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ANTI-VIRAL COMPOUNDS

BACKGROUND

Field

[0001] The present application relates to the fields of chemistry, biochemistry and medicine. Disclosed herein are compounds of Formula (I), or pharmaceutically acceptable salt thereof, pharmaceutical compositions that include a compound described herein (including pharmaceutically acceptable salts of a compound described herein) and methods of synthesizing the same. Also disclosed herein are methods of treating diseases and/or conditions with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Description

[0002] A positive-sense single-stranded RNA virus ((+)ssRNA virus) is a virus that uses positive sense, single stranded, RNA as its genetic material. Positive-sense single-stranded RNA viruses can be enveloped or non-enveloped. Coronaviridae, Picornaviridae and Norviruses are each a (+)ssRNA virus. Each of the aforementioned viruses are known to infect mammals, including humans.

SUMMARY

[0003] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0004] Some embodiments disclosed herein relate to a pharmaceutical composition that can contain an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0005] Some embodiments described herein relate to a method of treating a coronavirus infection that can include administering to a subject identified as suffering from the coronavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an

effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a coronavirus infection.

[0006] Some embodiments disclosed herein relate to a method of inhibiting replication of a coronavirus that can include contacting a cell infected with the coronavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication a coronavirus.

[0007] Some embodiments described herein relate to a method of treating a picornavirus infection that can include administering to a subject identified as suffering from the picornavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a picornavirus infection.

[0008] Some embodiments disclosed herein relate to a method of inhibiting replication of a picornavirus that can include contacting a cell infected with the picornavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication a picornavirus.

[0009] Some embodiments described herein relate to a method of treating a norovirus infection that can include administering to a subject identified as suffering from the

norovirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a norovirus infection.

[0010] Some embodiments disclosed herein relate to a method of inhibiting replication of a norovirus that can include contacting a cell infected with the norovirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication a norovirus.

[0011] These are other embodiments are described in greater detail below.

DETAILED DESCRIPTION

[0012] Coronaviridae viruses are a family of enveloped, positive-stranded, single-stranded, spherical RNA viruses. Coronaviruses are named for the crown-like spikes on their surface. The Coronaviridae family includes two sub-families, Coronavirus and Torovirus. The Coronavirus genus has a helical nucleocapsid, and Torovirus genus has a tubular nucleocapsid. The Coronaviridae family of viruses includes Middle East respiratory syndrome coronavirus (MERS-CoV), SARS and SARS-CoV-2.

[0013] Coronavirus disease 2019 (COVID-19) (also referred to as novel coronavirus pneumonia or 2019-nCoV acute respiratory disease) is an infectious disease caused by the virus severe respiratory syndrome coronavirus 2 (SARS-CoV-2) (also referred to as novel coronavirus 2019, or 2019-nCoV). The disease was first identified in December 2019 and spread globally, causing a pandemic. Symptoms of COVID-19 include fever, cough, shortness of breath, fatigue, headache, loss of smell, nasal congestion, sore throat,

coughing up sputum, pain in muscles or joints, chills, nausea, vomiting, and diarrhea. In severe cases, symptoms can include difficulty waking, confusion, blueish face or lips, coughing up blood, decreased white blood cell count, and kidney failure. Complications can include pneumonia, viral sepsis, acute respiratory distress syndrome, and kidney failure.

[0014] COVID-19 is especially threatening to public health. The virus is highly contagious, and studies currently indicate that it can be spread by asymptomatic carriers or by those who are pre-symptomatic. Likewise, the early stage of the disease is slow-progressing enough that carriers do not often realize they are infected, leading them to expose numerous others to the virus. The combination of COVID-19's ease of transmission, its high rate of hospitalization of victims, and its death rate make the virus a substantial public health risk, especially for countries without a healthcare system equipped to provide supportive care to pandemic-level numbers of patients. There is not yet a vaccine or specific antiviral treatment for COVID-19 and accordingly, there is a pressing need for treatments or cures.

[0015] SARS-CoV-2 is not the only coronavirus that causes disease. It is a β-coronavirus, a genus of coronaviruses that includes other human pathogens, including SARS-CoV (the causative agent of SARS), MERS-CoV (the causative agent of MERS), and HCoV-OC43 (a causative agent of the common cold). The infectivity of these viruses, and the severity of the diseases they cause, varies widely. β-coronavirus can also manifest as zoonotic infections, spread to and from humans and animals. Additionally, non-human species such as camels, bats, tigers, non-human primates, and rabbits can be susceptible to β-coronavirus. Accordingly, there is a pressing need for treatments or cures to multiple coronaviruses.

[0016] The present disclosure provides molecules useful against coronaviruses, and especially SARS-CoV-2, the causative agent of COVID-19 in humans. Accordingly, the present disclosure fulfills the need in the art for compounds that can be safely and effectively treat or prevent coronavirus infections in humans.

[0017] Picornaviruses are a family of positive strand RNA, nonenveloped viruses. A picornavirus has 60 identical subunits (vertices) which contain five protomers. Each protomer is made up of one copy of four proteins, named VP1, VP2, VP3 and VP4. There are several genera of picornaviruses, including, Enterovirus, Aphthovirus, Cardiovirus and

Hepatovirus. Enteroviruses known to infect human include, but are not limited to, Rhinovirus A, Rhinovirus B, Rhinovirus C, Coxsackievirus A, Coxsackievirus B and Poliovirus. There is no specific treatment for a picornavirus infection.

[0018] Noroviruses are single-stranded positive-sense RNA, non-enveloped viruses belonging to the Caliciviridae family. Noroviruses are often spread by the fecal-oral route, and are a common cause of gastroenteritis. Infected subjects can experience nausea, non-bloody diarrhea, vomiting and/or abdominal pain. Those suffering from a norovirus infection can become severely dehydrated and require medical attention. As with a picornavirus infection, there is no specific treatment for a norovirus infection. Accordingly, there is a need for compounds that effectively treat or prevent a picornavirus and/or a norovirus infection.

Definitions

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0020] Whenever a group is described as being "optionally substituted" that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being "unsubstituted or substituted" if substituted, the substituent(s) may be selected from one or more of the indicated substituents. If no substituents are indicated, it is meant that the indicated "optionally substituted" or "substituted" group may be substituted with one or more group(s) (such as 1, 2 or 3) individually and independently selected from deuterium, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, C-amido(alkyl), isocyanato, thiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl,

trihalomethanesulfonamido, an amino, a mono-substituted amine and a di-substituted amine.

[0021] As used herein, "C_a to C_b" in which "a" and "b" are integers refer to the number of carbon atoms in an alkyl, alkenyl or alkynyl group, or the number of carbon atoms in the ring of a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl group. That is, the alkyl, alkenyl, alkynyl, ring of the cycloalkyl, ring of the cycloalkenyl, ring of the aryl, ring of the heteroaryl or ring of the heterocyclyl can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, aryl, heteroaryl or heterocyclyl group, the broadest range described in these definitions is to be assumed.

[0022] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. The alkyl group may be substituted or unsubstituted.

[0023] As used herein, "alkenyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. The length of an alkenyl can vary. For example, the alkenyl can be a C_{2-4} alkenyl, C_{2-6} alkenyl or C_{2-8} alkenyl. Examples of alkenyl groups include allenyl, vinylmethyl and ethenyl. An alkenyl group may be unsubstituted or substituted.

[0024] As used herein, "alkynyl" refers to an alkyl group that contains in the

straight or branched hydrocarbon chain one or more triple bonds. The length of an alkynyl can vary. For example, the alkynyl can be a C_{2-4} alkynyl, C_{2-6} alkynyl or C_{2-8} alkynyl. Examples of alkynyls include ethynyl and propynyl. An alkynyl group may be unsubstituted or substituted.

[0025] As used herein, "cycloalkyl" refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused- or spiro-fashion. Cycloalkyl groups can contain 3 to 10 atoms in the ring(s). 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0026] As used herein, "cycloalkenyl" refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be "aryl," as defined herein). When composed of two or more rings, the rings may be connected together in a fused- or spiro-fashion. A cycloalkenyl can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkenyl group may be unsubstituted or substituted.

[0027] As used herein, "aryl" refers to a carbocyclic (all carbon) monocyclic or multicyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C_6-C_{14} aryl group, a C_6-C_{10} aryl group, or a C_6 aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0028] As used herein, "heteroaryl" refers to a monocyclic, bicyclic and tricyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1 to 5 heteroatoms), that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). Furthermore,

the term "heteroaryl" includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring, or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0029] As used herein, "heterocyclyl" refers to a monocyclic, bicyclic and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The number of atoms in the ring(s) of a heterocyclyl group can vary. For example, the heterocyclyl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused fashion. Additionally, any nitrogens in a heterocyclyl may be quaternized. Heterocyclyl groups may be unsubstituted or substituted. Examples of such "heterocyclyl groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine *N*-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and

their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and 3,4-methylenedioxyphenyl).

[0030] As used herein, "aryl(alkyl)" refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenyl(alkyl), 3-phenyl(alkyl), and naphthyl(alkyl).

[0031] As used herein, "heteroaryl(alkyl)" refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to 2-thienyl(alkyl), 3-thienyl(alkyl), furyl(alkyl), thienyl(alkyl), pyrrolyl(alkyl), pyridyl(alkyl), isoxazolyl(alkyl), imidazolyl(alkyl), and their benzo-fused analogs.

[0032] A "heterocyclyl(alkyl)" refer to a heterocyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a heterocyclyl(alkyl) may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl) and 1,3-thiazinan-4-yl(methyl).

[0033] "Lower alkylene groups" are straight-chained $-CH_2-$ tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$) and butylene ($-CH_2CH_2CH_2CH_2-$). A lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group with a substituent(s) listed under the definition of "substituted." Further, when a lower alkylene group is substituted, the lower alkylene can be substituted by replacing both hydrogens on the same carbon with a cycloalkyl group (e.g., ).

[0034] As used herein, "alkoxy" refers to the formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) is defined herein. A non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzyloxy. In some instances, an alkoxy can be –OR, wherein R is an unsubstituted C_{1-4} alkyl. An alkoxy may be substituted or

unsubstituted.

[0035] As used herein, "acyl" refers to a hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl and acryl. An acyl may be substituted or unsubstituted.

[0036] As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl and tri-haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0037] As used herein, "haloalkoxy" refers to a O-alkyl group and O-monocyclic cycloalkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di- haloalkoxy and tri- haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy, 2-fluoroisobutoxy, chloro-substituted cyclopropyl, fluoro-substituted cyclopropyl, chloro-substituted cyclobutyl and fluoro-substituted cyclobutyl. In some instances, a haloalkoxy can be –OR, wherein R is a $C_{1\text{-}4}$ alkyl substituted by 1, 2 or 3 halogens. A haloalkoxy may be substituted or unsubstituted.

[0038] A "sulfenyl" group refers to an "-SR" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0039] A "sulfinyl" group refers to an "-S(=O)-R" group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0040] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0041] An "O-carboxy" group refers to a "RC(=O)O-" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0042] The terms "ester" and "C-carboxy" refer to a "-C(=O)OR" group in which

R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0043] A "thiocarbonyl" group refers to a "-C(=S)R" group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0044] A "trihalomethanesulfonyl" group refers to an "X_3CSO_2-" group wherein each X is a halogen.

[0045] A "trihalomethanesulfonamido" group refers to an "$X_3CS(O)_2N(R_A)$-" group wherein each X is a halogen, and R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl).

[0046] The term "amino" as used herein refers to a $-NH_2$ group.

[0047] As used herein, the term "hydroxy" refers to a –OH group.

[0048] A "cyano" group refers to a "-CN" group.

[0049] The term "azido" as used herein refers to a $-N_3$ group.

[0050] An "isocyanato" group refers to a "-NCO" group.

[0051] A "thiocyanato" group refers to a "-CNS" group.

[0052] An "isothiocyanato" group refers to an "-NCS" group.

[0053] A "mercapto" group refers to an "-SH" group.

[0054] A "carbonyl" group refers to a -C(=O)- group.

[0055] An "S-sulfonamido" group refers to a "$-SO_2N(R_AR_B)$" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0056] An "N-sulfonamido" group refers to a "$RSO_2N(R_A)$-" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0057] An "O-carbamyl" group refers to a "$-OC(=O)N(R_AR_B)$" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An

O-carbamyl may be substituted or unsubstituted.

[0058] An "N-carbamyl" group refers to an "ROC(=O)N(R_A)-" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-carbamyl may be substituted or unsubstituted.

[0059] An "O-thiocarbamyl" group refers to a "-OC(=S)-N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.

[0060] An "N-thiocarbamyl" group refers to an "ROC(=S)N(R_A)-" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-thiocarbamyl may be substituted or unsubstituted.

[0061] A "C-amido" group refers to a "-C(=O)N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0062] An "N-amido" group refers to a "RC(=O)N(R_A)-" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0063] A "mono-substituted amine" refers to a "-NHR_A" in which R_A can be independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A mono-substituted amine may be substituted or unsubstituted. In some instances, a mono-substituted amine can be -NHR_A, wherein R_A can be an unsubstituted C_{1-6} alkyl or an unsubstituted or a substituted benzyl.

[0064] A "di-substituted amine" refers to a "-NR_AR_B" in which R_A and R_B can be independently can be independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A mono-substituted amine may be substituted or unsubstituted. In some instances, a mono-substituted amine can be -NR_AR_B, wherein R_A and R_B can be independently an

unsubstituted C_{1-6} alkyl or an unsubstituted or a substituted benzyl.

[0065] A "ketoamide" group refers to a –C(=O)-C(=O)N(R_AR_B) group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A ketoamide may be substituted or unsubstituted.

[0066] The term "halogen atom" or "halogen" as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0067] Where the numbers of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example "haloalkyl" may include one or more of the same or different halogens. As another example, "C_1-C_3 alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0068] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, Biochem. 11:942-944 (1972)).

[0069] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0070] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof. In addition, the term "comprising" is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

[0071] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality.

[0072] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of (R)-configuration or (S)-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0073] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g.,

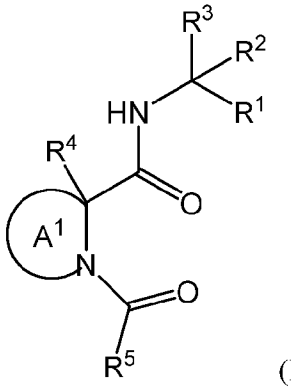
hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0074] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

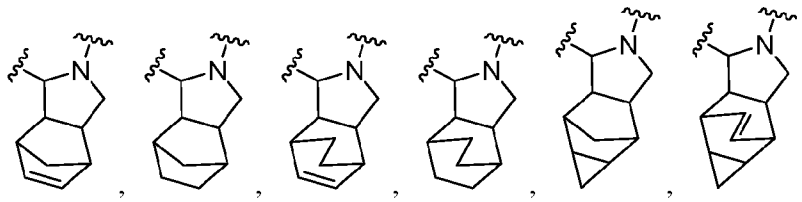
[0075] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

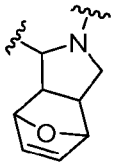
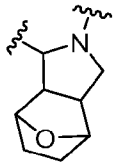
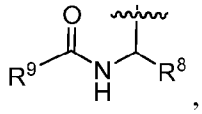
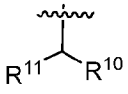
Compounds

[0076] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein: Ring A^1 can be  ,

 and  , and wherein Ring A^1 can be optionally substituted with one or more moieties independently selected from deuterium, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl; R^1 can be selected from cyano, an unsubstituted or a substituted C_{2-5} alkynyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted ketoamide, –CH(OH)-($S(=O)_2$-O^-), –CH(OH)(($P(=O)(OR^6)_2$) and –$C(=O)CH_2$-O-($(P(=O)(OR^7)_2$); each R^6 and each R^7 can be independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl); R^2 can be hydrogen, deuterium or halogen; R^3 can be an unsubstituted or a substituted monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl), an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) or an unsubstituted or a substituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl); R^4 can be hydrogen, deuterium or halogen; R^5 can be  ,  , a substituted monocyclic C_{3-6} cycloalkyl or a substituted 4- to 6-membered monocyclic heterocyclyl; R^8 and R^{10} can be independently selected from an unsubstituted or a substituted C_{2-6} alkyl, an unsubstituted or a substituted C_{2-6} alkenyl, an unsubstituted or a substituted C_{2-6} alkynyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted bicyclic C_{5-8} cycloalkyl and an unsubstituted or a substituted monocyclic 4- to 6-membered heterocyclyl, wherein when the C_{2-6} alkyl is substituted, the C_{2-6} alkyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, cyano, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl and an unsubstituted C_{1-4} alkoxy; wherein when the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted, the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4}

alkynyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl and an unsubstituted C_{1-4} alkoxy; R^9 can be selected from an unsubstituted C_{1-6} alkyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted bicyclic C_{5-6} cycloalkyl, an unsubstituted or a substituted monocyclic heteroaryl and an unsubstituted or a substituted monocyclic heterocyclyl, wherein the substituted monocyclic C_{3-6} cycloalkyl is substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl and an unsubstituted monocyclic C_{3-6} cycloalkyl; and R^{11} can be an optionally substituted monocyclic 4- to 6-membered heterocyclyl, $-(NH)_m-$an optionally substituted 5- to 6-membered monocyclic heteroaryl, –O–an optionally substituted C_{1-6} alkyl, –O–an optionally substituted C_{3-8} cycloalkyl and –O–an optionally substituted C_{3-8} cycloalkyl(C_{1-4} alkyl), wherein m can be 0 or 1.

