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(54) Titre : PEPTIDOMIMETIQUES POUR LE TRAITEMENT D'INFECTIONS PAR CORONAVIRUS ET PICORNAVIRUS
(54) Title: PEPTIDOMIMETICS FOR THE TREATMENT OF CORONAVIRUS AND PICORNAVIRUS INFECTIONS

(57) Abrégé/Abstract:
Compounds, compositions and methods for preventing, treating or curing a coronavirus, picornavirus, and/or Hepeviridae virus infection in human subjects or other animal hosts. Specific viruses that can be treated include enteroviruses. In one embodiment, the compounds can be used to treat an infection with a severe acute respiratory syndrome virus, such as human coronavirus 229E, SARS, MERS, SARS-CoV-1 (OC43), and SARS-CoV- 2. In another embodiment, the methods are used to treat a patient co-infected with two or more of these viruses, or a combination of one or more of these viruses and norovirus.

Date Submitted: 2021/11/29

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Abstract:

Compounds, compositions and methods for preventing, treating or curing a coronavirus, picornavirus, and/or Hepeviridae virus infection in human subjects or other animal hosts. Specific viruses that can be treated include enteroviruses. In one embodiment, the compounds can be used to treat an infection with a severe acute respiratory syndrome virus, such as human coronavirus 229E, SARS, MERS, SARS-CoV-1 (OC43), and SARS-CoV-2. In another embodiment, the methods are used to treat a patient co-infected with two or more of these viruses, or a combination of one or more of these viruses and norovirus.

PEPTIDOMIMETICS FOR THE TREATMENT OF CORONAVIRUS AND PICORNAVIRUS INFECTIONS

Cross-Reference to Related Application

This application claims priority to U.S. Provisional 62/857,674 filed June 5, 2019, entitled "PEPTIDOMIMETICS FOR THE TREATMENT OF CORONAVIRUS AND PICORNAVIRUS INFECTIONS".

Field of the Invention

The present invention is directed to compounds, methods and compositions for preventing, treating and/or curing Coronavirus infections, including Enterovirus infections. More specifically, the invention describes specifically modified peptidomimetics, pharmaceutically acceptable salts, or other derivatives thereof, and the use thereof in the treatment of these infections.

Background of the Invention

Coronaviruses are a species of virus belonging to the subfamily Coronavirinae in the family Coronaviridae, and are enveloped viruses with a positive-sense single-stranded RNA genome and with a nucleocapsid of helical symmetry.

Coronaviruses primarily infect the upper respiratory and gastrointestinal tract of mammals and birds, though several known strains infect humans as well. Coronaviruses are believed to cause a significant percentage of all common colds in human adults and children.

Coronaviruses, including the OC43 virus, cause colds with major symptoms, e.g., fever, throat congestion and adenoids, in humans primarily in the winter and early spring seasons. Coronaviruses can also cause pneumonia, either direct viral pneumonia or a secondary bacterial pneumonia, bronchitis, either direct viral bronchitis or a secondary bacterial bronchitis, and severe acute respiratory syndrome (SARS).

Coronaviruses also cause a range of diseases in farm animals and domesticated pets, some of which can be serious and are a threat to the farming industry. In chickens, the infectious

bronchitis virus (IBV), a coronavirus, targets not only the respiratory tract but also the urogenital tract. The virus can spread to different organs throughout the chicken.

Economically significant coronaviruses of farm animals include porcine coronavirus (transmissible gastroenteritis coronavirus, TGE) and bovine coronavirus, which both result in diarrhea in young animals. Feline Coronavirus: two forms, Feline enteric coronavirus is a pathogen of minor clinical significance, but spontaneous mutation of this virus can result in feline infectious peritonitis (FIP), a disease associated with high mortality. There are two types of canine coronavirus (CCoV), one that causes mild gastrointestinal disease and one that has been found to cause respiratory disease. Mouse hepatitis virus (MHV) is a coronavirus that causes an epidemic murine illness with high mortality, especially among colonies of laboratory mice.

Some strains of MHV cause a progressive demyelinating encephalitis in mice which has been used as a murine model for multiple sclerosis.

More recently a coronavirus pandemic has caused a dual threat to the health and the economy of the U.S. and the world. COVID-19 was first identified in December 2019 in Wuhan, Hubei province, China, resulting in the ongoing 2019-2020 pandemic. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Common symptoms of the disease include fever (88%), dry cough (68%), shortness of breath (19%), and loss of smell (15 to 30%). Complications may include pneumonia, viral sepsis, acute respiratory distress syndrome, diarrhea, renal disease, cardiac issues and encephalitis. As of June, 2020, the total number of infected worldwide stood at over 4 million and at least 102,753 had died, and, according to the Johns Hopkins University Coronavirus Resource Center, almost two million people had tested positive for coronavirus in the U.S. and over one hundred thousand people had died of the disease. Local transmission of the disease has been recorded in over 200 countries. Risk factors include travel and viral exposure, and prevention is assisted by social distancing and quarantine.

Enteroviruses are members of the picornavirus family, a large and diverse group of small RNA viruses characterized by a single positive-strand genomic RNA, and are associated with several human and mammalian diseases. Enteroviruses are named by their transmission-

route through the intestine (enteric meaning intestinal). On the basis of their pathogenesis in humans and animals, enteroviruses were originally classified into four groups, polioviruses, Coxsackie A viruses (CA), Coxsackie B viruses (CB), and echoviruses, though Enteroviruses isolated more recently are named with a system of consecutive numbers, for example, EV68, EV69, EV70, EV71, etc.

Enteroviruses affect millions of people worldwide each year and are often found in the respiratory secretions (e.g., saliva, sputum, or nasal mucus) and stool of an infected person. Historically, poliomyelitis was the most significant disease caused by an enterovirus, namely poliovirus.

Poliovirus, as well as coxsackie and echovirus, is spread through the fecal-oral route. Infection can result in a wide variety of symptoms, including those of: mild respiratory illness (the common cold), hand, foot and mouth disease, acute hemorrhagic conjunctivitis, aseptic meningitis, myocarditis, severe neonatal sepsis-like disease, acute flaccid paralysis, and the related acute flaccid myelitis.

Current treatments for these infections are mainly supportive, minimizing the symptoms rather than treating the underlying viral infection. For example, patients may be treated with analgesics to relieve pain, and patients with enteroviral carditis can be treated for complications such as arrhythmias, pericardial effusion, and cardiac failure.

It would be advantageous to provide new antiviral agents, compositions including these agents, and methods of treatment using these agents to treat coronaviruses and picornaviruses. The present invention provides such agents, compositions and methods.

Summary of the Invention

The present invention provides compounds, methods and compositions for preventing, treating and/or curing infections caused by coronaviruses, picornaviruses (e.g., an enterovirus or a rhinovirus) and/or viruses in the *Hepeviridae* family (e.g., hepatitis E) in a host, or reducing the activity of these viral infections in the host. In some embodiments,

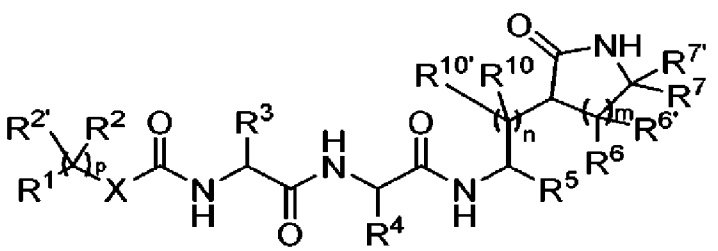
the host is a human, and in others, is an animal such as a cat or dog. Both human and veterinary embodiments are within the scope of the methods described herein.

The methods involve administering a therapeutically or prophylactically-effective amount of at least one compound as described herein to treat, cure or prevent an infection by, or an amount sufficient to reduce the biological activity of, a coronavirus, picornavirus, and/or *Hepeviridae* infection.

In one embodiment, the compounds are used to treat a patient suffering from multiple virus infections, such as hepatitis E and enterovirus (EV). The compounds can also be used to treat norovirus (noV) infections, so the combination of viral infections can include noV in addition to a coronavirus, picornovirus, and/or *hepeviridae* virus.

The pharmaceutical compositions include one or more of the compounds described herein, in combination with a pharmaceutically acceptable carrier or excipient, for treating a host infected with coronaviruses, picornaviruses, and/or *hepeviridae* viruses. The formulations can further include at least one other therapeutic agent. In addition, the present invention includes processes for preparing such compounds.

In one embodiment, the compounds have the following formula:



(I)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, specifically including –CH_2-napthyl, -CH_2-(hydroxy)phenyl, such as -CH_2-(4-hydroxy)phenyl, and –CH_2-(halo)phenyl, such as –CH_2-(4-halo)phenyl, including –CH_2-(fluoro)phenyl, specifically, –CH_2-(4-fluoro)phenyl. Alkylaryl and alkylheteroaryl are preferred variables.

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is -C(O)H, CH=C(CN)C(O)NH_2, -C(O)CF_3, -CH(OH)CF_3, -C(OH)SO_3^- (and an associated cation, such as Na^+), or an optionally-substituted epoxide ring, and is preferably –C(O)H,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl, and in one embodiment, are all H,

X is, independently, a bond, O or NH,

m, n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, N(R')$S(O)_2$R', $S(O)_2$R', $S(O)_2$N(R')$_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

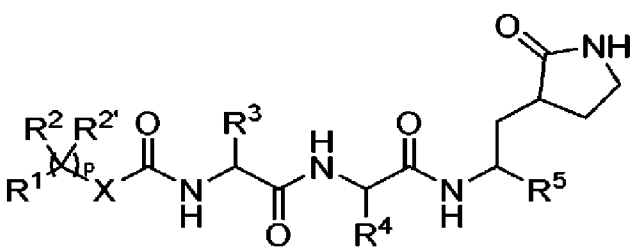
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom.

In yet another embodiment, the compounds have the following formula:

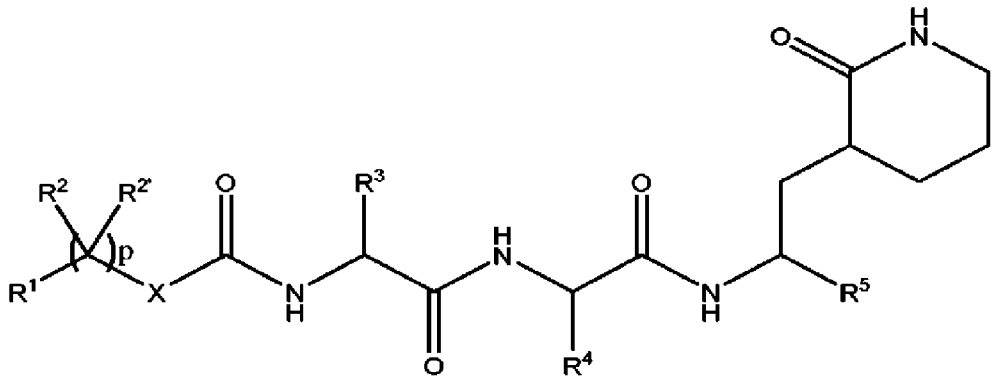


(II)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein p, X, R^1, R^2, $R^{2'}$, R^3, R^4 and R^5 are as defined above.

In still another embodiment, the compounds have the following formula:

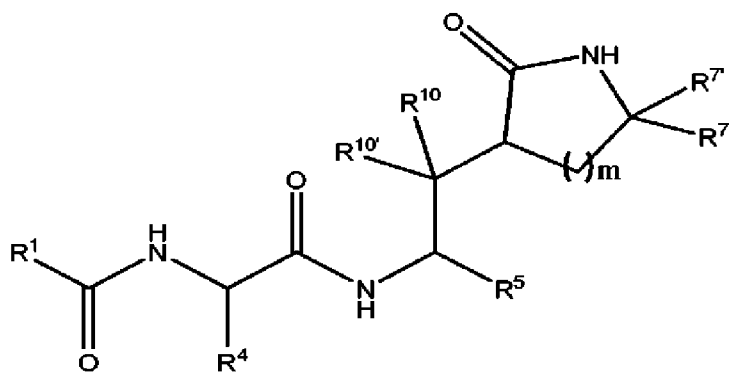


(III)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein p, X, R^1, R^2, $R^{2'}$, R^3, R^4 and R^5 are as defined above.

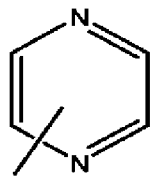
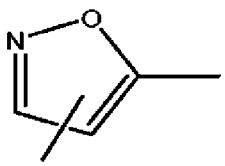
In still another embodiment, the compounds have the following formula:



(IV)

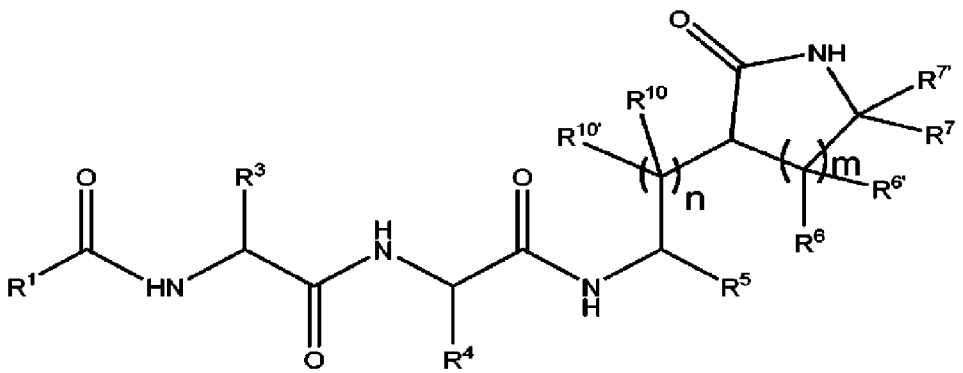
or a pharmaceutically acceptable salt or prodrug thereof,

wherein R^4, R^5, R^7, $R^{7'}$, R^{10}, and $R^{10'}$ are as defined above, and R^1 is an optionally-substituted C_{6-12} cycloalkyl, an optionally-substituted five or six membered ring heteroaryl,

such as or , and is preferably an optionally-substituted five or six membered ring heteroaryl.

In another embodiment, the compounds have the following formula:

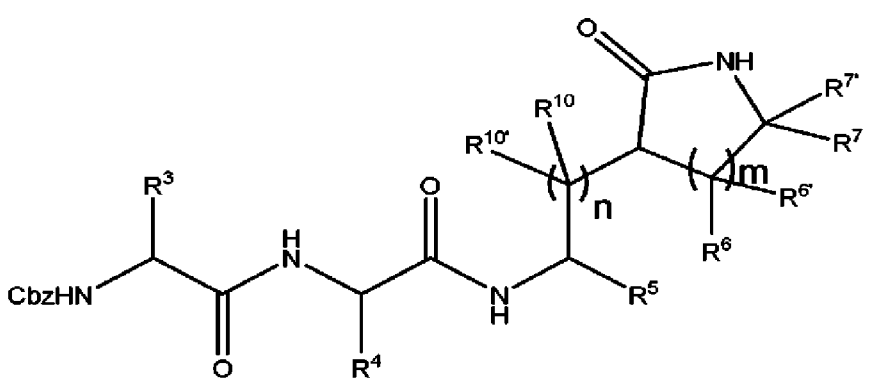


(V)

where R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^{10}, $R^{10'}$, m and n are as defined above, and R1 is a five or six membered ring heteroaryl,

and pharmaceutically-acceptable salts and prodrugs thereof.

In still another embodiment, the compounds have the following formula:

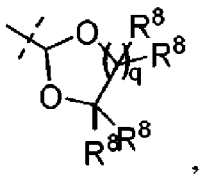
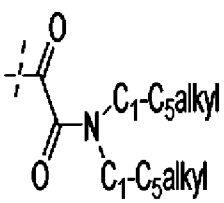
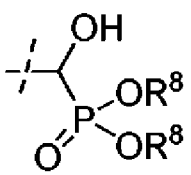
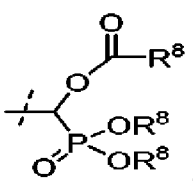
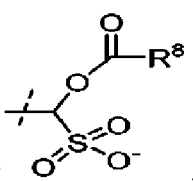


(VI)

or a pharmaceutically-acceptable salt or prodrug thereof,

wherein Cbz = carbobenzoxy, and R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^{10}, $R^{10'}$, m and n are as defined above.

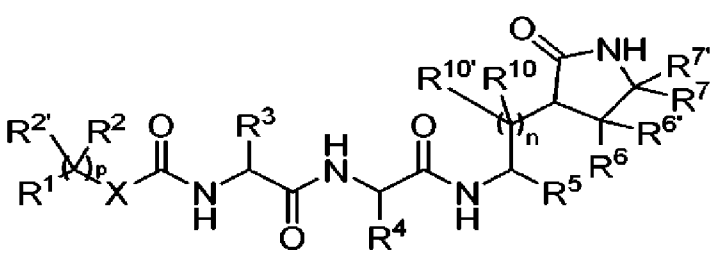
In another embodiment of the compounds of Formulas I-VI,

R^5 is $-(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN, ,  ,  ,  ,  , or  ,

where R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl.

In yet another embodiment, the compounds have the following formula:



(VII)

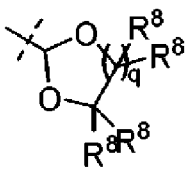
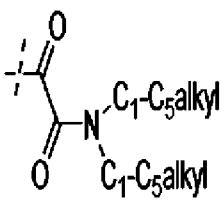
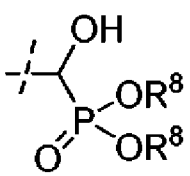
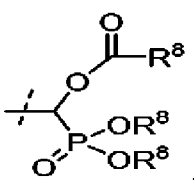
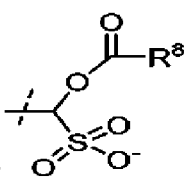
or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, -CH_2-(hydroxy)phenyl, and –CH_2-(halo)phenyl,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is –$(CH_2)_q$-SH,  , -$CH(OH)CF_3$, -CH(OH)CN, ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl,

heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

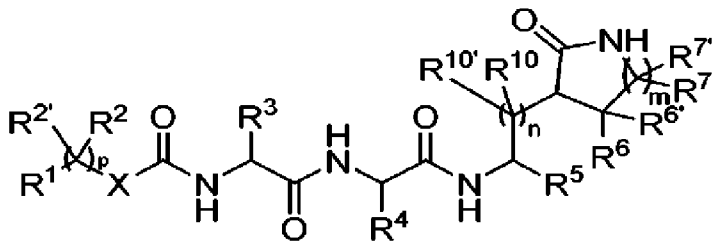
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

In yet another embodiment, the compounds have the following formula:



(VIII)

or a pharmaceutically acceptable salt or prodrug thereof,

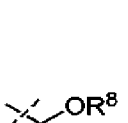
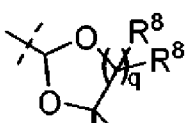
wherein:

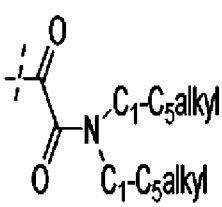
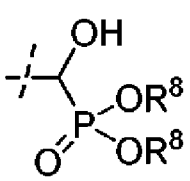
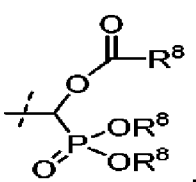
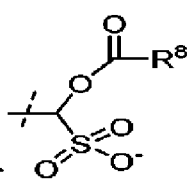
m = 2

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, -CH_2-(hydroxy)phenyl, and –CH_2-(halo)phenyl,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is –$(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN,  ,  ,

 ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

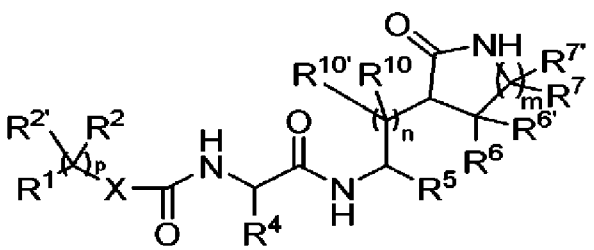
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

In still another embodiment, the compounds have the following formula:



(IX)

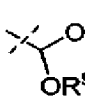
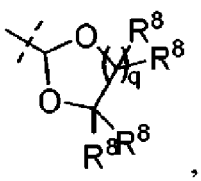
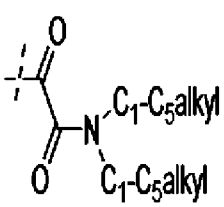
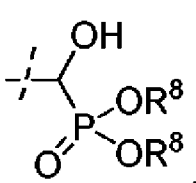
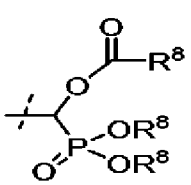
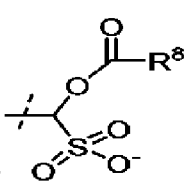
or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

m = 2 or 3

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is $-(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN,  ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

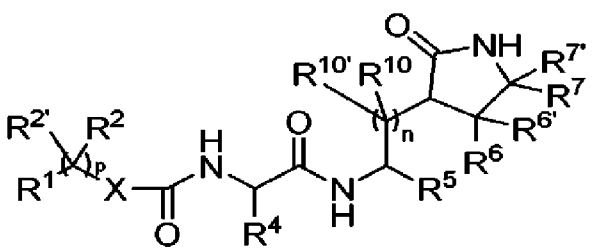
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

In still another embodiment, the compounds have the following formula:



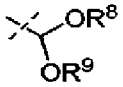
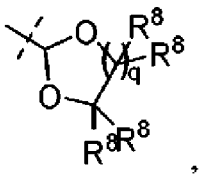
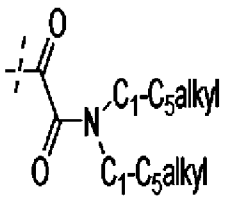
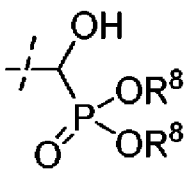
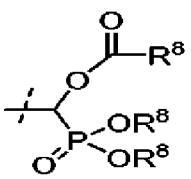
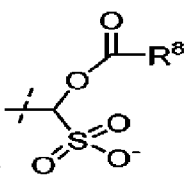
(X)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is $-(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN,  ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl,

acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

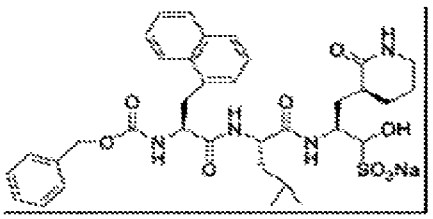
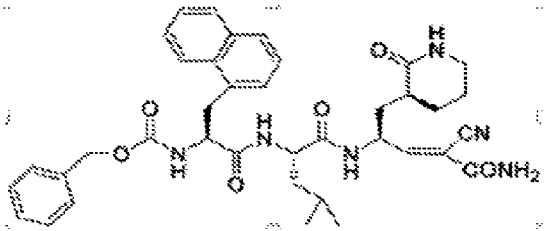
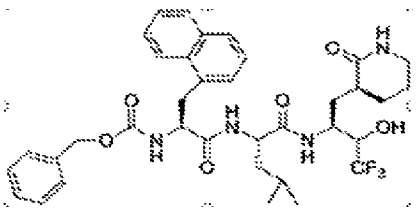
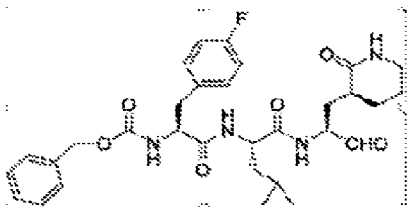
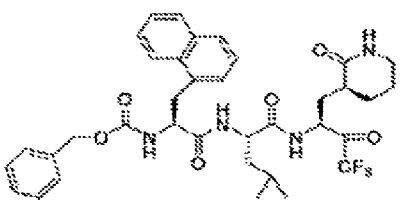
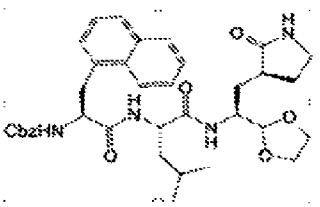
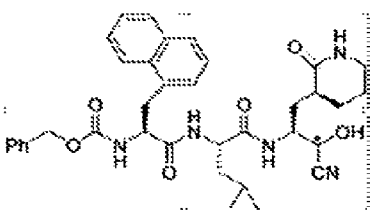
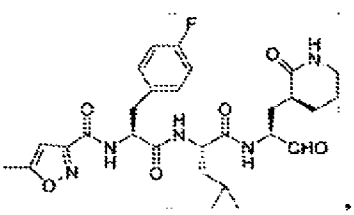
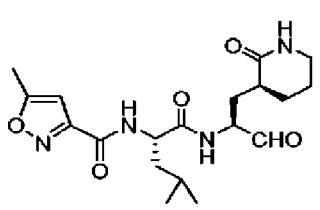
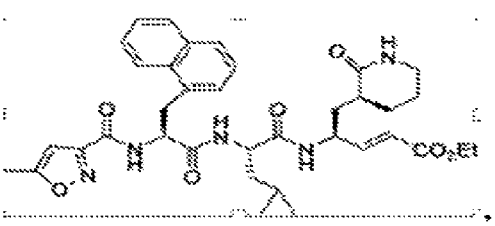
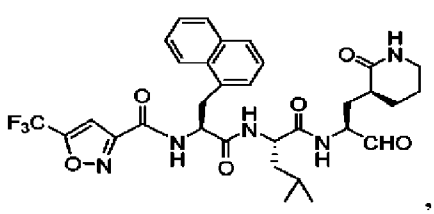
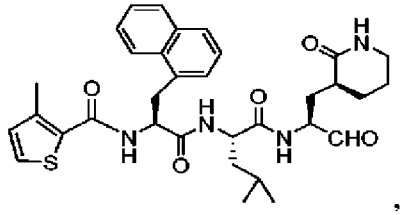
In certain embodiments of any of Formulas I – X, X is O, R^2 and $R^{2'}$ are H, and R^1 is an optionally substituted phenyl.

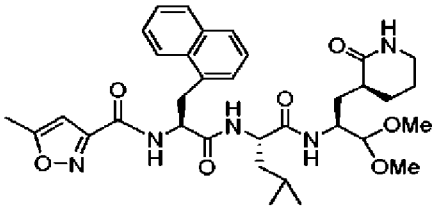
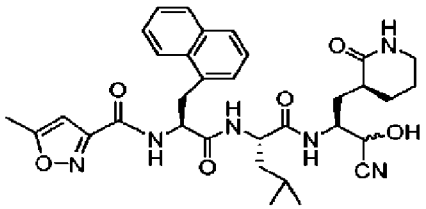
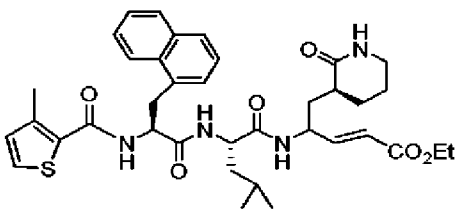
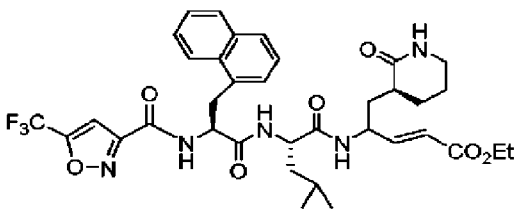
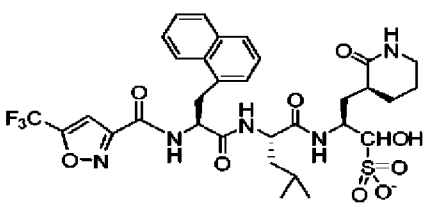
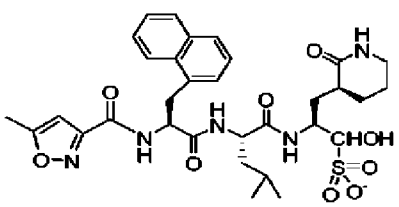
In certain embodiments of any of Formulas I – X, X = a covalent bond, p = 0, and R1 is an optionally substituted aryl or heteroaryl.

In certain embodiments of any of Formulas I – X, the heteroaryl ring is a pyrazine, thiophene, isoxazole, or oxazole ring.

In certain embodiments of any of Formulas I – X, R^3 is phenyl, halo-substituted phenyl, or naphthyl.

Representative compounds include the following:

, and , and pharmaceutically-acceptable salts and prodrugs thereof.

Detailed Description

In one embodiment, compounds and compositions useful in treating, preventing, or curing coronavirus, picornavirus, and/or *Hepeviridae* virus infections are disclosed. Methods for treating, preventing, or curing coronavirus, picornavirus, and/or *Hepeviridae* virus infections are also disclosed.

The compounds described herein show inhibitory activity against enterovirus infections in cell-based assays. Therefore, the compounds can be used to treat or prevent an enterovirus infection in a host, or reduce the biological activity of the virus. The host can be a mammal, and in particular, a human, infected with an enteroviral infection. The methods involve administering an effective amount of one or more of the compounds described herein.

Pharmaceutical formulations including one or more compounds described herein, in combination with a pharmaceutically acceptable carrier or excipient, are also disclosed. In one

embodiment, the formulations include at least one compound described herein and at least one further therapeutic agent.

The present invention will be better understood with reference to the following definitions:

I. Definitions

The term "independently" is used herein to indicate that the variable, which is independently applied, varies independently from application to application. Thus, in a compound such as R"XYR", wherein R" is "independently carbon or nitrogen," both R" can be carbon, both R" can be nitrogen, or one R" can be carbon and the other R" nitrogen.

As used herein, the term "enantiomerically pure" refers to a compound composition that comprises at least approximately 95%, and, preferably, approximately 97%, 98%, 99% or 100% of a single enantiomer of that compound.

As used herein, the term "substantially free of" or "substantially in the absence of" refers to a compound composition that includes at least 85 to 90% by weight, preferably 95% to 98% by weight, and, even more preferably, 99% to 100% by weight, of the designated enantiomer of that compound. In a preferred embodiment, the compounds described herein are substantially free of enantiomers.

Similarly, the term "isolated" refers to a compound composition that includes at least 85 to 90% by weight, preferably 95% to 98% by weight, and, even more preferably, 99% to 100% by weight, of the compound, the remainder comprising other chemical species or enantiomers.

The term "alkyl," as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbons, including both substituted and unsubstituted alkyl groups. The alkyl group can be optionally substituted with any moiety that does not otherwise interfere with the reaction or that provides an improvement in the process, including but not limited to but limited to halo, haloalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl,

sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference. Specifically included are CF_3 and CH_2CF_3.

In the text, whenever the term C(alkyl range) is used, the term independently includes each member of that class as if specifically and separately set out. The term "alkyl" includes C_{1-22} alkyl moieties, and the term "lower alkyl" includes C_{1-6} alkyl moieties. It is understood to those of ordinary skill in the art that the relevant alkyl radical is named by replacing the suffix "-ane" with the suffix "-yl".

As used herein, a "bridged alkyl" refers to a bicyclo- or tricyclo alkane, for example, a 2:1:1 bicyclohexane.

As used herein, a "spiro alkyl" refers to two rings that are attached at a single (quaternary) carbon atom.

The term "alkenyl" refers to an unsaturated, hydrocarbon radical, linear or branched, in so much as it contains one or more double bonds. The alkenyl group disclosed herein can be optionally substituted with any moiety that does not adversely affect the reaction process, including but not limited to but not limited to those described for substituents on alkyl moieties. Non-limiting examples of alkenyl groups include ethylene, methylethylene, isopropylidene, 1,2-ethane-diyl, 1,1-ethane-diyl, 1,3-propane- diyl, 1,2-propane-diyl, 1,3-butane-diyl, and 1,4-butane-diyl.

The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds. The alkynyl group can be optionally substituted with any moiety that does not adversely affect the reaction process, including but not limited to those described above for alkyl moieties. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, and hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals.

The term "alkylamino" or "arylamino" refers to an amino group that has one or two alkyl or aryl substituents, respectively.

The term "protected" as used herein and unless otherwise defined refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis, and are described, for example, in Greene et al., Protective Groups in Organic Synthesis, supra.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings can be attached together in a pendent manner or can be fused. Non-limiting examples of aryl include phenyl, biphenyl, or naphthyl, or other aromatic groups that remain after the removal of a hydrogen from an aromatic ring. The term aryl includes both substituted and unsubstituted moieties. The aryl group can be optionally substituted with any moiety that does not adversely affect the process, including but not limited to but not limited to those described above for alkyl moieties. Non-limiting examples of substituted aryl include heteroarylamino, N-aryl-N- alkylamino, N-heteroarylamino-N-alkylamino, heteroaralkoxy, arylamino, aralkylamino, arylthio, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, hydroxyaralkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl, and carboaralkoxy.

The terms "alkaryl" or "alkylaryl" refer to an alkyl group with an aryl substituent. The terms "aralkyl" or "arylalkyl" refer to an aryl group with an alkyl substituent.

The term "halo," as used herein, includes chloro, bromo, iodo and fluoro.

The term "acyl" refers to a carboxylic acid ester in which the non-carbonyl moiety of the ester group is selected from the group consisting of straight, branched, or cyclic alkyl or lower alkyl, alkoxyalkyl, including, but not limited to methoxymethyl, aralkyl, including, but not limited to, benzyl, aryloxyalkyl, such as phenoxymethyl, aryl, including, but not limited

to, phenyl, optionally substituted with halogen (F, Cl, Br, or I), alkyl (including but not limited to C_1, C_2, C_3, and C_4) or alkoxy (including but not limited to C_1, C_2, C_3, and C_4), sulfonate esters such as alkyl or aralkyl sulphonyl including but not limited to methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g., dimethyl-t-butylsilyl) or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group. The term "lower acyl" refers to an acyl group in which the non-carbonyl moiety is lower alkyl.

The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals having alkyl moieties, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals can be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and fluoropropoxy.

The term "alkylamino" denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical. The terms arylamino denotes "monoarylamino" and "diarylamino" containing one or two aryl radicals, respectively, attached to an amino radical. The term "aralkylamino", embraces aralkyl radicals attached to an amino radical. The term aralkylamino denotes "monoaralkylamino" and "diaralkylamino" containing one or two aralkyl radicals, respectively, attached to an amino radical. The term aralkylamino further denotes "monoaralkyl monoalkylamino" containing one aralkyl radical and one alkyl radical attached to an amino radical.

The term "heteroatom," as used herein, refers to oxygen, sulfur, nitrogen and phosphorus.

The terms "heteroaryl" or "heteroaromatic," as used herein, refer to an aromatic that includes at least one sulfur, oxygen, nitrogen or phosphorus in the aromatic ring.

The term "heterocyclic," "heterocyclyl," and cycloheteroalkyl refer to a nonaromatic cyclic group wherein there is at least one heteroatom, such as oxygen, sulfur, nitrogen, or phosphorus in the ring.

Nonlimiting examples of heteroaryl and heterocyclic groups include furyl, furanyl, pyridyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, isooxazolyl, pyrrolyl, quinazolinyl, cinnolinyl, phthalazinyl, xanthinyl, hypoxanthinyl, thiophene, furan, pyrrole, isopyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, pyrimidine or pyridazine, and pteridinyl, aziridines, thiazole, isothiazole, 1,2,3-oxadiazole, thiazine, pyridine, pyrazine, piperazine, pyrrolidine, oxaziranes, phenazine, phenothiazine, morpholinyl, pyrazolyl, pyridazinyl, pyrazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, adenine, N^6-alkylpurines, N^6-benzylpurine, N^6-halopurine, N^6- vinypurine, N^6-acetylenic purine, N^6-acyl purine,N^6-hydroxyalkyl purine, N^6-thioalkyl purine, thymine, cytosine, 6-azapyrimidine, 2-mercaptopyrmidine, uracil, N^5- alkylpyrimidines, N^5-benzylpyrimidines, N^5-halopyrimidines, N^5-vinylpyrimidine, N^5-acetylenic pyrimidine, N^5-acyl pyrimidine, N^5-hydroxyalkyl purine, and N^6-thioalkyl purine, and isoxazolyl. The heteroaromatic group can be optionally substituted as described above for aryl. The heterocyclic or heteroaromatic group can be optionally substituted with one or more substituents selected from the group consisting of halogen, haloalkyl, alkyl, alkoxy, hydroxy, carboxyl derivatives, amido, amino, alkylamino, and dialkylamino. The heteroaromatic can be partially or totally hydrogenated as desired. As a nonlimiting example, dihydropyridine can be used in place of pyridine. Functional oxygen and nitrogen groups on the heterocyclic or heteroaryl group can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl, trityl or substituted trityl, alkyl groups, acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenelsulfonyl. The heterocyclic or heteroaromatic group can be

substituted with any moiety that does not adversely affect the reaction, including but not limited to but not limited to those described above for aryl.

The term "host," as used herein, refers to a unicellular or multicellular organism in which the virus can replicate, including but not limited to cell lines and animals, and, preferably, humans. Alternatively, the host can be carrying a part of the viral genome, whose replication or function can be altered by the compounds of the present invention. The term host specifically refers to infected cells, cells transfected with all or part of the viral genome and animals, in particular, primates (including but not limited to chimpanzees) and humans. In most animal applications of the present invention, the host is a human being. Veterinary applications, in certain indications, however, are clearly contemplated by the present invention (such as for use in treating chimpanzees).

The term "peptide" refers to a natural or synthetic compound containing two to one hundred amino acids linked by the carboxyl group of one amino acid to the amino group of another.

The term "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any pharmaceutically acceptable form (such as an ester) compound which, upon administration to a patient, provides the compound.

The compounds can also be prepared in the form of water-soluble prodrugs. Water-soluble prodrugs are well-known to those of skill in the art, and include, for example, those disclosed in Bundgaard et al., "A novel solution-stable, water-soluble prodrug type for drugs containing a hydroxyl or an NH-acidic group," J. Med. Chem. 32(12):2503-2507, 1989, Matsumoto et al., Bioorganic & Medicinal Chemistry Letters, Vol. 11, Issue 4, 26 February 2001, Pages 605-609, and Stella et al., "Prodrug strategies to overcome poor water solubility," Advanced Drug Delivery Reviews, Volume 59, Issue 7, 30 July 2007, Pages 677-694.

As the name suggests, water-soluble prodrugs are formulated using the aqueous solubility of the drug and for enhancing the oral drug delivery, generally includes the addition of an ionizable progroup to the parent compound (such as phosphate, carboxylate, or sulfonate group). Water-soluble ester prodrugs can improve the aqueous solubility of poorly soluble drugs that contain a hydroxyl group. The most commonly used esters for forming prodrugs are those

containing ionizable groups such as dicarboxylic acid hemiesters. Phosphate esters, such as oxymethylphosphate (OMP) and oxyethylphosphate (OEP) prodrugs, offer one way to increase the oral bioavailability of many sparingly water soluble drugs. Pegylated prodrugs, either added to directly, or via a spacer, such as an amino acid spacer (Feng et al., Bioorganic & Medicinal Chemistry Letters, Volume 12, Issue 22, 18 November 2002, Pages 3301-3303), can also increase water-solubility.

Pharmaceutically-acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous other acids well known in the pharmaceutical art.

The term "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any pharmaceutically acceptable form (such as an ester) compound which, upon administration to a patient, provides the compound. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous other acids well known in the pharmaceutical art. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs include compounds that have biologically labile protecting groups on functional moieties of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. The prodrug forms of the compounds of this invention can possess antiviral activity, can be metabolized to form a compound that exhibits such activity, or both.

II. Active Compounds

Coronaviruses are a species of virus belonging to the subfamily Coronavirinae in the family Coronaviridae, and are enveloped viruses with a positive-sense single-stranded RNA genome and with a nucleocapsid of helical symmetry.

Picornaviruses belong to the family Picornaviridae, and are non-enveloped positive strand RNA viruses. Representative Picornaviruses include Enterovirus (including Rhinovirus and Poliovirus), Aphthovirus, Cardiovirus, and Hepatovirus genera.

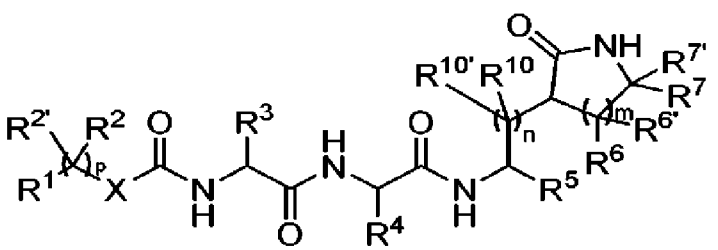
Viruses of the Hepeviridae family are single, positive stranded RNA viruses, and the family includes hepatitis E virus.

The compounds described herein are active against each of these viruses.

Enteroviral infections are believed to be associated with multiple sclerosis (MS), as infection by these viruses can cause demylenation. Accordingly, the compounds described herein can be used to treat or prevent multiple sclerosis which results, in whole or in part, from enteroviral infection.

While not wishing to be bound to a particular theory, it is believed that the compounds are effective at inhibiting a viral protease (e.g., a coronavirus 3CL protease, Picornavirus 3C protease, or Picornain 3C), and this is at least partially responsible for their effectiveness against these viruses.

In one embodiment, the compounds have the following formula:



(I)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, specifically including –CH_2--napthyl, -CH_2-(hydroxy)phenyl, such as -CH_2-(4-hydroxy)phenyl, and –CH_2-(halo)phenyl, such as –CH_2-(4-halo)phenyl, including –CH_2-(fluoro)phenyl, specifically, –CH_2-(4-fluoro)phenyl.

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is -C(O)H, CH=C(CN)C(O)NH_2, -C(O)CF_3, -CH(OH)CF_3, -C(OH)SO_3^- (and an associated cation, such as Na^+), or an optionally-substituted epoxide ring, and is preferably –C(O)H,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl, and in one embodiment, are all H,

X is, independently, a bond, O or NH,

m, n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, N(R')$S(O)_2$R', $S(O)_2$R', $S(O)_2$N(R')$_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl,

phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

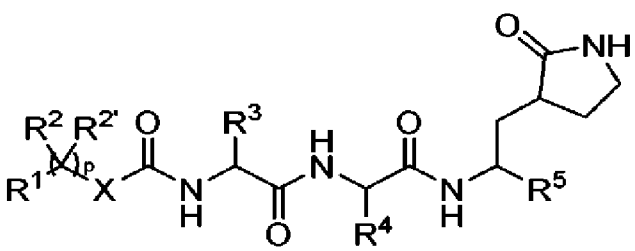
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom.

In yet another embodiment, the compounds have the following formula:

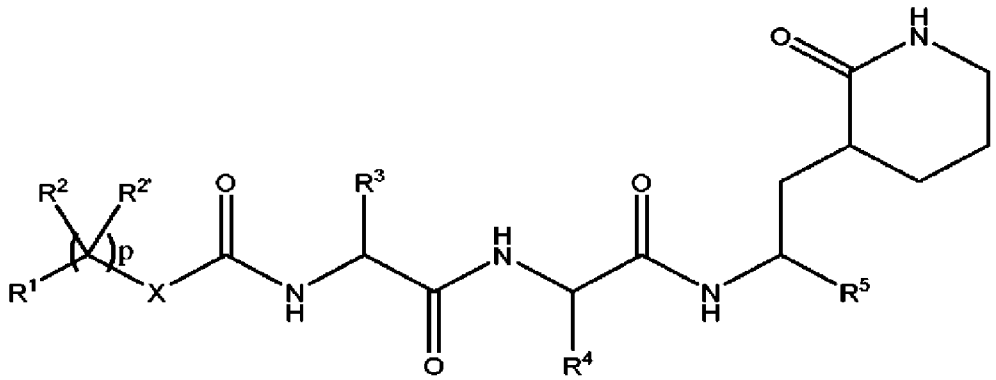


(II)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein p, X, R^1, R^2, $R^{2'}$, R^3, R^4 and R^5 are as defined above.

In still another embodiment, the compounds have the following formula:

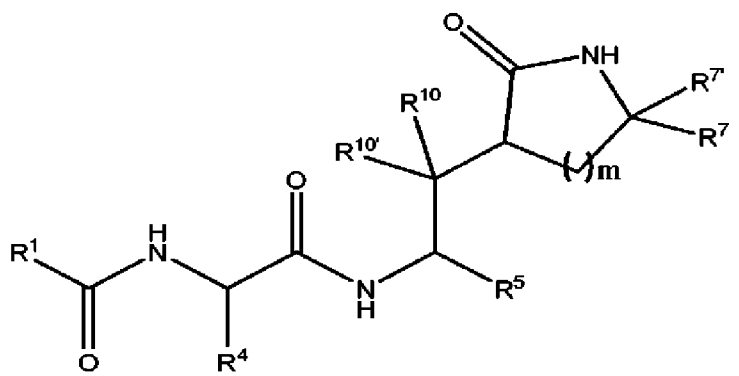


(III)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein p, X, R^1, R^2, $R^{2'}$, R^3, R^4 and R^5 are as defined above.

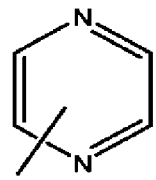
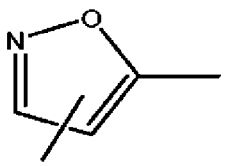
In still another embodiment, the compounds have the following formula:



(IV)

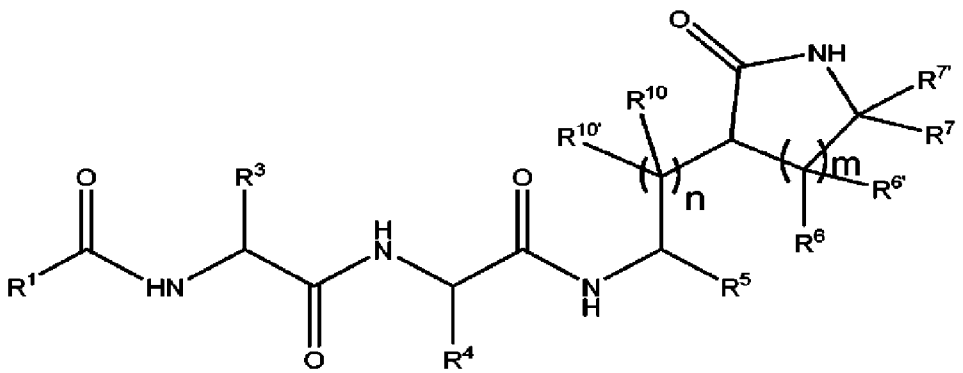
or a pharmaceutically acceptable salt or prodrug thereof,

wherein R^4, R^5, R^7, $R^{7'}$, R^{10}, and $R^{10'}$ are as defined above, and R^1 is an optionally-substituted C_{6-12} cycloalkyl, an optionally-substituted five or six membered ring heteroaryl,

such as or , and is preferably an optionally-substituted five or six membered ring heteroaryl.

In another embodiment, the compounds have the following formula:

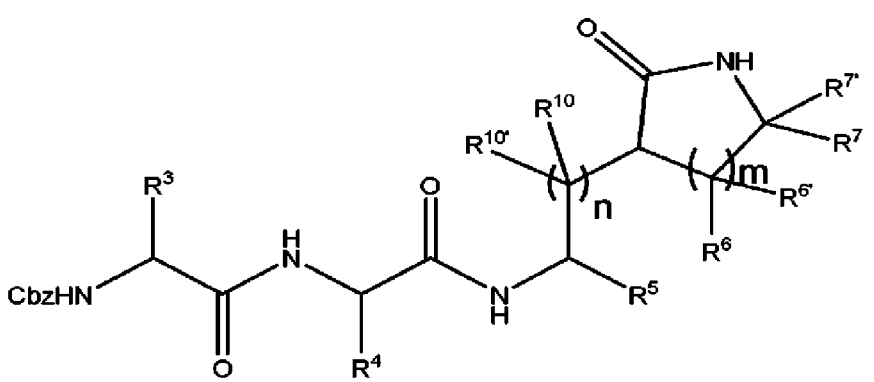


(V)

where R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^{10}, $R^{10'}$, m and n are as defined above, and R1 is a five or six membered ring heteroaryl,

and pharmaceutically-acceptable salts and prodrugs thereof.

In still another embodiment, the compounds have the following formula:

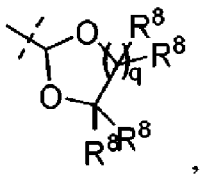
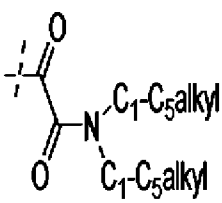
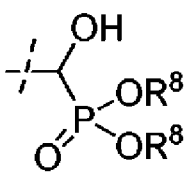
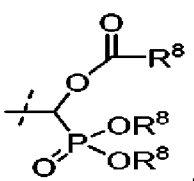
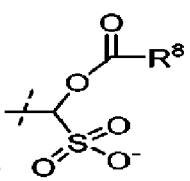


(VI)

or a pharmaceutically-acceptable salt or prodrug thereof,

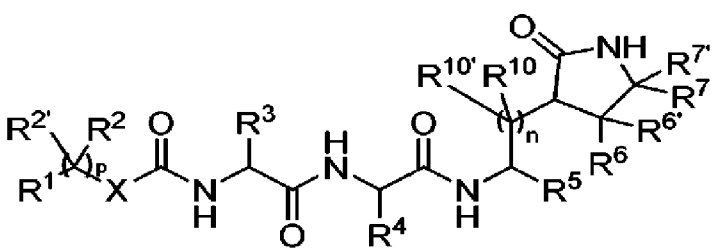
wherein Cbz = carbobenzoxy, and R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^{10}, $R^{10'}$, m and n are as defined above.

In another embodiment of the compounds of Formulas I-VI,

R^5 is $-(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN, ,  ,  ,  ,  , or  ,

where R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, and R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl.

In yet another embodiment, the compounds have the following formula:



(VII)

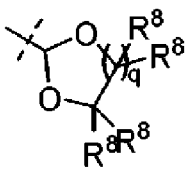
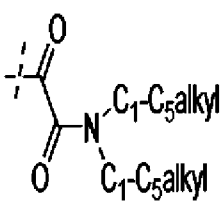
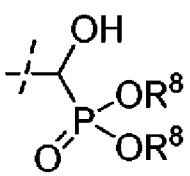
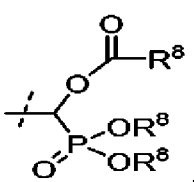
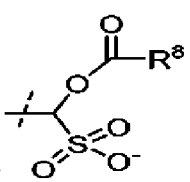
or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, -CH_2-(hydroxy)phenyl, and –CH_2-(halo)phenyl,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is –$(CH_2)_q$-SH,  , -$CH(OH)CF_3$, -CH(OH)CN, ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl,

heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

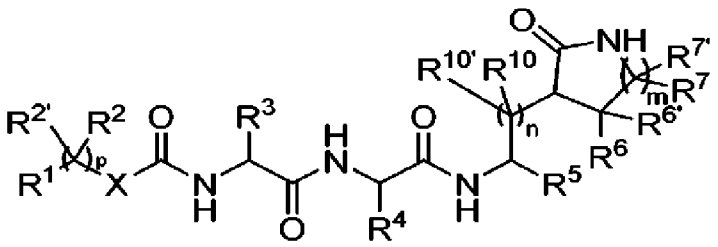
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

In yet another embodiment, the compounds have the following formula:



(VIII)

or a pharmaceutically acceptable salt or prodrug thereof,

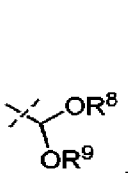
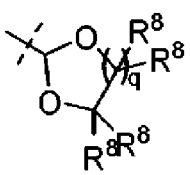
wherein:

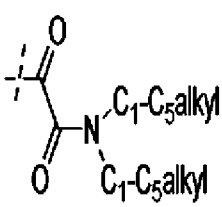
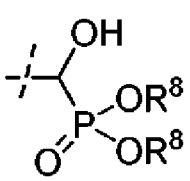
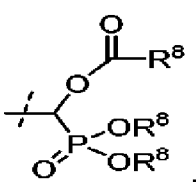
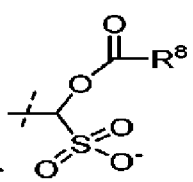
m = 2

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, -CH_2-(hydroxy)phenyl, and –CH_2-(halo)phenyl,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is –$(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN,  ,  ,

 ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

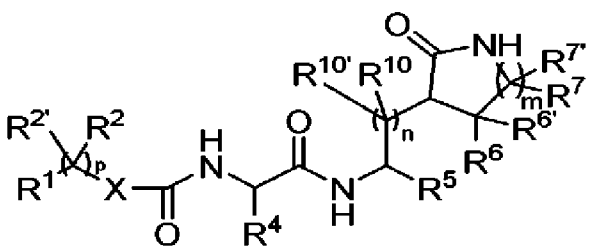
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

In still another embodiment, the compounds have the following formula:



(IX)

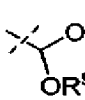
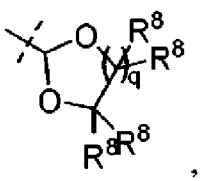
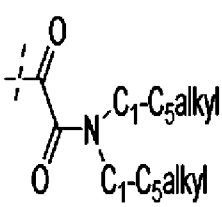
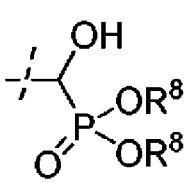
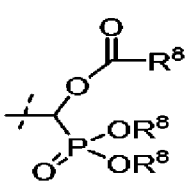
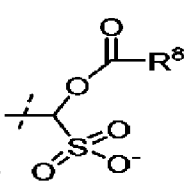
or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

m = 2 or 3

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is $-(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN,  ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

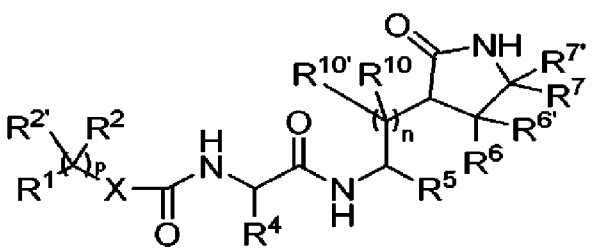
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

In still another embodiment, the compounds have the following formula:



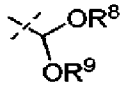
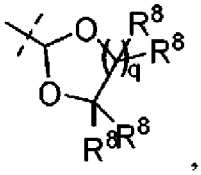
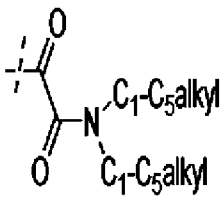
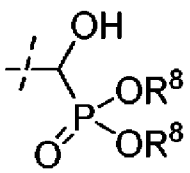
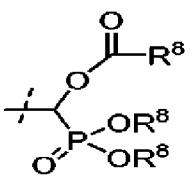
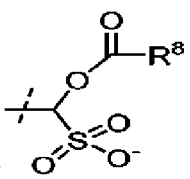
(X)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is $-(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN,  ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl,

acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

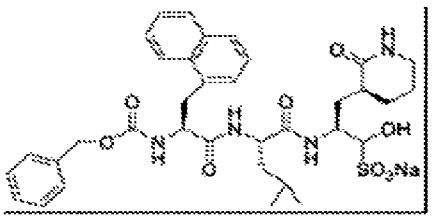
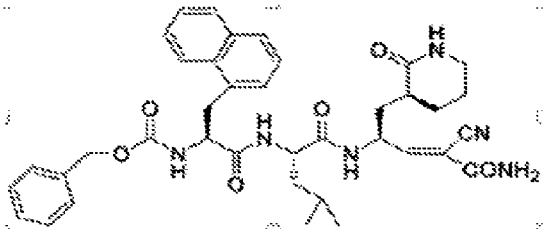
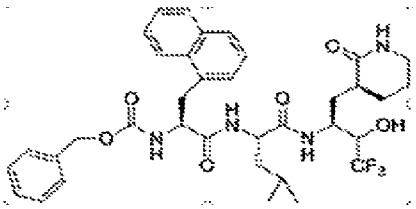
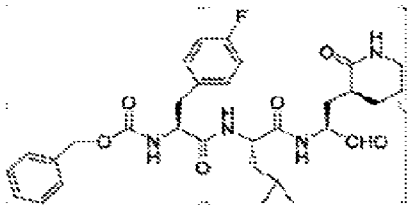
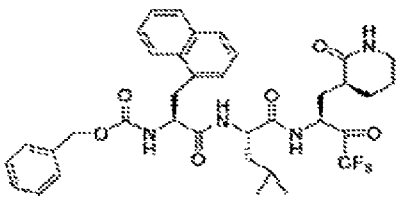
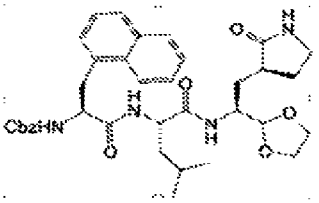
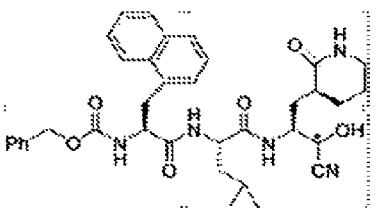
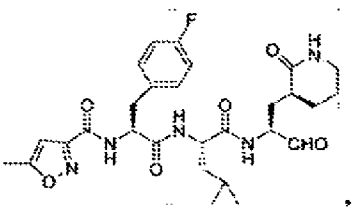
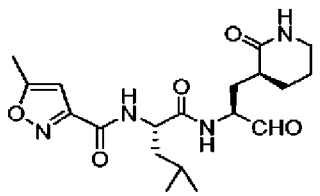
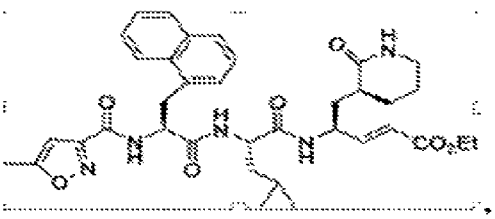
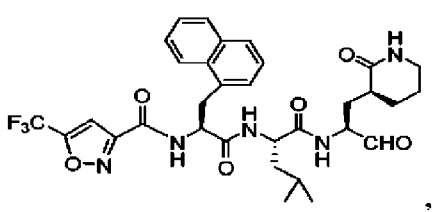
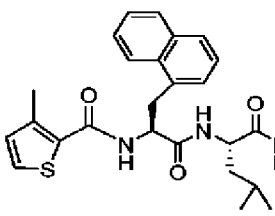
In certain embodiments of any of Formulas I – X, X is O, R^2 and $R^{2'}$ are H, and R^1 is an optionally substituted phenyl.

In certain embodiments of any of Formulas I – X, X = a covalent bond, p = 0, and R1 is an optionally substituted aryl or heteroaryl.

In certain embodiments of any of Formulas I – X, the heteroaryl ring is a pyrazine, thiophene, isoxazole, or oxazole ring.

In certain embodiments of any of Formulas I – X, R^3 is phenyl, halo-substituted phenyl, or naphthyl.

