR,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl}-sulfamoyl}-phenylamino}-2-cyclopentloxy carbonylamino-nonanoic acid methyl ester (TFA-salt), 82 mg (0.36 mmol) trans-rac-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-tert-butyl ester, 172 mg (0.45 mmol) HATU and 234 mg (1.8 mmol) DEPEA in 10 mL DCM.

HPLC (method A) tᵣ = 5.90 min

TLC, Rf(CH₂Cl₂/ZMeOH 9:1) = 0.69
Step 3

2-{(R,2S)-1-[2-((S)-8-carboxy-8-cyclopentylloxycarbonylamino-octylamino)-benzenesulfonyl-aminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2 (step 2) using 183 mg (0.20 mmol) 2-{(R,2S)-1-[2-(S)-8-cyclopentylloxycarbonyl-8-methoxycarbonyl-octylamino)-benzene-sulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (TFA-salt) and 49 mg (2.0 mmol) LiOH in 20 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) t_R = 5.42 min
TLC, Rf(CH₂Cl₂:MeOH 9:1) = 0.50

Step 4

(S)-9-[2-((R,2S)-1-[3-Aza-bicyclo[3.1.0]hexane-2-carbonyl)-amino]-2-vinyl-cyclopropane-carbonyl]-sulfamoyl)-phenylamino]-2-cyclopentylloxycarbonylamino-

nonanoic acid
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 157 mg (0.20 mmol) 2-[(R,R,S)-l-2-((S)-8-carboxy-8-cyclopentyl)oxycarbonylamino-octylamino)-benzenesulfonyl-aminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester and 0.5 mL TFA in 5 mL DCM.

HPLC (method A) \( t_R = 4.43 \) min
TLC, Rf (CH\(_2\)Cl\(_2\)/MeOH 9:1) = 0.37
MS (method D): 674 [M+]

**Example 27**

\((1R,2S,22'R,23a'S)-6'^\prime\'-Dioxido-1'^\prime'.1P'-trioxo-Z-vinylicosahydrodispiro[cyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8]thiatriazacyclohenicosine-7',r 1'-cyclopropan]-22'-yl 4-fluoro-1,3-dihydro-2//-isoiiidole-2-carboxylate\)
The title compound is prepared in analogy to the procedure described in Example 1 (last step) using 115 mg (0.14 mmol) 4-Fluoro-l,3-dihydro-isooindole-2-carboxylic acid (3R,5S)-5-{(1R,2S)-l-[l-(carboxy-undecyl)-cyclopropanesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester (trifluoroacetate) LC MS (method E) \( t_R = 5.135 \text{ min}, M+H = 687.3 \)
HPLC (method C) \( t_R = 5.681 \text{ min} \)

**Preparation of 4-Fluoro-1,3-dihydro-isooindole-2-carboxylic acid (3R,5S)-5-{(1R,2S)-l-[l-(carboxy-undecyl)-cyclopropanesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-pyrrolidin-3-yl ester (trifluoroacetate)**

**Step 1**

(12-Bromo-dodecyloxy)-tert-butyl-dimethyl-silane

To a mixture of 3.8 g (14.3 mmol) 12-Bromo-l-dodecanol and 1.2 g (17.2 mmol) imidazole in 8 mL DMF is added 2.6 g (17.2 mmol) tert-Butyl-chloro-dimethyl-silane. The mixture is stirred at RT for 5 h, then EtOAc is added and the mixture is washed with IN aq. HCl and water. The combined organic phases are dried over Na\(_2\)SO\(_4\) and concentrated in vacuo to give the product which was used in the next step without further purification.

TLC, \( R_f \) (EtOAc/hexane 1:9) = 0.70

**Step 2**

l-IlZ-^\( \text{ert-Butyl-dimethyl-silanyloxy} \)-dodecyl-cyclopropanesulfonylamine tert-butyl carbamate

To an ice-cold solution of 4.0 mL (28.2 mmol) diisopropylamine in 45 mL THF is added 17 mL (27 mmol) n-BuLi (1.6 M in hexanes). The mixture is stirred for 1 h at 0°C and cooled to -78°C. A mixture of 2.4 g (10.8 mmol) Cyclopropylsulfonylamine tert-butyl carbamate
(prepared as described in US2007/0010455) in 5 mL THF is added and the resulting mixture is stirred for an additional hour. Then 4.5 g (11.9 mmol) (12-Bromo-dodecyloxy)-tert-butyl-dimethyl-silane is added and the mixture is allowed to warm to RT and stirred overnight. Sat. aq. NH₄Cl-solution is added and the mixture is extracted with EtOAc. The combined organic layers are dried over Na₂SO₄ and concentrated in vacuo. The residue is purified by FC on silica (eluent: hexane to EtOAc/hexane 1:1) to give the title compound.

TLC, Rf (EtOAc/hexane 1:9) = 0.8

Step 3

l^[II]-Hydroxy-dodecyO-cyclopropanesulfonylamine tert-butyl carbamate

A mixture of 3.3 g (6.4 mmol) l-[12-(tert-Butyl-dimethyl-silyloxy)-dodecyl]-cyclopropanesulfonyl-amine tert-butyl carbamate and 13 mL TBAF (1 M in THF) in 400 mL THF is stirred for 4 h at RT. Sat. aq. NEL₄Cl-solution is added and the mixture is extracted with EtOAc. The combined organic layers are dried over Na₂SO₄ and concentrated in vacuo. The residue is purified by FC on silica (eluent: hexane to EtOAc/hexane 1:1) to give the title compound.

TLC, Rf (EtOAc/hexane 1:1) = 0.45

Step 4

l-(12-Oxo-dodecyl)-cyclopropanesulfonlamine tert-butyl carbamate

The title compound is prepared in analogy to the procedure described in Example 14 (step 3) using 1.8 g (4.4 mmol) l-[II]-Hydroxy-dodecyO-cyclopropanesulfonlamine tert-butyl carbamate, 1.4 g (6.7 mmol) PCC in 150 mL DCM.

TLC, Rf (EtOAc/hexane 1:19) = 0.7
Step 5
12-(l-tert-Butyl carbamoylsulfamoyl-cyclopropyl)-dodecanoic acid

The title compound is prepared in analogy to the procedure described in Example 16 (step 1) using 1.5 g (3.7 mmol) l-(12-Oxo-dodecyl)-cyclopropanesulfonfylamine tert-butyl carbamate.

TLC, Rf (EtOAc/hexane 1:19) = 0.42

Step 6
12-(l-Sulfamoyl-cyclopropyl)-dodecanoic acid methyl ester

A mixture of 1.5 g (3.6 mmol) 12-(l-tert-Butyl carbamoylsulfamoyl-cyclopropyl)-dodecanoic acid in 10 mL MeOH is cooled to -15 °C and 1.7 mL (23.6 mmol) thionylchloride is added. The mixture is stirred for 1 h at RT and heated to 60 °C overnight. At RT 1 mL of thionylchloride is added and the mixture is again warmed to 60 °C for 2 h before it is concentrated and filtered over a small plug of silica gel to give the title compound.

TLC, Rf (EtOAc/hexane 1:1) = 0.57

Step 7
12-{l-[(lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl}-cyclopropylj-dodecanoic acid methyl ester
A mixture of 610 mg (2.7 mmol) (lR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-
cyclopropane-carboxylic acid and 687 mg (4.0 mmol) CDI in 20 mL THF is refluxed for 1 h. The reaction mixture is cooled to RT and 0.6 mL (4.0 mmol) DBU and a mixture of 806 mg (2.4 mmol) 12-(l-Sulfamoyl-cyclopropyl)-dodecanoic acid methyl ester in 5 mL THF is added. The mixture is stirred at RT overnight, concentrated in vacuo, taken up in EtOAc and washed with 0.1 M aq. HCl. The combined organic phases are dried over Na₂SO₄ and concentrated in vacuo. The residue is purified by FC on silica (Eluent: EtOAc/hexane 1:3) to give the title compound.

LC-MS (method E) tᵣ = 5.132 min, M-H = 543.3
HPLC (method C) tᵣ = 4.472 min

Step 8

12-{l-[[((IR,2S)-l-Aminoo-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-cyclopropyl]-
dodecanoic acid methyl ester (hydrochloride)

A mixture of 343 mg (0.6 mmol) 12-{l-[[((IR,2S)-l-tert-Butoxycarbonylamino-2-vinyl-
cyclopropane-carbonyl)-sulfamoyl]-cyclopropyl]-dodecanoic acid methyl ester and 10 mL of a 4 M solution of HCl in dioxane in 10 mL dioxane is stirred at RT overnight. The mixture is concentrated and coevaporated twice with DCM. The obtained product is used without further purification.

LC-MS (method E) tᵣ = 4.103 min, M-H = 443.2
HPLC (method C) $t_R = 3.258$ min

**Step 9**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-L-tert-butoxycarbonyl-5-\{(1R,2S)-L-[L-(L-3-carboxy-undecyl)-cyclopropanesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-L-pyrrolidin-3-yl\} ester

To a mixture of 181 mL (0.46 mmol) (2S,4R)-L-(4-Fluoro-L,3-dihydro-isoindole-2-carbonyloxy)-pyrrolidine-L,2-dicarboxylic acid L-tert-butyl ester in 3 mL DMF is added 0.2 mL (1.25 mmol) DIPEA and 192 mg (0.50 mmol) HBTU at RT. After 30 min 200 mg (0.42 mmol) 12-\{(1R,2S)-L-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl\}-cyclopropyl] -dodecanoic acid methyl ester (hydrochloride) is added and the mixture is stirred at RT overnight. DCM is added and the mixture is washed with aq. $K_2CO_3$-solution. The aq. layer is extracted twice with DCM and the combined organic layers are washed with aq. 10% KH$SO_4$-solution and brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue is purified by FC (silica gel, eluent: EtOAc/hexane 1:3) to give the title compound.

LC MS (method E) $t_R = 4.317$ min, M+H = 819.4

HPLC (method C) $t_R = 4.681$ min

**Step 9**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-L-tert-butoxycarbonyl-5-\{(1R,2S)-L-[L-(L-carboxy-undecyl)-cyclopropanesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoylL-pyrrolidin-3-yl\} ester
A mixture of 137 mg (0.17 mmol) 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-{(1R,2S)-1-[(11-methoxycarbonyl-undecyl)-cyclopropanesulfonilaminocarbonyl]-2-vinyl-cyclopropyl carbamoyl}-pyrrolidin-3-yl ester and 21 mg (0.50 mmol) Lithiumhydroxid-monohydrate in 2 mL THF/MeOH/water (2:1:1) is stirred at RT overnight. The mixture is concentrated under reduced pressure, the residue is acidified with IN HCl and extracted with DCM (3x). The combined organic layers are dried over Na₂SO₄ and concentrated in vacuo to give the title compound which is used without further purification.

LC MS (method E) t_R = 4.623 min, M+H = 805.3

**Step 10**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-{(1R,2S)-1-[(11-carboxy-undecyl)-cyclopropanesulfonilaminocarbonyl]-2-vinyl-cyclopropyl carbamoyl}-pyrrolidin-3-yl ester (trifluoroacetate)
A mixture of 115 mg (0.14 mmol) 4-fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-[(1R,2S)-1-[11-carboxy-undecyl]-cyclopropanesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbaniyl]-pyrrolidin-3-yl ester and 0.2 mL (2.93 mmol) TFA in 2 mL DCM is stirred at RT for 1.5 h before the mixture is concentrated in vacuo. The crude product is used without further purification.

LC MS (method E) $t_R = 3.316 \text{ min, } M+H = 705.3$

**Example 28**

$(1R,2S,22'R,23a'S)-7'$-methyl-6',6'-dioxido-7,4',19'-trioxo-2-vinylicosahydro-7' $H$-spiro[cydoplane-1,3'-pyrrolo[2,1^-][1,2,5,8,21]thiatetraazyclohexicosin]-22'-yl 4-fluoro-1,3-dihydro-2//-isoindole-2-carboxylate

The title compound is prepared in analogy to the procedure described in Example 1 (last step) using 700 mg (0.75 mmol) of the title compound obtained in step 8 (trifluoroacetate)

LC MS (method E) $t_R = 4.613 \text{ min, } M-H = 674.2$
HPLC (method C) \( t_R = 4.275 \) min

Step 1
12-Methylamino-dodecanoic acid methyl ester

To a mixture of 5 g (21.8 mmol) 2-Methylamino-dodecanoic acid in 25 mL MeOH is added 5.5 mL (620 mmol) thionyl chloride at -15°C. The reaction mixture is refluxed overnight and concentrated under reduced pressure to yield the title compound which is used without further purification.

LC MS (method E) \( t_R = 1.819 \) min, M+H = 244.3

Step 2
Methyl 12-[(tert-butoxycarbonyl)amino]sulfanyl]methylamino]dodecanoate

A mixture of 100 mg (0.33 mmol) N-(tert-Butoxycarbonyl)-N-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide (prepared according to J.-Y. Winum et. al, Org. Lett. 2001, 3, 2241.) 97 mg (0.35 mmol) 12-Methylamino-dodecanoic acid methyl ester and 0.07 mL (0.40 mmol) DIPEA in 3 mL DCM is stirred at RT overnight. The reaction mixture is diluted with DCM and washed with 10% KHSCv solution. The aq. layer is extracted with DCM and the combined organic layers are washed with % KHSO\(_4\)-solution and brine, dried over \( \text{Na}_2\text{SO}_4 \) and concentrated under reduced pressure to give the title compound which is used without further purification.

LC MS (method E) \( t_R = 4.415 \) min, M+H = 423.1

Step 3
Methyl 12-[(aminosulfanyl)(methyl)amino]dodecanoate
A mixture of 9 g (21 mmol) of the title compound obtained in step 2 and 25 mL (330 mmol) TFA in 100 mL DCM is stirred at RT for 1.5 h before the mixture is concentrated in vacuo. The crude product is triturated with water, filtered, dried and used without further purification.

**LC-MS (method E)** $t_R = 4.00$ min, $M+H = 321.1$

**Step 4**

Methyl 12-[[((1R,2S)-1-tert-Butoxycarbonylamino)-2-vinylcyclopropyl]carbonyl]amino]-sulfonyl]-(methyl)amino]-dodecanoate

A mixture of 1.41 g (6.2 mmol) (1R,2S)-l-tert-Butoxycarbonylamino-2-vinyliccyclopropane-carboxylic acid and 1.52 mg (9.31 mmol) CDI in 30 mL THF is refluxed for 1 h. In a second flask to a mixture of 3.0 g (9.31 mmol) of the title compound obtained in step 3 in 30 mL THF 9.3 mL (9.3 mmol) LiHMDS (1 M in THF) is added at 0°C and the mixture is stirred for 30 min. Both mixtures are combined and stirred at RT overnight. Water is added and the mixture is extracted with DCM (3x). The combined organic layers are dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue is purified by FC (silica gel, eluent: EtOAc/hexane 1:3) to give the title compound.

**LC-MS (method E)** $t_R = 4.728$ min, $M-H = 530.2$

**Step 5**

Methyl 12-[[((1R,25)-1-amino-2-vinyliccyclopropyl]carbonyl]amino]-sulfonyl]- (methyl)amino]-dodecanoate (hydrochloride)
A mixture of 1.91 g (3.6 mmol) of the title compound obtained in step 4 and 18 mL of a 4 M solution of HCl in dioxane in 18 mL dioxane is stirred at RT for 6 h. The mixture is concentrated and coevaporated twice with DCM. The obtained product is used without further purification.

LC MS (method E) \( t_R = 3.642 \text{ min}, M+H = 432.3 \)

**Step 6**

(3R,5S)-l-(tert-butoxycarbonyl)-5-\[l(1R,25)-l-([\{(12-methoxy-12-oxododecyl)(methyI)amino\]-sulfonyl}carbarnoyl)-2-vinylcyclopropyl]carbamoyl]pyrrolidin-3-yl 4-fluoro-1,3-dihydro-2/ 5-isoindole-2-carboxylate

To a mixture of 447 mg (1.13 mmol) of the title compound obtained in step 5 in 10 mL DMF is added 0.5 mL (3.09 mmol) DIPEA and 474 mg (1.24 mmol) HBTU at RT. After 30 min 569 mg (1.03 mmol) 12-{l-[(lR,2S)-l-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-cyclopropyl}-dodecanoic acid methyl ester (hydrochloride) is added and the mixture is stirred at RT overnight. DCM is added and the mixture is washed with aq. \( \text{K}_2\text{CO}_3 \)-solution. The aq. layer is extracted twice with DCM and the combined organic layers are washed with aq. 10%
KHSC vs. solution and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue is purified by FC (silica gel, eluent: EtOAc/hexane 1:1) to give the title compound.

LC MS (method E) t<sub>R</sub> = 5.007 min, M+H = 806.3

**Step 7**


A mixture of 641 mg (0.79 mmol) of the title compound obtained in step 6 and 100 mg (2.38 mmol) Lithiumhydroxid-monohydrate in 8 mL THF/MeOH/water (2:1:1) is stirred at RT overnight. The mixture is concentrated under reduced pressure, the residue is acidified with IN HCl and extracted with DCM (3x). The combined organic layers are dried over Na₂SO₄ and concentrated in vacuo to give the title compound which is used without further purification.

LC MS (method E) t<sub>R</sub> = 4.574 min, M-H = 792.4

**Step 8**

A mixture of 600 mg (0.76 mmol) of the title compound obtained in step 7 and 0.5 mL (6.5 mmol) TFA in 12 mL DCM is stirred at RT for 1.5 h, before the mixture is concentrated in vacuo. The crude product is used without further purification.

LC MS (method E) t_R = 3.023 min, M-H = 692.2

Example 29

Cyclopentyl [(1S,2''S,5,6'R,22'a'R,24'a'R)-2,2-dimethyl-19't,19't-dioxido-5''l',24'-trioxo-2 M

hexadecahydrodispiro[cyclopropane-1,2'-pyrrolo[2,1-

benzothiatetraazacycloicosine-22',l''-cyclopropan]-6'-yl]carbamate

The title compound is prepared analogously as described for the title compound in Example 2 using 330 mg (0.35 mmol) ((S)-2-Cyclopentylxycarbonylamino-9-[2-((IR,2S)-1-[(3S,6S)-

1,1-dimethyl-5-aza-spiro[2.4]heptane-6-carbonyl]-amino]-2-vinyl-cyclopropanecarbonyl]-

sulfamoyl)-phenylamino]-nonanoic acid (TFA-salt), 452 mg (3.5 mmol) DIPEA and 665 mg
(1.75 mmol) HATU in 75 mL DCM and 1.5 mL DMF.
HPLC (method A) $t_R = 6.21$ min
TLC, $R_f (CH_2CVMeOH 19:1) = 0.40$
MS (method D): 698 [M+]

**Preparation of (3S,6S)-l,l-Dimethyl-5-aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-tert-butyl ester**

**Step 1**

(3R,7aS)-6-Hydroxymethyl-3-phenyl-tetrahydro-pyrrolo[1,2-c]oxazol-5-one

![Chemical Structure](image)

To a solution of DIPA (12.4 mL, 88.6 mmol, 1.2 equiv) in THF (400 mL) at -30°C is added n-BuLi (50 mL, 1.60 M in hexane, 81.0 mmol, 1.10 equiv). The solution is stirred at this temperature for 30 min, then a solution of (3R,7aS)-3-Phenyl-tetrahydro-pyrrolo[1,2-c]oxazol-5-one (15.0 g, 73.8 mmol, 1.0 equiv, prepared according to J. Org. Chem. 1986, 51, 3140.) is added and the solution is stirred at -30°C for 30 min.

A stream of CHO (22.0g, 738 mmol, 10 equiv) and N2 gas is bubbled through this solution over 10 mins. The reaction mixture is warmed up to 0°C over 30 mins and quenched by addition of 2.0 N HCl aq. solution until pH 3. EtOAc is added and the phases are separated. The aqueous layer is extracted 3 x with EtOAc, the combined organic layer is washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue was continued to the next step with no further purification.

**Step 2**

(3R,7aS)-6-Methylene-3-phenyl-tetrahydro-pyrrolo[1,2-c]oxazol-5-one
The residue from step 1 is dissolved in DCM (200 mL). To this solution at 0°C is added TEA (30.9 mL, 222 mmol, 3.0 equiv), DMAP (902 mg, 7.4 mmol, 0.1 equiv), followed by SLOW addition of MsCl (11.5 mL, 148 mmol, 2.0 equiv), while the reaction temperature is maintained below 5°C. The solution is stirred at rt for 2 h, quenched by addition of sat. aq. NH₄Cl and followed by 1/1 mixture of EtOAc/TBME. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried with Na₂SO₄ and concentrated.

The residue is dissolved in DCM/toluene (20 mL/20 mL). At 0°C, 15 mL of DBU are added and the internal temperature is kept below 20°C. After stirring for 2 h at RT the mixture is loaded directly to a silical gel column and flushed with hexane/EtOAc (2/1 to 1/1) to give the title compound (7.4 g). The product is used immediately in the next step to avoid polymerization.

LC-MS (method E) $t_R = 0.86$ min, M+H = 216.1

Step 3

1S^RS^S.Z-dimethyl-S'-phenyldihydro-l'H-spiro cyclopropane-l^'-pyrroloIl,|-c][l,3]oxazol]-5'-one

To a solution of isopropyl triphenyl phosphine iodide (10.4 g, 24.1 mmol, 1.4 equiv) in THF (70 mL) at -30°C is added n-BuLi (1.60 M, 13.9 mL, 22.4 mmol). The solution is stirred at 0°C for 30 min, then cooled to -30°C. A solution of (3R,7aS)-6-Methylene-3-phenyl-tetrahydro-pyrrolo[1,2-c]oxazol-5-one (3.7 g, 17.2 mmol, 1.0 equiv) is added and the reaction is warmed to rt over 1h and stirred at rt for 3h. The reaction is quenched by addition of sat. aq.
NaHCO₃ solution. After dilution with EtOAc, the mixture is filtered. The two phases are
separated and the aqueous layer is extracted with EtOAc. Organic layers are combined,
washed with brine, dried over Na₂SO₄ and concentrated. The residue is purified by silical gel,
hexane/EtOAc 3/1 to 2/1 to give the title compound.

TLC, Rf (EtOAc/heptane 1:2) = 0.53 (diastereomer 1) and 0.46 (diastereomer 2)

**Step 5**

((3S,6S)-5-Benzyl-l,l-dimethyl-5-aza-spiro[2.4]hept-6-yl)-methanol

To an ice-cold solution of 9.9 g (38 mmol) (lS,3'R,7a'S)-2,2-dimethyl-3'-phenylidihydro-l
H-spirocyclopropane-1,6'-pyrrolo[1,2-c][1,3]oxazorj-5'-one in 250 ml abs. THF is added 4.52
g (115 mmol) LiAlH₄ under Argon. The reaction is refluxed for 3 h and quenched at 0°C by
addition of 10 mL sat. aq. Na₂SO₄. After addition of 300 mL EtOAc and stirring for 30 min
the mixture is filtered and the filtrate is concentrated to give the titled compound, which is
used without further purification.