[0077] The substituent R^1 can be various moieties. In some embodiments, R^1 can be an unsubstituted ketoamide. In some embodiments, R^1 can be a substituted ketoamide. The ketoamide can have the structure $-C(=O)-C(=O)NR^{y1}R^{z1}$. In some embodiments, R^1 can be an acyl, for example, R^1 can be –C(=O)H, –C(=O)(an unsubstituted C_{1-4} alkyl), –C(=O)(an unsubstituted to a substituted benzyl), –C(=O)(an unsubstituted to a substituted monocyclic heteroaryl) or –C(=O)(an unsubstituted to a substituted bicyclic heteroaryl). In some embodiments, R^1 can be a substituted acyl. The acyl for R^1 can have the structure $-C(=O)R^{y2}$. When the acyl is substituted, the possible groups that can be present on the acyl include hydroxy, a substituted or an unsubstituted alkoxy (such as –O–(an unsubstituted C_{1-4} alkyl), –O–(an unsubstituted C_{3-6} cycloalkyl), a substituted or an unsubstituted phenoxy or a substituted or an unsubstituted benzyloxy) or –O-(C=O)-(an unsubstituted C_{1-6} alkyl). In some embodiments, R^1 can be an unsubstituted can be –C(=O)-N-sulfonamido.

[0078] R^{y1}, R^{y2} and R^{z1} can be a variety of groups. In some embodiments, R^{y1}, R^{y2} and R^{z1} can be independently selected from hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl (for example, a monocyclic C_{3-8} cycloalkyl), C_{3-8} cycloalkenyl (such as a monocyclic C_{3-8} cycloalkenyl), aryl (such as phenyl or naphthyl), heteroaryl (including a monocyclic or a bicyclic heteroaryl), heterocyclyl (for example, a monocyclic or a bicyclic heterocyclyl), aryl(alkyl) (such as benzyl), heteroaryl(alkyl) (including a monocyclic heteroaryl(CH_2)– and a monocyclic (heteroaryl(CH_2CH_2)–) or heterocyclyl(alkyl) (such as a

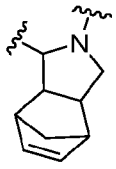
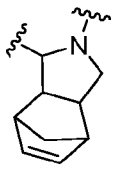
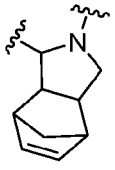
monocyclic heterocyclyl(CH_2)– and a monocyclic heterocyclyl(CH_2CH_2)–), wherein each of the aforementioned R^{y1}, R^{y2} and R^{z1} groups can be unsubstituted or substituted. In some embodiments, R^{y1}, R^{y2} and R^{z1} can be independently selected from H, C_{1-8} alkyl, an unsubstituted C_{1-4} haloalkyl (including $–CF_3$, $–CCl_3$, $–CHF_2$, $–C(CH_3)F_2$, $–CHCl_2$, $–CH_2F$, $–CH(CH_3)F$, $–CH_2CF_3$, $–CH_2Cl$, $–CH_2CH_2F$, $–CH_2CH_2Cl$, $–CH_2CH_2CH_2F$ and $–CH_2CH_2CH_2Cl$), $–C_{1-4}$ alkyl(OH) (including $–CH_2OH$, $–CH_2CH_2OH$ and $–CH(CH_3)OH$), $–C_{1-4}$ alkyl(C_{1-4} alkoxy) (such as $–CH_2O$(an unsubstituted C_{1-4} alkyl) and $–CH_2CH_2O$(an unsubstituted C_{1-4} alkyl)), $–C_{1-4}$ alkyl-O-(a monocyclic C_{3-6} cycloalkyl) (such as $–CH_2O$(a monocyclic C_{3-6} cycloalkyl), $–CH_2CH_2O$(a monocyclic C_{3-6} cycloalkyl)), $–C_{1-4}$ alkyl-O-(phenyl) (for example, $–CH_2O$(phenyl) and $–CH_2CH_2O$(phenyl)), $–C_{1-4}$ alkyl-O-(5- to 6-membered monocyclic heteroaryl) (such as $–CH_2O$(5- to 6-membered monocyclic heteroaryl) and $–CH_2CH_2O$(5- to 6-membered monocyclic heteroaryl)), $–C_{1-4}$ alkyl-O-(5- to 6-membered monocyclic heterocyclyl) (for example, $–CH_2O$(5- to 6-membered monocyclic heterocyclyl) and $–CH_2CH_2O$(5- to 6-membered monocyclic heterocyclyl)), $–C_{1-4}$ alkyl-O-(a monocyclic C_{3-6} cycloalkyl(C_{1-4} alkyl) (such as $–C_{1-4}$ alkyl-O-CH_2-(monocyclic C_{3-6} cycloalkyl) and $–C_{1-4}$ alkyl-O-CH_2CH_2-(monocyclic C_{3-6} cycloalkyl)), $–C_{1-4}$ alkyl-O-(benzyl) (for example, $–CH_2O$(benzyl) and $–CH_2CH_2O$(benzyl)), $–C_{1-4}$ alkyl-O-(5- to 6-membered monocyclic heteroaryl(C_{1-4} alkyl), $–C_{1-4}$ alkyl-O-(5- to 6-membered monocyclic heterocyclyl(C_{1-4} alkyl), $–C_{1-4}$ alkyl-O(C=O)(an unsubstituted C_{1-6} alkyl) (for example, $–CH_2O$(C=O)(an unsubstituted C_{1-6} alkyl)), a monocyclic C_{3-8} cycloalkyl (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl), a monocyclic heteroaryl (such as imidazole, 1,3,4-oxadiazole and pyridinyl), a monocyclic heterocyclyl (for example, tetrahydrofuran and tetrahydropyran), a bicyclic heteroaryl (for example, benzothiazole, benzoimidazole and benzooxazole), a bicyclic heterocyclyl, a monocyclic C_{3-6} cycloalkyl(alkyl), aryl(alkyl) (such as benzyl), heteroaryl(alkyl) (for example, a monocyclic heteroaryl–(CH_2)–, such as pyridinyl–(CH_2)–) and heterocyclyl(alkyl) (for example, a monocyclic heterocyclyl–(CH_2)–), wherein each of the aforementioned R^{y1}, R^{y2} and R^{z1} groups can be unsubstituted or substituted.

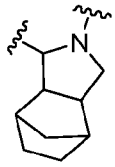
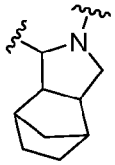
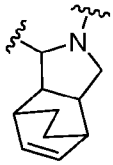
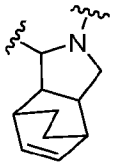
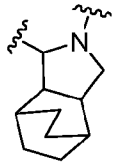
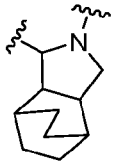
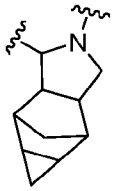
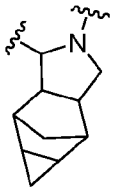
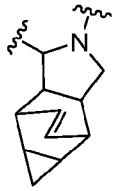
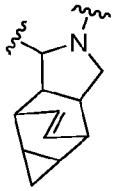
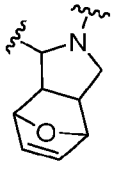
[0079] In some embodiments, R^1 can be $–C(=O)R^{y2}$, wherein R^{y2} can be $–C_{1-4}$ alkyl(OH) (such as $–CH_2OH$). In some embodiments, R^1 can be $–C(=O)$-$C(=O)NR^{y1}R^{z1}$; wherein R^{y1} can be H; and R^{z1} can be any of the moieties listed for R^{z1} in the previous

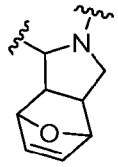
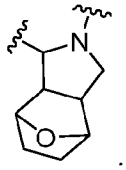
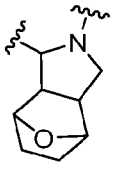
paragraph. In some embodiments, R^1 can be $-C(=O)-C(=O)NR^{y1}R^{z1}$; wherein R^{y1} can be H; and R^{z1} can be a monocyclic C_{3-8} cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl).

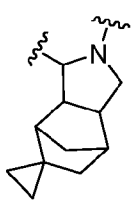
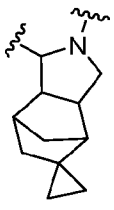
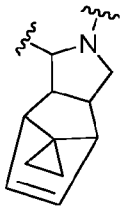
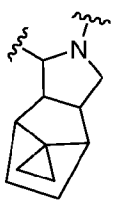
[0080] Prodrug-type and phosphate-containing moieties can be present at R^1. In some embodiments, R^1 can be $-CH(OH)-(S(=O)_2-O^-)$. In other embodiments, R^1 can be $-CH(OH)((P=O)(OR^6)_2)$, wherein each R^6 can be independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl). In still other embodiments, R^1 can be $-C(=O)CH_2-O-((P=O)(OR^7)_2)$, wherein each R^7 can be independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl). Other examples of R^6 and R^7 groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl (straight-chained and branched), hexyl (straight-chained and branched), ethenyl, propenyl, butenyl, pentenyl, hexenyl, chloromethyl, fluoromethyl, difluoromethyl, dichloromethyl, trifluoromethyl, trichloromethyl, an unsubstituted or a substituted phenyl and an unsubstituted or a substituted benzyl.

[0081] In some embodiments, R^1 can be cyano. In other embodiments, R^1 can be an unsubstituted C_{2-5} alkynyl. In still other embodiments, R^1 can be a substituted C_{2-5} alkynyl. The C_{2-5} alkynyl can have various structures. For example, the C_{2-5} alkynyl can have the structure $-(CH_2)_1-C_{2-4}$ alkynyl or $-(CH_2)_2-C_{2-3}$ alkynyl.

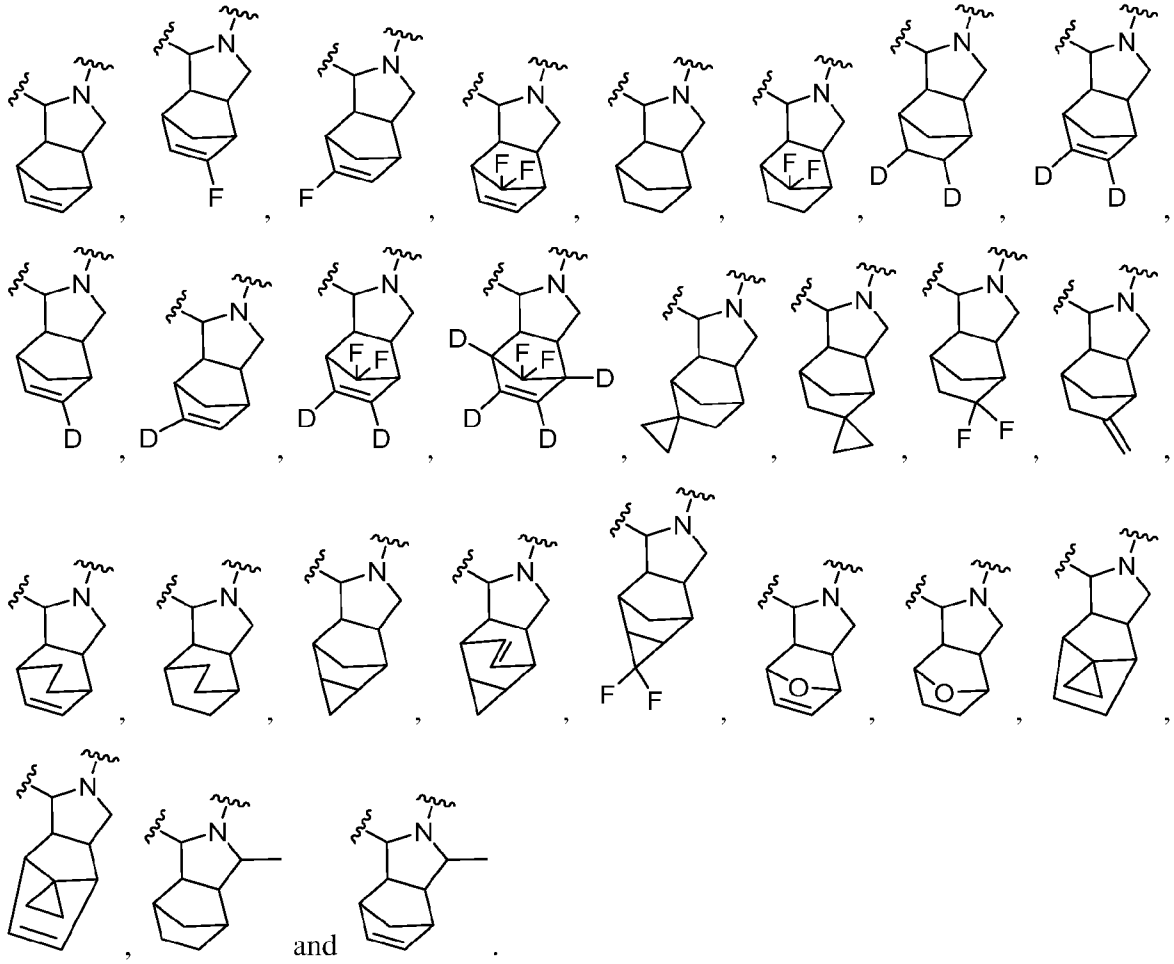
[0082] As described herein, Ring A^1 can be  , wherein Ring A^1 can be optionally substituted. In some embodiments, Ring A^1 can be an unsubstituted  . In other embodiments, Ring A^1 can be a substituted  . In still other embodiments, Ring

A^1 can be an unsubstituted  . In yet still other embodiments, Ring A^1 can be a substituted  . In some embodiments, Ring A^1 can be an unsubstituted  . In other embodiments, Ring A^1 can be a substituted  . In still other embodiments, Ring A^1 can be an unsubstituted  . In yet still other embodiments, Ring A^1 can be a substituted  . In some embodiments, Ring A^1 can be an unsubstituted  . In other embodiments, Ring A^1 can be a substituted  . In still other embodiments, Ring A^1 can be an unsubstituted  . In yet still other embodiments, Ring A^1 can be a substituted  . In some embodiments, Ring A^1 can be an unsubstituted  . In

other embodiments, Ring A^1 can be a substituted  In still other embodiments, Ring A^1 can be an unsubstituted  . In yet still other embodiments, Ring A^1 can be a substituted  .

[0083] As provided herein, Ring A^1 can be substituted with one or more moieties independently selected from deuterium, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl. Example of suitable substituents that can be present in Ring A^1 include halogen (such as F or Cl), an unsubstituted C_{1-4} alkyl (for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl), an unsubstituted C_{1-4} haloalkyl (including $-CF_3$, $-CCl_3$, $-CHF_2$, $-C(CH_3)F_2$, $-CHCl_2$, $-CH_2F$, $-CH(CH_3)F$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$ and $-CH_2CH_2CH_2Cl$), an unsubstituted C_{2-4} alkenyl (such as ethenyl, propenyl and butenyl) and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl). When Ring A^1 is substituted by an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl, the unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl can replace one hydrogen. In some embodiments, an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl can replace two hydrogens of Ring A^1 such that the unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl is connected to Ring A^1 in a spiro-fashion. Examples of an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl replacing two hydrogen of Ring A^1 includes the following:  ,  ,  and  , wherein

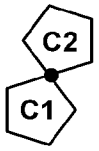
each can be unsubstituted or substituted as described herein. . Examples of Ring A^1 include, but are not limited to, the following:

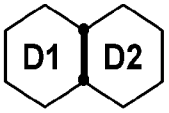


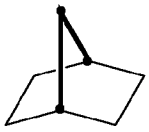
[0084] In some embodiments, R^4 can be hydrogen. In other embodiments, R^4 can be deuterium. In still other embodiments, R^4 can be halogen (such as fluoro or chloro).