Representative compounds include the following:

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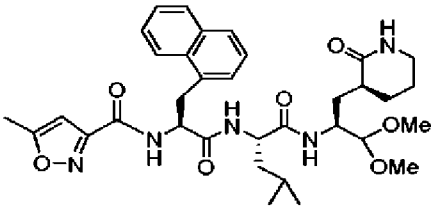
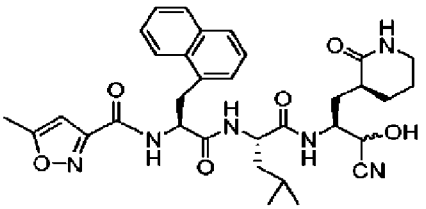
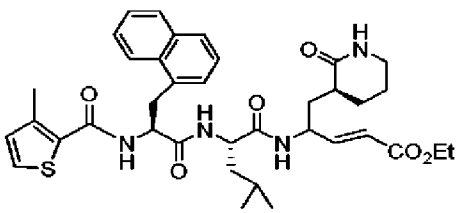
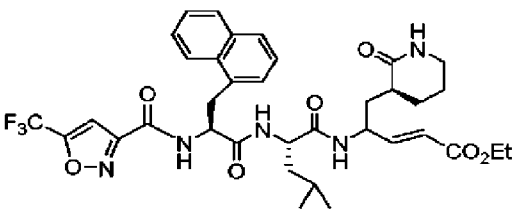
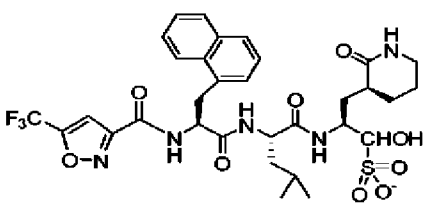
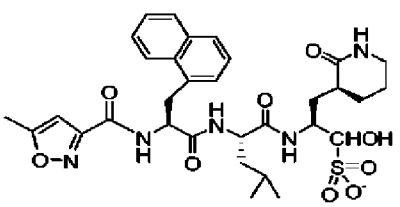
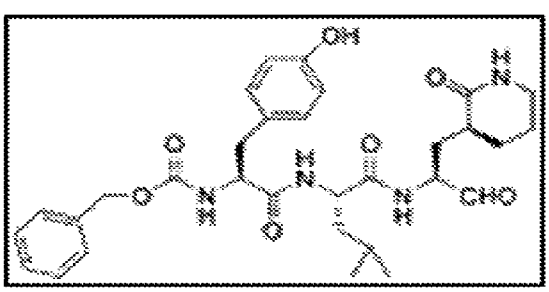
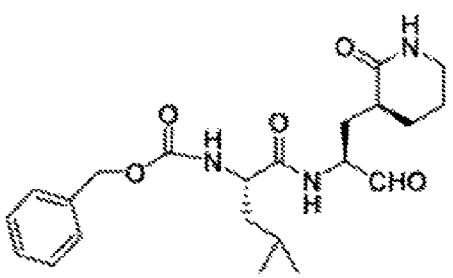
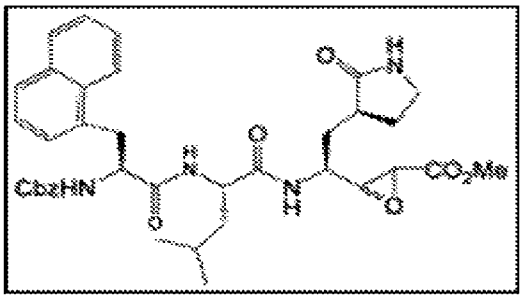
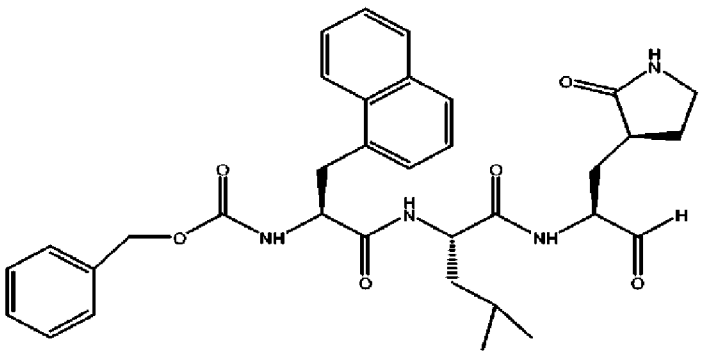







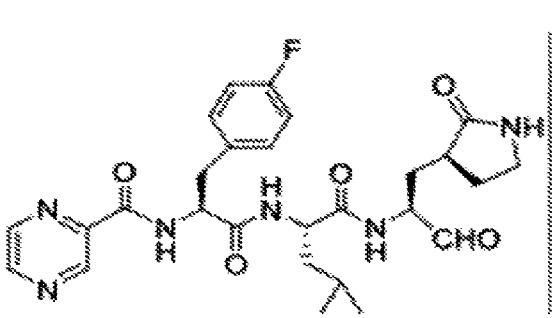
, and , and pharmaceutically-acceptable salts and prodrugs thereof.

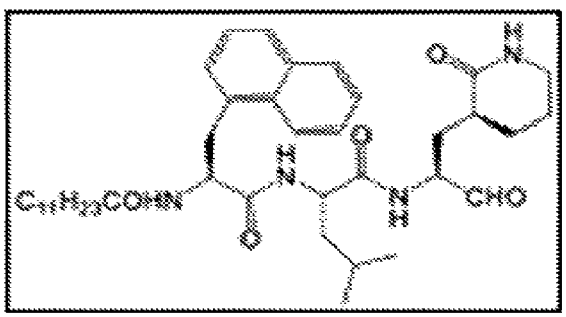
Representative compounds also include the following:

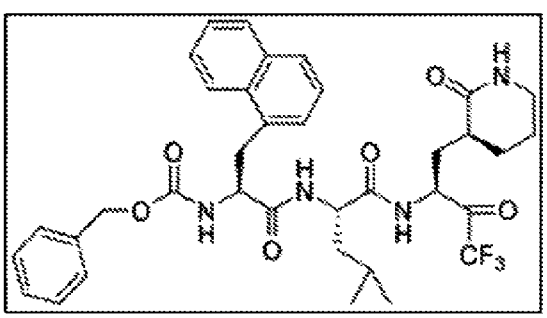



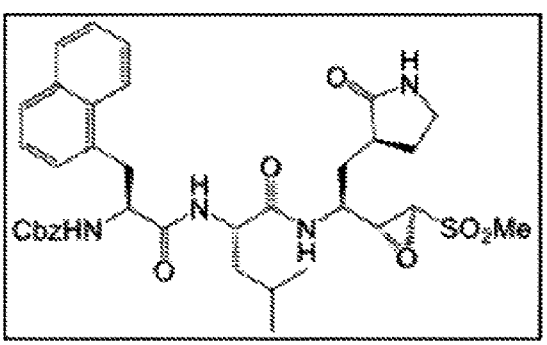


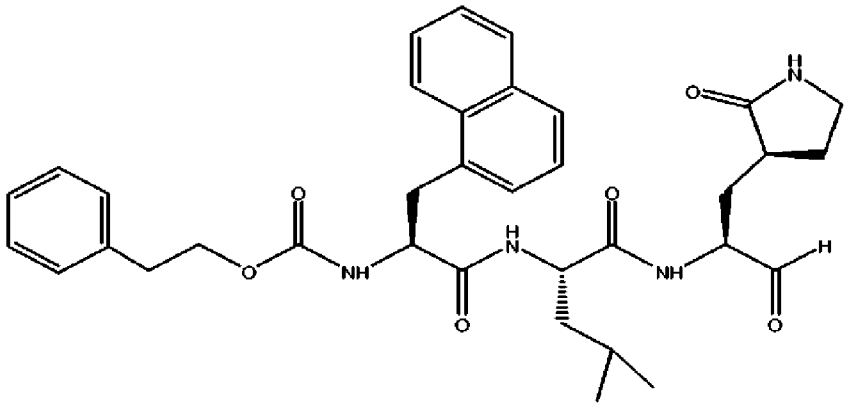


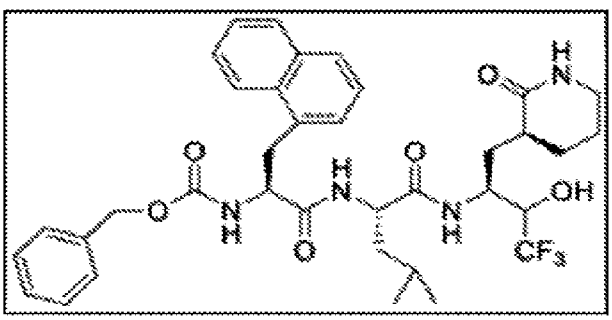


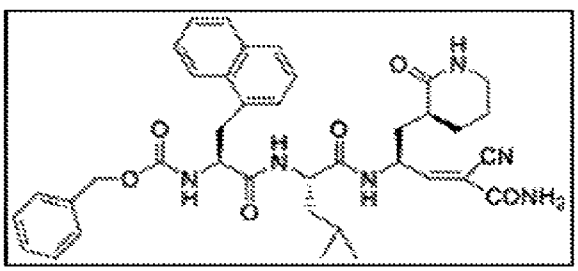


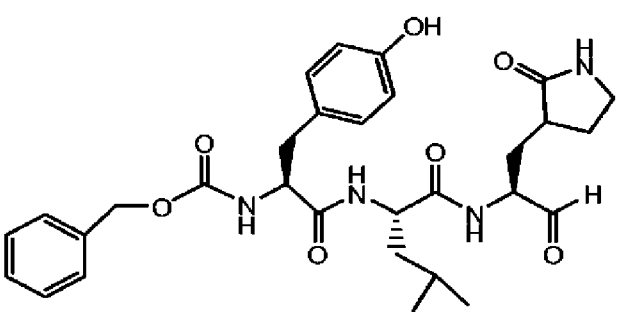


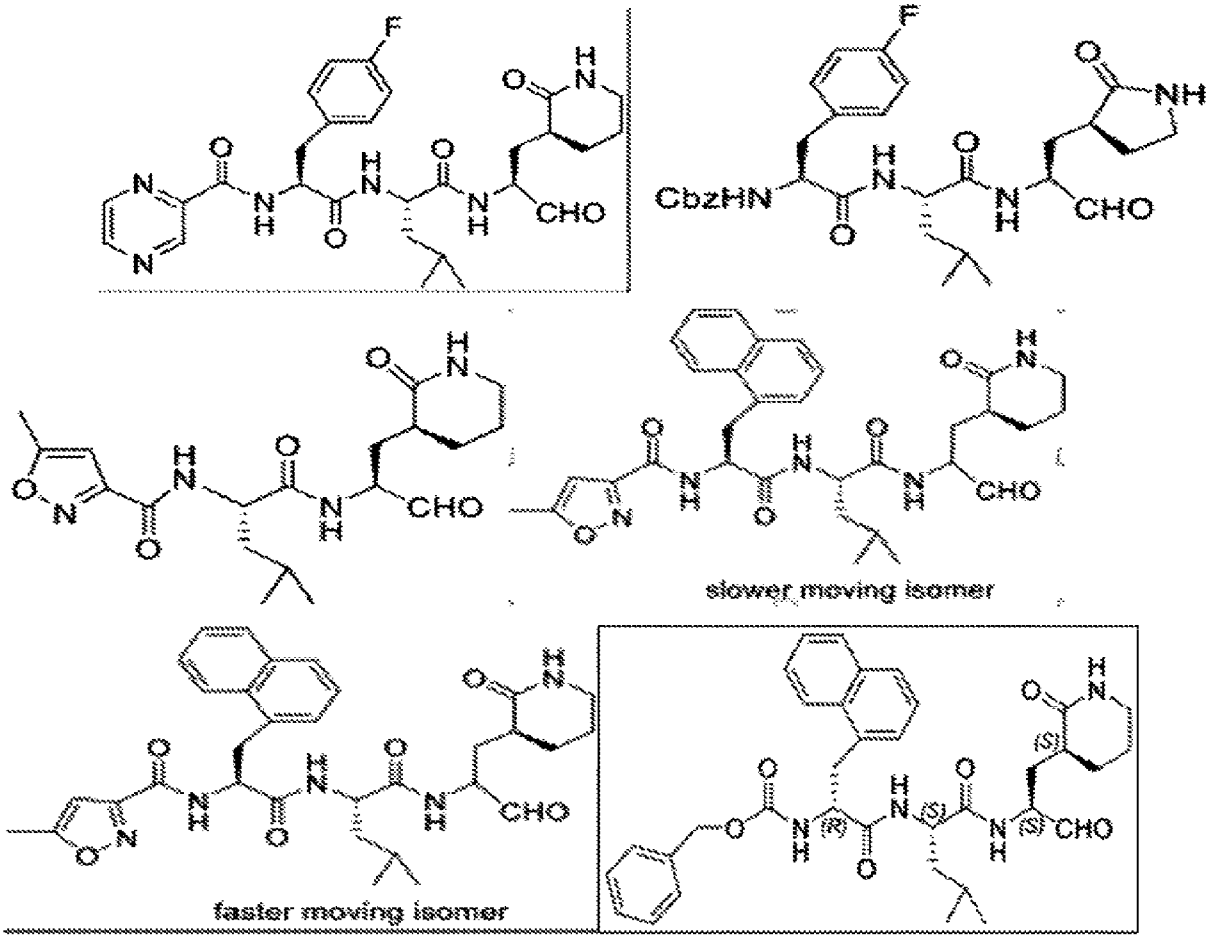


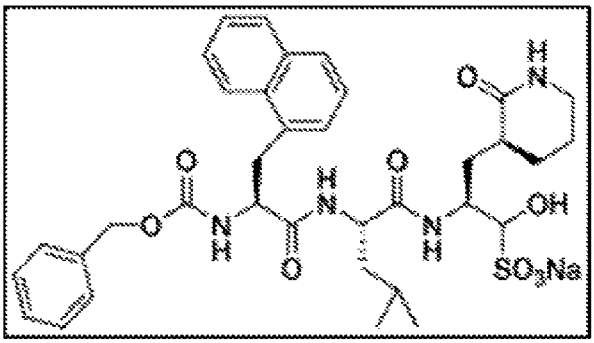


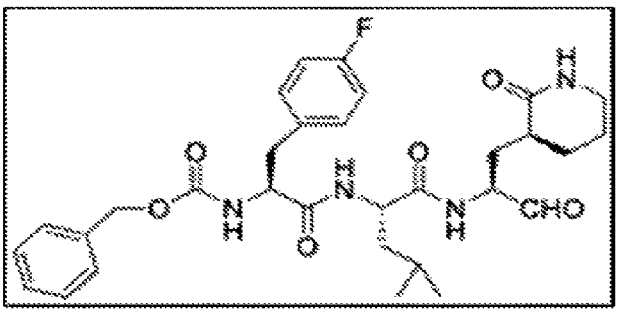


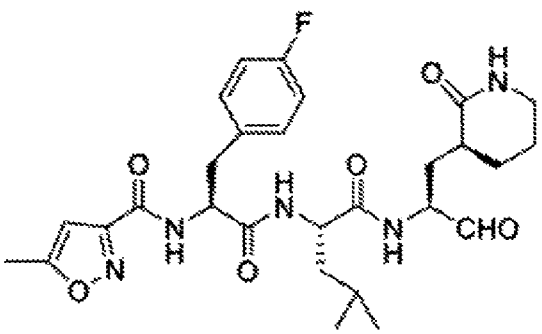


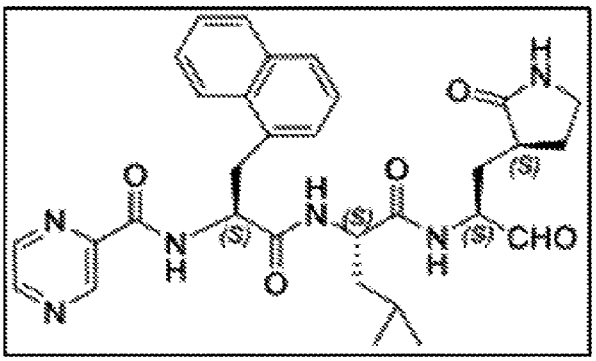



slower moving isomer
faster moving isomer



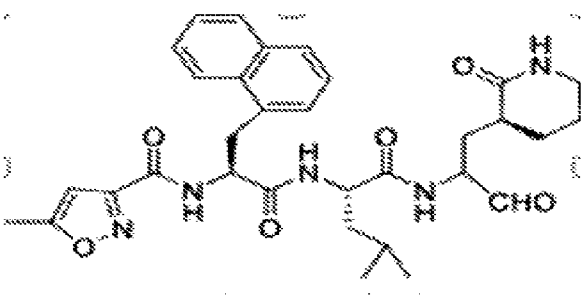


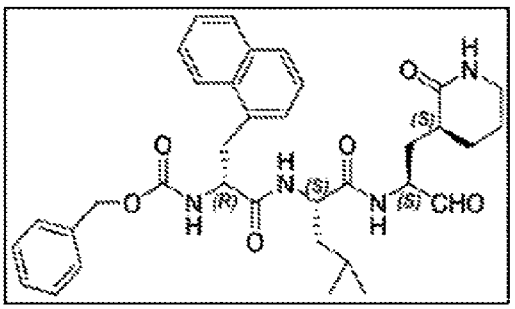


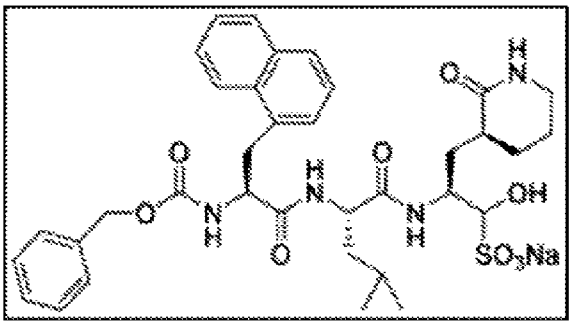


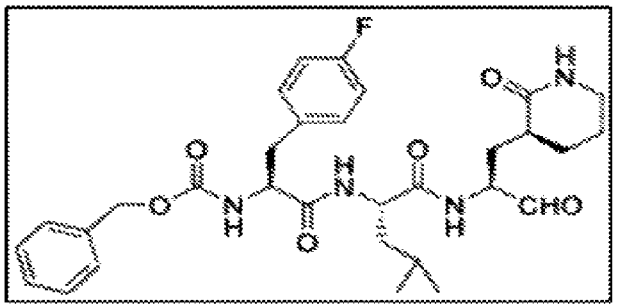
and pharmaceutically acceptable salts or prodrugs thereof.

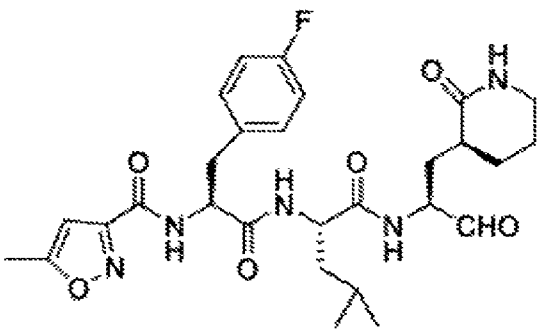
Preferred compounds include the following:

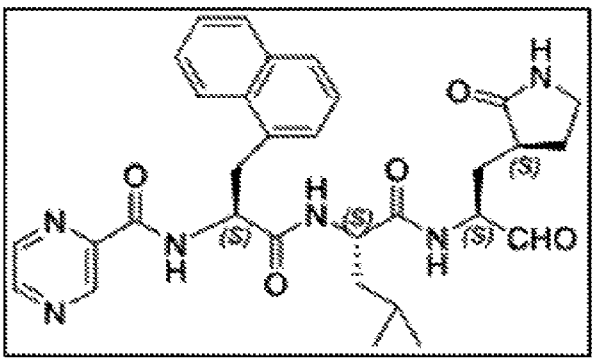












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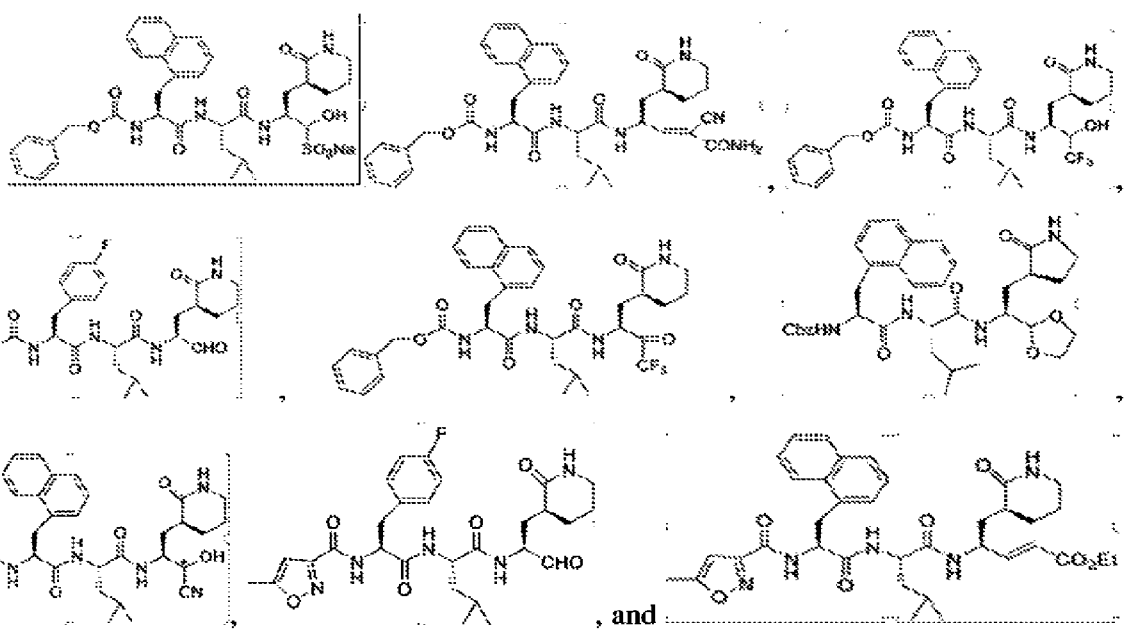
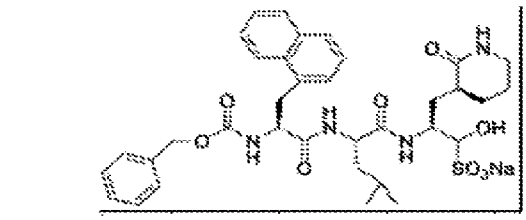
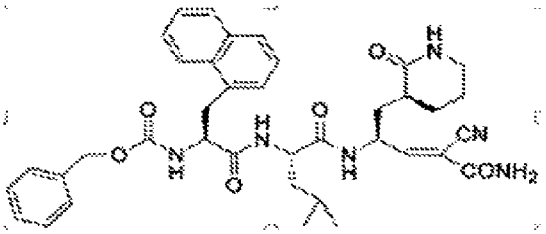
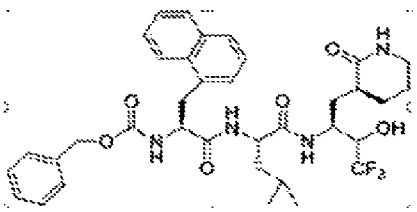
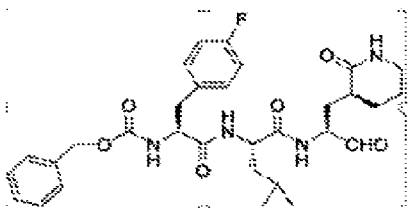
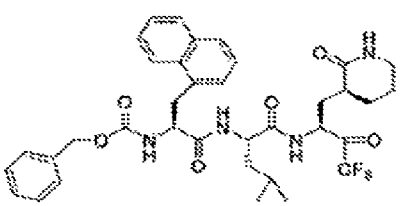
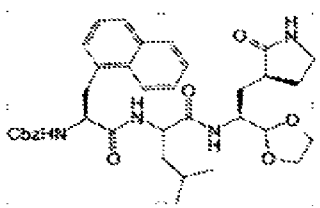
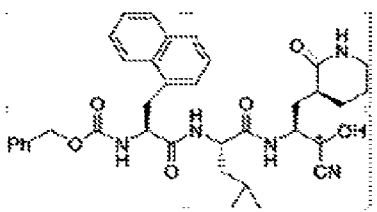
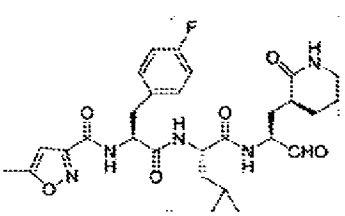
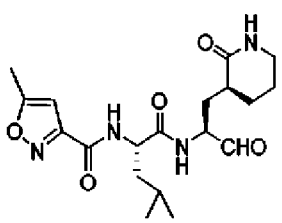
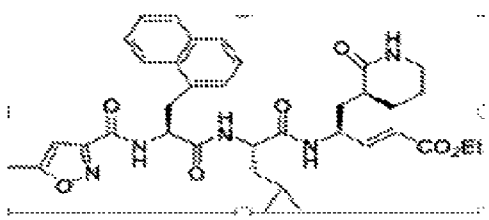
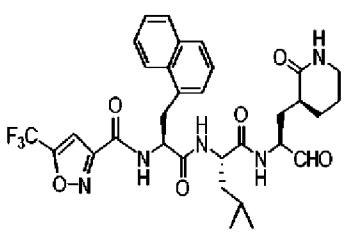
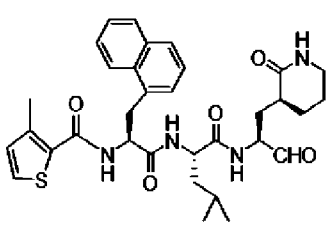
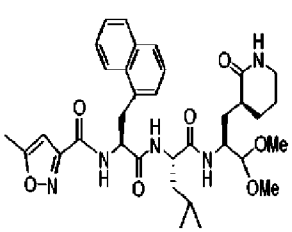
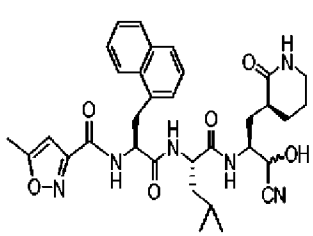
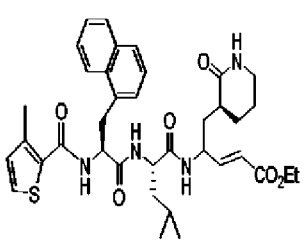
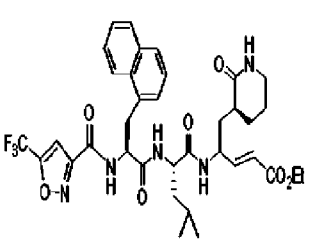
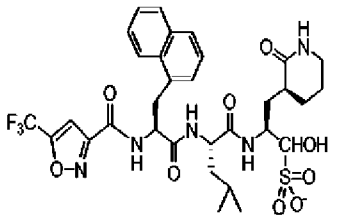
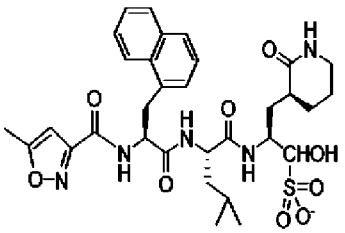


, and


, and 
, and pharmaceutically-acceptable salts and prodrugs thereof.

III. Stereoisomerism and Polymorphism

The compounds described herein can have asymmetric centers and occur as racemates, racemic mixtures, individual diastereomers or enantiomers, with all isomeric forms being included in the present invention. Compounds of the present invention having a chiral center can exist in and be isolated in optically active and racemic forms. Some compounds can exhibit polymorphism. The present invention encompasses racemic, optically-active, polymorphic, or stereoisomeric forms, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein. The optically active forms can be prepared by, for example, resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase or by enzymatic resolution. One can either purify the respective compound, then derivatize the compound to form the compounds described herein, or purify the compound themselves.

Optically active forms of the compounds can be prepared using any method known in the art, including but not limited to by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase.

Examples of methods to obtain optically active materials include at least the following.

i) physical separation of crystals: a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals

of the separate enantiomers exist, *i.e.*, the material is a conglomerate, and the crystals are visually distinct;

ii) simultaneous crystallization: a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;

iii) enzymatic resolutions: a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme;

iv) enzymatic asymmetric synthesis: a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer;

v) chemical asymmetric synthesis: a synthetic technique whereby the desired enantiomer is synthesized from an achiral precursor under conditions that produce asymmetry (*i.e.*, chirality) in the product, which can be achieved using chiral catalysts or chiral auxiliaries;

vi) diastereomer separations: a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

vii) first- and second-order asymmetric transformations: a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

viii) kinetic resolutions: this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

ix) enantiospecific synthesis from non-racemic precursors: a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

x) chiral liquid chromatography: a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase (including but not limited to via chiral HPLC). The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

xi) chiral gas chromatography: a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

xii) extraction with chiral solvents: a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent;

xiii) transport across chiral membranes: a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane that allows only one enantiomer of the racemate to pass through.

Chiral chromatography, including but not limited to simulated moving bed chromatography, is used in one embodiment. A wide variety of chiral stationary phases are commercially available.

IV. Salt or Prodrug Formulations

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid, which form a

physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate and α-glycerophosphate. Suitable inorganic salts can also be formed, including but not limited to, sulfate, nitrate, bicarbonate and carbonate salts. For certain transdermal applications, it can be preferred to use fatty acid salts of the compounds described herein. The fatty acid salts can help penetrate the stratum corneum. Examples of suitable salts include salts of the compounds with stearic acid, oleic acid, lineoleic acid, palmitic acid, caprylic acid, and capric acid.

Pharmaceutically acceptable salts can be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid, affording a physiologically acceptable anion. In those cases where a compound includes multiple amine groups, the salts can be formed with any number of the amine groups. Alkali metal (e.g., sodium, potassium or lithium) or alkaline earth metal (e.g., calcium) salts of carboxylic acids can also be made.

A prodrug is a pharmacological substance that is administered in an inactive (or significantly less active) form and subsequently metabolized in vivo to an active metabolite. Getting more drug to the desired target at a lower dose is often the rationale behind the use of a prodrug and is generally attributed to better absorption, distribution, metabolism, and/or excretion (ADME) properties. Prodrugs are usually designed to improve oral bioavailability, with poor absorption from the gastrointestinal tract usually being the limiting factor. Additionally, the use of a prodrug strategy can increase the selectivity of the drug for its intended target thus reducing the potential for off target effects.

V. Isotopes

Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. In other embodiments are examples of isotopes that are incorporated into the present compounds including isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, respectively. Certain isotopically-labeled compounds described

herein, for example those into which radioactive isotopes such as ^{2}H are incorporated, are useful in drug and/or substrate tissue distribution assays. Further, in some embodiments, substitution with isotopes such as deuterium, i.e., ^{2}H, can affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

VI. Methods of Treatment

In one embodiment, the compounds described herein can be used to prevent, treat or cure coronavirus, picornavirus infections, specifically including enterovirus infections, and/or *Hepeviridae* infections, specifically including hepatitis E infections.

The methods involve administering a therapeutically or prophylactically-effective amount of at least one compound as described herein to treat, cure or prevent an infection by, or an amount sufficient to reduce the biological activity of, a coronavirus, picornavirus, and/or Hepeviridae infection.

In one embodiment, the compounds are used to treat a patient suffering from multiple virus infections, such as hepatitis E and enterovirus (EV). The compounds can also be used to treat norovirus (noV) infections, so the combination of viral infections can include noV in addition to a coronavirus, picornovirus, and/or Hepeviridae virus.

In another embodiment, the compounds described herein can be used to inhibit a coronoviral and/or picornaviral protease (e.g., an enteroviral protease or a rhinoviral 3C protease) in a cell. The method includes contacting the cell with an effective amount of a compound described herein,

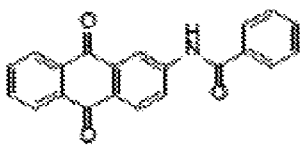
Hosts, including but not limited to humans infected with a coronavirus, picornavirus, *Hepeviridae* virus, or a gene fragment thereof, including humans co-infected with norovirus, can be treated by administering to the patient an effective amount of the active compound or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, transdermally, subcutaneously, or topically, in liquid or solid form.

VII. Combination of Alternation Therapy

In one embodiment, the compounds of the invention can be employed together with at least one other active agent, which can be an antiviral agent. In one aspect of this embodiment, the at least one other active agent is selected from the group consisting of fusion inhibitors, entry inhibitors, protease inhibitors, polymerase inhibitors, antiviral nucleosides, such as remdesivir, GS-441524, N4-hydroxycytidine, and other compounds disclosed in U.S. Patent No. 9,809,616, and their prodrugs, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2 (ACE2) inhibitors, SARS-CoV-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

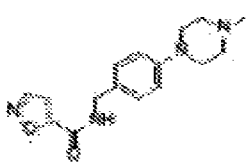
Umifenovir (also known as Arbidol) is a representative fusion inhibitor.

Representative entry inhibitors include Camostat, luteolin, MDL28170, SSAA09E2, SSAA09E1 (which acts as a cathepsin L inhibitor), SSAA09E3, and tetra-O-galloyl-β-D-glucose (TGG). The chemical formulae of certain of these compounds are provided below:



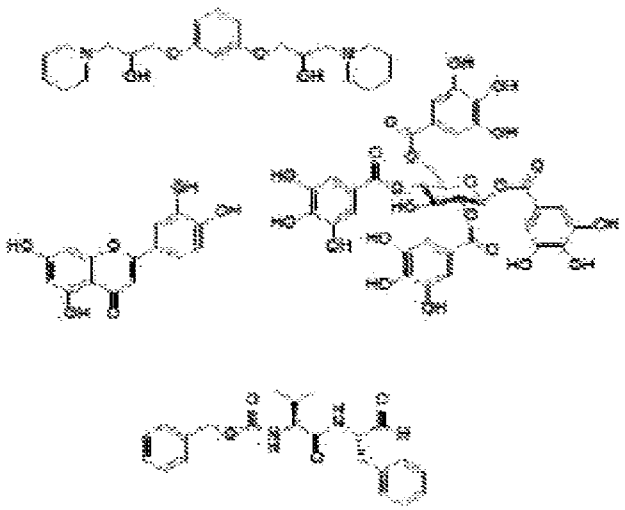
SSAA09E3

SSAA09E1

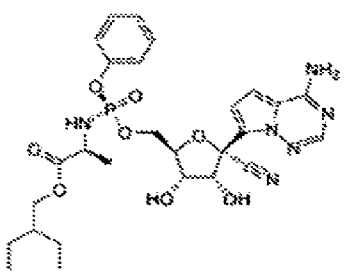


SSAA09E2

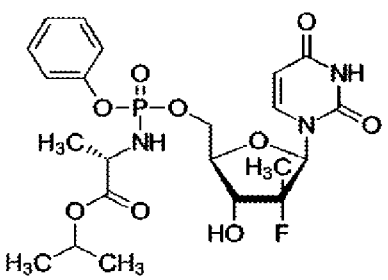
Other entry inhibitors include the following:



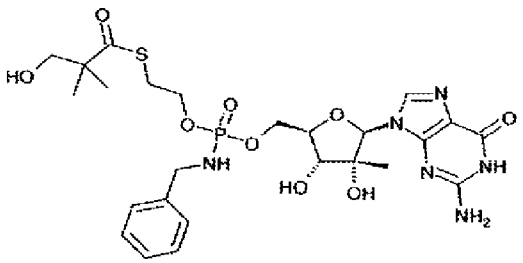
Remdesivir, Sofosbuvir, ribavirin, IDX-184 and GS-441524 have the following formulas:



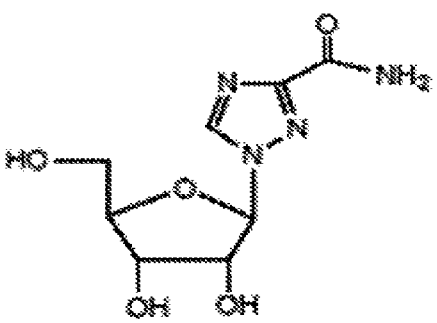
Remdesivir



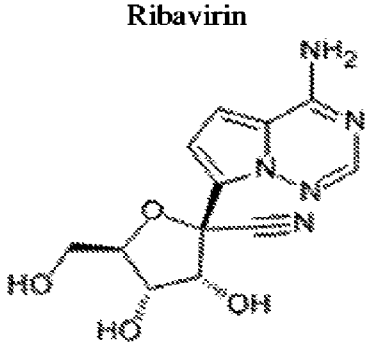
Sofosbuvir



IDX-184



Ribavirin



GS-441524

Additionally, one can administer compounds which inhibit the cytokine storm, anti-coagulants and/or platelet aggregation inhibitors that address blood clots, compounds which chelate iron ions released from hemoglobin by viruses such as COVID-19, cytochrome P-450 (CYP450) inhibitors and/or NOX inhibitors.

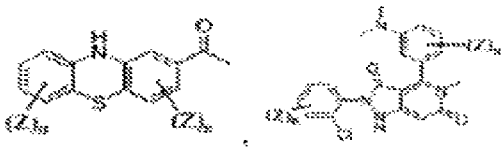
Representative NOX inhibitors are disclosed in PCT/US2018/067674, and include AEBSF, Apocyanin, DPI, GK-136901, ML171, Plumbagin, S17834, VAS2870, VAS3947,

GKT-831, GKT771, GTL003 or amido thiadiazole derivatives thereof, as described in AU2015365465, EP20140198597; and WO2015/59659, Schisandrin B, as described in CN104147001 and CN20131179455), bi-aromatic and tri-aromatic compounds described in U.S. Publication No. 2015045387, GB 20110016017, and WO201200725, methoxyflavone derivatives described in JP 2015227329, JP 20140097875, and JP 20150093939, peptides, such as NOX2ds-tat and PR-39, as described in U.S. Publication No. 2015368301, TN 2015000295, U.S. Publication No. 201514689803, U.S. Publication No. 201462013916, PCT WO 201450063, and EP 20130150187, piperazine derivatives described in U.S. Publication No. 2014194422, U.S. Patent No. 9428478, U.S. Publication No. 201214123877, U.S. Publication No. 201161496161, and PCT WO 2012US41988, pyrazole derivatives disclosed in KR101280198, KR20110025151, and KR20090082518, pyrazoline dione derivatives disclosed in HK1171748, PCT WO201054329, and EP 20090171466, pyrazolo piperidine derivatives disclosed in KR20130010109, KR20130002317, EP20100153927, PCT WO201150667, EP20100153929, and PCT WO2011IB50668, pyrazolo pyridine derivatives described in KR20170026643, HK1158948, HK1141734, HK1159096, HK1159092, EP20080164857, PCT WO200954156, PCT WO200954150, EP20080164853, PCT WO200853390, U.S. Publication No. 20070896284, EP20070109555, PCT WO 200954148, EP20080164847, PCT WO200954155, and EP20080164849, quinazoline and quinoline derivatives disclosed in EP2886120, U.S. Publication No. 2014018384, U.S. Publication No. 20100407925, EP20110836947, GB20110004600, and PCT WO 201250586, tetrahydroindole derivatives disclosed in U.S. Publication No. 2010120749, U.S. Patent No. 8,288,432, U.S. Publication No. 20080532567, EP20070109561, U.S. Publication No. 20070908414, and PCT WO 200853704, tetrahydroisoquinoline derivatives disclosed in U.S. Publication No. 2016083351, U.S. Publication No. 201414888390, U.S. Publication No. 201361818726, and PCT WO 201436402, Scopoletin, described in TW201325588 and TW20110147671, and 2,5-disubstituted benzoxazole and benzothiazole derivatives disclosed in TW201713650 and PCT WO 201554662. Representative NOX inhibitors also include those disclosed in PCT WO2011062864.

Exemplary Nox inhibitors also include 2-phenylbenzo[d]isothiazol-3(2H)-one, 2-(4-methoxyphenyl)benzo[d]isothiazol-3(2H)-one, 2-(benzo[d][1,3]dioxol-5-yl)benzo[d]isothiazol-3(2H)-one, 2-(2,4-dimethylphenyl)benzo[d]isothiazol-3(2H)-one, 2-(4-

fluorophenyl)benzo[d]isothiazol-3(2H)-one, 2-(2,4-dimethylphenyl)-5-fluorobenzo[d]isothiazol-3(2H)-one, 5-fluoro-2-(4-fluorophenyl)benzo[d]isothiazol-3(2H)-one, 2-(2-chloro-6-methylphenyl)-5-fluorobenzo[d]isothiazol-3(2H)-one, 5-fluoro-2-phenylbenzo[d]isothiazol-3(2H)-one, 2-(benzo[d][1,3]dioxol-5-yl)-5-fluorobenzo[d]isothiazol-3(2H)-one, methyl 4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, methyl 4-(5-fluoro-3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, ethyl 4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, tert-butyl 4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, methyl 2-methoxy-4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, methyl 3-chloro-4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, 4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzonitrile, methyl 2-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, 2-(4-acetylphenyl)benzo[d]isothiazol-3(2H)-one, 2-(4-nitrophenyl)benzo[d]isothiazol-3(2H)-one, 2-(4-hydroxyphenyl)benzo[d]isothiazol-3(2H)-one, methyl 6-(3-oxobenzo[d]isothiazol-2(3H)-yl)nicotinate, 6-(3-oxobenzo[d]isothiazol-2(3H)-yl)nicotinonitrile, 2-(4-(hydroxymethyl)phenyl)benzo[d]isothiazol-3(2H)-one, 2-benzylbenzo[d]isothiazol-3(2H)-one, N-methyl-4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzamide, 2-(4-hydroxyphenyl)benzo[d]isothiazol-3(2H)-one, 2-(2,4-dimethylphenyl)-l-methyl-lH-indazol-3(2H)-one, 2-(4-fluorophenyl)- 1 -methyl- 1 H-indazol-3 (2H)-one, 2-(2,4-dimethylphenyl)-lH-indazol-3(2H)-one, 1 -methyl-2-phenyl- 1 H-indazol-3 (2H)-one, 2-(l,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-phenyl-l,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-(ethylthio)-l,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-(methylthio)-l,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 5-fluoro-2-(l,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-(tert-butyl)-l,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-(4-bromophenyl)-l,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one 2-(4-methylthiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(4,5-dimethylthiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(benzo[d][1,3]dioxol-5-yl)-4,5-difluorobenzo[d][l,2]selenazol-3(2H)-one, 2-(benzo[d][l,3]dioxol-5-yl)-5-fluorobenzo[d][l,2]selenazol-3(2H)-one, 2-(2,3-dihydrobenzo[b][l,4]dioxin-6-yl)-5-fluorobenzo[d][l,2]selenazol-3(2H)-2-(4-(l,3-dioxolan-2-yl)phenyl)benzo[d][l,2]selenazol-3(2H)-one, 2-(benzo[d][l,3]dioxol-5-yl)-6, 7-dimethoxybenzo[d][l,2]selenazol-3(2H)-one, methyl 4-(3-oxobenzo[d][l,2]selenazol-2(3H)-yl)benzoate, methyl 4-(3-oxoisothiazolo[5,4-b]pyridin-2(3H)-yl)benzoate, and ethyl 4-(3-oxoisothiazol-2(3H)-yl)benzoate, and pharmaceutically acceptable salts and prodrugs thereof.

Additional representative NOX inhibitors include: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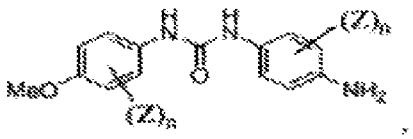
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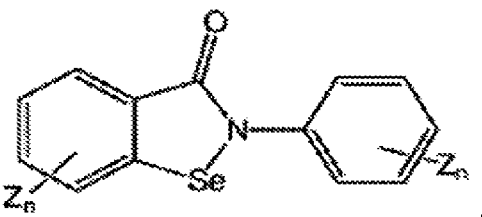
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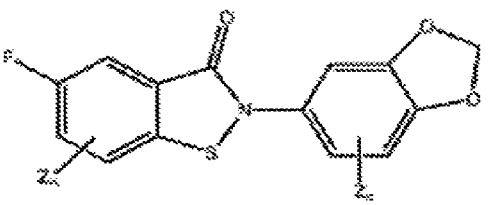
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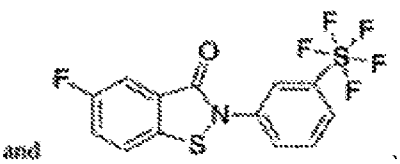

and

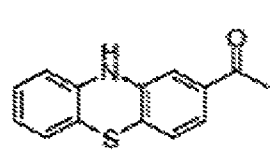
wherein

Z is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclic, alkylaryl, arylalkyl, hydroxyl, nitro, cyano, cyanoalkyl, azido, azidoalkyl, formyl, hydrazino, halo (F, Cl, Br, or 1), OR', NHR', SR', S(O)R', $S(O)_2$R', $S(O)_2$NHR', $S(O)_2$N(R')R', SF_5, COOR', COR', OCOR', NHCOR', N(COR')COR', SCOR', OCOOR', and NHCOOR', wherein each R' is independently H, a C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl , C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl, wherein the groups can be substituted with one or more substituents as defined above,

and n is an integer from 0-4,

or a pharmaceutically acceptable salt or prodrug thereof.

Specific examples of these compounds include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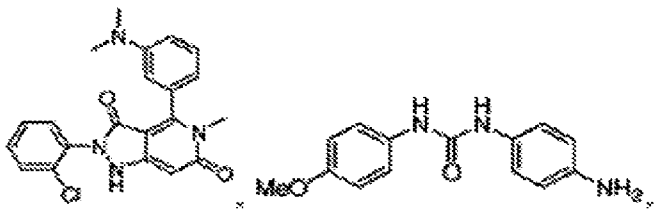

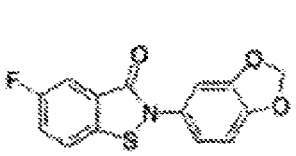

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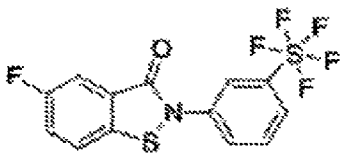


deuterated analogs thereof, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the NOX inhibitor is Ebselen, Neopterin, APBA, Diapocynin, or a deuterated analog thereof, or a pharmaceutically-acceptable salt or prodrug thereof.

In another embodiment, the NOX compounds are those disclosed in PCT WO 2010/035221.

In still another embodiment, the compounds are NOX inhibitors disclosed in PCT WO 2013/068972, which are selected from the group consisting of:

4-(2-fluoro-4-methoxyphenyl)-2-(2-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-methoxyphenyl)-5-(pyrazin-2-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(4-chlorophenyl)-2-(2-methoxyphenyl)-5-(pyrazin-2-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluoro-4-methoxyphenyl)-5-[(l-methyl-lH-pyrazol-3-yl) methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

4-(2-fluoro-5-methoxyphenyl)-2-(2-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-5-[(2-methoxypyridin-4-yl)methyl] -4-methyl-1H-pyrazo lo [4,3 -c] pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-methyl-5 -(pyridin-3-ylmethyl)-1H-pyrazo lo [4,3 -c]pyridine-3,6(2H,5H)-dione;

4-(4-chloro-2-fluorophenyl)-2-(2-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo [4,3-c] pyridine-3,6(2H,5H)-dione;

4-(5-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-3 -ylmethyl)- 1 H-pyrazo lo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-5-[(6-methoxypyridin-3-yl)methyl]-4-methyl-1H-pyrazolo[4,3-c] pyridine-3,6 (2H,5H)-dione;

4-(4-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-3-ylmethyl)-1H-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

4-(5-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

4-(2-fluoro-5-methoxyphenyl)-2-(2-methoxyphenyl)-5-[(1-methyl-1H-pyrazo-1-3-yl) methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

4-(5-chloro-2-fluorophenyl)-2-(2-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo [4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-methyl-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6 (2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(pyrazin-2-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6 (2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(4-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazo lo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-(3-methoxyphenyl)-5-[(1-methyl-1H-pyrazo-1-3-yl)methyl]-1 H-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluoro-4-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

4-(2-fluoro-4-methoxyphenyl)-2-(2-methoxyphenyl)-5-[(1-methyl-1H-pyrazo-1-3-yl) methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-[(1-methyl-1H-pyrazo-1-3-yl)methyl]-1 H-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-(3-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(4-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-[(2-methoxypyridin-4-yl)methyl]- lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluoro-4-methoxyphenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2,6-difluorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-methyl-5-[(l-methyl-lH-pyrazol-3-yl)methyl]-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(3-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-5-methyl-4-[3-(methylamino)phenyl]-1H-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(pyridin-2-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2,5-difluorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(l,3-thiazol-2-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-[(1-methyl-1H-pyrazol-3-yl) methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(3,5-dichlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(3-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-(pyridin-3-ylmethyl)-lH-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2,6-difluorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(2-fluoro-5-methoxyphenyl)-2-(2-methoxyphenyl)-5-(pyrazin-2-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2,5-difluorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione; and

2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-[(1-methyl-1H-pyrazol-3-yl) methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione.

Representative CYP450 inhibitors include, but are not limited to, amiodarone, amlodipine, apigenin, aprepitant, bergamottin (grapefruit), buprenorphine, bupropion, caffeine, cafestol, cannabidiol, celecoxib, chloramphenicol, chlorphenamine, chlorpromazine, cimetidine, cinacalcet, ciprofloxacin, citalopram, clarithromycin, clemastine, clofibrate, clomipramine, clotrimazole, cobicistat, cocaine,curcumin (turmeric), cyclizine, delavirdine, desipramine, disulfiram, diltiazem, diphenhydramine, dithiocarbamate, domperidone, doxepin, doxorubicin, duloxetine, echinacea, entacapone, erythromycin, escitalopram, felbamate, fenofibrate, flavonoids (grapefruit), fluoroquinolones (e.g., ciprofloxacin), fluoxetine, fluvoxamine, fluconazole, fluvastatin, gabapentin, gemfibrozil, gestodene, halofantrine, haloperidol, hydroxyzine, imatinib, indomethacin, indinavir, interferon, isoniazid, itraconazole, JWH-018, ketoconazole, letrozole, lovastatin, levomepromazine, memantine, methylphenidate, metoclopramide, methadone, methimazole, methoxsalen, metyrapone, mibefradil, miconazole, midodrine, mifepristone, milk thistle, moclobemide, modafinil, montelukast, moclobemide, naringenin (grapefruit), nefazodone, nelfinavir, niacin, niacinamide, nicotine, nicotinamide,nilutamide, norfloxacin, orphenadrine, paroxetine, perphenazine, pilocarpine, piperine, phenylbutazone, probenecid, promethazine, proton pump inhibitors (e.g., lansoprazole, omeprazole, pantoprazole, rabeprazole), quercetin, quinidine, ranitidine, risperidone, ritonavir, saquinavir, selegiline, sertraline, star fruit, St. John's wort, sulconazole, sulfamethoxazole, sulfaphenazole, telithromycin, teniposide, terbinafine, thiazolidinediones, thioridazine, ticlopidine, tioconazole, thiotepa, trimethoprim, topiramate, tranylcypromine, tripelennamine, valerian, valproic acid, verapamil, voriconazole, zafirlukast, and zuclopenthixol.

Representative ACE-2 inhibitors include sulfhydryl-containing agents, such as alacepril, captopril (capoten), and zefnopril, dicarboxylate-containing agents, such as enalapril (vasotec), ramipril (altace), quinapril (accupril), perindopril (coversyl), lisinopril (listril), benazepril (lotensin), imidapril (tanatril), trandolapril (mavik), and cilazapril (inhibace), and phosphonate-containing agents, such as fosinopril (fositen/monopril).

For example, when used to treat or prevent infection, the active compound or its prodrug or pharmaceutically acceptable salt can be administered in combination or alternation with another antiviral agent including, but not limited to, those of the formulae above. In general, in combination therapy, effective dosages of two or more agents are administered together, whereas during alternation therapy, an effective dosage of each agent is administered serially. The dosage will depend on absorption, inactivation and excretion rates of the drug, as well as other factors known to those of skill in the art. 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.

A number of agents for combination with the compounds described herein are disclosed in Ghosh et al., "Drug Development and Medicinal Chemistry Efforts Toward SARS-Coronavirus and Covid-19 Therapeutics," ChemMedChem 10.1002/cmdc.202000223.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include those listed below.

Compounds for Inhibiting the Cytokine Storm

Throughout its activation, the inflammatory response must be regulated to prevent a damaging systemic inflammation, also known as a "cytokine storm." A number of cytokines with anti-inflammatory properties are responsible for this, such as IL-10 and transforming growth factor β (TGF-β). Each cytokine acts on a different part of the inflammatory response. For example, products of the Th2 immune response suppress the Th1 immune response and vice versa.

By resolving inflammation, one can minimize collateral damage to surrounding cells, with little or no long-term damage to the patient. Accordingly, in addition to using the compounds described herein to inhibit the viral infection, one or more compounds which inhibit the cytokine storm can be co-administered.

Compounds which inhibit the cytokine storm include compounds that target fundamental immune pathways, such as the chemokine network and the cholinergic anti-inflammatory pathway.

JAK inhibitors, such as JAK 1 and JAK 2 inhibitors, can inhibit the cytokine storm, and in some cases, are also antiviral. Representative JAK inhibitors include those disclosed in U.S. Patent No. 10,022,378, such as Jakafi, Tofacitinib, and Baricitinib, as well as LY3009104/INCB28050, Pacritinib/SB1518, VX-509, GLPG0634, INC424, R-348, CYT387, TG 10138, AEG 3482, and pharmaceutically acceptable salts and prodrugs thereof.

Still further examples include CEP-701 (Lestaurtinib), AZD1480, INC424, R-348, CYT387, TG 10138, AEG 3482, 7-iodo-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(4-aminophenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N-(4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl) acrylamide, 7-(3-aminophenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl) acrylamide, N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, methyl 2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidine-7-carboxylate, N-(4-morpholinophenyl)-5H-pyrrolo[3,2-d]pyrimidin-2-amine, 7-(4-amino-3-methoxyphenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzene- sulfonamide, N,N-dimethyl-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, 1-ethyl-3-(2-methoxy-4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)urea, N-(4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)metha- nesulfonamide, 2-methoxy-4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)pheno- l, 2-cyano-N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)acetamide, N-(cyanomethyl)-2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidine-7-carboxamide, N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)methanesulfonamide, 1-

ethyl-3-(4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)-2-(trifluoromethoxy)phenyl)urea, N-(3-nitrophenyl)-7-phenylthieno[3,2-d]pyrimidin-2-amine, 7-iodo-N-(3-nitrophenyl)thieno[3,2-d]pyrimidin-2-amine, N1-(7-(2-ethylphenyl)thieno[3,2-d]pyrimidin-2-yl)benzene-1,3-diamine, N-tert-butyl-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, N1-(7-iodothieno[3,2-d]pyrimidin-2-yl)benzene-1,3-diamine, 7-(4-amino-3-(trifluoromethoxy)phenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(2-ethylphenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)aceta- mide, N-(cyanomethyl)-N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)methanesulfonamide, N-(cyanomethyl)-N-(4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)methanesulfonamide, N-(3-(5-methyl-2-(4-morpholinophenylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)phenyl)methanesulfonamide, 4-(5-methyl-2-(4-morpholinophenylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)b-enzenesulfonamide, N-(4-(5-methyl-2-(4-morpholinophenylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-y-l)phenyl)methanesulfonamide, 7-iodo-N-(4-morpholinophenyl)-5H-pyrrolo[3,2-d]pyrimidin-2-amine, 7-(2-isopropylphenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-bromo-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N7-(2-isopropylphenyl)-N2-(4-morpholinophenyl)thieno[3,2-d]pyrimidine-2,7-diamine, N7-(4-isopropylphenyl)-N2-(4-morpholinophenyl)thieno[3,2-d]pyrimidine-2,7-diamine, 7-(5-amino-2-methylphenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzamide, 7-iodo-N-(3-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(4-amino-3-nitrophenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(2-methoxypyridin-3-yl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, (3-(7-iodothieno[3,2-d]pyrimidin-2-ylamino)phenyl)methanol, N-tert-butyl-3-(2-(3-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, N-tert-butyl-3-(2-(3-(hydroxymethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, N-(4-morpholinophenyl)-7-(4-nitrophenylthio)-5H-pyrrolo[3,2-d]pyrimidin-2- -amine, N-tert-butyl-3-(2-(3,4,5-trimethoxyphenylamino)thieno[3,2-d]pyrimi- din-7-yl)benzenesulfonamide, 7-(4-

amino-3-nitrophenyl)-N-(3,4-dimethoxyphenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3,4-dimethoxyphenyl)-7-(2-methoxypyridin-3-yl)thieno[3,2-d]pyrimidin-2-amine, N-tert-butyl-3-(2-(3,4-dimethoxyphenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, 7-(2-aminopyrimidin-5-yl)-N-(3,4-dimethoxyphenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3,4-dimethoxyphenyl)-7-(2,6-dimethoxypyridin-3-yl)thieno[3,2-d]-pyrimidin-2-amine, N-(3,4-dimethoxyphenyl)-7-(2,4-dimethoxypyrimidin-5-yl)thieno[3,2-d]pyrim- idin-2-amine, 7-iodo-N-(4-(morpholinomethyl)phenyl)thieno[3,2-d]pyrimidin-2-amine, N-tert-butyl-3-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, 2-cyano-N-(4-methyl-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)acetamide, ethyl 3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzoate, 7-bromo-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3-(2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)acetamide, N-(cyanomethyl)-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzamide, N-tert-butyl-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzamide, N-tert-butyl-3-(2-(4-(1-ethylpiperidin-4-yloxy)phenylamino)thieno- [3,2-d]pyrimidin-7-yl)benzenesulfonamide, tert-butyl-4-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7- -yl)-1H-pyrazole-1-carboxylate, 7-bromo-N-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)thieno[3,2-d]pyrimidin- -2-amine, N-tert-butyl-3-(2-(4-((4-ethylpiperazin-1-yl)methyl)phenylamino)- thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, N-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-7-(1H-pyrazol-4-yl)thieno[3,2-d]pyrimidin-2-amine, N-(cyanomethyl)-3-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimi- din-7-yl)benzamide, N-tert-butyl-3-(2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)thieno[3,2-d]-pyrimidin-7-yl)benzenesulfonamide, tert-butyl pyrrolidin-1-yl)ethoxy)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzylcarb- amate, 3-(2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, 7-(3-chloro-4-fluorophenyl)-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)thieno-[3,2-d]pyrimidin-2-amine, tert-butyl 4-(2-(4-(1-ethylpiperidin-4-yloxy)phenylamino)thieno[3,2-d]pyrimidin-7-yl-)-1H-pyrazole-1-carboxylate, 7(benzo[d][1,3]dioxol-5-yl)-N-(4-(morpholinomethyl)phenyl)thieno[3,2-d]pyrimidin-2-amine, tert-butyl 5-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)-1H-indole-1-carboxylate, 7-(2-aminopyrimidin-5-yl)-N-(4-(morpholinomethyl)phenyl)thieno[3,2-d]pyrimidin-2-amine, tert-butyl 4-(2-(-4-(morpholinomethyl)phenylamino)thieno[3,2-

d]pyrimidin-7-yl)-5,6-di-hydropyridine-1(2H)-carboxylate, tert-butyl morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzylcarbamate, N-(3-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)phen- yl)acetamide, N-(4-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)phen- yl)acetamide, N-(3-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)phen- yl)methanesulfonamide, 7-(4-(4-methylpiperazin-1-yl)phenyl)-N-(4-(morpholinomethyl)phenyl)thieno-[3,2-d]pyrimidin-2-amine, N-(2-methoxy-4-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)acetamide, 7-bromo-N-(3,4,5-trimethoxyphenyl)thieno[3,2-d]pyrimidin-2-amine, (3-(2-(3,4,5-trimethoxyphenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)met- hanol, (4-(2-(3,4,5-trimethoxyphenylamino)thieno[3,2-d]pyrimidin-7-yl)phen-yl)methanol, (3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)methanol, (4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)methanol, N-(pyrrolidin-1-yl)ethoxy)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzyl)methanesulfonamide, tert-butyl morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzylcarbamate, N-(4-(morpholinomethyl)phenyl)-7-(3-(piperazin-1-yl)phenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(6-(2-morpholinoethylamino)pyridin-3-yl)-N-(3,4,5-trimethoxyphenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(2-ethylphenyl)-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(4-(aminomethyl)phenyl)-N-(4-(morpholinomethyl)phenyl)thieno[3,2-d]pyrimidin-2-amine, N-(4-(1-ethylpiperidin-4-yloxy)phenyl)-7-(1H-pyrazol-4-yl)thieno[3,2-d]pyrimidin-2-amine, N-(2,4-dimethoxyphenyl)-7-phenylthieno[3,2-d]pyrimidin-2-amine, 7-bromo-N-(3,4-dimethoxyphenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3,4-dimethoxyphenyl)-7-phenylthieno[3,2-d]pyrimidin-2-amine, and pharmaceutically acceptable salts and prodrugs thereof.

HMGB1 antibodies and COX-2 inhibitors can be used, which downregulate the cytokine storm. Examples of such compounds include Actemra (Roche). Celebrex (celecoxib), a COX-2 inhibitor, can be used. IL-8 (CXCL8) inhibitors can also be used.

Chemokine receptor CCR2 antagonists, such as PF-04178903 can reduce pulmonary immune pathology.

Selective α7Ach receptor agonists, such as GTS-21 (DMXB-A) and CNI-1495, can be used. These compounds reduce TNF-α. The late mediator of sepsis, HMGB1, downregulates IFN-γ pathways, and prevents the LPS-induced suppression of IL-10 and STAT 3 mechanisms.