HPLC (method A) tᵣ = 2.64 min

TLC, Rf(CH₂Cl₂/MeOH 9:1) = 0.48

MS (method D): 246 [M+H]

**Step 6**

((3S,6S)-l,l-Dimethyl-5-aza-spiro[2.4]hept-6-yl)-methanol

A suspension of 9.5 g (38 mmol) ((3S,6S)-5-Benzyl-l,l-dimethyl-5-aza-spiro[2.4]hept-6-yl)-
methanol and 10% Pd on charcoal (2 g) in 100 mL EtOAc/AcOH (1:1) is stirred for 2.5 h
under H₂ atmosphere. The reaction is filtered, washed with DCM and concentrated. After
addition of 2 N aq. NaOH, the aq. phase is extracted with DCM. The combined organic phases are washed with brine, dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is purified by FC (silica gel, eluent: DCM/MeOH 9:1 - 4:1) to give the title compound.

5  TLC, Rf(CH₂Cl₂/MeOH 4:1) = 0.29
MS (method D): 156 [M+H]

Step 7
(SS,6S)-6-Hydroxymethyl-1,1-dimethyl-S-aza-spiro[2.4]heptane-5-carboxylic acid tert-butyl ester

To an ice-cold solution of 1.4 g (9.0 mmol) ((3S,6S)-1,1-Dimethyl-5-aza-spiro[2.4]hept-6-yl)-methanol in 30 mL DCM is added 2.5 mL (18 mmol) NEt₃ and 2.8 g (12.6 mmol) (BOC)₂O and the mixture is stirred overnight at RT. The reaction is quenched by addition of aq. sat. bicarbonate and extracted with DCM. The combined organic phases are washed with brine, dried with Na₂SO₄, filtered and the solvent is removed in vacuo. The residue is purified by FC (silica gel, eluent: DCM/MeOH 19:1) to give the title compound.

TLC, Rf(CH₂Cl₂/MeOH 19:1) = 0.58
MS (method D): 200 [M-55]

Step 8
(3S,6S)-1,1-Di πethyl-5-aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-tert-butyl ester

To a solution of 1.7 g (6.7 mmol) (3S,6S)-6-Hydroxymethyl-1,1-dimethyl-5-aza-spiro[2.4]heptane-5-carboxylic acid tert-butyl ester in 30 mL DCM is added 235 mg (0.67 mmol) TPAP, 1.18 g (10 mmol) NMO followed by 300 mg molecular sieves 4A. The reaction is stirred for 2 h at RT, filtered through a pad of Celite, washed with DCM and the solvent is removed in vacuo. The residue is dissolved in 30 mL tert-butanol and 2.4 g (33.3
mmol) 2-Methyl-2-buten is added, followed by 3.1 g (20 mmol) NaH$_2$PO$_4$ (in 20 mL water) and 1.81 g (20 mmol) NaClO$_2$ (in 20 mL water). After 2 h at RT, 0.5 N aq. HCl is added and extracted with EtOAc. The solvent is removed in vacuo, the residue is dissolved in DCM and extracted 3 x with aq. NaHCO$_3$. The organic phase is discarded, while the bicarbonate phase is acidified with 4 N HCl to pH 1-2 and then extracted with DCM. The combined organic phase is dried with Na$_2$SO$_4$, filtered and the solvent is removed in vacuo to give the title compound, which is used without further purification.

TLC, Rf(CH$_2$Cl$_2$MeOH 19:1) = 0.16
MS (method D): 214 [M-55]

### Preparation

(3S,6S)-6-{((1R,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl)-sulfamoyl]-phenylamino]-nonanoic acid

#### Step 1

(3S,6S)-6-{(IR,2S)-1-I2-(S)-8-Cyclopentylxoycarboyloxyamino-8-methoxycarbonyloctyIamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbomoyl1}-1,l-
dimethyl-5-aza-spiro[2.4]heptane-5-carboxylic acid tert-butyl ester

![](image)

The title compound is prepared analogously as described for the title compound in Example 2 (step 1) using 403 mg (0.50 mmol) (S)-9-{{(IR,2S)-1-Amino-2-vinyl-cyclopropanecarbonyl}-sulfamoyl]-phenylamino]2-cyclopentylxycarbonylamino-nonanoic acid methyl ester (TFA-salt), 162 mg (0.60 mmol) (3S,6S)-1,l-Dimethyl-5-aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-tert-butyl ester, 285 mg (0.75 mmol) HATU and 388 mg (3.0 mmol) DIPEA in 15 mL DCM.

HPLC (method A) t$_R$ = 6.30 min
TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.40
MS (method D): 830 [M+]

**Step 2**

(3S,6S)-6-[(lR,2S)-l-[2-((S)-8-Carboxy-8-cyclopentyloxycarbonylamino-octylamino)-
benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl]-l,l-dimethyl-5-aza-
spho[2.4]heptane-5-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound in Example 2
(step 2) using 330 mg (0.35 mmol) (3S,6S)-6-[(lR,2S)-l-[2-((S)-8-
cyclopentyloxycarbonylamino-8-methoxycarbonyl-octylamino)-
benzenesulfonylamino-carbonyl]-2-vinyl-cyclopropylcarbamoyl]-l,l-dimethyl-5-aza-
spho[2.4]heptane-5-carboxylic acid tert-butyl ester (TFA-salt) and 84 mg (3.5 mmol) LiOH
in 20 mL THF/MeOH/H₂O (2:1:1).

HPLC (method A) t_R = 5.85 min
TLC, Rf (CH₂Cl₂/MeOH 9:1) = 0.50
MS (method D): 816 [M+]

**Step 3**

(S)-2-Cyclopentyloxycarbonylamino-9-[(lR,2S)-l-[(3S,6S)-l,l-dimethyl-5-aza-
spho[2.4]heptane-6-carbonyl]-amino]-2-vinyl-cyclopropanecarbonyl]-sulfainoyl-
phenylamino]-nonanoic acid
The title compound is prepared analogously as described for the title compound in Example 2 (step 3) using 258 mg (0.35 mmol) (3S,6S)-6-[(1R,2S)-1-[2-((S)-8-carboxy-8-cyclopentyloxycarbonylamino-octylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropylcarbamoyl]-1,1-dimethyl-5-aza-spiro[2.4]heptane-5-carboxylic acid tert-butyl ester and 1.0 mL TFA in 10 mL DCM.

HPLC (method A) \( t_R = 4.87 \) min

TLC, \( \text{Rf} \left( \text{CH}_2\text{Cl}_2\text{MeOH 85:15} \right) = 0.73 \)

MS (method D): 716 \([M+]\)

Scheme 3:

Synthetic scheme for Example 30
Example 30

((E)-(3S,13S)-3-Benzyl-7-cyclobutylmethyl-11-cyclopentylmethyl-2,5,6,9,12-pentaoxo-1,4,8,11-tetraaza-cyclononadec-16-en-13-yl)-carbamic acid tert-butyl ester

A solution of VI (85 mg, 0.12 mmol) with Hoveyda-Grubbs 2nd generation catalyst (3 mg, ~3 mol %) in Toluene (10 mL) degassed with N₂ is heated to 80 °C for 2.5 hours. After 2.5 hours the reaction is cooled to room temp and the catalyst is scavenged by adding the reaction...
to thiourea bound resin (4 equiv.). The reaction is stirred for 1 hour after which time the solution is filtered and the solvent removed. The crude product is run though a plug of silica gel with EtOAc and is purified by prep HPLC to yield VII.

LC-MS (method E): M+H = 694.9

**Preparation of** $[^{\text{SVl-But-S-enylcarbamoyl}}-{\text{pheiyl-ethylcarbamoyl}}}^{-1\text{-cyclobutylmethyl-2-oxo-ethylcarbamoyl}}^{-1\text{-methyl-}^{-1\text{-cyclopentylmethyl-carbamoyl}}}^{-1\text{-pent-4-enyl}}^{-\text{carbamic acid}}$ tert-butyl ester VI

**Step 1**

[2-((S)-1-But-3-enylcarbamoyl-2-phenyl-ethylcarbamoyl)-1-cyclobutylmethyl-2-hydroxy-ethyl]-carbamic acid tert-butyl ester

To a solution of I (500 mg, 1.57 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (2.0 mL) at 0 °C is added TFA (2.0 mL) and the solution is stirred at room temp for 1 hour. After 1 hour the solvent is removed under reduced pressure to yield a crude oil. A solution of II (640 mg, 2.30 mmol, 1.5 equiv), EDC (0.45 g, 2.30 mmol, 1.5 equiv), DIEA (2.0 mL, 11.5 mmol, 7.5 equiv) in CH$_2$Cl$_2$ (5.0 mL) is added at 0°C. The solution is brought to room temperature and stirred for 18 hours. The reaction mixture is diluted with EtOAc and washed with 0.5 N HCl. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue is purified by silica gel column chromatography (heptane/EtOAc, 1:3) to give product III.

LC-MS (method E): M+H = 474.3

**Step 2:**

[(S)-2-((S)-1-But-3-enylcarbamoyl-2-phenyl-ethylcarbamoyl)-1-cyclobutylmethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester
To a solution of III (150 mgs, 0.32 mmol, 1.0 equiv) in CH$_3$CN (10.0 mL) at °C is added DMP (0.39 mgs, 2.5 equiv.) and the solution is stirred at room temp for 1 hour. After 1 hour 3mL 1N sodium thiosulfate is added to the reaction mixture and the solution extracted with EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue is purified by silica gel column chromatography (heptane/EtOAc, 1:1) to give product IV.

LC-MS (method E): M+H = 472.3

**Step 3:**

\[](S)-l-[(2-((S)-l-But-3-enylcarbamoyl-2-phenyl-ethylcarbamoyl)-l-cyclobutylmethyl-2-oxo-ethylcarbamoyl]-methyl}-cyclo pentylmethyl-carbamoyl]-pent-4-enyl]-carbamic acid tert-butyl ester

To a solution of IV (102 mg, 0.22mmol, 1.0 equiv) a in CH$_2$Cl$_2$ (2.0 mL) at 0 °C is added TFA (2.0 mL) and the solution is stirred at room temp for 1 hour. After 1 hour the solvent is removed under reduced pressure to yield a crude oil to which is added a solution of V (85 mg, 0.22 mmol, 1.0 equiv), PyBrOP (108 mgs, 0.22 mmol, 1.0 equiv), DIEA (0.2 mL, 1.15 mmol, 5 equiv) in CH$_2$Cl$_2$ (5.0 mL) at 0 °C. The solution is brought to room temperature and stirred for 18 hours. The reaction mixture is diluted with EtOAc and washed with 0.5 N HCl. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue is purified by silica gel column chromatography (heptane/EtOAc, 1:3) to give product VI.
Example 3

Cyclopentyl ([1R,2S,2'R,6'S]-aSH'-hydroxy-^-IP'-dioxido-SSII'^'-trioxo-Z-vinyl-
1,2,3,5,6,7,8,9,10,11,12,13,14,16,18]-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-
g][1,2,5,8,18]benzothiatetraazacycloicosin]-6'-ylJcarbamate

The title compound can be prepared as described above for the final step in the synthesis of example 1.

LC MS (method E) \( t_R = 4.209 \) min, \( M+H = 660.3 \)

HPLC (method C) \( t_R = 3.993 \) min

Step 1

tert-butyl (2S,4R)-4-[[tert-butyl(dimethyl)silyl]oxy]-2-[[{(2S)-1-[(2S)-8-
((cyclopentyloxy)carbonyl]amino}-9-methoxy-9-
oxononyl]amino}phenyl]sulfonyl]carbamoyl]-2-
vinylicyclopropyl]carbamoyl]pyrro-idine-l-carboxylate

The title compound can be prepared as described above for the synthesis of (3R,5S)-l-tert-
butoxycarbonyl-5-[{(1R,2S)-1-[2-(8-methoxycarbonyl-octanoylamino)-benzenesulfonylaminocarbonyl]-2-vinyl-cyclopropyl]carbamoyl]pyrrolidin-3-yl ester

LC MS (method E) $t_R = 5.401$ min, M+H = 907.2

5 Step 2


The title compound can be prepared analogously as described for the title compound in example 21, step 11.

LC MS (method E) $t_R = 5.097$ min

15 Step 3

(2S)-2-[[[(cyclopentyloxy)carbonyl]amino]-9-[[2-[[((1R,2S)-1-[[[(4R)-4-[[[(2-nitrophenyl)-

The title compound can be prepared as described above for the synthesis of (2S)-2-[[[(cyclopentyloxy)carbonyl]amino]-9-[[2-[[((1R,2S)-1-[[[(4R)-4-[[[(2-nitrophenyl)-

LC MS (method E) \( t_R = 3.009 \text{ min}, M+H = 678.3 \)

**Example 32**

Cyclopentyl \{[(lR,2S,2'R,6'S,24a'S)-19',19'-dioxido-5',21',24'-trioxo-2'-[(quinolin-6-ylcarbonyl]-amino]-2-vinyl]-1',2',3',5',6',7',8',9',10',11'M2,1',13',14',20',21',23',24',24a'-octadecahydrospiro-[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-6'-yl} carbamate

To a mixture of 50 mg (0.07 mmol) Cyclopentyl \{[(lR,2S,2'R,6'S,24a'S)-2'-amino-19',19'-dioxido-5',21',24'-trioxo-2'-vinyl]-1',2',3',5',6',7',8',9',10',11'M2,1',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-6'-yl} carbamate, 0.037 mL (0.21 mmol) DIPEA and 40 mg (0.11 mmol) HATU in 0.7 mL DCM/DMF (50:1) are added at 0°C. 16 mg (0.09 mmol) 6-Quinoline carboxylic acid. The mixture is stirred for 72 h, concentrated in vacuo and purified by prep. HPLC (method C).

LC MS (method E) \( t_R = 4.254 \text{ min}, M+H = 814.3 \)

**Preparation of Cyclopentyl** \{[(lR,2S,2'R,6'S,24a'S)-2'-amino-19',19'-dioxido-5',21',24'-trioxo-2'-vinyl]-1',2',3',5',6',7',8',9',10',11'M2,1',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-6'-yl} carbamate

**Step 1**

1-tert-Butyl 2-methyl (2S,4R)-4-{{[2-nitrophenyl]sulfonyl]amino}pyrrolidine-1,2-dicarboxylate
To a mixture of 3 g (10.6 mmol) N-Boc-trans-4-amino-L-proline methyl ester hydrochloride, 14.8 mL (106 mmol) triethylamine in 260 mL DCM is added 3.6 g (15.9 mmol) 2-nitrobenzolsulfonyl chloride at 0°C. The mixture is stirred at rt overnight and extracted with brine. The organic layer is dried over Na₂SO₄, concentrated in vacuo and purified by FC on silica (eluent: DCM to DCMMeOH 95:5).

LC MS (method E) tᵣ = 3.284 min, M+H = 430.03
HPLC (method C) tᵣ = 3.306 min

Step 2

\[(4R)-1-(t\text{-}butoxycarbonyl)-4\{-[(2\text{-}nitropheny}l)sulfonyl]amino\}-L\text{-}proline\]

A mixture of 4.2 g (9.8 mmol) 1-tert-butyl 2-methyl (2S,4R)-4-{[(2-nitrophenyl)sulfonyl]amino}-1,2-pyrrolidine-1,2-dicarboxylate and 1.2 g (29 mmol) LiOH in 100 mL THF/water/MeOH (2:1:1) is stirred at rt for 4 h. The mixture is concentrated in vacuo and the residue is diluted with DCM and IN aq. HCl solution. The formed precipitate is filtered and dried.

LC MS (method E) tᵣ = 2.943 min, M-H = 414.1

Step 3

\[(2S)-2\{-[(cyclopentyloxy)carbonyl]amino\}-9\{-[(4R)-4\{-[(2\text{-}nitrophenyl)sulfonyl]amino\}-L\text{-}prolyl]amino\}-2\text{-}vinylcyclopropylcarbonylJamino-\}sulfonyl]phenyl\}amino\}-nonanoic acid
The title compound is prepared analogously as described for the title compound in example 21, step 10 using 3.3 g (5.4 mmol) methyl (2S)-9-({2-[[[(IR,2S)-l-amino-2-vinylcyclopropyl]carbonyl]amino]sulfonyl}phenyl)amino)-2-{{(cyclopentyloxy)carbonyl}amino}nonanoate hydrochloride, 2.8 g (6.8 mmol) (4R)-l-(tert-butoxycarbonyl)-4-{{(2-nitrophenyl)sulfonyl}amino}-L-proline, 2.6 g (6.9 mmol) HTBU and 3.0 mL (17 mmol) DIPEA in 50 mL DCM/DMF (50:1)

LC MS (method E) \( t_R = 4.644 \) min, M+H = 977.2
HPLC (method C) \( t_R = 4.346 \) min

**Step 4**

(2S)-9-{{2-[[[(IR,2S)-l-[(4R)-l-(tert-Butoxycarbonyl)]-4-{{(2-nitrophenyl)sulfonyl}amino}-L-prolyl]amino}-2-{{(cyclopentyloxy)carbonyl}amino}nonanoic acid

15

LC MS (method E) \( t_R = 4.240 \) min, M+H = 963.3

HPLC (method C) \( t_R = 4.083 \) min

10 Step 5

A mixture of 1.9 g (2.0 mmol) (2S)-9-\{[\{(IR,2S)-l-\{(4R)-l-(tert-Butoxycarbonyl)-4-\{(2-nitrophenyl)sulfonyl]amino\}-L-prolyl]amino\}-2-vinylcyclopropyl]carbonyl] amino)sulfonyl]phenyl] amino\}-2-\{(cyclopentyloxy)carbonyl]amino\}nonanoic acid, 20 mL 4 M HCl in dioxane and 20 mL dioxane is stirred at rt for 3 h. The mixture is concentrated in vacuo and the crude product is used without further purification.

LC MS (method E) \(t_R = 3.346\) min, M+H = 863.2
HPLC (method C) \(t_R = 3.484\) min

**Step 6**

Cyclopentyl ([IR,2S,2'R,6'S,24a'S]-2'-\{(2-nitrophenyl)sulfonyl]amino\}-19',19'-dioctadecahydrospiro-[cyclopropane-1,22'-pyrrolo[2,1-\(g\)][1,2,5,8,18]benzothiatetraazacycloicosin]-6'-yl]carbamate

The title compound can be prepared analogously as described for the title compound of example 21 using 2.1 g (2.1 mmol) (2S)-2-\{[(cyclopentyloxy)carbonyl]amino\}-9-\{[\{(IR,2S)-l-\{(4R)-l-(2-nitrophenyl)sulfonyl]amino\}-L-prolyl]amino\}-2-vinylcyclopropyl]carbonyl] amino)sulfonyl]phenyl] amino\}nonanoic acid (hydrochloride salt), 4.1 g (10.8 mmol) HATU and 3.8 mL (21.5 mmol) DIPEA in 300 mL DCM/DMF (50:1).

LC MS (method E) \(t_R = 4.470\) min, M-H = 842.2
HPLC (method C) \(t_R = 4.371\) min

**Step 7**
Cyclopentyl [(1R,2S,2'R,6'S,24a'S)-2'-amino-19',19'-dioxido-S'^l'^'-trioxo-Z-vinyl-1^l^l,2,3,5',6,7 f,8,9,10,1,12,13,14,20',21',23 f,24,24a'-octadecahydrospiro[cyclopane-1,22'-pyrrolo[2,1-g]][1,2,5,8,18]benzothiatetaazacycloicosin]-6'-yl]carbamate

A mixture of 670 mg (0.7 mmol) Cyclopentyl [(1R,2S,2'R,6'S,24a'S)-2'-[(2-nitrophenyl)sulfonyl]amino]-19',19'-dioxido-5',2'1',24'-trioxo-2-vinyl-1,2,3,5',6,7,8,9,10,1,12,13,14,14',20',21',23,24,24a'-octadecahydrospiro-[cyclopane-1,22'-pyrrolo[2,1-g]][1,2,5,8,18]benzothiatetaazacycloicosin]-6'-yl]carbamate, 0.2 mL (2.2 mmol) thiophenol and 404 mg (2.9 mmol) K2CO3 in 30 mL acetonitrile is stirred at rt overnight. The mixture is diluted with water and ethyl acetate. The organic layer is washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue is dissolved in hot DCM, ethyl ether is added and the precipitate is filtered and dried.

LC MS (method E) tR = 3.150 min, MIH = 659.3

Example 33

(1R,2S,1'6'S,2OR,2a'S)-6'-Ktert-butoxycarbonyOaminol^'-methyl-6^'-dioxido-l',4',17'-trioxo-2-vinlyoctadecahydro-7'H-spiro[cyclopane-1,3'-pyrrolo[2,1-g]][1,2,5,8,19]thiatetraazacyclonadecin]-20'-yl 5-(dimethylamino)-1,3-dihydro-2H-isoindole-2-carboxylate
A mixture of 150 mg (0.15 mmol) (1R,2S,3'S,2OR,21a'S)-1'α-amino-T'-methyl-6',β'-dioxido-1,4',17'-trioxo-2-vinyldecahydro-7'H-spiro[cyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8,19]thiatetrazacyclononadecin]-20'-yl 5-(dimethylamino)-1,3-dihydro-2Hisoindole-2-carboxylate, 37 mg (0.17 mmol) Boc2O and 0.03 mL (0.20 mmol) triethylamine in 4 mL DCM is stirred at rt overnight. The mixture is concentrated and purified by prep. HPLC.

LC MS (method E) t_R = 3.645 min, M+H = 788.2

Step 1

Ethyl (2S)-2-[(2-nitrophenyl)sulfonyl] amino)dec-9-enoate

To a mixture of 10 g (47 mmol) ethyl (2S)-2-aminodec-9-enoate (prepared as described above for (S)-2-Amino-non-8-enoic acid ethyl ester) and 67 mL (469 mmol) triethylamine in 800 mL DCM is added 16 g (70 mmol) o-nitro-benzenesulfonylchloride at 0°C. The mixture is stirred at rt overnight and partitioned between EtOAc and water. The aq. layer is extracted with EtOAc and the combined organic layers are dried over Na_2SO_4 and concentrated in vacuo. The crude product is purified by FC (silica gel).