[0085] As provided herein R^3 can be a non-hydrogen substituent selected from an unsubstituted or a substituted monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) and an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl). In some embodiments, R^3 can be an unsubstituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl). In other embodiments, R^3 can be a substituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl). In still other embodiments, R^3 can be an unsubstituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl). In yet still other embodiments, R^3 can be a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl). When R^3 is a bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl), the two rings of the bicyclic heterocyclyl can be

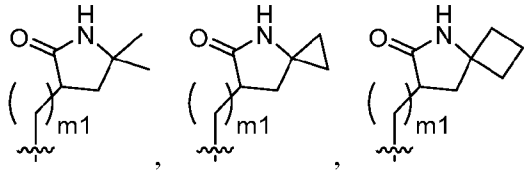
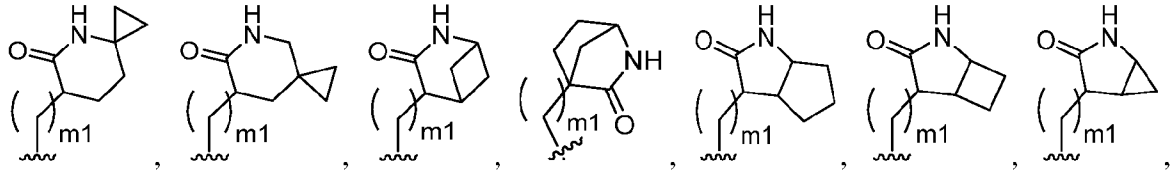
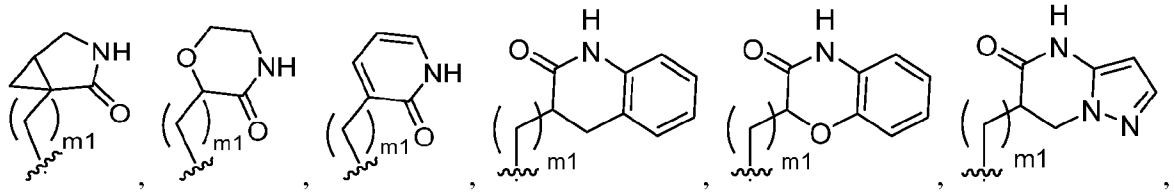
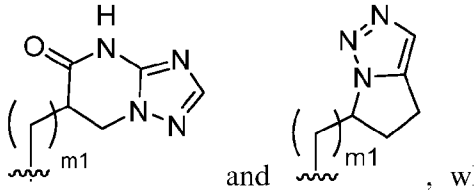
connected in a fused-fashion (including bridged-fashion) or a spiro-fashion. In some embodiments, R^3 can be an unsubstituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl). In other embodiments, R^3 can be a substituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl).

[0086] Those skilled in the art understand that when two rings are connected in a spiro-fashion, the two rings are connected by a single ring atom. For example, in the structure 

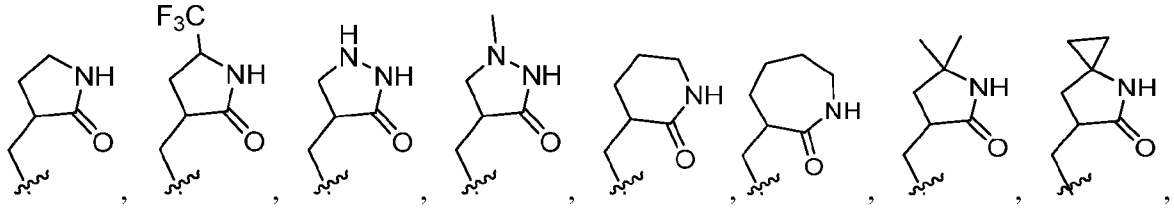
rings C1 and C2 are joined in a spiro-fashion. When two rings described herein are connected in a fused-fashion, the two rings are connected by two or more ring atoms. . In some instances, the two rings can be connected by two adjacent ring atoms. As an example, rings D1 and D1 are connected in a fused-fashion by two adjacent ring atoms 

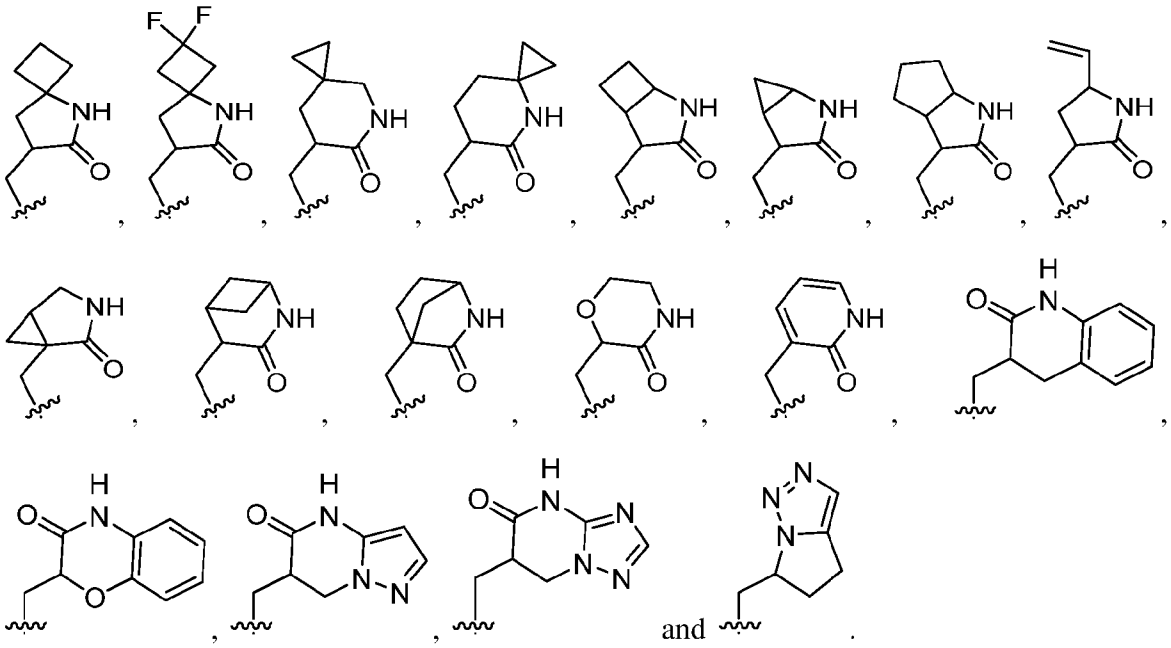
. In some instances, two rings described herein can be connected by three or more atoms are shared between the two rings. The following structure:  is an example of two rings being connected by three or more ring atoms. When two rings are connected by three or more ring atoms, the three or more ring atoms connecting the two rings would be referred to by those skilled in the art as "bridging" atoms. Further, those skilled in the art would understand based on the disclosure provided herein that two rings connected in a "bridged" fashion is an example of two rings connected in a fused-fashion.

[0087] The number of ring atoms for a monocyclic and a bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) can vary. Non-limiting examples include an unsubstituted or a substituted 5-membered monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl), 6-membered monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl), an unsubstituted or a substituted 9-membered bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) and 10-membered bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl). Examples of suitable R^3 groups include the following: azepan-2-one(C_{1-4} alkyl), imidazolidin-2-one(C_{1-4} alkyl), tetrahydropyrimidin-2-one(C_{1-4} alkyl), pyrrolidin-2-one(C_{1-4} alkyl), piperidin-2-

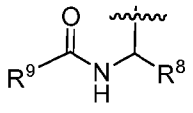
one(C_{1-4} alkyl), pyrazolidin-3-one(C_{1-4} alkyl),  ,  ,  ,  and , wherein each m1 can be independently 1, 2, 3 or 4, (including substituted or unsubstituted versions of the aforementioned). The R^3 groups provided herein can be substituted with one or more moieties independently selected from those listed for "optionally substituted." In some embodiments, a R^3 group provided herein can be substituted with one or more moieties selected from deuterium, halogen, hydroxy, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl an unsubstituted C_{1-4} alkoxy, amino, –(an unsubstituted C_{1-4} alkyl)-O-P-$(OH)_2$ (such as $–CH_2$-O-P-$(OH)_2$) and –(an unsubstituted C_{1-4} alkyl)-O-P-(O(an unsubstituted C_{1-4} alkyl))$_2$ (such as $–CH_2$-O-P-$(OCH_3)_2$).

[0088] Non-limiting examples of R^3 moieties include the following:





[0089] In some embodiments, R^2 can be hydrogen. In other embodiments, R^2 can be deuterium. In still other embodiments, R^2 can be halogen (for example, fluoro or chloro).

[0090] As provided herein, R^5 can be  . In some embodiments, R^9 can be an unsubstituted C_{1-6} haloalkyl. For example, R^9 can be $-CF_3$, $-CClF_2$, $-CCl_3$, $-CHF_2$, $-C(CH_3)F_2$, $-CHCl_2$, $-CH_2F$, $-CH(CH_3)F$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$ and $-CH_2CH_2CH_2Cl$. In some embodiments, R^9 can be $-CF_3$. In other embodiments, R^9 can be an unsubstituted C_{1-6} alkyl, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl (straight-chained or branched) and hexyl (straight-chained or branched). In still other embodiments, R^9 can be an unsubstituted or a substituted monocyclic heteroaryl. A variety of an unsubstituted or a substituted monocyclic heteroaryls can be present for R^9. For example, the heteroaryl can be a 5- or 6-membered heteroaryl that includes 1, 2 or 3 heteroatoms selected from nitrogen (N), oxygen (O) and sulfur (S). Exemplary heteroaryls for an unsubstituted or a substituted monocyclic heteroaryl include, but are not limited to, furane, isoxazole, isothiazole pyridine, pyridazine, pyrimidine and pyrazine. In yet still other embodiments, R^9 can be an unsubstituted or a substituted monocyclic heterocyclyl. A non-limiting list of monocyclic heterocyclyls for R^9 include oxetane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydropyran,

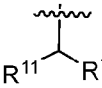
tetrahydrothiopyran, piperidine and morpholine. Various substituents can be present on a substituted heteroaryl and/or a substituted heterocyclyl of R^9. For example, the heteroaryl can be substituted 1, 2 or 3 times with a moiety selected from halogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{1-6} haloalkyl and an unsubstituted C_{1-6} alkoxy. Suitable halogens, unsubstituted C_{1-6} alkyls, unsubstituted C_{1-6} haloalkyls and unsubstituted C_{1-6} alkoxys are described herein.

[0091] In some embodiments, R^9 can be an unsubstituted monocyclic C_{3-6} cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In other embodiments, R^9 can be a halogen-substituted monocyclic C_{3-6} cycloalkyl. In still other embodiments, R^9 can be a monocyclic C_{3-6} cycloalkyl substituted with an unsubstituted C_{1-4} alkyl. In yet still other embodiments, R^9 can be a monocyclic C_{3-6} cycloalkyl substituted with an unsubstituted C_{2-4} alkenyl. In some embodiments, R^9 can be a monocyclic C_{3-6} cycloalkyl substituted with an unsubstituted C_{1-4} haloalkyl. In other embodiments, R^9 can be a monocyclic C_{3-6} cycloalkyl substituted with an unsubstituted monocyclic C_{3-6} cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments, R^9 can be an unsubstituted bicyclic C_{5-6} cycloalkyl. In other embodiments, R^9 can be a substituted bicyclic C_{5-6} cycloalkyl. The two rings of a bicyclic C_{5-6} cycloalkyl can be connected in a spiro-fashion or a fused-fashion. In some embodiments, R^9 can be a halogen-substituted bicyclic C_{5-6} cycloalkyl. In still other embodiments, R^9 can be a bicyclic C_{5-6} cycloalkyl substituted with an unsubstituted C_{1-4} alkyl. In yet still other embodiments, R^9 can be a bicyclic C_{5-6} cycloalkyl substituted with an unsubstituted C_{2-4} alkenyl. In some embodiments, R^9 can be a bicyclic C_{5-6} cycloalkyl substituted with an unsubstituted C_{1-4} haloalkyl. In other embodiments, R^9 can be a bicyclic C_{5-6} cycloalkyl substituted with an unsubstituted monocyclic C_{3-6} cycloalkyl (including cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl). A non-liming list of bicyclic C_{5-6} cycloalkyls include spiro[2.2]pentane, spiro[2.3]hexane, bicyclo[1.1.1]pentane and bicyclo[2.1.1]hexane.

[0092] Suitable halogen-substituted monocyclic C_{3-6} cycloalkyls include halogen-substituted cyclopropyl, halogen-substituted cyclobutyl, halogen-substituted cyclopentyl and halogen-substituted cyclohexyl. Additional monocyclic C_{3-6} cycloalkyls include cyclopropyl substituted with an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{1-4} haloalkyl and/or an unsubstituted monocyclic C_{3-6} cycloalkyl, cyclobutyl substituted

with an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{1-4} haloalkyl and/or an unsubstituted monocyclic C_{3-6} cycloalkyl, cyclopentyl substituted with an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{1-4} haloalkyl and/or an unsubstituted monocyclic C_{3-6} cycloalkyl and cyclohexyl substituted with an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{1-4} haloalkyl and/or an unsubstituted monocyclic C_{3-6} cycloalkyl. The number halogens on a halogen-substituted monocyclic C_{3-6} cycloalkyl and/or a bicyclic C_{5-6} cycloalkyl, the number of unsubstituted C_{1-4} alkyls on a monocyclic C_{3-6} cycloalkyl and/or a bicyclic C_{5-6} cycloalkyl, the number of unsubstituted C_{2-4} alkenyls on a monocyclic C_{3-6} cycloalkyl and/or a bicyclic C_{5-6} cycloalkyl, the number of unsubstituted C_{1-4} haloalkyls on a monocyclic C_{3-6} cycloalkyl and/or a bicyclic C_{5-6} cycloalkyl and the number of unsubstituted monocyclic C_{3-6} cycloalkyls on a monocyclic C_{3-6} cycloalkyl and/or a bicyclic C_{5-6} cycloalkyl can vary. For example, 1, 2, 3 or 4 halogens can be present on a halogen-substituted monocyclic C_{3-6} cycloalkyl, 1, 2, 3 or 4 unsubstituted C_{1-4} alkyls can be present on a monocyclic C_{3-6} cycloalkyl substituted with an unsubstituted C_{1-4} alkyl, 1, 2, 3 or 4 unsubstituted C_{2-4} alkenyls can be present on a monocyclic C_{3-6} cycloalkyl substituted with an unsubstituted C_{2-4} alkenyl, 1, 2, 3 or 4 unsubstituted C_{1-4} haloalkyls can be present on a monocyclic C_{3-6} cycloalkyl substituted with an unsubstituted C_{1-4} haloalkyl, 1 or 2 unsubstituted monocyclic C_{3-6} cycloalkyls can be present on a monocyclic C_{3-6} cycloalkyl, 1, 2, 3 or 4 halogens can be present on a halogen-substituted bicyclic C_{5-6} cycloalkyl, 1, 2, 3 or 4 unsubstituted C_{1-4} alkyls can be present on a bicyclic C_{5-6} cycloalkyl substituted with an unsubstituted C_{1-4} alkyl, 1, 2, 3 or 4 unsubstituted C_{2-4} alkenyls can be present on a bicyclic C_{5-6} cycloalkyl substituted with an unsubstituted C_{2-4} alkenyl 1, 2, 3 or 4 unsubstituted C_{1-4} haloalkyls can be present on a bicyclic C_{5-6} cycloalkyl substituted with an unsubstituted C_{1-4} haloalkyl and 1 or 2 unsubstituted monocyclic C_{3-6} cycloalkyls can be present on a bicyclic C_{5-6} cycloalkyl. In some embodiments, a monocyclic C_{3-6} cycloalkyl can be substituted with 1 or more substituents (such as 1, 2, 3 or 4 substituents) selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, and an unsubstituted C_{1-4} haloalkyl. In other embodiments, a bicyclic C_{5-6} cycloalkyl can be substituted with 1 or more substituents (such as 1, 2, 3 or 4 substituents) selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, and an unsubstituted C_{1-4} haloalkyl. Suitable halogens that can be present on a substituted monocyclic C_{3-6} cycloalkyl include, but are not limited to,

fluoro (F) and chloro (Cl). Examples of unsubstituted C_{1-4} haloalkyls include, but are not limited to, $-CF_3$, $-CCl_3$, $-CHF_2$, $-C(CH_3)F_2$, $-CHCl_2$, $-CH_2F$, $-CH(CH_3)F$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$ and $-CH_2CH_2CH_2Cl$.