Compounds for Treating or Preventing Blood Clots

Viruses that cause respiratory infections, including Coronaviruses such as Covid-19, can be associated with pulmonary blood clots, and blood clots that can also do damage to the heart.

The compounds described herein can be co-administered with compounds that inhibit blood clot formation, such as blood thinners, or compounds that break up existing blood clots, such as tissue plasminogen activator (TPA), Integrilin (eptifibatide), abciximab (ReoPro) or tirofiban (Aggrastat).

Blood thinners prevent blood clots from forming, and keep existing blood clots from getting larger. There are two main types of blood thinners. Anticoagulants, such as heparin or warfarin (also called Coumadin), slow down biological processes for producing clots, and antiplatelet aggregation drugs, such as Plavix, aspirin, prevent blood cells called platelets from clumping together to form a clot.

By way of example, Integrilin® is typically administered at a dosage of 180 mcg/kg intravenous bolus administered as soon as possible following diagnosis, with 2 mcg/kg/min continuous infusion (following the initial bolus) for up to 96 hours of therapy.

Representative platelet aggregation inhibitors include glycoprotein IIB/IIIA inhibitors, phosphodiesterase inhibitors, adenosine reuptake inhibitors, and adenosine diphosphate (ADP) receptor inhibitors. These can optionally be administered in combination with an anticoagulant.

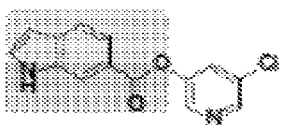
Representative anti-coagulants include coumarins (vitamin K antagonists), heparin and derivatives thereof, including unfractionated heparin (UFH), low molecular weight heparin (LMWH), and ultra-low-molecular weight heparin (ULMWH), synthetic pentasaccharide inhibitors of factor Xa, including Fondaparinux, Idraparinux, and Idrabiotaparinux, directly acting oral anticoagulants (DAOCs), such as dabigatran, rivaroxaban, apixaban, edoxaban and

betrixaban, and antithrombin protein therapeutics/thrombin inhibitors, such as bivalent drugs hirudin, lepirudin, and bivalirudin and monovalent argatroban.

Representative platelet aggregation inhibitors include pravastatin, Plavix (clopidogrel bisulfate), Pletal (cilostazol), Effient (prasugrel), Aggrenox (aspirin and dipyridamole), Brilinta (ticagrelor), caplacizumab, Kengreal (cangrelor), Persantine (dipyridamole), Ticlid (ticlopidine), Yosprala (aspirin and omeprazole).

Small Molecule Covalent CoV 3CLpro Inhibitors

Representative small molecule covalent CoV 3CLpro inhibitors include the following compounds: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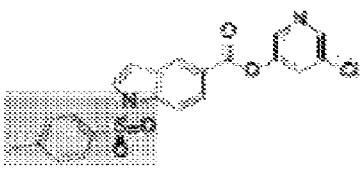
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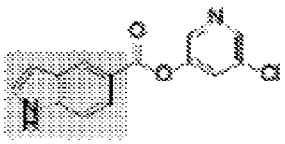
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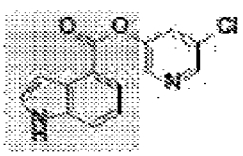

Non-Covalent CoV 3CLpro Inhibitors

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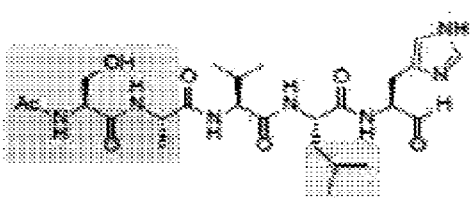
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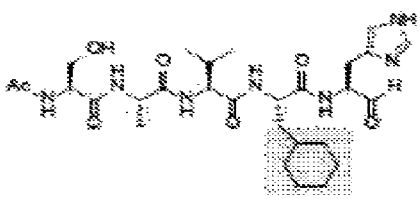
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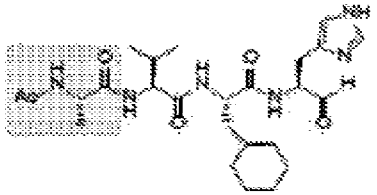
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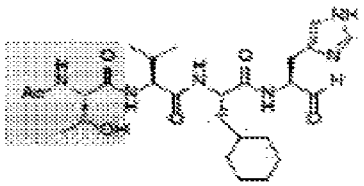
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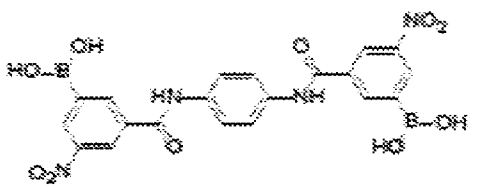
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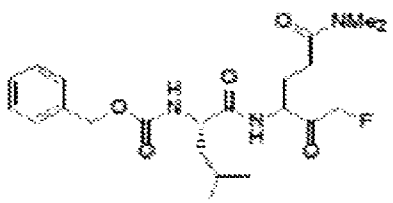
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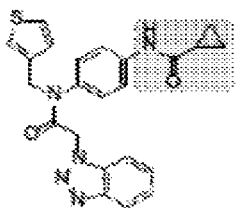
SARS-CoV PLpro Inhibitors

Representative SARS-Cov PLpro inhibitors include the following: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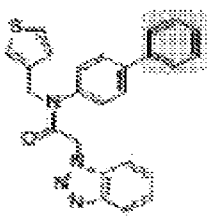
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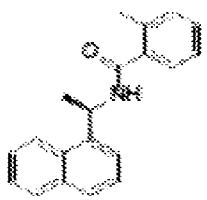
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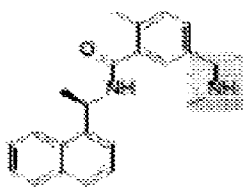
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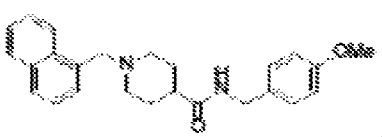
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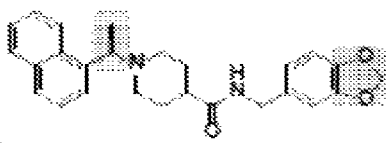
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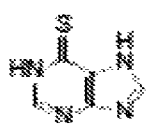
Additional compounds include the following: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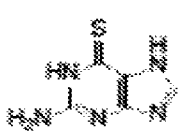
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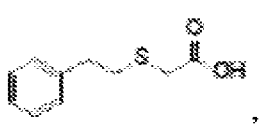
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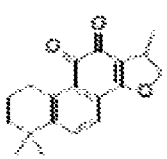
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Additional Compounds that can be Used

Additional compounds and compound classes that can be used in combination therapy include the following: Antibodies, including monoclonal antibodies (mAb), Arbidol (umifenovir), Actemra (tocilizumab), APN01 (Aperion Biologics), ARMS-1 (which includes Cetylpyridinium chloride (CPC)), ASC09 (Ascletis Pharma), AT-001 (Applied Therapeutics Inc.) and other aldose reductase inhibitors (ARI), ATYR1923 (aTyr Pharma, Inc.), Aviptadil (Relief Therapeutics), Azvudine, Bemcentinib, BLD-2660 (Blade Therapeutics), Bevacizumab, Brensocatib, Calquence (acalabrutinib), Camostat mesylate (a TMPRSS2 inhibitor), Camrelizumab, CAP-1002 (Capricor Therapeutics), CD24Fcm, Clevudine, (OncoImmune), CM4620-IE (CalciMedica Inc., CRAC channel inhibitor), Colchicine, convalescent plasma, CYNK-001 (Sorrento Therapeutics), DAS181 (Ansun Pharma), Desferal, Dipyridamole (Persantine), Dociparstat sodium (DSTAT), Duvelisib, Eculizumab, EIDD-2801 (Ridgeback Biotherapeutics), Emapalumab, Fadraciclib (CYC065) and seliciclib (roscovitine) (Cyclin-dependent kinase (CDK) inhibitors), Farxiga (dapagliflozin), Favilavir/Favipiravir/T-705/Avigan, Galidesivir, Ganovo (danoprevir), Gilenya (fingolimod) (sphingosine 1-phosphate receptor modulator), Gimsilumab, IFX-1, Ilaris (canakinumab), intravenous immunoglobulin, Ivermectin (importin α/β inhibitor), Kaletra/Aluvia (lopinavir/ritonavir), Kevzara (sarilumab), Kineret (anakinra), LAU-7b (fenretinide), Lenzilumab, Leronlimab (PRO 140), LY3127804 (an anti-Ang2 antibody), Leukine (sargramostim, a granulocyte macrophage colony stimulating factor), Losartan, Valsartan, and Telmisartan (Angiotensin II receptor antagonists), Meplazumab, Metablok (LSALT peptide, a DPEP1 inhibitor), Methylprednisolone and other corticosteroids, MN-166 (ibudilast, Macrophage migration inhibitory factor (MIF) inhibitor), MRx-4DP0004 (a strain of bifidobacterium breve, 4D Pharma), Nafamostat (a serine protease inhibitor), Neuraminidase inhibitors like Tamiflu (oseltamivir), Nitazoxanide (nucleocapsid (N) protein inhibitor), Nivolumab, OT-101 (Mateon), Novaferon (man-made Interferon), Opaganib (yeliva) (Sphingosine kinase-2 inhibitor), Otilimab, PD-1 blocking antibody, peginterferons, such as peginterferon lambda, Pepcid (famotidine), Piclidenoson (A3 adenosine receptor agonist), Prezcobix (darunavir), PUL-042 (Pulmotect, Inc., toll-like receptor (TLR) binder), Rebif (interferon beta-1a), RHB-107 (upamostat) (serine protease inhibitor, RedHill Biopharma Ltd.), Selinexor (selective inhibitor of nuclear export (SINE)), SNG001 (Synairgen, inhaled interferon beta-1a), Solnatide, stem cells, including mesenchymal stem cells, MultiStem (Athersys), and PLX (Pluristem Therapeutics), Sylvant

(siltuximab), Thymosin, TJM2 (TJ003234), Tradipitant (neurokinin-1 receptor antagonist), Truvada (emtricitabine and tenofovir), Ultomiris (ravulizumab-cwvz), Vazegepant (CGRP receptor antagonist or blocker), and Xofluza (baloxavir marboxil).

Repurposed Antiviral Agents

A number of pharmaceutical agents, including agents active against other viruses, have been evaluated against Covid-19, and found to have activity. Any of these compounds can be combined with the compounds described herein. Representative compounds include lopinavir, ritonavir, niclosamide, promazine, PNU, UC2, cinanserin (SQ 10,643), Calmidazolium (C3930), tannic acid, 3-isotheaflavin-3-gallate, theaflavin-3,3'-digallate, glycyrrhizin, S-nitroso-N-acetylpenicillamine, nelfinavir, niclosamide, chloroquine, hydroxychloroquine, 5-benzyloxygramine, ribavirin, Interferons, such as Interferon (IFN)-α, IFN-β, and pegylated versions thereof, as well as combinations of these compounds with ribavirin, chlorpromazine hydrochloride, triflupromazine hydrochloride, gemcitabine, imatinib mesylate, dasatinib, and imatinib.

VIII. Pharmaceutical Compositions

Hosts, including but not limited to humans, infected with a coronavirus, picornavirus, including enterovirus, and/or Hepeviridae virus, including hepatitis E virus, and, optionally, co-infected with norovirus, can be treated by administering to the patient an effective amount of the active compound or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, topically, or by inhalation or other form of delivery to the pulmonary tract, in liquid or solid form.

A preferred dose of the compound for will be in the range of between about 0.01 and about 10 mg/kg, more generally, between about 0.1 and 5 mg/kg, and, preferably, between about 0.5 and about 2 mg/kg, of body weight of the recipient per day. The effective dosage

range of the pharmaceutically acceptable salts and prodrugs can be calculated based on the weight of the parent compound to be delivered. If the salt or prodrug exhibits activity in itself, the effective dosage can be estimated as above using the weight of the salt or prodrug, or by other means known to those skilled in the art.

The compound is conveniently administered in unit any suitable dosage form, including but not limited to but not limited to one containing 7 to 600 mg, preferably 70 to 600 mg of active ingredient per unit dosage form. An oral dosage of 1-400 mg is usually convenient.

The concentration of active compound in the drug composition will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. 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 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, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient can be administered at once, or can be divided into a number of smaller doses to be administered at varying intervals of time.

Oral Formulations

A preferred mode of administration of the active compound is oral, although for certain patients a sterile injectable form can be given sc, ip or iv. Oral compositions will generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum

tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, unit dosage forms can contain various other materials that modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup can contain, in addition to the active compound(s), sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable prodrug or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti- inflammatories or other antiviral compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid; buffers, such as acetates, citrates or phosphates, and agents for the adjustment of tonicity, such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

Transdermal Formulations

In some embodiments, the compositions are present in the form of transdermal formulations, such as that used in the FDA-approved agonist rotigitine transdermal (Neupro patch). Another suitable formulation is that described in U.S. Publication No. 20080050424, entitled "Transdermal Therapeutic System for Treating Parkinsonism." This formulation

includes a silicone or acrylate-based adhesive, and can include an additive having increased solubility for the active substance, in an amount effective to increase dissolving capacity of the matrix for the active substance.

The transdermal formulations can be single-phase matrices that include a backing layer, an active substance-containing self-adhesive matrix, and a protective film to be removed prior to use. More complicated embodiments contain multiple-layer matrices that may also contain non-adhesive layers and control membranes. If a polyacrylate adhesive is used, it can be crosslinked with multivalent metal ions such as zinc, calcium, aluminum, or titanium ions, such as aluminum acetylacetonate and titanium acetylacetonate.

When silicone adhesives are used, they are typically polydimethylsiloxanes. However, other organic residues such as, for example, ethyl groups or phenyl groups may in principle be present instead of the methyl groups. Because the active compounds are amines, it may be advantageous to use amine-resistant adhesives. Representative amine- resistant adhesives are described, for example, in EP 0 180 377.

Representative acrylate-based polymer adhesives include acrylic acid, acrylamide, hexylacrylate, 2-ethylhexylacrylate, hydroxyethylacrylate, octylacrylate, butylacrylate, methylacrylate, glycidylacrylate, methacrylic acid, methacrylamide, hexylmethacrylate, 2-ethylhexylmethacrylate, octylmethacrylate, methylmethacrylate, glycidylmethacrylate, vinylacetate, vinylpyrrolidone, and combinations thereof.

The adhesive must have a suitable dissolving capacity for the active substance, and the active substance most be able to move within the matrix, and be able to cross through the contact surface to the skin. Those of skill in the art can readily formulate a transdermal formulation with appropriate transdermal transport of the active substance.

Certain pharmaceutically acceptable salts tend to be more preferred for use in transdermal formulations, because they can help the active substance pass the barrier of the stratum corneum. Examples include fatty acid salts, such as stearic acid and oleic acid salts. Oleate and stearate salts are relatively lipophilic, and can even act as a permeation enhancer in the skin.

Permeation enhancers can also be used. Representative permeation enhancers include fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerol or its fatty acid esters, N-methylpyrrolidone, terpenes such as limonene, alpha-pinene, alpha- terpineol, carvone, carveol, limonene oxide, pinene oxide, and 1,8-eucalyptol.

The patches can generally be prepared by dissolving or suspending the active agent in ethanol or in another suitable organic solvent, then adding the adhesive solution with stirring. Additional auxiliary substances can be added either to the adhesive solution, the active substance solution or to the active substance-containing adhesive solution. The solution can then be coated onto a suitable sheet, the solvents removed, a backing layer laminated onto the matrix layer, and patches punched out of the total laminate.

Formulations for Pulmonary Administration

In some embodiments, the compounds are administered to the pulmonary tract (i.e., via pulmonary administration). In one specific embodiment, pulmonary administration comprises inhalation of the compounds, typically in the form of particles or droplets, such as by nasal, oral inhalation, or both. The particles or droplets can be administered in two or more separate administrations (doses).

In one aspect of this embodiment, particles may be formulated as an aerosol (i.e.: liquid droplets of a stable dispersion or suspension of particles which include one or more of the compounds described herein in a gaseous medium). Particles delivered by aerosol may be deposited in the airways by gravitational sedimentation, inertial impaction, and/or diffusion. Any suitable device for generating the aerosol may be used, including but not limited to pressured meter inhalers (pMDI), nebulizers, dry powder inhalers (DPI), and soft-mist inhalers.

In one specific embodiment, the methods comprise inhalation of particles including one or more of the compounds described herein aerosolized via nebulization. Nebulizers generally use compressed air or ultrasonic power to create inhalable aerosol droplets of the particles or suspensions thereof. In this embodiment, the nebulizing results in pulmonary delivery to the subject of aerosol droplets of the particles or suspension thereof.

In another embodiment, the methods comprise inhalation of particles aerosolized via a pMDI, wherein the particles or suspensions thereof are suspended in a suitable propellant system (including but not limited to hydrofluoroalkanes (HFAs) containing at least one liquefied gas in a pressurized container sealed with a metering valve. Actuation of the valve results in delivery of a metered dose of an aerosol spray of the particles or suspensions thereof.

Biodegradable particles can be used for the controlled-release and delivery of the compounds described herein. Aerosols for the delivery of therapeutic agents to the respiratory tract have been developed. Adjei, A. and Garren, J. Pharm Res. 7, 565-569 (1990); and Zanen, P. and Lamm, J.-W. J. Int. J. Pharm. 114, 111-115 (1995).

The respiratory tract encompasses the upper airways, including the oropharynx and larynx, followed by the lower airways, which include the trachea followed by bifurcations into the bronchi and bronchioli. The upper and lower airways are called the conducting airways. The terminal bronchioli then divide into respiratory bronchioli which then lead to the ultimate respiratory zone, the alveoli, or deep lung. Gonda, I. "Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract," in Critical Reviews in Therapeutic Drug Carrier Systems 6:273-313, 1990. The deep lung, or alveoli, are the primary target of inhaled therapeutic aerosols for systemic drug delivery.

Accordingly, it can be important to deliver antiviral particles to the deep lung (i.e., the alveolar regions of the lung). Relatively large particles tend to get trapped in the oropharyngeal cavity, which can lead to excessive loss of the inhaled drug. Relatively smaller particles can be delivered to the deep lung, but can be phagocytosed. One way to deliver relatively large particles (sized to avoid phagocytosis), which are light enough to avoid excessive entrapment in the oropharyngeal cavity, is to use porous particles.

In one embodiment, the particles for delivering the compounds described herein to the alveolar regions of the lung are porous, "aerodynamically-light" particles, as described in U.S. Patent No. 6,977,087. Aerodynamically light particles can be made of a biodegradable material, and typically have a tap density less than 0.4 g/cm^{3}and a mass mean diameter between 5 μm and 30 μm. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of a functionalized polyester graft

copolymer consisting of a linear alpha-hydroxy-acid polyester backbone having at least one amino acid group incorporated herein and at least one poly(amino acid) side chain extending from an amino acid group in the polyester backbone. In one embodiment, aerodynamically light particles having a large mean diameter, for example greater than 5 μm, can be used for enhanced delivery of one or more of the compounds described herein to the alveolar region of the lung.

Nanoparticulate Compositions

The compounds described herein can also be administered in the form of nanoparticulate compositions.

In one embodiment, the controlled release nanoparticulate formulations comprise a nanoparticulate active agent to be administered and a rate-controlling polymer which functions to prolong the release of the agent following administration. In this embodiment, the compositions can release the active agent, following administration, for a time period ranging from about 2 to about 24 hours or up to 30 days or longer. Representative controlled release formulations including a nanoparticulate form of the active agent are described, for example, in U.S. Patent No. 8,293,277.

Nanoparticulate compositions comprise particles of the active agents described herein, having a non-crosslinked surface stabilizer adsorbed onto, or associated with, their surface.

The average particle size of the nanoparticulates is typically less than about 800 nm, more typically less than about 600 nm, still more typically less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, or less than about 50 nm. In one aspect of this embodiment, at least 50% of the particles of active agent have an average particle size of less than about 800, 600, 400, 300, 250, 100, or 50 nm, respectively, when measured by light scattering techniques.

A variety of surface stabilizers are typically used with nanoparticulate compositions to prevent the particles from clumping or aggregating. Representative surface stabilizers are selected from the group consisting of gelatin, lecithin, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate,

cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, poloxamers, poloxamines, poloxamine 908, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, an alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), SA9OHCO, decanoyl-N-methylglucamide, n-decyl -D-glucopyranoside, n-decyl-D- maltopyranoside, n-dodecyl-D-glucopyranoside, n-dodecyl-D-maltoside, heptanoyl-N-methylglucamide, n-heptyl-D-glucopyranoside, n-heptyl-D-thioglucoside, n-hexyl-D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl-D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl-D-glucopyranoside, and octyl-D-thioglucopyranoside. Lysozymes can also be used as surface stabilizers for nanoparticulate compositions. Certain nanoparticles such as poly(lactic-co-glycolic acid) (PLGA)-nanoparticles are known to target the liver when given by intravenous (IV) or subcutaneously (SQ).

In one embodiment, the nanoparticles or other drug delivery vehicles are targeted to the liver. One such type of liver-targeted drug delivery vehicle is described in Park, et al., Mol Imaging. Feb 2011; 10(1): 69–77, and uses Glypican-3 (GPC3) as a molecular target. Park taught using this target for hepatocellular carcinoma (HCC), a primary liver cancer frequently caused by chronic persistent hepatitis.

In one aspect of this embodiment, this drug delivery vehicle is also used to target therapeutics to the liver to treat viral infections. Further, since the compounds described herein have anti-cancer uses, this type of system can target the compounds to the liver and treat liver cancers. GPC3 is a heparan sulfate proteoglycan that is not expressed in normal adult tissues, but significantly over-expressed in up to 80% of human HCC's. GPC3 can be targeted, for example, using antibody-mediated targeting and binding (See Hsu, et al., Cancer Res. 1997; 57:5179–84).

Another type of drug delivery system for targeting the liver is described in U.S. Patent No. 7,304,045. The '045 patent discloses a dual-particle tumor or cancer targeting system that includes a first ligand-mediated targeting nanoparticle conjugated with galactosamine, with the ligand being on a target cell. The first nanoparticle includes poly(γ-glutamic acid)/poly(lactide) block copolymers and n antiviral compound, which in this case is a compound described herein, and in the '045 patent, was gancyclovir. A second nanoparticle includes poly(γ-glutamic acid)/poly(lactide) block copolymers, an endothelial cell-specific promoter, and a (herpes-simplex-virus)-(thymidine kinase) gene constructed plasmid, and provides enhanced permeability and retention-mediated targeting. The first and said second nanoparticles are mixed in a solution configured for delivering to the liver. When the disorder to be treated is a liver tumor or cancer, the delivery can be directly to, or adjacent to, the liver tumor or cancer.

Representative rate controlling polymers into which the nanoparticles can be formulated include chitosan, polyethylene oxide (PEO), polyvinyl acetate phthalate, gum arabic, agar, guar gum, cereal gums, dextran, casein, gelatin, pectin, carrageenan, waxes, shellac, hydrogenated vegetable oils, polyvinylpyrrolidone, hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropyl methylcelluose (HPMC), sodium carboxymethylcellulose (CMC), poly(ethylene) oxide, alkyl cellulose, ethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydrophilic cellulose derivatives, polyethylene glycol, polyvinylpyrrolidone, cellulose acetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, polyvinyl acetaldiethylamino acetate, poly(alkylmethacrylate), poly(vinyl acetate), polymers derived from acrylic or methacrylic acid and their respective esters, and copolymers derived from acrylic or methacrylic acid and their respective esters.

Methods of making nanoparticulate compositions are described, for example, in U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Nanoparticulate compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" U.S. Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticulate NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat.

No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate

Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,428,814 for "Bioadhesive nanoparticulate compositions having cationic surface stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" and U.S. Pat. No. 6,432,381 for "Methods for targeting drug delivery to the upper and/or lower gastrointestinal tract," all of which are specifically incorporated by reference. In addition, U.S. Patent Application No. 20020012675 A1, published on Jan. 31, 2002, for "Controlled Release Nanoparticulate Compositions," describes nanoparticulate compositions, and is specifically incorporated by reference.

The nanoparticle formulations including the compounds described herein, and also in the form of a prodrug or a salt, can be used to treat or prevent infections by coronaviruses, picornaviruses, and/or viruses in the *Hepeviridae* family, which includes the hepatis E virus.

Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water- Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

Controlled Release Formulations

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including but not limited to implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters and polylactic acid. For example, enterically coated compounds can be used to protect cleavage by stomach acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Suitable materials can also be obtained commercially.

Liposomal suspensions (including but not limited to liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in US Pat. No. 4,522,811 (incorporated by reference). For example, liposome formulations can be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

The terms used in describing the invention are commonly used and known to those skilled in the art. As used herein, the following abbreviations have the indicated meanings:

Boc_2O	Di-tert-butyl dicarbonate
CbzCl	Benzyl chloroformate
CDI	N,N'-Carbonyldiimidazole
DCE	dichloroethane
DCM	Dichloromethane
DIPEA	diisopropyl ethyl amine (Hünig's base)

DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride
Et_3N	Triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
h	hour
HOBt	Hydroxybenzotriazole
KOAC	Potassium acetate
LiHMDS	Lithium bis(trimethylsilyl)amide
M	molar
mCPBA	meta-Chloroperoxybenzoic acid
MeOH	Methanol
$MePPh_3Br$	Methyltriphenylphosphonium bromide
MsCl	Methanesulfonyl chloride
min	minute
$Py.SO_3$	Sulfur trioxide pyridine complex
rt or RT	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin layer chromatography
$TMSCF_3$	trimethyl(trifluoromethyl)silane

NEED TO ADD AEROSOL (inhalable therapeutic)

FOR RESPIRATORY VIRUSES

IX. General Methods for Preparing Active Compounds

Methods for the facile preparation of active compounds are known in the art and result from the selective combination of known methods. The compounds disclosed herein can be prepared as described in detail below, or by other methods known to those skilled in the art. It will be understood by one of ordinary skill in the art that variations of detail can be made without departing from the spirit and in no way limiting the scope of the present invention.

The various reaction schemes are summarized below.

Scheme 1 is a non-limiting example of the synthesis of active compounds of the present invention, and in particular, a synthetic approach to compound **A**.

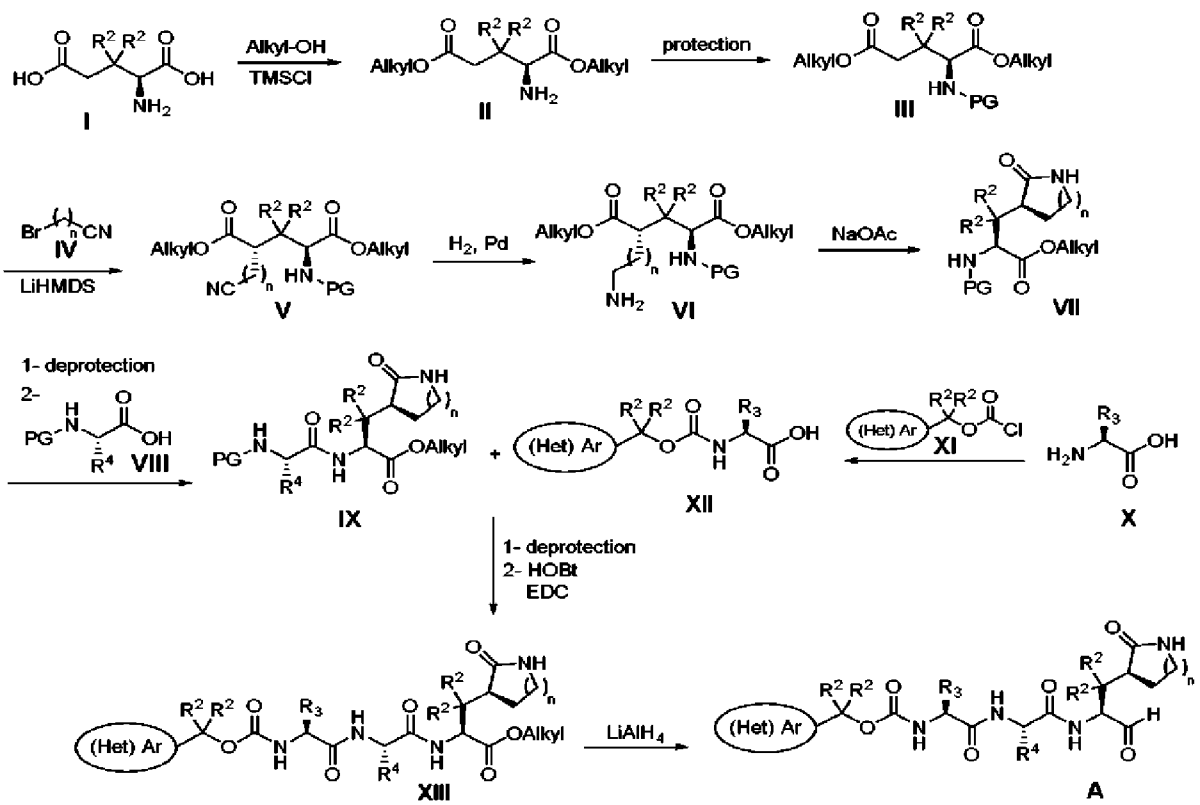
Scheme 2 is a non-limiting example of the synthesis of intermediates of the present invention, and in particular, a synthetic approach to compound **XVI**, **XVIII**, **XIX** and **XXI**.

Scheme 3 is a non-limiting example of the synthesis of active compounds of the present invention, and in particular, a synthetic approach to compound **B-D**.

Scheme 4 is a non-limiting example of the synthesis of active compounds of the present invention, and in particular, a synthetic approach to compound **E**.

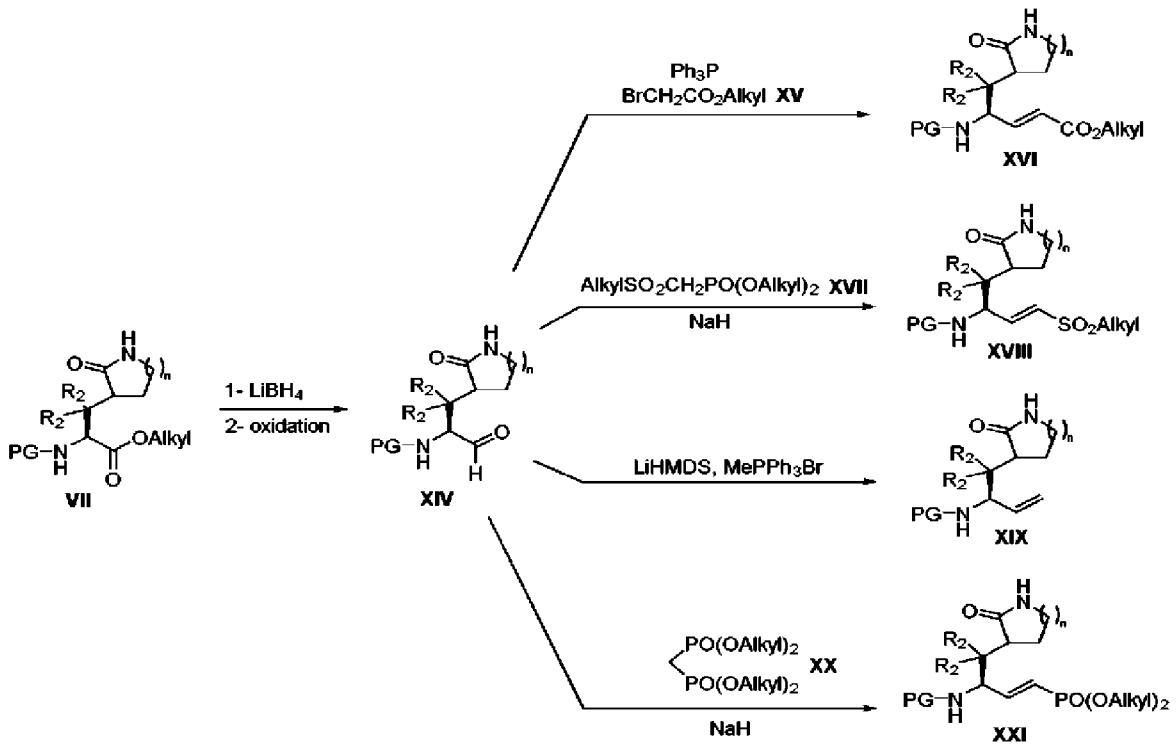
Compounds of formula **A** can be prepared by first reaction of an amino acid derivative of general formula **I** with an alcohol. Intermediate **II** can be then N-protected for example, by treatment with Boc_2O in the presence of a base such as Et_3N and then reacted with a compound of general formula **IV** in presence of a base such as LiHMDS. Cyano derivative of general formula **V** can be then reduced and finaly cyclized to give **VII**. Intermediate **VII** can be deprotected for example, in the presence of TFA when Boc was used as a protecting group, and reacted with an amino acid of general formula **VIII** in the presence

of peptide coupling reagents like EDC and HOBt. After deprotection for example, in the presence of TFA when Boc was used as a protecting group, compound of general formula **IX** can be reacted in presence peptide coupling reagents like EDC and HOBt with compound **XII**, prepared by reaction of amino acid of general formula **X** and halogenated reagent **XI** in the presence of a base such as $NaHCO_3$. Esters of general formula **XIII** can then be reduced with, for instance, $LiAlH_4$ to give compounds of general formula **A**.



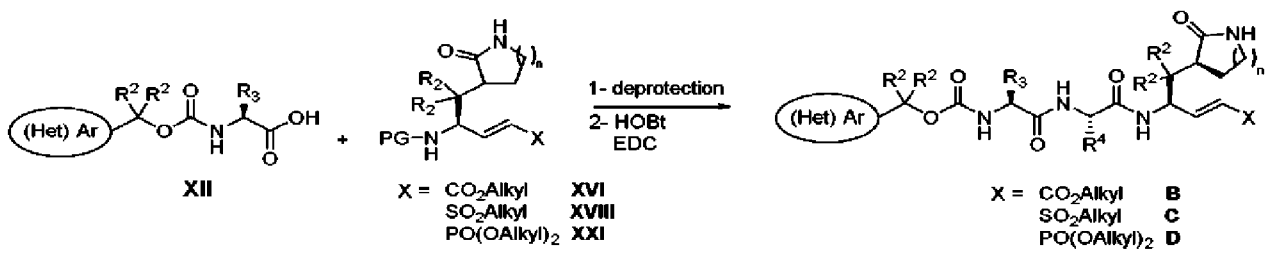
Scheme 1 A synthetic approach to compound **A**

Intermediates of formula **XVI**, **XVIII**, **XIX** and **XXI** can be prepared by first reduction of compound of general formula **VI**, with a reducing agent such as for instance $LiBH_4$ followed by oxidation to form aldehyde of general formula **XIV** and then reaction with either compounds **XV**, **XVII**, **XX** or $MePPh_3Br$.



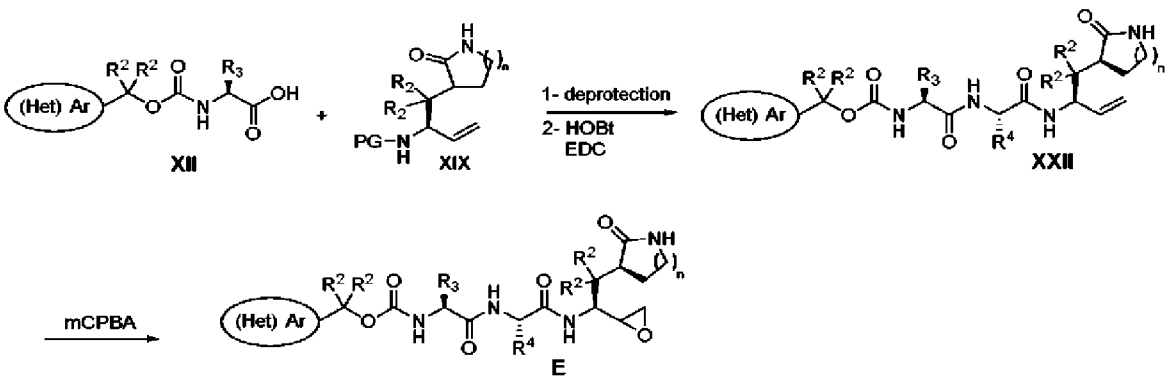
Scheme 2 A synthetic approach to intermediates **XVI**, **XVIII**, **XIX** and **XXI**

Compounds of formula **B-D** can be prepared by first deprotection of compound of general formula **XVI**, **XVIII** or **XXI**, for example, in the presence of TFA when Boc was used as a protecting group, and reaction with a carboxylic acid of general formula **XII** in the presence of peptide coupling reagents like EDC and HOBt.



Scheme 3 A synthetic approach to compounds **B-D**

Compounds of formula **E** can be prepared by first deprotection of compound of general formula **XIX**, for example, in the presence of TFA when Boc was used as a protecting group; reaction with a carboxylic acid of general formula **XII** in the presence of peptide coupling reagents like EDC and HOBt and epoxidation using for instance mCPBA.



Scheme 3 A synthetic approach to compounds **E**

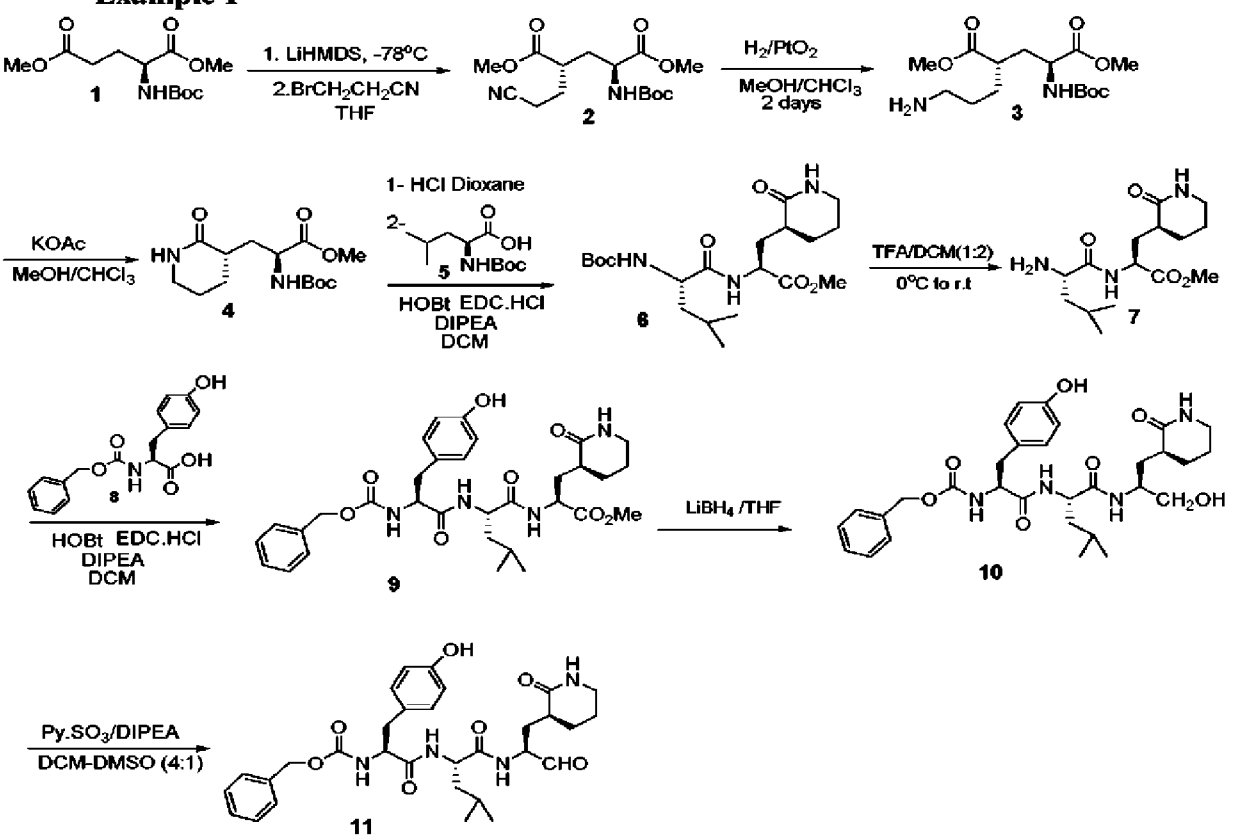
Specific Examples

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The present compounds can also be used as intermediates in subsequent examples to produce additional compounds of the present invention. No attempt has necessarily been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

Anhydrous solvents were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI) and EMD Chemicals Inc. (Gibbstown, NJ). Reagents were purchased from commercial sources. Unless noted otherwise, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods

known to one skilled in the art of chemical synthesis. ^{1}H and ^{13}C NMR spectra were taken on a Bruker Ascend™ 400 MHz Fourier transform spectrometer at room temperature and reported in ppm downfield from internal tetramethylsilane. Deuterium exchange, decoupling experiments or 2D-COSY were performed to confirm proton assignments. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), br (broad), bs (broad singlet), m (multiplet). All *J*- values are in Hz. Mass spectra were determined on a Micromass Platform LC spectrometer using electrospray techniques. Analytic TLC were performed on Sigma-Aldrich® aluminum supported silica gel (25 μm) plates. Column chromatography was carried out on Silica Gel or *via* reverse-phase high performance liquid chromatography.

Example 1



Dimethyl (2*S*,4*S*)-2-((tert-butoxycarbonyl)amino)-4-(2-cyanoethyl)pentanedioate (**2**)

To a solution of *N*-Boc-L-glutamic acid dimethyl ester (**1**, 16.5 g, 60.0 mmol) in THF (180 mL) was added dropwise a solution of lithium bis(trimethylsilyl)amide in THF (130 mL,

1 M, 130 mmol) at -78 °C under an argon atmosphere. The resulting mixture was stirred at -78 °C for 1.5 h. At the same time, 3-bromopropionitrile (9.63 g, 71.9 mmol) was added dropwise to the dianion solution over a period of 1 h while maintaining the temperature below -70 °C. The reaction mixture was stirred at -78 °C for an additional 3 h. The reaction was quenched with aqueous NH_4Cl (80 mL). The reaction mixture was allowed to warm up to room temperature and then EtOAc (140 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was evaporated to dryness. The crude residue was purified by flash column chromatography (hexanes/ethyl acetate = 4/1) to give product **2** (5.25g , 27%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.08 (1H, d, J = 8.0 Hz), 4.38 (1H, m), 3.74 (3H, s), 3.71 (3H, s), 2.62-2.65 (1H, m), 2.35-2.42 (2H, m), 1.97-2.04 (4H, m), 1.44 (9H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 15.16, 27.31, 28.26, 34.47, 40.77, 51.55, 52.20, 52.60, 80.37, 118.70, 115.38, 172.36, 174.42. ESI-MS (*m/z*): 329.4 $(M + H)^+$.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopiperidin-3-yl)propanoate (**4**)

In a hydrogenation flask was placed compound **2** (2.15 g, 6.55 mmol), 5 mL of chloroform and 60 mL of methanol before addition of PtO_2 (160 mg, 0.65 mmol). The resulting mixture was mechanically stirred at room temperature for 2 days under hydrogen pressure (50 Psi). The mixture was then filtered over a pad of silica gel. KOAc (1.27 g, 13 mmol) was added to the filtrate and the resulting mixture was stirred at 60 °C for 12 h. After removal of the solvents, the crude residue was purified by silica gel column chromatography (DCM/MeOH = 50:1 to 20:1) to give the product **4** as a colorless oil (1.21 g, 62%, over two steps). ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.41 (1H, s), 5.64 (1H, d, J = 8.0 Hz), 4.30-4.36 (1H, m), 3.31-3.33 (1H, m), 2.38-2.42 (1H, m), 2.25-2.34 (1H, m), 2.13-2.16 (1H, m), 1.81-1.93 (3H, m), 1.71-1.79 (1H, m), 1.52-1.61 (1H, m), 1.47 (9H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 21.54, 26.53, 28.29, 34.28, 37.97, 42.35, 51.70, 52.30, 79.81, 155.92, 173.18, 174.58. ESI-MS (*m/z*): 301.4 $(M + H)^+$.

Methyl (5*S*, 8*S*, 11*S*)-5-(4-hydroxybenzyl)-8-isobutyl-3, 6, 9-trioxo-11-(((*S*)-2-oxopiperidin-3-yl)methyl)-1-phenyl-2-oxa-4, 7, 10-triazadodecan-12-oate (**9**)

To a solution of **4** (300 mg, 1.0 mmol) in dioxane was added a solution of 4 M HCl in

dioxane. The reaction was stirred for 2 h at room temperature and then concentrated. The crude HCl salt was suspended in DCM (10 mL) and (*tert*-butoxycarbonyl)-*L*-leucine (254 mg, 1.1 mmol), 1-hydroxybenzotriazole (169 mg, 1.25 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (240 mg, 1.25 mmol) and *N,N*-diisopropylethyl amine (0.7 mL, 4.0 mmol) were added at 0°C. The ice bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with EtOAc (100 mL) and washed with 1N HCl, $NaHCO_3$ (5%) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (DCM/MeOH 30:1 to 10:1) to give compound **6** (262 mg, 63%). Compound **6** (200 mg, 0.48 mmol) was dissolved in a 1:2 TFA-DCM solution (10 mL) and stirred 2 h at room temperature and then concentrated under vacuum. The crude HCl salt was suspended in DCM (10 mL) and ((benzyloxy)carbonyl)-*L*-tyrosine **8** (166 mg, 0.53 mmol), 1-hydroxybenzotriazole (82 mg, 0.61 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (161 mg, 0.61 mmol) and N,N-diisopropylethyl amine (0.33 mL, 1.92 mmol) at were added at 0°C. The ice bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (100 mL) and washed with 1N HCl, $NaHCO_3$ (5%) and brine.The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (DCM/MeOH 30:1 to 10:1) to give compound **9** (170 mg, 58%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.39 – 7.20 (m, 5H), 7.12 – 7.03 (m, 2H), 6.80 – 6.65 (m, 2H), 5.13 – 4.94 (m, 2H), 4.64 (s, 1H), 4.54 (dd, J = 11.5, 4.2 Hz, 1H), 4.40 (ddd, J = 17.8, 9.2, 5.5 Hz, 2H), 3.72 (s, 3H), 3.31 – 3.20 (m, 2H), 3.05 (dd, J = 14.0, 4.9 Hz, 1H), 2.76 (dd, J = 14.0, 9.4 Hz, 1H), 2.41 (dt, J = 9.9, 5.0 Hz, 1H), 2.30 (ddd, J = 15.5, 11.6, 4.1 Hz, 1H), 2.04 – 1.88 (m, 2H), 1.88 – 1.80 (m, 1H), 1.79 – 1.58 (m, 4H), 1.52 (dtt, J = 13.3, 10.3, 4.4 Hz, 2H), 0.95 (dd, J = 13.9, 6.1 Hz, 6H).^{13}C NMR (101 MHz, MeOD) δ 175.04, 173.48, 172.75, 172.45, 156.89, 155.80, 136.77, 130.01, 128.05, 127.22, 114.83, 66.16, 56.45, 51.83, 51.43, 49.83, 41.56, 40.48, 37.32, 36.82, 32.76, 25.52, 24.31, 21.99, 20.85, 20.81.ESI-MS (*m/z*): 611.4 $(M + H)^+$.

Benzyl ((*S*)-1-(((*S*)-1-(((*S*)-1-hydroxy-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (**10**)

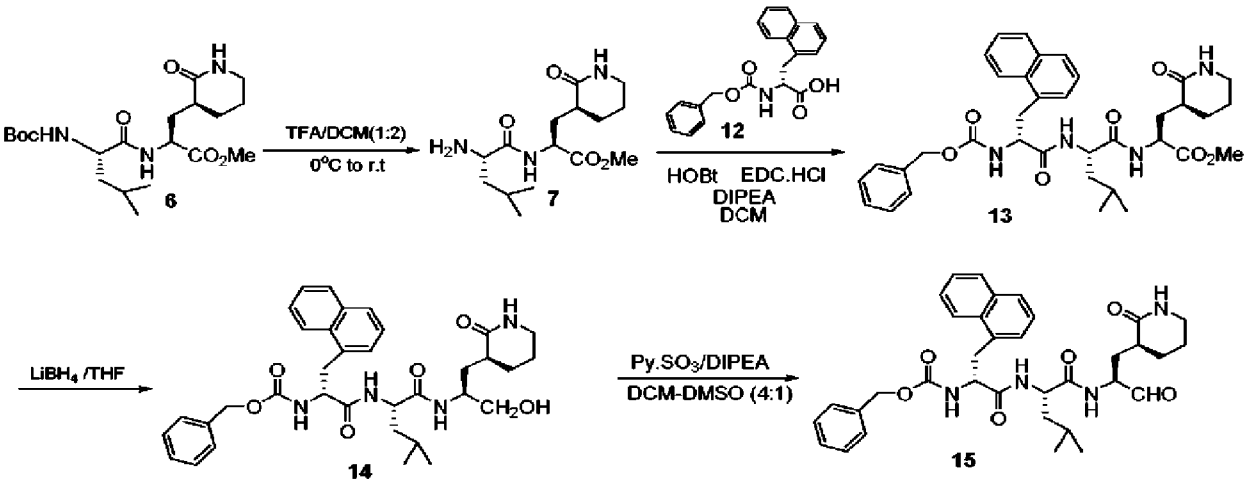
To a solution of **9** (120 mg, 0.2 mmol) in THF (3 mL) was added $LiBH_4$ (4M in THF,

0.3 mL, 1.2 mmol) dropwise at 0°C. The reaction mixture was stirred at room temperature for 2 h and then quenched with 1N HCl (15 mL). After being stirred for 1 h at room temperature, the suspension was extracted with ethyl acetate, and washed with $NaHCO_3$ and brine. The organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (DCM/MeOH 30:1 to 10:1) to give compound. to afford **10** (83 mg, 73%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44 – 7.23 (m, 5H), 7.08 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 5.18 – 4.97 (m, 3H), 4.62 (s, 1H), 4.43 – 4.28 (m, 2H), 4.09 – 3.91 (m, 1H), 3.51 (qd, J = 11.0, 5.7 Hz, 2H), 3.33 (t, J = 1.7 Hz, 1H), 3.06 (dd, J = 14.1, 5.0 Hz, 1H), 2.80 (dd, J = 14.1, 9.1 Hz, 1H), 2.30 (d, J = 9.6 Hz, 1H), 2.16 – 1.94 (m, 2H), 1.79 (d, J = 9.4 Hz, 1H), 1.75 – 1.56 (m, 5H), 1.56 – 1.46 (m, 1H), 1.01 – 0.88 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 176.01, 173.42, 172.89, 157.15, 155.87, 136.70, 129.99, 128.05, 127.62, 127.55, 127.34, 114.88, 66.33, 64.15, 56.75, 52.22, 41.63, 40.51, 37.29, 36.60, 32.74, 25.66, 24.38, 22.11, 20.64, 20.56. ESI-MS (*m/z*): 583.5 $(M + H)^+$.

Benzyl ((*S*)-3-(4-hydroxyphenyl)-1-(((*S*)-4-methyl-1-oxo-1-(((*S*)-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-1-oxopropan-2-yl)carbamate (**11**)

To a solution of **10** (50 mg, 0.086 mmol) in dichloromethane-DMSO (4:1, 1 mL) were added sulfur trioxide pyridine complex (55 mg, 0.34 mmol) and *N*,*N*-diisopropylethyl amine (0.06 mL, 0.34 mmol). The resulting mixture was stirred at room temperature for 12 h and then quenched with 1N HCl (5 mL). The suspension was extracted with ethyl acetate washed with a saturated solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative TLC (DCM/ MeOH = 12/1) to give product **11** as a white solid (28 mg, 56%). ^{1}H NMR (400 MHz, MeOD) δ 7.39-7.23 (m, 5H), 7.08 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 5.01 (dd, J = 25.6, 12.8 Hz, 1H), 4.65 (s, 1H), 4.53 – 4.45 (m, 1H), 4.37 (dd, J = 9.5, 4.3 Hz, 2H), 4.01 (d, J = 2.8 Hz, 1H), 3.36 (s, 1H), 3.23 (d, J = 4.1 Hz, 2H), 3.06 (dd, J = 14.1, 4.3 Hz, 1H), 2.77 (dd, J = 13.4, 10.4 Hz, 1H), 2.27 (d, J = 6.4 Hz, 1H), 2.15 (t, J = 13.1 Hz, 1H), 2.01 (dd, J = 6.9, 3.5 Hz, 1H), 1.84 – 1.43 (m, 6H), 1.01-0.87 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 176.10, 173.55, 173.46, 172.89, 172.80, 157.02, 155.82, 136.75, 129.98, 128.05, 127.74, 127.51, 127.25, 114.84, 98.40, 98.32, 66.21, 56.57, 54.07, 53.77, 52.22, 50.72, 50.62, 41.62, 40.66, 40.59, 37.05, 37.02, 36.77, 30.50, 29.93, 25.43, 24.38, 24.32, 21.97, 20.85, 20.52. ESI-MS (*m/z*): 581.4 $(M + H)^+$.

Example 2



6 7 13 14 15

Methyl (5*R*, 8*S*, 11*S*)-8-isobutyl-5-(naphthalen-1-ylmethyl)-3, 6, 9-trioxo-11-(((*S*)-2-oxopiperidin-3-yl)methyl)-1-phenyl-2-oxa-4, 7, 10-triazadodecan-12-oate (**13**)

Compound **13** was prepared from (*R*)-2-(((benzyloxy)carbonyl)amino)-3-(naphthalen-1-yl)propanoic acid using a similar procedure as that used in the synthesis of compound **9**. White solid 188 mg (83% yield). ^{1}H NMR (400 MHz, MeOD) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.1 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.24 (m, 7H), 5.08 (d, *J* = 3.0 Hz, 2H), 4.63 (s, 2H), 4.52 (dd, *J* = 15.4, 6.8 Hz, 3H), 4.21 (dd, *J* = 10.9, 3.8 Hz, 2H), 3.66 (s, 3H), 3.50 (t, *J* = 7.3 Hz, 2H), 3.25 – 3.16 (m, 2H), 2.50 – 2.28 (m, 3H), 1.99 – 1.85 (m, 3H), 1.80 (d, *J* = 13.8 Hz, 2H), 1.69 (d, *J* = 13.5 Hz, 2H), 1.54 – 1.37 (m, 3H), 1.15 (t, *J* = 11.4 Hz, 1H), 0.99 (dd, *J* = 16.3, 5.6 Hz, 1H), 0.63-0.67 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 175.11, 173.65, 172.72, 172.29, 156.89, 136.72, 134.10, 132.56, 131.94, 128.48, 128.09, 127.63, 127.58, 127.37, 125.99, 125.37, 125.15, 123.33, 66.42, 56.53, 51.56, 51.36, 49.68, 41.51, 39.70, 37.24, 34.36, 32.53, 25.23, 23.64, 22.03, 20.66, 20.20. ESI-MS (*m/z*): 645.4 $(M + H)^+$.

Benzyl ((*R*)-1-(((*S*)-1-(((*S*)-1-hydroxy-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**14**)

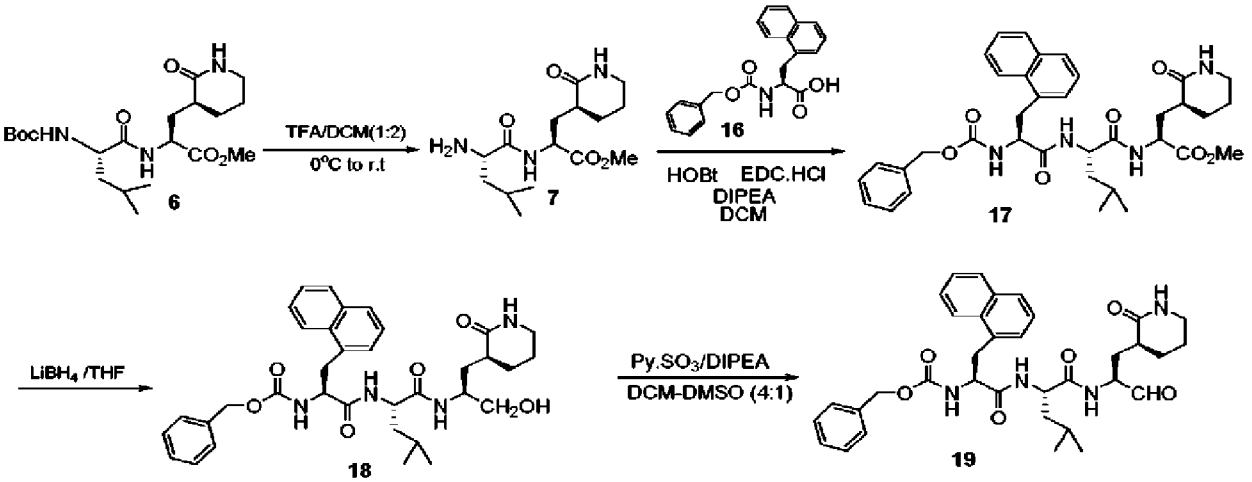
Prepared from **13** using a similar procedure as that used in the synthesis of compound

10. White solid 83 mg (75% yield). ^{1}H NMR (400 MHz, MeOD) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.52 (dt, *J* = 14.7, 6.9 Hz, 2H), 7.43 – 7.26 (m, 6H), 5.12 (dd, *J* = 29.6, 12.4 Hz, 2H), 5.07(s, 1H), 4.48 (dd, *J* = 9.6, 6.0 Hz, 1H), 4.13 (dd, *J* = 11.4, 3.3 Hz, 1H), 4.02 – 3.93 (m, 1H), 3.71 (dt, *J* = 12.2, 6.1 Hz, 1H), 3.57 – 3.37 (m, 5H), 3.19 (t, *J* = 5.8 Hz, 2H), 2.26 – 2.02 (m, 2H), 1.93 (dd, *J* = 6.7, 3.8 Hz, 1H), 1.77 (dd, *J* = 12.7, 4.6 Hz, 1H), 1.63 (t, *J* = 11.3 Hz, 3H), 1.52 – 1.36 (m, 3H), 1.13 (d, *J* = 6.1 Hz, 7H), 0.62-0.57 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 176.05, 173.35, 173.26, 156.99, 136.61, 134.11, 132.37, 131.90, 128.53, 128.15, 127.71, 127.67, 127.59, 127.46, 126.08, 125.45, 125.22, 123.32, 68.72, 66.53, 64.10, 56.79, 51.82, 41.58, 39.88, 37.18, 34.07, 32.70, 25.30, 23.46, 22.19, 21.74, 20.26, 20.04. ESI-MS (*m/z*): 617.4 $(M + H)^+$.

Benzyl ((*R*)-1-(((*S*)-4-methyl-1-oxo-1-(((*S*)-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**15**)

Prepared from compound **14** using a similar procedure as that used in the synthesis of compound **11**. White solid 13 mg (41% yield). ^{1}H NMR (400 MHz, MeOD) δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.51 (tt, *J* = 18.1, 9.0 Hz, 2H), 7.37 (dd, *J* = 14.9, 7.7 Hz, 2H), 7.29 (s, 2H), 7.22 (d, *J* = 7.2 Hz, 2H), 5.05 – 4.92 (m, 2H), 4.59 (dt, *J* = 21.6, 10.7 Hz, 1H), 4.48 (t, *J* = 3.9 Hz, 1H), 4.43 (dd, *J* = 9.9, 4.6 Hz, 1H), 4.10 (dt, *J* = 19.3, 9.6 Hz, 1H), 4.02 (ddd, *J* = 11.3, 7.7, 3.5 Hz, 1H), 3.73 (dd, *J* = 14.5, 4.4 Hz, 1H), 3.34 (dd, *J* = 18.8, 7.1 Hz, 4H), 3.26 – 3.11 (m, 3H), 2.28 (s, 1H), 2.17 (t, *J* = 12.4 Hz, 1H), 2.08 – 1.96 (m, 1H), 1.85 – 1.44 (m, 8H), 1.47 (d, *J* = 9.7 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 1H), 1.03 – 0.85 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 176.08, 173.45, 173.43, 172.71, 172.61, 156.86, 136.69, 134.03, 133.09, 131.99, 128.45, 128.01, 127.53, 127.49, 127.27, 125.86, 125.26, 125.00, 123.28, 98.40, 98.32, 98.25, 66.26, 66.17, 55.83, 55.61, 52.36, 52.28, 52.22, 50.72, 50.54, 41.61, 40.64, 40.57, 40.29, 38.11, 37.08, 37.04, 34.53, 34.36, 30.44, 29.89, 26.44, 25.49, 25.46, 24.44, 24.38, 22.14, 21.92, 21.13, 20.90, 20.56. ESI-MS (*m/z*): 615.4 $(M + H)^+$.