LC MS (method E) t_R = 4.361 min, M+H = 399.1

HPLC (method C) t_R = 4.335 min

Step 2

Ethyl (2S)-10-hydroxy-2-[(2-nitrophenyl)sulfonyl]amino)decanoate
This compound can be prepared as described above for the synthesis of (S)-2-
Cyclopentyloxy carbonylamino-9-hydroxy-nonanoic acid methyl ester

LC MS (method E) t_R = 3.550 min, M+H = 417.1
HPLC (method C) t_R = 3.635 min

5

**Step 3**

Ethyl (2S)-10-(methylamino)-2-\{[(2-nitrophenyl)sulfonyl]amino\}decanoate

\[
\text{To a mixture of 13 g (31 mmol) Ethyl (2S)-10-hydroxy-2-\{[(2-nitrophenyl)sulfonyl]amino\}decanoate in 300 mL DCM is added 2.9 mL (37 mmol)}
\]

methanesulfonylchloride and 8.6 mL (61 mmol) triethylamine at 0°C. After 1 h water is
added and the mixture is extracted with DCM. The combined organic layers are dried over
Na_2SO_4 and concentrated. The crude is taken up in 150 mL DMSO and 42 mL methylamine
(8 M in EtOH) and the mixture is stirred at rt overnight. The mixture is partitioned between
water and ether and the aq. phase is extracted with ether. The combined organic layers are
dried over Na_2SO_4 and concentrated in vacuo to give the title compound which is used
without further purification in the next step.

LC MS (method E) t_R = 0.930 min, M+H = 430.1

20 **Step 4**

Ethyl (2S)-10-\{[(tert-butoxycarbonyl)amino]sulfonyl\}(methyl)amino)-2-\{[(2-
nitrophenyl)sulfonyl]amino\}decanoate
This compound can be prepared using the method described by J.Y. Winum et al. *Org. Lett.* 2001, 3, 2241.

LC MS (method E) $t_R = 4.121$ min, $M+H = 609.3$

HPLC (method C) $t_R = 4.580$ min

**Step 5**

Ethyl (2S)-10-[(aminosulfonyl)(methyl)amino]-2-[(2-nitrophenyl)sulfonyl]amino]decanoate

A mixture of 11 g (16 mmol) ethyl (2S)-10-[[tert-butoxycarbonyl]amino]sulfonyl] (methyl)amino]-2-[(2-nitrophenyl)sulfonyl]amino]decanoate and 200 mL HCl in dioxane (4 M) is stirred overnight at rt. The mixture is concentrated and the crude is purified by FC (silica gel, eluent: hexanes to hexanes/EtOAc 1:1).

LC MS (method E) $t_R = 3.559$ min, $M+H = 509.0$

HPLC (method C) $t_R = 3.900$ min

**Step 6**

The title compound can be prepared as described above for the synthesis of [(IR,2S)-1-(2-Amino-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester (example 1, step 1)

5 LC MS (method E) \( t_R = 4.270 \text{ min} \), \( M-H = 718.2 \)
HPLC (method C) \( t_R = 4.289 \text{ min} \)

**Step 7**

ethyl (2S)-10-{{(1R,2S)-1-amino-2-vinylcyclopropyl} carboxylic acid} (methyl)amine-2-[(2-nitrophenyl)sulfonyl]amino}decanoate

The title compound can be prepared as described above for the synthesis of 8-{2-[[IR,2S]-1-Amino-2-vinyl-cyclopropanecarbonyl]-sulfamoyl]-phenylcarbamoyl} -octanoic acid methyl ester (example 1, step 3)

15 LC MS (method E) \( t_R = 3.368 \text{ min} \), \( M+H = 618.1 \)
HPLC (method C) \( t_R = 3.279 \text{ min} \)

**Step 8**

The title compound can be prepared as described above for the synthesis of 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-(tert-butoxycarbonyl)-5-((1R,2S)-1-[2-(8-methoxycarbonyl-octanoylamino)-benzenesulfonylamino]carbonyl]-2-vinylcyclopropylcarbamoyl]pyrrolidin-3-yl ester (example 3, step 4) using (4R)-1-(tert-butoxycarbonyl)-4-[[5-(dimethylamino)-1,3-dihydro-2H-isoindol-2-yl]carbonyl]oxy-L-proline which can be prepared as described in example 3, steps 1 and 2.

LC-MS (method E) $t_R = 4.439$ min, M+H = 1020.4

**Step 9**

The title compound can be prepared as described above for the synthesis of (2S)-2-\{[(cyclopentyloxy)carbonyl]amino\}-9-\{2-[\{[(lR,2S)-l-\{[(4R)-4-\{[(2-nitrophenyl)sulfonyl]amino \}-L-prolyl]amino \}-2-vinylcyclopropyl]carbonyl]amino\}-sulfonyl]phenyl \}-amino)nonanoic acid (hydrochloride salt) (step 4 and 5)

LC MS (method E) $t_R = 2.934$ min, M+H = 892.3

Step 10

$\text{H}_{12}\text{S}_1\text{O}^*\text{SH}^*\text{methyH} \quad \text{6}',6'-\text{dioxido-1',4',17'-trioxo-2-vinloctadecahydro-7'H-spiro[cyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8,19]thiatetraazacyclononadecin]-20'-yl 5-(dimethylamino)-1,3-dihydro-2H-isoindole-2-carboxylate}$

The title compound can be prepared as described above for the final step in the synthesis of example 1.
LC MS (method E) $t_R = 3.927$ min, M+H = 874.2

**Step 11**

$\{(1R,2S,16'S,20'R,21a'S)-16'$-amino-7'-methyl-6',6'$-dioxido-1',4',17'$-trioxo-2$-vinyl\}$octadeca$hydrono$$-7H$-spiro$[cyclopropane-1,3'$-pyrrolo[2,1-g][1,2,5,8,19]thiatetraazacyclononadecin]-20'$-yl 5-(dimethylamino)-1,3-dihydro-2H-isooindole-2-carboxylate

A mixture of 760 mg (0.9 mmol) $(lR,2S,16'S,20'R,21a'S)-7'$-methyl-16'-[[[(2'$-$nitrophenyl)sulfonyl]amino]-6',6'$-dioxido-1',4',17'$-trioxo-2$-vinyl$]$octadecahydro-7H$-spiro$[cyclopropane-1,3'$-pyrrolo[2,1-g][1,2,5,8,19]thiatetraazacyclononadecin]-20'$-yl 5-(dimethylamino)-1,3-dihydro-2H-isooindole-2-carboxylate, 0.3 mL (4.4 mmol) 2-mercapto$ethanol$ and 0.7 mL (4.4 mmol) DBU in 2 mL acetonitrile is stirred at rt for 5 h. The mixture is partitioned between EtOAc and water. The organic layer is washed with water, dried over $Na_2SO_4$ and concentrated to give the crude product which is used in the next step without further purification.

LC MS (method E) $t_R = 1.806$ min, M+H = 688.1

**Example 34**

To a solution of 2.24 g (2.45 mmol) (1/?,25,2 1/?5,24a/?5)-17-fluoro-6'-{[(2-nitrophenyl)-sulfonyl] amino }-19', 19'-dioxido-5',2 1',24'-trioxo-2- vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24'a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2, 1-g// 1,2,5,8, 18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro- 1,3-dihydro-2 H-isooindole-2-carboxylate (prepared analogously as described starting from ethyl (2S)-2-[(2-nitrophenyl)sulfonyl]-amino}dec-9-enoate) in 230 mL acetonitrile is added at it 1.85 mL (12.3 mmol) DBU followed by 1.9 mL (27 mmol) 2-mercaptoethanole. After 90 min the reaction mixture is concentrated, aq. bicarbonate is added and extracted with DCM. The organic layer is dried over Na$_2$SO$_4$, concentrated in vacuo and purified by FC on silica (eluent: DCM/MeOH 19:1 -> 9:1).

MS (method ): M+ = 729.2
HPLC (method ) $t_R = 4.60$ min

The following compounds (Table 1) can be prepared according to one of the methods described above.
### TABLE 1

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>Example 35: 4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (8S,10R,14S)-14-cyclopentyloxy carbonyl-amino-5-[(1R,2S)-1-carboxylamino-2-ethyl-cyclopropyl]-2,2,4,7,13-pentaaxo-2A<em>6</em>-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>mass</th>
<th>( t_R ) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M+1 = 825</td>
<td>6.04</td>
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<td>MS method D</td>
<td>HPLC method A</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>mass</th>
<th>( t_R ) (min)</th>
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</thead>
<tbody>
<tr>
<td>M+ = 837.2</td>
<td>5.987</td>
</tr>
<tr>
<td>MS method D</td>
<td>HPLC method A</td>
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</table>

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<tr>
<th>mass</th>
<th>( t_R ) (min)</th>
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<tbody>
<tr>
<td>M+ = 837.2</td>
<td>5.97</td>
</tr>
<tr>
<td>MS method D</td>
<td>HPLC method A</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>Example 38: (1R,2S,2'R,6'S,24a'S)-6-{(cyclopentloxy)carbonyl</td>
</tr>
<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>4.863; M-H = 817.3</td>
<td>4.516</td>
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<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<tr>
<td>4.673; M-H = 821.2</td>
<td>4.426</td>
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<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<tr>
<td>4.663; M-H = 861.3</td>
<td>4.438</td>
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<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
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<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<tr>
<td>4.675; M+H = 826.3</td>
<td>4.499</td>
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<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
</tbody>
</table>

$t_R$ (min); mass | $t_R$ (min)
--- | ---
3.767; M-H = 804.3 | 3.492
LC MS method E | HPLC method C


$t_R$ (min); mass | $t_R$ (min)
--- | ---
4.380; M+H = 773.3 | 4.157
LC MS method E | HPLC method C


$t_R$ (min); mass | $t_R$ (min)
--- | ---
4.296; M-H = 804.3 | 3.774
LC MS method E | HPLC method C

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<th>Name</th>
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</table>

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<tr>
<th>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</th>
<th>t&lt;sub&gt;R&lt;/sub&gt; (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.897; M+H = 851.3 LC MS method E</td>
<td>3.614 HPLC method C</td>
</tr>
<tr>
<td>4.850; M-H = 837.3 LC MS method E</td>
<td>4.546 HPLC method C</td>
</tr>
<tr>
<td>4.645; M+H = 771.3 LC MS method E</td>
<td>4.439 HPLC method C</td>
</tr>
<tr>
<td>4.761; M+H = 849.3 LC MS method E</td>
<td>4.274 HPLC method C</td>
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<table>
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<th>Structure</th>
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<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>3.240; M-H = 841.3 LC MS method E</td>
<td>3.572 HPLC method C</td>
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</table>
dydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl5-(4-methylpiperazin-1-yl)-1,3-dihydro-2H-isooindole-2-carboxylate | 
| t\(_R\) (min); mass | t\(_R\) (min) |
| 3.290; M+H = 904.3 LC MS method E | 3.609 HPLC method C |
| Example 55: (1R,2S,2'R,6'S,24a'S)-6'-(((cyclopentyloxy)carbonyl)amino)-19',19'-
dydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl4-pyridin-2-ylpiperazine-1-carboxylate | 
| t\(_R\) (min); mass | t\(_R\) (min) |
| 3.773; M+H = 850.3 LC MS method E | 3.608 HPLC method C |
| Example 56: (1R,2S,2'R,6'S,24a'S)-6'-(((cyclopentyloxy)carbonyl)amino)-19',19'-
dydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl5-(methylamino)-3,4-dihydroisoquinoline-2(1H)-carboxylate | 
<p>| t(_R) (min); mass | t(_R) (min) |
| 4.619; M+H = 849.4 LC MS method E | 3.828 HPLC method C |</p>
<table>
<thead>
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<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
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<td><img src="image1.png" alt="Structure" /></td>
<td>Example 57: (1R,2S,2'R,6'S,24a'S)-6'- {{(cyclopentylloxycarbonyl)amino}}-19'19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5-(dimethylamino)-3,4-dihydroisoquinoline-2(1H)-carboxylate</td>
</tr>
<tr>
<td>tr&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>4.185; M+H = 863.3</td>
<td>3.659</td>
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<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
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<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>Example 58: (1R,2S,2'R,6'S,24a'S)-6'- {{(cyclopentylloxycarbonyl)amino}}-19'19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-carboxylate</td>
</tr>
<tr>
<td>tr&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>4.205; M+H = 810.3</td>
<td>4.059</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>Example 59: (1R,2S,2'R,6'S,24a'S)-6'- {{(cyclopentylloxycarbonyl)amino}}-19'19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-pyrimidin-2-ylpiperazine-1-carboxylate</td>
</tr>
<tr>
<td>tr&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>4.512; M+H = 851.3</td>
<td>4.220</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td><strong>Example 60:</strong> (1R,2S,2'R,6'S,24a'S)-6'-{(cyclopentylxoy)carbonyl]amino}-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g]][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5-pyrrolidin-1-yl-1,3-dihydro-2H-isooindole-2-carboxylate</td>
</tr>
<tr>
<td>(t_R) (min); mass</td>
<td>(t_R) (min)</td>
</tr>
<tr>
<td>4.849; M+H = 875.3</td>
<td>4.344</td>
</tr>
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<td>HPLC method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td><strong>Example 61:</strong> (1R,2S,2'R,6'S,24a'S)-6'-{(cyclopentylxoy)carbonyl]amino}-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g]][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-1,3-dihydro-2H-isooindole-2-carboxylate</td>
</tr>
<tr>
<td>(t_R) (min); mass</td>
<td>(t_R) (min)</td>
</tr>
<tr>
<td>3.424; M-H = 916.3</td>
<td>3.601</td>
</tr>
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<td>HPLC method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td><strong>Example 62:</strong> (1R,2S,2'R,6'S,24a'S)-6'-{(cyclopentylxoy)carbonyl]amino}-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g]][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5-(1-oxidothiomorpholin-4-yl)-1,3-dihydro-2H-isooindole-2-carboxylate</td>
</tr>
<tr>
<td>(t_R) (min); mass</td>
<td>(t_R) (min)</td>
</tr>
<tr>
<td>4.166</td>
<td>5.166</td>
</tr>
<tr>
<td>HPLC method C</td>
<td>HPLC method C</td>
</tr>
</tbody>
</table>
Example 63: (1R,2S,2'R,6'S,24a'S)-6'-
{[(cyclopentyl)oxy]carbonyl}[amino]-19'-
dioxidol-5',21',24'-trioxy-2-vinyl-1',2',3',5',6',7',8',
hydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothia
tetraazacycloicosin]-2'-yl
3,4-dihydroquinoline-1(2H)-carboxylate

<table>
<thead>
<tr>
<th>tᵣ (min); mass</th>
<th>tᵣ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.776; M+H = 819.3</td>
<td>4.591</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
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</table>

Example 64: (1R,2S,2'R,6'S,24a'S)-6'-
{[(cyclopentyl)oxy]carbonyl}[amino]-17'-fluoro-
19',19'-dioxidol-5',21',24'-trioxy-2-vinyl-
4',24a'-octadecahydrspirot[cyclopropane-1,22'-
pyrrolo[2,1-g][1,2,5,8,18]benzothieta
tetraazacycloicosin]-2'-yl
5,6-dihydro[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate

<table>
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<th>tᵣ (min)</th>
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<tr>
<td>4.101; M+H = 828.3</td>
<td>4.176</td>
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<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
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</table>

Example 65: (1R,2S,2'R,6'S,24a'S)-6'-
{[(cyclopentyl)oxy]carbonyl}[amino]-17'-fluoro-
19',19'-dioxidol-5',21',24'-trioxy-2-vinyl-1',2',3',5',
octadecahydrspirot[cyclopropane-1,22'-
pyrrolo[2,1-g][1,2,5,8,18]benzothieta
tetraazacycloicosin]-2'-yl
4-pyridin-2-yl-1,4-
diazepane-1-carboxylate

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<th>tᵣ (min); mass</th>
<th>tᵣ (min)</th>
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</thead>
<tbody>
<tr>
<td>3.506; M+H = 882.3</td>
<td>3.792</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
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<tr>
<td>Structure</td>
<td>Name</td>
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<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>$t_R$ (min); mass</td>
<td>$t_R$ (min)</td>
</tr>
<tr>
<td>3.988; M+H = 878.3</td>
<td>3.872</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
</tbody>
</table>

| $t_R$ (min); mass | $t_R$ (min) |
| 3.473; M+H = 907.3 | 3.663 |
| LC MS method E | HPLC method C |

<p>| $t_R$ (min); mass | $t_R$ (min) |
| 4.418; M+H = 896.2 | 4.330 |
| LC MS method E | HPLC method C |</p>
<table>
<thead>
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<th>Structure</th>
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</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Example 69" /></td>
<td>Example 69: ((1R,2S,2'R,6'S,24a'S)-6'-({([\text{cyclopentylloxy}]\text{carbonyl})\text{amino}})-17-\text{fluoro}-19',19'-\text{dioxido}-5',21',24'\text{-trioxo}-2\text{-vinyl}-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-\text{octadecahydrospiro}[\text{cyclopropane}-1,22'-\text{pyrrolo}[2,1-g][1,2,5,8,18]\text{benzothiatetraazacyclocoicosin}]\text{-2'-yl thiomorpholine}-4\text{-carboxylate 1-oxide})</td>
</tr>
<tr>
<td>(t_R) (min); mass</td>
<td>(t_R) (min)</td>
</tr>
<tr>
<td>4.076; M-H = 821.2</td>
<td>4.038</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td><img src="image2" alt="Example 70" /></td>
<td>Example 70: ((1R,2S,2'R,6'S,24a'S)-6'-({([\text{cyclopentylloxy}]\text{carbonyl})\text{amino}})-19',19'-\text{dioxido}-5',21',24'\text{-trioxo}-2\text{-vinyl}-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-\text{octadecahydrospiro}[\text{cyclopropane}-1,22'-\text{pyrrolo}[2,1-g][1,2,5,8,18]\text{benzothiatetraazacyclocoicosin}]\text{-2'-yl 5-(1-aminocyclopropyl)}-1,3\text{-dihydro-2H-isoindole-2-carboxylate})</td>
</tr>
<tr>
<td>(t_R) (min); mass</td>
<td>(t_R) (min)</td>
</tr>
<tr>
<td>3.396; M+H = 879.3</td>
<td>3.610</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td><img src="image3" alt="Example 71" /></td>
<td>Example 71: ((1R,2S,2'R,6'S,24a'S)-6'-{([\text{cyclopentylloxy}]\text{carbonyl})\text{amino}))-19',19'-\text{dioxido}-5',21',24'\text{-trioxo}-2\text{-vinyl}-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-\text{octadecahydrospiro}[\text{cyclopropane}-1,22'-\text{pyrrolo}[2,1-g][1,2,5,8,18]\text{benzothiatetraazacyclocoicosin}]\text{-2'-yl 1,3\text{-dihydro-2H-isoindole-2-carboxylate})</td>
</tr>
<tr>
<td>(t_R) (min); mass</td>
<td>(t_R) (min)</td>
</tr>
<tr>
<td>4.709; M-H = 803.3</td>
<td>4.394</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td>Structure</td>
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</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td><strong>Example 73</strong>: (1R,2S,2'R,6'S,24a'S)-6'-{(cyclo pentyloxy)carbonyl]amino}-17'-fluoro-19',19'-dioxido-5,21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecaehydrospiro[cyclopropane-1,22''-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-(6-methoxy pyridin-2'-yl)piperazine-1-carboxylate</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td><strong>Example 74</strong>: (1R,2S,2'R,6'S,24a'S)-6'-{(cyclo pentyloxy)carbonyl]amino}-17'-fluoro-19',19'-dioxido-5,21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecaehydrospiro[cyclopropane-1,22''-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-(1-methyl-6-oxo-1,6-dihydropyridin-2'-yl)piperazine-1-carboxylate</td>
</tr>
<tr>
<td><img src="image4.png" alt="Data" /></td>
<td><img src="image5.png" alt="Data" /></td>
</tr>
<tr>
<td><img src="image6.png" alt="Data" /></td>
<td><img src="image7.png" alt="Data" /></td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>Example 75: (1R,2S,2'R,6'S,24'a'S)-6'-{(cyclopentloxy)carbonyl}[amino]-17'-fluoro-19',19'-dioxido-5',21',24'-trixo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24'a'-octadecahydrodipiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothietetraazacycloicosin]-2'-yl 4-(6-methylpyridin-2-yl)piperazine-1-carboxylate</td>
</tr>
<tr>
<td>3.778; M+H = 882.3</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass 3.721</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>Example 76: (1R,2S,2'R,6'S,24'a'S)-6'-{(cyclopentloxy)carbonyl}[amino]-17'-fluoro-19',19'-dioxido-5',21',24'-trixo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24'a'-octadecahydrodipiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothietetraazacycloicosin]-2'-yl 1,4-diazepane-1-carboxylate</td>
</tr>
<tr>
<td>3.234; M+H = 804.3</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>5.227; M+H = 738.3</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass 5.008</td>
</tr>
<tr>
<td>4.539; M+H = 674.2</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass 4.319</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
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<tr>
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</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>Example 82: (1R,2S,2'R,6'S,24a'S)-6'-{{(cyclopentlyloxy)carbonyl}amino}-17'-fluoro-19',19'-dioxido-5',21',24'-triexo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo][2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5-(dimethyl amino)-1,3-dihy dro-2H-isoin dole-2-carboxylate</td>
</tr>
<tr>
<td>mass</td>
<td>866.2</td>
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<tr>
<td>$t_R$ (min)</td>
<td>3.31</td>
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<td>MS method D</td>
<td>HPLC method A</td>
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<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>Example 82: (1R,2S,2'R,6'S,24a'S)-6'-{{(cyclopentlyloxy)carbonyl}amino}-17'-fluoro-19',19'-dioxido-5',21',24'-triexo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo][2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 8-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate</td>
</tr>
<tr>
<td>mass</td>
<td>855.2</td>
</tr>
<tr>
<td>$t_R$ (min)</td>
<td>7.13</td>
</tr>
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<td>HPLC method A</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>Example 83: (1R,2S,2'R,6'S,24a'S)-6'-{{(cyclopentlyloxy)carbonyl}amino}-17'-fluoro-19',19'-dioxido-5',21',24'-triexo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo][2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate</td>
</tr>
<tr>
<td>mass</td>
<td>827.2</td>
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<td>$t_R$ (min)</td>
<td>6.23</td>
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<td>HPLC method A</td>
</tr>
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<td>Structure</td>
<td>Name</td>
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<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>Example 84: (1R,2S,2'R,6'S,24a'S)-6'-([(cyclopentloxy)carbonyl]amino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-(g)][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate</td>
</tr>
<tr>
<td>mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>M⁺ = 839.2</td>
<td>6.27</td>
</tr>
<tr>
<td>MS method D</td>
<td>HPLC method A</td>
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<tbody>
<tr>
<td>mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>M⁺ = 882.2</td>
<td>5.70</td>
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<td>HPLC method A</td>
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<td><img src="image3.png" alt="Structure 3" /></td>
<td>Example 86: (1R,2S,2'R,6'S,24a'S)-6'-([(cyclopentloxy)carbonyl]amino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-(g)][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 2-methyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate</td>
</tr>
<tr>
<td>mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>M⁺ = 839.2</td>
<td>6.16</td>
</tr>
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<td>HPLC method A</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td><strong>Example 87:</strong> 1R,2S,2'R,6'S,24a'S)-6'-([(cyclopentloxy)carbonyl]amino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',2,4',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclocosin]-2'-yl 8-chloro-3,4-dihydroisoquinoiline-2(1H)-carboxylate</td>
</tr>
<tr>
<td>mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>M+ = 871.2</td>
<td>7.27</td>
</tr>
<tr>
<td>MS method D</td>
<td>HPLC method A</td>
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<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td><strong>Example 88:</strong> 1R,2S,2'R,6'S,24a'S)-6'-([(cyclopentloxy)carbonyl]amino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',2,4',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclocosin]-2'-yl 1-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine-6-carboxylate</td>
</tr>
<tr>
<td>mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>M+ = 841.2</td>
<td>6.21</td>
</tr>
<tr>
<td>MS method D</td>
<td>HPLC method A</td>
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<tbody>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td><strong>Example 89:</strong> 1R,2S,2'R,6'S,24a'S)-6'-([(cyclopentloxy)carbonyl]amino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',2,4',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclocosin]-2'-yl 4-methoxy-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate</td>
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<tr>
<td>mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<td>M+ = 869.2</td>
<td>6.41</td>
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<td>M+ = 883.2</td>
<td>5.89</td>
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<td>M+ = 915.2</td>
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<tr>
<td>mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<td>M+ = 945.3</td>
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<td>MS method D</td>
<td>HPLC method A</td>
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<tr>
<td>Structure</td>
<td>Name</td>
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<td>-----------</td>
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<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>Example 93: (1R,2S,2'R,6'S,24a'S)-6'-([(cyclopentyl oxy)carbonyl]amino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadeca hydrospirocyclopropane-1,2,2'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraa zacycloicosin]-2'-yl 1-phenyl-4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate</td>
</tr>
</tbody>
</table>
| ![Structure 2](image2.png) | M+ = 889.3  
MS method D  
HPLC method A |
| ![Structure 3](image3.png) | Example 94: (1R,2S,2'R,6'S,24a'S)-6'-([(cyclopentyl oxy)carbonyl]amino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadeca hydrospirocyclopropane-1,2,2'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraaza cycloicosin]-2'-yl 3-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate |
| ![Structure 4](image4.png) | M+ = 848.8  
MS method D  
HPLC method A |
| ![Structure 5](image5.png) | Example 95: (1R,2S,2'R,6'S,24a'S)-6'-([(cyclopentyl oxy)carbonyl]amino)-17'-fluoro-24a'-methyl-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadeca hydrospirocyclopropane-1,2,2'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoidole-2-carboxylate |
| ![Structure 6](image6.png) | M+ = 854.7  
MS method D  
HPLC method A |