[0093] In some embodiments, R^5 can be  , wherein R^{10} can be independently selected from an unsubstituted or a substituted C_{2-6} alkyl, an unsubstituted or a substituted C_{2-6} alkenyl, an unsubstituted or a substituted C_{2-6} alkynyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted bicyclic C_{5-8} cycloalkyl and an unsubstituted or a substituted monocyclic 4- to 6-membered heterocyclyl, wherein when the C_{2-6} alkyl is substituted, the C_{2-6} alkyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen and an unsubstituted C_{1-4} alkoxy; wherein when the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted, the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{1-4} haloalkyl and an unsubstituted C_{1-4} alkoxy; and R^{11} can be $-(NH)_m-$an optionally substituted 5- to 6-membered monocyclic heteroaryl, wherein m can be 0 or 1. In some embodiments, R^{11} can be an optionally substituted monocyclic 4- to 6-membered heterocyclyl. Examples of heterocyclyls for R^{11} include optionally substituted 4- to 6-membered monocyclic heterocyclyls that include 1, 2 or 3 heteroatoms independently selected from N (nitrogen), O (oxygen) and S (sulfur). A non-limiting list of heterocyclyl for R^{11} include the following: azetidine, pyrrolidine and piperidine. In other embodiment, m can be 0; and R^{11} can be an unsubstituted 5- to 6-membered monocyclic heteroaryl. In other embodiment, m can be 0; and R^{11} can be a substituted 5- to 6-membered monocyclic heteroaryl. In still other embodiment, m can be 1; and R^{11} can be an $-(NH)-$unsubstituted 5- to 6-membered monocyclic heteroaryl. In other embodiment, m can be 1; and R^{11} can be a $-(NH)-$substituted 5- to 6-membered monocyclic heteroaryl. An example of a 5- to 6-membered monocyclic heteroaryl that can be present for R^{11} include a 5- to 6-membered monocyclic heteroaryl that includes 1, 2 or 3 heteroatoms independently selected from N (nitrogen), O

(oxygen) and S (sulfur). Examples of suitable 5- to 6-membered monocyclic heteroaryls include, but are not limited to, imidazole, pyrazole, oxazole, thiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-oxadiazole and 1,3,4-thiadiazole. In still other embodiments, R^{11} can be –O–an optionally substituted C_{1-6} alkyl. In yet still other embodiments, R^{11} can be –O–an optionally substituted C_{3-8} cycloalkyl. In some embodiments, R^{11} can be –O–an optionally substituted C_{3-8} cycloalkyl(C_{1-4} alkyl). The cycloalkyl of –O–an optionally substituted C_{3-8} cycloalkyl and –O–an optionally substituted C_{3-8} cycloalkyl(C_{1-4} alkyl) can be a monocyclic C_{3-6} cycloalkyl or a bicyclic C_{5-8} cycloalkyl. The C_{1-4} alkyl of –O–an optionally substituted cycloalkyl(C_{1-4} alkyl) can be $–CH_2–$, $–CH_2CH_2–$, $–CH_2CH_2CH_2–$ or $–CH_2CH_2CH_2CH_2–$. As described herein, R^{11} can be substituted. Exemplary groups that can be present on R^{11} include halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} alkoxy and an unsubstituted C_{1-4} haloalkyl.

[0094] The R^8 and/or R^{10} moieties can be a substituted or an unsubstituted version of a C_{2-6} alkyl, a C_{2-6} alkenyl, a C_{2-6} alkynyl, a monocyclic C_{3-6} cycloalkyl, a bicyclic C_{5-8} cycloalkyl or a monocyclic 4- to 6-membered heterocyclyl. In some embodiments, R^8 and/or R^{10} can be an unsubstituted C_{2-6} alkyl. In other embodiments, R^8 and/or R^{10} can be a substituted C_{2-6} alkyl. Exemplary C_{2-6} alkyls include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl (straight-chained and branched) and hexyl (straight-chained and branched). In some embodiments, R^8 and/or R^{10} can be an unsubstituted C_{2-6} alkenyl. In other embodiments, R^8 and/or R^{10} can be a substituted C_{2-6} alkenyl. In still other embodiments, R^8 and/or R^{10} can be an unsubstituted C_{2-6} alkynyl. In yet still other embodiments, R^8 and/or R^{10} can be a substituted C_{2-6} alkynyl.

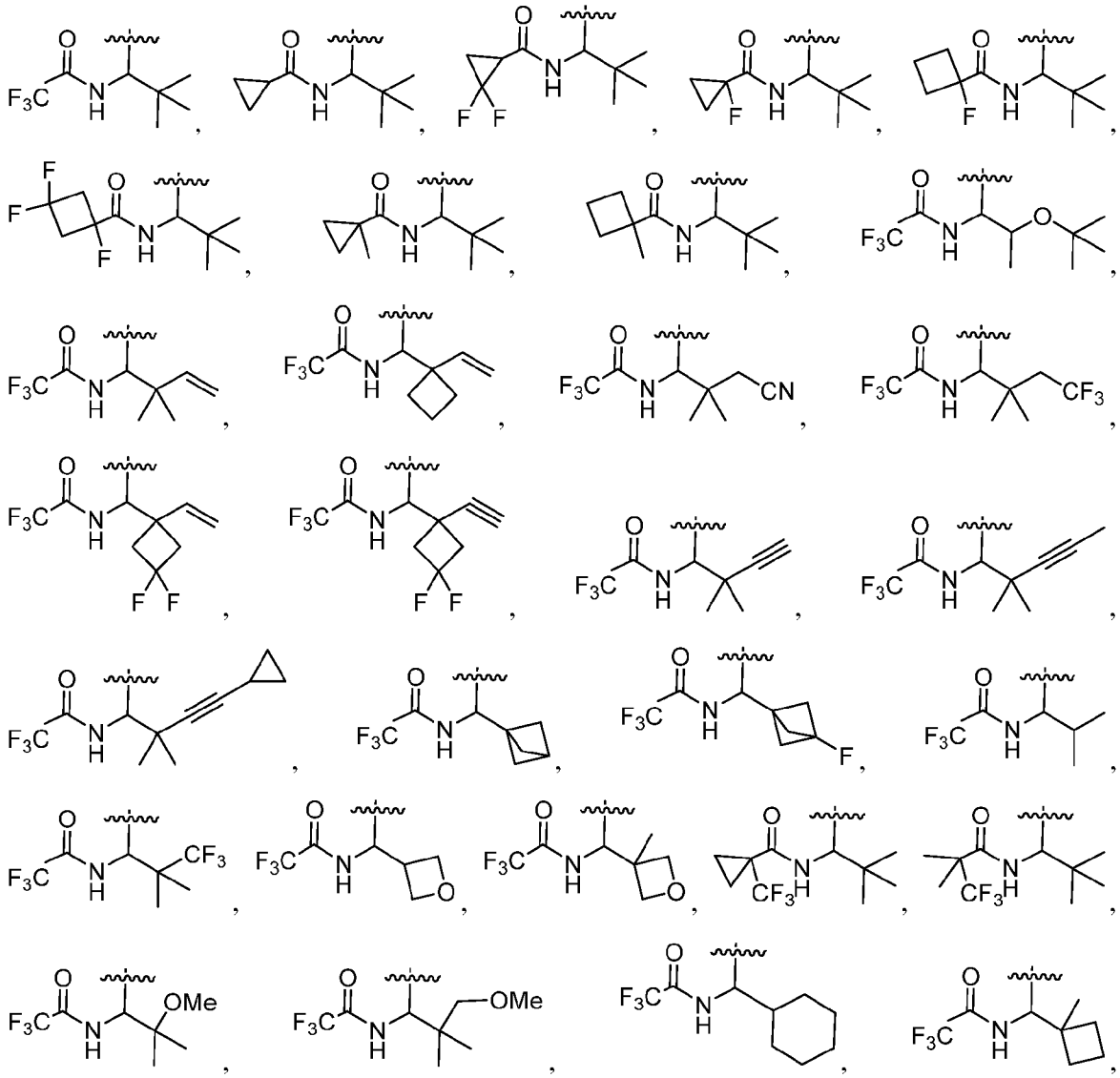
[0095] Cyclic moieties, including monocyclic and bicyclic moieties, can also be present for R^8 and/or R^{10}. In some embodiments, R^8 and/or R^{10} can be an unsubstituted monocyclic C_{3-6} cycloalkyl. In some embodiments, R^8 and/or R^{10} can be a substituted monocyclic C_{3-6} cycloalkyl. For example, R^8 and/or R^{10} can be a substituted or an unsubstituted cyclopropyl, a substituted or an unsubstituted cyclobutyl, a substituted or an unsubstituted cyclopentyl or a substituted or an unsubstituted cyclohexyl. In some embodiments, R^8 and/or R^{10} can be an unsubstituted bicyclic C_{5-8} cycloalkyl. In other embodiments, R^8 and/or R^{10} can be an unsubstituted bicyclic C_{5-8} cycloalkyl. The two rings of the bicyclic C_{5-8} cycloalkyl can joined in a fused or a spiro-fashion. Examples of rings

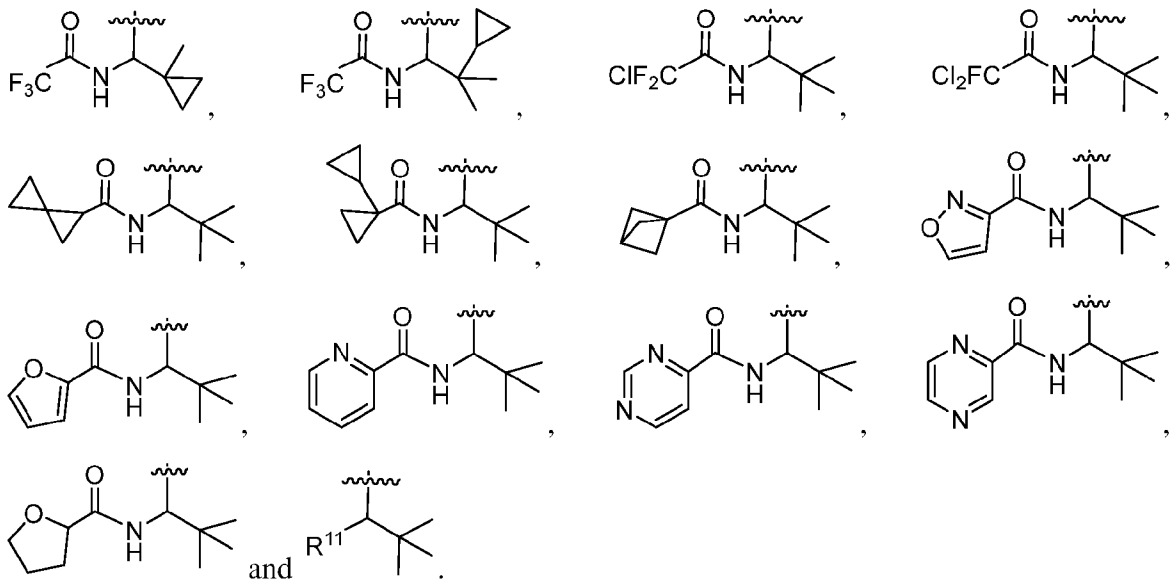
connected in a fused and a spiro-fashion are provided herein. In some embodiments, R^8 and/or R^{10} can be an unsubstituted or a substituted bicyclo[1.1.1]pentyl. In still other embodiments, R^8 and/or R^{10} can be an unsubstituted monocyclic 4- to 6-membered heterocyclyl. In yet still other embodiments, R^8 and/or R^{10} can be an unsubstituted monocyclic 4- to 6-membered heterocyclyl. The number of heteroatoms present in a monocyclic 4- to 6-membered heterocyclyl for R^8 and/or R^{10} can vary. Suitable heteroatoms include, but are not limited to, O (oxygen), S (sulfur) and N (nitrogen). Examples of monocyclic 4- to 6-membered heterocyclyls are oxetane, thietane, azetidine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrahydropyran, tetrahydrothiopyran and piperidine (including unsubstituted or substituted versions of each of the aforementioned).

[0096] As described herein, R^8 and/or R^{10} can be substituted. In some embodiments, when R^8 and/or R^{10} is a C_{2-6} alkyl that is substituted, the C_{2-6} alkyl can be substituted 1, 2, 3 or 4 times with a substituents independently selected from halogen, cyano, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl and an unsubstituted C_{1-4} alkoxy. Each halogen can be independently F (fluoro) or Cl (chloro). Suitable unsubstituted C_{1-4} alkoxys that can be substituted on a C_{2-6} alkyl of R^8 and/or R^{10} include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy. In some embodiments, when R^8 and/or R^{10} is a substituted C_{2-6} alkenyl, a substituted C_{2-6} alkynyl, a substituted monocyclic C_{3-6} cycloalkyl, a substituted bicyclic C_{5-8} cycloalkyl or a substituted monocyclic 4- to 6-membered heterocyclyl, each of the aforementioned can be substituted 1, 2, 3 or 4 times with a substituents independently selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl and an unsubstituted C_{1-4} alkoxy. Examples of unsubstituted C_{1-4} alkyls, an unsubstituted C_{2-4} alkenyl and an unsubstituted C_{2-4} alkynyl that can be substituted on a substituted C_{2-6} alkenyl, a substituted C_{2-6} alkynyl, a substituted monocyclic C_{3-6} cycloalkyl, a substituted bicyclic C_{5-8} cycloalkyl or a substituted monocyclic 4- to 6-membered heterocyclyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl. Suitable halogens and unsubstituted C_{1-4} alkoxys that can be present on a substituted C_{2-6} alkenyl, a substituted C_{2-6} alkynyl, a substituted monocyclic C_{3-6} cycloalkyl, a substituted bicyclic C_{5-8} cycloalkyl or a substituted monocyclic 4- to 6-

membered heterocyclyl are described herein, such as in this paragraph. Non-limiting list of unsubstituted and substituted monocyclic C_{3-6} cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and halogen-substituted monocyclic C_{3-6} cycloalkyls. Examples of unsubstituted C_{1-6} haloalkyls that can be present on a substituted C_{2-6} alkenyl, a substituted C_{2-6} alkynyl, a substituted monocyclic C_{3-6} cycloalkyl, a substituted bicyclic C_{5-8} cycloalkyl or a substituted monocyclic 4- to 6-membered heterocyclyl include, but are not limited to, $-CF_3$, $-CCl_3$, $-CHF_2$, $-C(CH_3)F_2$, $-CHCl_2$, $-CH_2F$, $-CH(CH_3)F$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$ and $-CH_2CH_2CH_2Cl$.

[0097] Exemplary R^5 groups include the following:

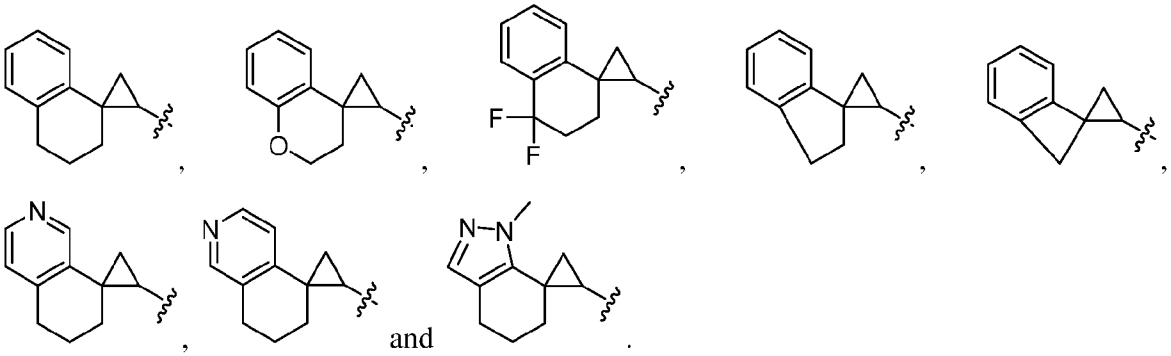




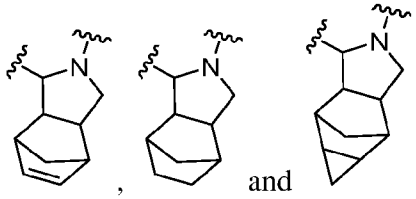
[0098] As described herein, in some embodiments, R^5 can be a substituted monocyclic C_{3-6} cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In other embodiments, R^5 can be a substituted 4- to 6-membered monocyclic heterocyclyl. For example, R^5 can be a substituted 4- to 6-membered monocyclic heterocyclyl that includes 1, 2 or 3 heteroatoms selected from N (nitrogen), O (oxygen) and S (sulfur). The substituted monocyclic C_{3-6} cycloalkyl and/or the substituted 4- to 6-membered monocyclic heterocyclyl can be substituted 1, 2 or 3 times with a moiety selected from deuterium, halogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{1-6} haloalkyl and an unsubstituted C_{1-6} alkoxy.