Example 3



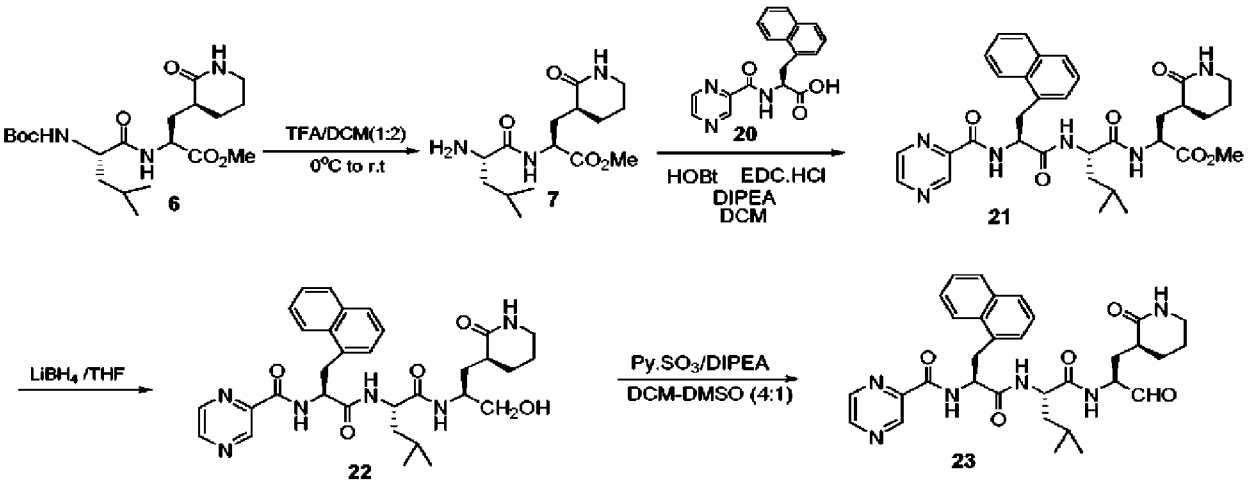
Methyl (5*S*, 8*S*, 11*S*)-8-isobutyl-5-(naphthalen-1-ylmethyl)-3, 6, 9-trioxo-11-(((*S*)-2-oxopiperidin-3-yl)methyl)-1-phenyl-2-oxa-4, 7, 10-triazadodecan-12-oate (**17**)

Compound **17** was prepared from (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(naphthalen-1-yl)propanoic acid **16** using a similar procedure as that used in the synthesis of compound **9**. White solid 120 mg (80% yield). ^{1}H NMR (400 MHz, MeOD) δ 8.21 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.1 Hz, 1H), 7.52 (dt, *J* = 20.4, 7.1 Hz, 2H), 7.43 – 7.34 (m, 2H), 7.30 (d, *J* = 7.1 Hz, 2H), 7.22 (d, *J* = 7.2 Hz, 2H), 5.01(2H, overlapped with water peak), 4.71 – 4.59 (m, 2H), 4.54 (dt, *J* = 26.7, 11.3 Hz, 1H), 4.51 – 4.39 (m, 1H), 3.79 – 3.67 (m, 4H), 3.32 (t, *J* = 5.8 Hz, 2H), 3.29 – 3.17 (m, 2H), 2.47 – 2.38 (m, 1H), 2.35 – 2.31 (m, 1H), 2.32 (dd, *J* = 18.3, 7.5 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.95 – 1.86 (m, 1H), 1.77 (d, *J* = 16.4 Hz, 1H), 1.75 – 1.65 (m, 2H), 1.66 – 1.53 (m, 2H), 1.03 – 0.85 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 175.04, 173.57, 173.48, 172.62, 172.48, 156.80, 136.69, 134.02, 133.05, 132.01, 128.45, 128.03, 127.51, 127.25, 125.86, 125.27, 125.01, 123.29, 66.16, 55.53, 51.98, 51.42, 49.92, 49.82, 41.55, 40.43, 37.33, 34.51, 32.78, 25.54, 24.36, 21.95, 20.87, 20.83. ESI-MS (*m/z*): 645.5 $(M + H)^+$.

Benzyl ((*S*)-1-(((*S*)-4-methyl-1-oxo-1-(((*S*)-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**19**)

Compound **19** was synthesized from compound **17** using a similar procedure as that used in the synthesis of compound **11**. White solid 11 mg (41% yield). ^{1}H NMR (400 MHz, MeOD) δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.51 (tt, *J* = 18.1, 9.0 Hz, 2H), 7.37 (dd, *J* = 15.0, 7.8 Hz, 2H), 7.27 (d, *J* = 15.0 Hz, 2H), 7.23 (t, *J* = 7.0

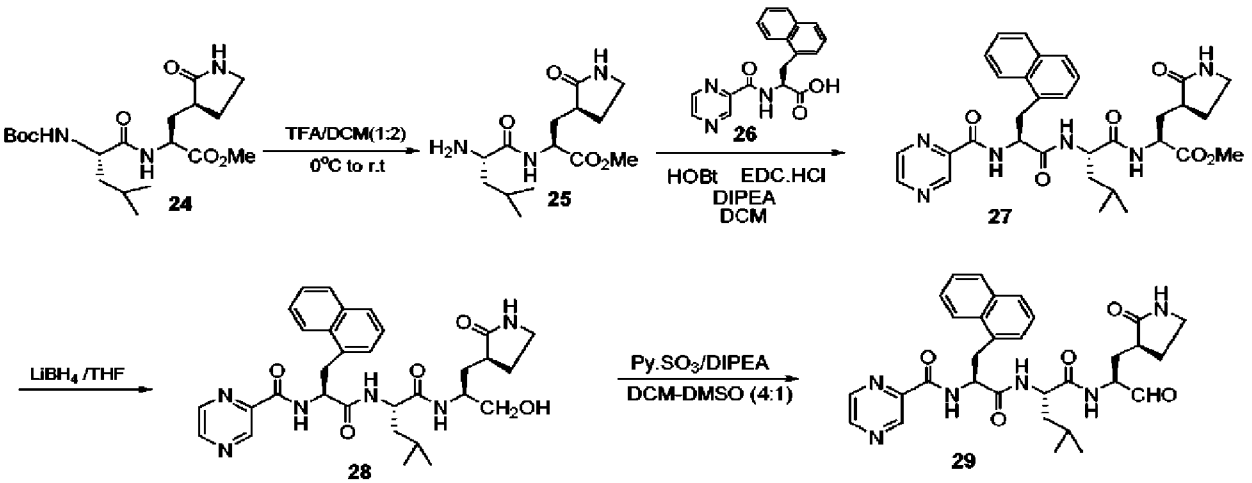
Hz, 2H), 4.97 (d, *J* = 9.8 Hz, 2H), 4.60 (dd, *J* = 9.5, 4.4 Hz, 1H), 4.47 (dd, *J* = 10.1, 6.1 Hz, 1H), 4.44 – 4.35 (m, 1H), 4.02 (ddd, *J* = 11.3, 7.7, 3.5 Hz, 1H), 3.73 (dd, *J* = 14.5, 4.4 Hz, 1H), 3.40 – 3.32 (m, 3H), 3.26 – 3.12 (m, 3H), 2.46 – 2.35 (m, 1H), 2.28 (s, 1H), 2.17 (t, *J* = 12.4 Hz, 1H), 1.84 – 1.55 (m, 7H), 1.47 (d, *J* = 9.7 Hz, 1H), 1.02 – 0.83 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 176.08, 173.45, 173.43, 172.71, 172.61, 156.86, 136.69, 134.03, 133.09, 131.99, 128.45, 128.01, 127.53, 127.49, 127.27, 125.86, 125.26, 125.00, 123.28, 98.32, 98.25, 66.26, 66.17, 55.61, 52.36, 52.28, 52.22, 50.72, 50.54, 41.61, 40.64, 40.57, 40.29, 38.11, 37.08, 37.04, 34.53, 34.36, 30.44, 29.89, 26.44, 25.49, 25.46, 24.44, 24.38, 22.14, 21.92, 21.13, 20.90, 20.56. ESI-MS (*m/z*): 615.5 $(M + H)^+$.



N-((S)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)pyrazine-2-carboxamide (23)

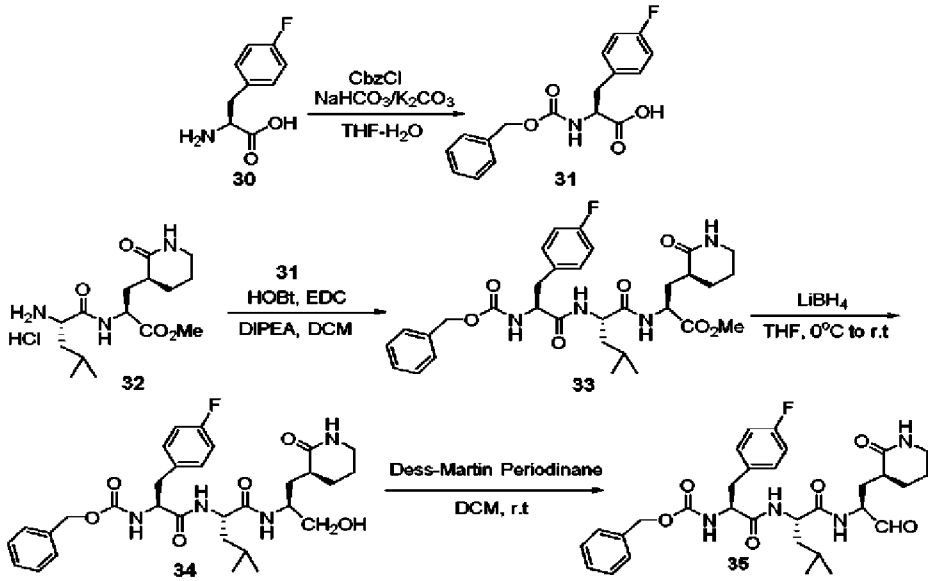
Compound **23** was synthesized from compound **6** using a similar procedure as that used in the synthesis of compound **11**. ^{1}H NMR (400 MHz, Methanol-d4) δ 9.09 (dd, J = 16.5, 1.4 Hz, 1H), 8.75 (dd, J = 4.9, 2.4 Hz, 1H), 8.63 (td, J = 2.5, 1.4 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 7.85 (dd, J = 8.3, 5.0 Hz, 1H), 7.76 (t, J = 7.3 Hz, 1H), 7.60 – 7.43 (m, 3H), 7.37 (dt, J = 9.7, 7.5 Hz, 1H), 5.14 – 5.00 (m, 1H), 4.59 – 4.37 (m, 2H), 4.25 – 4.12 (m, 1H), 4.08 – 3.99 (m, 1H), 3.89 (ddd, J = 19.4, 9.9, 3.8 Hz, 1H), 3.62 – 3.46 (m, 1H), 3.25 (td, J = 9.3, 8.4, 3.7 Hz, 2H), 2.41 (dt, J = 10.3, 5.7 Hz, 1H), 2.31 (d, J = 8.8 Hz, 1H), 2.18 (ddd, J = 14.7, 8.8, 3.3 Hz,

1H), 2.04 (tt, J = 9.8, 5.0 Hz, 1H), 1.93 – 1.58 (m, 4H), 1.07 – 0.82 (m, 6H). ESI-MS (m/z): 587.5 (M + H)+.



N-((S)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)pyrazine-2-carboxamide (29)

Compound **29** was synthesized from compound **24** using a similar procedure as that used in the synthesis of compound **11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.09 (dd, J = 20.6, 1.4 Hz, 1H), 8.75 (dd, J = 6.2, 2.5 Hz, 1H), 8.62 (tt, J = 2.6, 1.3 Hz, 1H), 8.29 (d, J = 8.5 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.75 (t, J = 9.2 Hz, 1H), 7.51 (dq, J = 27.0, 7.3 Hz, 3H), 7.37 (dt, J = 15.0, 7.6 Hz, 1H), 5.16 – 4.97 (m, 1H), 4.58 – 4.36 (m, 2H), 4.09 (dq, J = 8.5, 4.3 Hz, 1H), 4.03 – 3.93 (m, 1H), 3.87 (td, J = 15.6, 14.5, 5.2 Hz, 1H), 3.53 (ddd, J = 19.6, 14.2, 9.0 Hz, 1H), 2.60 – 2.43 (m, 1H), 2.41 – 2.29 (m, 1H), 2.22 (dt, J = 14.0, 4.7 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.89 (q, J = 10.7, 9.9 Hz, 1H), 1.83 – 1.54 (m, 4H), 0.97-0.91 (m, 6H). ESI-MS (m/z): 573.5 (M + H)$^+$.



(S)-2-(((Benzyloxy)carbonyl)amino)-3-(4-fluorophenyl)propanoic acid (**31**)

To a solution of *p*-fluoro-L-phenylalanine (2.56 g, 13.98 mmol), $NaHCO_3$ (1.76 g, 21 mmol), K_2CO_3 (2.90 g, 21 mmol) in THF-H_2O (v/v=1:1, 50 mL) was added CbzCl (2.2 mL, 15.4 mmol). The reaction mixture was stirred overnight at room temperature. After evaporation of the volatils , the reaction mixture was washed with ethyl acetate (10 mL) and then the pH of the water phase was adjusted to pH =1 by addition of 1N HCl. The water layer was finally extracted with ethyl acetate (30 mL x 4) and the combined organic layers dried over Na_2SO_4, to give, after evaporation, compound **31** (4.2 g, 95%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.37 – 7.12 (m, 7H), 6.96 (t, J = 8.8 Hz, 2H), 5.11 – 4.93 (m, 2H), 4.47 (dd, J = 9.3, 5.0 Hz, 1H), 3.19 (dd, J = 14.0, 5.0 Hz, 1H), 2.92 (dd, J = 14.0, 9.3 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 173.61, 163.03, 160.62, 156.94, 136.74, 133.08, 133.05, 130.72, 130.64, 128.08, 127.61, 127.34, 114.78, 114.57, 66.20, 55.37, 36.45. ^{19}F NMR (377 MHz, Methanol-d_4) δ -119.46 . LC-MS: m/z $[M+H]^+$ calcd. for $C_{17}H_{17}FNO_4$: 318.1, found: 318.2.

Methyl (5S,8S,11S)-5-(4-fluorobenzyl)-8-isobutyl-3,6,9-trioxo-11-(((S)-2-oxopiperidin-3-yl)methyl)-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (**33**)

To a solution of compound **32** (230 mg, 0.66 mmol) and amino acid **31** (250 mg, 0.79 mmol) in DCM (6.0 mL) was added 1-hydroxybenzotriazole (135 mg, 1.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (190 mg, 1.0 mmol) and *N,N*-diisopropylethyl amine (0.7 mL, 4.0 mmol) at 0°C. After being stirred at room temperature overnight, the reaction mixture was diluted with EtOAc (50 mL) and washed with 1N HCl, $NaHCO_3$ (5%) and a saturated solution of NaCl. The organic layer was dried over Na_2SO_4. The solvent was concentrated in vacua and was purified by flash chromatography (DCM/MeOH 20:1) to afford compound **33** (280 mg, 69%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.64 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 7.28 (m, 4H), 7.08 – 6.90 (m, 3H), 5.16 – 4.94 (m, 2H), 4.42 (ddd, J = 8.3, 5.7, 3.1 Hz, 2H), 3.72 (s, 4H), 3.29 – 3.20 (m, 2H), 3.14 (dd, J = 14.0, 4.7 Hz, 1H), 2.82 (dd, J = 14.0, 9.7 Hz, 1H), 2.47 – 2.18 (m, 2H), 2.08 – 1.78 (m, 2H), 1.73-1.51 (m, J = 4H), 0.93 and 0.98 (2s, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 175.01, 173.60, 173.51, 172.52, 172.45, 172.43, 163.01, 160.59, 156.90, 156.85, 136.79, 133.19, 133.15, 130.77, 130.69, 130.61, 128.03, 127.55, 127.31, 127.28, 114.69, 114.48, 66.16, 66.07, 56.19, 52.00, 51.97, 51.91, 51.87, 51.37, 49.94, 49.84, 41.56, 40.55, 40.51, 37.35, 36.77, 32.83, 32.79, 25.58, 24.34, 21.97, 20.85, 20.82. ^{19}F NMR (377 MHz, Methanol-d_4) δ -119.88 – -119.94 (m). LC-MS: m/z $[M+H]^+$ calcd. for $C_{32}H_{42}FN_4O_7$: 613.3, found: 613.5.

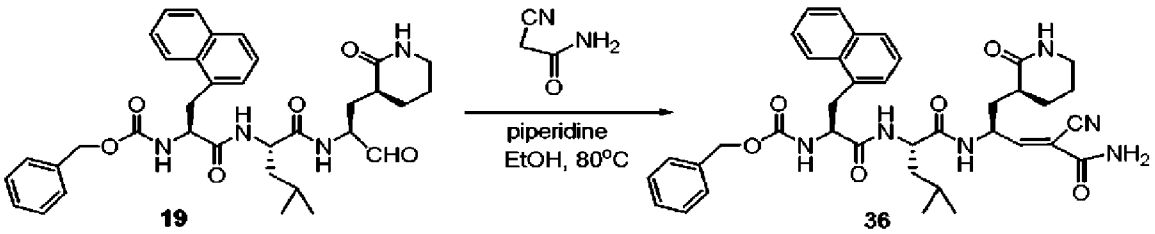
Benzyl ((S)-3-(4-fluorophenyl)-1-(((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-1-oxopropan-2-yl)carbamate (**34**)

To a solution of **33** (230 mg, 0.38 mmol) in THF (2.0 mL) was added $LiBH_4$ (4M in THF, 0.25 mL, 1.0 mmol) dropwise at 0°C. The reaction mixture was stirred at room temperature for 2 h. Then the reaction was quenched with 1N HCl (5 mL) and stirred for 1 h at room temperature. Ethyl acetate (30 mL) was added to the mixture, and the organic layer was washed with 1N HCl, $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and the filtrate evaporated to dryness. The residue was purified by was purified by flash chromatography (DCM/MeOH 30:1 to 10:1) to afford product **34** (174 mg, 80%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (d, J = 8.9 Hz, 1H), 7.38 – 7.21 (m, 6H), 6.98 (t, J = 8.8 Hz, 2H), 5.16 – 4.96 (m, 2H), 4.39 (dt, J = 12.9, 6.2 Hz, 3H), 4.02 (ddd, J = 8.9, 5.8, 2.9 Hz, 1H), 3.60 – 3.42 (m, 2H), 3.25 (t, J = 4.7 Hz, 2H), 3.15 (dd, J = 14.1, 4.7 Hz, 1H), 2.85 (dd, J = 14.1,

9.5 Hz, 1H), 2.31 (d, J = 8.7 Hz, 1H), 2.18 – 1.96 (m, 2H), 1.90 – 1.77 (m, 1H), 1.72 – 1.57 (m, 5H), 0.95 (d, J = 5.7 Hz, 3H), 0.92 (d, J = 5.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.98, 173.48, 173.40, 172.53, 163.02, 160.60, 157.06, 136.71, 133.11, 130.75, 130.67, 128.02, 127.56, 127.38, 127.29, 114.72, 114.50, 66.29, 64.16, 56.42, 52.26, 52.22, 41.62, 40.52, 37.29, 36.57, 32.76, 25.71, 24.42, 22.07, 20.62. ^{19}F NMR (377 MHz, Methanol-d_4) δ -119.74 – -119.82 (m). LC-MS: m/z $[M+H]^+$ calcd. for $C_{31}H_{42}FN_4O_6$: 585.3, found: 585.5.

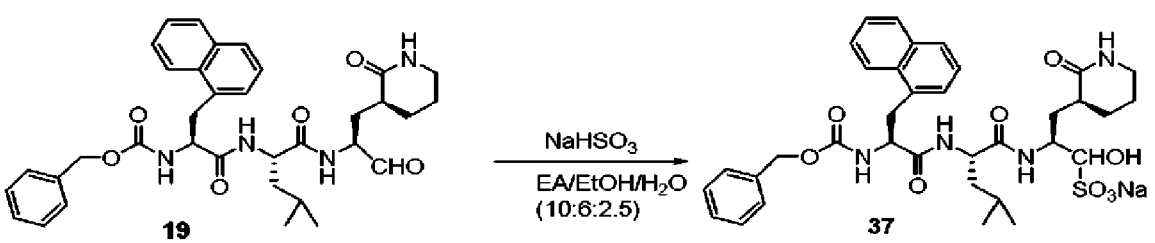
Benzyl ((S)-3-(4-fluorophenyl)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-1-oxopropan-2-yl)carbamate (**35**)

To a solution of compound **34** (123 mg, 0.21 mmol) in dichloromethane (2.0 mL) was added Dess-Martin periodinane (43 mg, 0.1 mmol). The reaction mixture was stirred at room temperature for 2 h then filtered through a silica gel pad, washed with ethyl acetate. The filtrate was evaporated to dryness and the residue was purified by flash chromatography (DCM/MeOH 30:1 to 12:1) to afford product **35** (70 mg, 57%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18 (dd, J = 7.5, 4.1 Hz, 1H), 7.86 (d, J = 9.3 Hz, 1H), 7.42 – 7.15 (m, 12H), 6.98 (t, J = 8.8 Hz, 3H), 5.16 – 4.95 (m, 3H), 4.41 (qd, J = 6.2, 3.8, 3.3 Hz, 3H), 4.02 (ddt, J = 9.1, 5.8, 2.7 Hz, 1H), 3.23 (t, J = 4.9 Hz, 3H), 3.15 (dd, J = 14.1, 4.9 Hz, 2H), 2.83 (dd, J = 13.7, 10.0 Hz, 1H), 2.35 – 2.24 (m, 1H), 2.23 – 2.11 (m, 2H), 2.02 (dt, J = 10.5, 3.5 Hz, 1H), 1.75 – 1.57 (m, 7H), 0.94 (dd, J = 13.6, 6.1 Hz, 10H). ^{13}C NMR (101 MHz, MeOD) δ 176.05, 173.53, 173.50, 172.51, 172.42, 163.00, 160.59, 156.92, 136.75, 133.17, 130.75, 130.67, 128.04, 128.02, 127.54, 127.35, 127.32, 114.75, 114.71, 114.54, 114.49, 98.39, 98.32, 66.19, 56.26, 54.03, 53.80, 53.73, 52.28, 52.24, 50.80, 50.62, 41.62, 40.71, 40.64, 40.40, 37.07, 37.03, 36.77, 30.45, 29.92, 26.46, 25.50, 25.47, 24.41, 24.35, 22.15, 21.97, 21.94, 21.14, 20.89, 20.85, 20.57, 20.54. ^{19}F NMR (377 MHz, Chloroform-d) δ -117.12 – -117.37 (m). LC-MS: m/z $[M+H]^+$ calcd. for $C_{31}H_{40}FN_4O_6$: 583.3, found: 583.5.



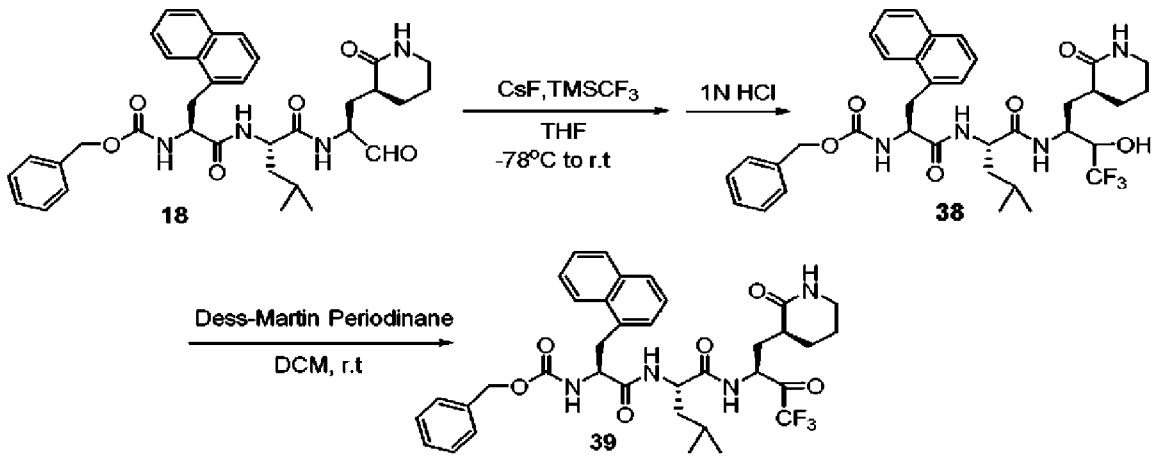
Benzyl ((S)-1-(((S)-1-(((S,E)-5-amino-4-cyano-5-oxo-1-((S)-2-oxopiperidin-3-yl)pent-3-en-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**36**)

To a solution of 2-cyanoacetamide (6.5 mg, 0.08 mmol) and **19** (50 mg, 0.08 mmol) in ethanol (0.2 mL) was added piperidine (0.66 M in ethanol, 12 μL, 0.008 mmol). The reaction vessel was then placed into a microwave reactor (CEM Discover), and irradiated for 25 minutes at 80°C. After removal of the volatils under vacuo, the reaction mixture was purified by preparative TLC (EtOAc/MeOH 20/1) to give 2-cyano-3-(substituted phenyl)acrylamide product **36** as a white solid (8 mg, 15%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 (q, J = 12.1, 10.0 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.84 – 7.72 (m, 1H), 7.53 (dt, J = 22.7, 7.3 Hz, 2H), 7.45 – 7.36 (m, 1H), 7.36 – 7.17 (m, 6H), 5.00 (d, J = 8.2 Hz, 1H), 4.62 (d, J = 10.2 Hz, 1H), 4.45 – 4.26 (m, 1H), 3.78 – 3.65 (m, 1H), 3.28 – 3.16 (m, 4H), 2.50 – 2.16 (m, 1H), 2.04 (s, 1H), 1.85 (d, J = 15.2 Hz, 1H), 1.64 (dd, J = 8.4, 4.7 Hz, 1H), 1.06 – 0.73 (m, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 175.97, 175.49, 173.37, 172.76, 157.28, 156.97, 136.65, 134.03, 132.99, 131.98, 128.45, 128.03, 128.00, 127.51, 127.31, 127.26, 125.88, 125.27, 125.00, 123.26, 114.64, 113.42, 66.27, 64.16, 55.77, 52.35, 52.19, 41.61, 41.56, 40.09, 37.34, 37.30, 34.30, 24.56, 24.46, 22.06, 20.81, 20.66, 20.51. LC-MS: m/z $[M+H]^+$ calcd. for $C_{38}H_{44}N_6O_6$: 680.3, found: 680.5.



Sodium (5S,8S,11S)-12-hydroxy-8-isobutyl-5-(naphthalen-1-ylmethyl)-3,6,9-trioxo-11-(((S)-2-oxopiperidin-3-yl)methyl)-1-phenyl-2-oxa-4,7,10-triazadodecane-12-sulfonate (**37**)

A solution of **19** (19 mg, 0.03 mmol) and sodium bisulfite (4.5 mg, 0.04 mmol) in a mixture of EtOAc/EtOH/H_20 (1:0.6:0.25, 0.2 mL) was stirred for 3 h at 55°C and then allowed to cool down to room temperature. The precipitate formed was vacuum filtered and the solid was thoroughly washed with absolute ethanol. The filtrate was then dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to yield a yellowish oil which was treated with ethyl ether to form a white solid. Careful removal of the solvent using a pipette yielded compound **37** (15 mg, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 8.3 Hz, 2H), 7.92 (dd, J = 7.7, 3.6 Hz, 1H), 7.85 – 7.74 (m, 2H), 7.70 – 7.49 (m, 2H), 7.30 (dt, J = 9.1, 5.6 Hz, 3H), 7.24 – 7.13 (m, 2H), 4.45 (q, J = 10.8, 9.2 Hz, 1H), 4.39 – 4.18 (m, 1H), 3.87 (d, J = 4.8 Hz, 0H), 3.21 – 2.97 (m, 3H), 2.17 (ddd, J = 21.8, 11.5, 4.6 Hz, 1H), 2.01 (d, J = 14.7 Hz, 1H), 1.96 – 1.79 (m, 1H), 1.76 – 1.63 (m, 2H), 1.57 – 1.41 (m, 4H), 0.92 (d, J = 4.8 Hz, 3H), 0.88 (d, J = 4.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 201.42, 173.16, 173.00, 172.94, 171.82, 171.72, 156.25, 137.40, 134.19, 133.83, 132.07, 129.03, 128.72, 128.08, 127.87, 127.75, 127.70, 127.48, 126.52, 126.00, 125.77, 124.19, 65.63, 61.62, 56.05, 55.81, 55.69, 51.70, 41.68, 41.55, 41.40, 34.98, 26.18, 24.66, 23.54, 23.37, 22.27, 22.12, 21.85, 21.77, 15.60. LC-MS: m/z $[M+H]^+$ calcd. for $C_{35}H_{45}N_4O_9S$: 697.3, found: 697.5.



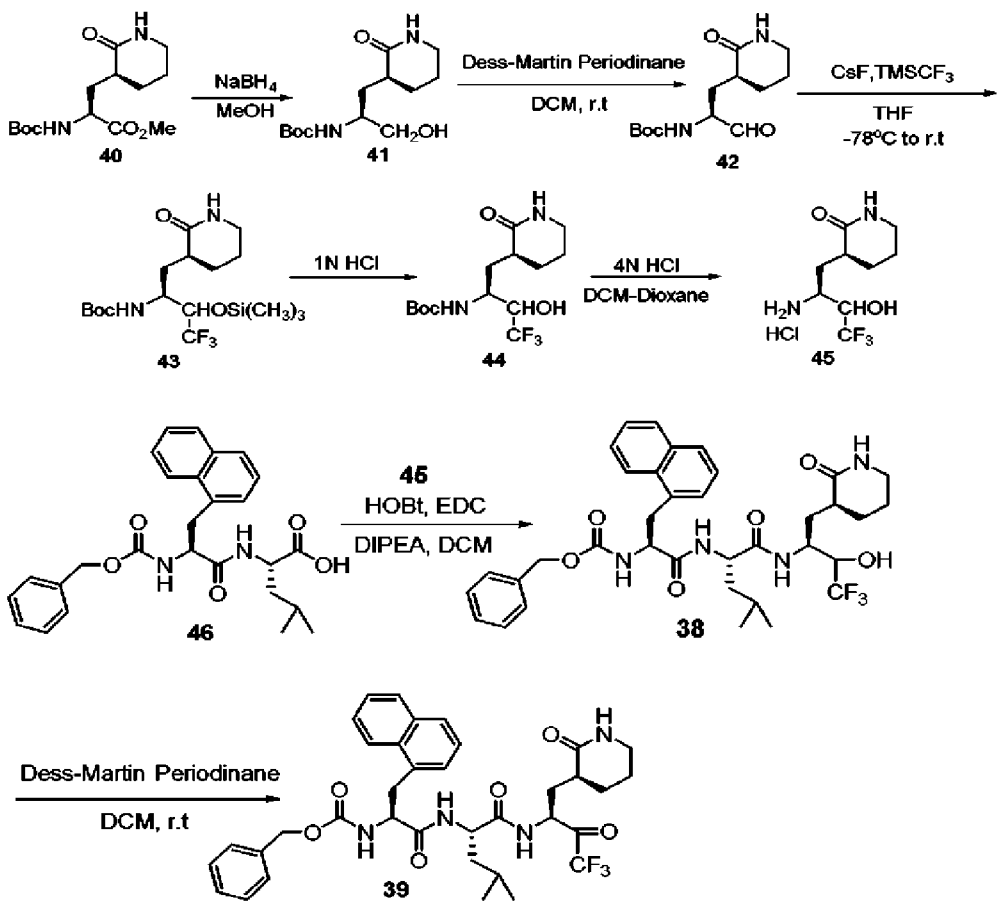
Benzyl ((2S)-1-(((2S)-4-methyl-1-oxo-1-(((2S)-4,4,4-trifluoro-3-hydroxy-1-((S)-2-oxopiperidin-3-yl)butan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**38**)

To a solution of compound **19** (61 mg, 0.1 mmol) and cesium fluoride in THF (76 mg, 0.5 mmol) was added Me_3SiCF_3 (2M in THF, 0.1 mL, 0.2 mmol) at -78 °C dropwise over 5 minutes. The reaction mixture was then stirred at room temperature for 2 h and quenched with 1N HCl (0.5 mL). After 1 h, EtOAc (10 mL) was added to the reaction mixture and the organic layer was washed with 1N HCl, $NaHCO_3$ and water. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative TLC (DCM/MeOH 20:1) to provide compound **38** (19 mg, 28%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 8.08 (s, 1H), 7.98 – 7.80 (m, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.45 (m, 1H), 7.36 (d, *J* = 15.8 Hz, 5H), 6.70 – 6.38 (m, 2H), 5.99 (d, *J* = 33.3 Hz, 1H), 5.66 – 5.40 (m, 1H), 5.04 (s, 1H), 4.66 (d, *J* = 8.5 Hz, 1H), 4.46 (d, *J* = 8.9 Hz, 1H), 4.33 (t, *J* = 7.4 Hz, 1H), 3.76 – 3.62 (m, 1H), 3.46 – 3.36 (m, 1H), 3.24 (s, 2H), 2.22 (s, 1H), 2.10 – 1.86 (m, 3H), 1.75 (s, 2H), 0.98 – 0.78 (m, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 175.83, 174.65, 173.21, 172.79, 172.58, 156.79, 136.72, 134.04, 133.08, 132.87, 131.99, 128.45, 128.03, 128.00, 127.51, 127.36, 127.28, 125.86, 125.26, 125.00, 123.25, 66.22, 55.64, 52.55, 41.68, 41.57, 39.75, 38.56, 37.11, 36.84, 34.59, 26.45, 24.52, 24.42, 22.22, 22.09, 21.54, 20.53, 20.30. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -75.94, -77.58. LC-MS: m/z $[M+H]^+$ calcd. for $C_{36}H_{44}F_3N_4O_6$: 685.3, found: 685.5.

Benzyl ((S)-1-(((S)-4-methyl-1-oxo-1-(((S)-4,4,4-trifluoro-3-oxo-1-((S)-2-oxopiperidin-3-yl)butan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**39**)

A solution of compound **38** (19 mg, 0.03 mmol) and Dess-Martin periodinane (45 mg, 0.11 mmol) in dichloromethane (0.8 mL) was stirred at room temperature for 1 h. The reaction mixture was then filtered through silica gel pad, washed with ethyl acetate and concentrated under vacuum. The residue was purified by two successive preparative TLCs (DCM/methanol = 20/1 then 100% ethyl acetate) to give compound **39** as a white solid (10 mg, 53%). ^{1}H NMR

(400 MHz, Methanol-d_4) δ 8.22 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.52 (dt, J = 15.2, 7.6 Hz, 2H), 7.38 (d, J = 9.6 Hz, 2H), 7.30 (d, J = 6.3 Hz, 3H), 7.21 (d, J = 7.2 Hz, 2H), 4.95 (s, 1H), 4.69 – 4.55 (m, 1H), 4.47 (dd, J = 10.2, 6.1 Hz, 1H), 4.38 (d, J = 11.6 Hz, 1H), 3.73 (d, J = 14.7 Hz, 1H), 3.28 – 3.16 (m, 2H), 2.40 – 2.18 (m, 2H), 2.04 (s, 1H), 1.85 – 1.67 (m, 1H), 1.60 (dt, J = 13.3, 7.3 Hz, 2H), 1.44 (d, J = 11.1 Hz, 1H), 1.03 – 0.81 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 176.01, 175.84, 173.66, 173.39, 172.79, 172.66, 156.79, 136.70, 134.03, 133.09, 131.99, 128.45, 128.01, 127.48, 127.30, 127.22, 125.85, 125.25, 125.00, 123.25, 66.13, 66.09, 55.49, 52.29, 52.05, 49.71, 49.43, 41.57, 40.32, 37.00, 36.87, 34.58, 30.12, 29.99, 29.36, 25.62, 25.43, 24.35, 24.32, 22.06, 21.98, 20.76, 20.72, 20.62. ^{19}F NMR (377 MHz, CD_3OD) δ -79.48, -79.97. LC-MS: m/z $[M+H]^+$ calcd. for $C_{36}H_{42}F_3N_4O_6$: 683.3, found: 683.5 and 701.5 $[M + H_2O]^+$.



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tert-Butyl ((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamate (**41**)

To a solution of compound **40** (600 mg, 2.0 mmol) in MeOH (10 mL) was added $NaBH_4$ (152 mg, 4.0 mmol) at 0°C. The reaction mixture was stirred at room temperature for 3 h then quenched with 1N HCl (5 mL) and finaly stirred for 1 h at room temperature. The suspension was extracted with ethyl acetate (3 x 30 mL), and washed with $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and then evaporated to dryness. The residue was purified by flash chromatography on silica gel (DCM/MeOH 50:1 to 10:1) to afford compound **41** (480 mg, 88%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.42 (s, 1H), 5.57 (d, *J* = 8.1 Hz, 1H), 3.70 (dt, *J* = 24.3, 5.3 Hz, 2H), 3.63 – 3.51 (m, 2H), 3.48 (s, 0H), 3.32 (qd, *J* = 4.8, 2.2 Hz, 2H), 2.38 (dt, *J* = 11.0, 5.5 Hz, 1H), 2.17 (s, 1H), 2.01-2.1 (m, 1H), 1.96 – 1.81 (m, 1H), 1.80 – 1.66 (m, 2H), 1.56 (dtd, *J* = 13.5, 10.5, 3.0 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.78, 156.55, 79.31, 65.64, 53.43, 50.66, 50.47, 42.45, 38.10, 32.80, 28.39, 26.90, 21.64. LC-MS: m/z $[M+H]^+$ calcd. for $C_{13}H_{25}N_2O_4$: 273.2, found: 273.5.

Tert-Butyl ((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamate (**42**)

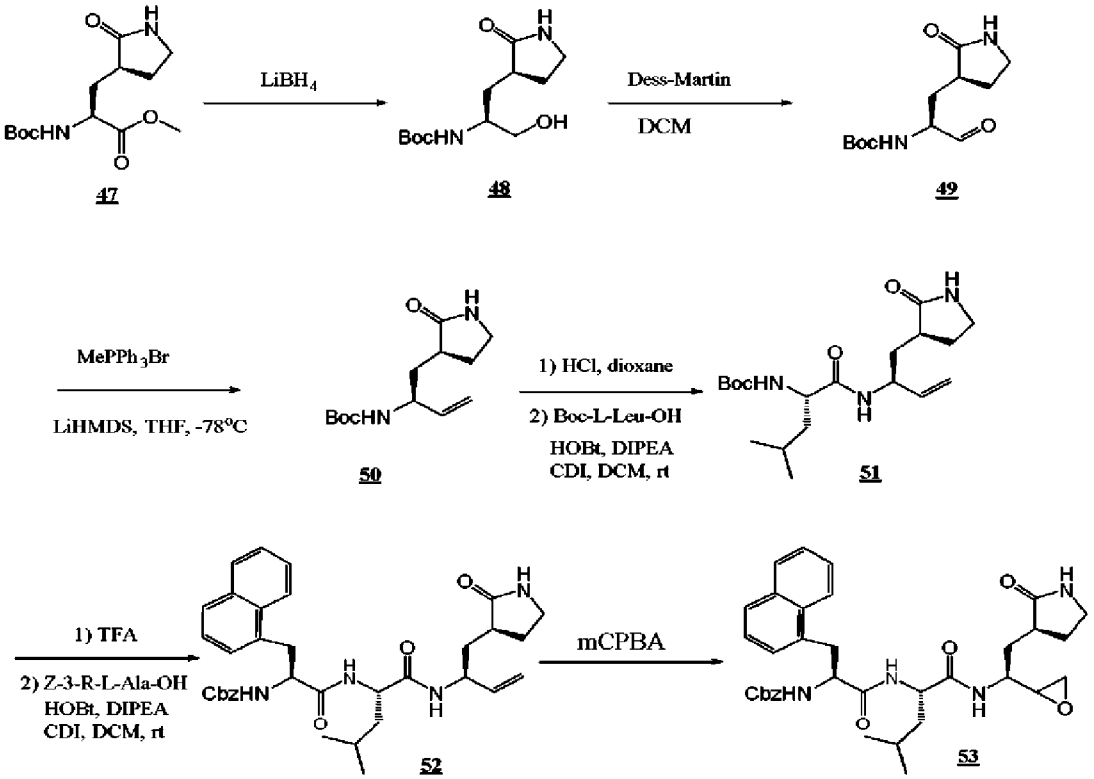
A solution of compound **41** (400 mg, 1.47 mmol) and Dess-Martin periodinane (750 mg, 1.77 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was filtered through a celite pad and washed with ethyl acetate (50 mL). The organic layer was washed with a solution of sodium thiosulfate (0.4 N, 10 mL) and a solution of $NaHCO_3$ (5%, 10 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure to give the crude product **42** (364 mg, 92%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.55 (s, 1H), 6.33 – 6.14 (m, 1H), 4.28 – 4.15 (m, 1H), 3.43 – 3.20 (m, 4H), 2.47 – 2.25 (m, 1H), 2.19 (ddd, *J* = 14.2, 8.6, 7.1 Hz, 1H), 1.88 (tt, *J* = 8.5, 4.4 Hz, 2H), 1.75 (dtd, *J* = 13.8, 7.3, 3.3 Hz, 1H), 1.64 – 1.51 (m, 1H), 1.45 (d, *J* = 12.1 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.77, 174.84, 156.18, 79.94, 60.40, 58.30, 42.39, 37.34, 31.50, 28.40, 28.32, 27.38, 21.31. LC-MS: m/z $[M+H]^+$ calcd. for $C_{13}H_{23}N_2O_4$: 271.2, found: 271.5.

tert-Butyl ((2S)-4,4,4-trifluoro-3-hydroxy-1-((S)-2-oxopiperidin-3-yl)butan-2-yl)carbamate (**44**)

To a solution of crude product **42** (270 mg, 1.0 mmol) and CsF (180 mg, 1.18 mmol) in THF (3.0 mL) was added at -78°C, $TMSCF_3$ (2.0M in THF, 0.7 mL, 1.4 mmol) dropwise over 10 minutes. After addition, the reaction mixture was then stirred at room temperature for 1 h, quenched by addition of a 1 N HCl solution (10 mL) and stirred for another 30 minutes. The reaction mixture was extracted with ethyl acetate (30 ml x 3), washed with a saturated solution of $NaHCO_3$ and water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel column (DCM/MeOH 30:1 to 10:1) to afford compound **44**. LC-MS: m/z $[M+H]^+$ calcd. for $C_{14}H_{24}F_3N_2O_4$: 341.2, found: 341.5.

Benzyl ((2S)-1-(((2S)-4-methyl-1-oxo-1-(((2S)-4,4,4-trifluoro-3-hydroxy-1-((S)-2-oxopiperidin-3-yl)butan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**38**)

To a solution of crude product **44** (50 mg, 0.18 mmol) in DCM (1.5 mL) was added 4N HCl in dioxane (0.6 mL, 2.4 mmol). The reaction mixture was stirred for 2 h at room temperature and then the volatils were remove under reduced pressure. The residue was dissolved in DCM (1.0 mL) and compound **46** (46 mg, 0.1 mmol), 1-hydroxybenzotriazole (28 mg, 0.2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (38 mg, 0.2 mmol) and *N,N*-diisopropylethyl amine (0.14 mL, 0.8 mmol) were added at 0°C. The reaction mixture was stirred at room temperature overnight before being diluted with EtOAc (20 mL). The organic layer was washed with a 1N HCl solution, a solution of $NaHCO_3$ (5%) and brine. The organic layer was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (DCM/MeOH 30:1 to 15:1) to afford product **38**. LC-MS: m/z $[M+H]^+$ calcd. for $C_{36}H_{44}F_3N_4O_6$: 685.3, found: 685.5.



tert-Butyl ((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (**49**)

To a solution of compound **47** (1.0 g, 3.49 mmol) in methanol (40 mL) was added $NaBH_4$ (0.53 g, 14 mmol) at room temperature. The reaction mixture was stirred at this temperature for 2 h, then quenched with water (30 mL). The suspension was extracted with EtOAc (50 mL x 3) and the combined organic layers were dried over Na_2SO_4 and finaly evaporated under vacuum. The residue was then dissolved in dichloromethane (20 mL) and Dess-Martin periodinane (1.48 g, 3.49 mmol) and $NaHCO_3$ (0.37 g, 3.49 mmol) were added. The resulting mixture was stirred at room temperature for 5 h. The mixture was diluted with EtOAc (150 mL) and the organic layer was washed with an aqueous solution of 10% $Na_2S_2O_4$, a saturated solution of $NaHCO_3$, a solution of 1N HCl, and brine successively. The organic layer was dried over Na_2SO_4 and then concentrated to give product **49** as a white solid which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 9.73 (1H, s), 6.02 (1H, br), 5.48 (1H, d, J = 7.8 Hz), 4.36–4.25 (1H, m), 3.38–3.32 (2H, m), 2.50–2.44 (2H, m), 2.11–2.03 (1H, m), 1.88–1.76 (2H, m), 1.43 (9H, s). LCMS-ESI (m/z): 257 $(M + H)^+$.

tert-Butyl((S)-1-((S)-2-oxopyrrolidin-3-yl)but-3-en-2-yl)carbamate (**50**)

To a suspension of methyltriphenylphosphonium bromide (3.29 g, 9.29 mmol) in THF (10 mL) at -78 °C was added LiHMDS (30.3 g, 152 mmol). The resulting yellow suspension was warmed up to room temperature and stirred at the same temperature for 1 hour. After the reaction mixture was cooled down to -78°C, a solution of aldehyde **49** (1.07 g, 4.4 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at 0 °C overnight. The reaction was quenched with MeOH (0.5 mL) and the resulting mixture was poured into 1 N HCl solution (20 mL). Extraction with Et_2O (3 x 20 mL), drying over Na_2SO_4 and evaporation of the solvent in vacuo afforded an orange semi-solid that was purified by silica gel chromatography (DCM/MeOH = 20/1) to afford **50** as a white solid (0.36 g, 32 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.89 (s, 1H), 5.72 – 5.80 (m, 1H), 5.03 – 5.20 (m, 3 H), 4.14 (s, br, 1H), 3.23 – 3.31 (m, 2H), 2.40 – 2.46 (m, 2H), 1.72-1.77 (m, 1 H), 1.45-1.52 (m, 1 H), 1.40 (s, 9 H).

tert-Butyl ((S)-4-methyl-1-oxo-1-(((S)-1-((S)-2-oxopyrrolidin-3-yl)but-3-en-2-yl)amino)pentan-2-yl)carbamate (**51**)

To a solution of **50** (250 mg, 1.04 mmol) in dioxane (5 mL) was added a solution of 4 M HCl in dioxane (2 mL). The reaction was stirred at room temperature for 3 h and then the volatils were removed under vacuum. The residue was finally coevaporated with toluene the deprotected deprotected product as a colorless oil. To a solution of this amino derivative in DCM (20 mL) was added EDC (250 mg, 1.3 mmol), HOBt (176 mg, 1.3 mmol), Boc-L-Leu-OH (280 mg, 1.2 mmol) and DIPEA (0.84 mL, 4.8 mmol). The solution was stirred at room temperature overnight before being diluted with ethyl acetate (80 mL). The organic layer was washed successively with aq. HCl (1M), sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4. After removal of the volatils under vacuum, the title compound **51** was obtained as a colorless oil (250 mg, 67 %). LCMS-ESI (m/z): 368 $(M + H)^+$.

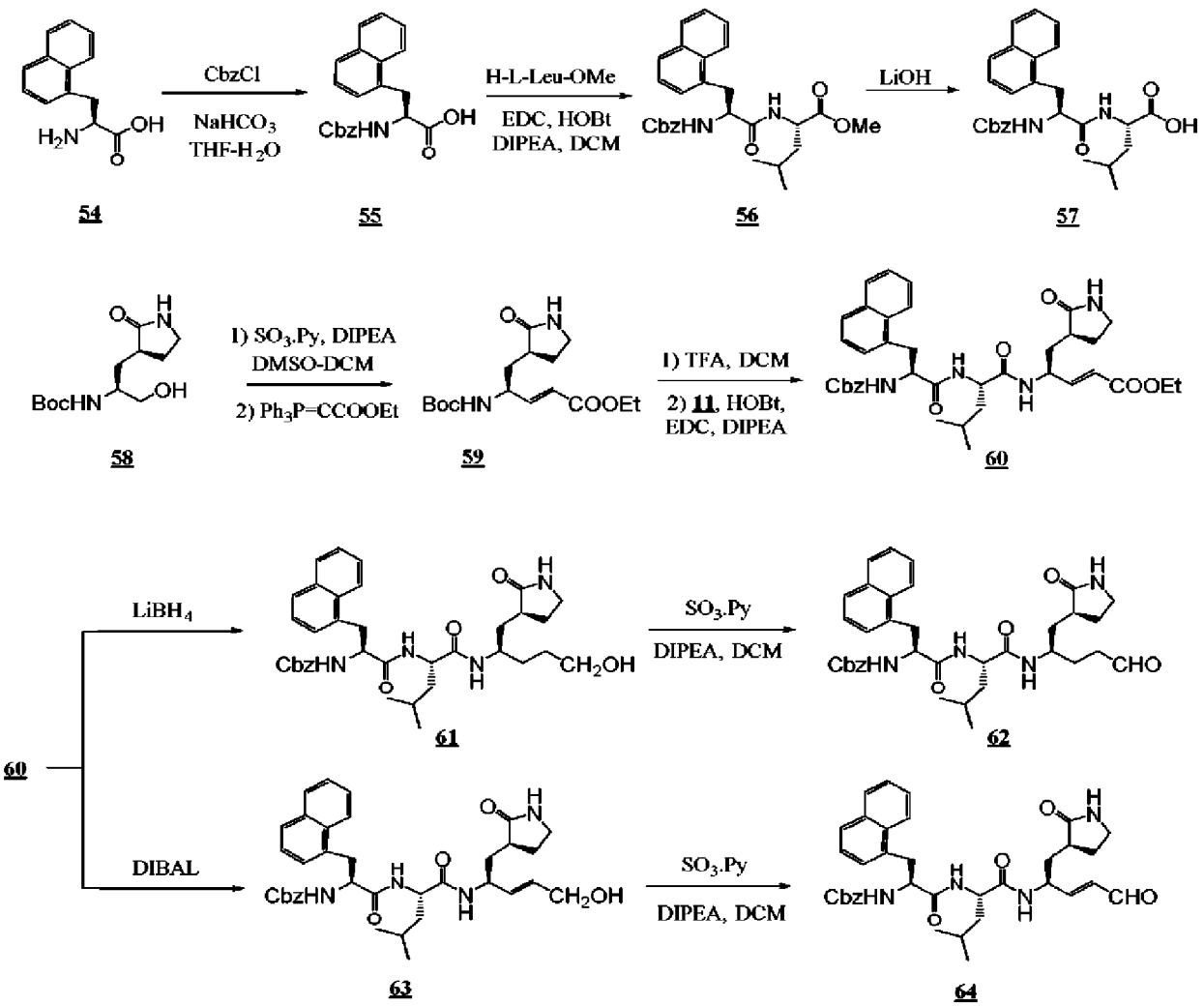
Benzyl ((S)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-((S)-2-oxopyrrolidin-3-yl)but-3-en-2-yl)amino) pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**52**)

Compound **51** (370 mg, 1.0 mmol) was dissolved in DCM (6 mL) and treated with trifluoroacetic acid (2 mL). The solution was stirred at room temperature for 3 h and the solvent was removed under vacuum. The crude compound was dried under vacuum for 5 h and used in the next step without further purification. To a solution of the deprotected amino acid in DCM (20 mL) was added EDCI (230 mg, 1.2 mmol), HOBt (160 mg, 1.2 mmol), Z-L-Ala(-1-naphthyl)-OH (350 mg, 1.0 mmol) and DIPEA (0.7 mL, 4.0 mmol). After being stirred at room temperature overnight, the reaction mixture was diluted with ethyl acetate (80 mL). The organic layer was washed successively with aq. HCl (1M), sat. aq. $NaHCO_3$ and brine. The organic layer was then dried over Na_2SO_4 and the solvent removed under vacuum. The residue was purified by column chromatography (DCM:MeOH = 20:1) to give title compound **52** as a white solid (320 mg, 54 %). ^{1}H NMR (400 MHz, MeOH-*d4*) δ 8.18 (t, J = 10.1 Hz, 2 H), 7.87 (d, J = 7.6 Hz, 1 H), 7.76 (d, J = 7.3 Hz, 1 H), 7.48-7.54 (m, 2 H), 7.21-7.40 (m, 7 H), 5.80-5.85 (m, 1 H), 5.21 (dt, J_1 = 1.4 Hz, J_2 = 17.2 Hz, 1 H), 5.17 (dt, J_1 = 1.4 Hz, J_2 = 10.4 Hz, 1 H), 4.95-4.97 (m, 2 H), 4.59-4.65 (m, 1 H), 4.40-4.52 (m, 2 H), 3.67-3.73 (m, 1 H), 3.16-3.28 (m, 2 H), 2.47-2.49 (m, 1 H), 2.24-2.27 (m, 1 H), 1.47-1.77 (m, 4 H), 0.91-0.96 (m, 6 H); ^{13}C NMR (100 MHz, MeOH-*d4*) δ 181.02, 172.93, 171.58, 156.92, 138.32, 136.69, 134.04, 132.98, 131.98, 128.48, 128.03, 127.52, 127.29, 125.90, 125.30, 125.02, 123.25, 113.62, 66.23, 60.14, 55.81, 52.43, 49.33, 40.68, 40.10, 38.28, 35.58, 34.53, 27.51, 24.40, 21.97, 20.84, 19.49, 13.09; LCMS-ESI (m/z): 599 $(M + H)^+$.

Benzyl ((2S)-1-(((2S)-4-methyl-1-(((1S)-1-(oxiran-2-yl)-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**53**)

To a solution of compound **52** (50 mg, 0.08 mmol) in DCM (5 mL) containing *aq.* $Na_2HP_3O_4$ (6 M, 40μL, 0.24 mmol) was added mCPBA (70%, 62 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 24 h. EtOAc (30 mL) was added and the solution was washed with a saturated solution of $NaHCO_3$, 1 N HCl, brine, and dried over Na_2SO_4. After concentration under vacuum, the residue was purified on preparative TLC to afford compound **53** as a white solid (20 mg, 39%). ^{1}H NMR (400 MHz, MeOH-*d4*) δ 8.11-8.23 (m, 1 H), 7.94-

8.01 (m, 1 H), 7.89 (d, J = 7.7 Hz, 1 H), 7.78 (d, J = 7.2 Hz, 1 H), 7.23-7.61 (m, 8 H), 4.98 (s, 2 H), 4.59-4.62 (m, 1 H), 4.35-4.40 (m, 1 H), 4.02-4.10 (m, 1 H), 3.69-3.74 (m, 1 H), 3.21-3.28 (m, 2 H), 3.04-3.07 (m, 1 H), 2.75-2.77 (m, 1 H), 2.58-2.60 (m, 1 H), 2.45-2.52 (m, 1 H), 2.09-2.33 (m, 2 H), 1.53-1.81 (m, 4 H), 1.30-1.37 (m, 1 H), 0.88-0.98 (m, 6 H); ^{13}C NMR (100 MHz, MeOH-*d4*) δ 180.88, 173.64, 173.56, 172.75, 156.87, 136.69, 134.03, 133.00, 132.19, 131.98, 129.67, 128.44, 128.01, 127.50, 127.26, 127.20, 125.87, 125.28, 124.99, 123.24, 66.20, 55.57, 53.29, 52.40, 44.06, 40.51, 40.06, 38.05, 34.38, 32.54, 27.43, 24.50, 21.95, 20.66; LCMS-ESI (m/z): 615 $(M + H)^+$, 633 $(M + H + H_2O)^+$



Methyl ((S)-2-(((benzyloxy)carbonyl)amino)-3-(naphthalen-1-yl)propanoyl)-L-leucinate (**56**)

To a solution of Cbz-L-Ala(1-Naphthyl)-OH **55** (0.78 g, 2.25 mmol) and L-Leu-OMe (0.45 g, 2.48 mmol) in DCM (50 mL) was added EDCI (560 mg, 2.9 mmol), HOBt (400 mg, 2.9 mmol), and DIPEA (1.6 mL, 9 mmol). The reaction mixture was stirred overnight at room temperature at which time H_2O (100 mL) and EtOAc (200 mL) were added. The organic layer was washed successively with aq. HCl (1 M, 50 mL), sat. aq. $NaHCO_3$ (200mL) and brine (100mL), and then dried over Na_2SO_4. The solvent was removed under vacuum to give the title compound as a yellow solid after crystallization from ethyl acetate (0.9 g, 85%). ^{1}H NMR (400 MHz, MeOH-*d4*) δ 7.89 (d, *J* = 9.0 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.49-7.58 (m, 2 H), 7.36-7.41 (m, 8 H), 5.82 (d, *J* = 8.0 Hz, 1 H), 5.51-5.53 (m, 1 H), 5.08-5.16 (m, 2 H), 4.60-4.65 (m, 1 H), 4.44-4.59 (m, 1 H), 4.09-4.23 (m, 2 H), 3.21-3.27 (m, 2 H), 2.48-2.52 (m, 1 H), 1.57-1.80 (m, 4 H), 1.21-1.40 (m, ; LCMS-ESI (m/z): 477 $(M + H)^+$.

((S)-2-(((Benzyloxy)carbonyl)amino)-3-(naphthalen-1-yl)propanoyl)-L-leucine (**57**)

To a solution of methyl ester **56** (2.0 g, 4.2 mmol) in MeOH (19 mL) was added a solution of $LiOH·H_2O$ (270 mg, 6.3 mmol) in H_2O (1 mL). The reaction mixture was stirred overnight at room temperature. The volatiles were removed under vacuum to give a colourless residue that was partitioned between EtOAc and *aq.* HCl (1M). The organic layer was separated, washed successively with *aq.* HCl (1M) and brine, then dried over $MgSO_4$, and the solvent removed under vacuum to give a glassy solid. Recrystallization from EtOAc gave the title compound **57** as a white solid (1.86 g, 96%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13-8.21 (m, 1 H), 7.89 (s, br, 1 H), 7.79 (s, 1 H), 7.25-7.57 (m, 9 H), 5.02-5.17 (m, 1 H), 4.33-4.59 (m, 1 H), 3.34-3.56 (m, 1 H), 1.34-1.54 (m, 3 H), 0.84-0.88 (m, 6 H); LCMS-ESI (m/z): 463 $(M + H)^+$.

Methyl (5S,8S,11S,E)-8-isobutyl-5-(naphthalen-1-ylmethyl)-3,6,9-trioxo-11-(((S)-2-oxopyrrolidin-3-yl)methyl)-1-phenyl-2-oxa-4,7,10-triazatetradec-12-en-14-oate (**60**)

To a solution of compound **59** (330 mg, 1.0 mmol) in dioxane (5 mL) was added HCl (4 M in dioxane, 2 mL). The reaction was stirred at room temperature for 3 h and then the volatils were removed under vacuum to give the crude deprotected amine which was used directly in the next step. This compound was thus dissolved in DCM (20 mL) and EDC (250 mg, 1.3 mmol), HOBt (176 mg, 1.3 mmol), dipeptide **57** (460 mg, 1.0 mmol) and DIPEA (0.84 mL, 4.8 mmol) were added. The solution was stirred at room temperature overnight and then diluted with ethyl acetate (80 mL). The organic layer was washed successively with *aq.* HCl (1M), *sat. aq.* $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent removed under vacuum. The residue was purified by column chromatography to give **60** as a white solid (460 mg, 70 %).^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18-8.21 (m, 1 H), 7.74-7.94 (m, 3 H), 7.23-7.68 (m, 8H), 6.91 (dd, J = 15.5, 5.3 Hz, 1 H), 5.90-6.02 (m, 1H), 4.95-5.01 (m, 1 H), 4.60-4.65 (m, 1 H), 4.32-4.86 (m, 1 H), 4.01-4.23 (m, 2 H), 3.70-3.75 (m, 1 H), 3.21-3.27 (m, 2 H), 2.48-2.52 (m, 1 H), 2.40-2.66 (m, 1 H), 1.58-1.80 (m, 4 H), 1.20-1.40 (m, 6 H), 0.89-1.10 (m, 6 H); LCMS-ESI (m/z): 657 $(M + H)^+$.