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<td>mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<td>M+ = 824.6</td>
<td>6.26</td>
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<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<td>3.480</td>
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<td>HPLC method C</td>
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<tr>
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<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<tr>
<td>3.398; M+H = 868.3</td>
<td>3.673</td>
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<td>HPLC method C</td>
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<td>Structure</td>
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<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td><strong>Example 100:</strong> (1R,2S,2'R,6'S,24a'S)-6'-{(cyclopentylcarbonyl)amino}-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-(3-methylpyridin-2-yl)piperazine-1-carboxylate</td>
</tr>
<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<tr>
<td>4.189; M+H = 882.3</td>
<td>3.771</td>
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<td><img src="image2.png" alt="Structure 2" /></td>
<td><strong>Example 101:</strong> (1R,2S,2'R,6'S,24a'S)-6'-{(cyclopentylcarbonyl)amino}-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5-cyano-1,3-dihydro-2H-isoinole-2-carboxylate</td>
</tr>
<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<tr>
<td>4.387; M-H = 846.3</td>
<td>4.524</td>
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<tr>
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<td>HPLC method C</td>
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<td><img src="image3.png" alt="Structure 3" /></td>
<td><strong>Example 102:</strong> (1R,2S,2'R,6'S,24a'S)-6'-{(cyclopentylcarbonyl)amino}-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-(3-cyanopyridin-2-yl)piperazine-1-carboxylate</td>
</tr>
<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
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<td>4.456; M+H = 893.2</td>
<td>4.583</td>
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<td><img src="image1" alt="Chemical Structure" /></td>
<td>Example 103: 2-(4-Methyl-piperazin-1-yl)-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid (8S,10R,14S)-14-cyclopentylxoxycarbonyl-amino-5-[(1R,2S)-1-carboxylamino-2-vinyl-cyclopropyl]-26-fluoro-2,2,4,7,13-pentaaxo-2Λ<em>6</em>-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
</tr>
<tr>
<td>Mass</td>
<td>t_R (min)</td>
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<td>M+1 = 923</td>
<td>5.27</td>
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<td>HPLC method A</td>
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<td><img src="image2" alt="Chemical Structure" /></td>
<td>Example 104: 2-Dimethylamino-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid (8S,10R,14S)-14-cyclopentylxoxycarbonyl-amino-5-[(1R,2S)-1-carboxylamino-2-vinyl-cyclopropyl]-26-fluoro-2,2,4,7,13-pentaaxo-2Λ<em>6</em>-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
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<tr>
<td>Mass</td>
<td>t_R (min)</td>
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<td>M+1 = 868</td>
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<td>HPLC method A</td>
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<td><img src="image3" alt="Chemical Structure" /></td>
<td>Example 105: 2-Pyrrolidin-1-yl-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid (8S,10R,14S)-14-cyclopentylxoxycarbonyl-amino-5-[(1R,2S)-1-carboxylamino-2-vinyl-cyclopropyl]-26-fluoro-2,2,4,7,13-pentaaxo-2Λ<em>6</em>-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
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<tr>
<td>Mass</td>
<td>t_R (min)</td>
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<td>5.82</td>
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<td>HPLC method A</td>
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<tr>
<td>Structure</td>
<td>Name</td>
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<td>-----------</td>
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<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>Example 106: 3,4,5,6-Tetrahydro-2H-[4,4']bipyridinyl-1-carboxylic acid (8S,10R,14S)-14-cyclopentylxocarbonyl-amino-5-[(1R,2S)-1-carbonylamo-2-vinyl-cyclopropyl]-26-fluoro-2,2,4,7,13-penta-o-2A<em>6</em>-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
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<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>Example 107: 3-Pyridin-2-yl-pyrrolidine-1-carboxylic acid (8S,10R,14S)-14-cyclopentylxocarbonyl-amino-5-[(1R,2S)-1-carbonylamo-2-vinyl-cyclopropyl]-26-fluoro-2,2,4,7,13-penta-o-2A<em>6</em>-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
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<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>Example 108: 3-Pyridin-4-yl-pyrrolidine-1-carboxylic acid (8S,10R,14S)-14-cyclopentylxocarbonyl-amino-5-[(1R,2S)-1-carbonylamo-2-vinyl-cyclopropyl]-26-fluoro-2,2,4,7,13-penta-o-2A<em>6</em>-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
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<td><img src="image4.png" alt="Structure 4" /></td>
<td>Example 109: 5-(4-Methyl-piperazine-1-carbonyl)-1,3-dihydro-isooindole-2-carboxylic acid (8S,10R,14S)-14-cyclopentylxocarbonyl-amino-5-[(1R,2S)-1-carbonylamo-2-vinyl-cyclopropyl]-26-fluoro-2,2,4,7,13-penta-o-2A<em>6</em>-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
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<th>Mass</th>
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<td>M - 1 = 865</td>
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<tr>
<td>M - 1 = 851</td>
<td>5.42 HPLC method A</td>
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<tr>
<td>M - 1 = 851</td>
<td>5.36 HPLC method A</td>
</tr>
<tr>
<td>M - 1 = 948</td>
<td>5.35 HPLC method A</td>
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<tr>
<td>Structure</td>
<td>Name</td>
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<td>-----------</td>
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<tr>
<td><img src="image1" alt="Structure Image" /></td>
<td>Example 110: 5-(1-Oxo-1(\Lambda^4)-thiomorpholine-4-carbonyl)-1,3-dihydro-isooindole-2-carboxylic acid (8S,10R,14S)-14-cyclopentyleoxy carbonyl-amino-5-{(1R,2S)-1-carbonylamino-2-vinyl-cyclopropyl}-26-fluo-ro-2,2,4,7,13-penta oxo-2(\Lambda^6)-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
</tr>
<tr>
<td><img src="image2" alt="Structure Image" /></td>
<td>Example 111: 2-Morpholin-4-yl-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid (8S,10R,14S)-14-cyclopentyleoxy carbonyl-amino-5-{(1R,2S)-1-carbonylamino-2-vinyl-cyclopropyl}-26-fluoro-2,2,4,7,13-penta oxo-2(\Lambda^6)-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
</tr>
<tr>
<td><img src="image3" alt="Structure Image" /></td>
<td>Example 112: 5,6-Dimethoxy-1,3-dihydro-isooindole-2-carboxylic acid (8S,10R,14S)-14-cyclopentyleoxy carbonyl-amino-5-{(1R,2S)-1-carbonylamino-2-vinyl-cyclopropyl}-26-fluoro-2,2,4,7,13-penta oxo-2(\Lambda^6)-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
</tr>
<tr>
<td><img src="image4" alt="Structure Image" /></td>
<td>Example 113: 2-Phenyl-piperazine-1,4-dicarboxylic acid 1-tert-butyl ester (8S,10R,14S)-14-cyclopentyleoxy carbonyl-amino-5-{(1R,2S)-1-carbonylamino-2-vinyl-cyclopropyl}-26-fluoro-2,2,4,7,13-penta oxo-2(\Lambda^6)-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0<em>8,12</em>]heptacosa-1(23),24,26-trien-10-yl ester</td>
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<td>M-1 = 967</td>
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<td>M+1 = 910</td>
<td>6.46 (HPLC method A)</td>
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<td>M+1 = 884</td>
<td>6.62 (HPLC method A)</td>
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<td>M+1 = 967</td>
<td>7.35 (HPLC method A)</td>
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<td>Structure</td>
<td>Name</td>
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| ![Structure Image](image1) | Example 114: 3-Phenyl-piperazine-1-carboxylic acid (8S,10R,14S)-14-cyclopentloxy carbonyl-amino-5-((1R,2S)-1-carboxylamino-2-vinyl-cyclopropyl)-26-fluoro-2,2,4,7,13-pentaoxo-2\*6*-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0
8,12*]heptacosa-1(23),24,26-trien-10-yl ester |
| Mass | t<sub>R</sub> (min) |
| M+1 = 967 | 5.62 |
| MS method D | HPLC method A |

| ![Structure Image](image2) | Example 115: 4-Dimethylamino-5,7-dihydro pyrrolo[3,4-d]pyrimidine-6-carboxylic acid (8S,10R,14S)-14-cyclopentloxy carbonyl-amino-5-((1R,2S)-1-carboxylamino-2-vinyl-cyclopropyl)-26-fluoro-2,2,4,7,13-pentaoxo-2\*6*-thia-3,6,12,22-tetraaza-tricyclo[21.4.0.0
8,12*]heptacosa-1(23),24,26-trien-10-yl ester |
| Mass | t<sub>R</sub> (min) |
| M+1 = 868 | 5.44 |
| MS method D | HPLC method A |

g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoindole-2-carboxylate |
| Mass | t<sub>R</sub> (min) |
| M+H = 711.2 | 4.51 |
| MS method D | HPLC method A |

g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoindole-2-carboxylate |
<p>| Mass | t&lt;sub&gt;R&lt;/sub&gt; (min) |
| M+H = 810.3 | 5.51 |
| MS method D | HPLC method A |</p>
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<td><img src="image1" alt="Structure" /></td>
<td>Example 118: (1R,2S,2'R,6'S,24a'S)-6'-(cyclopentylcarbamoyl)amino]-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydro spiro[cyclopropane-1,22'-pyrrolo[2,1-g]]1,2,5,8,18 benzothiatetraazaacacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoxindole-2-carboxylate</td>
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<td>M+H = 822.3</td>
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<td>Example 119: (1R,2S,2'R,6'S,24a'S)-6'-(cyclohexylcarbamoyl)amino]-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydro spiro[cyclopropane-1,22'-pyrrolo[2,1-g]]1,2,5,8,18 benzothiatetraazaacacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoxindole-2-carboxylate</td>
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<td><img src="image3" alt="Structure" /></td>
<td>Example 120: (1R,2S,2'R,6'S,24a'S)-6'-(tert-butoxycarbonyl)amino]-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydro spiro[cyclopropane-1,22'-pyrrolo[2,1-g]]1,2,5,8,18 benzothiatetraazaacacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoxindole-2-carboxylate</td>
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<td>Mass</td>
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<td>M+H = 811.2</td>
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<td>t_R (min)</td>
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<td>5.87</td>
</tr>
<tr>
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<td>HPLC method A</td>
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<tr>
<td><img src="image4" alt="Structure" /></td>
<td>Example 121: (1R,2S,2'R,6'S,24a'S)-19',19'-dioxido-5',21',24'-trioxo-6'-(tetrahydro-2H-pyran-4-yloxy)carbonyl)amino]-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydro spiro[cyclopropane-1,22'-pyrrolo[2,1-g]]1,2,5,8,18 benzothiatetraazaacacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoxindole-2-carboxylate</td>
</tr>
<tr>
<td></td>
<td>Mass</td>
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<tr>
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<td>M+H = 839.3</td>
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<tr>
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<td></td>
<td>t_R (min)</td>
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<tr>
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<td>5.38</td>
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<tr>
<td><strong>Mass</strong></td>
<td><strong>t_R (min)</strong></td>
</tr>
<tr>
<td>M+ = 837.2</td>
<td>6.10</td>
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<td>HPLC method A</td>
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<tbody>
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<td><strong>Mass</strong></td>
<td><strong>t_R (min)</strong></td>
</tr>
<tr>
<td>M+ = 809.2</td>
<td>5.79</td>
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<tr>
<td><strong>Mass</strong></td>
<td><strong>t_R (min)</strong></td>
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<td>M+ = 837.2</td>
<td>6.16</td>
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<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>Example 125: (1R,2S,2'R,6'S,24a'S)-19',19'-dioxido-5',21',24'-trioxo-6'-{{(3R)-tetrahydrofuran-3'-yloxy</td>
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<table>
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<tr>
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<td>M+ = 825.3</td>
<td>5.26</td>
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<td>HPLC method A</td>
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</table>

| ![Structure](image2) | Example 126: (1R,2S,2'R,6'S,24a'S)-6'{{(cyclopropylacetilamino)-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro|cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isindole-2-carboxylate |

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</thead>
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<td>M+ = 793.2</td>
<td>5.32</td>
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<td>HPLC method A</td>
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</tbody>
</table>

| ![Structure](image3) | Example 127: (1R,2S,2'R,6'S,24a'S)-6'{{(2-methoxyethoxy)|carbonyl| amino}-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro|cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isindole-2-carboxylate |

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<td>HPLC method A</td>
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<tbody>
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<td>M+ = 801.2</td>
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<td>MS method D</td>
<td>HPLC method A</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>Example 129: (1R,2S,2'R,6'S,24a'S)-6'-(1-tertbutoxycarbonylpiperidin-4-ylacetyl)amino)-19',19'-dixido-5',21',24'-trixo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate</td>
</tr>
<tr>
<td><img src="image2" alt="Structure" /></td>
<td>Example 130: (1R,2S,2'R,6'S,24a'S)-19',19'-dixido-5',21',24'-trixo-6'-(piperidin-4-yl acetyl)amino)-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate</td>
</tr>
<tr>
<td><img src="image4" alt="Structure" /></td>
<td>Example 132: (1R,2S,2'R,6'S,24a'S)-6'-((1-methylpiperidin-4-yl)acetyl)amino)-19',19'-dixido-5',21',24'-trixo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate</td>
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<tbody>
<tr>
<td>M+ = 936.5</td>
<td>5.72</td>
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<td>HPLC method A</td>
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<td>M+ = 936.2</td>
<td>4.54</td>
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<td>HPLC method A</td>
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<tr>
<td>M+ = 823.3</td>
<td>5.13</td>
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<td>HPLC method A</td>
</tr>
<tr>
<td>M+ = 823.3</td>
<td>5.13</td>
</tr>
<tr>
<td>MS method D</td>
<td>HPLC method A</td>
</tr>
</tbody>
</table>
### Example 133:
(1R,2S,2′R,6′S,24a′S)-6′-(((1-methylpiperidin-4-yl)oxy)carbonyl)amino)-19′,19′-dioxido-5′,21′,24′-trioxo-2-vinyl-1′,2′,2′,5′,6′,7′,8′,9′,10′,11′,12′,13′,14′,20′,21′,23′,24′,24a′-octadecahydrospiro[cyclopropane-1,22′-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2′-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate

<table>
<thead>
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<th>Mass</th>
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</thead>
<tbody>
<tr>
<td>M+ = 850.5</td>
<td>4.64</td>
</tr>
<tr>
<td>MS method D</td>
<td>HPLC method A</td>
</tr>
</tbody>
</table>

### Example 134:
(1R,2S,2′R,6′S,24a′S)-6′-(((2-methylalananyl)amino)-19′,19′-dioxido-5′,21′,24′-trioxo-2-vinyl-1′,2′,3′,5′,6′,7′,8′,9′,10′,11′,12′,13′,14′,20′,21′,23′,24′,24a′-octadecahydrospiro[cyclopropane-1,22′-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2′-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate

<table>
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<td>M+ = 796.3</td>
<td>4.55</td>
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<tr>
<td>MS method D</td>
<td>HPLC method A</td>
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### Example 135:
(1R,2S,2′R,6′S,24a′S)-19′,19′-dioxido-5′,21′,24′-trioxo-6′-((tetrahydro-2H-pyran-4-ylacetyl)amino)-2-vinyl-1′,2′,3′,5′,6′,7′,8′,9′,10′,11′,12′,13′,14′,20′,21′,23′,24′,24a′-octadecahydrospiro[cyclopropane-1,22′-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2′-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate

<table>
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<th>Mass</th>
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<tbody>
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<td>M+ = 837.2</td>
<td>5.19</td>
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<td>Structure</td>
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</tr>
<tr>
<td>Mass</td>
<td>t&lt;sub&gt;R&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>M+ = 850.5</td>
<td>4.77</td>
</tr>
<tr>
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<td>HPLC method A</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image of structure" /></td>
<td>Example 137: (1R,2S,2'R,6'S,24a'S)-6'-(2-methyl-2-morpholin-4-ylpropanoyl)amino)-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoindole-2-carboxylate</td>
</tr>
<tr>
<td>Mass</td>
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<tr>
<td>M+ = 866.3</td>
<td>4.70</td>
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<td>HPLC method A</td>
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<tr>
<td>Mass</td>
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</tr>
<tr>
<td>M+ = 837.5</td>
<td>4.57</td>
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<td>HPLC method A</td>
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<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
</tbody>
</table>
| ![Structure 1](image1.jpg) | Example 139: (1R,2S,2'R,6'S,24a'S)-6'\-[\text{morpholin-4-ylcarbonyl}amide]-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadeca-
hydropyrrolo[cyclopropane-1,22'-pyrrolo[2,1-
g][1,2,5,8,18]benzothiatetrazacycloicosin]-2'-yl
4-fluoro-1,3-dihydro-2H-isoinole-2-carboxylate |
|          | Mass | t<sub>R</sub> (min) |
|          | M+ = 824.2 | 5.15 |
|          | MS method D | HPLC method A |

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<th>Structure</th>
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hydropyrrolo[cyclopropane-1,22'-pyrrolo [2,1-g][1,2,5,8,18]benzothiatetrazacycloicosin]-
2'-yl 4-fluoro-1,3-dihydro-2H-isoinole-2-
| Mass | t<sub>R</sub> (min) |
| M+ = 811.2 | 5.16 |
| MS method D | HPLC method A |

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</table>
| ![Structure 3](image3.jpg) | Example 141: (1R,2S,2'R,6'S,24a'S)-6'\-[\text{1-(2,2-
difluoroethyl)piperidin-4-yl}acetamide]-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadeca-
hydropyrrolo[cyclopropane-1,22'-pyrrolo [2,1-g][1,2,5,8,18]benzothiatetrazacycloicosin]-
2'-yl 4-fluoro-1,3-dihydro-2H-isoinole-2-
<p>| Mass | t&lt;sub&gt;R&lt;/sub&gt; (min) |
| M+ = 900.3 | 4.67 |
| MS method D | HPLC method A |</p>
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<tr>
<td>Example 142: ((1R,2S,2'R,6'S,24a'S)-19',19'-dioxido-5',21',24'-trioxo-6'-({{(1-(2,2,2-trifluoroethyl)piperidin-4-yl}acetyl}}amino)-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate)</td>
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<td>Mass</td>
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<tbody>
<tr>
<td>Example 143: ((1R,2S,2'R,6'S,24a'S)-19',19'-dioxido-5',21',24'-trioxo-6'-({{(1-(2,2,2-trifluoroethyl)piperidin-4-yl}oxy}carbonyl)amino)-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate)</td>
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<td>Mass</td>
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<td>Example 144: ((1R,2S,2'R,6'S,24a'S)-6'-({{(1-(2-fluoroethyl)piperidin-4-yl}acetyl}amino)-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadeca hydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate)</td>
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<td>Mass</td>
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<td>HPLC method A</td>
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<tr>
<td>Structure</td>
<td>Name</td>
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<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image2" alt="Structure Image" /></td>
<td>Example 146: (1R,2S,2'2'R,6'S,24a'S)-6'-[({4-(2-fluoroethyl)piperazin-1-yl}carbonyl)amino]-19',19'-dioxido-5',21',24'-triox-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospirocyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isioindole-2-carboxylate</td>
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<tbody>
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</tr>
<tr>
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<td>HPLC method A</td>
</tr>
<tr>
<td>M+ = 869.2</td>
<td>4.62</td>
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<td>HPLC method A</td>
</tr>
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<td>M+ = 884.2</td>
<td>4.71</td>
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<td>HPLC method A</td>
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<tr>
<td>Structure</td>
<td>Name</td>
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<td>------</td>
</tr>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>Example 148: ((1R,2S,2'R,6'S,24a'S)-6'-({[(2S)-1-isopropylpiperidin-2-yl]carbonyl} amino)-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclocoicn]-2'-yl 4-fluoro-1,3-dihydro-2H-isoindole-2-carboxylate</td>
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<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>Example 149: ((1R,2S,2'R,6'S,24a'S)-6'-({1-(2-methoxyethyl)piperidin-4-yl)oxy} carbonyl) amino)-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicoisin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoindole-2-carboxylate</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>Example 150: ((1R,2S,2'R,6'S,24a'S)-6'-({(2R)-1-isopropylpiperidin-2-yl)carbonyl} amino)-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicoisin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoindole-2-carboxylate</td>
</tr>
<tr>
<td><img src="image4" alt="Structure 4" /></td>
<td>Example 151: ((1R,2S,2'R,6'S,24a'S)-6'-({(1-isopropylpiperidin-4-yl)oxy} carbonyl) amino)-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicoisin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoindole-2-carboxylate</td>
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<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>M⁺ = 880.2, MS method D</td>
<td>tᵣ (min) 4.848, HPLC method A</td>
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</tbody>
</table>