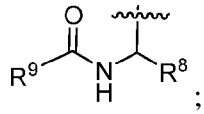
[0099] Further, when R^5 is a monocyclic C_{3-6} cycloalkyl or a 4- to 6-membered monocyclic heterocyclyl, the monocyclic C_{3-6} cycloalkyl or the 4- to 6-membered monocyclic heterocyclyl can be substituted in a spiro-fashion by an unsubstituted or a substituted bicyclic cycloalkenyl or an unsubstituted or a substituted bicyclic heterocyclyl. The bicyclic cycloalkenyl can be an unsubstituted or a substituted 8- to 10-membered bicyclic cycloalkenyl. An unsubstituted or a substituted bicyclic heterocyclyl can be an unsubstituted or a substituted 8- to 10-membered bicyclic heterocyclyl, for example, an unsubstituted or a substituted 8- to 10-membered bicyclic heterocyclyl that includes 1, 2 or 3 heteroatoms in the rings selected from N (nitrogen), O (oxygen) and S (sulfur). In some embodiments, the bicyclic cycloalkenyl and/or the bicyclic heterocyclyl can be substituted one or more times (such as 1, 2, 3 or 4 times) with a moiety independently selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-6} haloalkyl (such as $-CF_3$, $-CCl_3$, –

CHF_2, $-C(CH_3)F_2$, $-CHCl_2$, $-CH_2F$, $-CH(CH_3)F$, $-CH_2CF_3$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CH_2Cl$) and an unsubstituted C_{1-4} alkoxy. Examples of R^5 as a monocyclic C_{3-6} cycloalkyl or a 4- to 6-membered monocyclic heterocyclyl substituted in a spiro-fashion by an unsubstituted or a substituted bicyclic cycloalkenyl or an unsubstituted or a substituted bicyclic heterocyclyl include the following:



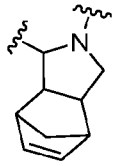
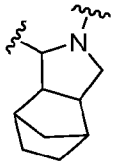
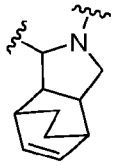
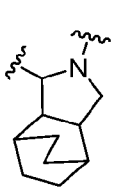
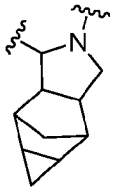
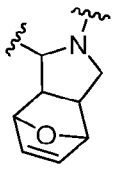
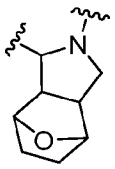
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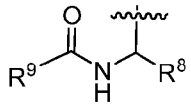
[0100] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be where: Ring A^1 can be 

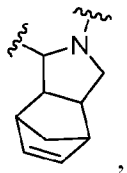
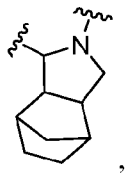
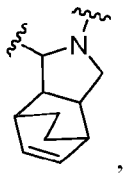
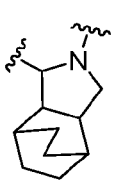
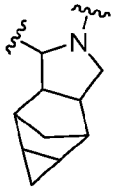
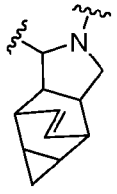
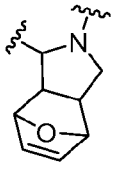
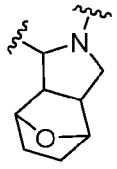
, and , and wherein Ring A^1 can be optionally substituted with one or more moieties independently selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl; R^1 can be selected from cyano, an unsubstituted or a substituted C_{2-5} alkynyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted ketoamide, $-CH(OH)-(S(=O)_2-O^-)$, $-CH(OH)((P=O)(OR^6)_2)$ and $-C(=O)CH_2-O-((P=O)(OR^7)_2)$; each R^6 and each R^7 can be independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl); R^2 can be hydrogen, deuterium or halogen; R^3 can be an unsubstituted or a substituted monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) or an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl); R^4 can be hydrogen, deuterium or halogen; R^5 can be 

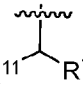
; R^8 can be selected from an unsubstituted or a substituted C_{2-6} alkyl, an unsubstituted or a substituted C_{2-6} alkenyl, an

unsubstituted or a substituted C_{2-6} alkynyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted bicyclic C_{5-8} cycloalkyl and an unsubstituted or a substituted monocyclic 4- to 6-membered heterocyclyl, wherein when the C_{2-6} alkyl is substituted, the C_{2-6} alkyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen and an unsubstituted C_{1-4} alkoxy; wherein when the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted, the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{1-4} alkoxy; and R^9 can be selected from an unsubstituted C_{1-6} alkyl, an unsubstituted C_{1-6} haloalkyl and an unsubstituted to a substituted monocyclic C_{3-6} cycloalkyl, wherein the substituted monocyclic C_{3-6} cycloalkyl is substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{1-4} haloalkyl.

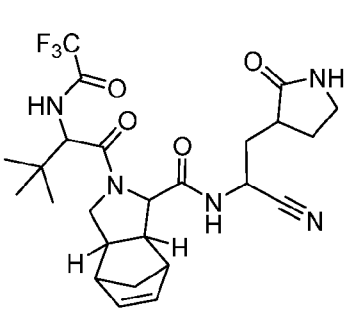
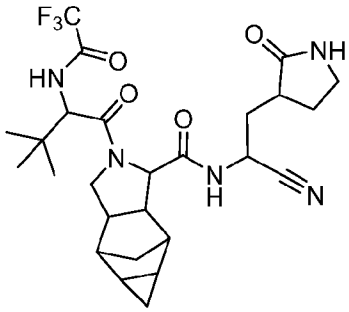
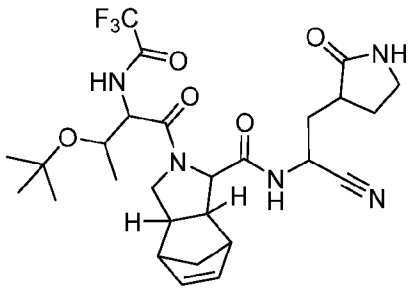
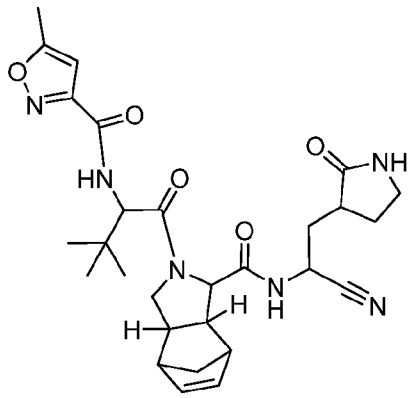
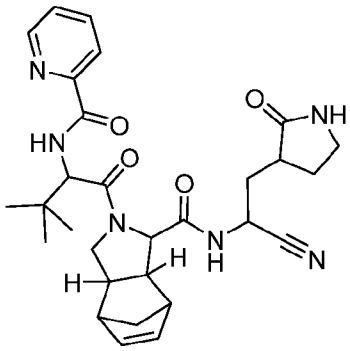
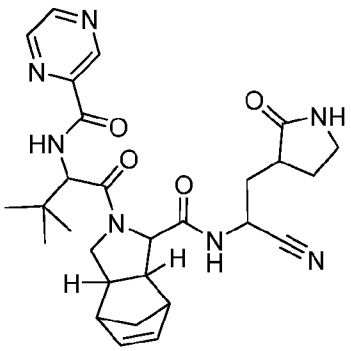
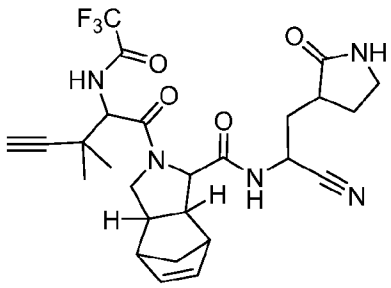
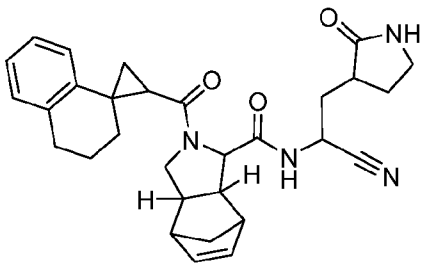
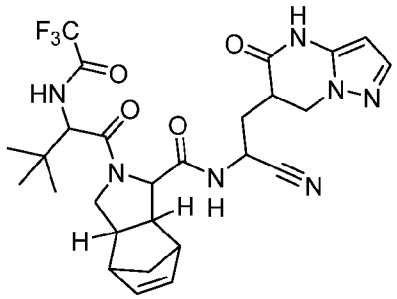
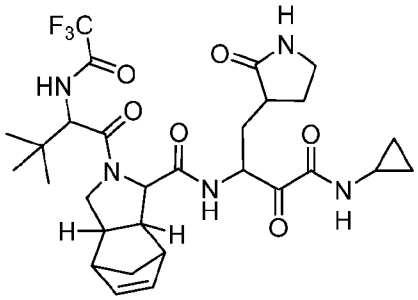
[0101] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be where: Ring A^1 can be  ,  ,  ,  ,  ,  and  , and wherein Ring A^1 can be optionally substituted with one or more moieties independently selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl; R^1 can be selected from cyano, an unsubstituted or a substituted C_{2-5} alkynyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted ketoamide, $-CH(OH)-(S(=O)_2-O^-)$, $-CH(OH)((P=O)(OR^6)_2)$ and $-C(=O)CH_2-O-((P=O)(OR^7)_2)$; each R^6 and each R^7 can be independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl); R^2 can be hydrogen, deuterium or halogen; R^3 can be an unsubstituted or a substituted monocyclic nitrogen-

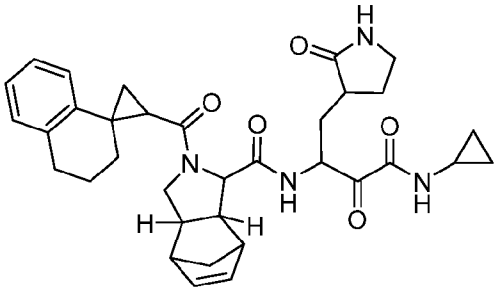
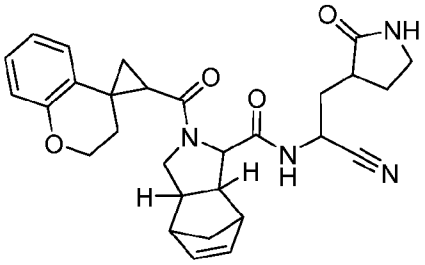
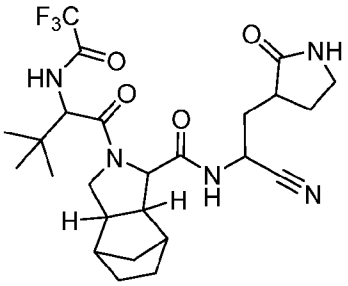
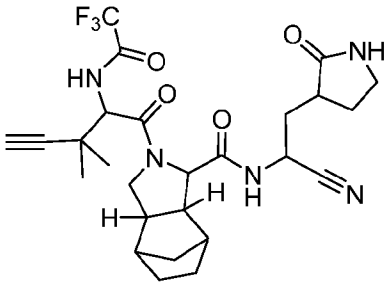
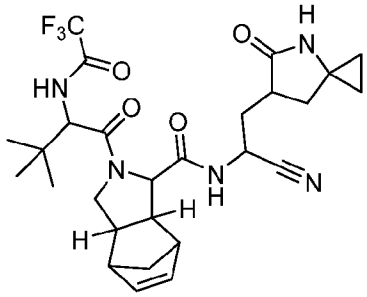
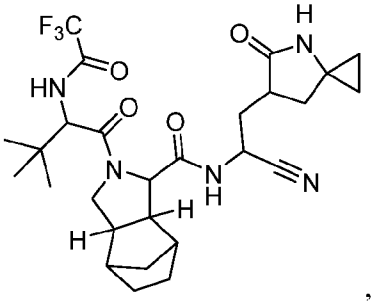
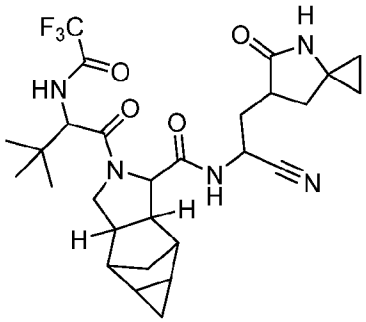
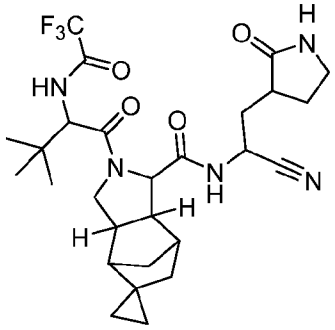
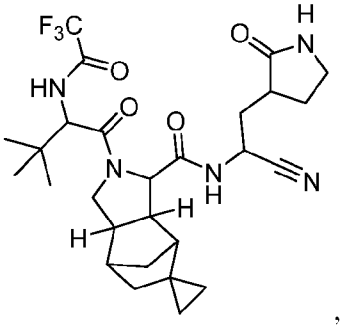
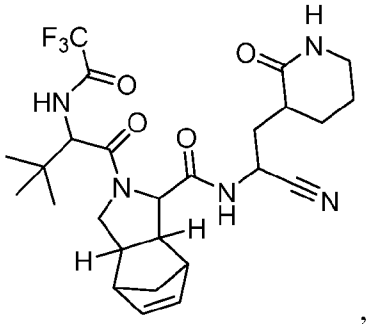
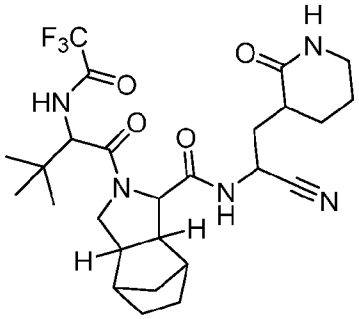
containing heterocyclyl(C_{1-4} alkyl) or an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl); R^4 can be hydrogen, deuterium or halogen; R^5 can be  , a substituted monocyclic C_{3-6} cycloalkyl or a substituted 4- to 6-membered monocyclic heterocyclyl; R^8 can be selected from an unsubstituted or a substituted C_{2-6} alkyl, an unsubstituted or a substituted C_{2-6} alkenyl, an unsubstituted or a substituted C_{2-6} alkynyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted bicyclic C_{5-8} cycloalkyl and an unsubstituted or a substituted monocyclic 4- to 6-membered heterocyclyl, wherein when the C_{2-6} alkyl is substituted, the C_{2-6} alkyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen and an unsubstituted C_{1-4} alkoxy; wherein when the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted, the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl and an unsubstituted C_{1-4} alkoxy; and R^9 can be selected from an unsubstituted C_{1-6} alkyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted monocyclic heteroaryl and an unsubstituted or a substituted monocyclic heterocyclyl, wherein the substituted monocyclic C_{3-6} cycloalkyl is substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{1-4} haloalkyl.