Benzyl ((S)-1-(((S)-1-(((R)-5-hydroxy-1-((S)-2-oxopyrrolidin-3-yl)pentan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**61**)

To a solution of methyl ester **60** (34 mg, 0.05 mmol) in dry THF (3 mL) was added $LiBH_4$ (2M in THF, 0.03 mL, 0.06 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h and then quenched with aq. HCl (1M). Ethyl acetate (20 mL) was added and the organic layer was further washed with H_2O, dried over Na_2SO_4, and the solvent removed under vacuum to give a white solid. Recrystallization from EtOAc gave **61** as a white solid (9 mg, 29%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 (d, J = 8.3 Hz, 1H), 7.97 – 7.71 (m, 3H), 7.52 (dt, J = 14.6, 7.5 Hz, 2H), 7.45 – 7.20 (m, 9H), 5.10 – 4.94 (m, 2H), 4.58 (dd, J = 9.5, 5.3 Hz, 1H), 4.46 – 4.29 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.97 (d, J = 10.6 Hz, 1H), 3.70 (dd, J = 14.0, 5.0 Hz, 1H), 3.30 – 3.17 (m, 2H), 2.59 – 2.20 (m, 5H), 2.05 – 1.38 (m, 7H), 1.37 – 1.16 (m, 4H), 0.93 (td, J = 12.7, 10.8, 5.7 Hz, 6 H); LCMS-ESI (m/z): 631 $(M + H)^+$.

Benzyl ((S)-1-(((S)-4-methyl-1-oxo-1-(((R)-5-oxo-1-((S)-2-oxopyrrolidin-3-yl)pentan-2-yl)amino) pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**62**)

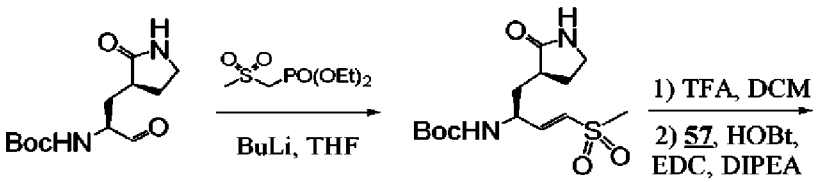
To a solution of **61** (47 mg, 0.075 mmol) in DCM (4 mL) and DMSO (1 mL) was added DIPEA (50 µL, 0.3 mmol) at 0 °C. The solution was stirred for 30 min before addition of SO_3·pyridine complex (47 mg, 0.3 mmol). The reaction mixture was stirred for 3 h at room temperature, and then diluted with EtOAc (50 mL). The organic phase was separated and then washed successively with *aq.* HCl (1M), *sat. aq.* $NaHCO_3$, and brine, dried over Na_2SO_4 . After removal of the voaltils under vacuum, the residue was purified by preparative TLC (DCM:MeOH 20:1) to give **62** as a white solid. LCMS-ESI (m/z): 629 $(M + H)^+$.

Benzyl ((S)-1-(((S)-1-(((S,E)-5-hydroxy-1-((S)-2-oxopyrrolidin-3-yl)pent-3-en-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**63**)

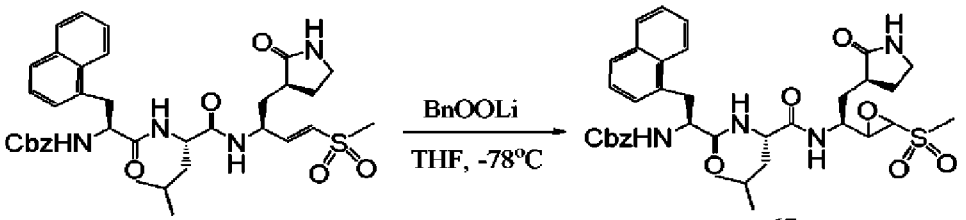
To a solution of **60** (67 mg, 0.1 mmol) in DCM (3 mL) was added DIBAL (1 M, 0.2 mL, 0.3 mmol) at 0 °C. The reaction was stirred for 2 h at 0 °C and then quenched with 1 M HCl (0.1 mL). The reaction mixture was warmed up to room temperature and diluted with EtOAc (15 mL). The organic layer was washed successively with 1 M HCl (5 mL), *sat. aq.* $NaHCO_3$ (5 mL), and brine , dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by silica gel chromatography (DCM:MeOH = 20:1) to give **63**. ^1H NMR (400 MHz, Methanol-d_4) δ 8.22 (d, J = 8.4 Hz, 1 H), 7.84 (dd, J = 41.9, 7.7 Hz, 2 H), 7.53 (dt, J = 14.5, 7.6 Hz, 1 H), 7.44 – 7.13 (m, 7 H), 5.81 – 5.63 (m, 1 H), 4.68 – 4.27 (m, 4 H), 4.07 (d, J = 5.0 Hz, 1 H), 3.80 – 3.62 (m, 1 H), 2.60 – 2.17 (m, 3 H), 2.03 (dd, J = 24.1, 7.1 Hz, 2 H), 1.82 – 1.45 (m, 6 H), 1.31 (s, H), 1.04 – 0.85 (m, 6 H); LCMS-ESI (m/z): 629 $(M + H)^+$.

Benzyl ((S)-1-(((S)-4-methyl-1-oxo-1-(((S,E)-5-oxo-1-((S)-2-oxopyrrolidin-3-yl)pent-3-en-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**64**)

To a solution of alcohol **63** (56 mg, 0.09 mmol) in DCM (4 mL) and DMSO (1 mL) was added DIPEA (0.13 mL, 0.36 mmol) at 0 °C. The solution was stirred for 30 min before addition of SO_3·pyridine complex (60 mg, 0.36 mmol). The reaction mixture was then stirred at 0 °C overnight and then diluted with EtOAc (25mL). The organic phase was separated and then washed successively with *aq.* HCl (1M, 10 mL), *sat. aq.* $NaHCO_3$ (10 mL), and brine, dried over Na_2SO_4. After removal of the volatils under vacuum, the residue was purified by preparative TLC to give **64** as a white solid (mg, 75%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.55 (dd, J = 1.6, 7.8 Hz, 1 H), 8.21 (d, J = 8.4 Hz, 1 H), 7.88 (d, J = 7.4 Hz, 1 H), 7.78 (d, J = 6.6 Hz, 1 H), 7.48-7.57 (m, 2 H), 7.23-7.41 (m, 7 H), 6.91-6.97 (m, 1 H), 6.14-6.20 (m, 1 H), 4.99 (s, 2 H), 4.74-4.85 (m, 1 H), 4.59-4.63 (m, 1 H), 4.37-4.41 (m, 1 H), 3.68-3.74 (m, 1 H), 3.24-3.29 (m, 2 H), 2.45-2.61 (m, 1 H), 2.24-2.32 (m, 1 H), 1.62-1.84 (m, 5 H), 0.89-0.98 (m, 6 H); LCMS-ESI (m/z): 627 $(M + H)^+$.



49 **65**



66 **67**

tert-Butyl ((S,E)-4-(methylsulfonyl)-1-((S)-2-oxopyrrolidin-3-yl)but-3-en-2-yl)carbamate (**65**)

To a solution of diethyl ((methylsulfonyl)methyl)phosphonate (1.46 g, 6.3 mmol) in THF (60 mL) was added BuLi (1 M, 6.5 mL, 6.5 mmol) dropwise at -78°C. After stirred for 30 min, aldehyde **49** (1.35 g, 5.3 mmol) in THF (10 mL) was added over 30 min. The reaction mixture was warmed up to rt over 1 h and stirred for further 3 h. Quenched the reaction by

addition of MeOH (1 mL), and the solvent was removed in vacuum. The residue was partitioned between EtOAc (150 mL) and *aq.* 1N HCl (80 mL), and the organic phase was washed respectively with *aq.* $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated, and the residue was purified by silica gel chromatography (DCM:MeOH = 20:1) to afford **65** (25%). LCMS-ESI (m/z): 333 [M+H].

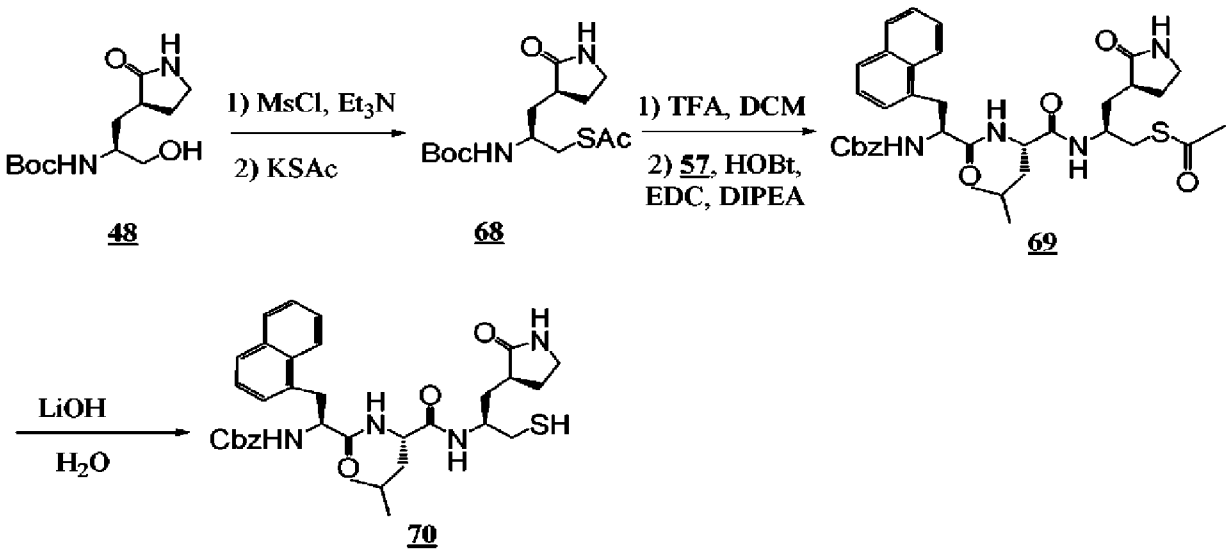
Benzyl ((S)-1-(((S)-4-methyl-1-(((S,E)-4-(methylsulfonyl)-1-((S)-2-oxopyrrolidin-3-yl)but-3-en-2-yl)amino)-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**66**)

A solution of compound **65** (330 mg, 1 mmol) and trifluoroacetic acid (2 mL) in DCM (6 mL) was stirred at room temperature for 3 h. The solvent was removed under vacuum and the residue coevaporated three times with toluene. The residue was then dissolved in DCM (30 mL) and dipeptide **57** (480 mg, 1.05 mmol), EDCI (250 mg, 1.3 mmol), HOBt (180 mg, 1.3 mmol), and DIPEA (0.7 mL, 4 mmol) were added. The solution was stirred at room temperature overnight before being diluted with EtOAc (80 mL). The organic layer was washed successively with *aq.* HCl (1M), *sat. aq.* $NaHCO_3$ and brine, dried over Na_2SO_4. Removal of the volatils under vacuum and recristalization of the residue from EtOAc gave **66** as a white solid (27mg, 31%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 (d, J = 8.72 Hz, 1 H), 7.89 (d, J = 7.76 Hz, 1 H), 7.79 (d, J = 4.84 Hz, 1 H), 7.48-7.59 (m, 2 H), 7.25-7.40 (m, 7 H), 6.86 (dd, J = 4.8, 15.32 Hz, 1 H), 6.7 (d, J = 15.16 Hz, 1 H), 5.01-5.05 (m, 2 H), 4.70-4.72 (m, 1 H), 4.56-4.60 (m, 1 H), 4.31-4.34 (m, 1 H), 3.66-3.73 (m, 1 H), 2.99 (s, 3 H), 2.51-2.54 (m, 1 H), 2.27-2.29 (m, 1 H), 1.61-1.84 (m, 4 H), 0.91-0/98 (m, 6 H); LCMS-ESI (m/z): 677 $(M + H)^+$.

Benzyl ((2S)-1-(((2S)-4-methyl-1-(((1S)-1-(3-(methylsulfonyl)oxiran-2-yl)-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**67**)

To a solution of TBHP (5.5 M, 50 µL, 0.27 mmol) in THF (5 mL) was added MeLi (2.5 M, 0.1 mL, 0.25 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 15 min and

then a solution of compound **66** (123 mg, 0.18 mmol) in THF (1 mL) was added dropwise. The resulting mixture was stirred at 0 °C overnight. Solid Na_2SO_3 (200 mg) was added and the suspension was stirred for 15 min. After dilution with *sat. aq.* NH_4Cl solution, extraction with EtOAc (30 mL x 3), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude oil was purified by column chromatography (DCM:MeOH = 20:1) to give **67** as a pale yellow solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.23 (d, J = 8.6 Hz, 1 H), 7.88 (d, J = 8.2 Hz, 1 H), 7.78 (d, J = 7.3 Hz, 1 H), 7.53 (dd, J = 17.7, 7.7 Hz, 1 H), 7.45 – 7.18 (m, 6 H), 4.98 (d, J = 3.6 Hz, 1 H), 4.72 (q, J = 7.2, 6.7 Hz, 1 H), 4.60 (q, J = 3.8 Hz, 1 H), 4.47 (dd, J = 26.2, 3.5 Hz, 1 H), 4.19 – 4.05 (m, 2 H), 3.69 (dt, J = 13.1, 6.2 Hz, 1 H), 3.38 (d, J = 6.7 Hz, 1 H), 2.58 (d, J = 10.3 Hz, 1 H), 2.43 – 2.30 (m, 1 H), 2.05 – 1.92 (m, 1 H), 1.82 (ddd, J = 13.2, 8.8, 4.4 Hz, 1 H), 1.75 – 1.44 (m, 2 H), 1.40 – 1.21 (m, 2H), 0.94 (hept, J = 6.7 Hz, 6 H); LCMS-ESI (m/z): 693 $(M + H)^+$.



48 68 69 70

S-((S)-2-((tert-Butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propyl) ethanethioate (**32**)

To a solution of N-[1-(hydroxymethyl)cyclopropyl]carbamic acid-t-butyl ester **2** (3.74 g, 20.0 mmol) and NEt_3 (3.4 mL, 24.0 mmol) in CH_2Cl_2 (100 mL), methanesulfonyl chloride (1.9 mL, 24.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 20 h at

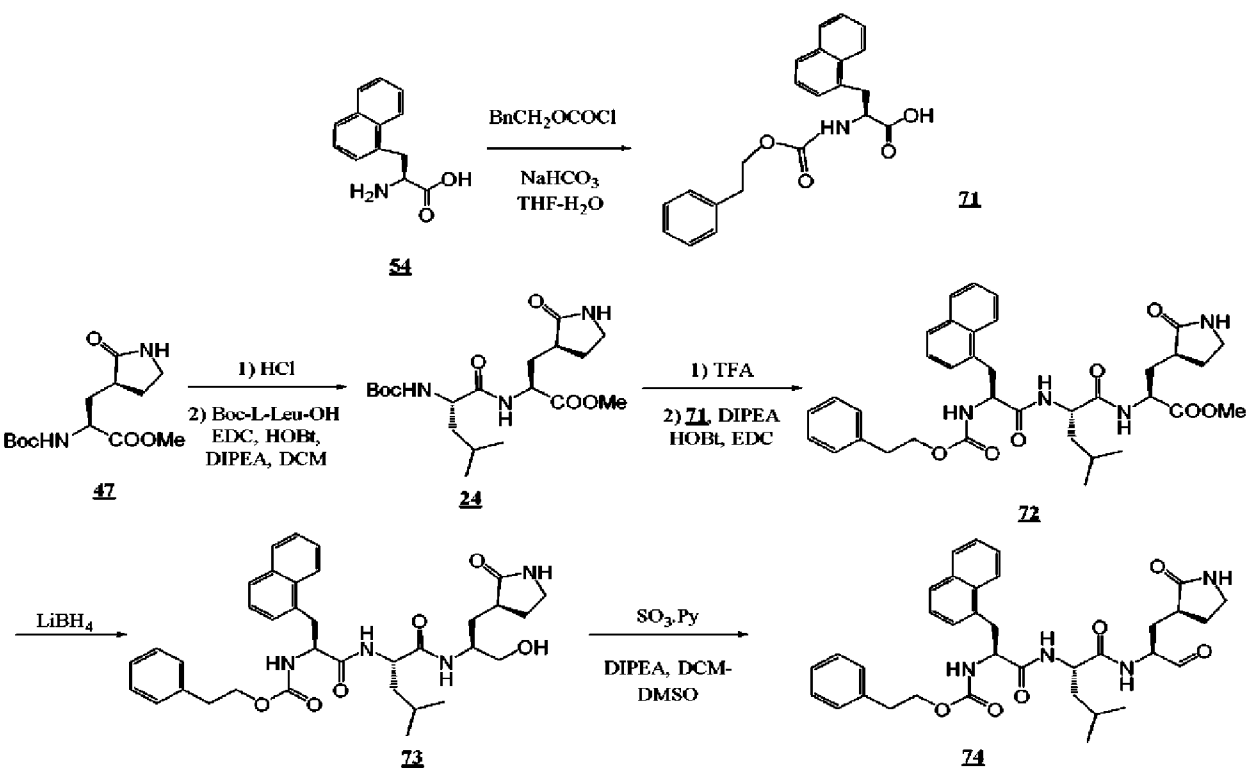
0 °C and after removal of the volatile components under reduced pressure, the residue was diluted with H_2O (60 mL). The aqueous phase was extracted with EtOAc (3 x 60 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. To a solution of the residue in DMF (90 mL) was added K_2CO_3 (6.78 g, 20.8 mmol) and thioacetic acid (1.5 mL, 20.8 mmol).The reaction mixture was stirred for 24 h at room temperature and then the volatile components were removed under reduced pressure. 1N HCl (90 mL) was added to the residue and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. Recrystallization of the residue from hexane/Et_2O yielded **68** (2.97 g, 12.1 mmol, 61 %) as pale yellow solid. LCMS-ESI (m/z): 317 [M+H].

S-((5S,8S,11S)-8-Isobutyl-5-(naphthalen-1-ylmethyl)-3,6,9-trioxo-11-(((S)-2-oxopyrrolidin-3-yl)methyl)-1-phenyl-2-oxa-4,7,10-triazadodecan-12-yl) ethanethioate (**69**)

A solution of compound **68** (130 mg, 0.41 mmol) in DCM (6 mL) and trifluoroacetic acid (2 mL) was stirred at room temperature for 2 h. The solvent was removed under vacuum, the residue coevaporated three times with toluene. To a solution of the dry residue in DCM (20 mL) was added dipeptide **57** (200 mg, 0.43 mmol), EDCI (103 mg, 0.54 mmol), HOBt (73 mg, 0.54 mmol), and DIPEA (0.3 mL, 1.72 mmol). The solution was stirred at room temperature overnight before being diluted with EtOAc (80 mL). The organic layer was washed successively with aq. HCl (1M), sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4. After removal of the solvent under vacuum and reccrystalization from EtOAc, the thioacetate **69** was obtained as a white solid (227 mg, 50%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (d, J = 8.4 Hz, 1 H), 7.89 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.48-7.59 (m, 2 H), 7.30-7.44 (m, 7 H), 5.32 (d, J = 12.4 Hz, 1 H), 5.13 (d, J = 12.4 Hz, 1 H), 4.42-4.47 (m, 1 H), 3.97-4.07 (m, 2 H), 3.45-3.51 (m, 1 H), 3.24-3.30 (m, 1 H), 3.16-3.20 (m, 1 H), 2.87-2.93 (m, 1 H), 2.29 (s, 3 H), 1.67-1.73 (m, 1 H), 1.48-1.52 (m, 1 H), 1.35-1.42 (m, 1 H), 1.09-1.16 (m, 1 H), 0.92-0.97 (m 1 H), 0.60 (d, J = 6.4 Hz, 3 H), 0.52 (d, J = 6.4 Hz, 3 H); LCMS-ESI (m/z): 661 [M+H].

Benzyl ((S)-1-(((S)-1-(((S)-1-mercapto-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**70**)

A solution of thioacetate **60** (21 mg, 0.03 mmol) and LiOH (2.4 mg, 0.1 mmol) in methanol (1 ml), and the mixture was stirred for 3 days in room temperature. The solvent was removed under vaccum and the residue was purified by preparative TLC (DCM:MeOH = 20:1) to give solid thiol **70** in quantitative yield. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (d, J = 8.4 Hz, 1 H), 7.89 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.48-7.59 (m, 2 H), 7.30-7.44 (m, 7 H), 5.32 (d, J = 12.4 Hz, 1 H), 5.13 (d, J = 12.4 Hz, 1 H), 4.42-4.47 (m, 1 H), 3.97-4.07 (m, 2 H), 3.45-3.51 (m, 1 H), 3.24-3.30 (m, 1 H), 3.16-3.20 (m, 1 H), 2.87-2.93 (m, 1 H), 1.67-1.73 (m, 1 H), 1.48-1.52 (m, 1 H), 1.35-1.42 (m, 1 H), 1.09-1.16 (m, 1 H), 0.92-0.97 (m 1 H), 0.60 (d, J = 6.4 Hz, 3 H), 0.52 (d, J = 6.4 Hz, 3 H); LCMS-ESI (m/z): 619 [M+H].



(S)-3-(naphthalen-1-yl)-2-((phenethoxycarbonyl)amino)propanoic acid (**71**)

To a mixture of amino acid **54** (545 mg, 2.53 mmol), $NaHCO_3$ (320 mg, 3.8mmol) in THF-H_2O (2:3, 20 mL) was added $PhCH_2CH_2OCOCl$ (0.33 mL, 2.78 mmol) at 0 °C. The reaction mixture stirred at rt for 5 h and the acidified with 1 N HCl (8-10 mL) to pH 2.0. organic solvents were then removed under vaccum and the remaing aqueous phase extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried, and concentrated under vacuum to give **71** as a white solid after recrystallization from EtOAc. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 8.2 Hz, 1 H), 7.54 (q, *J* = 8.1, 7.1 Hz, 2 H), 7.15-7.48 (m, 7 H), 5.13 (m, 1 H), 4.79 (m, 1 H), 4.27 (m, 2 H), 3.76 (d, *J* = 13.7 Hz, 1 H), 3.50 (m, 1 H), 2.89 (m , 2 H). LCMS-ESI (m/z): 364 [M+H].

Methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (**24**)

To a solution of compound **47** (4.14g, 14.47 mmol) in dioxane (30 mL) was added HCl (4 M in dioxane, 20 mL). The reaction mixture was stirred at room temperature for 2 h and the solvent removed under vacuum. The residue was carfully dried in vacuo for 5 h and then used directely in the next step without further purification. The residue was dissolved in DCM (100 mL) and Boc-L-Leu-OH (4.02 g, 17.4 mmol), EDCI (3.61 g, 18.8 mmol), HOBt (2.54 g, 18.8 mmol), and DIPEA (10.4 mL, 60 mmol) were added. The solution was stirred at room temperature overnight before solvents were removed under vaccum. EtOAc (200 mL) was then added and the organic layer was washed successively with aq. HCl (1M), sat. aq. $NaHCO_3$ and brine and finaly dried over Na_2SO_4. After removal of the solvent under vacuum and recrystallization from EtOAc, compound **24** was obtained as a white solid (72%). LCMS-ESI (m/z): 400 [M+H].

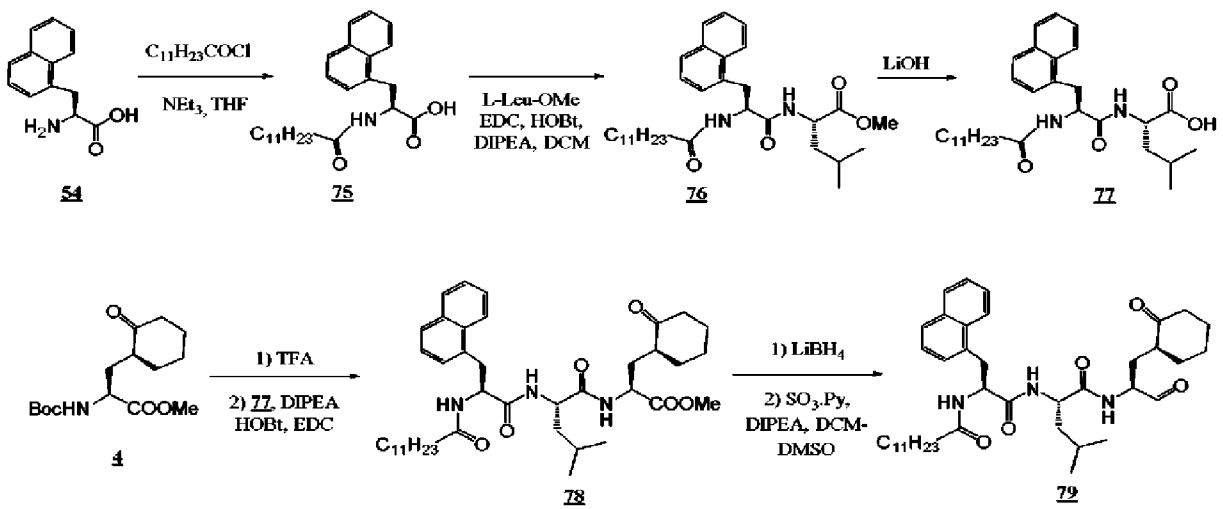
Methyl (6S,9S,12S)-9-isobutyl-6-(naphthalen-1-ylmethyl)-4,7,10-trioxo-12-(((S)-2-oxopyrrolidin-3-yl)methyl)-1-phenyl-3-oxa-5,8,11-triazatridecan-13-oate (**72**)

A solution of compound **24** (520 mg, 1.3 mmol) and TFA (5 mL) in DCM (20 mL) was stirred at room temperature for 3 h. The solvent was removed under vaccum and the residue used in the next step without further purification. The residue was dissolved in DCM (40 mL) and compound **71** (494 mg, 1.2 mmol mmol), EDCI (310 mg, 1.62 mmol), HOBt (220 mg, 1.62 mmol), and DIPEA (0.88 mL, 5 mmol) were added The solution was stirred at room temperature overnight before solvents were removed under vaccum. EtOAc (100 mL) was then added and the organic layer was washed successively with aq. HCl (1M), sat. aq. $NaHCO_3$ and brine and finaly dried over Na_2SO_4. After removal of the solvent under vacuum and recrystallization from EtOAc, compound **72** was obtained as a white solid (62%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.16 (d, J = 8.4 Hz, 1 H), 7.89 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 7.9 Hz, 1 H), 7.54 (dt, J = 27.5, 7.3 Hz, 2 H), 7.44 – 7.20 (m, 7 H), 4.64 (m, 1 H), 4.52 – 4.40 (m, 1 H), 4.34 – 4.11 (m, 3 H), 3.72 (d, J = 15.2 Hz, 1 H), 3.64 (s, 2 H), 3.47 (d, J = 7.8 Hz, 1 H), 3.30 – 3.18 (m, 1 H), 2.91 (t, J = 6.9 Hz, 1 H), 2.50 (d, J = 10.7 Hz, 1 H), 2.28 (ddd, J = 34.9, 17.0, 7.3 Hz, 2 H), 1.92 – 1.37 (m, 2 H), 1.14 (d, J = 6.0 Hz, 1 H), 0.64 (d, J = 12.8 Hz, 6 H); LCMS-ESI (m/z): 645 [M+H].

Phenethyl ((S)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**74**)

To a solution of methyl ester **72** (420 mg, 0.65 mmol) in THF-EtOH (2:3, 10 mL) were added $LiBH_4$ (4M, 250 µL, 1 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h and then quenched with aq. HCl (1 M). Ethyl acetate (50 mL) was added and the organic phase was further washed with brine and dried over Na_2SO_4 After removal of the solvent under vacuum compound **73** was obtained as a white solid. To a solution of alcohol **73** in a mixture of DCM (16 mL) and DMSO (4 mL) was added at 0 °C DIPEA (360 µL, 2.07 mmol). The resulting solution was stirred for 30 min before addition of SO_3-pyridine complex (330 mg, 2.06 mmol). The reaction mixture was stirred overnight at 0 °C and then diluted with EtOAc (100 mL). The organic phase was then washed successively with aq. HCl (1M), sat. aq. $NaHCO_3$, and brine and dried over Na_2SO_4. After removal of the solvent under vacuum and recrystallization from EtOAc, compound **74** was obatined as a white solid (68%). ^{1}H NMR (400

MHz, Methanol-d_4) δ 8.16 (d, J = 8.4 Hz, 1 H), 7.89 (d, J = 7.8 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.64 – 7.44 (m, 2 H), 7.15-7.46 (m, 7 H), 4.53 – 4.41 (m, 1 H), 4.31 – 4.14 (m, 3 H), 3.69 (s, 1 H), 3.64 (s, 2 H), 3.51 – 3.44 (m, 1 H), 3.29 – 3.14 (m, 2 H), 2.90 (q, J = 7.2 Hz, 2 H), 2.59 – 2.44 (m, 1 H), 2.39 – 2.14 (m, 1 H), 1.91 – 1.64 (m, 1 H), 1.64 – 1.37 (m, 1 H), 0.72 – 0.51 (m, 6 H); LCMS-ESI (m/z): 615 [M+H].



(S)-2-Dodecanamido-3-(naphthalen-1-yl)propanoic acid (**75**)

To a mixture of amino acid **54** (215 mg, 1 mmol), $NaHCO_3$ (125 mg, 1.5 mmol) in THF-H_2O (2:3, 10 mL) was added $C_{11}H_{23}COCl$ (0.33 mL, 2.78 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h and then acidified with 1 N HCl (8-10 mL) to reach pH 2.0. After removal of the solvent the aqueous layer was extracted with EtOAc (20 mL x 3), and the combined organic phases were washed with brine, dried over Na_2SO_4. After removal of the solvent under vacuum and recrystallization from EtOAc, compound **75** (73%) was obtained as a white solid. LCMS-ESI (m/z): 398 [M+H].

Methyl ((S)-2-dodecanamido-3-(naphthalen-1-yl)propanoyl)-L-leucinate (**76**)

To a solution of compound **75** (380 mg, 1.05 mmol) and L-Leu-OMe (230 mg, 1.27 mmol) in DCM (30 mL) were added added EDCI (260 mg, 1.35 mmol), HOBt (185 mg, 1.34 mmol), and DIPEA (0.73 mL, 4.2 mmol). The reaction mixture was stirred overnight at room temperature and then H_2O (800 mL) and EtOAc (100 mL) were added. The organic phase was washed successively with aq. HCl (1 M, 50 mL), sat. aq. $NaHCO_3$ (50mL) and brine (500mL), and then dried over Na_2SO_4. After removal of the solvent under vacuum and recrystallization from EtOAc, compound **76** (350 mg, 65%) was obtained. LCMS-ESI (m/z): 525 [M+H].

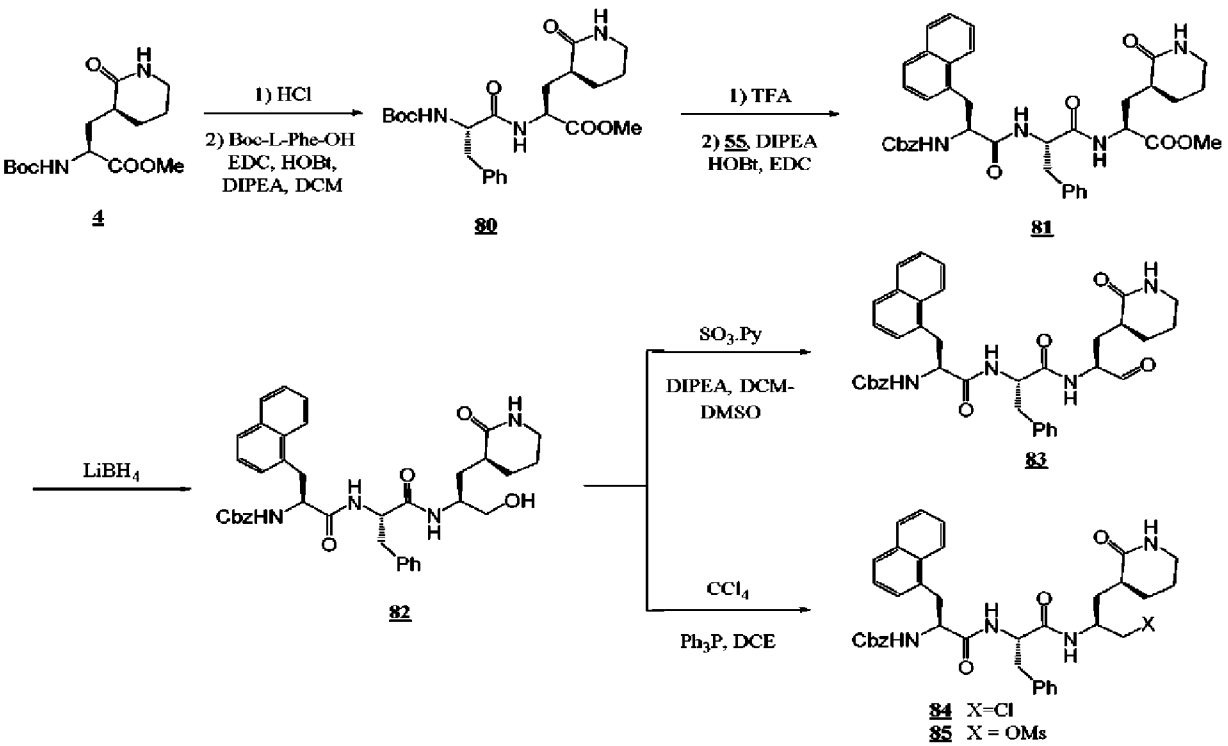
((S)-2-Dodecanamido-3-(naphthalen-1-yl)propanoyl)-L-leucine (**77**)

To a solution of methyl ester **76** (345 mg, 0.66 mmol) in THF-MeOH-H_2O (3:1:1, 10 mL) was added a solution of $LiOH \cdot H_2O$ (32 mg, 1.33 mmol) in H_2O (1 mL). The reaction mixture was stirred overnight at room temperature. The volatiles were removed under vacuum to give a colourless residue that was partitioned between EtOAc and aq. HCl (1M). The organic layer was separated, washed successively with aq. HCl (1M) and brine, then dried over Na_2SO_4, After removal of the solvent under vacuum and recrystallization from EtOAc, compound **77** was obtained as a white solid (430 mg, 96%). LCMS-ESI (m/z): 692 [M+H].

N-((S)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxocyclohexyl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)dodecanamide (**79**)

To a solution of methyl ester **4** (466 mg, 0.67 mmol) in THF-EtOH (2:3, 20 mL) was added $LiBH_4$ (2 M, 440 µL, 0.88 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h and then quenched with aq. HCl (1 M). After addition of ethyl acetate (50 mL) the organic phase was separated and further washed with brine and dried over Na_2SO_4. Removal of the solvent under vacuum afforded compound **78** as a white solid which was used directly in the next without further purification. To a solution of alcohol **78** (70 mg, 0.11 mmol) in a mixture of DCM (3 mL) and DMSO (1 mL) was added at 0 °C DIPEA (90 µL, 0.5 mmol). The solution was stirred at this temperature for 10 min before addition of SO_3·pyridine complex (70 mg, 0.43 mmol). The reaction mixture was stirred overnight at 0 °C and then diluted with

EtOAc (50 mL). The organic phase was separated and then washed successively with aq. HCl (1M), sat. aq. $NaHCO_3$, and brine, dried over Na_2SO_4. After removal of the solvent under vacuum and recrystallization from EtOAc, compound **79** was obtained as a white solid (48 %). ^1H NMR (400 MHz, Methanol-d_4) δ 8.23 (d, J = 6.4 Hz, 1 H), 7.87 (d, J = 6.8 Hz, 1 H), 7.75-7.78 (m, 1 H), 7.48-7.59 (m, 2 H), 7.37 – 7.42 (m, 2 H), 4.37-4.44 (m, 1 H), 3.95-4.04 (m, 1 H), 3.67-3.75 (m, 1 H), 3.45-3.55 (m, 2 H), 3.21-3.28 (m, 2 H), 2.27-2.35 (m, 1 H), 2.08-2.18 (m, 4 H), 1.60-1.82 (m, 7 H), 1.19-1.43 (m, 18 H), 0.90-0.98 (m, 9 H); LCMS-ESI (m/z): 662 [M+H].



Methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-((S)-2-oxocyclohexyl) propanoate (**80**)

To a solution of compound **4** (630 mg, 2.1 mmol) in dioxane (8 mL) was added HCl (4M in dioxane, 8 mL). The solution was stirred at room temperature for 3 h and the solvent was removed under reduced pressure. The obtained residue was used in the next step without

further purification. To a solution of the residue in DCM (80 mL) was added L-Phe-OH (725 mg, 2.73 mmol), EDCI (564 mg, 2.94 mmol), HOBt (400 mg, 2.94 mmol), and DIPEA (1.54 mL, 8.83 mmol). The reaction mixture was stirred at room temperature overnight before evaporation of the solvent unde vaccum. EtOAc (200 mL) was added to the residue and the organic layer was washed successively with *aq.* HCl (1 M), *sat. aq.* $NaHCO_3$, brine and dried over Na_2SO_4. After removal of the solvent under vacuum and recrystallization from EtOAc, compound **80** was obtained as a white solid (72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 7.5 Hz, 1 H), 7.34 – 7.16 (m, 7 H), 6.36 (s, 1 H), 5.19 (d, *J* = 8.4 Hz, 1 H), 4.56 (dd, *J* = 19.2, 10.7 Hz, 2 H), 3.71 (s, 3 H), 3.16 (dd, *J* = 13.9, 5.5 Hz, 1 H), 3.03 (dd, *J* = 14.1, 7.0 Hz, 1 H), 2.35 (ddd, *J* = 14.0, 11.3, 5.1 Hz, 1 H), 2.24 (dq, *J* = 14.9, 5.7 Hz, 1 H), 2.15 – 2.00 (m, 2 H), 1.88 (dtd, *J* = 14.3, 7.9, 3.9 Hz, 2 H), 1.80 – 1.61 (m, 1 H), 1.60 – 1.46 (m, 1 H), 1.37 (d, *J* = 17.7 Hz, 9 H); LCMS-ESI (m/z): 413 [M+H].

Methyl (5S,8S,11S)-8-benzyl-5-(naphthalen-1-ylmethyl)-3,6,9-trioxo-11-(((S)-2-oxopiperidin-3-yl)methyl)-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (**81**)

A solution of compound **80** (592 mg, 1.28 mmol) and TFA (5 mL) in DCM (15 mL) was stirred at room temperature for 2 h. The solvent was removed under vaccum and the residue used in the next step without further purification. The residue was dissolved in DCM (50 mL) and compound **9** (540 mg, 1.54 mmol mmol), EDCI (320 mg, 1.68 mmol), HOBt (225 mg, 1.67 mmol), and DIPEA (0.9 mL, 5.2 mmol) were added. The solution was stirred at room temperature overnight before removal of the solvent under vacuum and addition of EtOAc (150 mL). The organic layer was washed successively with *aq.* HCl (1M), *sat. aq.* $NaHCO_3$,brine and dried over Na_2SO_4. After removal of the solvent under vacuum and recrystallization from EtOAc, compound **81** was obtained as a white solid (62 %). LCMS-ESI (m/z): 679 [M+H].

Benzyl ((S)-1-(((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**82**)

To a solution of methyl ester **81** (870 mg, 1.28 mmol) in THF-EtOH (2:3, 30 mL) was added $LiBH_4$ (2 M, 1 mL, 2 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h and then quenched with aq. HCl (1 M). Ethyl acetate (50 mL) was added and the organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvent under vaccum gave **82** as a white solid which was used in the next step without further purification. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.14 (d, J = 8.5 Hz, 1 H), 7.85 (d, J = 8.3 Hz, 2 H), 7.74 (d, J = 8.1 Hz, 1 H), 7.49 (dq, J = 14.6, 7.2 Hz, 2 H), 7.27 (tdd, J = 16.9, 11.8, 7.9 Hz, 12 H), 4.96 (d, J = 4.2 Hz, 2 H), 4.58 (dt, J = 19.6, 7.1 Hz, 2 H), 4.02 – 3.89 (m, 1 H), 3.55 (dd, J = 14.3, 5.4 Hz, 1 H), 3.48 – 3.06 (m, 4 H), 2.98 (dd, J = 13.6, 8.0 Hz, 1 H), 2.24 (h, J = 5.7, 4.5 Hz, 1 H), 1.98 (dtq, J = 12.7, 6.3, 3.5 Hz, 3 H), 1.79 – 1.53 (m, 4 H), 1.50 – 1.35 (m, 1 H); LCMS-ESI (m/z): 651 [M+H].

Benzyl ((S)-3-(naphthalen-1-yl)-1-oxo-1-(((S)-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-phenylpropan-2-yl)amino)propan-2-yl)carbamate (**83**)

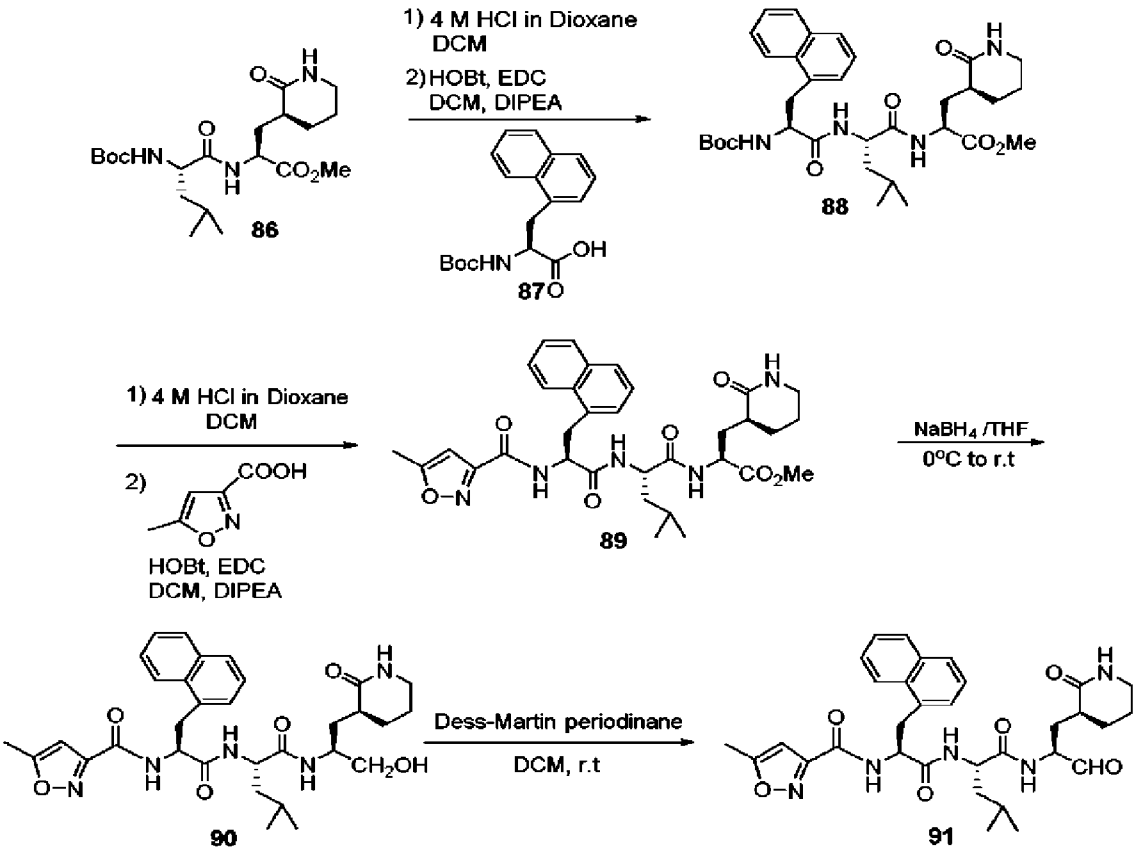
To a solution of **82** (70 mg, 0.11 mmol) in a mixture of DCM (3 mL) and DMSO (1 mL) was added at 0 °C DIPEA (90 µL, 0.5 mmol). After 10 minutes at this temperature, SO_3·pyridine complex (70 mg, 0.43 mmol) was added and the reaction mixture was stirred overnight at 0 °C. After addition of EtOAc (50 mL), the organic layer was washed successively with aq. HCl (1M), sat. aq. $NaHCO_3$, brine and dried over Na_2SO_4. After removal of the solvent under vacuum and recrystallization from EtOAc, compound **83** as a white solid (56 %). ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.22 (s, 0.3 H), 8.22 – 8.07 (m, 1 H), 7.87 (d, J = 8.1 Hz, 1 H), 7.76 (d, J = 8.1 Hz, 1 H), 7.51 (dq, J = 14.6, 7.1 Hz, 2 H), 7.39 – 7.12 (m, 12 H), 5.06 – 4.94 (m, 2 H), 4.69 – 4.46 (m, 1 H), 4.35 – 4.21 (m, 1 H), 3.98 (d, J = 12.3 Hz, 1 H), 3.57 (dt, J = 14.2, 7.7 Hz, 1 H), 3.28 – 2.95 (m, 5 H), 2.29 – 1.93 (m, 1 H), 1.81 (d, J = 14.4 Hz, 1 H), 1.66 (s, 1 H), 1.46 (q, J = 11.5, 10.3 Hz, 1 H), 1.35 – 1.18 (m, 1 H); LCMS-ESI (m/z): 649 [M+H].

Benzyl ((S)-1-(((S)-1-(((S)-1-chloro-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**84**)

A solution of **82** (32 mg, 0.05 mmol), Ph_3P (50 mg, 0.19 mmol), CCl_4 (0.1 mL) in 1,2-dichloroethane (0.5 mL) was heated at 80 °C for 3 min under microwave irradiation. After removal of the solvent under vacuum, the residue was purified by preparative TLC to give **84** (78%) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.51 (dq, J = 15.3, 7.5 Hz, 2H), 7.27 (tdd, J = 20.7, 9.9, 5.4 Hz, 13H), 4.96 (d, J = 19.5 Hz, 2H), 4.57 (dq, J = 21.7, 6.2, 5.1 Hz, 2H), 4.19 – 4.09 (m, 1H), 3.67 – 3.37 (m, 2H), 3.27 – 2.96 (m, 5H), 2.27 (s, 1H), 2.19 – 1.88 (m, 2H), 1.85 – 1.52 (m, 3H); LCMS-ESI (m/z): 669 [M + H].

Benzyl ((S)-3-(naphthalen-1-yl)-1-oxo-1-(((S)-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-phenylpropan-2-yl)amino)propan-2-yl)carbamate (**85**)

To a solution of **82** (41 mg, 0.06 mmol) and NEt_3 (30 μL, 0.2 mmol) in CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (9 μL, 0.09 mmol) at 0 °C. The reaction mixture was stirred for 1 h at this temperature. After removal of the volatile components under reduced pressure, the residue was subjected to preparative TLC to give **85** as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.05 (m, 2 H), 7.87 (d, J = 7.9 Hz, 1 H), 7.77 (t, J = 8.2 Hz, 1 H), 7.51 (dd, J = 13.4, 7.6 Hz, 2 H), 7.27 (tt, J = 17.2, 7.0 Hz, 6 H), 5.06 – 4.96 (m, 2 H), 4.64 – 4.44 (m, 1 H), 4.07 (q, J = 7.7, 5.7 Hz, 1 H), 3.65 – 3.49 (m, 1 H), 3.23 (d, J = 5.0 Hz, 3 H), 3.04 (s, 3 H), 2.37 – 2.21 (m, 2 H), 2.22 – 1.94 (m, 1 H).



Methyl (6S,9S,12S)-9-isobutyl-2,2-dimethyl-6-(naphthalen-1-ylmethyl)-4,7,10-trioxo-12-(((S)-2-oxopiperidin-3-yl)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (88)

To a solution of **86** (930 mg, 2.25 mmol) (Y. Zhai, Y. Ma, F. Ma, Q. Nie, X. Ren, Y.Wang, L. Shang, Z.Yin, *Eur. J. Med. Chem*, **2016**, 124, 559-573.) in CH_2Cl_2 (10 mL) was added 4 M HCl in dioxane (2.3 mL) dropwise. The reaction mixture was stirred for 2 h at room temperature and then concentrated under vacuum. The resulting amine was suspended in DCM (10 mL) and (*S*)-*N*-Boc-*L*-(1-naphthyl)alanine **87** (710 mg, 2.25 mmol), 1-hydroxybenzotriazole (405 mg, 3.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (575 mg, 3.0 mmol) and *N*,*N*-diisopropylethyl amine (2.1 mL, 12.0 mmol) were added at 0 °C. After being stirred at room temperature overnight, the reaction mixture was diluted with EtOAc (80 mL) and the organic layer washed with 1 M HCl, 5% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. After removal of the volatiles under vacuum, the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 20/1 to 10/1) to afford **88** (1.02 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 7.3 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dddd, *J* = 20.7, 8.0, 6.8, 1.3 Hz, 2H), 7.40 – 7.29 (m, 2H), 7.17 (d, *J* = 8.5 Hz, 1H), 6.79 (s, 1H), 5.09 (d, *J* = 8.1 Hz, 1H), 4.67 (td, *J* = 8.8, 4.7 Hz, 1H), 4.59 – 4.41 (m, 2H), 3.70 (s, 3H), 3.37 (dd, *J* = 14.5, 8.2 Hz, 1H), 3.23 (d, *J* = 11.8 Hz, 2H), 2.47 – 2.22 (m, 2H), 2.05 (m, 1H), 1.83 (dp, *J* = 11.5, 3.6 Hz, 2H), 1.67 (ddt, *J* = 19.1, 15.7, 6.1 Hz, 3H), 1.56 – 1.42 (m, 2H), 1.34 (s, 9H), 1.05 (s, 1H), 0.93 – 0.90 (overlap two s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 172.7, 172.5, 171.5, 155.5, 133.9, 133.2, 132.2, 128.8, 127.6, 127.5, 126.3, 125.6, 125.4, 125.6, 123.7, 80.0, 55.3, 52.3, 51.8, 50.1, 42.3, 42.1, 37.7, 34.9, 33.5, 28.2, 28.0, 26.2, 24.6, 22.9, 22.1, 21.4. ESI-MS (*m/z*): 611.4 $(M + H)^+$.

Methyl (S)-2-((S)-4-methyl-2-((S)-2-(5-methylisoxazole-3-carboxamido)-3-(naphthalen-1-yl)propanamido)pentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (89)

To a solution of **88** (610 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added 4 M HCl in dioxane (1.0 mL) dropwise. The reaction mixture was stirred for 2 h at room temperature and then concentrated under vacuum. The residue was suspended in CH_2Cl_2 (10 mL) before addition of 5-methylisoxazole-3-carboxylic acid (165 mg, 1.3 mmol), 1-hydroxybenzotriazole (176 mg, 1.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (248 mg, 1.3 mmol) and *N,N*-diisopropylethyl amine (0.7 mL, 4.0 mmol) at 0 °C. After being stirred at room temperature overnight, the reaction mixture was diluted with EtOAc (60 mL) and the organic layer washed with 1M HCl, 5% aqueous $NaHCO_3$ and brine and finally dried over Na_2SO_4. After removal of the volatile under vacuum, the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 30/1 to 15/1) to afford **89** (396 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.21 (m, 1H), 8.16 (d, *J* = 7.0 Hz, 1H), 7.83 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.78 – 7.69 (m, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.53 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.47 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.42 – 7.31 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 1H), 6.81 (s, 1H), 6.35 (d, *J* = 1.1 Hz, 1H), 5.03 (td, *J* = 7.8, 6.3 Hz, 1H), 4.62 (td, *J* = 8.5, 5.4 Hz, 1H), 4.50 (ddd, *J* = 11.4, 7.0, 3.7 Hz, 1H), 3.70 (s, 3H), 3.55 (dd, *J* = 14.3, 7.6 Hz, 1H), 3.36 – 3.20 (m, 2H), 2.43 (d, *J* = 0.9 Hz, 3H), 2.39 – 2.27 (m, 2H), 2.10 -2.03 (m, 1H), 1.89 -1.82 (m, 2H), 1.72 – 1.43 (m, 5H), 0.88 (d, *J* = 1.8 Hz, 3H), 0.87 (d, *J* = 1.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 172.3, 171.2, 170.1, 159.1, 158.2, 133.9, 132.5, 132.0, 128.8, 127.9, 127.7, 126.4,

125.7, 125.3, 123.7, 101.4, 54.0, 52.3, 52.00, 50.8, 42.2, 41.8, 38.0, 35.4, 33.4, 26.8, 24.6, 22.8, 22.1, 21.5, 12.3. ESI-MS (*m/z*): 620.4 $(M + H)^+$.

N-((S)-1-(((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)-5-methylisoxazole-3-carboxamide (90)

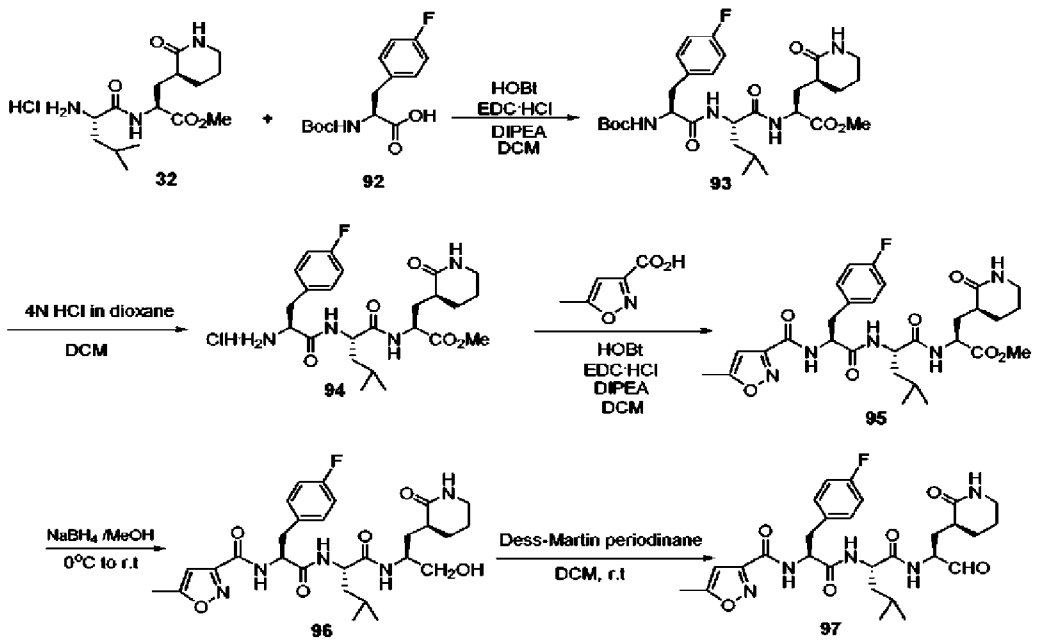
To a solution of **89** (370 mg, 0.6 mmol) in methanol (6.0 mL) was added $NaBH_4$ (46 mg, 1.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then quenched with a saturated solution of NH_4Cl and finally stirred for another hour at room temperature. After evaporation of the volatiles under vacuum, ethyl acetate (60 mL) was added. The organic layer was washed with a saturated solution of NH_4Cl and water and finally dried over Na_2SO_4. After removal of the volatiles under vacuum, the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 30/1 to 12/1) to afford **90** (245 mg, 69%).
^1H NMR (400 MHz, MeOD) δ 8.26 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.56 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.52 -7.47 (m, 1H), 7.46-7.41 (m, 1H), 7.37 (dd, *J* = 8.1, 7.0 Hz, 1H), 6.33 (d, *J* = 1.0 Hz, 1H), 5.02 (dd, *J* = 9.3, 5.1 Hz, 1H), 4.41 (dd, *J* = 8.6, 6.2 Hz, 1H), 4.03 (ddq, *J* = 11.3, 5.6, 2.8 Hz, 1H), 3.82 (dd, *J* = 14.4, 5.1 Hz, 1H), 3.60 – 3.40 (m, 3H), 3.27 – 3.18 (m, 2H), 2.43 (s, 3H), 2.40 – 2.28 (m, 1H), 2.15 – 2.01 (m, 2H), 1.84 – 1.74 (m, 1H), 1.72 – 1.57 (m, 4H), 1.54 – 1.43 (m, 1H), 0.96 (d, *J* = 6.3 Hz, 3H), 0.93 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.0, 173.4, 173.3, 171.7, 171.6, 160.0, 158.06, 134.0, 132.7, 132.0, 128.4, 127.4, 127.3, 125.9, 125.3, 125.0, 123.2, 100.5, 64.2, 54.0, 52.5, 52.5, 41.6, 40.5, 37.3, 34.3, 32.6, 25.7, 24.5, 22.0, 20.7, 10.6. ESI-MS (*m/z*): 592.4 $(M + H)^+$.

5-Methyl-N-((S)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)isoxazole-3-carboxamide (91)

To a solution of **90** (150 mg, 0.25 mmol) in CH_2Cl_2 (3.0 mL) was slowly added Dess-Martin periodinane (161 mg, 0.38 mmol). The resulting mixture was stirred at room temperature for 2 h and then quenched with 5% aqueous $NaHCO_3$ (3 mL) and 10% aqueous Na_2SO_3 (3 mL). The mixture was extracted with dichloromethane (15 mL x 2) and the combined organic layers

were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 30/1 to 10/1) and then preparative TLC (DCM/MeOH, 15/1) to give **91** (79 mg, 53%).

^{1}H NMR (400 MHz, MeOD) δ 8.31 – 8.22 (m, 1H), 7.86 (dt, *J* = 8.2, 2.0 Hz, 1H), 7.75 (dd, *J* = 8.2, 4.0 Hz, 1H), 7.56 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.37 (ddd, *J* = 8.2, 7.0, 5.9 Hz, 1H), 6.33 (dd, *J* = 1.5, 0.9 Hz, 0.4H), 6.31 (d, *J* = 1.0 Hz, 0.6H), 5.06 -5.01 (m, 1H), 4.54 -4.48 (m, 1H), 4.46 – 4.41 (m, 1H), 4.20 – 4.12 (m, 0.4H), 4.06 – 4.0 (m, 0.6H), 3.89 -3.79 (m, 1H), 3.53 – 3.40 (m, 1H), 3.37 – 3.34 (overlap two d, *J* = 0.9 Hz, 3H), 2.44 – 2.41 (overlap two d, *J* = 0.9 Hz, 3H), 2.33 – 2.29 (m, 1H), 2.22 – 2.14 (m, 1H), 2.07 – 2.0 (m, 0.6H), 1.96 – 1.92 (m, 0.4H), 1.81 – 1.60 (m, 5H), 1.01 – 0.88 (m, 6H).^{13}C NMR (101 MHz, MeOD) δ 176.1, 173.4, 171.7, 171.6, 171.5, 159.8, 158.0, 134.0, 134.0, 132.7, 132.0, 128.4, 127.4, 125.9, 125.9, 125.3, 125.0, 123.3, 100.6, 100.5, 98.4, 98.3, 54.0, 53.8, 53.7, 52.5, 52.3, 50.7, 50.5, 40.6, 40.5, 38.1, 37.1, 34.4, 30.3, 29.8, 26.4, 25.5, 24.5, 24.4, 22.1, 21.9, 21.9, 21.1, 20.9, 20.9, 20.6, 20.6, 10.6. ESI-MS (*m/z*): 590.3 $(M + H)^+$.