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<thead>
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<th>tᵣ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M⁺ = 990.0, MS method D</td>
<td>5.36, HPLC method A</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Mass</th>
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</tr>
</thead>
<tbody>
<tr>
<td>M⁺ = 840.2, MS method D</td>
<td>4.82, HPLC method A</td>
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<tr>
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</thead>
<tbody>
<tr>
<td>M⁺ = 840.2, MS method D</td>
<td>4.75, HPLC method A</td>
</tr>
<tr>
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<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>Mass</td>
</tr>
<tr>
<td></td>
<td>M+ = 881.2</td>
</tr>
<tr>
<td></td>
<td>MS method D</td>
</tr>
<tr>
<td></td>
<td>Example 156: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-6'-[(2-(trifluoromethyl)benzyl)amino]-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isoindole-2-carboxylate</td>
</tr>
<tr>
<td></td>
<td>Mass</td>
</tr>
<tr>
<td></td>
<td>M+ = 887.2</td>
</tr>
<tr>
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<td>MS method D</td>
</tr>
<tr>
<td></td>
<td>Mass</td>
</tr>
<tr>
<td></td>
<td>M+ = 811.2</td>
</tr>
<tr>
<td></td>
<td>MS method D</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>Example 159: (1R,2S,2'R,6'S,24a'S)-6'-(bis(cyclopentylmethylamino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecaahydrorspirocyclopropane-1,22'-'pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclocoisin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>Example 160: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-6'-(1S)-2-methyl-1-((4-methylpiperazin-1-yl)methyl)[propyl][carbamoyl]amino)-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecaahydrorspirocyclopropane-1,22'-'pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclocoisin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Mass</th>
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<tbody>
<tr>
<td>M+ = 783.3</td>
<td>4.84</td>
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<tr>
<td>M+ = 893.3</td>
<td>5.62</td>
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<tr>
<td>M+ = 940.3</td>
<td>4.64</td>
</tr>
</tbody>
</table>


Example 164: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-6'-(pyridin-4-ylmethyl)amino)-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadehydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothietetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isindole-2-carboxylate

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>Example 166: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-6'-(methylsulfonyl)amino-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octodecahydro spiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isindolet-2-carboxylate</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>Example 167: (1R,2S,2'R,6'S,24a'S)-6'- (benzoylemino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octodecahydro spiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isindolet-2-carboxylate</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>Example 168: (1R,2S,2'R,6'S,24a'S)-6'-(1-(2,2-difluoroethyl)piperidin-4-yl)acetyl)amino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octodecahydro spiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraaza cycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isindolet-2-carboxylate</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Example 171</strong>: (1R,2S,2'R,6'S,24a'S)-6'-[(3,4-difluorobenzyl)amino]-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraaza cycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate</td>
<td></td>
</tr>
<tr>
<td><strong>Example 172</strong>: (1R,2S,2'R,6'S,24a'S)-6'-(1-ethyl-3-ylcarbonyl)amino]-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraaza cycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate</td>
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<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M+ = 868.2</strong> MS method D</td>
<td>4.81 HPLC method A</td>
</tr>
<tr>
<td><strong>M+ = 855.3</strong> MS method D</td>
<td>5.10 HPLC method A</td>
</tr>
<tr>
<td><strong>M+ = 855.3</strong> MS method D</td>
<td>5.03 HPLC method A</td>
</tr>
<tr>
<td><strong>M+ = 868.2</strong> MS method D</td>
<td>4.91 HPLC method A</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
</tbody>
</table>
| Example 173: \((1R,2S,2'R,6'S,24a'S)-6'-(\{(1-(2,2-difluoroethyl)piperidin-4-yl)oxy\}carbonyl)amino\)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate | Mass | \(M^+ = 903.3\) 
MS method D | \(t_R\) (min) | 4.427
HPLC method A |
MS method D | \(t_R\) (min) | 3.07
HPLC method A |
MS method D | \(t_R\) (min) | 5.10
HPLC method A |
<table>
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<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>Example 177: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-6'·{[3-(trifluoromethyl)benzyl]amino}-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiaterazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isouindole-2-carboxylate</td>
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<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>Example 178: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-6'·{[(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbonyl]amino}-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiaterazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isouindole-2-carboxylate</td>
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<th>Mass</th>
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<td>3.38</td>
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<td>HPLC method A</td>
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<td>M+ = 887.2</td>
<td>3.04</td>
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<td>HPLC method A</td>
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<tr>
<td>M+ = 864.2</td>
<td>3.628</td>
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<td>HPLC method A</td>
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<tr>
<td>Structure</td>
<td>Name</td>
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<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>Mass</td>
<td>t_R (min)</td>
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<tr>
<td>M+ = 905.2</td>
<td>3.07</td>
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<td>MS method D</td>
<td>HPLC method A</td>
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<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>Example 180: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-6'-[(1-methyl-2-oxopiperidin-3-yl)carbonyl]amino]-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isindoide-2-carboxylate (2 diastereoisomers)</td>
</tr>
<tr>
<td>Mass</td>
<td>t_R (min)</td>
</tr>
<tr>
<td>M+ = 868.2</td>
<td>3.21 (Isomer A)</td>
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<tr>
<td>MS method D</td>
<td>3.42 (Isomer B)</td>
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<tr>
<td>HPLC method A</td>
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<tr>
<td>Mass</td>
<td>t_R (min)</td>
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<td>M+ = 1007.5</td>
<td>3.51</td>
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<td>MS method D</td>
<td>HPLC method A</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td><img src="image2" alt="Structure" /></td>
<td>Mass</td>
</tr>
<tr>
<td></td>
<td>M+ = 873.3</td>
</tr>
<tr>
<td></td>
<td>MS method D</td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>Example 183: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-6'-%[(1,6-naphthyridin-2-ylcarbonyl)amino]-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraaza cycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isooindole-2-carboxylate</td>
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<td><img src="image4" alt="Structure" /></td>
<td>Mass</td>
</tr>
<tr>
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<td>M+ = 585.3</td>
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<td>MS method D</td>
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<tr>
<td><img src="image6" alt="Structure" /></td>
<td>Mass</td>
</tr>
<tr>
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<td>M+ = 873.3</td>
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<td>MS method D</td>
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<tr>
<td>Structure</td>
<td>Name</td>
</tr>
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<td><img src="image2.png" alt="Structure 2" /></td>
<td><img src="image3.png" alt="Structure 3" /></td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>Example 187: (1R,2S,18'S,22'R,23a'S)-18'-(1-cyclopentoloxycarbonylamino)-7'-ethyl-6',6'-dioxido-1',4',19'-trioxo-2-vinlyicosahydro-7H-spiro[cyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8,21]thiatetrazacyclogenicosin]-22'-yl 4-fluoro-1,3-dihydro-2H-isindole-2-carboxylate</td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>Example 188: (1R,2S,16'S,20'R,21a'S)-16'-(1-cyclopentoloxycarbonylamino)-7'-methyl-6',6'-dioxido-1',4',17'-trioxo-2-vinlyoctadecahydro-7'H-spiro[cyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8,19]thiatetrazacyclononadecin]-20'-yl 4-fluoro-1,3-dihydro-2H-isindole-2-carboxylate</td>
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<tr>
<td><img src="image8.png" alt="Structure 8" /></td>
<td><img src="image9.png" alt="Structure 9" /></td>
</tr>
<tr>
<td><img src="image10.png" alt="Structure 10" /></td>
<td><img src="image11.png" alt="Structure 11" /></td>
</tr>
<tr>
<td><img src="image12.png" alt="Structure 12" /></td>
<td><img src="image13.png" alt="Structure 13" /></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</th>
<th>t&lt;sub&gt;R&lt;/sub&gt; (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.136; M+H = 824.2</td>
<td>4.179</td>
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<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td>4.676; M+H = 803.3</td>
<td>4.555</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td>4.875; M+H = 817.3</td>
<td>4.652</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td>4.330; M+H = 775.3</td>
<td>4.419</td>
</tr>
<tr>
<td>LC MS method E</td>
<td>HPLC method C</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>Example 189: (1R,2S,20'R,21'a'S)-6',6'-dioxido-1',4',17'-trioxo-2-vinylactadecahydrodispirocyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8]thiatriazacyclonadecine-7',1''-cyclopropan]-20'-yl 4-fluoro-1,3-dihydro-2H-isoindole-2-carboxylate</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>t&lt;sub&gt;R&lt;/sub&gt; (min); mass</th>
<th>t&lt;sub&gt;R&lt;/sub&gt; (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.281; M+H = 659.0 LC MS method E</td>
<td>4.072 HPLC method C</td>
</tr>
<tr>
<td>M+ = 825.3 MS method D</td>
<td>5.284 HPLC method A</td>
</tr>
<tr>
<td>M+ = 825.3 MS method D</td>
<td>5.63 HPLC method A</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
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</tbody>
</table>
| ![Structure 1](image1.png) | **Example 192**: (1R,2S,2'R,6'S,24a'S)-6'\-
)((cyclopentloxy)carbonyl]amino)-19',19'\-
diido-5',21',24'-truxo-2-vinyl-
pyrrolo[2,1-
g][12,1,2,5,8,18]benzoxathietetrazacycloicosin] \-
2'-yl 4-fluoro-1,3-dihydro-2H-isoidole-2-
carboxylate |
| **Mass** | **t_R (min)** |
| M+ = 825.3 | 5.45 |
| MS method D | HPLC method A |

| ![Structure 2](image2.png) | **Example 193**: (1R,2S,2'R,6'S,24a'S)-6'\-
)((cyclopentloxy)carbonyl]amino)-19',19'\-
diido-5',21',24'-truxo-2-vinyl-
1',2',3',5',6',7',8',9',10',13',14',20',21',23',24',24a'\-hexadecahydro-12'H-spiro[cyclopropane-1,22'-
pyrrolo[2,1-
g][15,1,2,5,8,18]benzoxathietetrazacycloicosin] \-
2'-yl 4-fluoro-1,3-dihydro-2H-isoidole-2-
carboxylate |
| **Mass** | **t_R (min)** |
| M+H = 825.3 | 5.28 |
| MS method D | HPLC method A |

| ![Structure 3](image3.png) | **Example 194**: (1R,2S,2'R,6'S,24a'S)-6'\-
)((cyclopentloxy)carbonyl]amino)-7'-7'-
dimethyl-19',19'-diido-5',21',24'-truxo-2-vinyl-
pyrrolo[2,1-
g][1,2,5,8,18]benzothietetrazacycloicosin]-2'-yl \-
4-fluoro-1,3-dihydro-2H-isoidole-2-carboxylate |
<p>| <strong>Mass</strong> | <strong>t_R (min)</strong> |
| M+ = 851.2 | 6.42 |
| MS method D | HPLC method A |</p>
<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mass</strong></td>
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</tr>
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<td>HPLC method A</td>
</tr>
<tr>
<td>M+ = 841.3</td>
<td>6.120</td>
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<td>HPLC method A</td>
</tr>
<tr>
<td>M+ = 801.2</td>
<td>4.88</td>
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<td>MS method D</td>
<td>HPLC method A</td>
</tr>
<tr>
<td>M+ = 837.2</td>
<td>5.63</td>
</tr>
<tr>
<td>MS method D</td>
<td>HPLC method A</td>
</tr>
<tr>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td><strong>mass</strong></td>
<td><strong>t_R (min)</strong></td>
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<tr>
<td>M+ = 823.3</td>
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<td>HPLC method A</td>
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<tr>
<td><strong>mass</strong></td>
<td><strong>t_R (min)</strong></td>
</tr>
<tr>
<td>M+ = 739.2</td>
<td>4.28</td>
</tr>
<tr>
<td>MS method D</td>
<td>HPLC method A</td>
</tr>
<tr>
<td><strong>mass</strong></td>
<td><strong>t_R (min)</strong></td>
</tr>
<tr>
<td>M+ = 809.2</td>
<td>5.748</td>
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<td><img src="image1.png" alt="Structure" /></td>
<td>Example 207: (1R,2S,2'R,6'S,24a'S)-6'-(((cyclopentyl oxy)carbonyl)amino)-19',19'-dioxido-5',21',24'-tri oxo-2-vinyl-1',2',3',5',6', 7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1- g][1,2,5,8,12,18]benzothiapentaaza cycloicosin]-2'-yl 4-fluoro-1,3-dihydro-2H-isindo le-2-carboxylate</td>
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<td>M+ = 824.2</td>
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<td>3.371; M-H = 848.3</td>
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<td><img src="image3.png" alt="Structure" /></td>
<td>Example 209: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-19',19'-dio xido-5',21',24'-tri oxo-6'-(((3R) -tetrahydrofuran-3-yloxy)carbonyl)amino)-2 vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20', 21',23',24',24a'-octadecahydrospiro [cyclopropane-1,22'-pyrrolo[2,1- g][1,2,5,8,18]benzothiatetraaza cycloicosin]-2'-yl 5-chloro-1,3-dihydro-2H-isindo le-2-carboxylate</td>
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<td>4.366; M+H = 859.3</td>
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<td><img src="image4.png" alt="Structure" /></td>
<td>Example 210: (1R,2S,16'S,20'R,21a'S)-16'-(((tert butoxy carbonyl)amino)-7'-methyl-6',6'-dioxido 1',4',17'-tri oxo-2-vinylotic adecahydro-7'H-spiro [cyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8,19] thiatetraazacyclononadecin]-20'-yl 5,7-dihydro- 6H-pyrrolo[3,4-b]pyridine-6-carboxylate</td>
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<td>3.977; M+H = 746.3</td>
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<td><img src="image1.png" alt="Structure 1" /></td>
<td>Example 211: (1R,2S,16'S,20'R,21a'S)-16'-{(cyclopentylxoy)carbonyl}amino}-7'-methyl-6',6'-dioxido-1',4',17'-trioxo-2-vinloctadeca hydro-7'H-spiro[cyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8,19]thietazaazacyclonadecin]-20'-yl 5-(dimethylamino)-1,3-dihydro-2H-isoinole-2-carboxylate</td>
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<td><img src="image2.png" alt="Structure 2" /></td>
<td>3.597; M+H = 800.2 LC MS method E HPLC method C</td>
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<td>Example 212: (1R,2S,16'S,20'R,21a'S)-16'-{(tert-butoxy)carbonyl}amino}-7'-methyl-6',6'-dioxido-1',4',17'-trioxo-2-vinloctadeca hydro-7'H-spiro[cyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8,19]thietazaazacyclonadecin]-20'-yl 5-(dimethylamino)-1,3-dihydro-2H-isoinole-2-carboxylate</td>
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<td><img src="image4.png" alt="Structure 4" /></td>
<td>3.645; M+H = 788.2 LC MS method E</td>
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<td><img src="image5.png" alt="Structure 5" /></td>
<td>Example 213: (1R,2S,16'S,20'R,21a'S)-16'-{(cyclopentylxoy)carbonyl}amino}-7'-methyl-6',6'-dioxido-1',4',17'-trioxo-2-vinloctadeca hydro-7'H-spiro[cyclopropane-1,3'-pyrrolo[2,1-g][1,2,5,8,19]thietazaazacyclonadecin]-20'-yl 5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate</td>
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<td><img src="image6.png" alt="Structure 6" /></td>
<td>3.909; M+H = 758.2 LC MS method E 3.714 HPLC method C</td>
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<td><img src="image7.png" alt="Structure 7" /></td>
<td>Example 214: (1R,2S,2'R,6'S,24a'S)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-6'-{(3R)-tetrahydrofuran-3-yloxy)carbonyl}amino}-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro [cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothietazaazacycloicosin]-2'-yl 5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate</td>
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<td><img src="image8.png" alt="Structure 8" /></td>
<td>M+ = 826.2 MS method D 4.74 HPLC method A</td>
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<td><img src="image1" alt="Structure 1" /></td>
<td>Example 215: (1R,2S,2'R,6'S,24a'S)-6'-[(tert-butoxycarbonyl)amino]-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclocoisin]-2'-yl 5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate</td>
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<td>Example 217: (1R,2S,2'R,6'S,24a'S)-6'-[(cyclopropylacetyl)amino]-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacyclocoisin]-2'-yl 5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate</td>
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<td>Example 218: (1R,2S,2'R,6'S,24a'S)-6'-([{1-(2,2-difluoroethyl)piperidin-4-yl}acetyl]amino)-17'-fluoro-19',19'-dioxido-5',21',24'-trioxo-2-vinyl-1',2',3',5',6',7',8',9',10',11',12',13',14',20',21',23',24',24a'-octadecahydrospiro[cyclopropane-1,22'-pyrrolo[2,1-g][1,2,5,8,18]benzothiatetraazacycloicosin]-2'-yl 5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate</td>
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### Example 226
4- Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (2R,5S,18aS)-16-cyclobutylmethyl-5-cyclopentyl oxycarbonylamino-4,14,15,18-tetraoxo-octadecahydro-3a,13,17-triaza-cyclopenta cycloheptadecen-2-yl ester
A solution of 0.01 g (0.014 mmol) of 4-fluoro-1,3-dihydro-isooindole-2-carboxylic acid (2R,5S,18aS)-16-cyclobutylmethyl-S-cyclopentyloxycarbonylamino-15-hydroxy-4,14,18-trioxo-octadecahydro-3a,13,17-triaza-cyclopentacycloheptadecen-2-yl ester in 0.1 mL of DMSO is treated with 0.012 g (0.042 mmol) of EBX for 3 hours and chromatographed by RP-HPLC (method G) to give the title compound; MS (method D): 712 [M+1]; HPLC (method A) $t_R$ (min) 5.24

Preparation of 4-fluoro-1,3-dihydro-isooindole-2-carboxylic acid (2R,5S,18aS)-16-cyclobutylmethyl-5-cyclopentyloxycarbonylamino-15-hydroxy-4,14,18-trioxo-octadecahydro-3a,13,17-triaza-cyclopentacycloheptadecen-2-yl ester
Step 1

(S)-2-Cyclopentyl Oxycarbonylamino-non-8-enoic acid methyl ester

A solution of 18.1 g (63.87 mmol) of (S)-2-cyclopentyl oxycarbonylamino-non-8-enoic acid in 300 mL of acetone is treated with 10.232 g (102.2 mmol) of ICHCO\textsubscript{3} and 22.666 g (159.69 mmol) of iodomethane and then heated up to reflux. Upon completion the reaction mixture is cooled down, salts are filtered-off and the filtrate is concentrated, taken up in EtOAc, washed with saturated aqueous NaHCO\textsubscript{3} and brine. The organics are dried over Na\textsubscript{2}SO\textsubscript{4}, concentrated in vacuo to give the title compound; MS (method D): 298 [M+1]

Step 2

(S)-2-Cyclopentyl Oxycarbonylamino-9-hydroxy-nonanoic acid methyl ester

A solution of 25.65 g (86.25 mmol) of (S)-2-cyclopentyl oxycarbonylamino-non-8-enoic acid methyl ester in 400 mL of absolute THF is cooled to 0 °C and treated by drop wise addition
of 275 mL (120.7 mmol) of 9-BBN (0.5 M in THF solution) while maintaining temperature below 5 °C. The reaction mixture is stirred at RT under completion, cooled to 0 °C, treated by drop wise addition of 80 mL of a 5% NaHCO₃ aqueous solution, then by careful addition of 16.3 mL of 35% H₂O₂ in water while maintaining the temperature below 12 °C. The reaction mixture is stirred at RT for 1.5 hour, treated with 100 mL of saturated aqueous NaHCO₃ and 100 mL water. The organics are washed with brine and water, combined, dried (Na₂SO₄), concentrated and chromatographed on silica gel (eluent Hexane / EtOAc 1:1) to give the title compound; MS (method D): 316 [M+1]

Step 3

(S)-9-Bromo-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester

A solution of 5.5 g (17.44 mmol) of (S)-2-cyclopentyloxycarbonylamino-9-hydroxy-nonanoic acid methyl ester in 60 mL of CH₂Cl₂ is treated with 4.851 g (18.31 mmol) of triphenylphosphine and 3.36 g (18.31 mmol) of N-bromosuccinimide and stirred overnight at RT. The crude reaction mixture is chromatographed on silica gel (eluent Hexane / EtOAc 7:2) to give the title compound; MS (method D): 378 [M+1]

Step 4

(S)-9-Azido-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester

A solution of 1.8 g (4.76 mmol) of (S)-9-bromo-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester in 20 mL DMF is treated with 1.25 g (19.03 mmol) of sodium azide and stirred at 50 °C for 2 hours. The reaction mixture is quenched with saturated aqueous NaHCO₃ and extracted with ethylether. The organics are washed with brine, dried over Na₂SO₄ and concentrated to give the title compound; MS (method D): 341 [M+1]

Step 5

(S)-9-Amino-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester

A solution of 1.41 g (4.14 mmol) of (S)-9-azido-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester in 50 mL ethanol is hydrogenated over Pd/Carbon (0.2 g, 10 %) at RT under H₂ atmosphere. The reaction mixture is filtered through Celite and the filtrate concentrated to give the title compound; MS (method D): 315 [M+1]

Step 6
(S)-9-(3-tert-Butoxycarbonylamino-4-cyclobutyl-2-hydroxy-butyrylamino)-2-
cyclopentyloxycarbonylamino-nonanoic acid methyl ester

A solution of 0.4 g (1.27 mmol) of (S)-9-amino-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester and 0.417 g (1.52 mmol) of 3-tert-butoxycarbonylamino-4-cyclobutyl-2-hydroxy-butyric acid in 10 mL CH₂Cl₂ is treated with 0.212 g (1.53 mmol) of 1-hydroxy-7-azabenzotriazole and 0.443 g (2.29 mmol) of N-(3-dimethylaminopropyl)-N'-ethyl-
carbodiimide hydrochloride, followed by 0.217 mL (1.53 mmol) of triethylamine. The reaction mixture is stirred overnight at RT and chromatographed on silica gel (eluent Hexane / EtOAc 3:2) to give the title compound; MS (method D): 570 [M+1]

Step 7

(S)-9-(3-Amino-4-cyclobutyl-2-hydroxy-butyrylaminino)-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester