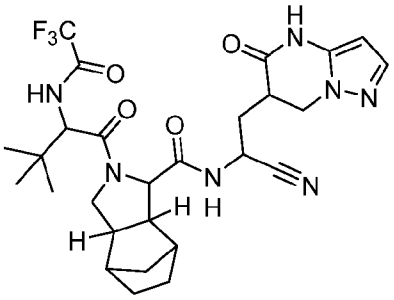
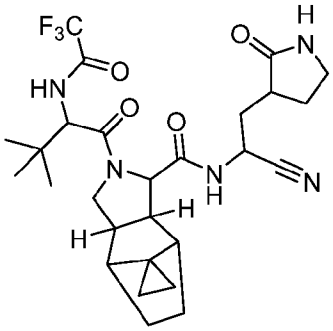
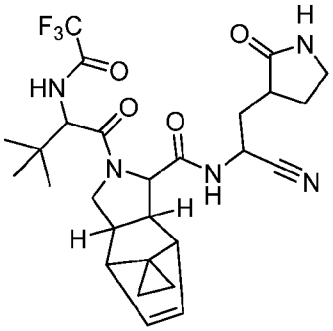
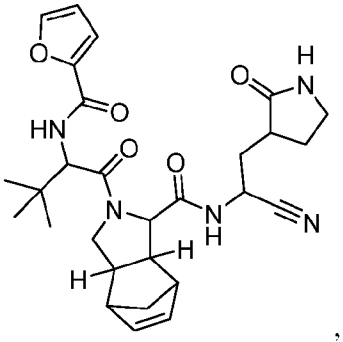
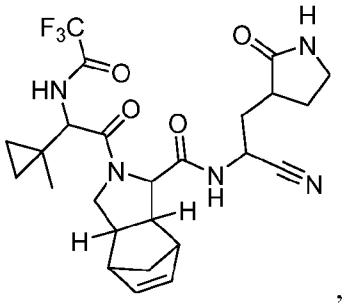
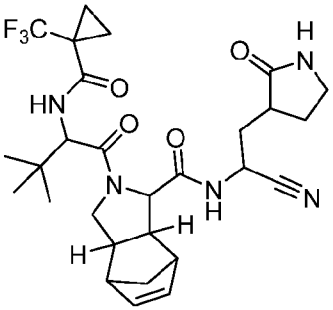
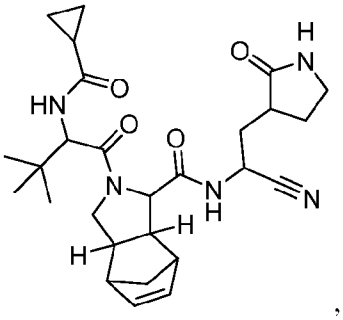
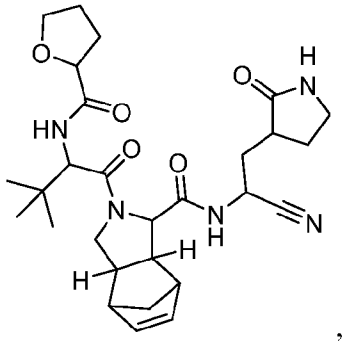
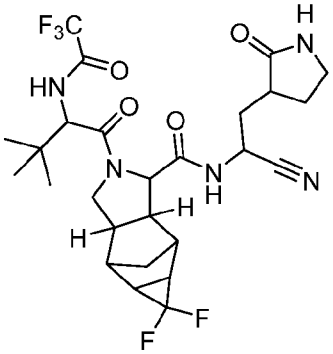
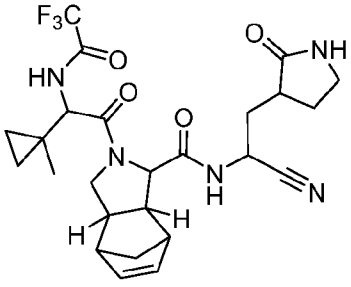
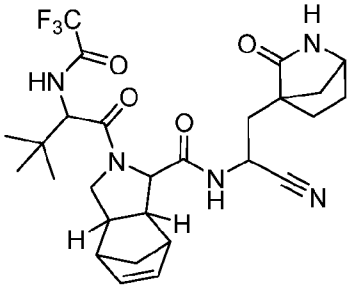
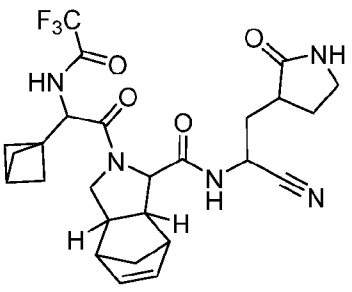
[0102] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be where: Ring A^1 can be  ,  ,  ,  ,  ,  ,  and  , and wherein Ring A^1 can be optionally substituted with one or more moieties independently selected from deuterium,

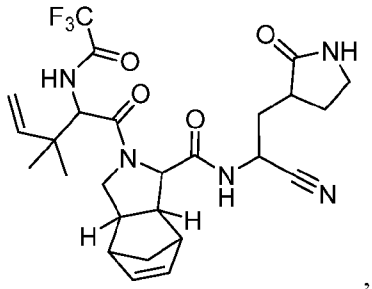
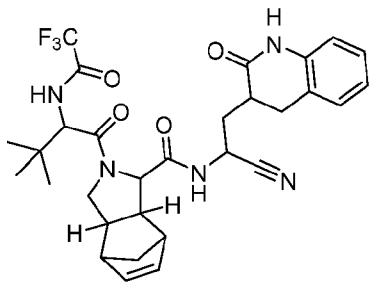
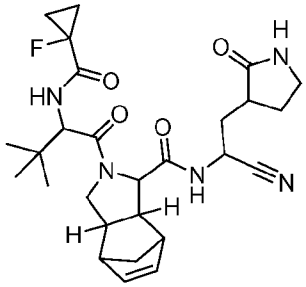
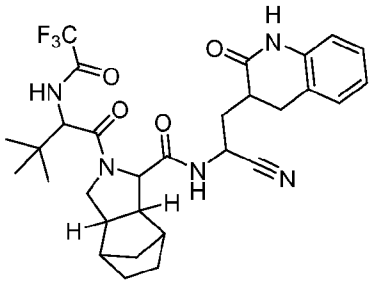
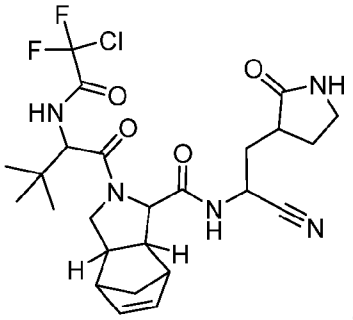
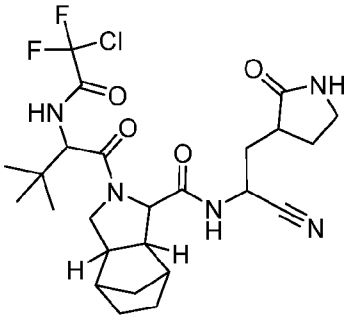
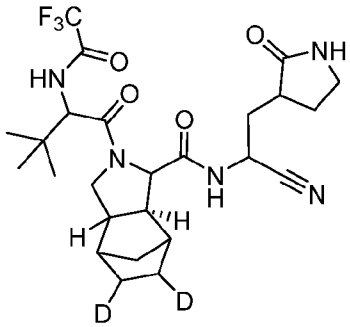
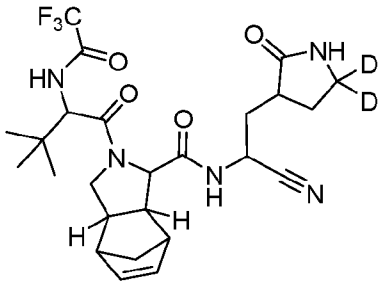
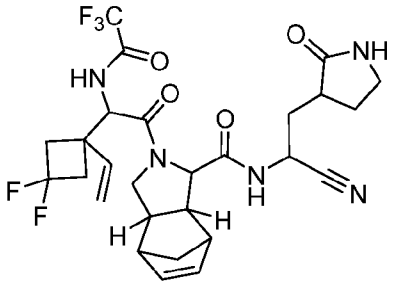
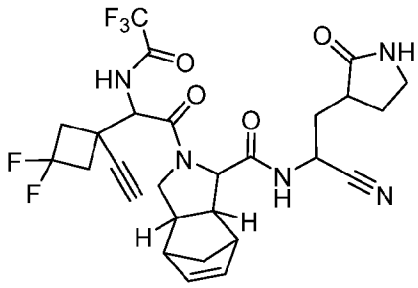
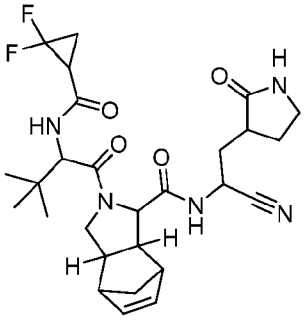
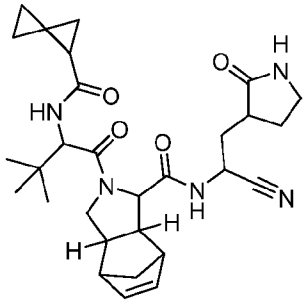
halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl; R^1 can be selected from cyano, an unsubstituted or a substituted C_{2-5} alkynyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted ketoamide, $-CH(OH)-(S(=O)_2-O^-)$, $-CH(OH)((P=O)(OR^6)_2)$ and $-C(=O)CH_2-O-((P=O)(OR^7)_2)$; each R^6 and each R^7 can be independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl); R^2 can be hydrogen, deuterium or halogen; R^3 can be an unsubstituted or a substituted monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl), an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl), an unsubstituted or a substituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl); R^4 can be hydrogen, deuterium or halogen; and R^5 can be  ; R^{10} can be selected from an unsubstituted or a substituted C_{2-6} alkyl, an unsubstituted or a substituted C_{2-6} alkenyl, an unsubstituted or a substituted C_{2-6} alkynyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted bicyclic C_{5-8} cycloalkyl and an unsubstituted or a substituted monocyclic 4- to 6-membered heterocyclyl, wherein when the C_{2-6} alkyl is substituted, the C_{2-6} alkyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen and an unsubstituted C_{1-4} alkoxy; wherein when the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted, the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{1-4} haloalkyl and an unsubstituted C_{1-4} alkoxy; and R^{11} can be an optionally substituted monocyclic 4- to 6-membered heterocyclyl, $-(NH)_m-$an optionally substituted 5- to 6-membered monocyclic heteroaryl, –O–an optionally substituted C_{1-6} alkyl, –O–an optionally substituted C_{3-8} cycloalkyl and –O–an optionally substituted C_{3-8} cycloalkyl(C_{1-4} alkyl), wherein m can be 0 or 1.

[0103] Examples of compounds of Formula (I), include the following:


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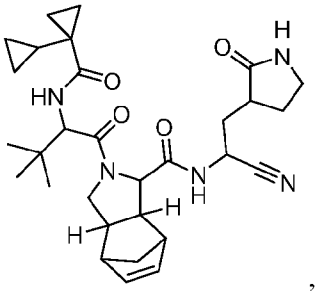
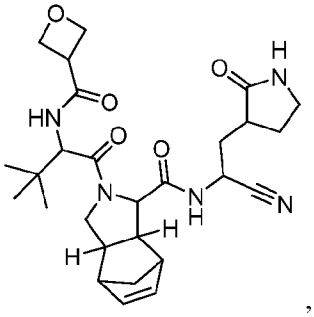
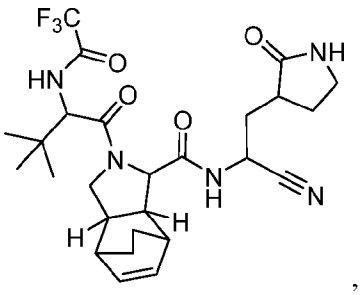
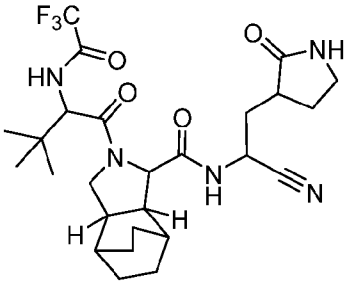
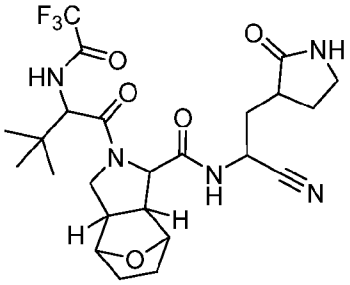
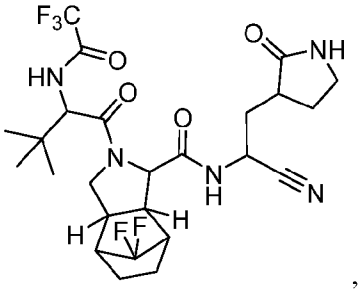
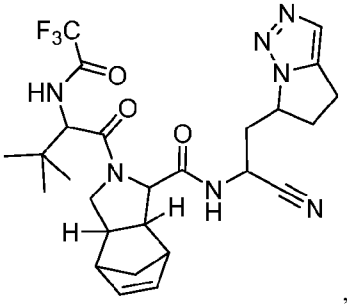
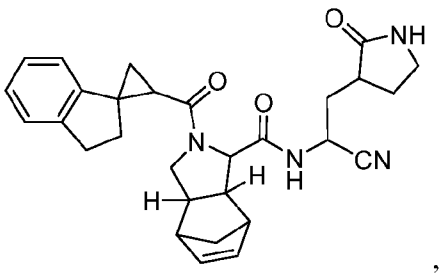
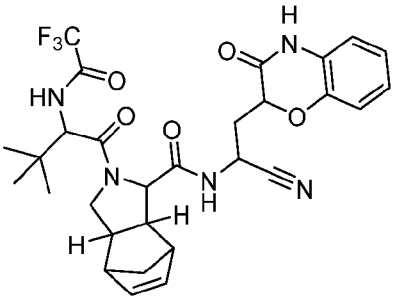
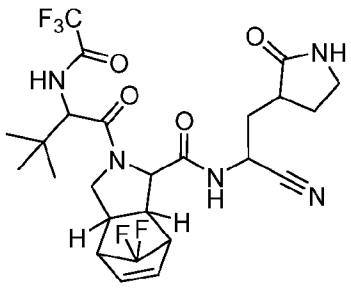
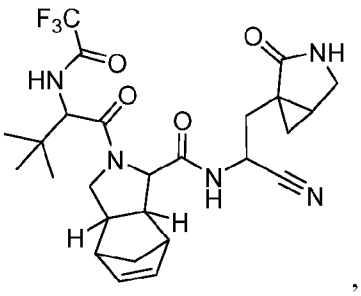
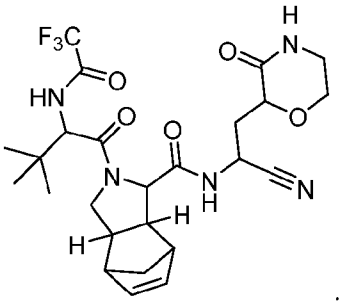
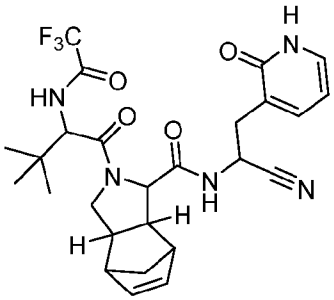
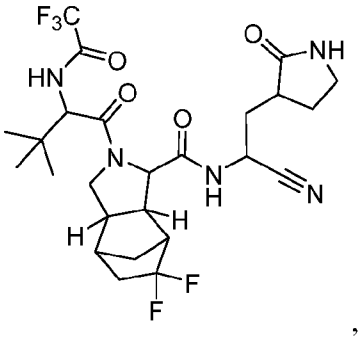

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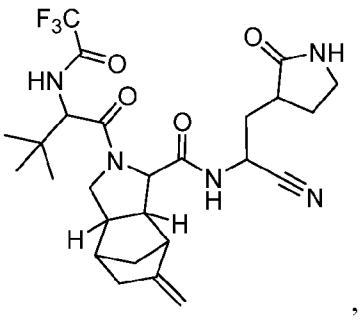
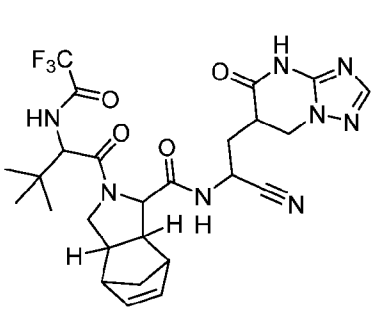
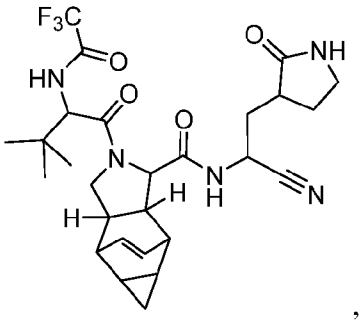
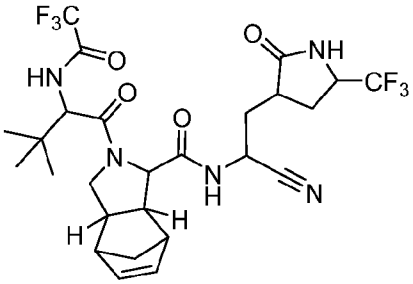
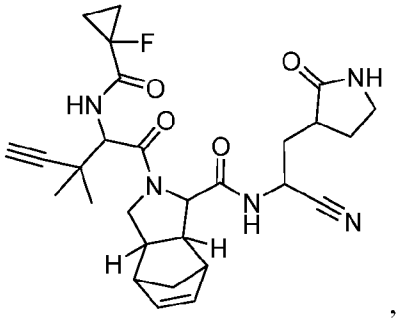
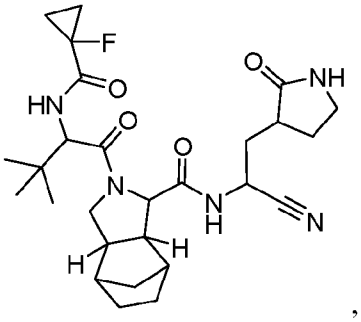
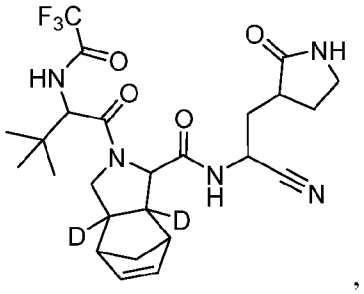
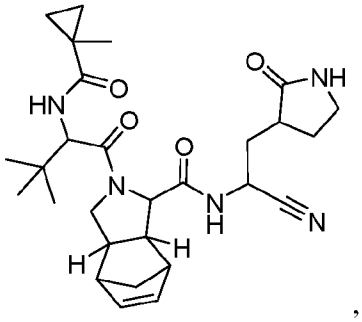
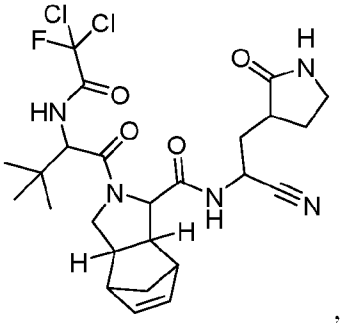
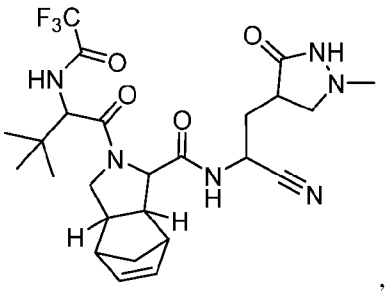
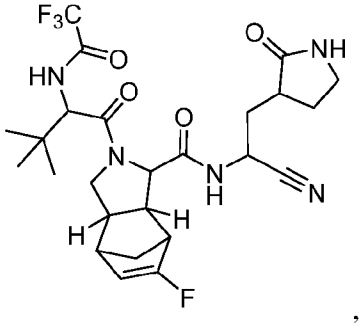