Methyl (6S,9S,12S)-6-(4-fluorobenzyl)-9-isobutyl-2,2-dimethyl-4,7,10-trioxo-12-(((S)-2-oxopiperidin-3-yl)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (**93**)

A solution of compound **32** (350 mg, 1.0 mmol) and (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-fluorophenyl)propanoic acid (compound **92**, 286 mg, 1.0 mmol) in DCM (10 mL) was treated with 1-hydroxybenzotriazole (200 mg, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (287 mg, 1.5 mmol) and *N,N*-diisopropylethyl amine (0.7 mL, 4.0 mmol) at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (70 mL) and the organic layer washed with 1N HCl, $NaHCO_3$ (5%) and saturated brine and dried over Na_2SO_4. The solvent was evaporated and the crude mixture was purified on silica gel, eluting with mixtures of DCM/MeOH (30:1 to 20:1) to give product **93** (450 mg, 78%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 7.2 Hz, 1H), 7.24 – 7.10 (m, 3H), 6.94 (t, *J* = 8.6 Hz, 3H), 5.15 (d, *J* = 8.4 Hz, 1H), 4.65 (td, *J* = 8.8, 4.7 Hz, 1H), 4.56 – 4.44 (m, 1H), 4.45 – 4.32 (m, 1H), 3.71 (s, 3H), 3.28 (dt, *J* = 9.4, 3.0 Hz, 2H), 3.10 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.94 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.46 – 2.21 (m, 2H), 2.12 – 1.98 (m, 1H), 1.95 – 1.79 (m, 2H), 1.78 – 1.59 (m, 3H), 1.59 – 1.44 (m, 2H), 1.38 (s, 9H), 0.92 (s, 3H), 0.91 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.22 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.51, 172.50, 172.30, 170.94, 161.79 (d, *J* = 244.6 Hz), 155.40, 132.45, 130.92, 130.84, 115.22 (d, *J* = 21.2 Hz), 80.15, 55.45, 52.27, 51.66, 50.46, 42.20, 37.92, 37.31, 33.39, 28.22, 26.56, 24.54, 22.88, 22.05, 21.45. ESI-MS (*m/z*): 579.3 $(M + H)^+$.

Methyl (S)-2-((S)-2-((S)-3-(4-fluorophenyl)-2-(5-methylisoxazole-3-carboxamido)propanamido)-4-methylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (**95**)

To a solution of compound **93** (139 mg, 0.24 mmol) in DCM (2.5 mL) was added 4N HCl in dioxane (0.25 mL, 1.0 mmol) dropwise. The reaction mixture was stirred for 1 h at room temperature and then concentrated to yield compound **94** as a crude HCl salt. A solution of the crude HCl salt and 5-methylisoxazole-3-carboxylic acid (38 mg, 0.3 mmol) in DCM (3 mL) was treated with 1-hydroxybenzotriazole (40 mg, 0.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (57 mg, 0.3 mmol) and *N,N*-diisopropylethyl amine (0.21 mL, 1.2 mmol) at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (30 mL) and the organic layer washed with 1N HCl, $NaHCO_3$ (5%) and saturated brine

and then dried over Na_2SO_4. The solvent was evaporated, and the crude mixture was purified on silica gel, eluting with mixtures of DCM/MeOH (30:1 to 20:1) to afford product **95** (86 mg, 61%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 6.9 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.23 – 7.10 (m, 2H), 6.99 – 6.85 (m, 3H), 6.39 (d, *J* = 1.0 Hz, 1H), 4.90 (ddd, *J* = 8.4, 7.3, 5.7 Hz, 1H), 4.67 (td, *J* = 8.6, 5.3 Hz, 1H), 4.49 (ddd, *J* = 11.3, 6.9, 3.7 Hz, 1H), 3.71 (s, 3H), 3.33 – 3.24 (m, 2H), 3.19 (dd, *J* = 14.1, 5.7 Hz, 1H), 3.06 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.61 (s, 1H), 2.45 (d, *J* = 0.9 Hz, 3H), 2.44 – 2.37 (m, 1H), 2.37 – 2.28 (m, 1H), 2.05 (ddt, *J* = 12.8, 5.7, 2.7 Hz, 1H), 1.86 (ddd, *J* = 13.6, 7.9, 3.6 Hz, 2H), 1.78 – 1.56 (m, 2H), 1.51 (ddd, *J* = 12.5, 6.3, 2.9 Hz, 2H), 0.89 (d, *J* = 4.0 Hz, 3H), 0.89 (d, *J* = 4.0 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.92 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.54, 172.68, 172.33, 171.23, 169.84, 161.83 (d, *J* = 244.9 Hz), 158.94, 158.20, 132.07, 130.92 (d, *J* = 7.9 Hz), 115.27 (d, *J* = 21.2 Hz), 101.40, 54.15, 52.27, 51.78, 50.78, 42.21, 41.93, 37.99, 37.47, 33.34, 26.66, 24.59, 22.77, 22.09, 21.48, 12.30. ESI-MS (*m/z*): 588.3 $(M + H)^+$.

N-((S)-3-(4-fluorophenyl)-1-(((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-1-oxopropan-2-yl)-5-methylisoxazole-3-carboxamide (**96**)

To a solution of compound **95** (60 mg, 0.1 mmol) in methanol (2 mL) was added $NaBH_4$ (38 mg, 1.0 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h and quenched with 1N HCl (5 mL). The resultion mixture was stirred for 1 h at room temperature before being extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ and brine and then dried over Na_2SO_4. The filtrate was evaporated to dryness and the crude product was purified on silica gel, eluting with mixtures of DCM/MeOH (20:1 to 15:1) to afford product **96** as a white solid (45 mg, 81%).

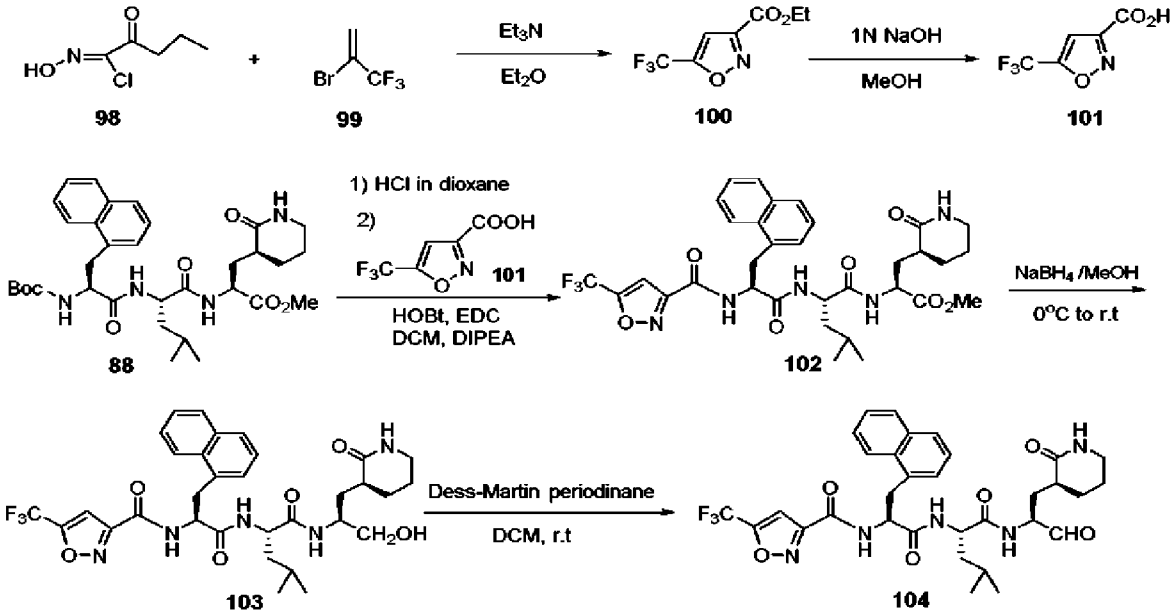
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 7.3 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.21 – 7.10 (m, 2H), 6.97 – 6.86 (m, 2H), 6.60 (s, 1H), 6.36 (d, *J* = 1.0 Hz, 1H), 4.94 (td, *J* = 7.6, 5.8 Hz, 1H), 4.54 (td, *J* = 8.5, 5.4 Hz, 1H), 4.00 (tt, *J* = 6.9, 4.3 Hz, 1H), 3.90 (t, *J* = 6.4 Hz, 1H), 3.59 (d, *J* = 4.8 Hz, 2H), 3.27 (dq, *J* = 7.4, 3.8, 2.9 Hz, 2H), 3.19 (dd, *J* = 14.1, 5.8 Hz, 1H), 3.09 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.45 (d, *J* = 0.9 Hz, 3H), 2.36 (s, 1H), 2.29 (dd, *J* = 10.4, 5.6 Hz, 1H), 2.22 – 1.96 (m, 2H), 1.85 (dt, *J* = 13.7, 4.9 Hz, 1H), 1.77 – 1.59

(m, 2H), 1.53 (tq, *J* = 12.4, 4.8, 3.5 Hz, 3H), 0.89 (s, 3H), 0.86 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.76 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.71, 172.94, 171.35, 170.03, 161.86 (d, *J* = 245.0 Hz),159.21, 158.13, 132.03, 130.90 (d, *J* = 7.8 Hz) , 115.34 (d, *J* = 21.2 Hz), 101.35, 65.64, 54.28, 52.40, 50.40, 42.38, 41.83, 38.29, 37.23, 32.73, 27.17, 24.83, 22.85, 22.00, 21.50, 12.31. ESI-MS (*m/z*): 560.3 $(M + H)^+$.

N-((S)-3-(4-fluorophenyl)-1-(((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-1-oxopropan-2-yl)-5-methylisoxazole-3-carboxamide (**97**)

The procedure described for the synthesis of compound **91** was used with compound **96** (37 mg, 0.067 mmol) as a starting material to give compound **97** (18 mg, 49%).

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.25 – 7.15 (m, 2H), 6.94 – 6.82 (m, 2H), 6.28 (d, *J* = 1.0 Hz, 1H), 4.74 – 4.68 (m, 1H), 4.36 (t, *J* = 4.0 Hz, 1H), 4.27 (ddd, *J* = 8.2, 6.9, 2.9 Hz, 1H), 3.97 – 3.81 (m, 1H), 3.14 (dt, *J* = 8.9, 4.6 Hz, 3H), 2.89 (dd, *J* = 14.0, 9.3 Hz, 1H), 2.35 (s, 3H), 2.19 (dddd, *J* = 11.4, 9.0, 6.0, 3.2 Hz, 1H), 2.11 – 1.97 (m, 1H), 1.91 (ddt, *J* = 9.7, 6.3, 3.2 Hz, 1H), 1.77 – 1.66 (m, 1H), 1.64 – 1.44 (m, 4H), 1.43 – 1.32 (m, 1H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H). ^{19}F NMR (377 MHz, MeOD) δ -118.43(s). ^{13}C NMR (101 MHz, MeOD) δ 176.10, 173.37, 171.66, 171.36, 161.88 (d, *J* = 243.6 Hz), 159.80, 158.14, 132.76, 130.77 (d, *J* = 7.9 Hz), 114.64 (d, *J* = 21.4 Hz), 100.52, 54.31, 52.39, 50.61, 41.61, 40.60, 37.03, 36.55, 29.79, 25.52, 24.40, 21.86, 20.83, 20.60, 10.57. ESI-MS (*m/z*): 558.3 $(M + H)^+$.



98 99 100 101 88 102 103 104

5-(Trifluoromethyl)isoxazole-3-carboxylic acid (**101**)

A solution of triethylamine (1.48 mL, 8.0 mmol) in diethyl ether (8.0 mL) was added dropwise with syringe pump over 7 h to a solution of ethyl chlorooximidoacetate **98** (500 mg, 3.3 mmol) and 3,3,3-trifluoro-2-bromopropene **99** (1.2 mL, 11 mmol) in diethyl ether (11 mL). After addition, the reaction mixture was stirred overnight at room temperature and then quenched with water. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and partially concentrated. MeOH (7.0 mL) and 1N NaOH (7.0 mL) were added. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was partitioned between 1N HCl and CH_2Cl_2.The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and partially concentrated to give the crude product **101**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.10 (s, 1H), 7.11 (s, 1H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -64.34 (s). ESI-MS (*m/z*): 204.2 $(M + Na)^+$.

Methyl (S)-2-((S)-4-methyl-2-((S)-3-(naphthalen-1-yl)-2-(5-(trifluoromethyl)isoxazole-3-carboxamido)propanamido)pentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (**102**)

Compound **102** was prepared by following the protocol described for the preparation of compound **89**.

^{1}H NMR (400 MHz, Acetone-d_6) δ 8.35 (dd, J = 16.6, 7.7 Hz, 2H), 8.28 (dd, J = 8.4, 1.2 Hz, 1H), 7.94 – 7.84 (m, 2H), 7.78 (d, J = 8.2 Hz, 1H), 7.59 – 7.47 (m, 3H), 7.43 – 7.34 (m, 2H), 6.98 (s, 1H), 5.22 – 5.07 (m, 1H), 4.64 – 4.55 (m, 1H), 4.49 (ddd, J = 11.3, 7.2, 4.1 Hz, 1H), 3.88 (dd, J = 14.4, 5.0 Hz, 1H), 3.67 (s, 3H), 3.56 (dd, J = 14.4, 9.0 Hz, 1H), 3.30 – 3.21 (m, 2H), 2.90 (d, J = 5.1 Hz, 2H), 2.44 – 2.24 (m, 2H), 2.15 (s, 1H), 1.82 (ddd, J = 10.6, 6.4, 4.4 Hz, 1H), 1.77 – 1.63 (m, 2H), 1.62 – 1.45 (m, 2H), 0.91 (d, J = 4.9 Hz, 3H), 0.89 (d, J = 4.9 Hz, 3H). ^{19}F NMR (377 MHz, Acetone-d_6) δ -64.81 (s). ESI-MS (m/z): 674.2 $(M + H)^+$.

N-((S)-1-(((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)-5-(trifluoromethyl)isoxazole-3-carboxamide (**103**)

Compound **103** was prepared by following the protocol described for the preparation of compound **90**.

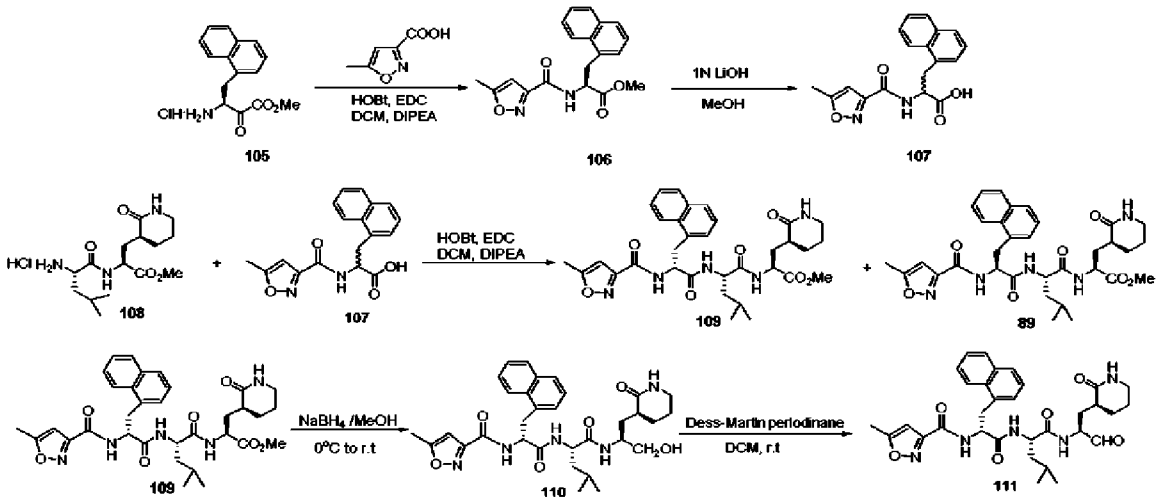
^{1}H NMR (400 MHz, Methanol-d_4) δ 8.28 – 8.18 (m, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.83 (dd, J = 8.2, 1.4 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.52 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.37 (dd, J = 8.2, 7.0 Hz, 1H), 7.25 (d, J = 1.1 Hz, 1H), 5.09 (dd, J = 9.5, 5.0 Hz, 1H), 4.45 (dd, J = 8.3, 6.3 Hz, 1H), 4.04 (ddq, J = 8.8, 6.2, 3.3 Hz, 1H), 3.83 (dd, J = 14.4, 5.0 Hz, 1H), 3.61 – 3.42 (m, 3H), 3.20 (dd, J = 7.9, 5.0 Hz, 2H), 2.42 – 2.28 (m, 1H), 2.12 -2.07 (m, 1H), 2.05 – 1.96 (m, 1H), 1.86 – 1.74 (m, 1H), 1.65 (qd, J = 10.1, 8.9, 5.7 Hz, 4H), 1.53 – 1.40 (m, 1H), 0.95 (d, J = 6.1 Hz, 3H), 0.91 (d, J = 6.1 Hz, 3H). ^{19}F NMR (377 MHz, Methanol-d_4) δ -65.62 (s). ESI-MS (m/z): 646.2 $(M + H)^+$.

N-((S)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)-5-(trifluoromethyl)isoxazole-3-carboxamide (**104**)

Compound **104** was prepared by following the protocol described for the preparation of compound **91**.

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.25 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.51 – 7.42 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.25 (s, 1H), 5.08 (dd, J = 9.7, 4.8 Hz, 1H), 4.54 – 4.40 (m, 2H), 4.04 (ddq, J = 11.6, 7.2, 3.8 Hz, 1H), 3.84 (dd, J = 14.4, 4.8 Hz, 1H), 3.46 (dd, J = 14.5, 9.7 Hz, 1H), 3.40 – 3.30 (m, 1H), 3.27 – 3.16 (m,

2H), 2.32 (dtd, *J* = 11.8, 5.7, 3.0 Hz, 1H), 2.26 – 2.14 (m, 1H), 2.10 – 1.98 (m, 1H), 1.84 – 1.57 (m, 4H), 1.48 (qt, *J* = 9.8, 3.4 Hz, 1H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H). ^{19}F NMR (377 MHz, MeOD) δ -65.69 (s). ESI-MS (*m/z*): 644.2 $(M + H)^+$.



Methyl (S)-2-(5-methylisoxazole-3-carboxamido)-3-(naphthalen-1-yl)propanoate (**106**)

A solution of compound **105** (530 mg, 2.0 mmol) and 5-methylisoxazole-3-carboxylic acid (254 mg, 2.0 mmol) in DCM (10 mL) was treated with 1-hydroxybenzotriazole (350 mg, 2.6 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (497 mg, 2.6 mmol) and *N,N*-diisopropylethyl amine (1.48 mL, 8.0 mmol) at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with EtOAc (60 mL) and the organic layer washed with 1N HCl, $NaHCO_3$ (5%) and brine and finally dried over Na_2SO_4. The solvent was evaporated, and the crude mixture was purified on silica gel, eluting with mixtures of DCM/MeOH (50:1 to 30:1) to afford product **106** (470 mg, 70%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.93 – 7.82 (m, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.62 – 7.31 (m, 4H), 6.40 (s, 1H), 5.17 (q, *J* = 7.2 Hz, 1H), 3.77 – 3.65 (m, 2H), 3.63 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.58, 171.26, 158.88, 158.15, 133.91, 132.07, 131.98, 128.92, 128.10, 127.53, 126.45, 125.81, 125.31, 123.35, 101.33, 53.16, 52.38, 35.53, 12.26. ESI-MS (*m/z*): 339.2 $(M + H)^+$.

Methyl 2-(5-methylisoxazole-3-carboxamido)-3-(naphthalen-1-yl)propanoate (**107**)

To a solution of compound **106** (450 mg, 1.33 mmol) in THF (7.0 mL) was added 2N LiOH (1.33 mL, 2.66 mmol) dropwise at 0 °C. The reaction was mixture was then stirred at room temperature for 2 h before addition of 1N HCl (adjusted to pH = 1~2). The reaction mixture was extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated to give compound **107** (358 mg, 83%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 9.02 (t, J = 6.4 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.72 – 7.25 (m, 4H), 6.45 (d, J = 4.8 Hz, 1H), 4.77 (dp, J = 12.2, 4.1 Hz, 1H), 3.92 – 3.67 (m, 1H), 3.52 (td, J = 12.1, 10.2, 3.7 Hz, 1H), 2.43 (d, J = 5.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.97, 171.68, 159.23, 158.83, 134.23, 133.91, 131.85, 129.23, 127.81, 127.70, 126.76, 126.10, 125.82, 123.66, 101.69, 53.41, 33.69, 12.25. ESI-MS (m/z): 325.2 $(M + H)^+$.

N-((R)-1-(((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)-5-methylisoxazole-3-carboxamide (**111**)

A solution of compound **108** (112 mg, 0.32 mmol) and compound **107** (105 mg, 0.32 mmol) in DCM (3 mL) was treated with 1-hydroxybenzotriazole (47 mg, 0.35 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (67 mg, 0.35 mmol) and *N*,*N*-diisopropylethyl amine (0.26 mL, 1.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight before being diluted with EtOAc (30 mL). The solution was then washed with 1N HCl, $NaHCO_3$ (5%) and brine and dried over Na_2SO_4. The solvent was evaporated, and the crude mixture was purified with preparative TLC (DCM/MeOH = 25:1) to afford the less polar compound **109** (57 mg, 29%) and the more polar compound **89** (90 mg, 45%).

Compound **109**: ^{1}H NMR (400 MHz, Chloroform-d) δ 8.91 (d, J = 4.9 Hz, 1H), 8.78 (d, J = 9.1 Hz, 1H), 8.28 – 8.18 (m, 1H), 7.87 – 7.79 (m, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.55 – 7.39 (m, 3H), 7.35 (dd, J = 8.2, 7.0 Hz, 1H), 6.66 (s, 1H), 6.40 (d, J = 1.0 Hz, 1H), 6.11 (d, J = 9.3 Hz, 1H), 5.30 (dt, J = 8.9, 6.5 Hz, 1H), 4.70 (td, J = 9.9, 4.4 Hz, 1H), 4.10 (ddd, J = 12.0, 4.9, 3.3 Hz, 1H), 3.88 (dd, J = 14.0, 6.1 Hz, 1H), 3.74 (s, 3H), 3.71 – 3.65 (m, 1H), 3.36 – 3.22 (m, 2H), 2.46 (d, J = 0.9 Hz, 3H), 2.18 – 2.09 (m, 1H), 2.07 – 1.84 (m, 3H), 1.78 – 1.65 (m, 2H), 1.56 (td, J = 12.2, 3.2 Hz, 1H), 1.43 (ddt, J = 11.4, 6.6, 3.3 Hz, 1H), 1.30 – 1.13 (m, 1H), 0.86 (dd, J = 18.5, 6.6 Hz, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.14, 172.26, 172.03, 171.11, 169.93,

159.14, 158.48, 133.87, 133.25, 132.47, 128.57, 128.41, 127.47, 126.25, 125.59, 125.46, 124.09, 102.00, 54.46, 53.40, 52.30, 51.52, 42.05, 40.93, 39.88, 35.02, 33.01, 28.73, 24.60, 23.07, 21.82, 21.48, 12.32.

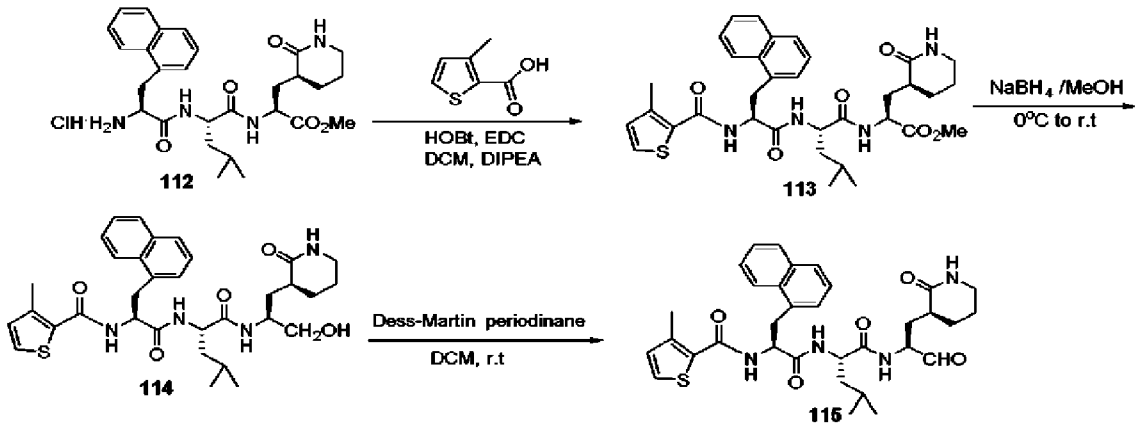
Compound **110** (37 mg, 67%) was prepared from compound **109** (57 mg, 0.093 mmol) by following the protocol described for the preparation of compound **90**.

Compound **110**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.75 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 5.8 Hz, 1H), 8.22 – 8.10 (m, 1H), 7.80 (dd, *J* = 6.9, 2.6 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.46 (ddt, *J* = 9.6, 6.8, 3.5 Hz, 2H), 7.41 – 7.31 (m, 2H), 6.75 (s, 1H), 6.55 (d, *J* = 8.8 Hz, 1H), 6.36 (d, *J* = 1.2 Hz, 1H), 5.15 (q, *J* = 7.3 Hz, 1H), 4.53 (dq, *J* = 12.7, 4.1 Hz, 1H), 4.17 (d, *J* = 6.3 Hz, 1H), 3.83 (dd, *J* = 14.0, 6.3 Hz, 1H), 3.79 – 3.69 (m, 1H), 3.62 (dd, *J* = 14.1, 7.3 Hz, 1H), 3.54 (p, *J* = 6.3, 5.8 Hz, 2H), 3.34 – 3.15 (m, 2H), 2.43 (s, 3H), 2.10 – 1.94 (m, 1H), 1.94 – 1.75 (m, 2H), 1.65 (dtd, *J* = 13.1, 10.1, 8.4, 4.6 Hz, 2H), 1.56 – 1.34 (m, 2H), 1.34 – 1.16 (m, 3H), 0.81 (d, *J* = 6.3 Hz, 3H), 0.78 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.90, 173.25, 171.24, 170.37, 159.29, 158.29, 133.83, 133.01, 132.26, 128.62, 128.24, 127.58, 126.23, 125.53, 125.43, 123.95, 101.88, 66.45, 54.68, 52.66, 52.18, 42.17, 40.64, 39.16, 34.87, 33.01, 28.41, 24.59, 23.11, 21.69, 21.30, 12.30. ESI-MS (*m/z*): 592.3 $(M + H)^+$.

5-Methyl-N-((R)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)isoxazole-3-carboxamide **(111)**

Compound **111** (17 mg, 48%) was prepared from compound **110** (35 mg, 0.06 mmol) by following the protocol described for the preparation of compound **91**.

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.29 – 8.18 (m, 1H), 7.89 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.83 – 7.76 (m, 1H), 7.61 – 7.44 (m, 2H), 7.44 – 7.35 (m, 2H), 6.50 (ddd, *J* = 9.5, 2.4, 1.0 Hz, 1H), 4.51 – 4.38 (m, 1H), 4.21 – 4.01 (m, 1H), 4.00 – 3.86 (m, 1H), 3.64 (td, *J* = 9.1, 3.0 Hz, 2H), 3.33 (m, 1H), 3.29-3.25 (m, 2H), 3.26 (s, 1H), 3.20 (dt, *J* = 8.9, 6.2 Hz, 2H), 2.49 (dt, *J* = 2.1, 1.0 Hz, 3H), 2.38 – 2.11 (m, 2H), 1.95 (ddt, *J* = 13.3, 6.4, 3.2 Hz, 1H), 1.88 – 1.54 (m, 2H), 1.52 – 1.33 (m, 1H), 1.25 – 1.04 (m, 1H), 0.68 (d, *J* = 5.3 Hz, 3H), 0.65 (d, *J* = 5.3 Hz, 3H). ESI-MS (*m/z*): 590.3 $(M + H)^+$.



Methyl (S)-2-((S)-4-methyl-2-((S)-2-(3-methylthiophene-2-carboxamido)-3-(naphthalen-1-yl)propanamido)pentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (**113**)

A solution of compound **112** (162 mg, 0.3 mmol) and 3-methylthiophene-2-carboxylic acid (43 mg, 0.3 mmol) in DCM (3.5 mL) was treated with 1-hydroxybenzotriazole (55 mg, 0.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (78 mg, 0.4 mmol) and *N,N*-diisopropylethyl amine (0.22 mL, 1.26 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight before being diluted with EtOAc (30 mL). The solution was washed with 1N HCl, $NaHCO_3$ (5%) and brine and the organic layer was dried over Na_2SO_4. The solvent was evaporated, and the crude mixture was purified on silica gel, eluting with mixtures of DCM/MeOH (50:1 to 20:1) to afford compound **113** (142 mg, 75%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 – 8.17 (m, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.82 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.79 – 7.69 (m, 1H), 7.55 – 7.43 (m, 3H), 7.42 – 7.32 (m, 2H), 7.21 (d, *J* = 4.9 Hz, 1H), 6.84 (s, 1H), 6.78 (d, *J* = 5.0 Hz, 1H), 6.60 (d, *J* = 7.3 Hz, 1H), 5.02 (td, *J* = 7.5, 6.2 Hz, 1H), 4.59 (dtd, *J* = 22.8, 8.1, 7.5, 4.4 Hz, 2H), 3.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 3.70 (d, *J* = 2.3 Hz, 3H), 3.66 – 3.53 (m, 2H), 3.18 (ddd, *J* = 7.4, 4.3, 2.0 Hz, 2H), 2.48 – 2.30 (m, 2H), 2.25 (s, 3H), 2.14 – 2.01 (m, 1H), 1.84 (ddt, *J* = 15.7, 13.3, 4.3 Hz, 2H), 1.66 (tdd, *J* = 12.9, 6.9, 2.4 Hz, 2H), 1.59 – 1.45 (m, 2H), 0.89 (d, *J* = 4.0 Hz, 3H), 0.87 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.50, 172.45, 172.38, 170.90, 163.02, 140.99, 133.87, 132.82, 132.19, 131.85, 130.87, 128.74, 127.83, 127.35, 126.45, 125.75, 125.32, 123.85, 67.08, 54.40, 52.29, 52.18, 50.50, 42.19, 41.82, 37.99, 34.87, 33.70, 26.64, 24.68, 22.88, 22.03, 21.44, 15.56. ESI-MS (*m/z*): 635.2 $(M + H)^+$.

N-((S)-1-(((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)-3-methylthiophene-2-carboxamide (**114**)

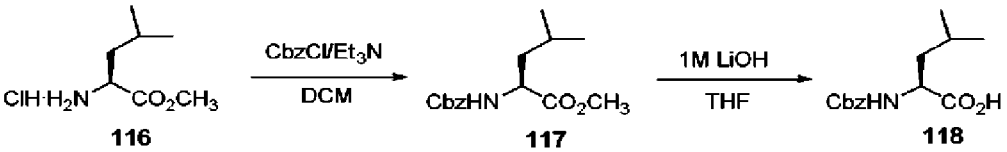
Compound **114** (103 mg, 85%) was prepared from compound **113** (130 mg, 0.2 mmol) by following the protocol described for the preparation of compound **90**.

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.24 – 8.08 (m, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.72 (dd, J = 8.0, 1.4 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.37 (dddd, J = 24.4, 8.1, 6.8, 1.3 Hz, 3H), 7.31 – 7.21 (m, 2H), 6.69 (d, J = 5.0 Hz, 1H), 4.90 (dd, J = 9.5, 5.0 Hz, 1H), 4.33 (dd, J = 8.9, 6.0 Hz, 1H), 4.06 – 3.83 (m, 1H), 3.69 (dd, J = 14.4, 5.0 Hz, 1H), 3.50 – 3.28 (m, 3H), 3.27 – 3.15 (m, 1H), 3.05 (dd, J = 7.6, 5.1 Hz, 2H), 2.32 – 2.13 (m, 1H), 2.05 (s, 3H), 1.71 – 1.57 (m, 2H), 1.51 (ddt, J = 12.6, 10.3, 4.1 Hz, 3H), 1.33 (ddt, J = 13.4, 10.1, 5.2 Hz, 1H), 1.20 – 1.06 (m, 1H), 0.84 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.93, 173.50, 172.26, 164.07, 140.98, 134.03, 133.00, 132.10, 131.19, 130.30, 128.47, 127.49, 127.38, 125.98, 125.36, 125.05, 123.38, 64.22, 60.15, 54.42, 52.50, 52.46, 41.62, 40.75, 37.31, 34.00, 32.69, 32.66, 25.78, 24.51, 22.10, 20.69, 14.21. ESI-MS (*m/z*): 607.2 $(M + H)^+$.

3-Methyl-N-((S)-1-(((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)thiophene-2-carboxamide (**115**)

Compound **115** (61 mg, 64%) was prepared from compound **114** (95 mg, 0.16 mmol) by following the protocol described for the preparation of compound **91**.

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.14 (dd, J = 8.5, 5.5 Hz, 1H), 7.73 (ddd, J = 8.2, 3.3, 1.3 Hz, 1H), 7.64 (dd, J = 8.2, 4.3 Hz, 1H), 7.41 (tdd, J = 7.0, 3.7, 1.4 Hz, 1H), 7.35 (ddt, J = 8.4, 6.9, 3.4 Hz, 2H), 7.31 – 7.17 (m, 2H), 6.70 (t, J = 5.2 Hz, 1H), 4.90 (dt, J = 9.2, 4.6 Hz, 1H), 4.46 – 4.30 (m, 2H), 4.12 – 3.86 (m, 1H), 3.80 – 3.64 (m, 1H), 3.43 – 3.28 (m, 1H), 3.20 (p, J = 1.6 Hz, 1H), 3.06 (dd, J = 7.6, 4.8 Hz, 2H), 2.31 – 2.14 (m, 1H), 2.05 (m, 4H), 1.94 - 1.80 (m, 1H), 1.73 – 1.43 (m, 4H), 1.16 (s, 1H), 0.84 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H). ESI-MS (*m/z*): 605.2 $(M + H)^+$.



116 117 118

Methyl ((benzyloxy)carbonyl)-L-leucinate (**117**)

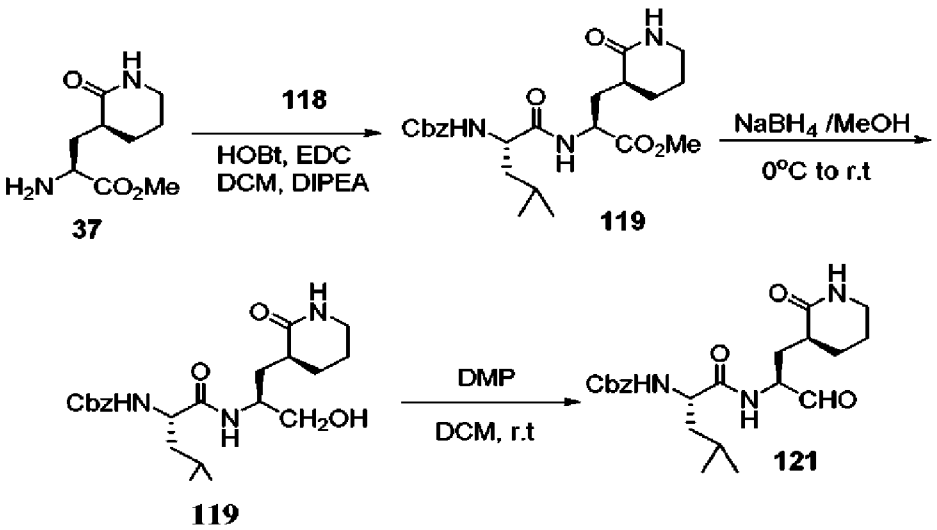
To a solution of compound **116** (360 mg, 2.0 mmol) in DCM (10 mL) was added benzyl carbonochloridate (340 mg, 2.0 mmol) and Et_3N (0.54 mL, 4.0 mmol). The reaction mixture was stirred overnight at room temperature and then diluted with DCM (30 mL). The solution was washed with 1N HCl, $NaHCO_3$ (5%) and brine and the organic layer was dried over Na_2SO_4. The solvent was evaporated, and the crude mixture was purified on silica gel, eluting with mixtures of Hex/EA (5:1 to 2:1) to afford compound **117** (447 mg, 80%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.28 (m, 5H), 5.29 (d, *J* = 7.4 Hz, 1H), 5.10 (s, 2H), 4.40 (td, *J* = 9.1, 5.1 Hz, 1H), 3.72 (s, 3H), 1.77 – 1.58 (m, 2H), 1.52 (ddd, *J* = 13.5, 9.3, 5.5 Hz, 1H), 0.94 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.65, 156.00, 136.29, 128.50, 128.14, 128.08, 66.96, 52.48, 52.26, 41.72, 24.73, 22.82, 21.82. ESI-MS (*m/z*): 280.1 $(M + H)^+$.

((Benzyloxy)carbonyl)-L-leucine (**118**)

To a solution of compound **117** (430 mg, 1.54 mmol) in THF (10 mL) was added LiOH (1M, 1.85 mL, 1.85 mmol). The reaction mixture was stirred for 1.5 h at room temperature. The pH of the solution was then adjusted to ~1-2 by addition of 1N HCl. The reaction mixture was extracted with ethyl acetate, dried over Na_2SO_4, filtrated and concentrated to give compound **118** (335 mg, 82%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.20 (s, 1H), 7.49 – 7.30 (m, 6H), 5.26 – 5.06 (m, 3H), 4.42 (td, *J* = 9.1, 4.7 Hz, 1H), 1.85 – 1.64 (m, 2H), 1.56 (ddd, *J* = 13.4, 9.4, 5.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.24, 156.15, 136.10, 128.55, 128.24, 128.12, 67.19, 52.39, 41.46, 24.77, 22.83, 21.73. ESI-MS (*m/z*): 266.1 $(M + H)^+$.



Methyl (S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-4-methylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (**119**)

A solution of compound **37** 280 mg (1.06 mmol) and compound **118** (350 mg, 1.0 mmol) in DCM (5 mL) was treated with 1-hydroxybenzotriazole (176 mg, 1.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (250 mg, 1.3 mmol) and *N,N*-diisopropylethyl amine (0.74 mL, 4.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight before being diluted with EtOAc (40 mL). The solution was then washed with 1N HCl, $NaHCO_3$ (5%) and brine and the organic layer dried over Na_2SO_4. The solvent was evaporated, and the residue was purified on silica gel, eluting with mixtures of DCM/MeOH (50:1 to 20:1) to afford compound **119** (312 mg, 70%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 7.3 Hz, 1H), 7.39 – 7.29 (m, 5H), 6.81 (s, 1H), 5.73 (d, *J* = 8.9 Hz, 1H), 5.08 (s, 2H), 4.52 (ddd, *J* = 11.5, 7.3, 3.8 Hz, 1H), 4.42 (td, *J* = 8.9, 5.4 Hz, 1H), 3.69 (s, 3H), 3.28 – 3.16 (m, 3H), 2.48 – 2.18 (m, 2H), 2.11 – 1.98 (m, 1H), 1.85 (dtd, *J* = 17.2, 8.6, 4.7 Hz, 2H), 1.78 – 1.59 (m, 2H), 1.59 – 1.47 (m, 2H), 0.96 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.54, 173.03, 172.44, 156.06, 136.45, 128.47, 128.05, 127.91, 66.74, 53.34, 52.24, 50.39, 42.51, 42.15, 37.86, 33.30, 26.47, 24.59, 22.91, 22.15, 21.47. ESI-MS (*m/z*): 448.2 $(M + H)^+$.

Benzyl ((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (**120**)

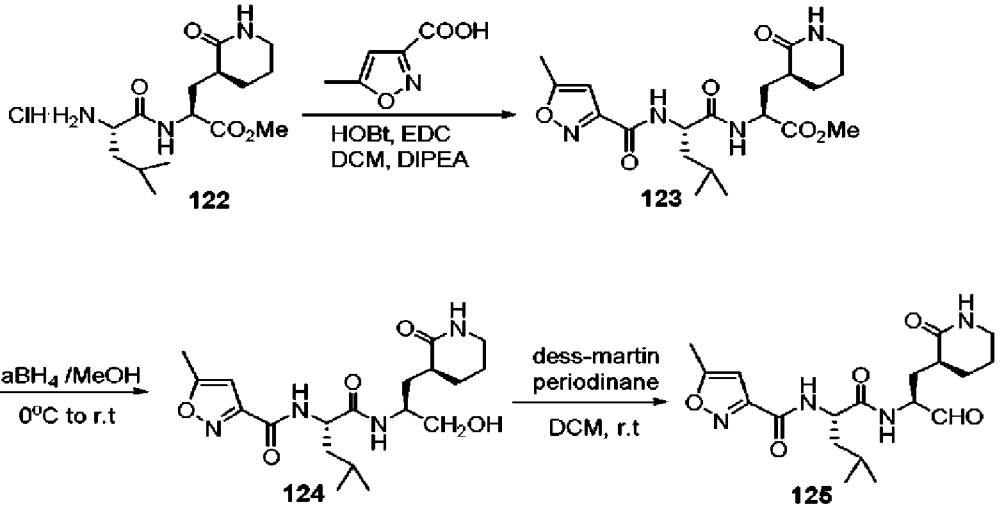
Compound **120** (161 mg, 64%) was prepared from compound **119** (270 mg, 0.6 mmol) by following the protocol described for the preparation of compound **90**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.1 Hz, 1H), 7.31 (m, 5H), 6.79 (s, 1H), 5.99 (d, *J* = 8.4 Hz, 1H), 5.07 (d, *J* = 4.0 Hz, 2H), 4.27 (td, *J* = 9.0, 5.0 Hz, 1H), 4.05 (td, *J* = 7.1, 3.8 Hz, 2H), 3.55 (q, *J* = 5.6 Hz, 2H), 3.19 (dt, *J* = 7.7, 4.1 Hz, 2H), 2.32 – 2.13 (m, 3H), 2.04 – 1.98 (m, 1H), 1.82 – 1.76 (m, 1H), 1.71 – 1.44 (m, 5H), 0.93 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.84, 173.39, 156.20, 136.41, 128.47, 128.06, 127.92, 66.77, 65.58, 53.92, 49.38, 42.24, 37.87, 32.70, 26.66, 24.76, 23.02, 22.01, 21.33. ESI-MS (*m/z*): 420.2 $(M + H)^+$.

Benzyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (**121**)

Compound **121** (17 mg, 48%) was prepared from compound **120** (35 mg, 0.084 mmol) by following the protocol described for the preparation of compound **91**.

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.30 – 7.14 (m, 5H), 5.08 – 4.89 (m, 2H), 4.34 (dd, *J* = 4.1, 2.1 Hz, 1H), 4.03 (dt, *J* = 8.1, 4.2 Hz, 1H), 3.89 (tt, *J* = 9.3, 3.7 Hz, 1H), 3.24 – 3.18 (m, 1H), 3.18 – 3.02 (m, 2H), 2.16 (dtd, *J* = 11.6, 5.8, 2.9 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.95 – 1.81 (m, 1H), 1.74 – 1.40 (m, 4H), 1.39 – 1.27 (m, 1H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.15, 174.40, 156.95, 136.88, 128.07, 127.58, 127.39, 127.37, 98.36, 66.15, 53.92, 50.60, 41.60, 40.82, 36.97, 29.80, 25.34, 24.42, 21.95, 20.55. ESI-MS (*m/z*): 418.2 $(M + H)^+$.



Methyl (S)-2-((S)-4-methyl-2-(5-methylisoxazole-3-carboxamido)pentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (**123**)

A solution of compound **122** (139 mg, 0.4 mmol) and 5-methylisoxazole-3-carboxylic acid (51 mg, 0.4 mmol) in DCM (5 mL) was treated with 1-hydroxybenzotriazole (68 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (96 mg, 0.5 mmol) and *N,N*-diisopropylethyl amine (0.35 mL, 2.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight before being diluted with EtOAc (40 mL). The solution was washed with 1N HCl, $NaHCO_3$ (5%) and brine and the organic layer was dried over Na_2SO_4. The solvent was evaporated, and the residue was purified on silica gel, eluting with mixtures of DCM/MeOH (30:1 to 20:1) to afford compound **123** (145 mg, 86%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 7.3 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 6.82 (s, 1H), 6.40 (d, *J* = 1.0 Hz, 1H), 4.81 (td, *J* = 8.8, 5.1 Hz, 1H), 4.54 (ddd, *J* = 11.5, 7.3, 3.9 Hz, 1H), 3.71 (s, 3H), 3.30 (ddd, *J* = 7.5, 4.5, 2.4 Hz, 2H), 2.47 (s, 3H), 2.45 – 2.28 (m, 2H), 2.13 – 2.00 (m, 2H), 1.88 (ddd, *J* = 13.4, 7.7, 3.8 Hz, 2H), 1.83 – 1.61 (m, 3H), 1.61 – 1.47 (m, 1H), 0.98 (m, 3H), 0.96 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.82, 172.32, 172.14, 171.08, 158.88, 158.46, 101.41, 52.30, 51.65, 50.61, 42.25, 42.11, 37.90, 33.33, 26.61, 24.71, 22.87, 22.10, 21.40, 12.31. ESI-MS (*m/z*): 423.2 $(M + H)^+$.

N-((S)-1-(((S)-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-5-methylisoxazole-3-carboxamide (**124**)

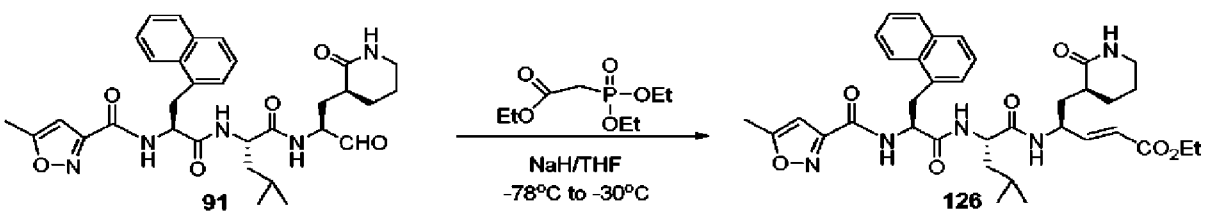
Compound **124** (86 mg, 82%) was prepared from compound **123** (110 mg, 0.27 mmol) by following the protocol described for the preparation of compound **90**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 1H), 6.41 (d, *J* = 1.1 Hz, 1H), 4.72 (td, *J* = 8.5, 4.2 Hz, 1H), 4.06 (td, *J* = 7.5, 3.9 Hz, 1H), 3.59 (t, *J* = 4.4 Hz, 2H), 3.39 – 3.20 (m, 2H), 2.46 (d, *J* = 0.9 Hz, 3H), 2.37 – 2.26 (m, 1H), 2.19 (ddd, *J* = 14.1, 10.9, 4.6 Hz, 1H), 2.05 (ddq, *J* = 11.1, 5.9, 2.9 Hz, 1H), 1.92 – 1.78 (m, 1H), 1.79 – 1.59 (m, 6H), 1.58 – 1.38 (m, 1H), 0.95 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.81, 172.46, 171.09, 158.98, 158.49, 101.50, 65.63, 52.17, 49.61, 42.35, 41.98, 38.00, 32.62, 26.78, 24.86, 22.98, 21.99, 21.43, 12.30. ESI-MS (*m/z*): 395.2 $(M + H)^+$.

5-Methyl-N-((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)pentan-2-yl)isoxazole-3-carboxamide (**125**)

Compound **125** (26 mg, 53%) was prepared from compound **124** (52 mg, 0.13 mmol) by following the protocol described for the preparation of compound **91**.

^{1}H NMR (400 MHz, Methanol-d_4) δ 6.56 – 6.44 (m, 1H), 4.60 (tdd, *J* = 8.5, 5.6, 2.6 Hz, 1H), 4.56 – 4.39 (m, 1H), 4.24 – 3.88 (m, 1H), 3.36 (d, *J* = 3.7 Hz, 2H), 3.30 – 3.20 (m, 2H), 2.50 (dd, *J* = 2.2, 0.9 Hz, 3H), 2.34 (dddd, *J* = 20.4, 11.7, 6.6, 3.3 Hz, 1H), 2.23 – 2.09 (m, 1H), 2.03 (ddt, *J* = 13.1, 6.4, 3.2 Hz, 1H), 1.89 – 1.60 (m, 3H), 1.57 – 1.40 (m, 1H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.99 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.10, 173.19, 171.63, 159.95, 158.32, 100.64, 98.33, 53.80, 52.39, 50.56, 41.61, 40.55, 37.01, 29.80, 25.40, 24.62, 21.90, 20.83, 10.62. ESI-MS (*m/z*): 393.2 $(M + H)^+$.



91 126

Ethyl (S,E)-4-((S)-4-methyl-2-((S)-2-(5-methylisoxazole-3-carboxamido)-3-(naphthalen-1-yl)propanamido)pentanamido)-5-((S)-2-oxopiperidin-3-yl)pent-2-enoate (**126**)

To a solution of triethyl phosphonoacetate (20 mg, 0.09 mmol) in anhydrous THF (0.5 mL), at -78 °C under an argon atmosphere, was added sodium hydride (2.0 mg, 0.05 mmol). The suspension was stirred for 30 min at the same temperature, and a solution of compound **91** (12.5

mg, 0.021 mmol) in anhydrous THF was added dropwise. The reaction was gradually warmed to -30 °C and stirred for 1 h and upon completion was quenched by the addition of saturated aqueous NH_4Cl. The mixture was diluted with AcOEt (15 mL) and the water layer was extracted with AcOEt. The combined organic layer was dried over Na_2SO4, and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC (DCM/MeOH, 20/1) to give compound **126** (8.1 mg, 58%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 6.8 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.55 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 2H), 7.48 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.44 – 7.33 (m, 2H), 6.80 (dd, *J* = 15.7, 5.4 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.37 (d, *J* = 1.0 Hz, 1H), 6.01 (s, 1H), 5.91 (dd, *J* = 15.7, 1.5 Hz, 1H), 4.98 (q, *J* = 7.3 Hz, 1H), 4.46 (td, *J* = 8.7, 8.2, 4.7 Hz, 2H), 3.78-3.72 (m, 4H), 3.59 (dd, *J* = 14.3, 7.2 Hz, 1H), 3.32 – 3.18 (m, 2H), 2.45 (s, 3H), 2.22 (dd, *J* = 10.6, 5.5 Hz, 1H), 2.02 – 1.96 (m, 2H), 1.84-1.79 (m, 2H), 1.70-1.62 (m, 2H), 1.53 – 1.42 (m, 4H), 1.40 – 1.25 (m, 3H), 0.86 (d, J = 4.4Hz, 3H), 0.84 (d, J = 4.4Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.93, 171.81, 171.28, 170.02, 166.77, 159.39, 158.14, 147.83, 133.94, 132.45, 132.00, 128.85, 128.02, 127.84, 126.45, 125.75, 125.47, 123.75, 120.66, 101.32, 54.22, 52.30, 51.57, 49.50, 42.32, 41.49, 38.71, 35.86, 35.04, 27.93, 24.79, 22.92, 21.83, 21.50, 12.32. ESI-MS (*m/z*): 660.3 $(M + H)^+$.

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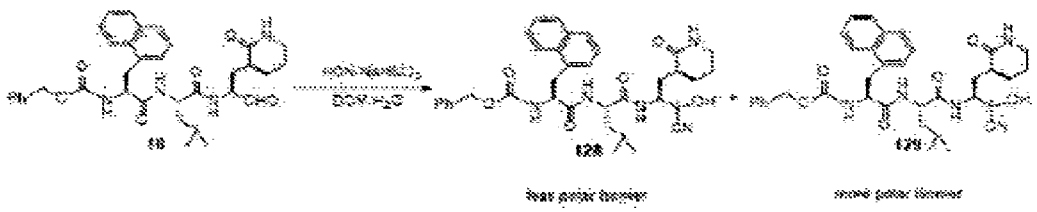
N-((S)-1-(((S)-1-(((S)-1,1-dimethoxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)-5-methylisoxazole-3-carboxamide (**127**)

To a solution of compound **91** (23 mg, 0.039 mmol) in MeOH (2 mL) was added TsOH (0.5 mg). The reaction mixture was stirred overnight at room temperature. After removal of the solvent, the residue was purified with preparative TLC (DCM/MeOH = 20:1) to give compound **127** (16.3 mg, 66%).

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.27 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.56 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.53 – 7.41 (m, 2H), 7.37 (dd, *J*

= 8.2, 7.0 Hz, 1H), 6.32 (d, *J* = 1.1 Hz, 1H), 5.03 (ddd, *J* = 9.5, 5.0, 1.9 Hz, 1H), 4.42 (t, *J* = 7.5 Hz, 1H), 4.31 – 4.22 (m, 1H), 4.22 – 4.09 (m, 1H), 3.82 (dd, *J* = 14.4, 4.9 Hz, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.38 – 3.36 (m, 1H), 3.23 (tt, *J* = 7.2, 3.8 Hz, 3H), 2.43 (d, *J* = 0.9 Hz, 3H), 2.31 (dddd, *J* = 11.8, 9.2, 5.9, 3.1 Hz, 1H), 2.16 (ddd, *J* = 14.2, 12.2, 3.3 Hz, 1H), 2.10 – 2.03 (m, 1H), 1.84 – 1.54 (m, 4H), 1.53 – 1.41 (m, 1H), 1.37 (dd, *J* = 7.0, 5.1 Hz, 1H), 0.98 (dd, *J* = 6.4 Hz, 3H), 0.95 (dd, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.92, 173.39, 173.31, 171.61, 171.57, 159.89, 158.08, 134.04, 132.72, 131.99, 128.44, 127.39, 127.34, 125.92, 125.31, 124.99, 123.24, 105.88, 100.52, 54.62, 53.83, 52.55, 41.61, 40.57, 37.05, 34.38, 30.70, 25.50, 24.41, 21.83, 20.93, 20.70, 10.55. ESI-MS (*m/z*): 604.2 $(M - OCH_3)^+$.



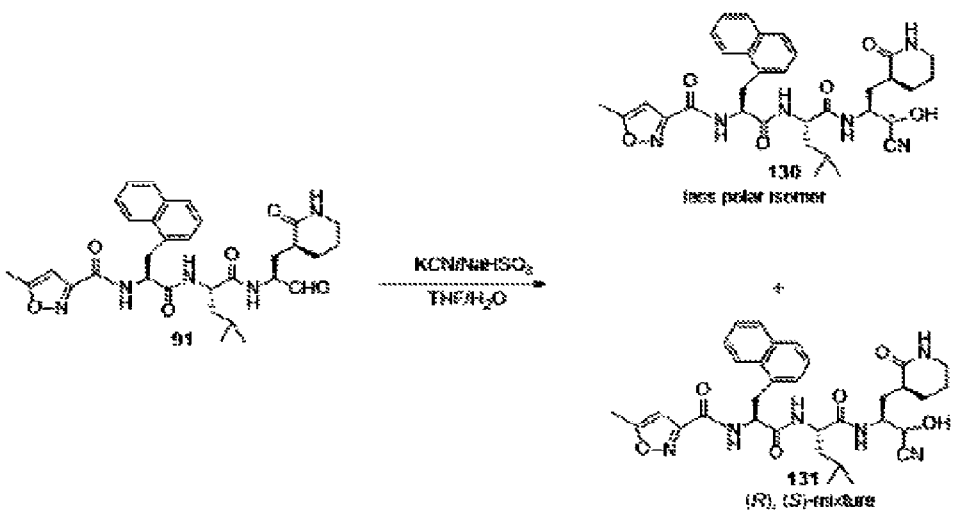
Benzyl ((S)-1-(((S)-1-(((1R,2S)-1-cyano-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate and benzyl ((S)-1-(((S)-1-(((1S,2S)-1-cyano-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (**128** and **129**)

To a solution of **18** (31 mg, 0.05 mmol) in DCM (0.5 mL) was added $NaHSO_3$ (1M, 0.06 mL, 0.06 mmol). The mixture was stirred at room temperature for 30 minutes, and then a solution of KCN (1M, 0.06 mL, 0.06 mmol) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM (30 mL) and washed with water. The organic layer was dried over Na_2SO4, and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC (DCM/MeOH, 20/1) to give the less polar isomer **128** (11 mg, 34%) and the more polar isomer **129** (14 mg, 43%).

Compound **128**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.76 (dt, *J* = 8.1, 1.8 Hz, 1H), 7.66 (dt, *J* = 7.1, 3.1 Hz, 1H), 7.49 – 7.34 (m, 2H), 7.34 – 7.24 (m, 2H), 7.21 – 7.16 (m, 2H), 7.16 – 7.02 (m, 3H), 4.90 – 4.87 (m, 1H), 4.60 – 4.40 (m, 1H), 4.40 – 4.20 (m, 2H), 4.15 – 4.08 (m, 1H), 3.67 - 3.56 (m, 1H), 3.18 – 2.98 (m, 3H), 2.37 – 2.02 (m, 2H), 1.97 – 1.85 (m, 1H), 1.78 – 1.42 (m, 7H), 1.34 (t, *J* = 11.2 Hz, 1H), 0.92 – 0.75 (m, 6H). ^{13}C NMR

(101 MHz, MeOD) δ 175.51, 175.44, 173.86, 172.71, 156.88, 136.69, 134.06, 133.11, 132.01, 128.48, 128.04, 127.50, 127.27, 125.86, 125.27, 125.00, 123.33, 118.89, 66.19, 63.62, 55.91, 52.30, 49.58, 41.55, 40.59, 37.62, 36.97, 34.46, 31.42, 25.77, 24.47, 21.26, 20.52. ESI-MS (*m/z*): 642.3 $(M + H)^+$.

Compound **129**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.22 (d, J = 8.3 Hz, 1H), 7.88(d, J = 8.1 Hz, 1H), 7.77 (dd, J = 6.7, 2.9 Hz, 1H), 7.61 – 7.46 (m, 2H), 7.45 – 7.36 (m, 2H), 7.34 – 7.28 (m, 3H), 7.26 – 7.14 (m, 2H), 5.06 – 4.97 (m, 2H), 4.85 -4.77 (m, 1H), 4.63 (dq, J = 15.8, 6.1, 5.4 Hz, 1H), 4.50 – 4.33 (m, 1H), 4.22 (dt, J = 12.1, 3.8 Hz, 1H), 4.02 (ddd, J = 9.7, 5.2, 2.6 Hz, 1H), 3.73 (dt, J = 14.5, 4.2 Hz, 1H), 3.36 (d, J = 4.0 Hz, 1H), 3.28 – 3.12 (m, 3H), 2.37 (tdd, J = 17.6, 10.4, 4.0 Hz, 1H), 2.24 – 2.09 (m, 1H), 2.08 – 1.96 (m, 1H), 1.87 – 1.52 (m, 4H), 1.52 – 1.40 (m, 1H), 0.98 – 0.91 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 176.09, 175.51, 173.96, 172.67, 156.81, 136.70, 134.03, 133.11, 132.03, 128.44, 128.01, 127.49, 127.28, 127.25, 125.83, 125.26, 125.00, 123.33, 123.28, 118.68, 66.16, 62.90, 55.61, 52.29, 49.58, 41.55, 40.60, 37.09, 34.46, 30.66, 25.77, 24.38, 21.90, 20.72. ESI-MS (*m/z*): 642.3 $(M + H)^+$.