A solution of 0.358 g (0.63 mmol) of (S)-9-(3-tert-butoxycarbonylamino-4-cyclobutyl-2-
hydroxy-butyrylamino)-2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester in 1.57 mL of 4N HCl in dioxane is stirred at RT. Upon completion the reaction mixture is concentrated in vacuo to give the title compound; MS (method D): 470 [M+1]

Step 8

4-Fluoro-1,3-dihydro-isoindoIe-2-carboxylic acid (3R,5S)-l-tert-butoxycarbonyl-5-[l-
cyclobutylmethyl-2-(S)-8-cyclopentyloxycarbonylamino-8-methoxycarbonyl-
octylcarbamoyl]- hydroxy-ethylcarbamoyl]-pyrrolidin-S-yl ester

A solution of 0.306 g (0.65 mmol) of (S)-9-(3-amino-4-cyclobutyl-2-hydroxy-butyrylamino)-
2-cyclopentyloxycarbonylamino-nonanoic acid methyl ester and 0.283 g (0.72 mmol) of
(2S,4R)-4-(4-fluoro- 1,3-dihydro-isoindoIe-2-carbonyloxy)-pyrrolidine- 1,2-dicarboxylic acid
1-tert-butyl ester 15 mL CH₂Cl₂ is treated with 0.109 g (0.78 mmol) of 1-hydroxy-7-
azabenzotriazole and 0.139 mL (0.98 mmol) of triethylamine, followed by 0.227 g (1.17 mmol) of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride. The reaction mixture is stirred overnight at RT and chromatographed by RP-HPLC (method G) to give the title compound; MS (method D): 846 [M+1]
4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-[2-((S)-8-carboxy-8-cyclopentylcarbonylamino-octylcarbamoyl)-l-cyclobutylmethyl-2-hydroxy-ethylcarbamoyl]-pyrrolidin-3-yl ester

A suspension of 0.353 g (0.42 mmol) of 4-fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-[1-cyclobutylmethyl-2-((S)-8-cyclopentyloxycarbonylamino-octylcarbamoyl)-2-hydroxy-ethylcarbamoyl]-pyrrolidin-3-yl ester in 5 mL methanol and 5 mL water is treated with 0.204 g (8.34 mmol) of LiOH and stirred overnight at RT. Methanol is removed in vacuo, the resulting aqueous phase is acidified to pH 6 with 2N HCl and extracted with CH₂Cl₂. The organics are dried over Na₂SO₄ to give the title compound; MS (method D): 832 [M+H]

**Step 10**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-[2-((S)-8-carboxy-8-cyclopentylcarbonylamino-octylcarbamoyl)-1-cyclobutylmethyl-2-hydroxy-ethylcarbamoyl]-pyrrolidin-3-yl ester

The title compound is obtained from 0.302 g (0.254 mmol) of 4-fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-1-tert-butoxycarbonyl-5-[2-((S)-8-carboxy-8-cyclopentylcarbonylamino-octylcarbamoyl)-1-cyclobutylmethyl-2-hydroxy-ethylcarbamoyl]-pyrrolidin-3-yl ester according to the procedure described in step 7; MS (method D): 732 [M+H]

**Step 11**

4-Fluoro-1,3-dihydro-isoindole-2-carboxylic acid (2R,5S,18aS)-16-cyclobutylmethyl-5-cyclopentylcarbonylamino-15-hydroxy-4,14,18-trioxo-octadecahydro-3a,13,17-triaza-cyclopentacycloheptadecen-2-yl ester

A solution of 0.293 g (0.28 mmol) of 4-fluoro-1,3-dihydro-isoindole-2-carboxylic acid (3R,5S)-5-[2-((S)-8-carboxy-8-cyclopentylcarbonylamino-octylcarbamoyl)-1-cyclobutylmethyl-2-hydroxy-ethylcarbamoyl]-pyrrolidin-3-yl ester in 30 mL of CH₂Cl₂ is treated with 0.479 mL (2.8 mmol) of Hunig's base, followed by 0.532 g (1.4 mmol) of HATU. The reaction mixture is stirred at RT under completion and chromatographed by RP-HPLC (method G) to give the title compound; MS (method D): 714 [M+H]
Synthesis of intermediates

Preparation of 5-chloroisoindoline


Preparation of 5-morpholin-4-ylisoindoline

Step 1

5-bromoisoindoline

To a mixture of 4.5 g (20 mmol) 5-bromo-1H-isoindole-1,3(2H)-dione in 10 mL THF is added 81 mL Borane-THF complex (1 M) and the mixture is refluxed overnight. After cooling to rt 150 mL MeOH and 80 mL 6 N aq. HCl are carefully added and the mixture is refluxed for 1 h. The mixture is concentrated under reduced pressure, water and DCM are added and the aq. layer is extracted with DCM (2x) and ether (2x). The pH of the aq. layer is adjusted to 11 using cone. Aq. NaOH and extracted with DCM (4x). The combined organic layers of this last extraction are dried over Na2SO4, concentrated in vacuo and the residue is used without further purification.

LC MS (method E) t_R = 0.346 min, M+H = 200.1

Step 2

terf-butyl 5-bromo-1,3-dihydro-2/y-isoindole-2-carboxylate

To a mixture of 2.2 g (11 mmol) 5-bromoisoindoline in 90 mL DCM is added at 0°C a solution of 2.9 g (13 mmol) Boc2O in 20 mL DCM followed by 3.0 mL (20 mmol) TMEDA. The mixture is stirred at 5°C overnight and 250 mL 2 N aq. HCl is added and the mixture is stirred for additional 20 min at 5°C. The aq. layer is extracted with DCM and the combined
organic layers are dried over Na2SO4 and concentrated under reduced pressure. The residue is purified by FC on silica.
HPLC (method C) $t_R = 4.141$ min

**Step 3**

**tert-butyl** 5-morpholin-4-yl-1,3-dihydro-2//-isoindole-2-carboxylate

A mixture of 600 mg (2.0 mmol) tert-butyl 5-bromo-1,3-dihydro-2//-isoindole-2-carboxylate, 0.2 mL (2.4 mmol) morpholine, 268 mg (2.8 mmol) sodium tert.butoxide, 18 mg (0.02 mmol) Pd2(dbac)3 and 37 mg (0.06 mmol) rac-BINAP in 4 mL toluene is stirred at 80°C for 3 h. The mixture is cooled to rt, ethyl ether is added and the precipitate is filtered off and dried.
LC MS (method E) $t_R = 3.592$ min, M+H = 305.2
HPLC (method C) $t_R = 2.870$ min

**Step 4**

5-morpholin-4-ylisoindoline (hydrochloride)

A mixture of 130 mg (0.4 mmol) tert-butyl 5-morpholin-4-yl-1,3-dihydro-2//-isoindole-2-carboxylate, 4 mL 4 M HCl in dioxane and 4 mL dioxane is stirred for 3.5 h at rt. The mixture is concentrated and the crude is used without further purification.
LC MS (method E) $t_R = 0.264$ min, M+H = 205.1

The following isoindoline can be prepared as described above:
Preparation of 1-(2,3-Dihydro-1H-isoindol-5-yl)cyclopropanamine

Step 1
S-Cyano-l^-dihydro-isoindole^-carboxylic acid tert-butyl ester

A mixture of 0.5 g (1.5 mmol) tert-butyl 5-bromo-l,3-dihydro-2H-isoindole-2-carboxylate, 626 mg (2.0 mmol) Zinc cyanide and 367 mg (0.2 mmol) Pd(PPh3)4 in 15 mL DMF is heated to 80°C for 2h. The mixture is partitioned between water and EtOAc and the aq. layer is extracted with EtOAc. The combined organic layers are washed with brine, dried and concentrated under reduced pressure to give a crude product which is purified by FC (silica gel)-LC MS (method E) t_R = 4.161 min, M+H = 244.9

Step 2
5-(l-Amino-cyclopropyl)-l,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester

To a mixture of 250 mg (1.1 mmol) S-Cyano-l^-dihydro-isoindole^-carboxylic acid tert-butyl ester and 0.3 mL (1.2 mmol) titanium-(VI)-isopropoxide in 5 mL ether is added 0.8 mL (2.3 mmol) ethylmagnesium bromide (3 M in ether) at -70°C. After 5 min the mixture is allowed to reach rt over 1 h and 0.3 mL (2.1mmol) BF3*Et2O is added. After 1 h the mixture is quenched with IN HCl and ether and a basic pH is adjusted using NaOH solution. The aq.
layer is extracted with ether and the combined organic layers are dried and concentrated under reduced pressure. The crude product is purified by FC (silica gel)

**Step 3**

5 l-(2,3-D'hydro-lH-isoindol-5-yl)cyclopropanamine (dihydrochloride)

95 mg (0.3 mmol) of the 5-(l-Amino-cyclopropyl)-l,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester is dissolved in 2 mL dioxane and 2 mL 4M HCl in dioxane are added. The mixture is stirred at rt for 3 h and concentrated in vacuo to yield the product which is used in the next step without further purification.

**Preparation of** N-methyl-1,2,3,4-tetrahydroisoquinolin-5-amine

**Step 1**

15 5-Amino-3,4-dihydro-lH-isoquinoline-2-carboxylic acid tert-butyl ester

To a mixture of 5 g (34 mmol) 1,2,3,4-tetrahydro-5-aminoisoquinoline in 150 mL dioxane are added 11 mL aq. NaOH (3M) and 7.4 g (34 mmol) Boc2O at 0°C. The mixture is stirred at rt overnight, ice water is added and the mixture is extracted with EtOAc. The combined organic layers are washed with sat. NaHCO3-solution and brine, dried and concentrated in vacuo. The crude product is used in the next step without further purification.

LC MS (method E) \( t_R = 2.636 \text{ min}, \ M\text{-Boc+H} = 149.2 \)

25 **Step 2**

5-Methylamino-3,4-dihydro-lH-isoquinoline-2-carboxylic acid tert-butyl ester and 5-Dimethylamino-3,4-dihydro-lH-isoquinoline-2-carboxylic acid tert-butyl ester
To a mixture of 8.2 g (33 mmol) 5-Amino-3,4-dihydro-lH-isoquinoline-2-carboxylic acid tert-butyl ester in 200 mL THF is added 3.3 g (83 mmol) NaH (60% in mineral oil) at 0°C. After 15 min 6.2 mL (99 mmol) methyl iodide is added and the mixture is stirred at rt for 48 h. The mixture is poured on ice water and extracted with EtOAc. The combined organic layer is dried and concentrated to give a mixture of mono- and dimethylated product. The crude product is triturated with MeOH and the unsoluble solid is filtered off to give the pure monomethylated product. The filtrate is concentrated to give a mixture of mono- and dimethylated product.

LC-MS (method E) t_R = 2.076 min, M + H = 277.1 (dimethyl)
LC-MS (method E) t_R = 3.261 min, M-Boc+H = 263.2 (monomethyl)

**Step 3**

Methyl-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-amine (dihydrochloride salt)

300 mg (1.2 mmol) of the pure 5-Methylamino-3,4-dihydro-lH-isoquinoline-2-carboxylic acid tert-butyl ester obtained in step 2 is dissolved in 5 mL dioxane and 5 mL 4M HCl in dioxane are added. The mixture is stirred at rt for 3 h and concentrated in vacuo to yield the product which is used in the next step without further purification.

LC-MS (method E) t_R = 0.256 min, M + H = 163.1

**Preparation of** N,N-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-amine (dihydrochloride)

**Step 1**

Dimethylamino-3,4-dihydro-lH-isoquinoline-2-carboxylic acid tert-butyl ester
1 g of the mixture of mono- and dimethyl product of step 2 of the previous example is dissolved in 10 mL THF and 190 mg NaH (60% in mineral oil) is added at 0°C. After 15 min 0.35 mL methyl iodide is added and the mixture is stirred at rt overnight. The mixture is poured on ice water and extracted with EtOAc. The combined organic layer is dried and concentrated to give the dimethylated product.

LC MS (method E) \( t_R = 2.076 \text{ min}, \ M + H = 277.1 \)

**Step 2**

10 N,N-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-amine (dihydrochloride)

1.3 g (4.7 mmol) of the pure Dimethylamino-3,4-dihydro-lH-isoquinoline-2-carboxylic acid tert-butyl ester obtained in step 1 is dissolved in 15 mL dioxane and 15 mL 4M HCl in dioxane are added. The mixture is stirred at rt overnight and concentrated in vacuo to yield the product which is used in the next step without further purification.

LC MS (method E) \( t_R = 0.349 \text{ min}, \ M + H = 177.3 \)

**Preparation of 2-(4-methyl-piperazin-l-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine**

20 **Step 1**

3-[l-Dimethylamino-methylidene]-4-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester
A mixture of 15.72 g (84.87 mmol) of N-(tert-butoxycarbonyl)-3-pyrrolidinone and 82 mL of N,N-dimethylformamide dimethylacetal is heated up at reflux for 1.5 hour. Excess of N,N-dimethylformamide dimethylacetal is removed in vacuo, the residue is triturated with n-hexane to provide a solid that is dried in vacuo; MS (method D): 241 [M+I]

Step 2

Z-\(^-\)Methyl-piperazin-1-yO-S^-dihydro-pyrrolo[3\(^-\)dlpyrimidine-6-carboxylic acid tert-butyl ester

A mixture of 0.39 g (1.62 mmol) of 3-[1-dimethylamino-methylidene]-4-oxo-pyrrolidine-l-carboxylic acid tert-butyl ester, 0.98 g (2.43 mmol) of 4-methylpiperazine-l-carboximidamide and 1.35 mL of sodium methoxide (5.4M in methanol) in 10 mL of ethanol is heated up at reflux overnight. The reaction mixture is poured into ice-water and extracted with EtOAc, the organics are washed with brine and dried over Na\(_2\)SO\(_4\). Purification by RP-HPLC (method G) gives the title compound; MS (method D): 320 [M+I]

Step 3

2-(4-Methyl-piperazin-1-yl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine

A solution of 0.16 g (0.5 mmol) of 2-(4-methyl-piperazin-1-yl)-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid tert-butyl ester in 1 mL 1,4-dioxane is treated with 1.9 mL of 4N HCl in dioxane and stirred at RT under completion. The reaction mixture is concentrated in vacuo, taken up in 2N NaOH aqueous solution and extracted with EtOAc. The organics are dried over Na\(_2\)SO\(_4\) and concentrated in vacuo to give the title compound; MS (method D): 220 [M+I]

The following compounds are prepared in an analogous manner

(6,7-Dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)-dimethyl-amine: MS (method D): 165 [M+I]

2-Pyrrolidin-1-yl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine: MS (method D): 191 [M+I]

2-Morpholin-4-yl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine: MS (method D): 207 [M+I]
Preparation of (6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)-dimethyl-amine

**Step 1**

1-Chloro^δ^dimethylamino-S.T-dihydro-pyrroloP^-dlpyrimidine-6-carboxylic acid tert-butyl ester

A solution of 0.2 g (0.66 mmol) of 2,4-dichloro-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid tert-butyl ester in 8 mL of ethanol is treated with 0.103 mL (0.73 mmol) of triethylamine and 0.118 mL of a dimethylamine solution in ethanol (5.6 M). The vial is sealed and the reaction mixture is stirred at RT for 3 hours. The solvent is removed in vacuo and the residue is chromatographed on silica gel (eluent Hexane/EtOAc 4:1) to give the title compound; MS (method D): 299 [M+1], Rf 0.25 (eluent Hexane/EtOAc 3:1)

**Step 2**

4Dimethylamino-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid tert-butyl ester

A solution of 0.08 g (0.27 mmol) of 2-chloro-4-dimethylamino-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid tert-butyl ester in 10 mL of methanol is treated with 4 mL of triethylamine and degassed. Pd on Carbon (10%, 20 mg) is added and the reaction is allowed to stir overnight under an H₂ atmosphere. Under completion the catalyst is removed by filtration and the filtrate is chromatographed on silica gel (eluent Hexane / EtOAc 1:1) to afford the title compound; MS (method D): 265 [M+1]

**Step 3**

(6,7-Dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl)-dimethyl-amine

A solution of 0.067 g (0.25 mmol) of 4-dimethylamino-5,7-dihydro-pyrrolo[3,4-d]pyrimidine-6-carboxylic acid tert-butyl ester in 1 mL of 1,4-dioxane is treated with 0.95
mL of 4N HCl in 1,4-dioxane. Under completion the reaction mixture is freeze-dried to give the title compound; MS (method D): 165 [M+1]

**Preparation of (S)-3-(3-chloro-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-eiie-7,8-dicarboxylic acid 7-tert-butyl ester**

**Step 1**

(S)-4-Oxo-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

A solution of 2.14 g (10.01 mmol) of sodium metaperiodate in 25 mL of water is added to a well stirred suspension of 0.168 g (1.26 mmol) of ruthenium(IV)oxide hydrate in 10 mL CCl₄ at 0 °C to give a yellow organic phase. A solution of 1.23 g (5.02 mmol) of Boc-Cis-HYP-OMe in chloroform is added in one portion. The ice bath is removed and the reaction mixture is allowed to stir at RT for 1.5 hour. The organic layer is separated, the water phase is extracted with ethylether. The organics are treated with 2-propanol, dried over Na₂SO₄, filtered over Celite and concentrated in vacuo to afford the title compound; MS (method D): 242 [M-I]

**Step 2**

(S)-4-Methylene-pyrroldine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

A suspension of 0.3 g (2.59 mmol) of potassium tert-butoxide 20 mL of ethylether at 0°C is treated with 0.944 g (2.59 mmol) of methyl-triphenylphosphoniumbromide, followed by 0.45 g (1.85 mmol) of (S)-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester after 15 minutes. The resulting brown mixture is heated up to reflux for 4 hours, poured into an ice-cold solution of ammonium chloride, and extracted with ethylether. The organic phase is dried over Na₂SO₄, concentrated and chromatographed on silica gel (eluent Hexane / EtOAc 6:1) to give the title compound; Rf 0.44 (eluent Hexane/EtOAc 3:1)
Step 1
3-Chloro-benzaldehyde oxime
To a solution of 7.24 g (51.51 mmol) of 3-chlorobenzaldehyde and 3.941 g (56.14 mmol) of hydroxylamine hydrochloride in water (13 mL) and ethanol (13 mL) is added ice (25 g), followed by a 50% NaOH solution (5 mL). The resulting solution is stirred for 1 hour, acidified with concentrated HCl, and extracted with CH₂Cl₂. The organics are washed with water, dried over Na₂SO₄ and concentrated to give the title compound; MS (method D): 154 [M-I]

Step 2
3-Chlorobenzohydroximinoyl chloride
A mixture of 0.5 g (3.21 mmol) of 3-chloro-benzaldehyde oxime and 0.447 g (3.21 mmol) of N-chlorosuccinimide in 5 mL DMF is stirred at 60 °C for 45 min. The reaction mixture is poured into ice-water, extracted with ethylether. The organics are washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the title compound; HPLC (method A) tₚ (min) 4.17

Step 1
(S)-3-(3-Chloro-phenyl)-l-oxa-2,7-diaza-spiro[4.4]non-2-ene-7,8-dicarboxylic acid 7-tert-butyl ester 8-methyl ester
A solution of 0.15 g (0.62 mmol) of (S)-4-methylene-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester in 10 mL of EtOAc is treated with 0.154 g (0.81 mmol) of 3-chlorobenzohydroximinoyl chloride below 7 °C, followed by 0.114 mL (0.81 mmol) of triethylamine. The reaction mixture is stirred at RT overnight, poured into ice-water / EtOAc.
The organics are washed with brine, dried over Na$_2$SO$_4$, concentrated and chromatographed to give the title compound; HPLC (method A) t$_R$ (min) 4.8 and 4.9 (4:1 ratio)

**Step 2**

(S)-3-(3-Chloro-phenyl)-l-oxa-2,7-diaza-spiro[4.4]non-2-ene-7,8-dicarboxylic acid 7-tert-butyl ester

A solution of 0.12 g (0.30 mmol) of (S)-3-(3-chloro-phenyl)-l-oxa-2,7-diaza-spiro[4.4]non-2-ene-7,8-dicarboxylic acid 7-tert-butyl ester 8-methyl ester in methanol (3 mL) and water 1.5 mL is treated with 0.371 g (15.2 mmol) of LiOH and stirred at RT for 1 hour. The reaction mixture is poured into 6N HCl, extracted with CH$_2$Cl$_2$. The organics are combined, dried over Na$_2$SO$_4$ and concentrated to give the title compound; MS (method D): 379 [M-I]

The following compound is prepared in an analogous manner:

(SVS-Pyridin-S-yH-oxa^^-diaza-spiro^^Jnon^-ene^.-dicarboxylic acid 7-tert-butyl ester: MS (method D): 348 [M+I]

**Preparation of (2S,4R)-4-(6-chloro-benzo[d]isoxazol-3-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester**

A solution of 1 g (4.08 mmol) of Boc-cis-HYP-OMe in 70 mL of THF is cooled to 0°C, treated with 0.784 g (4.48 mmol) of 6-chlorobenzo(d)isoxazol-3-ol, 1.62 g (6.12 mmol) of triphenylphosphine and after 5 minutes, 1.26 mL (6.12 mmol) of diisopropyl azodicarboxylate. The reaction mixture is stirred at RT overnight, concentrated and...
chromatographed by RP-HPLC (method G) to give the title compound; MS (method D): 297 [M-Boc+1]

**Step 2**

(2S,4R)-4-(6-Chloro-benzo[d]isoxazol-3-yloxy)-pyrroolidine-1,2-dicarboxylic acid 1-tert-butyl ester

A solution of 1.24 g (3.12 mmol) of (2S,4R)-4-(6-chloro-benzo[d]isoxazol-3-yloxy)-pyrroolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester in methanol (3 mL) and water 1.5 mL is treated with 0.382 g (15.6 mmol) of LiOH and stirred at RT for 1 hour. The reaction mixture is poured into 6N HCl, extracted with CH₂Cl₂. The organics are combined, dried over Na₂SO₄ and concentrated to give the title compound; MS (method D): 381 [M-I]

**The following compounds are prepared in an analogous manner:**

(2S,4R)-4-(Isoxazolo[4,5-b]pyridin-3-yloxy)-pyrroolidine-1,2-dicarboxylic acid 1-tert-butyl ester: MS (method D): 348 [M-I]

(2S,4R)-4-(Isoxazolo[5,4-c]pyridin-3-yloxy)-pyrroolidine-1,2-dicarboxylic acid 1-tert-butyl ester: MS (method D): 348 [M-I]

**Preparation of (lR,2R)-l-tert-butoxycarbonylamino-2-ethyl-cyclopropanecarboxylic acid methyl ester**

A solution of 15.94 g (66 mmol) of (lR,2S)-l-tert-butoxycarbonylamino-2-vinyl-cyclopropanecarboxylic acid methyl ester in 300 mL t-butyl-methyl ether is hydrogenated over 1.6 g of Pd(OH)₂ on Carbon (20%, wet) under H₂ atmosphere at RT, and under atmospheric pressure. The catalyst is filtered-off and the residue concentrated in vacuo to give the title compound; MS (method D): 242 [M-I]

**BIOLOGICAL ACTIVITY**

Example 227: HCV NS3-4A protease assay
The inhibitory activity of certain compounds of Table A against HCV NS3-4A serine protease is determined in a homogenous assay using the full-length NS3-4A protein (genotype Ia, strain HCV-I) and a commercially available internally-quenched fluorogenic peptide substrate as described by Taliani, M., et al. 1996 Anal. Biochem. 240:60-67, which is incorporated by reference in its entirety.