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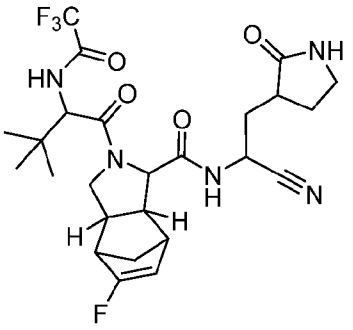
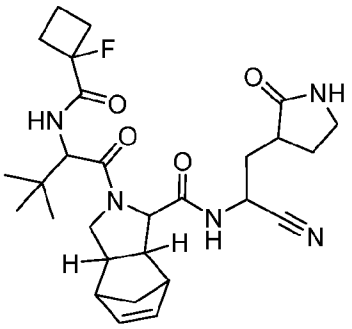
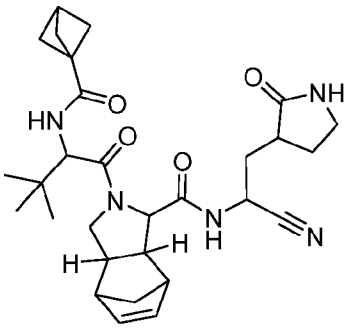
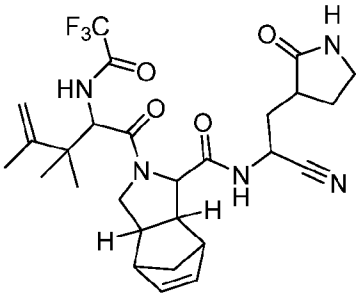
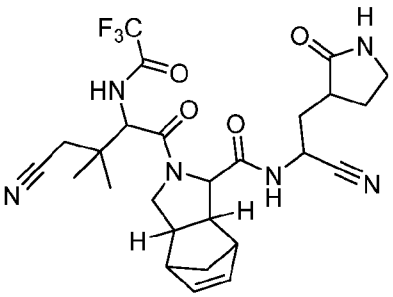
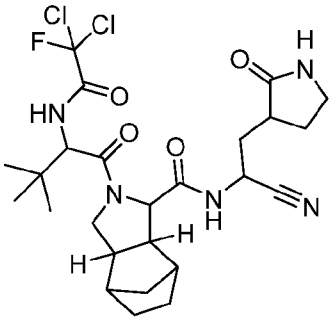
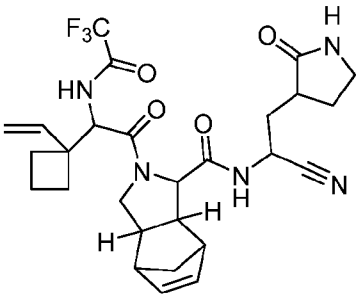
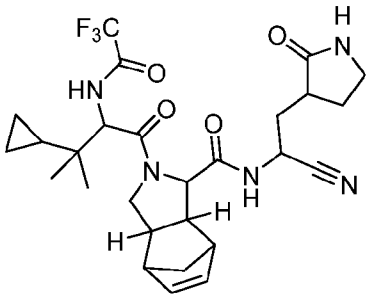
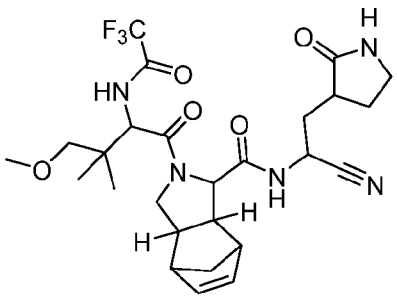
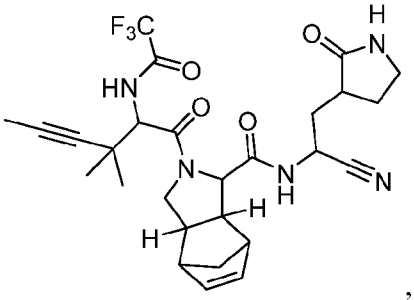
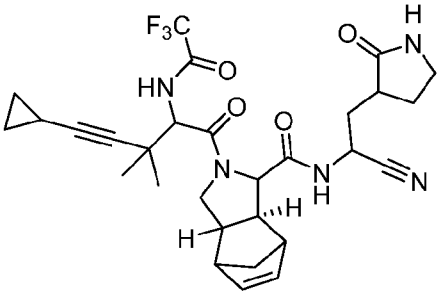
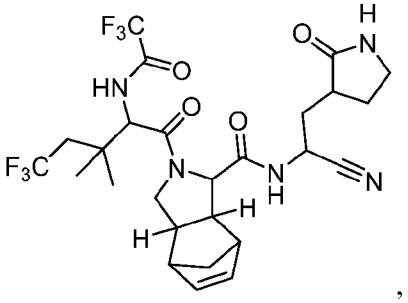
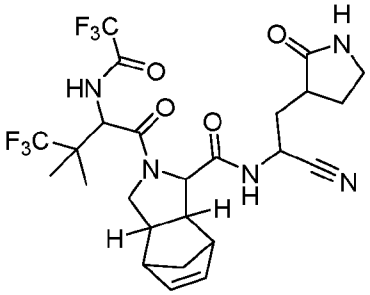
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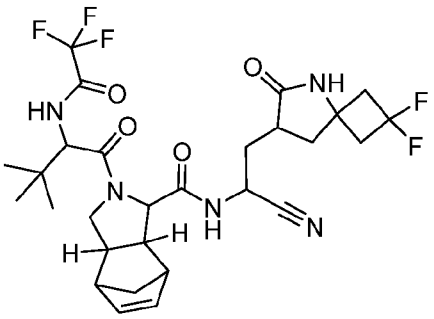
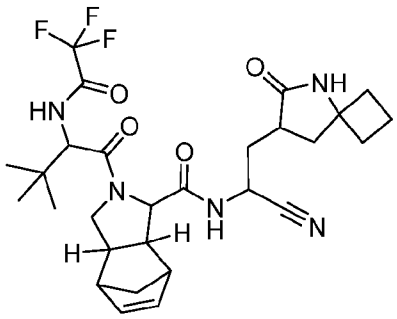
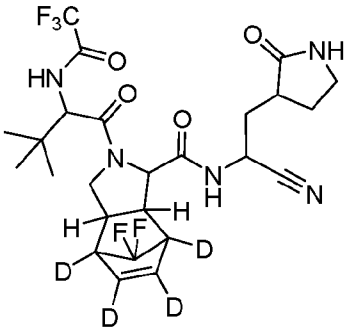
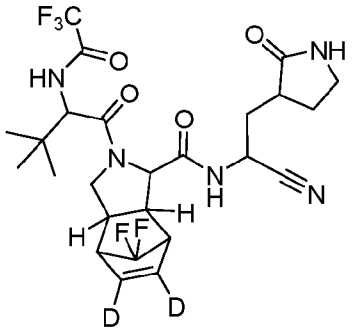
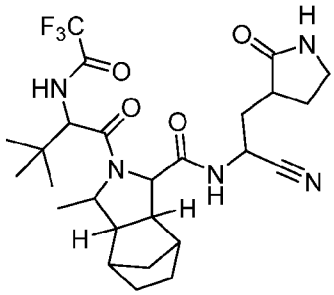
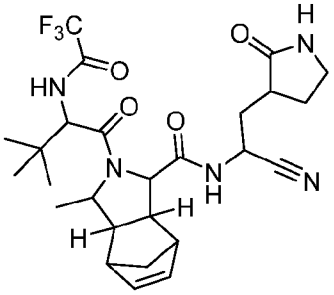
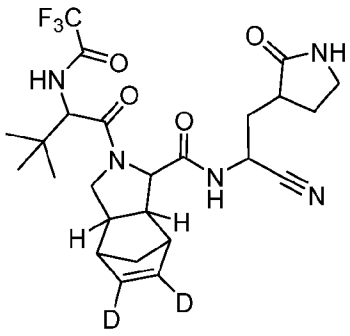
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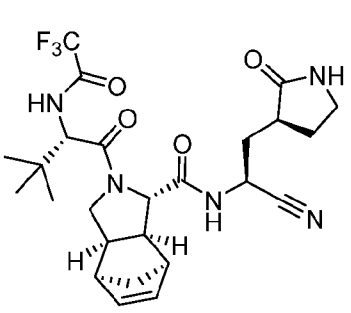
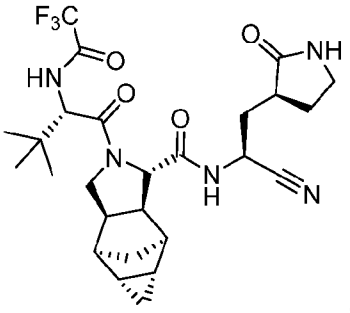
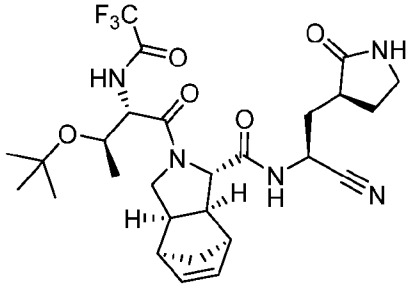

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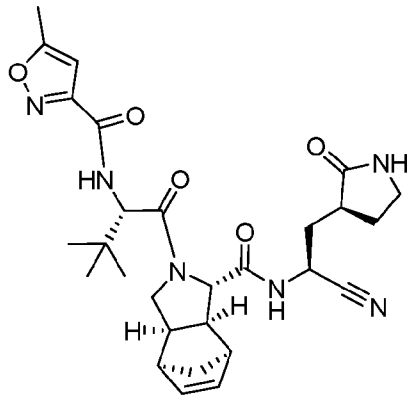
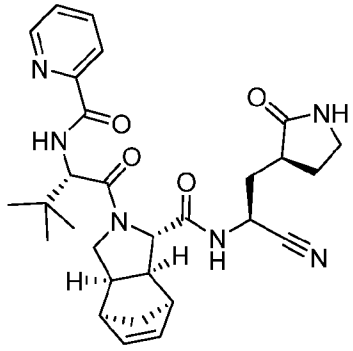
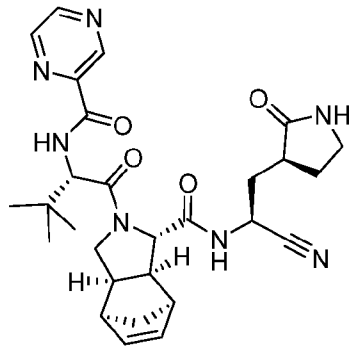
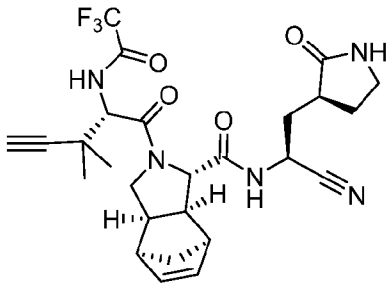
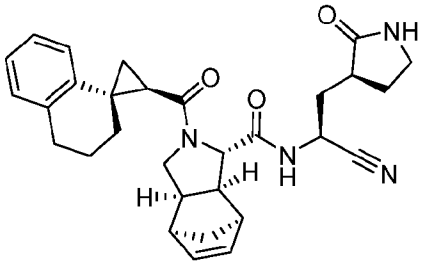
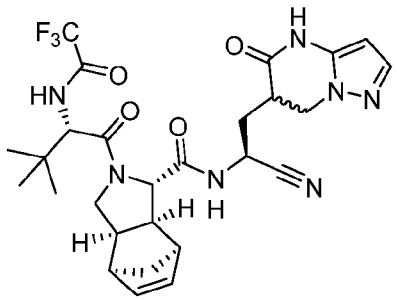
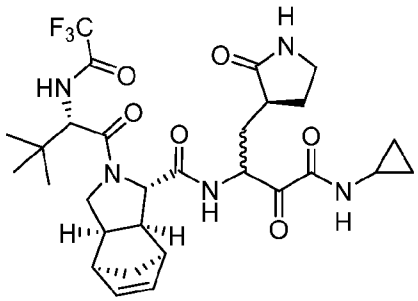
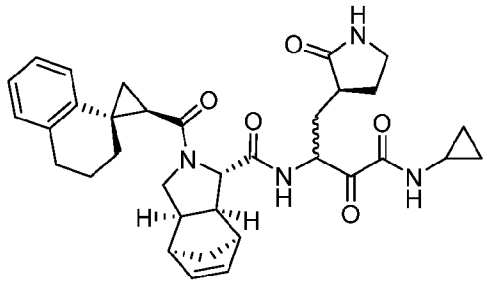
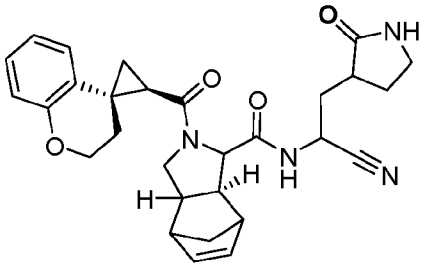
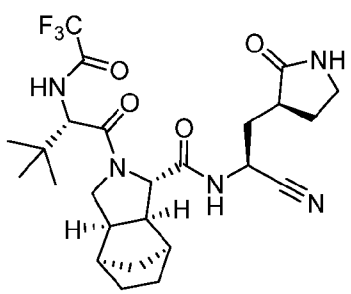
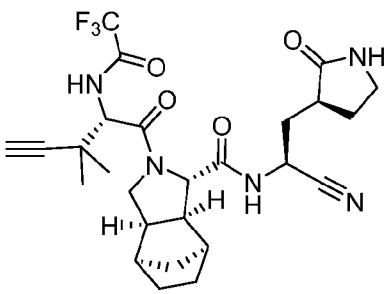
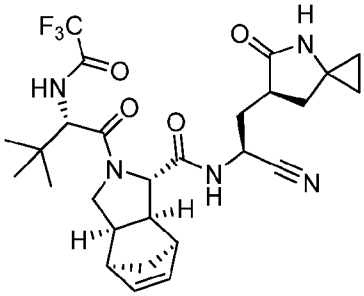