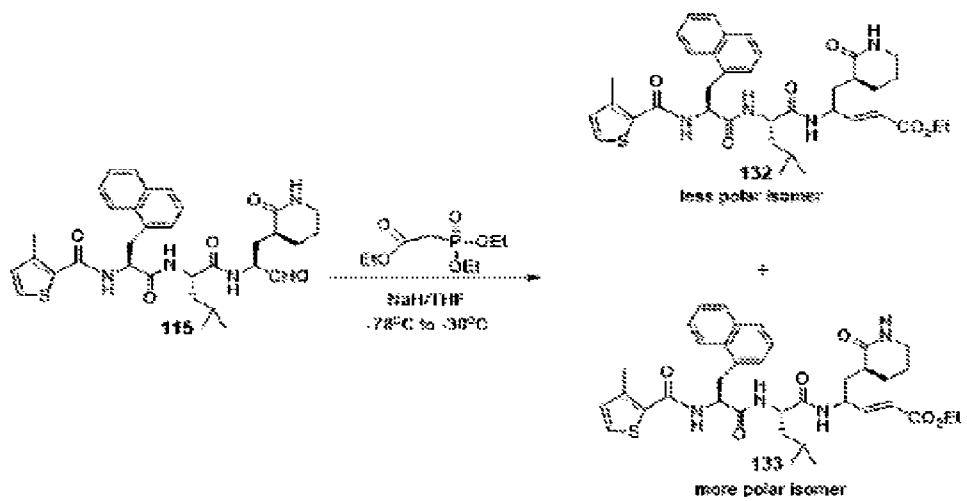


N-((2S)-1-(((2S)-1-(((2S)-1-cyano-1-hydroxy-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)-5-methylisoxazole-3-carboxamide (**130** and **131**)

Cyanohydrins **130** and **131** were synthesized from **91** by following the procedure described for the preparation of compound **128** and **129**. After purification, one fraction was

isolated as a single isomer (**130**, configuration unknown) while the other fractions were mixtures of (*R*)- and (*S*)-isomers (**131**).

Compound **130**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 7.2 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.89 – 7.64 (m, 3H), 7.46 (dtd, *J* = 10.1, 6.8, 1.7 Hz, 3H), 7.38 – 7.28 (m, 2H), 6.64 (s, 1H), 6.27 (s, 1H), 5.98 (d, *J* = 7.7 Hz, 1H), 5.06 (td, *J* = 8.0, 6.0 Hz, 1H), 4.56 (dd, *J* = 7.7, 3.7 Hz, 1H), 4.49 (td, *J* = 8.2, 5.5 Hz, 1H), 4.22 (ddt, *J* = 11.5, 7.5, 3.7 Hz, 1H), 3.70 (dd, *J* = 14.5, 5.9 Hz, 1H), 3.51 (dd, *J* = 14.4, 8.3 Hz, 1H), 3.29 – 3.10 (m, 2H), 2.38 (s, 3H), 2.29 (ddd, *J* = 22.3, 12.0, 4.6 Hz, 2H), 1.97 (tt, *J* = 8.9, 4.0 Hz, 1H), 1.77 (dt, *J* = 13.5, 4.2 Hz, 1H), 1.71 – 1.38 (m, 5H), 0.82 (dd, *J* = 2.2 Hz, 3H), 0.80 (dd, *J* = 2.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.17, 173.96, 171.34, 170.79, 159.45, 158.04, 133.87, 132.51, 131.97, 128.82, 127.86, 127.70, 126.44, 125.76, 125.42, 123.62, 118.45, 101.31, 65.16, 54.07, 52.77, 51.78, 42.24, 41.12, 37.79, 34.93, 31.49, 27.09, 24.75, 22.75, 21.96, 21.24, 12.27. ESI-MS (*m/z*): 617.3 $(M + H)^+$.



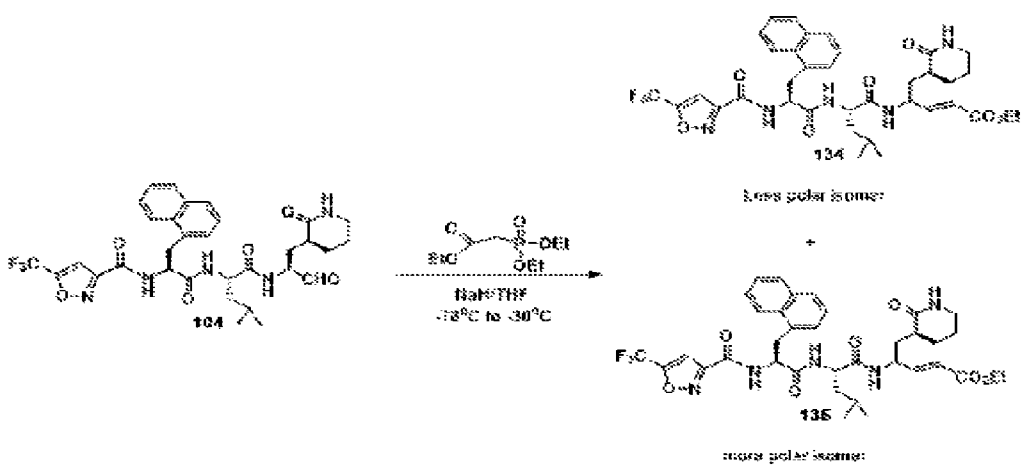
Ethyl (E)-4-((S)-4-methyl-2-((S)-2-(3-methylthiophene-2-carboxamido)-3-(naphthalen-1-yl)propanamido)pentanamido)-5-((S)-2-oxopiperidin-3-yl)pent-2-enoate (**132** and **133**)

Compounds **132** and **133** were synthesized from **115** by following the procedure described for the preparation of compound **126**.

Compound **132**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 8.5 Hz, 1H), 7.89 – 7.79 (m, 2H), 7.79 – 7.70 (m, 1H), 7.51 (dddd, *J* = 23.8, 8.0, 6.8, 1.3 Hz, 2H), 7.46 – 7.34 (m, 2H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.87 – 6.76 (m, 2H), 6.50 (d, *J* = 7.2 Hz, 1H), 5.93 (ddd, *J* = 17.2, 13.9, 3.0

Hz, 2H), 5.00 (q, *J* = 7.2 Hz, 1H), 4.48 (td, *J* = 9.3, 8.8, 4.8 Hz, 2H), 4.18 (qd, *J* = 7.2, 2.9 Hz, 3H), 3.83 – 3.56 (m, 2H), 3.22 (s, 1H), 2.97 (dd, *J* = 21.6, 6.4 Hz, 1H), 2.33 (d, *J* = 2.2 Hz, 3H), 2.28 – 2.15 (m, 1H), 2.06 – 1.89 (m, 1H), 1.81 (dd, *J* = 9.0, 4.5 Hz, 1H), 1.69 (ddt, *J* = 13.3, 9.1, 4.5 Hz, 1H), 1.58 – 1.41 (m, 3H), 1.35 (t, *J* = 7.1 Hz, 1H), 1.30 – 1.22 (m, 4H), 0.88 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.88, 171.95, 170.84, 166.34, 163.26, 147.48, 141.24, 133.96, 132.75, 132.19, 131.97, 130.76, 128.84, 128.00, 127.92, 127.47, 126.49, 125.78, 125.49, 123.93, 121.16, 60.41, 54.60, 52.31, 49.36, 42.34, 41.44, 38.66, 36.03, 34.78, 27.88, 24.83, 23.03, 21.73, 21.43, 15.66, 14.25. ESI-MS (*m/z*): 675.3 $(M + H)^+$.

Compound **133**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.35 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 7.2 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.57 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.46 – 7.35 (m, 2H), 7.00 – 6.79 (m, 2H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 7.1 Hz, 1H), 5.90 (dd, *J* = 15.6, 1.7 Hz, 1H), 5.82 (s, 1H), 5.07 (q, *J* = 7.2 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.43 (td, *J* = 9.3, 4.4 Hz, 1H), 4.18 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.80 (dd, *J* = 14.4, 6.6 Hz, 1H), 3.76 – 3.63 (m, 2H), 3.22 (d, *J* = 7.0 Hz, 3H), 2.32 (s, 3H), 2.02 – 1.94 (m, 2H), 1.93 – 1.81 (m, 1H), 1.77 – 1.56 (m, 4H), 1.50 – 1.40 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.85 (dd, *J* = 1.7 Hz, 3H), 0.82 (dd, *J* = 1.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.88, 171.34, 171.31, 166.28, 163.56, 147.12, 141.49, 134.00, 132.90, 132.15, 132.02, 130.52, 128.91, 127.97, 127.91, 127.54, 126.66, 125.89, 125.52, 123.85, 121.72, 60.45, 54.53, 52.48, 48.36, 42.52, 41.22, 37.84, 34.68, 34.14, 27.60, 24.81, 23.05, 21.87, 21.52, 15.64, 14.26. ESI-MS (*m/z*): 675.3 $(M + H)^+$.



Ethyl (E)-4-((S)-4-methyl-2-((S)-3-(naphthalen-1-yl)-2-(5-(trifluoromethyl)isoxazole-3-carboxamido)propanamido)pentanamido)-5-((S)-2-oxopiperidin-3-yl)pent-2-enoate (**134** and **135**)

Compounds **134** and **135** were synthesized from **104** by following the procedure described for the preparation of compound **126**.

Compound **134**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 6.6 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.52 (dddd, *J* = 26.4, 8.0, 6.8, 1.3 Hz, 2H), 7.45 – 7.32 (m, 2H), 7.08 (t, *J* = 0.9 Hz, 1H), 6.79 (dd, *J* = 15.7, 5.4 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 5.92 (d, *J* = 1.6 Hz, 1H), 5.01 (q, *J* = 7.2 Hz, 1H), 4.45 (td, *J* = 10.4, 8.3, 5.0 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.79 – 3.56 (m, 2H), 3.26 (d, *J* = 12.9 Hz, 3H), 2.35 – 2.23 (m, 1H), 2.09 – 1.91 (m, 2H), 1.87 – 1.60 (m, 4H), 1.60 – 1.37 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.88 (dd, *J* = 1.7 Hz, 3H), 0.86 (dd, *J* = 1.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.17, 171.74, 169.67, 166.31, 158.17, 157.27, 147.31, 133.97, 132.13, 131.98, 128.93, 128.23, 127.99, 126.55, 125.85, 125.48, 123.65, 121.22, 105.33, 105.30, 60.45, 54.39, 52.35, 49.88, 42.39, 41.62, 38.85, 36.13, 35.35, 28.22, 24.80, 22.90, 21.87, 21.44, 14.24. ^{19}F NMR (377 MHz, $CDCl_3$) δ -64.01. ESI-MS (*m/z*): 714.3 $(M + H)^+$.

Compound **135**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 7.0 Hz, 1H), 8.29 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.73 – 7.65 (m, 1H), 7.60 – 7.53 (m, 2H), 7.51 – 7.46 (m, 2H), 7.41 – 7.37 (m, 1H), 6.86 (dd, *J* = 15.6, 4.4 Hz, 1H), 6.22 (d, *J* = 7.8 Hz, 1H), 6.10 (s, 1H), 5.96 (dd, *J* = 15.6, 1.8 Hz, 1H), 5.16 (q, *J* = 7.4 Hz, 1H), 4.70 (d, *J* = 6.2 Hz, 1H), 4.31 (ddd, *J* = 9.8, 7.9, 4.8 Hz, 1H), 4.26 – 4.12 (m, 3H), 3.77 (dd, *J* = 14.3, 7.3 Hz, 1H), 3.68 (dd, *J* = 14.4, 7.0 Hz, 1H), 3.25 (s, 3H), 2.35 – 2.25 (m, 1H), 1.96 – 1.87 (m, 2H), 1.70 (ddt, *J* = 16.6, 12.5, 6.3 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.81 (d, *J* = 4.2 Hz, 3H), 0.79 (d, *J* = 4.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.30, 170.83, 169.81, 166.31, 158.36, 157.28, 146.91, 133.99, 132.42, 132.16, 131.97, 128.99, 128.45, 128.13, 127.99, 126.63, 125.89, 125.57, 123.53, 122.05, 105.47, 60.53, 54.19, 52.86, 48.51, 42.49, 40.70, 37.48, 35.16, 28.33, 24.74, 22.94, 21.64, 21.60, 14.26. ^{19}F NMR (377 MHz, $CDCl_3$) δ -64.01. ESI-MS (*m/z*): 714.3 $(M + H)^+$.

Example 2

Cellular Toxicity Assays

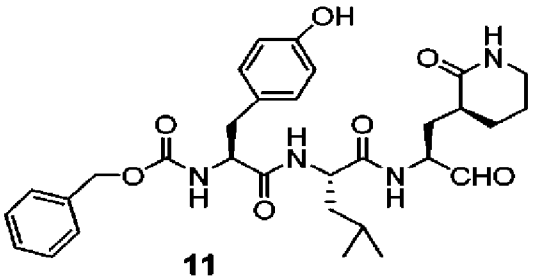
The toxicity of the compounds was assessed in Vero, human PBM, CEM (human lymphoblastoid), MT-2, and HepG2 cells, as described previously (see Schinazi R.F., Sommadossi J.-P., Saalmann V., Cannon D.L., Xie M.-Y., Hart G.C., Smith G.A. & Hahn E.F. *Antimicrob. Agents Chemother.* **1990**, 34, 1061-67). Cycloheximide was included as positive cytotoxic control, and untreated cells exposed to solvent were included as negative controls. The cytotoxicity CC_{50} was obtained from the concentration-response curve using the median effective method described previously (see Chou T.-C. & Talalay P. *Adv. Enzyme Regul.* **1984**, 22, 27-55; Belen'kii M.S. & Schinazi R.F. Antiviral Res. **1994**, 25, 1-11). The results are shown in Table 1 below:

Table 1

Cytotoxicity, CC_{50}, µM (% inhibition)

Compound	PBM	CEM	VERO	Huh7
11	>100	>100	>100	>10
19	24	32	20	>10
23	>100	39	>100	>10
29	>100	38	>100	>10
35	52	35	>100	60
36	45	9	>100	8
37	44	18	>100	11
38	18	6	22	13
39	39	2	11	14
67	>100	64	>100	ND

In the Table, compounds 11, 19, 28, 29, 35-39 and 67 have the following structures:



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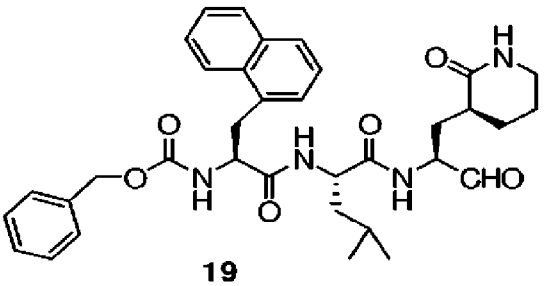

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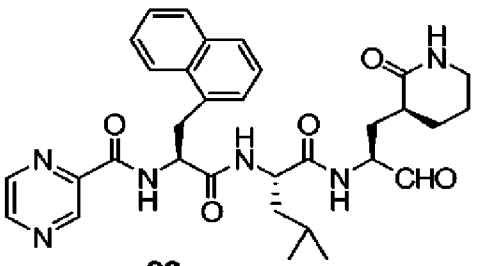

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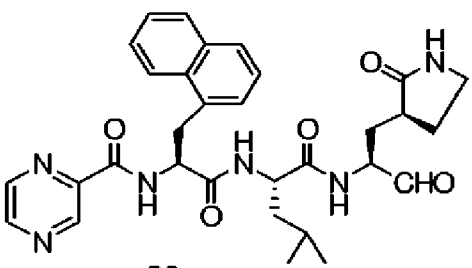

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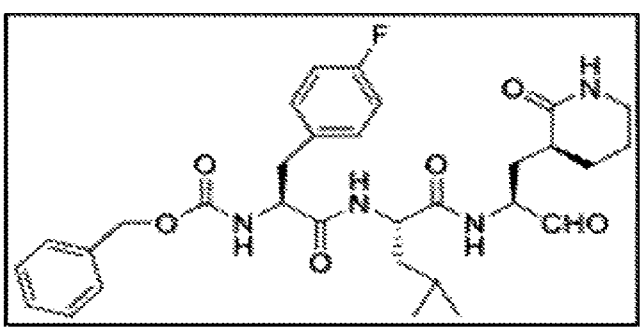

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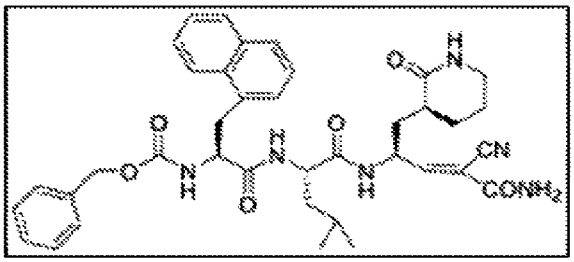

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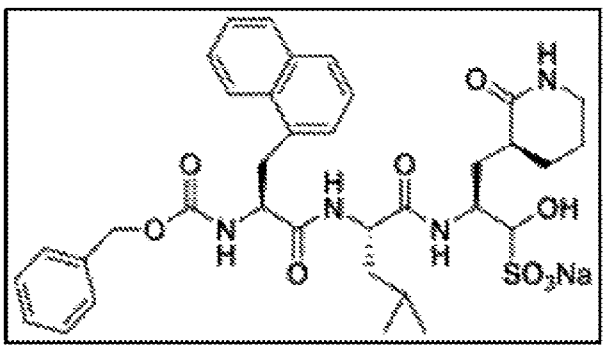

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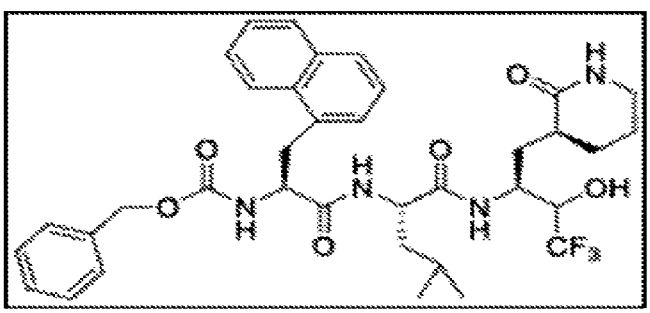

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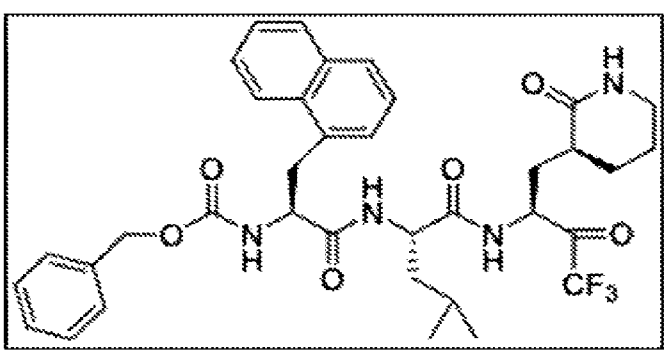

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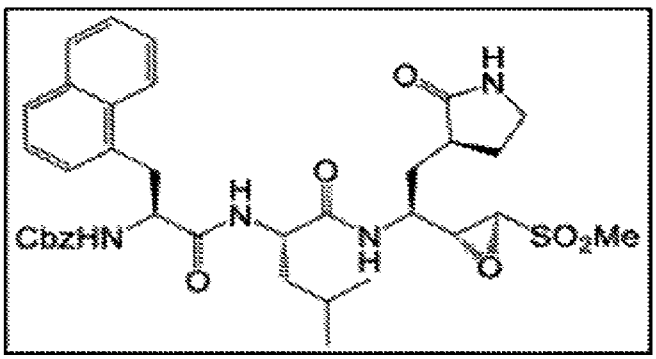


67

Example 3

Mitochondrial Toxicity Assays in HepG2 Cells:

i) Effect of Compounds on Cell Growth and Lactic Acid Production: The effect on the growth of HepG2 cells was determined by incubating cells in the presence of 0 μM, 0.1 μM, 1 μM, 10 μM and 100 μM drug. Cells (5 x 10^4 per well) were plated into 12-well cell culture clusters in minimum essential medium with nonessential amino acids supplemented with 10% fetal bovine serum, 1% sodium pyruvate, and 1% penicillin/streptomycin and incubated for 4 days at 37°C. At the end of the incubation period the cell number was determined using a hemocytometer. Also taught by Pan-Zhou X-R, Cui L, Zhou X-J, Sommadossi J-P, Darley-Usmer VM. "Differential effects of antiretroviral nucleoside analogs on mitochondrial function in HepG2 cells," Antimicrob. Agents Chemother. **2000**; 44: 496-503.

To measure the effects of the compounds on lactic acid production, HepG2 cells from a stock culture were diluted and plated in 12-well culture plates at 2.5 x 10^4 cells per well. Various concentrations (0 μM, 0.1 μM, 1 μM, 10 μM and 100 μM) of compound were added, and the cultures were incubated at 37°C in a humidified 5% CO_2 atmosphere for 4 days. At day 4, the number of cells in each well was determined and the culture medium collected. The culture medium was then filtered, and the lactic acid content in the medium was determined using a colorimetric lactic acid assay (Sigma-Aldrich). Since lactic acid product

can be considered a marker for impaired mitochondrial function, elevated levels of lactic acid production detected in cells grown in the presence of test compounds would indicate a drug-induced cytotoxic effect.

ii)Effect of Compounds on Mitochondrial DNA Synthesis: a real-time PCR assay to accurately quantify mitochondrial DNA content has been developed (see Stuyver LJ, Lostia S, Adams M, Mathew JS, Pai BS, Grier J, Tharnish PM, Choi Y, Chong Y, Choo H, Chu CK, Otto MJ, Schinazi RF. Antiviral activities and cellular toxicities of modified 2',3'-dideoxy-2',3'-didehydrocytidine analogs. Antimicrob. Agents Chemother. **2002**; 46: 3854-60). This assay was used in all studies described in this application that determine the effect of compounds on mitochondrial DNA content. In this assay, low-passage-number HepG2 cells were seeded at 5,000 cells/well in collagen-coated 96-well plates. Test compounds were added to the medium to obtain final concentrations of 0 μM, 0.1 μM, 10 μM and 100 μM. On culture day 7, cellular nucleic acids were prepared by using commercially available columns (RNeasy 96 kit; Qiagen). These kits co-purify RNA and DNA, and hence, total nucleic acids are eluted from the columns. The mitochondrial cytochrome c oxidase subunit II (COXII) gene and the ß-actin or rRNA gene were amplified from 5 μl of the eluted nucleic acids using a multiplex Q-PCR protocol with suitable primers and probes for both target and reference amplifications. For COXII the following sense, probe and antisense primers were used, respectively: 5'- TGCCCGCCATCATCCTA-3', 5'-tetrachloro-6-carboxyfluorescein-TCCTCATCGCCCTCCCATCCC-TAMRA-3' and 5'-CGTCTGTTATGTAAAGGATGCGT-3'. For exon 3 of the ß-actin gene (GenBank accession number E01094) the sense, probe, and antisense primers are 5'- GCGCGGCTACAGCTTCA-3', 5'-6-FAMCACCACGGCCGAGCGGGATAMRA-3' and 5'-TCTCCTTAATGTCACGCACGAT-3', respectively. The primers and probes for the rRNA gene are commercially available from Applied Biosystems. Since equal amplification efficiencies are obtained for all genes, the comparative CT method was used to investigate potential inhibition of mitochondrial DNA synthesis. The comparative CT method uses arithmetic formulas in which the amount of target (COXII gene) is normalized to the amount of an endogenous reference (the ß-actin or rRNA gene) and is relative to a calibrator (a control with no drug at day 7). The arithmetic formula for this approach is given by 2-ΔΔCT, where ΔΔCT is (CT for average target test sample - CT for target control) - (CT for average reference

test -CT for reference control) (see Johnson MR, K Wang, JB Smith, MJ Heslin, RB Diasio. Quantitation of dihydropyrimidine dehydrogenase expression by real-time reverse transcription polymerase chain reaction. Anal. Biochem. 2000; 278:175-184). A decrease in mitochondrial DNA content in cells grown in the presence of drug indicated mitochondrial toxicity.

Example 4

Mitochondrial Toxicity Assays in Neuro2A Cells

To estimate the potential of the compounds of this invention to cause neuronal toxicity, mouse Neuro2A cells (American Type Culture Collection 131) can be used as a model system (see Ray AS, Hernandez-Santiago BI, Mathew JS, Murakami E, Bozeman C, Xie MY, Dutschman GE, Gullen E, Yang Z, Hurwitz S, Cheng YC, Chu CK, McClure H, Schinazi RF, Anderson KS. Mechanism of anti-human immunodeficiency virus activity of beta-D-6-cyclopropylamino-2',3'-didehydro-2',3'-dideoxyguanosine. *Antimicrob. Agents Chemother.* **2005**, 49, 1994-2001). The concentrations necessary to inhibit cell growth by 50% (CC_{50}) can be measured using the 3-(4,5-dimethyl-thiazol-2-yl)-2,5- diphenyltetrazolium bromide dye-based assay, as described. Perturbations in cellular lactic acid and mitochondrial DNA levels at defined concentrations of drug can be carried out as described above. ddC and AZT can be used as control nucleoside analogs.

Example 5

Assay for Bone Marrow Cytotoxicity

Primary human bone marrow mononuclear cells can be obtained commercially from Cambrex Bioscience (Walkersville, MD). CFU-GM assays is carried out using a bilayer soft agar in the presence of 50 units/mL human recombinant granulocyte/macrophage colony-stimulating factor, while BFU-E assays used a ethylcellulose matrix containing 1 unit/mL erythropoietin (see Sommadossi JP, Carlisle R. Toxicity of 3'-azido-3'-deoxythymidine and 9-(1,3-dihydroxy-2-propoxymethyl) guanine for normal human hepatopoietic progenitor cells *in vitro*. Antimicrob. Agents Chemother. 1987; 31: 452-454; Sommadossi, JP, Schinazi, RF, Chu, CK, and Xie, MY. Comparison of cytotoxicity of the (-) and (+) enantiomer of 2',3'-

dideoxy-3'-thiacytidine in normal human bone marrow progenitor cells. Biochem. Pharmacol. 1992; 44:1921- 1925). Each experiment can be performed in duplicate in cells from three different donors. AZT is used as a positive control. Cells can be incubated in the presence of the compound for 14-18 days at 37°C with 5% CO_2, and colonies of greater than 50 cells can be counted using an inverted microscope to determine the IC50. The 50% inhibitory concentration (IC_{50}) can be obtained by least-squares linear regression analysis of the logarithm of drug concentration *versus* BFU-E survival fractions. Statistical analysis can be performed with Student's t test for independent non-paired samples.

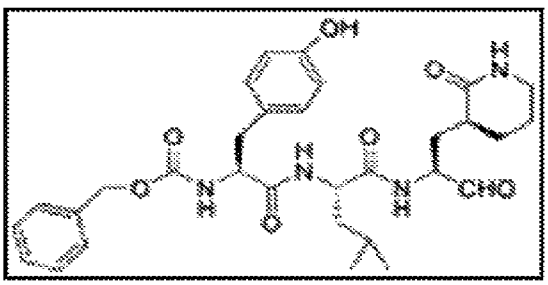
Example 6

Anti-Enterovirus Activity

Compounds are tested for cytotoxicity using a MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) method and the CC_{50} (IC_{50}) values (cytotoxic concentrations of drug required to reduce cell viability by 50%) are determined for each test compound in human rhabdomyosarcoma (RD) cell line. In addition, the maximum non-toxic concentrations (MNTC) are also determined for each compound. To avoid potential drug toxicity that would interfere with viral cytopathic effect (CPE), compounds are evaluated at nontoxic concentrations. The resultant inhibitory effect of each test compound is calculated as a percentage of decrease in EV-71 CPE. Briefly, a monolayer of RD cells is prepared in a 96-well plates. The cells are then infected with 1 MOI of EV-71 (BrCr strain) followed by treatment with a single non-toxic dose of each compound in triplicate. The vehicle control wells are treated with 0.1% DMSO diluted in the working media. The plate is then incubated for 48 h at which time the virus-control wells produced detectable CPE. To determine the probable CPE inhibitory effect of test compounds, an MTS assay is performed and effective compounds are chosen for further studies to identify the potency of the compounds and their concentration-dependent manner. The dose-response antiviral activity of each compound is determined by a virus yield reduction assay method. Briefly, confluent monolayers of RD cells in 96-wells microplate are infected with 0.1 MOI of EV-71 followed by treatment with compounds. Effective compounds are further quantified and confirmed with a virus-yield-reduction assay using an optimized in house qRT-PCR to determine the EV-71 RNA copy number after 2 days post-treatment from collected supernatants. qRT-PCR is performed using the EV-71 specific

probe/primer mix and qScript-Tough master mix (Quantibio, USA). Quantitative PCR measurement was performed using StepOnePlus real time PCR system (Roche, Germany) according to manufacturer's protocol. The median effective concentration (EC_{50}) and the concentration with 90% of inhibitory effect (EC_{90}) are calculated using GraphPad PRISM for Windows, version 5 (GraphPad Software Inc., San Diego, CA, 2005) as the means ± standard deviation (SD) of the mean from triplicate assay from three independent experiments.

The median effective concentrations (EC_{50}) ranges of several of the compounds described herein against Enterovirus EV-71 (BrCr strain) is shown below:

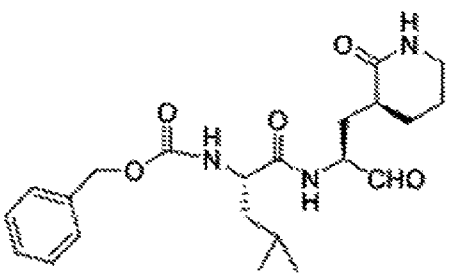


Compound 11

$EC_{50} = 0.19\ \mu M$

$EC_{90} = 0.36\ \mu M$

$CC_{50} = >100\ \mu M$

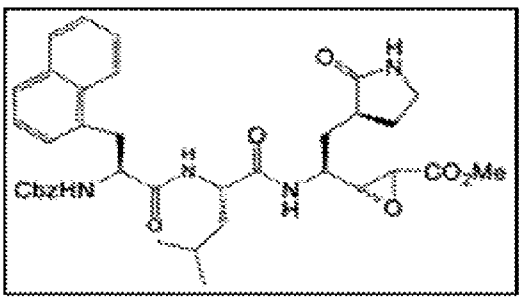


RS-3240

$EC_{50} = 0.05\ \mu M$

$EC_{90} = 0.13 \mu M$

CC_{50} = >100 μM

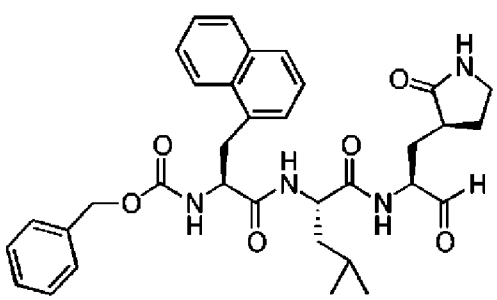


RS-3146

EC_{50} = 0.19 μM

EC_{90} = 0.36 μM

CC_{50} = 80.2 μM

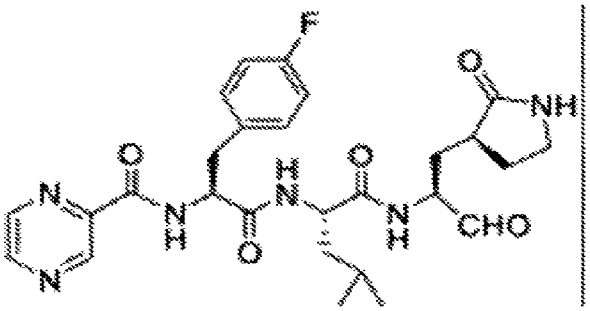


RS-2608

EC_{50} = 0.09 μM

EC_{90} = 0.26 μM

CC_{50} = >100 μM

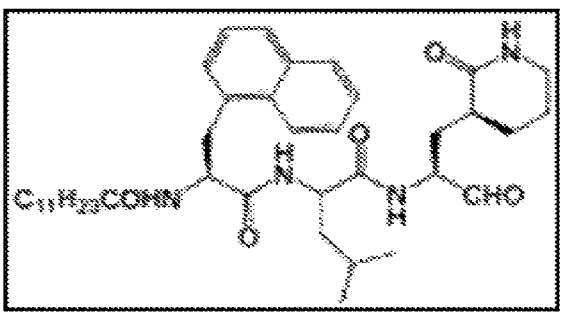


RS-3206

IC_{50} = 0.09 μM

IC_{90} = 0.57 μM

CC_{50} = >100 μM

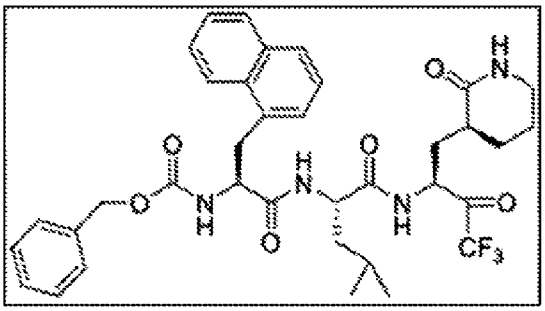


Compound 79

EC_{50} = 0.70 μM

EC_{90} = 1.31 μM

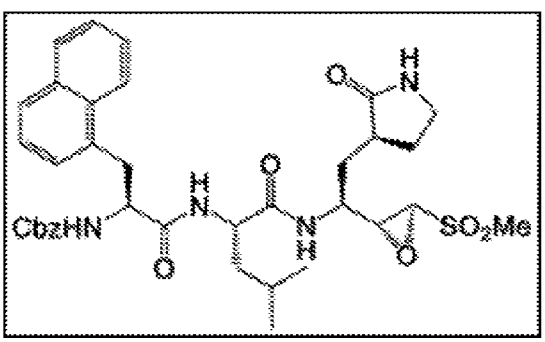
CC_{50} = 32.4 μM



Compound 39

$EC_{50} = 0.32\ \mu M$

$EC_{90} = 0.58\ \mu M$; $CC_{50} = 65\ \mu M$

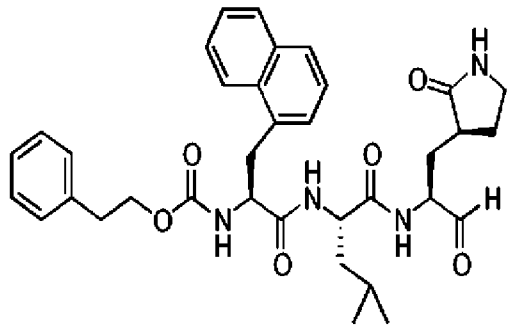


Compound 67

$EC_{50} = 1.44\ \mu M$

$EC_{90} = 5.02\ \mu M$

$CC_{50} = >100\ \mu M$

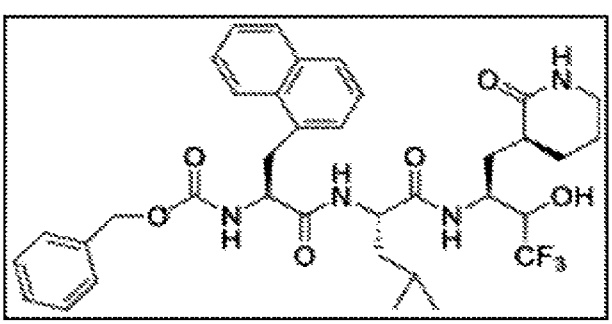


Compound 74

$EC_{50} = 0.75\ \mu M$

$EC_{90} = 2.11\ \mu M$

$CC_{50} = 42.5\ \mu M$

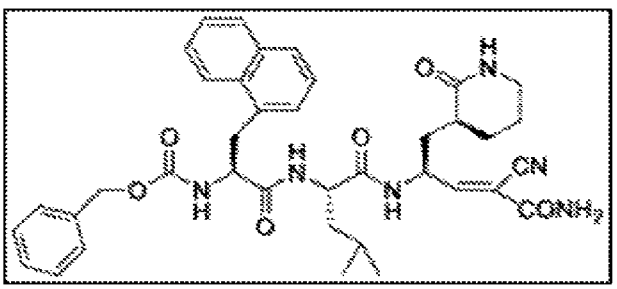


Compound 38

$EC_{50} = 0.31\ \mu M$

$EC_{90} = 0.58\ \mu M$

$CC_{50} = 25\ \mu M$

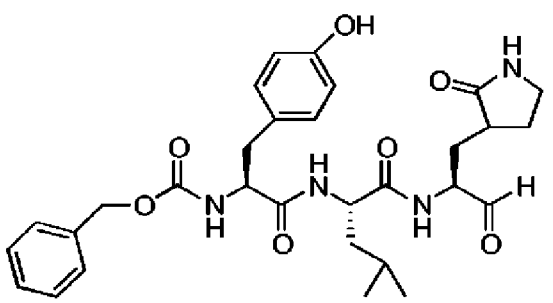


Compound 36

$EC_{50} = 0.03\ \mu M$

$EC_{90} = 0.12\ \mu M$

$CC_{50} = 42.5\ \mu M$

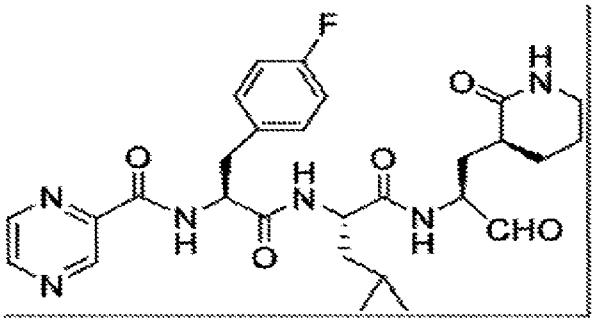


RS-2592

$EC_{50} = 2.3\ \mu M$

$EC_{90} = 4.8\ \mu M$

$CC_{50} > 100$

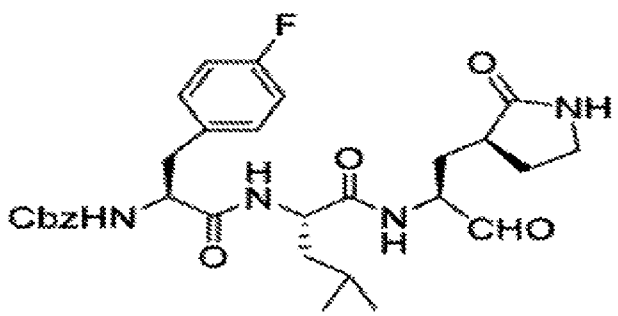


RS-3204

$EC_{50} = 0.28\ \mu M$

$EC_{90} = 0.57\ \mu M$

$CC_{50} = >100\ \mu M$

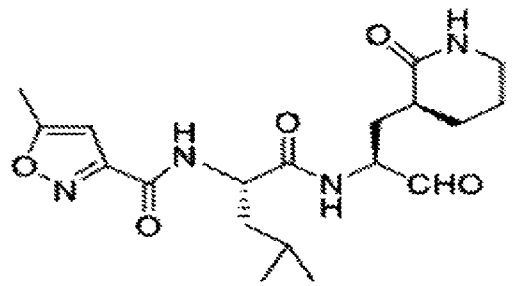


RS-3205

$EC_{50} = 0.03\ \mu M$

$EC_{90} = 0.06\ \mu M$

$CC_{50} = >100\ \mu M$

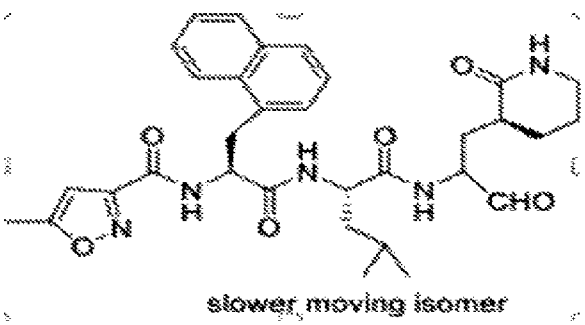


RS-3295

EC_{50} = 1.1 μM

EC_{90} = 4.0 μM

CC_{50} = >100 μM

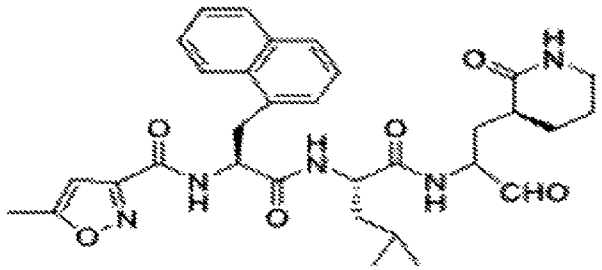


Compound 91

EC_{50} = 1.7 nM

EC_{90} = 7.5 nM

CC_{50} = >100 μM

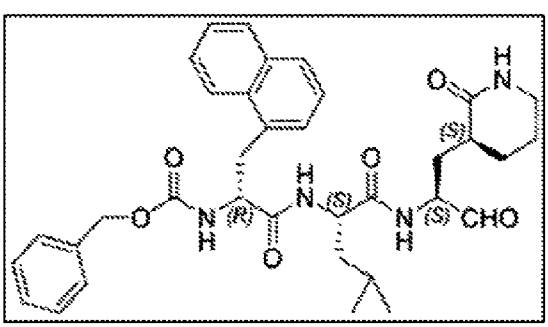


Compound 91A (isomer of Compound 91)

EC_{50} = 8.5 nM

EC_{90} = 21.4 nM

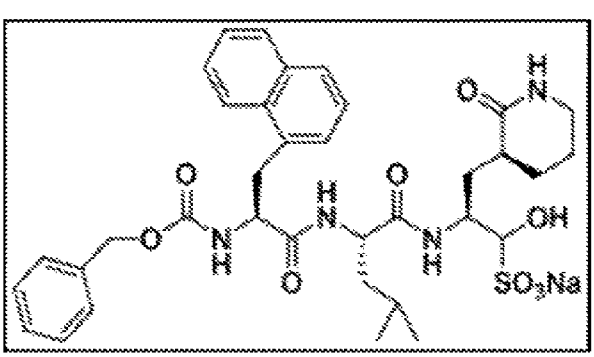
CC_{50} = >100 μM



Compound 19

IC_{50} = 8.8 nM

IC_{90} = 30.0 nM; CC_{50} = 32.5 μM

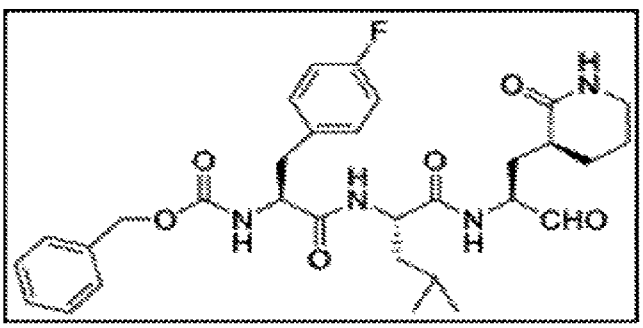


Compound 37

IC_{50} = 11.8 nM

IC_{90} = 30.0 nM

CC_{50} = 95 μM

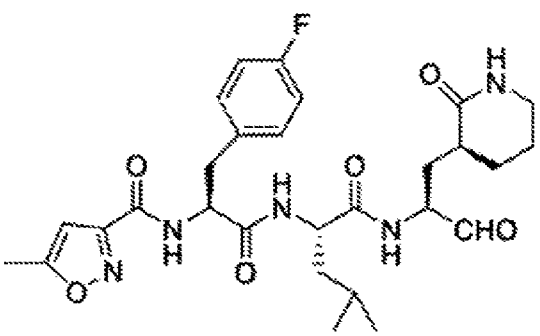


Compound 35

IC_{50} = 10.3 nM

IC_{90} = 29.1 nM

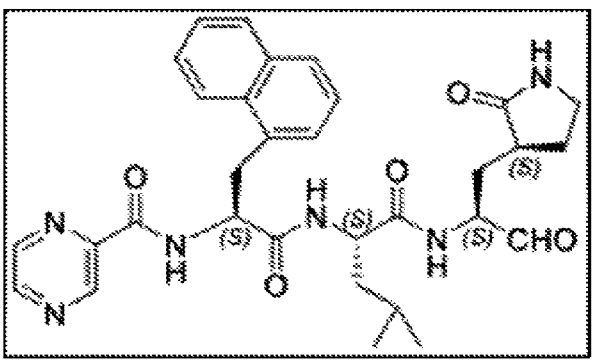
CC_{50} = >100 μM



RS-3294

EC_{50} = 9.4 nM

EC_{90} = 16.6 nanoM; CC_{50} = >100 μM

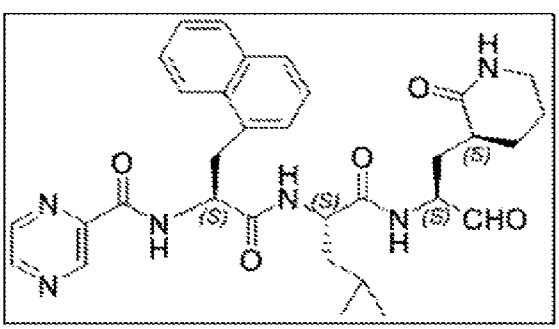


Compound 29

IC_{50} = 17.2 nM

IC_{90} = 64.0 nM

CC_{50} = >100 μM



Compound 23

EC_{50} = 15.8 nM

EC_{90} = 47.5 nM; CC_{50} = >100 μM

Thus, numerous compounds within the formulas described herein have nanomolar EC_{50} values, and excellent therapeutic windows (i.e., CC_{50} values >100 μM).

Example 7

In Vitro Assay for SARS

A fusion protein, prepared by fusing a severe acute respiratory syndrome 3CL protease to E. coli maltose-binding protein (MBP), can be expressed in E coli BL21 (DE3) pLys S cells (Novagen, Oakland, Calif.). Fusion protein thus obtained can be purified by amylose-affinity chromatography and cleaved with factor Xa to release the severe acute respiratory syndrome 3CL protease. Subsequently, the recombinant protease can be purified to homogeneity using phenyl Sepharose CL-4B column (Pharmacia, Uppsala, Sweden) and concentrated to form a 25 μM solution.

The enzymatic activity of severe acute respiratory syndrome 3CL protease (75 nM) can be determined by incubation with a solution containing 15 μM of a substrate peptide (SITSAVLQSGFRKMA, SEQ ID No: 1) at 25° C. for 30 minutes in a medium containing 20 mM Tris-HCl (pH 7.5), 200 mM NaCl, 1 mM EDTA, 1 mM dithiothretol, and 1 mg/mL bovine serum albumin. The reaction can be terminated by adding an equal volume of 0.2% trifluoroacetic acid. The reaction mixture can be analyzed by reverse-phase HPLC using a C18 column. Cleaved products can be resolved using a 5-95% linear gradient of acetonitrile in 0.9% trifluoroacetic acid. Quantification of peak areas can be used to determine the extent of substrate conversion.

Compounds can be tested for their efficacy in inhibiting severe acute respiratory syndrome 3CL protease. Specifically, a test compound and the severe acute respiratory syndrome 3CL protease can be pre-incubated at 25° C for 20 minutes before they are incubated with the substrate peptide.

Example 8

In vitro assay for SARS-CoV-2 and HCoV (OC43):

In order to determine the potential effect of each selected compound against *in vitro* replication of SARS-CoV-2 in Vero cells or HCoV (OC43) in Huh7 cells, a confluent cell monolayer in a 96-wells cell culture microplate can be infected at a multiplicity of infection (MOI) of 0.1 and treated with a maximum non-toxic concentration (MNTC) of each compound.

To assess the antiviral activity, a virus yield reduction assay using specific qRT-PCR for each virus can be performed.

Dose-Dependent Antiviral Assay. The antiviral effect of each compound selected through the antiviral evaluation assay can be further confirmed by virus yield reduction assay using the optimized qRT-PCR by measuring the RNA copy number for each virus in the supernatant of treated-infected cells. A positive control, such as remdesivir, can be used for each assay.

Statistical analysis. The half-maximal effective concentration (EC_{50}) and the concentration with 90% of inhibitory effect (EC_{90}) can be calculated using GraphPad PRISM for Windows, version 5 (GraphPad Software Inc., San Diego, CA, 2005) or the Chou and Talalay Method.

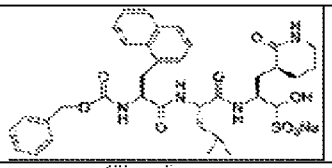
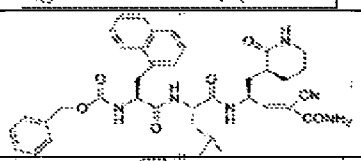
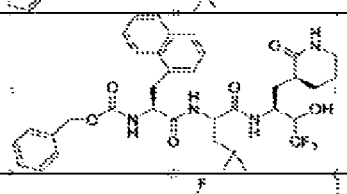
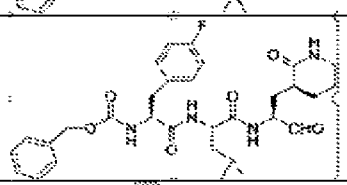
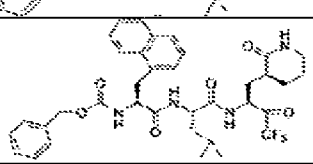
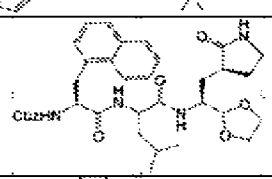
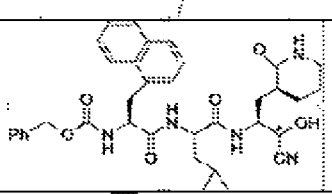
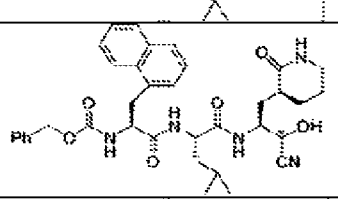
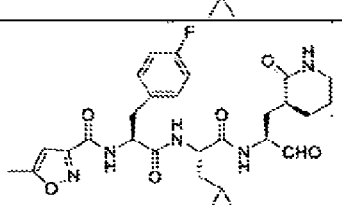
These methods were used to evaluate certain of the compounds described herein.

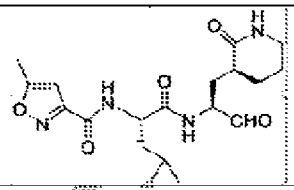
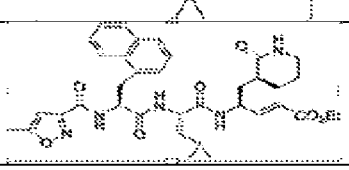
SARS-CoV-2 strain was provided by BEI Resources (NR-52281: USA-WA/2020) . The virus was propagated in Vero cells (African Green Monkey Kidney: ATCC) and titrated by median tissue culture infectious dose ($TCID_{50}$) method. Viral stock was stored as aliquots at -80°C until further use.

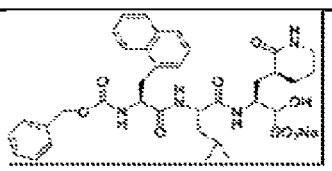
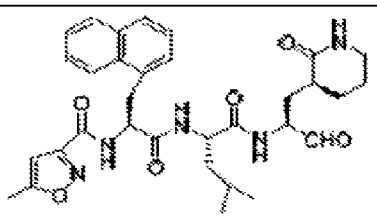
A qRT-PCR assay was used to specifically to quantify the yield of SARS-CoV-2 in the cell-based assays. A one-step qRT-PCR was carried out in a final volume of 20µl containing extracted viral RNA, probe/primer mix (Forward Primer: 5'-GAC CCC AAA ATC AGC GAA AT- 3'; Reverse Primer: 5'-TCT GGT TAC TGC CAG TTG AAT CTG-3'; Probe: 5'-FAM-ACC CCG CAT TAC GTT TGG TGG ACC-BHQ1-3') recommended by CDC and synthesized by IDT DNA Technology, and qScript-Tough master mix. Quantitative PCR measurement was performed using StepOnePlus real time PCR system (Roche, Germany).

Virus kinetic replication assay: To determine the best time point for virus yield assay a kinetic replication of SARS-CoV-2 in Vero cells was performed and the yield of progeny virus production was assessed from supernatants at interval time points using a specific q-RT PCR for SARS-CoV-2. It was observed that 48 h post-infection, a significant increase in virus yield was achieved.

Compound	Structure	OC43	SARS-CoV-2 Inhibition

		Inhibition at 10 μM (%)	at 10 μM (%)
37		99.9	99.9
36		99.9	99.8
38		95	85.1
35		99.9	99.8
39		99.4	68.0
136		99.3	99.8
128		100	99.9
129		99.9	99.9
97		99.9	99.8

43		99.9	99.9
44		99.7	99.5

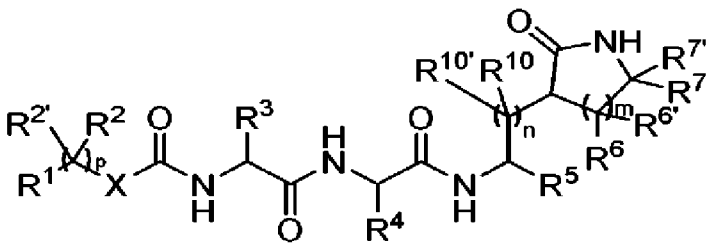
Compound	Structure	Activity against SARS-CoV-2	
		EC_{50}	EC_{90}
37		0.3	4.5
91		0.6	2.3

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties for all purposes.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

We claim:

1. Use of a compound of any of Formulas I-VI in the preparation of a medicament for treating a coronavirus, picornavirus, and/or Hepeviridae virus infection, preventing a coronavirus, picornavirus, or Hepeviridae virus infection, or reducing the biological activity of an infection with a coronavirus, picornavirus, or Hepeviridae virus:



(I)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, -CH_2-(hydroxy)phenyl, and –CH_2-(halo)phenyl,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is -C(O)H, CH=C(CN)C(O)NH_2, -C(O)CF_3, -CH(OH)CF_3, -C(OH)SO_3^- (and an associated cation, such as Na^+), or an optionally-substituted epoxide ring,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

m, n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

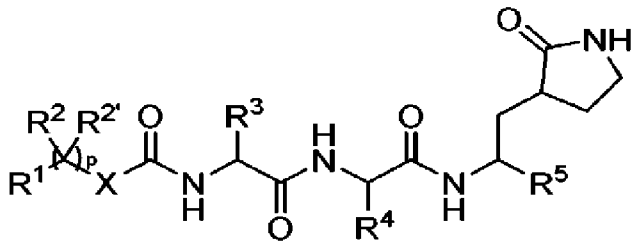
the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

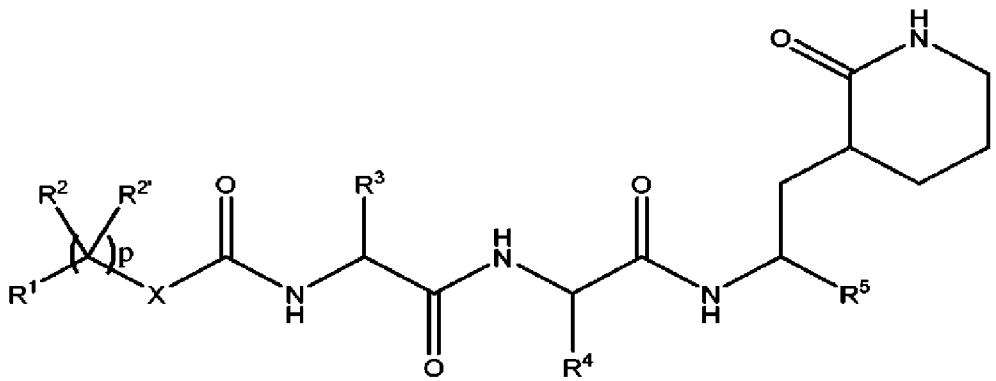
R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;



(II)

or a pharmaceutically acceptable salt or prodrug thereof,

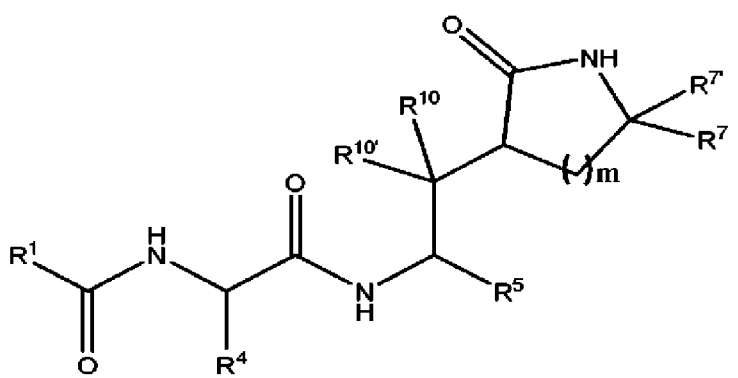
wherein p, X, R^1, R^2, $R^{2'}$, R^3, R^4 and R^5 are as defined above with respect to Formula I;



(III)

or a pharmaceutically acceptable salt or prodrug thereof,

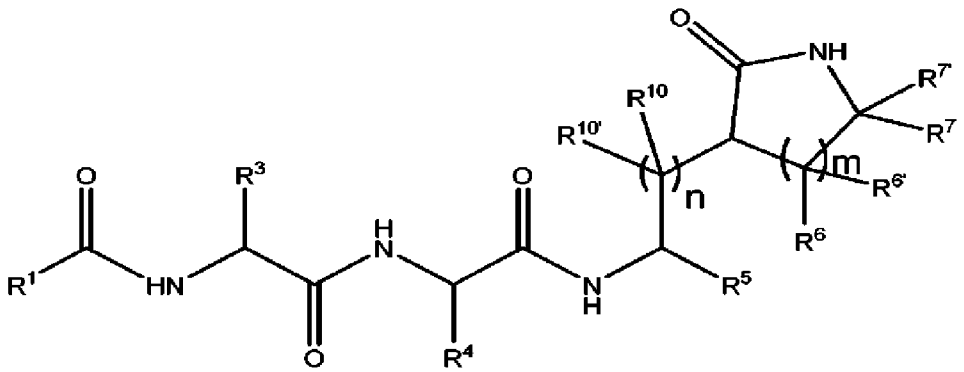
wherein p, X, R^1, R^2, $R^{2'}$, R^3, R^4 and R^5 are as defined above with respect to Formula I;



(IV)

or a pharmaceutically acceptable salt or prodrug thereof,

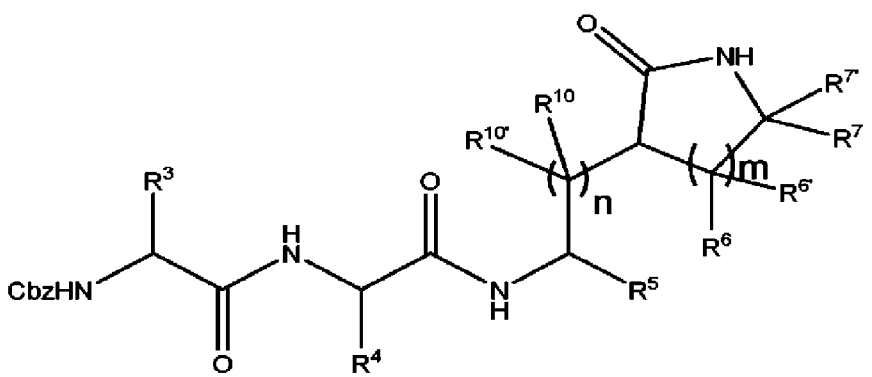
wherein R^4, R^5, R^7, $R^{7'}$, R^{10}, and $R^{10'}$ are as defined above with respect to Formula I, and R^1 is an optionally-substituted C_{6-12} cycloalkyl, or an optionally-substituted five or six membered ring heteroaryl;



(V)

where R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^{10}, $R^{10'}$, m and n are as defined above with respect to Formula I, and R^1 is a five or six membered ring heteroaryl,

and pharmaceutically-acceptable salts and prodrugs thereof; and



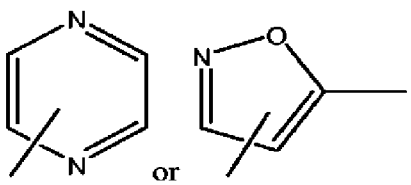
(VI)

or a pharmaceutically-acceptable salt or prodrug thereof,

wherein Cbz = carbobenzoxy, and R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^{10}, $R^{10'}$, m and n are as defined above with respect to Formula I.

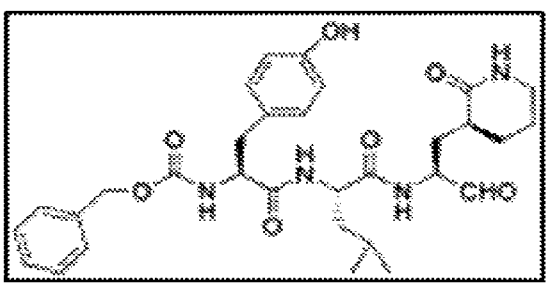
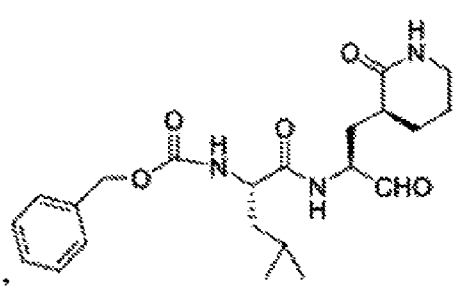
2. The use of Claim 1, wherein R^5 is C(O)H.