**Example 228: Luciferase-based HCV replicon assay**

The antiviral activity and cytotoxicity of certain compounds of Table A is determined using a subgenomic genotype 1b HCV replicon cell line (Huh-Luc/neo-ET) containing a luciferase reporter gene, the expression of which is under the control of HCV RNA replication and translation. Briefly, 5,000 replicon cells are seeded in each well of 96-well tissue culture plates and are allowed to attach in complete culture media without G418 overnight. On the next day, the culture media are replaced with media containing a serially diluted compound of Table A in the presence of 10% FBS and 0.5% DMSO. After a 48-h treatment with the compound of Table A, the remaining luciferase activities in the cells are determined using BriteLite reagent (Perkin Elmer, Wellesley, Massachusetts) with a LMaxII plate reader (Molecular Probe, Invitrogen). Each data point represents the average of four replicates in cell culture. \( IC_{50} \) is the concentration of the at which the luciferase activity in the replicon cells is reduced by 50%. The cytotoxicity of the compound of Table A is evaluated using an MTS-based cell viability assay.

Compounds Table A *supra* have been tested in at least one of the protease assay of Example 227 or the replicon assay of Example 228 and exhibit an \( IC_{50} \) of less than about 10 \( \mu \text{M} \) or less in at least one of the assays recited in Example 227 and 228.

**Equivalents**

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.
What is claimed is:

1. A compound of formula I:

![Diagram of compound I]

and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof;

wherein the macrocycle:

![Diagram of macrocycle]

comprises between 15 to 40 ring atoms;

m, x and z are each independently selected from 0 or 1;

p is selected at each occurrence from the group consisting of 0, 1 and 2;

R_i and R_2 are independently selected, at each occurrence, from hydrogen or cyano, or from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, alkoxy, and cycloalkyloxy, each of which is unsubstituted or substituted with 1-6 moieties which can be the same or different and are independently selected from the group consisting of hydroxy, oxo, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, heteroaryl sulfonamido, arylaminosulfonyl, heteroarylaminosulfonyl, mono and dialkylaminosulfonyl, carboxy, carbalkoxy, amid, carboxamido, alkoxy carbonylamino, aminocarbonyloxy, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from...
alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroaralkyl;

\[ R_3 \text{ is selected from the group consisting of } H \text{ and } \text{Ci}-4\text{-alkyl}; \]

\[ E \text{ is a divalent residue selected from the group consisting of } \text{CF}(\text{O})\text{NR}_{23}, \text{NR}_{23}\text{S(O)}_p\text{NR}_{23}; \]

\[ \text{Li and } L_2 \text{ are divalent residues independently selected from the group consisting of } \text{Co}^\text{alkylene}, (\text{CH}_2)_k\text{-FG-}(\text{CH}_2)_k, (\text{CH}_2)_n\text{C}_3, \text{cycloheteroalkylene-(CH}_2)_k, \text{alkenylene}, \text{alkynylene, arylenes, heteroarylenes, cycloalkylene and heterocycloalkylene, each of which is substituted with } 0 \text{ to } 4 \text{ independently selected } X_1 \text{ or } X_2 \text{ groups;} \]

\[ i \text{ and } k \text{ are independently selected integers of from } 0 \text{ to } 7; \]

\[ L_3 \text{ is a Co}_4\text{-alkylene or a divalent ethylene or acetylene residue, wherein the } \text{Co}_4\text{-alkylene and divalent ethylene residues are substituted by } 0-2 \text{ substituents selected from alkyl, aryl, heteroaryl, mono- or di-alkylamino-Co-C}_6\text{alkyl, hydroxyl alkyl or alkoxyalkyl;} \]

\[ \text{FG is absent or a divalent residue selected from the group consisting of } O, \text{S(O)}_p\text{NR}_{23}, \text{C(O), (C(O)NR}_{23}, \text{OC(O)NR}_{23}, \text{NR}_{23}\text{C(O)NR}_{23}, \text{S(O)}_p\text{NR}_{23}, \text{NR}_{23}\text{S(O)}_p\text{NR}_{23}; \]

\[ R_{23} \text{ is independently selected at each occurrence from hydrogen or the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heteroaralkyl, aralkyl and heteroaralkyl, each of which is substituted with } 0-2 \text{ substituents independently selected from halogen, alkyl, alkoxy, and mono- and di-alkylamino; or } \]

\[ \text{Two } R_{23} \text{ residues, taken in combination, form a monocyclic, bicyclic or tricyclic heterocyclic ring system which is saturated, partially unsaturated, or aromatic, and which is substituted with } O \text{ to } 3 \text{ substituents independently selected from } C_6\text{alkyl, C}_1\text{-alkoxy, Q}_a \text{alkoxy Ci}_6\text{-alkoxy, mono- and di-C}_1\text{-alkylaminoC}_1\text{-alkoxy, C}_1\text{-haloalkyl, C}_1\text{-haloalkoxy, mono- and di-C}_1\text{-alkylamino, halogen, 4 to } 7 \text{ member heterocycloalkyl, aryl, heteroaryl, and } 3 \text{ to } 6 \text{ member spirocycloalkyl or spiroheterocycloalkyl, each of which is substituted with } O \text{ to } 3 \text{ substituents independently selected from the group consisting of } C_1\text{-alkyl, Ci}_4\text{-alkoxy, hydroxy, amino, and mono- and di-C}_1\text{-alkylamino;} \]

\[ R_7, \text{RiO, } \text{RN, } \text{Ri}_2, \text{Ri}_3, \text{Ri}_4, \text{Ri}_6, \text{RN, and } R_{22} \text{ are each, independently, selected from hydrogen or the group consisting of alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkoxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkyloxy, amino, alkylamino,} \]
aryl amino, alkyl-aryl amino, aryl amino, heteroaryl amino, cycloalkyl amino, carboxy alkyl amino, aralkyloxy and heterocyclyl amino; all of which may be further substituted 0 to 5 times with substituents independently selected from X₁ and X₂;

R₉ is absent or selected from hydrogen, C¹alkyl, C₃₋₇cycloalkyl-Co¹alkyl, or hydroxy;

X₁ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclylalkyl, heterocyclylalkyl, aryl, alkyaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclyl amino, alkylheteroaryl, or heteroa ralkyl; wherein X₁ can be independently substituted with one or more of the same or different and are independently selected;

X₂ is hydroxy, oxo, alkyl, aryloxy, heterocyclylalkyl, alkylamino, heteroaryl, thio, alkythio, ary thio, heteroarylthio, amino, alkyamin o, arylamino, heteroarylamino, alkylsulfonyl, arylsulfonyl, heterocyclylsulfonyl, alkyaminosulfonyl, arylaminosulfonyl, heterocyclylsulfonyl, mono and dialkyaminosulfonyl, carboxy, carbalkoxy, amido, carbamid o, alkoxy carb onylamino, aminocarbonyloxy, alkoxy carb onyl oxy, carbamoyl, ureido, arylureido, arylureido, halogen, cyano, or nitro; wherein each of said alkyl, arkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, alky laryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclyl amino, alkylheteroaryl and heteroa ralkyl;

Z₁ is Co¹alkylene, oxygen or NR₁₀;

Z₂ is CR₁⁰, O or N;

R₁₄ is C(O) or S(O)₁₀;

V is selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, heteroaryl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-alkyloxy, arlyloxy, heteroaryl, heterocyclyloxy, cycloalkylox y, amino, alkylamino, arylamin o, alkyarylamin o, arylamin o, heteroarylamin o, cycloalkylamin o, carbox yalkylamin o, mono- and di-alkylcarboxamide, aralkyloxy and heterocyclyl amino; each of which may be further independently substituted one or more times with X₁ and X₂;

wherein X₁ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arlyloxy, arylthio, arylheteroaryl, heteroaryl, heterocyclyl amino, alkylheteroaryl, or heteroarylalkyl; wherein X₁ can be independently substituted with one or more X₂ moieties which can be the same or different and are independently selected; wherein X₂ is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl.
heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, thio, alkylthio, amino, mono- and di-
alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido,
carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyl,
alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each X₂
residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently
substituted with one or more moieties which can be the same or different and are
independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl,
heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl,
heterocyclylamino, alkylnitroaryl and heteroaralkyl;

or V is selected from the group consisting of Q'-Q₂, wherein Q¹ is absent, C(O),
S(O)₂, N(H), N(Ci-4-alkyl), C-N(CN), C=N(SO₂CH₃), C=N-COH-Cₘ-alkyl, or C=N-COH,
and Q² is hydrogen or is selected from the group consisting of Ci-4-alkyl, O-C^-alkyl, NH₂,
N(H)-C i-4-alkyl, N(Ci-4-alkyl)₂, SO₂-aryl, SO₂-heteroaryl, SO₄-C^-alkyl, C₃₄-cycloalkyl-C₀-
₄-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one
or more times with a halogen atom, Ci-4-alkyl, C₁₄-alkyl substituted by one or more halogen
atoms, or C₃₆-cycloalkyl;

or R₂₂ and Rᵢ₆ may together form a 3, 4, 5, 6 or 7-membered ring and may contain
one or more heteroatoms, wherein the ring may be further substituted one or more times;

or R₇ and Rᵢ₃ may together form a 3, 4, 5, 6 or 7-membered ring and may contain one
or more heteroatoms, wherein the ring may be further substituted one or more times;

or Rᵢ₅ and Rᵦ may together form a 3, 4, 5, 6 or 7-membered ring and may contain one
or more heteroatoms, wherein the ring may be further substituted one or more times;

or Rᵢ₅ and Rᵦ₆ may together form a 4, 5, 6 or 7-membered ring and may contain one
or more heteroatoms, wherein the ring may be further substituted one or more times;

or Rᵢ₅ and Rᵦ₆ may together form an arylene or heteroarylene ring and R₇ and R₂₂ are
absent, wherein the ring may be further substituted one or more times;

or Rᵦ and R₂ may together form a 3, 4, 5, 6 or 7-membered ring that is saturated or
partially unsaturated and may contain one or more heteroatoms, which ring is substituted with
0-3 residues independently selected from C^alkyl, Ci^alkoxy, C₂₄-alkenyl, C₂₄-alkynyl,
halogen, hydroxy, C₃₆-cycloalkyl and C₃₆-spiroalkyl;

or Rᵦ₇ and Rᵦ₈ may together form a 4, 5, 6, 7 or 8-membered ring of the formula:
wherein

n and g are each, independently, 0, 1 or 2;
X is O, S, N, C or CR₅₆;
R₄ is hydrogen or is selected from the group consisting of Ci^a-alkyl, C₃₋₇-cycloalkyl, aryl, heterocycle and heteroaryl, all of which may be independently substituted one or more times with a halogen atom or Ci-4-alkyl;
R₅ is absent, hydrogen or oxo or is selected from the group consisting of hydroxyl, C₁₋₈-alkyl, C₂₋₈-alkenyl, C₂₋₈-alkynyl, C₃₋₈-cycloalkyl-Co₋₄-alkyl, aryl-C₀₋₄-alkyl, heterocycle-Co₋₄-alkyl, heteroaryl-Co₋₄-alkyl, C₃₋₈-cycloalkyloxy, aryloxy, NR₂₋₃COR₂₋₃, CONR₂₋₃R₂₋₃, NR₂₋₃CONHR₂₋₃, OCONR₂₋₃, NR₂₋₃COOR₂₋₃, OCOR₂₋₃, aryl-C(O)O, aryl-C(O)NR₂₋₃, heteroaryl-C(O)O, heterocycle-C(O)O, heteroaryl-C(O)NR₂₋₃, heterocycle-C(O)NR₂₋₃, each of which may be independently substituted one or more times (or more preferably 0, 1, 2, 3, 4, or 5 times) with halogen, Ci₋₄-alkyl, C^a-alkoxy, haloCi₋₄-alkoxy, amino, mono- and di-C₁^a-alkylaminoCo^a-alkyl, mono- and di-Q.

4alkylaminoC₀₋₄alkoxy, C₃₋₇cycloalkyl, fused- or spiroyclic 3-7 membered ring, heterocycleC₀₋₄alkoxy, heterocycleCo^aalkyl, aryl, or heteroaryl;
R₅a is selected from the group consisting of H, hydroxyl, C₁₋₈-alkyl, C₂₋₈-alkenyl, C₂₋₈-alkynyl, C₃₋₈-cycloalkyl-Co₋₄-alkyl, aryl-Co₋₄-alkyl and heteroaryl-Co₋₄-alkyl,
or R₄ and R₅ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, heteroaryl, trihalomethyl, C^a-alkoxy or C₁₋₄-alkyl;
or R₅ and R₅a may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C₁₋₈-alkyl, C₂₋₈-alkenyl, C₂₋₈-alkynyl, Ci₋₄-alkoxy-Co₋₄alkyl, Ci₋₄-haloalkyl, C₂₋₈-haloalkenyl, C₂₋₈-haloalkynyl, Ci₋₄-haloalkoxy, Q. 8-alkylthio, C₁₋₈-alkylsulfenyl, Ci.g-alkylsulfoxy, C₁₋₄-alkanoyl, Cg-alkoxy carbonyl, C₃₋₇-cycloalkyl-Co₋₄-alkyl, aryl-Co₋₄-alkyl, heteroaryl-Co₋₄-alkyl, COOH, C(O)NH₂, mono- and di-C₁₋₄-alkyl-carboxamides, mono- and di-Ci₋₄-alkyl-amino-Co₋₄alkyl, SO₂H, SO₂NH₂, and mono-and di-Ci₋₄-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S,
which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from
cyano, halogen, amino, thiol, C\(_1\)-C\(_4\)-alkyl, C\(_2\)-C\(_8\)-alkenyl, C\(_1\)-C\(_8\)-alkoxy-Co-
4alkyl, C\(_1\)-C\(_8\)-haloalkyl, C\(_2\)-C\(_8\)-haloalkenyl, C\(_2\)-C\(_8\)-haloalkynyl, C\(_1\)-C\(_8\)-alkylthio, C\(_1\)-
alloylsulfonyl, C\(_1\)-C\(_8\)-alkylsulfuryl, C\(_1\)-C\(_8\)-alkanoyl, C\(_1\)-C\(_8\)-alkoxycarbonyl, C\(_3\)-C\(_7\)-cycloalkyl-Co-
4alkyl, aryl-C\(_0\)-alkyl, heteroaryl-C\(_0\)-alkyl, COOH, C(0)NH\(_2\), mono- and di-C\(_1\)-C\(_4\)alkyl-
carboxamide, mono- and di-C\(_1\)-C\(_4\)-alkylaminocarbonyl, SO\(_3\)H, SO\(_2\)NH\(_2\), and mono-and di-Ci-
4alkylsulfonamide; and

R\(_6\) is independently selected at each occurrence from the group consisting of
hydrogen, hydroxy, amino, C\(_1\)-C\(_4\)-alkyl, C\(_1\)-C\(_4\)-alkoxy, and mono- and di-Ci-alkylamino, and C\(_3\).

\(8\) CycloalkylCo^alkyl;

or two R\(_6\) residues may together form a spirocyclic ring having between 3 and 7 ring
atoms and having \(0, 1, 2\) ring heteroatoms, which is optionally substituted by 0-4
substituents selected from cyano, halogen, hydroxy, amino, thiol, C\(_1\)-C\(_4\)-alkyl, C\(_2\)-C\(_8\)-alkenyl, C\(_2\)-C\(_8\)-haloalkyl, C\(_1\)-C\(_8\)-alkoxy-Co-
4alkyl, C\(_1\)-C\(_8\)-haloalkenyl, C\(_2\)-C\(_8\)-haloalkenyl, C\(_1\)-C\(_8\)-haloalkynyl, C\(_1\)-C\(_8\)-
alloyxycarbonyl, C\(_3\)-C\(_7\)-cycloalkyl-Co-
4alkyl, aryl-C\(_0\)-alkyl, heteroaryl-C\(_0\)-alkyl, COOH, C(0)NH\(_2\), mono- and di-Ci-alkyl-
carboxamide, mono- and di-Ci-alkylaminocarbonyl, SO\(_3\)H, SO\(_2\)NH\(_2\), and mono-and di-Ci-
4alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having \(0, 1, 2\) ring heteroatoms selected
from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected
substituents selected from halogen, C\(_1\)-C\(_4\)-alkyl, C\(_1\)-C\(_4\)-alkoxy, C\(_1\)-C\(_4\)-alkanoyl, mono- and di-Ci-alkylamino, mono- and di-Q^alkyl-carboxamide, C\(_1\)-C\(_4\)-alkoxycarbonyl, and phenyl.

2. A compound of claim 1, wherein R\(_1\) and R\(_2\) taken in combination form a 3, 4,
5, or 6-membered saturated carbocyclic ring which is substituted with 0-2 substituents
independently selected from halogen, alkyl, alkenyl, alkoxy and C\(_3\)-C\(_6\)cycloalkyl.

3. A compound of claim 1 wherein R\(_2\) and one occurrence of R\(_i\) taken in
combination form a cyclopropyl ring which is substituted with 0 or 1 substituents selected Ci-
4alkyl, vinyl or cyclopropyl; E is C(O)NH, NHS(O)\(_2\), NHSO\(_2\)N(Me), NHSO\(_2\)N(Et) or
NHSO\(_2\)N(cyclopropyl).

4. The compound of claim 1, wherein the macrocycle:
5. The compound of claim 1, wherein the macrocycle:

comprises between 15 to 25 ring atoms.

6. The compound of claim 1, wherein

5  
L₁ is CrQalkylene, C₃-C₇ cycloalkylene, arylene or heteroarylene each of which is substituted by 0-4 residues independently selected from Ci-Cialkyl, Ci-C₄ alkoxy, hydroxyl, amino, mono- and di-Ci-C₄ alkylamino, halogen, cyano, Ci-C₄ fluoroalkyl, Ci-C₄ fluoroalkoxy, COOH, carboxamide (CONH₂), mono- and di-Ci-C₄ alkyl carboxamide, aryl, heteroaryl and 5 or 6 membered saturated heterocycles;

10  
L₂ is selected from Ci-C₆ alkyleny and C₂-C₆ alkenylene, each of which is substituted by 0-4 residues independently selected from Ci-C₄ alkyl, Ci-C₄ alkoxy, hydroxyl, amino, mono- and di-Ci-C₄ alkylamino, halogen, cyano, Ci-C₄ fluoroalkyl, Ci-C₄ fluoroalkoxy, COOH, carboxamide (CONH₂), mono- and di-Ci-C₄ alkyl carboxamide, aryl, heteroaryl, and 5 or 6 membered saturated heterocycles; and

15  
L₃ is absent or a divalent ethylene residue which is substituted by 0 to 2 independently selected methyl or ethyl residues.

7. The compound of claim 6, wherein L₁ is a divalent residue selected from C₂-C₄ alkylene, 1,2-phenylene, 1,3-phenylene, 2,4-pyridylene, 2,3-pyridylene, 3,4-pyridylene or 1,7-indolylene, 2,7-indolylene, each of which is substituted with 0-3 residues selected from Ci-C₄ alkyl, Ci-C₄ alkoxy, hydroxyl, amino, mono- and di-Ci-C₄ alkylamino, halogen, cyano, Ci-C₄ fluoroalkyl, Ci-C₄ fluoroalkoxy, COOH, carboxamide (CONH₂), and mono- and di-Q-
C₄alkylcarboxamide.

8. The compound of claim 1, wherein R₅ is a residue of the formula:

wherein

- n and g are integers independently selected from 0, 1, or 2;
- Z₃ is NR₂₃ or O;
- Z₄, Z₅, Z₆, and Z₇ are each independently selected from the group consisting of N, CH, and CR₈; and
- R₈ and R₉ are each independently represent 0 to 2 groups, each of which is independently selected at each occurrence of R₈ and R₉ from the group consisting of hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, haloC₁-C₄ alkyl, haloC₁-C₄ alkoxy, amino, mono- and di-C₁₋₄ alkylaminoC₀₋₄alkyl, mono- and di-C₂₋₃ cycloalkylC₀₋₄alkyl.

9. The compound of claim 1, wherein
- E is C(O)NH;
- R₁ is H or C₁₋₄ alkyl; and
- R₂ is H, C₂₋₄ alkyl, C₂₋₄ fluoroalkyl, C₂₋₄ alkenyl, or C₃₋₇ cycloalkylC₀₋₂ alkyl.

10. A compound of claim 1 wherein the compound is a compound of formula II:

and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers,
diastereomers, or racemates thereof.

11. The compound of claim 10, wherein
   x is 0 or 1;
   n is 0 or 1;
   \( R_{14} \) is C(O) or S(O)\(_2\);
   \( Z_1 \) is absent or NH;
   \( Z_2 \) is nitrogen or CH;
   \( R_1 \) is selected from the group consisting of \( H \) and \( C^1\)-alkyl;
   \( R_2 \) is selected from the group consisting of \( C_i-4\)-alkyl, \( C(O)C_i-alkyl \), \( C(O)OC_i-alkyl \), and \( (CH_2)_0-4-alkyl \);
   or \( R_1 \) and \( R_2 \) together form a cyclopropyl ring which is substituted with 0 or 1 substituents selected \( C_i^1\)-alkyl, vinyl or cyclopropyl;
   \( R_3 \) is selected from the group consisting of \( H \) and \( C_i-4\)-alkyl;
   \( X \) is \( N \), \( R_5 \) or \( C_R^8 \);  
   \( R_4 \) is hydrogen or is selected from the group consisting of \( C_i-4\)-alkyl, \( C_{3,6}\)-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times with a halogen atom or \( d^1\)-alkyl;
   \( R_5 \) is hydrogen or oxo or is selected from the group consisting of hydroxyl, \( C_{2,8}\)-alkenyl, \( C_{2,8}\)-alkynyl, \( C_{3,8}\)-cycloalkyl-\( C_{-4}\)-alkyl, \( aryl-C_0-4\)-alkyl, arylxy, heteroarylxy, heterocycle-\( C_{0,4}\)-alkyl and heteroaryl-\( C_{-4}\)-alkyl, each of which may be independently substituted one or more times with a halogen atom, aryl, heteroaryl, trihalomethyl, \( C_{i-4}\)-alkoxy or \( d^-\)-alkyl; or
   \( R_3 \) is a residue of the formula:

   ![Diagram](attachment:image.png)

   wherein
   n and g are integers independently selected from 0, 1, or 2;
   \( Z_3 \) is \( NR_2 \) or \( O \);
   \( Z_4, Z_5, Z_6, \) and \( Z_7 \) are each independently selected from the group consisting of \( N \), \( CH \), and \( CR_8 \);
R₈ and R₉₈ each independently represent 0 to 2 groups, each of which is independently selected at each occurrence of R₈ and R₉₈ from the group consisting of hydrogen, halogen, C₁⁻Ci₄-alkyl, Ci₄-alkoxy, haloC₁₄⁻alkyl, haloCi₄-alkoxy, amino, mono- and di-Ci⁻alkylaminoCo⁻₄alkyl, mono- and Ci₁₄alkylaminoCo₄alkoxy, heterocycleC₀.₄alkoxy, heterocycleCo⁻₄alkylamino, and heterocycleCo⁻₄alkyl;

R₅₃ is selected from the group consisting of H, hydroxyl, Ci₄-alkyl, C₂₈-alkenyl, C₂₈-alkynyl, C₃₈-cycloalkyl-Co⁻₄alkyl, aryl-Co⁻₄alkyl and heteroaryl-C₀.₄alkyl,

or R₄ and R₅ may together form a fused dimethyl cyclopentyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, heteroaryl, trihalomethyl, Ci⁻₄alkoxy or Ci⁻₄alkyl;

or R₅ and R₅₄ may together form a spirocarbocyclic saturated ring having between 3 and 6 carbon ring atoms which is optionally substituted by 0-2 substitutents selected from halogen, Ci⁻₆alkyl, C₂₆-alkenyl, C₂₆-alkynyl, Ci₁₆alkoxide, Ci₃.₇-cycloalkyl-Co⁻₄alkyl, phenyl-Co⁻₄alkyl, naphthyl-Co⁻₄alkyl, heteroaryl-Co⁻₄alkyl, or two substitutents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or C⁻alkyl groups;

Rio and Rn are each, independently, selected from the group consisting of H and Ci⁻₄alkyl;

R₆ and Ri₃ is H;

Ri₂ is selected from the group consisting of H, Ci⁻₄alkyl and C₃.₆-cycloalkyl; and

V is selected from the group consisting of Q⁻Q⁻², wherein Q⁻¹ is absent, C(O), N(H), N(Ci⁻₄alkyl), C=N(CN), C=N(SO₂CH₃), or C=N-COH, and Q² is H, Ci⁻₄alkyl, C=N-COH-Ci⁻₄alkyl, Ci⁻₄alkoxy, C₃.₇cycloalkyloxy, heterocycloalkyloxy, NH₂, N(H)-C⁻i⁻alkyl, N(Q⁻₄alkyl)², SO²-aryl, SO²-C⁻i⁻alkyl, C₃.₆-cycloalkyl-Co⁻₄alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, Ci⁻₄alkyl, Ci⁻alkoxy, C₂⁻C₄alkenyl, C₂⁻C₄alkynyl, Ci⁻₄alkyl substituted by one or more halogen atoms, or C₃.₆-cycloalkyl;

or when x is 0, Rio and V can form a cyclopropyl ring that may be further substituted by an amide group.

The compound of claim 10, wherein X is CR₅R₅₃, R₄ is H, and R₅ and R₅₄ taken in combination form a 3 to 6 member spirocyclic carbocycle substituted with 0-2 substitutents selected from halogen, Ci⁻₆alkyl, C₂⁻₆alkenyl, C₂⁻₆alkynyl, Ci⁻₆alkoxide, C₃.₇cycloalkyl-Co⁻₄alkyl, phenyl-Co⁻₄alkyl, naphthyl-Co⁻₄alkyl, heteroaryl-Co⁻₄alkyl, or two
substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or C\textsuperscript{\textdagger}^-alkyl groups.

13. The compound of claim 10, wherein V is R\textsuperscript{20} or C(O)-R\textsuperscript{20}, wherein R\textsuperscript{20} is selected from the group consisting of C\textsubscript{3-6}-cycloalkyl, mono- and di-C\textsubscript{1-4}alkylamino, phenyl, pyrazine, benzoxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, CF\textsubscript{3}, C\textsuperscript{\textdagger}^-alkyl, C\textsubscript{1-4}alkoxy, C\textsubscript{2-4}alkenyloxy, C\textsubscript{2-4}alkynloxy, or C\textsubscript{3-6}-cycloalkyl.

14. The compound of claim 10, wherein V is hydrogen or selected from R\textsuperscript{20} or C(O)R\textsuperscript{20}, wherein R\textsuperscript{20} is selected from the group consisting of

![Chemical structures](image-url)
wherein \( b \) is 0, 1, or 2; and \( R_i \) is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and \( C^i\)-alkyl.

15. The compound of claim 10 according to Formula IIa:

wherein

\( \pi_{a} \)

\( Z_2 \) is nitrogen or CH;

\( k_1 \) and \( k_2 \) are 0 or 1 such that a sum of \( k_1 \) and \( k_2 \) equals 1 or 2;

\( R_a \) is hydrogen, \( C^i\)alkyl, or phenyl;

\( R_b \) is hydrogen, \( C_{1-4}\)alkyl, \( C_{1-4}\)alkoxy-\( C_{0-4}\)alkyl, mono- and di-\( C_{1-4}\)alkylamino\( C_{0-4}\)alkyl, mono- and di-\( C_{1-4}\)alkyl carboxamide, \( C_{1-4}\)alkanoyl, \( C_{1-4}\)alkoxycarbonyl, or phenyl

or \( R_a \) and \( R_b \) taken together form a fused or spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, \( C_{1-4}\)alkyl, \( C_{1-4}\)alkoxy, \( Q \) .
alkanoyl, and phenyl; and

$R_c$ represents 0 to 4 substituents which are independently selected at each occurrence of $R_c$ from the group consisting of halogen, alkyl, and phenyl, or two geminal $R_c$ substituents, taken in combination form a 3 to 6 member spirocyclic ring.

16. The compound of claim 15, wherein the divalent residue:

\[ \text{is selected from the group consisting of:} \]

\[ \text{\begin{align*}
&\text{, } \text{, } \text{, } \text{, } \\
&\text{, } \text{, } \text{, } \text{, } \\
&\text{, } \text{, } \text{, } \text{, } \\
&\text{, } \text{, } \text{, } \text{, } \\
&\text{, } \text{, } \text{, } \text{, } \\
&\text{, } \text{, } \text{, } \text{, } \\
\end{align*}} \]
17. The compound of claim 10, wherein X is CRsRs; and

R₅ and R₃, taken in combination, form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which spirocyclic ring is substituted with a spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, and wherein each of the spirocyclic rings has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, C₁₋₈-alkyl, C₂₋₈-alkenyl, C₂₋₈-alkynyl, C₁₋₈-alkoxy-Co₄-alkyl, C₁₋₈-haloalkyl, C₂₋₈-haloalkenyl, C₂₋₈-haloalkynyl, C₁₋₈-haloalkoxy, C₁₋₈-alkylthio, C₁₋₈-alkylsulfonyl, C₁₋₈-alkylsulfoxo, C₁₋₈-alkanoyl, C₁₋₈-alkoxycarbonyl, C₃₋₇-cycloalkyl-Co₄-alkyl, aryl-Co₄-alkyl, heteroaryl-Co₄-alkyl, COOH, C(O)NH₂, mono- and di-CM-alkyl-carboxamide, mono- and di-C₁₋₄-alkyl-amino-Co₄-alkyl, SO₂H, SO₂NH₂, and mono-and di-C₁₋₄-alkylsulfonamide.

18. The compound of claim 10 according to Formula lib:
$Z_2$ is nitrogen or CH;

$k_1$ and $k_2$ are 0 or 1 such that a sum of $k_1$ and $k_2$ equals 1 or 2;

$R_a$ and $R_b$ taken together form a spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C^alkyl, C^alkoxy, C_i^4alkanoyl, and phenyl;

$R_c$ represents 0 to 2 substituents which are independently selected at each occurrence of $R_c$ from the group consisting of halogen, C^alkyl, and phenyl, or two geminal $R_c$ substitents, taken in combination form a 3 to 6 member spirocyclic ring;

$R_4$ represents 0, 1, or 2 substituents each of which is independently selected from H and Q - 4 - alkyl; and

$R_{ss}$ is hydrogen or C^alkyl.

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

![Chemical structures](image)

20. A compound of claim 1, wherein the compound is a compound of formula III:
and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof.

21. The compound of claim 20, wherein:

Z₂ is nitrogen or CH;

Z₁ is absent or NRᵢ₀;

R₃ is selected from the group consisting of H, Q₁, Q₂, and C₄₋₆-cycloalkylCo-

C₄alkyl;

Rₙ, R₁₁ and R₂₂ are selected from the group consisting of H, alkyl-aryl, Cᵢ₋₄-alkyl, O-Ci-4-alkyl, N(H)-Cᵢ₋₄-alkyl, and C₃₋₆-cycloalkylCo₀-C₄alkyl;

R₉ and R₁₇ are each, independently, selected from the group consisting of H, Cᵢ₋₄-alkyl and (CH₂)₀₋₄-C₃₋₆-cycloalkyl; or

R₁₅ and R₆₁ may together form a 3, 4, 5, 6 or 7-membered ring that may comprise between 0 to 3 additional heteroatoms, wherein the ring may be further substituted with 0-5 substitutents; or

R₁₆ and R₁₇ may together form a 3, 4, 5, 6 or 7-membered ring that may comprise between 0 to 3 additional heteroatoms, wherein the ring may be further substituted with 0-5 substitutents; and

V is selected from the group consisting of Q₁, Q₂, wherein Q¹ is absent, C(O), N(H), N(Cᵢ₋₄-alkyl), C=N(CN), C=N(SO₂CH₃), or C=N-COH, and Q² is H, Cᵢ₋₄-alkyl, C=N-COH-Cᵢ⁻alkyl, Cᵢ₋₄-alkoxy, Cᵢ₋₄-cycloalkyloxy, heterocycloalkyloxy, NH₂, N(H)-Cᵢ₋₄-alkyl, N(Q₁₋₄-alkyl)₂, SO₂-aryl, SO₂-Cᵢ₋₄-alkyl, C₃₋₆-cycloalkyl-Co-4-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, Cᵢ₋₄-alkyl, Cᵢ⁻alkoxy, C₂₋₄alkenylxy, C₂₋₄alkynloxy, Ci-4-alkyl substituted by one or more
halogen atoms, or C_{3-6}-CyClOaIlCyI.

22. The compound of claim 20, wherein
   \( R_3 \) is selected from the group consisting of H and Ci-4-alkyl;
   \( R_{13} \) is H;
   Rio and Rn are each, independently, selected from the group consisting of H, Ci-4-alkyl, and C_{3-7}cycloalkylC_{0-4}alkyl;
   \( R_9 \) and Ri_2 are each, independently, selected from the group consisting of H, Ci-4-alkyl and (CH_2)_{0-4}C_{3-6}-cycloalkyl; and
   \( V \) is selected from the group consisting of Q’-Q’’, wherein Q’ is absent, C(O), N(H), N(Ci-4-alkyl), C=N(CN), C=N(SO_2CH_3), or C=N-COH, and Q’’ is H, C^alkyl, C=N-COH-Ci-4-alkyl, C^alkoxy, C_{3-7}cycloalkyloxy, heterocycloalkyloxy, NH_2, N(H)-Ci-4-alkyl, N(Ci-4-alkyl)_2, SO_2-aryl, SO_2-C_i-4-alkyl, C^cycloalkyl-Q’’-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, Ci-4-alkyl, C^alkoxy, C_2-C_4alkenyloxy, C_2-C_4alkynloxy, C_{1-4}-alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl.

23. The compound of claim 20, wherein \( V \) is C(O)-R_20, wherein R_20 is selected from the group consisting of tert-butyl, C_{3-6}-cycloalkyl, phenyl, pyrazine, benzoxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, thiazole, benzothiazole, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with 0-5 substitutents selected from halogen atom, CF_3, Ci-4-alkyl or C_{3-6}-cycloalkyl.

24. The compound of claim 20, wherein \( V \) is selected from the group consisting of C_{3-6}-cycloalkyl, phenyl, pyrazine, benzoxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, thiazole, benzothiazole, benzothiazole 1,1-dioxide and quinazoline, all of which may be further independently substituted with a halogen atom, CF_3, Ci-4-alkyl, Q^alkoxy, C_2-C_4alkenyloxy, C_2-C_4alkynloxy, or C^cycloalkyl.

25. A compound of claim 1, wherein the compound is a compound of formula FV:
and pharmaceutically acceptable salts, enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof.

26. The compound of claim 25, wherein

Z₂ is nitrogen or CH;
R₃ is selected from the group consisting of H and C⁻alkyl;
R₁₇ is selected from hydrogen or the group consisting of C₁₋₄-alkyl, C₁₋₆-cycloalkyl, (CH₂)₁₋₄-C₃₋₆-cycloalkyl, aryl, alkyl-aryl and heterocycle, each of which may be independently substituted one or more times;
Rᵢₒ and Rᵢₙ are each, independently, selected from the group consisting of H and C₁₋₄-alkyl;
V is selected from the group consisting of Q¹⁻Q², wherein Q¹ is absent, C(O), N(H), Ntd⁻alkyl, C=N(CN), C=N(SO₂CH₃), or C=N-COH, and Q² is H, C₁₋₄-alkyl, C=N-COH-C₃₋₆-cycloalkyl-Co-C₂-alkyl, O-C₁₋₄-alkyl, NH₂, N(H)-C₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, SO₂-aryl, SO₂-C₃₋₆-alkyl, C₃₋₆-cycloalkyl-Co-C₄-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, C₁₋₄-alkyl, C⁻alkyl substituted by one or more halogen atoms, or C₃₋₆-cycloalkyl;

or Rᵢ₁ and V form the following 5-membered ring which may be further substituted:

27. The compound of claim 25, wherein Rᵢ₇ is selected from the group consisting of H, cyclopropyl-Co-C₂-alkyl, cyclopentyl-Co-C₂-alkyl, phenyl-Co-C₂-alkyl, and naphthyl-Co-C₂-alkyl,
C_{2}alkyl.

28. The compound of claim 25, wherein V is C(O)-N(H)-M>utyl or C(O)-R_{20}, wherein R_{20} is selected from the group consisting of C_{3-6}-cycloalkyl, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, thiazole, benzothiazole, benzothiazole 1,1-dioxide and quinazoline, all of which may be further independently substituted with a halogen atom, CF_{3}, C_{1-4}-alkyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy, or C_{3-6}-cycloalkyl.

29. The compound of claim 25, wherein V is selected from the group consisting of C_{3-6}-cycloalkyl, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, thiazole, benzothiazole, benzothiazole 1,1-dioxide and quinazoline, all of which may be further independently substituted with a halogen atom, CF_{3}, C_{1-4}-alkyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynloxy, or C_{3-6}-cycloalkyl.

30. The compound of claim 1, wherein V is R_{2} or C(O)-R_{20}, wherein R_{2} is a residue of the formula:

![Diagram](image)

wherein

Z_{g} is absent or selected from NR_{33} or oxygen;

g and f are independently selected integers selected from the group consisting of 0, 1, 2, 3 and 4;

j is an integer selected from the group consisting of 1, 2, 3 and 4, wherein the sum of f + g + j is less than or equal to 5 and greater than or equal to 2 when Z_{g} is absent and the sum of f + g + jk is less than or equal to 4 and greater than or equal to 1 when Z_{g} is oxygen;

R_{33} is independently selected at each occurrence from the group consisting of hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxyC_{1-4}alkyl, and C_{1-4}alkoxyC_{1-4}alkyl; and

R_{34} represents zero to three residues each independently selected at each occurrence from the group consisting of halogen, hydroxy, amino, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}alkoxy, mono- and di-C_{1-4}alkylamino, hydroxyC_{1-4}alkyl, and C_{1-4}alkoxyC_{1-4}alkyl.

31. The compound of claim 1, wherein V is R_{2} or C(O)-R_{20}, wherein R_{2} is a residue of the formula:
wherein

g is an integer selected from the group consisting of 0, 1, 2, 3 and 4;

j is an integer selected from the group consisting of 1, 2, 3 and 4, wherein the sum of

g + j is less than or equal to 5 and greater than or equal to 2;

R\textsuperscript{33} is independently selected at each occurrence from the group consisting of

hydrogen, C\textsubscript{1-4}alkyl, haloC\textsubscript{1-4}alkyl, C\textsubscript{3-6}cycloalkyl, hydroxyC\textsubscript{1-4}alkyl, and C\textsubscript{1-4}alkoxyC\textsubscript{1-4}alkyl; and

R\textsuperscript{34} represents zero to three residues each independently selected at each occurrence

from the group consisting of halogen, hydroxy, amino, C^alkyl, Ca^cycloalkyl, C^alkoxy, mono-and di-C\textsubscript{1-4}alkylamino, hydroxyC^alkyl, and C^alkoxyC^alkyl.

32. A pharmaceutical composition comprising at least one compound according to any one of claims 1-31 and a pharmaceutically acceptable carrier.

33. The pharmaceutical composition of claim 32, wherein the composition further comprises at least one additional HCV-modulating compound.

34. The pharmaceutical composition of claim 32, wherein the additional HCV-modulating compound is selected from the group consisting of Sch 503034 and VX-950.

35. The pharmaceutical composition of claim 32, wherein the additional HCV-modulating compound is interferon or derivatized interferon.

36. The pharmaceutical composition of claim 32, wherein the interferon is selected from the group consisting of interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, lymphoblastoid interferon, and interferon tau; and said compound having anti-hepatitis C virus activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, double stranded RNA, double stranded RNA complexed with tobramycin, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

37. The pharmaceutical composition of claim 32, wherein the additional HCV-modulating compound is a cytochrome P450 monooxygenase inhibitor.
38. The pharmaceutical composition of claim 37, wherein the cytochrome P450 inhibitor is selected from the group consisting of ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazone.

39. A method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound according to any one of claims 1-31.

40. The method of claim 39, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

41. A method of treating an HIV infection comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound according to any one of claims 1-31.

42. A method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound according to any one of claims 1-31.

43. . A method of inhibiting the activity of a serine protease, comprising the step of contacting said serine protease with a compound according to any one of claims 1-31.

44. The method of claim 43, wherein the activity of the NS2 protease is inhibited.

45. The method of claim 43, wherein the activity of the NS3 protease is inhibited.

46. The method of claim 43, wherein the activity of the NS3 helicase is inhibited.

47. The method of claim 43, wherein the activity of the NS5a protein is inhibited.

48. The method of claim 43, wherein the activity of the NS5b polymerase is inhibited.

49. The method of claim 43, wherein the interaction between the NS3 protease and NS4A cofactor is disrupted.

50. The method of claim 43, wherein the severing of one or more of the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions of the HCV is prevented or altered.

51. The method of any one of claims 43-50, wherein an HCV-associated disorder is treated in a subject in need thereof.

52. The method of claim 51, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.
53. A method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound according to any one of claims 1-31, wherein the compound interacts with any target in the HCV life cycle.

54. The method of claim 53, wherein the target is selected from the group consisting of NS2 protease, NS3 protease, NS3 helicase, NS5a protein and NS5b polymerase.

55. A method of decreasing the HCV RNA load in a subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound according to any one of claims 1-31, such that the HCV RNA load in the subject is decreased.

56. A method of treating an HCV-associated disorder in a subject, comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound according to any one of claims 1-31, and a pharmaceutically acceptable carrier, such that the HCV-associated disorder is treated.

57. A method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of a compound according to any one of claims 1-31, in combination with a pharmaceutically effective amount of an additional HCV-modulating compound, such that the HCV-associated disorder is treated.

58. The method of claim 57, wherein the additional HCV-modulating compound is selected from the group consisting of ITMNI 91, Sch 503034 and VX-950.

59. The method of claim 57, wherein the additional HCV-modulating compound is interferon or derivatized interferon.

60. The method of claim 59, wherein the interferon is selected from the group consisting of interferon alpha 2B, pegylated interferon alpha, albufuron, consensus interferon, interferon alpha 2A, lymphoblastoid interferon, and interferon tau; and said compound having anti-hepatitis C virus activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, double stranded RNA, double stranded RNA complexed with tobramycin, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimartadine.

61. The method of claim 57, wherein the additional HCV-modulating compound is a cytochrome P450 monooxygenase inhibitor.

62. The method of claim 61, wherein the cytochrome P450 inhibitor is selected from the group consisting of ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole,
cyclosporin, and clomethiazole.

63. The method of claim 57, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

64. A method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell with a compound according to any one of claims 1-31.

65. A packaged HCV-associated disorder treatment, comprising an HCV-modulating compound according to any one of claims 1-31, packaged with instructions for using an effective amount of the HCV-modulating compound to treat an HCV-associated disorder.

66. The treatment of claim 65, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

67. A method of treating HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinemia, non-Hodgkin's lymphoma, and/or a suppressed innate intracellular immune response in subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound according to any one of claims 1-31.

68. The method of claim 39, wherein the HCV is selected from any HCV genotype.

69. The method of claim 39, wherein the HCV is selected from HCV genotype 1, 2 and/or 3.

70. A method of preventing liver damage in a liver transplant patient, the method comprising administration of a compound of any one of claims 1-31 to a patient who has received a liver transplant or is scheduled for a liver transplant operation.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D257/02 C07D285/00 C07D487/04 C07D487/08 C07D498/04
C07D513/04 C07D515/04 C07D519/00 C07K5/02

According to International Patent Classification (IPC) and/or both national classification and IPC

B. RELES SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practical search terms used)
EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate of the relevant passages</th>
<th>Relevant to claim No</th>
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<td>A</td>
<td>WO 97/30080 A (ORTHO PHARMA CORP [US]); 21 August 1997 (1997-08-21) Claims 1-53; Formula [II]; examples</td>
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<td>E</td>
<td>WO 2008/033389 A (NOVARTIS AG [CH]; BRANDL TRIKI [CH]; COTTENS SYLVAIN [CH]; EHRHARDET CL) 20 March 2008 (2008-03-20) Claims 1-110; Formula [I]; examples</td>
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Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
15 July 2008

Date of mailing of the international search report
29/07/2008

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Authorized officer
Kirsch, Ceci l

Form PCT/ISA/210 (second sheet) (April 2005)
### Box No. II  Observations where certain claims were found unsearchable

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:  
   Although claims 39-70 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **☐** Claims Nos.:  
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically.

3. **☐** Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III  Observations where unity of invention is lacking

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**  
- [ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- [ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- [ ] No protest accompanied the payment of additional search fees.
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