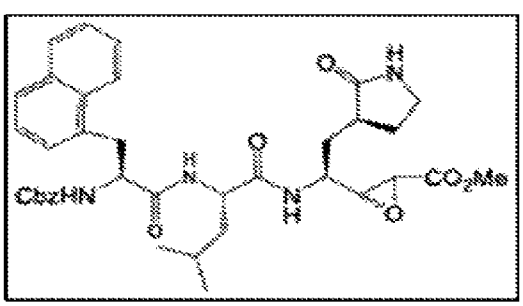
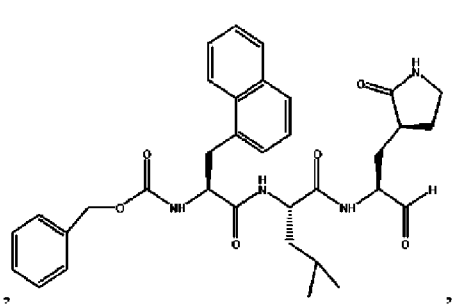
3. The use of Claim 1, wherein R^3 is alkylaryl or alkylheteroaryl.

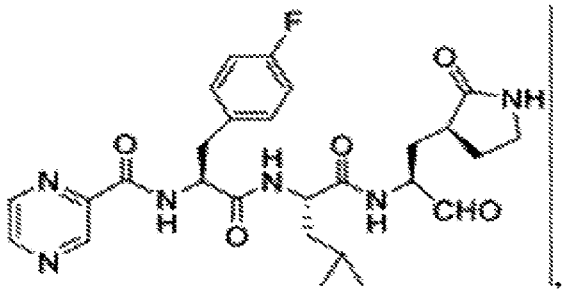
4. The use of Claim 1, wherein R^1 is  or .

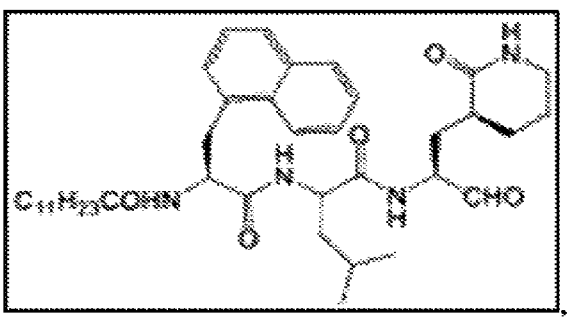
5. The use of Claim 1, wherein R^1 is a thiophene.

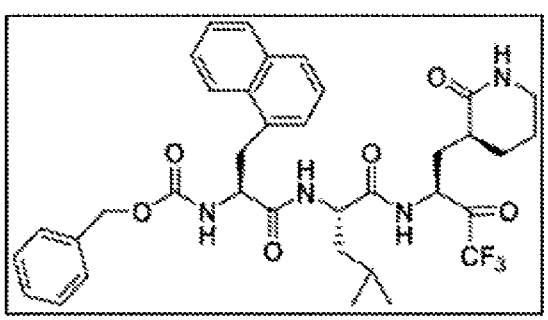
6. The use of Claim 1, wherein the compound has one of the following formulas:

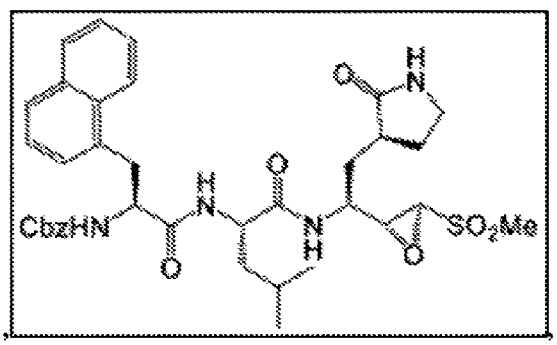
 , 

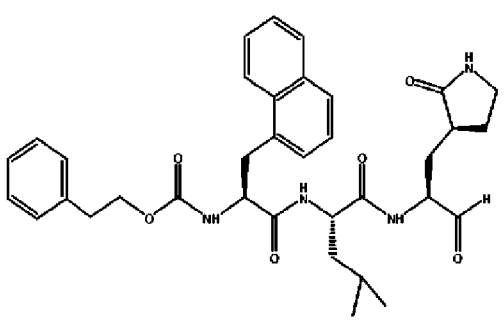
 ,  ,

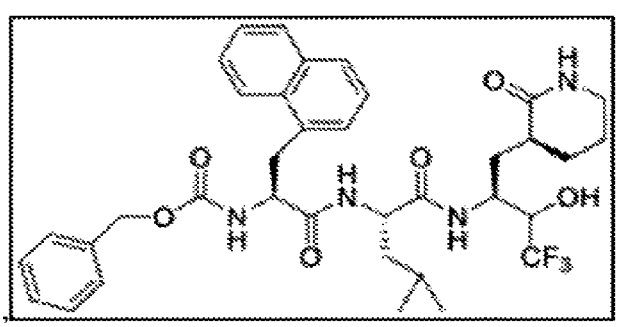


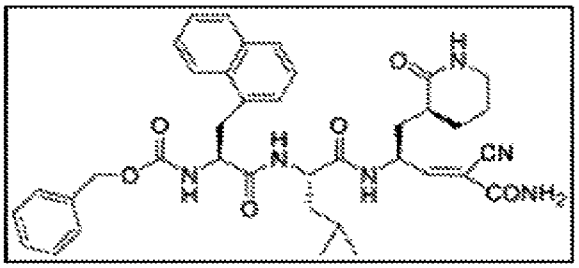


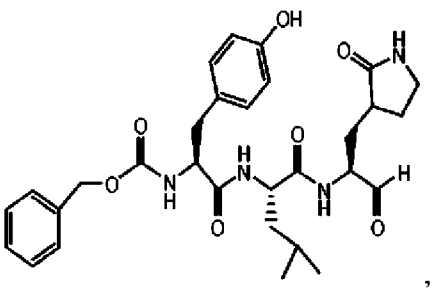


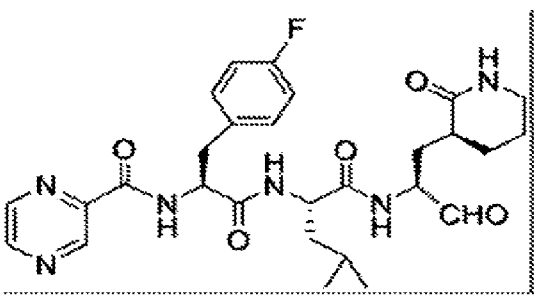


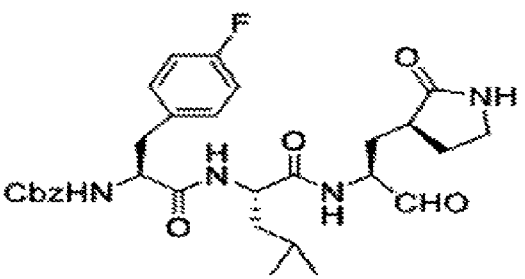


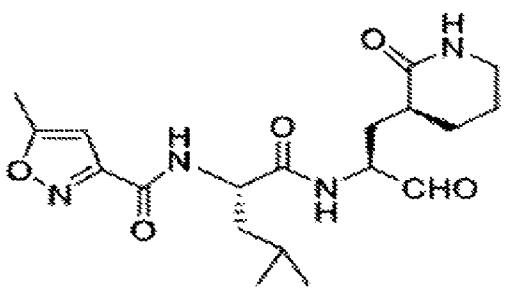


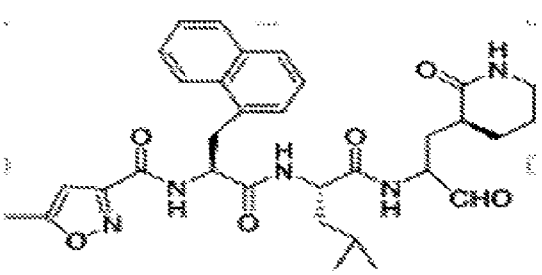


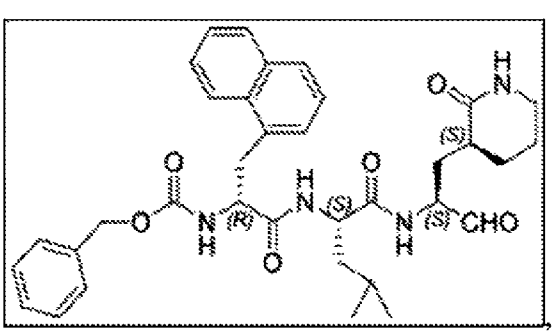


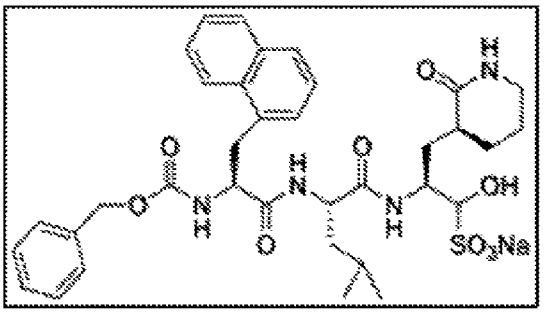
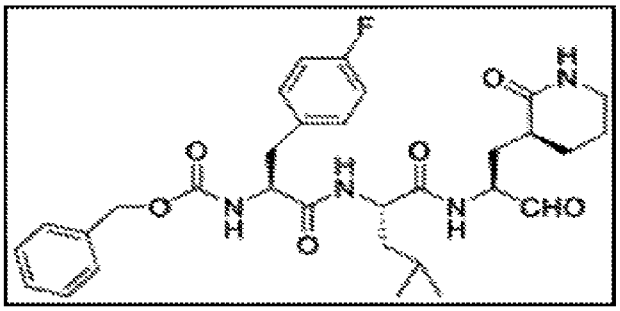
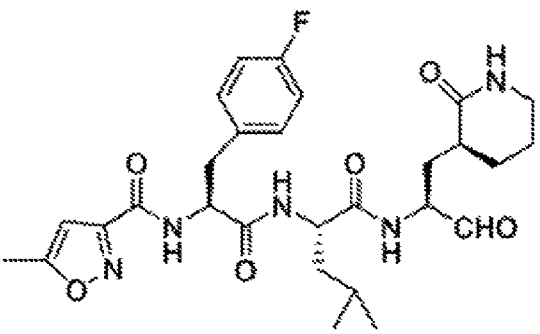
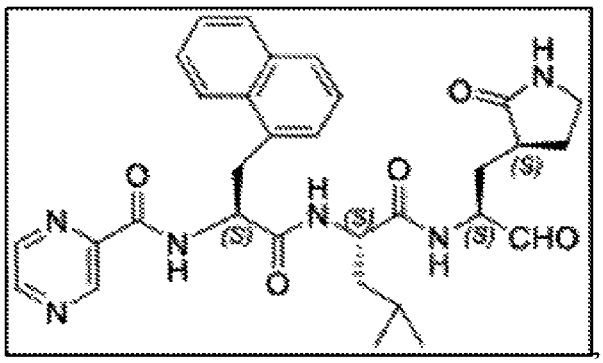






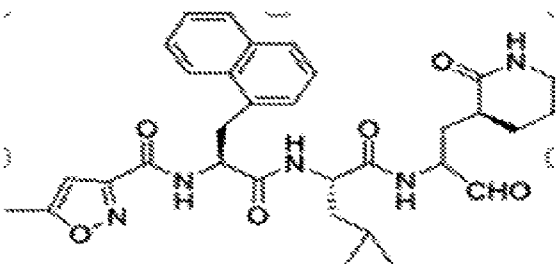
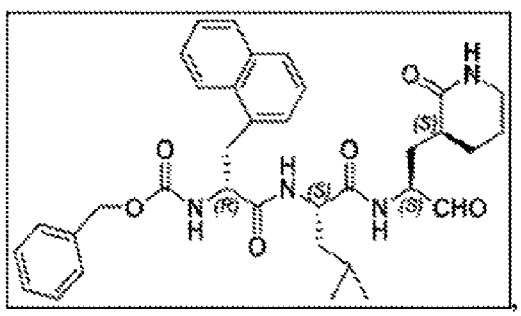


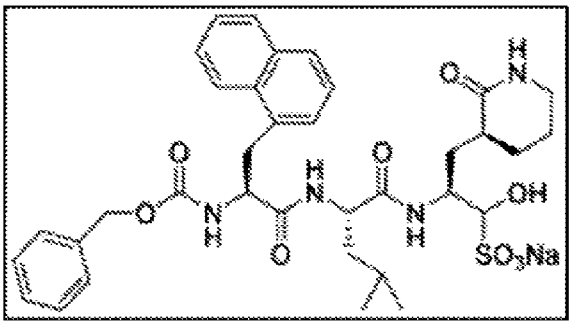


and pharmaceutically acceptable salts or prodrugs thereof.

7. The use of Claim 1, wherein the compounds have one of the following structures:



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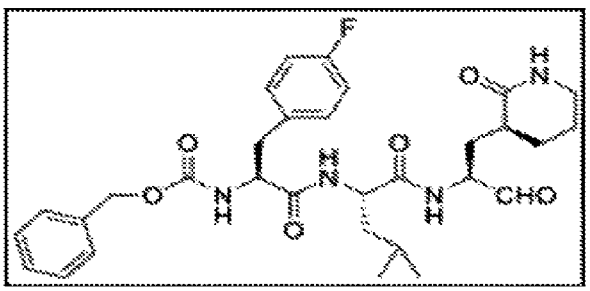

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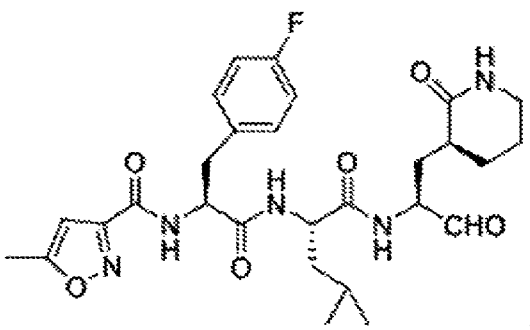
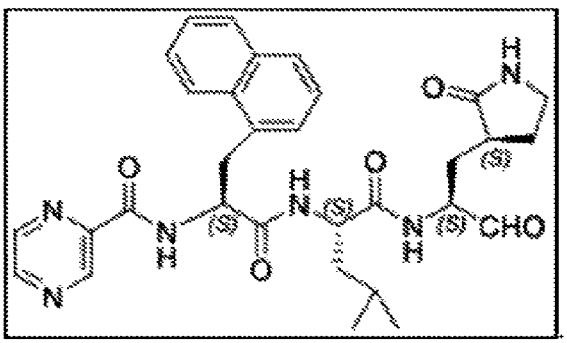


, or



.

8. The use of Claim 1, wherein X is O, R^2 and $R^{2'}$ are H, and R^1 is an optionally substituted phenyl.

9. The use of Claim 1, wherein X = a covalent bond, p = 0, and R^1 is an optionally substituted aryl or heteroaryl.

10. The use of Claim 9, wherein the heteroaryl ring is a pyrazine, thiophene, isoxazole, or oxazole ring.

11. The use of Claim 1, wherein R^3 is phenyl, halo-substituted phenyl, or naphthyl.

12. The use of Claim 1, wherein the Hepeviridae virus is the hepatitis E virus.

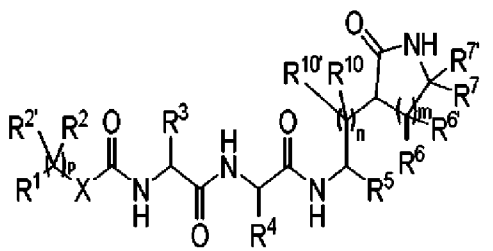
13. The use of Claim 1, wherein the picornavirus is an enterovirus.

14. The use of Claim 1, wherein the virus is a causative agent for multiple sclerosis, SARS, MERS, or COVID-19.

15. The use of Claim 13, wherein the enterovirus is a causative agent for a respiratory infection.

16. A method for treating a host infected with a coronavirus, picornavirus or hepeviridae virus, preventing a coronavirus, picornavirus or hepeviridae virus infection, curing

an a coronavirus, picornavirus or hepeviridae virus infection, or reducing the biological activity of an infection with a coronavirus, picornavirus or hepeviridae virus in a host, comprising administering an effective amount of a compound of any of Formulas I-VI to a patient in need of treatment thereof:



(I)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, specifically including $–CH_2$--napthyl, $-CH_2$-(hydroxy)phenyl, such as $-CH_2$-(4-hydroxy)phenyl, and $–CH_2$-(halo)phenyl, such as $–CH_2$-(4-halo)phenyl, including $–CH_2$-(fluoro)phenyl, specifically, $–CH_2$-(4-fluoro)phenyl.

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is -C(O)H, $CH=C(CN)C(O)NH_2$, $-C(O)CF_3$, $-CH(OH)CF_3$, $-C(OH)SO_3^-$ (and an associated cation, such as Na^+), or an optionally-substituted epoxide ring, and is preferably –C(O)H,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

m, n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

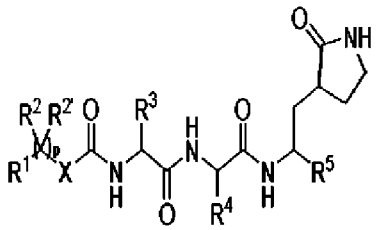
the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

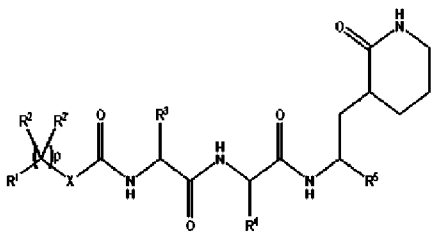
R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;



(II)

or a pharmaceutically acceptable salt or prodrug thereof,

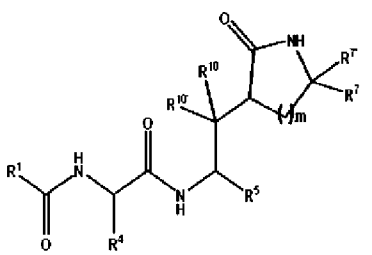
wherein p, X, R^1, R^2, $R^{2'}$, R^3, R^4 and R^5 are as defined above with respect to Formula I;



(III)

or a pharmaceutically acceptable salt or prodrug thereof,

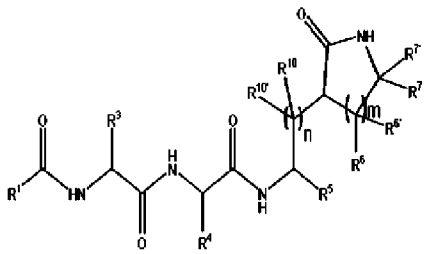
wherein p, X, R^1, R^2, $R^{2'}$, R^3, R^4 and R^5 are as defined above with respect to Formula I;



(IV)

or a pharmaceutically acceptable salt or prodrug thereof,

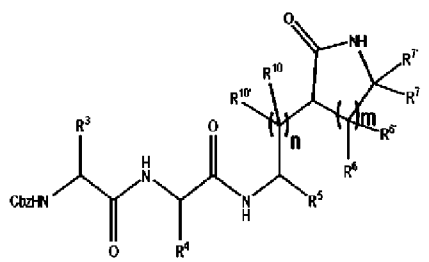
wherein R^4, R^5, R^7, $R^{7'}$, R^{10}, and $R^{10'}$ are as defined above with respect to Formula I, and R^1 is an optionally-substituted C_{6-12} cycloalkyl, or an optionally-substituted five or six membered ring heteroaryl;



(V)

where R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^{10}, $R^{10'}$, m and n are as defined above with respect to Formula I, and R^1 is a five or six membered ring heteroaryl,

and pharmaceutically-acceptable salts and prodrugs thereof; and



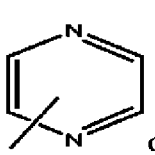
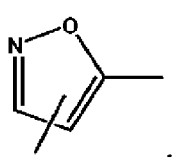
(VI)

or a pharmaceutically-acceptable salt or prodrug thereof,

wherein Cbz = carbobenzoxy, and R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^{10}, $R^{10'}$, m and n are as defined above with respect to Formula I.

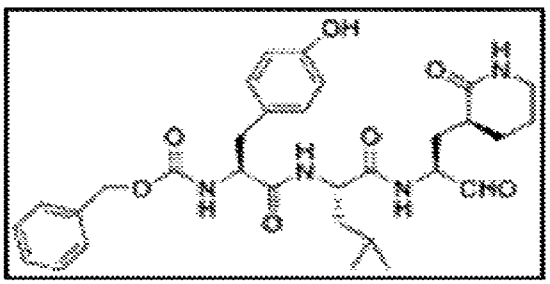
17. The method of Claim 16, wherein R^5 is C(O)H.

18. The method of Claim 16, wherein R^3 is alkylaryl or alkylheteroaryl.

19. The method of Claim 16, wherein R^1 is  or  .

20. The method of Claim 11, wherein R^1 is thiophene.

21. The method of Claim 16, wherein the compound has one of the following formulas:



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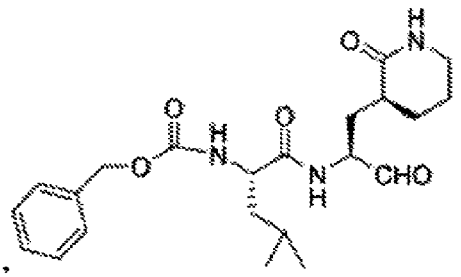

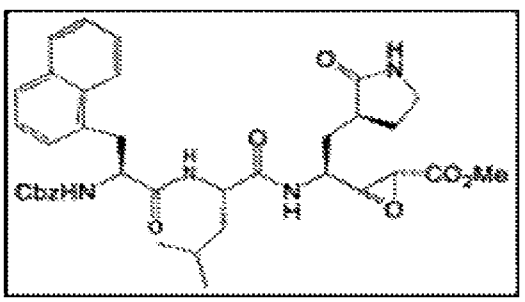

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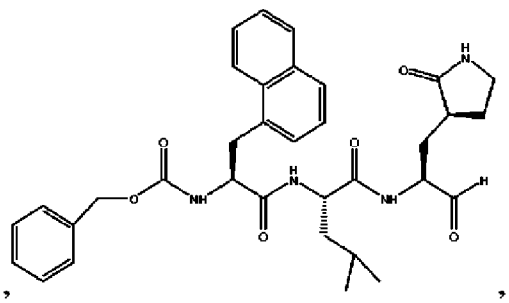

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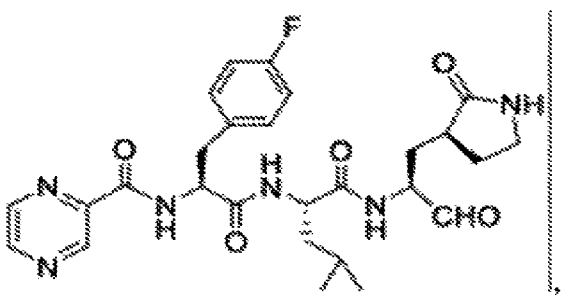

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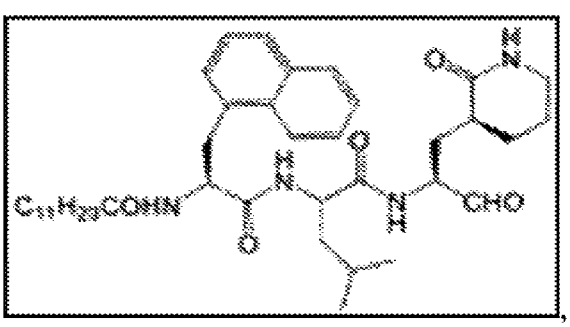

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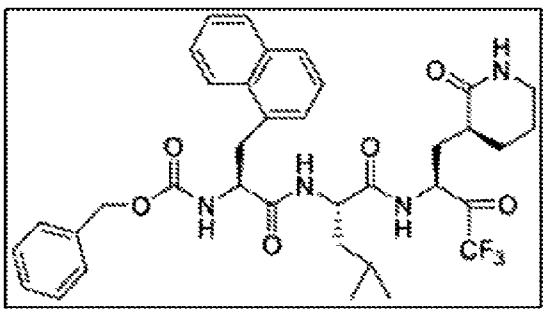
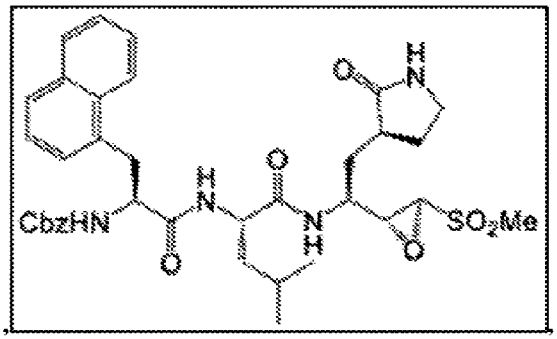
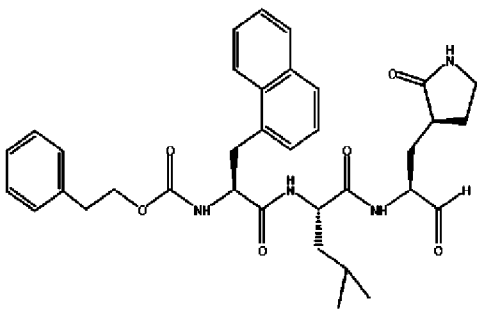
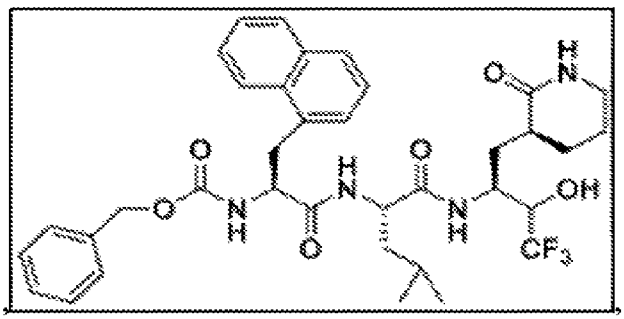
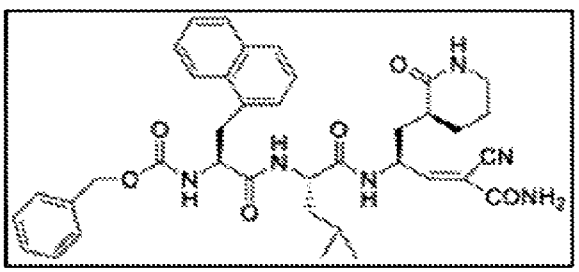
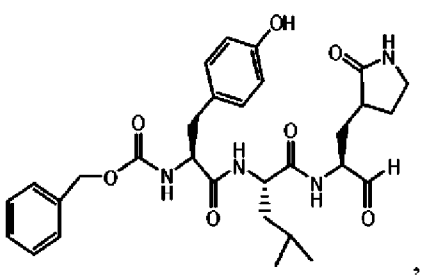

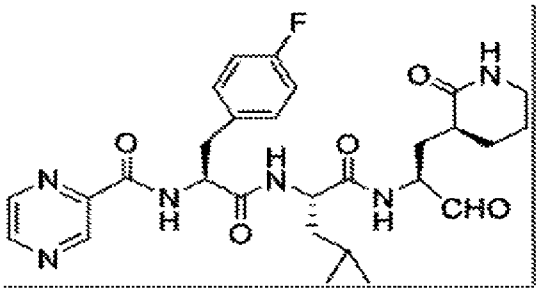
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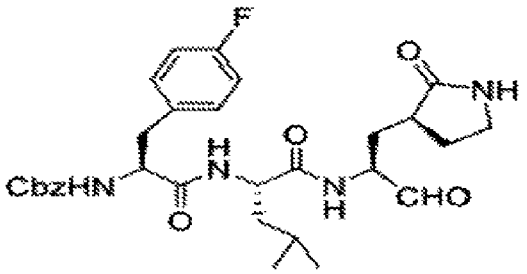
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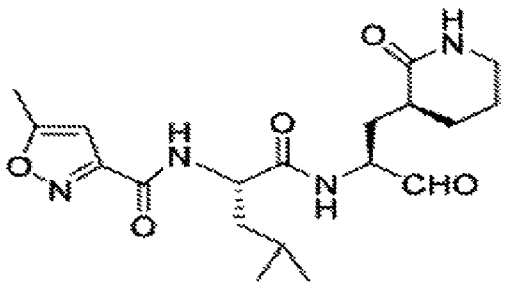
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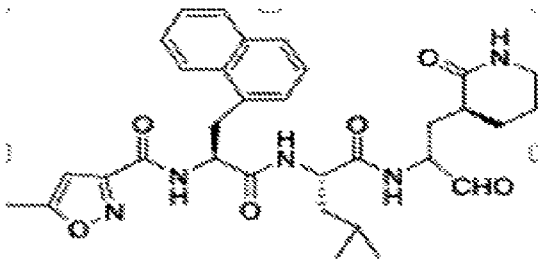
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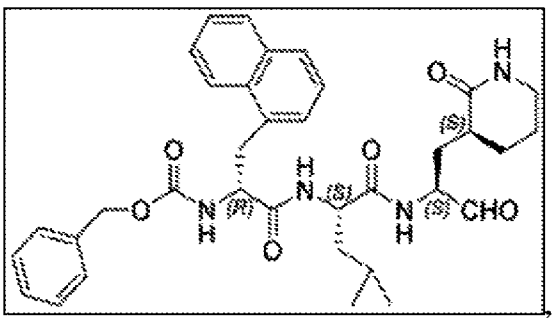
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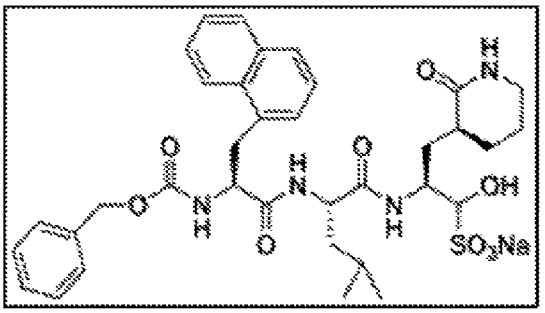
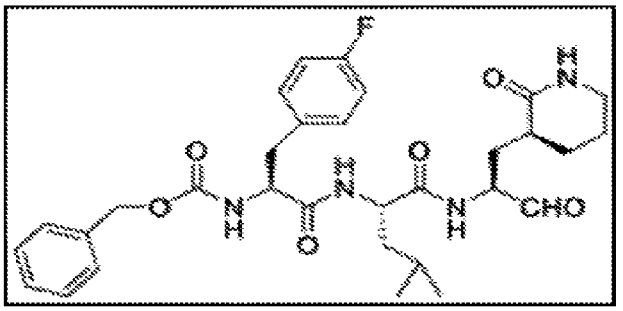
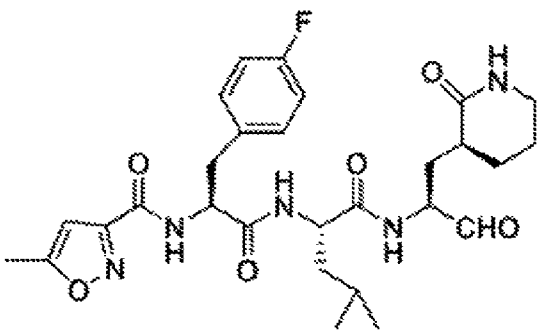
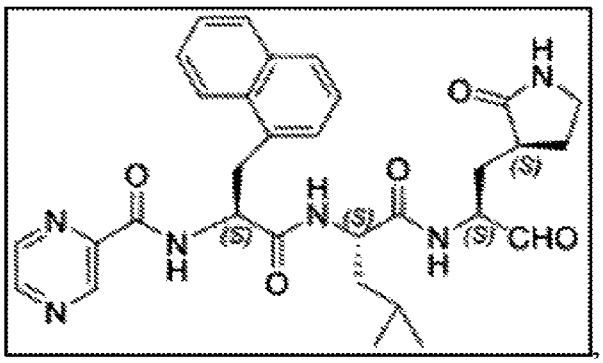
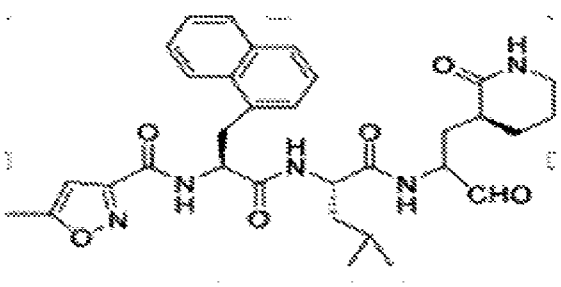
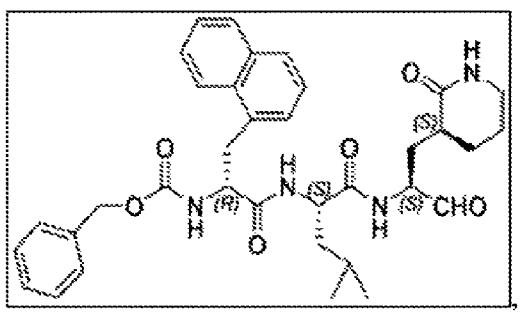
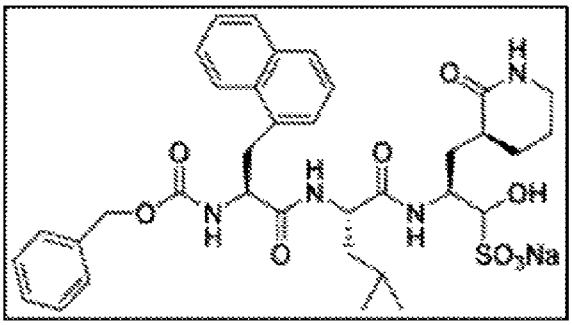
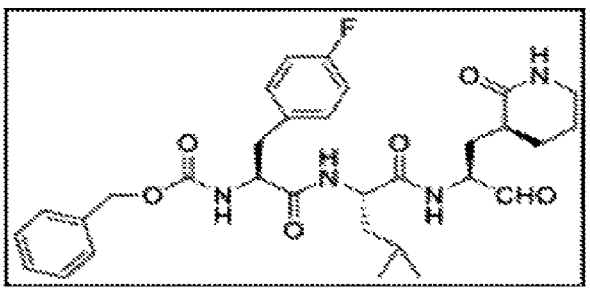
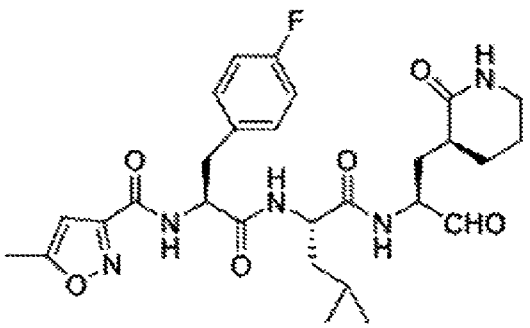
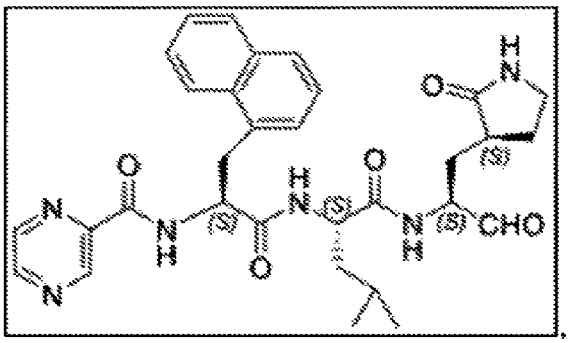





and pharmaceutically acceptable salts or prodrugs thereof.

22. The method of Claim 16, wherein the compounds have one of the following structures:

pharmaceutically-acceptable salts and prodrugs thereof.

23. The method of Claim 16, wherein X is O, R^2 and $R^{2'}$ are H, and R^1 is an optionally substituted phenyl.

24. The method of Claim 16, wherein X = a covalent bond, p = 0, and R^1 is an optionally substituted aryl or heteroaryl.

25. The method of Claim 24, wherein the heteroaryl ring is a pyrazine, thiophene, isoxazole, or oxazole ring.

26. The method of Claim 16, wherein R^3 is phenyl, halo-substituted phenyl, or naphthyl.

27. The method of Claim 16, wherein the Hepeviridae virus is the hepatitis E virus.

28. The method of Claim 16, wherein the picornavirus is an enterovirus.

29. The method of Claim 16, wherein the virus is a causative agent for multiple sclerosis, SARS, MERS, or COVID-19.

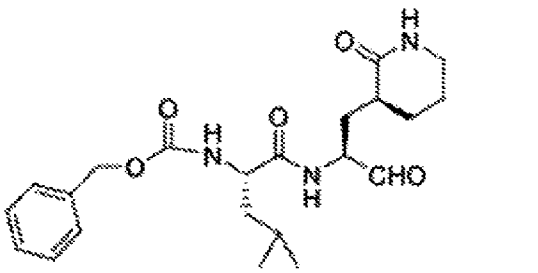
30. The method of Claim 16, wherein the virus is a causative agent for a respiratory infection.

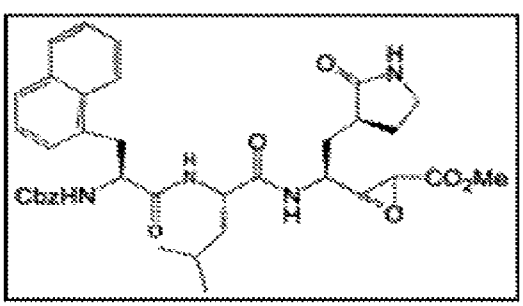
31. The method of Claim 16, wherein the method further comprising administering another anti-coronavirus or picornavirus virus agent in combination or alternation with the compound of any of Formulas I-VI.

32. The use of Claim 1, wherein the medicament is also useful for treating a patient co-infected with norovirus.

33. The method of Claim 16, wherein the patient is co-infected with norovirus, and the compound is also effective at treating the norovirus co-infection.

34. A compound having the formula:





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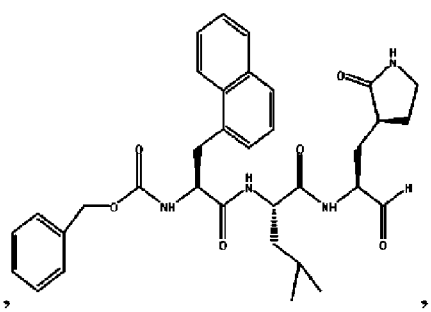

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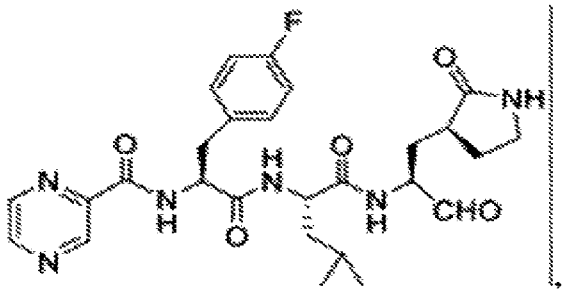
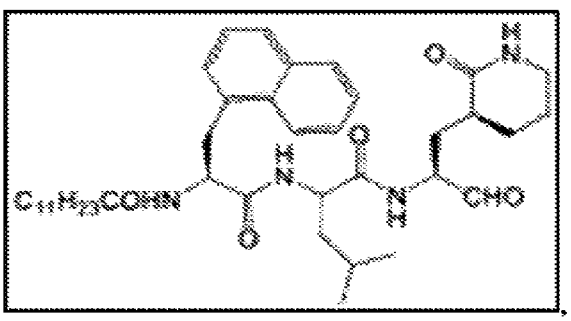
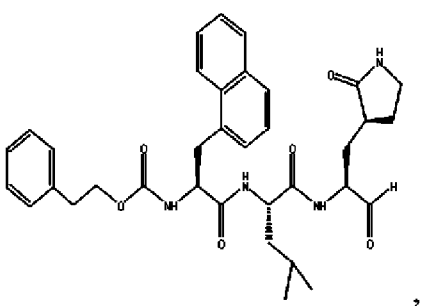
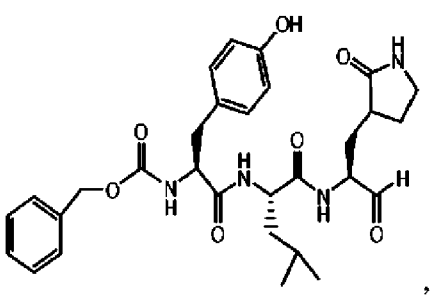
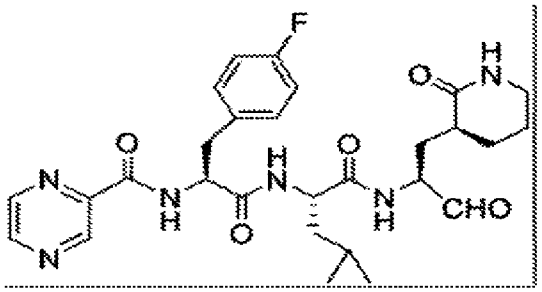
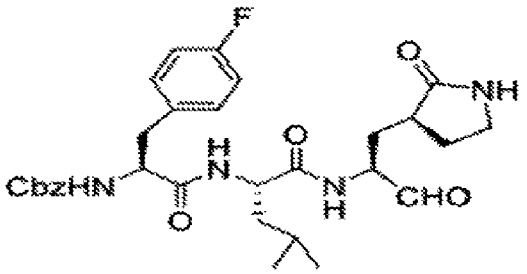
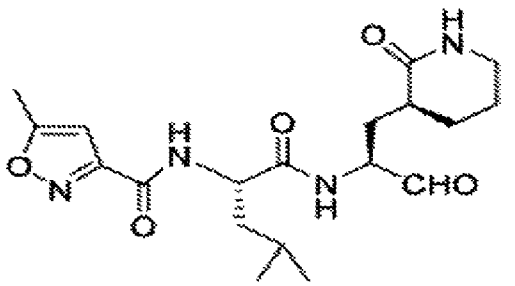
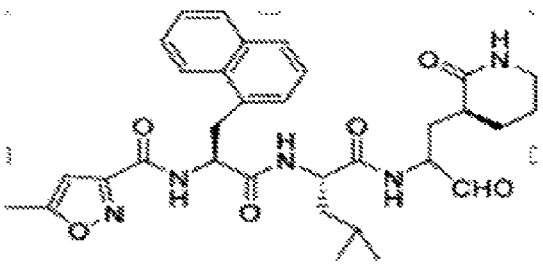
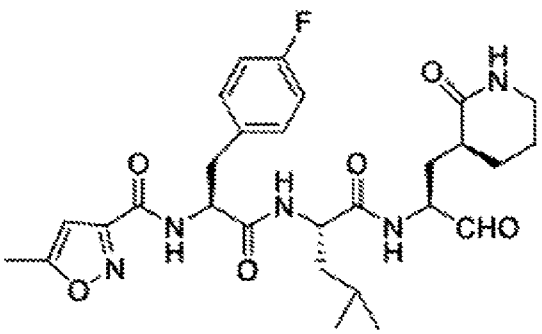




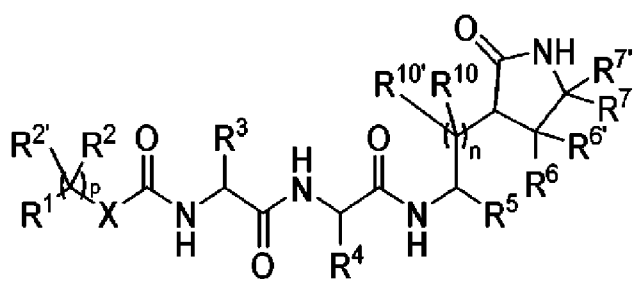




, and pharmaceutically-acceptable salts and prodrugs thereof.

35. Use of a compound of Formula VII in the preparation of a medicament for treating a coronavirus, picornavirus, and/or Hepeviridae virus infection, preventing a coronavirus, picornavirus, or Hepeviridae virus infection, or reducing the biological activity of an infection with a coronavirus, picornavirus, or Hepeviridae virus:



(VII)

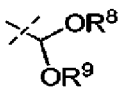
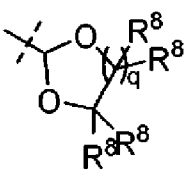
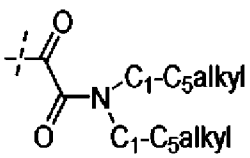
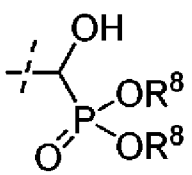
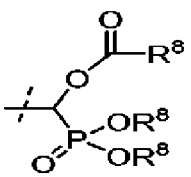
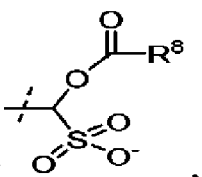
or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, -CH_2-(hydroxy)phenyl, and –CH_2-(halo)phenyl,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is –$(CH_2)_q$-SH,  , -$CH(OH)CF_3$, -CH(OH)CN,  ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, N(R')$S(O)_2$R', $S(O)_2$R', $S(O)_2$N(R')$_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl,

alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

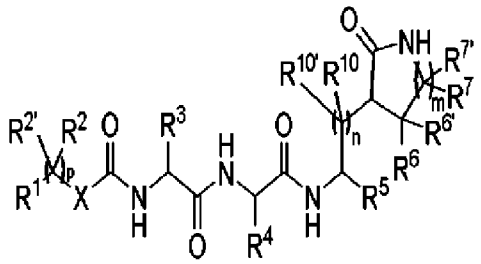
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

36. Use of a compound of Formula VIII in the preparation of a medicament for treating a coronavirus, picornavirus, and/or Hepeviridae virus infection, preventing a coronavirus, picornavirus, or Hepeviridae virus infection, or reducing the biological activity of an infection with a coronavirus, picornavirus, or Hepeviridae virus:



(VIII)

or a pharmaceutically acceptable salt or prodrug thereof,

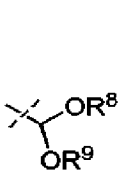
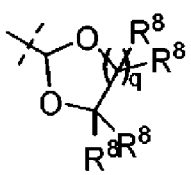
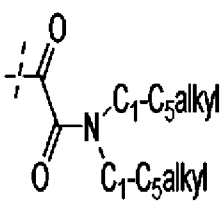
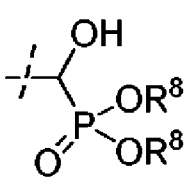
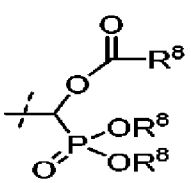
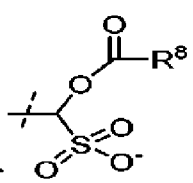
wherein:

m = 2

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^3 is an optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl, -CH_2-(hydroxy)phenyl, and –CH_2-(halo)phenyl,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is –$(CH_2)_q$-SH,  , -$CH(OH)CF_3$, -CH(OH)CN,  ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

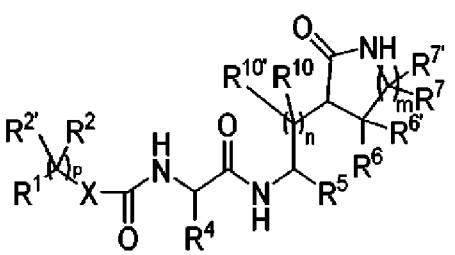
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

37. Use of a compound of Formulas IX in the preparation of a medicament for treating a coronavirus, picornavirus, and/or Hepeviridae virus infection, preventing a coronavirus, picornavirus, or Hepeviridae virus infection, or reducing the biological activity of an infection with a coronavirus, picornavirus, or Hepeviridae virus:



(IX)

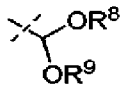
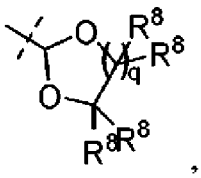
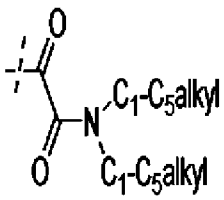
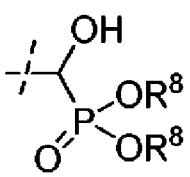
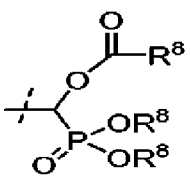
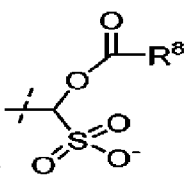
or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

m = 2 or 3

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is $-(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN,  ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl,

acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

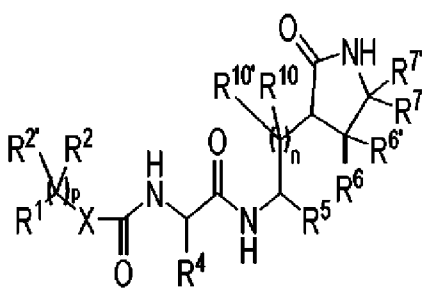
two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

38. Use of a compound of Formulas X in the preparation of a medicament for treating a coronavirus, picornavirus, and/or Hepeviridae virus infection, preventing a coronavirus, picornavirus, or Hepeviridae virus infection, or reducing the biological activity of an infection with a coronavirus, picornavirus, or Hepeviridae virus:



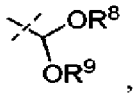
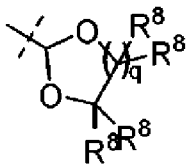
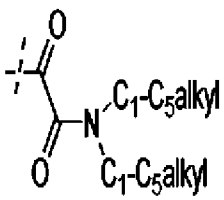
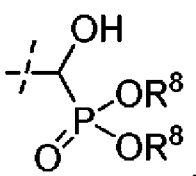
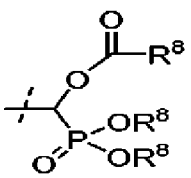
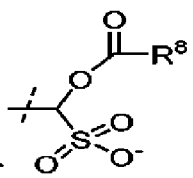
(X)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is optionally substituted C_{1-10} alkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, or heteroarlalkoxy,

R^4 is an optionally substituted C_{1-6} alkyl,

R^5 is $-(CH_2)_q$-SH,  , -CH(OH)CF_3, -CH(OH)CN,  ,  ,  ,  ,  , or  ,

R^8 is independently H, an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

R^9 is an optionally substituted C_{1-10} alkyl, C_{2-10} alkene, C_{2-10} alkyne, aryl, heteroaryl, arylalkyl, alkylaryl, heteroarylalkyl, or alkylheteroaryl,

q is 1, 2 or 3,

R^2, $R^{2'}$, R^{10} and $R^{10'}$ are, independently, hydrogen, CF_3, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{2-6} alkenyl,

X is, independently, a bond, O or NH,

n and p are, independently, 0, 1, 2, or 3;

R^6 and $R^{6'}$ are, independently, hydrogen, halogen, CF_3, hydroxy, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl,

heterocyclylalkyl, or C_{1-6} hydroxyalkyl; or R^6 and $R^{6'}$, together with the carbon to which they are attached, form a carbonyl,

each R' is, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, alkylaryl, or arylalkyl,

the R' groups can optionally be substituted with one or more substituents, which substituents are, independently, halo, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, carboxyl, acyl, aryl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, alkoxyalkyl, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, or phosphonate;

two R' residing on the same carbon or nitrogen atom can come together to form a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^6 and $R^{6'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom;

R^7 and $R^{7'}$ are, independently, hydrogen, CF_3, $N(R')S(O)_2R'$, $S(O)_2R'$, $S(O)_2N(R')_2$, C_{1-6} alkoxy, C_{2-6} alkenyl, cyano, C_{2-6} alkynyl, C_{3-6} alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C_{1-6} alkyl, arylalkoxycarbonyl, carboxy, C_{1-6} haloalkyl, heterocyclylalkyl, or C_{1-6} hydroxyalkyl; and

R^7 and $R^{7'}$ can come together to form an optionally substituted double bond or a C_{3-6} ring optionally containing a N, O, or S heteroatom, and pharmaceutically-acceptable salts and prodrugs thereof.

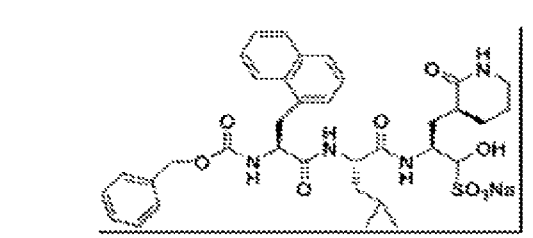
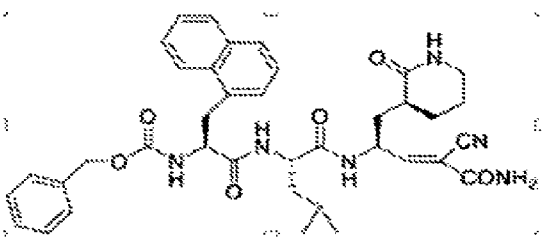
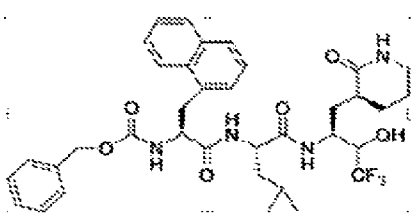
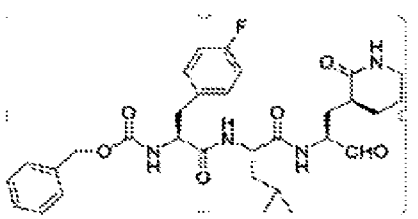
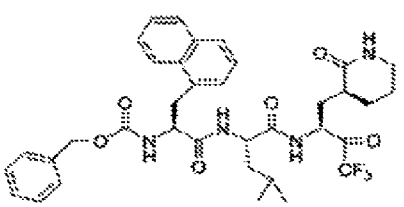
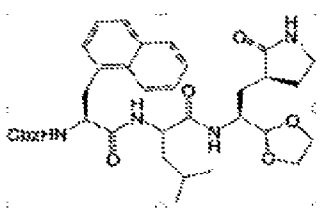
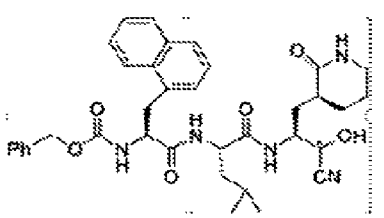
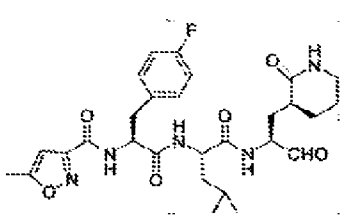
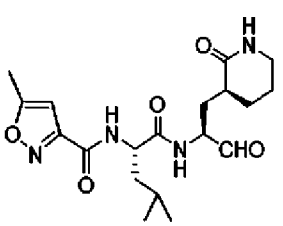
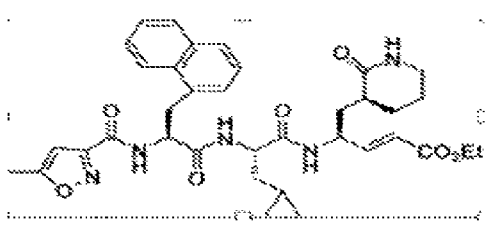
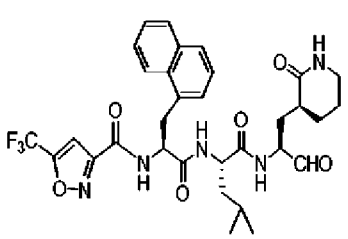
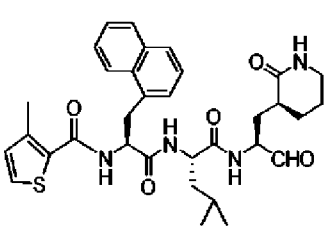
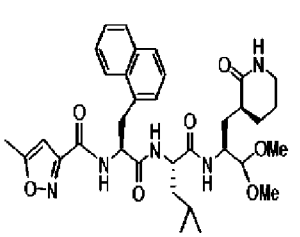
39. The use of any of Claims 35-38, wherein X is O, R^2 and $R^{2'}$ are H, and R^1 is an optionally substituted phenyl.

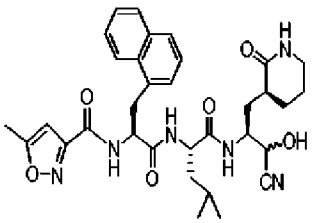
40. The use of any of Claims 35-38, wherein X = a covalent bond, p = 0, and R1 is an optionally substituted aryl or heteroaryl.

41. The use of any of Claims 41, wherein the heteroaryl ring is a pyrazine, thiophene, isoxazole, or oxazole ring.

42. The use of any of Claims 35-38, wherein R^3 is phenyl, halo-substituted phenyl, or naphthyl.

43. A compound having the formula: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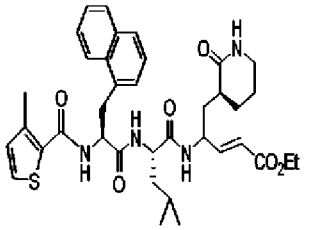
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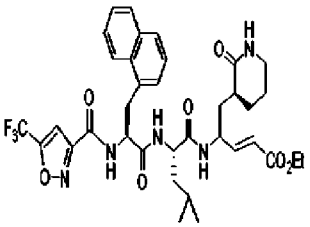
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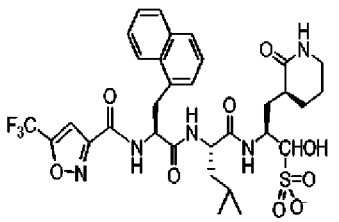
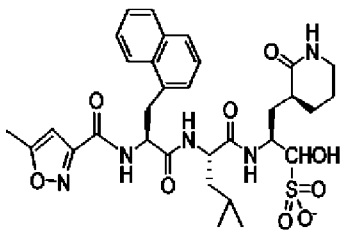

, and

, and pharmaceutically-acceptable salts and prodrugs thereof.

44. The use of a compound of Claim 43 in the preparation of a medicament for treating a coronavirus, picornavirus, and/or Hepeviridae virus infection, preventing a coronavirus, picornavirus, or Hepeviridae virus infection, or reducing the biological activity of an infection with a coronavirus, picornavirus, or Hepeviridae virus.

45. The use of any of Claims 1-15, 35-42, or 44, wherein the medicament further comprises one or more additional active compounds.

46. The use of Claim 45, wherein the one or more additional active compounds are selected from the group consisting of fusion inhibitors, entry inhibitors, protease inhibitors, polymerase inhibitors, antiviral nucleosides, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2 (ACE2) inhibitors, SARS-CoV-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

47. The use of Claim 46, wherein the one or more additional active agents comprise remdesivir, N-hydroxy cytidine, or a pharmaceutically-acceptable salt or prodrug thereof.

48. The use of Claim 46, wherein the one or more additional active agents comprise Jakafi, Tofacitinib, Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof.

49. The use of Claim 46, wherein the one or more additional active agents comprise an anticoagulant or a platelet aggregation inhibitor.

50. The use of Claim 46, wherein the one or more additional active agents comprise an ACE-2 inhibitor, a CYP-450 inhibitor, or NOX inhibitor.

51. A method for treating a host infected with a coronavirus, picornavirus or Hepeviridae virus, preventing an a coronavirus, picornavirus or Hepeviridae virus infection, curing an a coronavirus, picornavirus or Hepeviridae virus infection, or reducing the biological activity of an infection with a coronavirus, picornavirus or Hepeviridae virus in a host, comprising administering an effective amount of a compound of any of Formulas VII-X to a patient in need of treatment thereof.

52. A method for treating a host infected with a coronavirus, picornavirus or Hepeviridae virus, preventing a coronavirus, picornavirus or Hepeviridae virus infection, curing a coronavirus, picornavirus or Hepeviridae virus infection, or reducing the biological activity of an infection with a coronavirus, picornavirus or Hepeviridae virus in a host, comprising administering an effective amount of a compound of Claim 43 to a patient in need of treatment thereof.

53. The use of any of Claims 1-15, 35-42, 44, or 48-50, wherein the virus is SARS-CoV-2.