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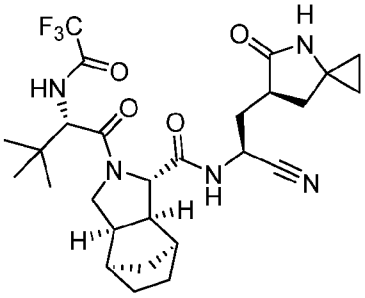
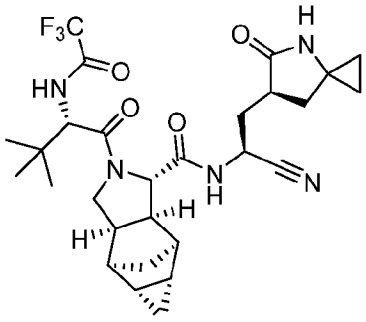
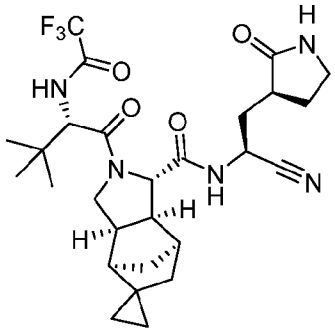
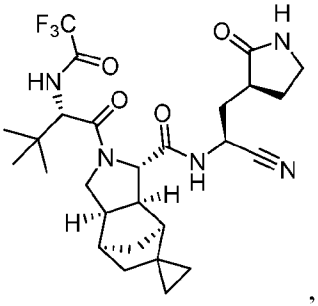
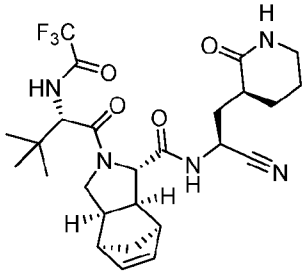
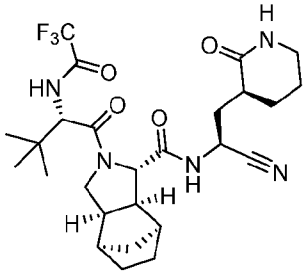
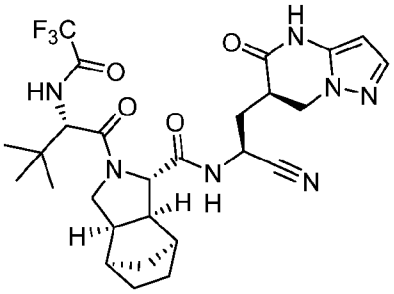
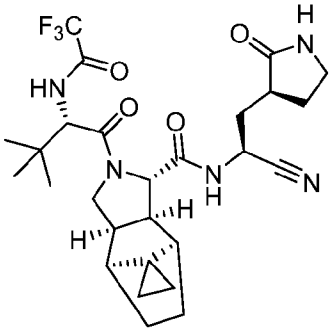
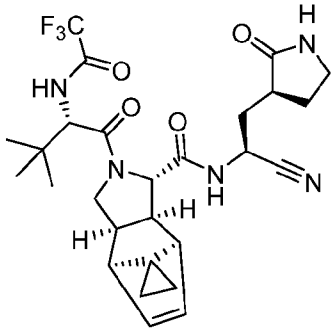
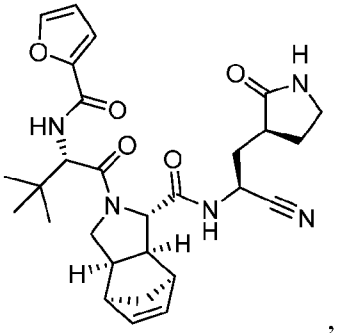
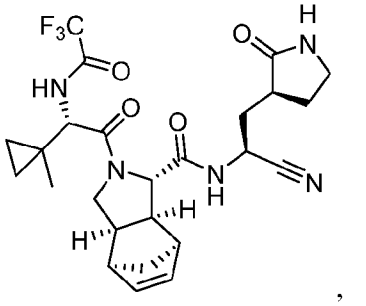
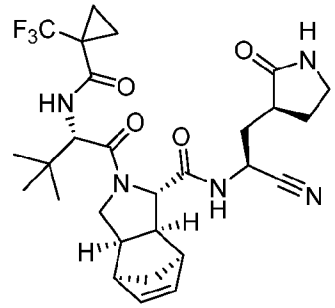

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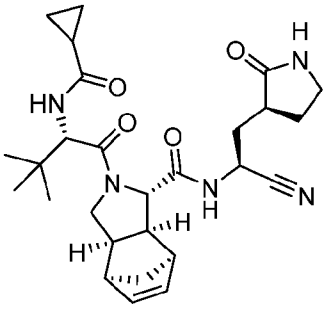
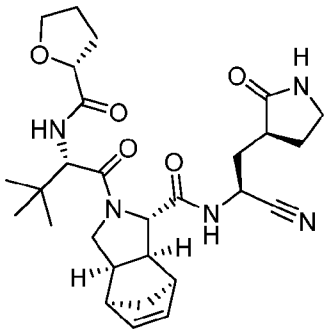
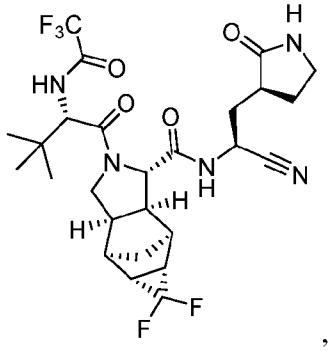
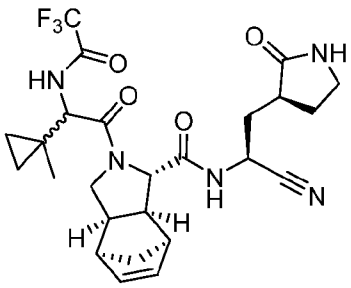
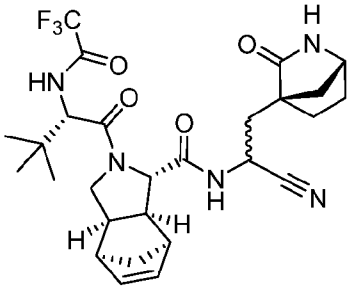
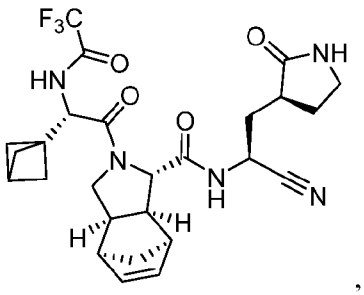
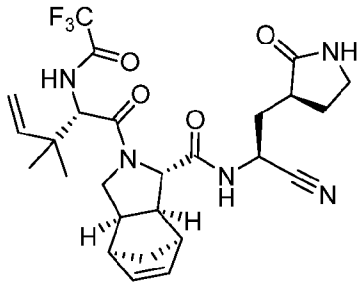
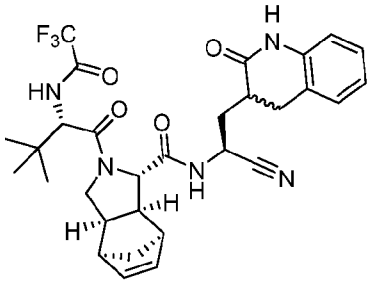
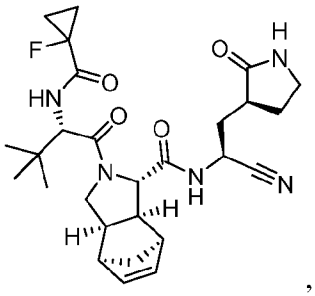
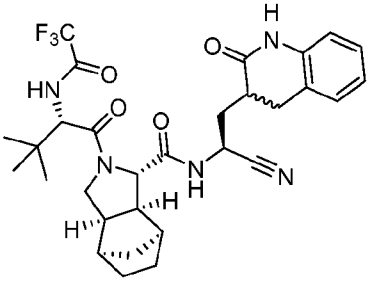
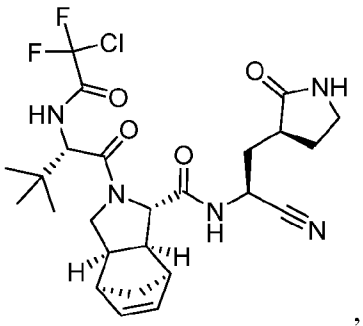
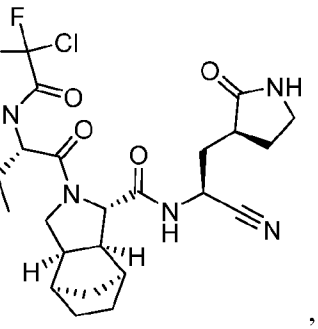

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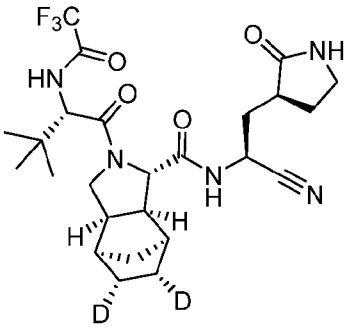
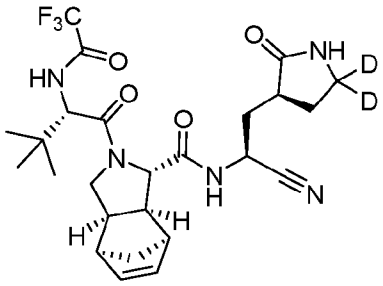
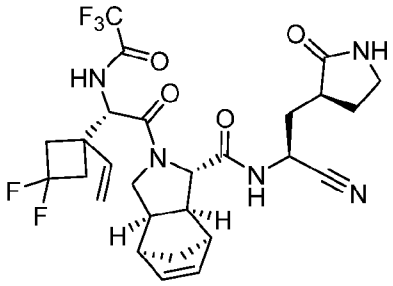
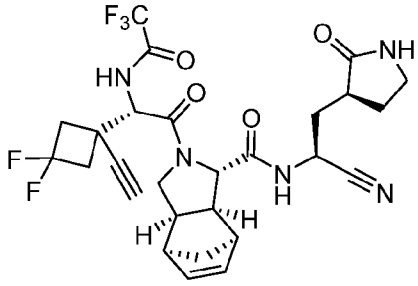
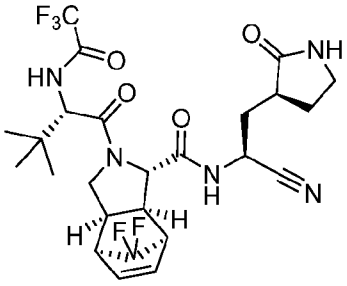
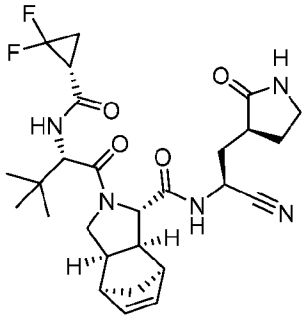
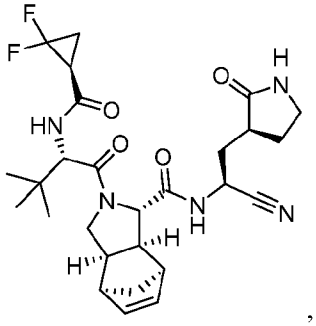
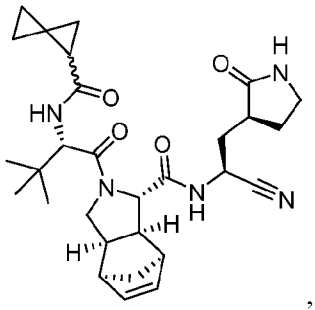
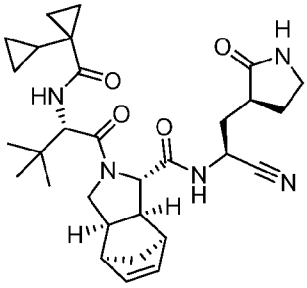
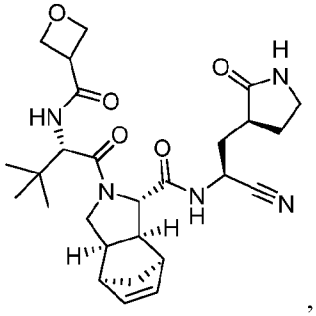
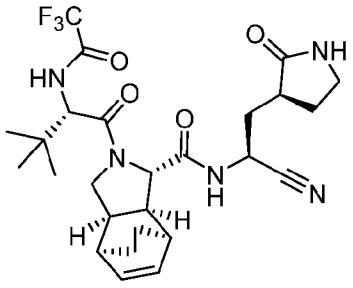
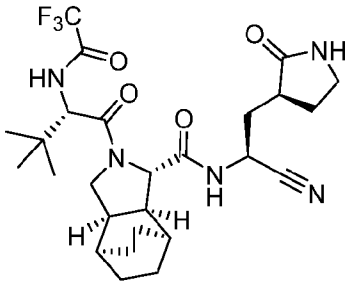
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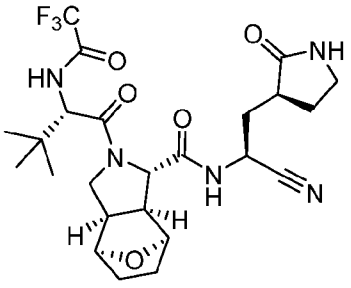
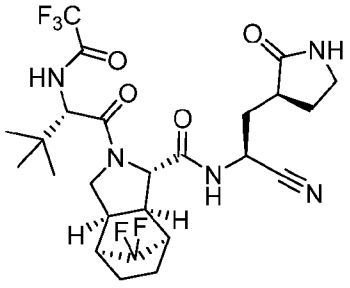
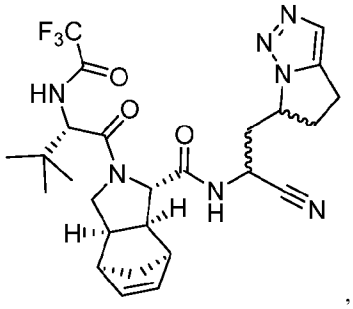
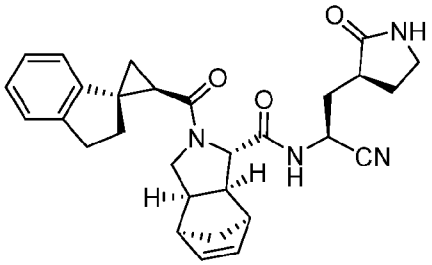
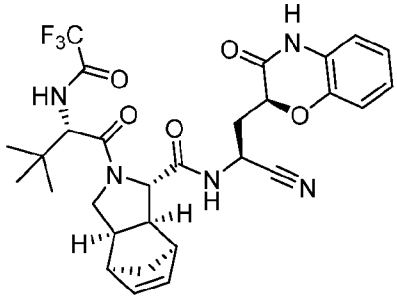
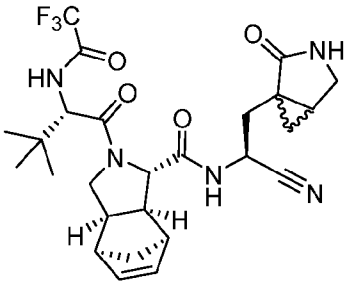
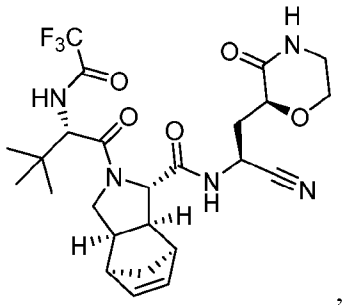
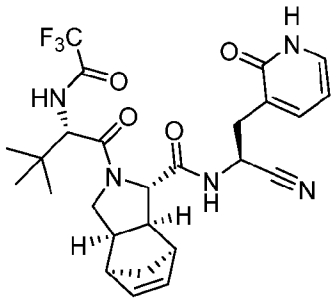
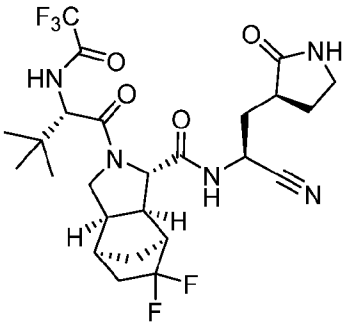
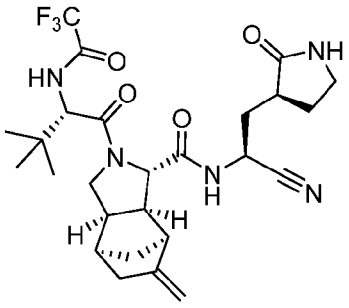
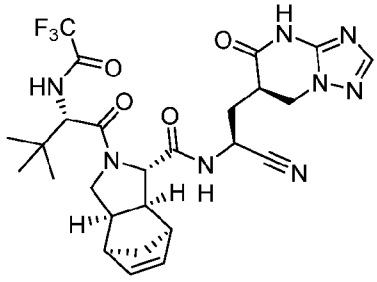
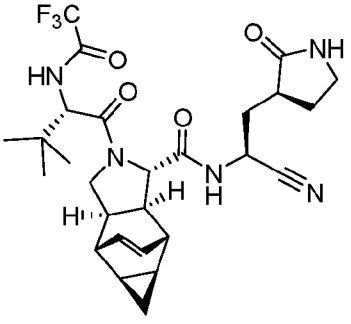
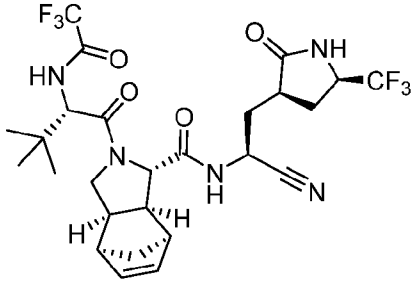

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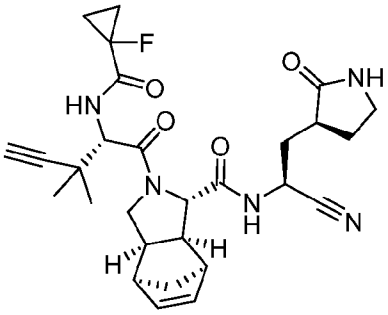
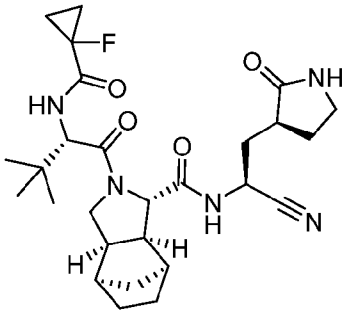
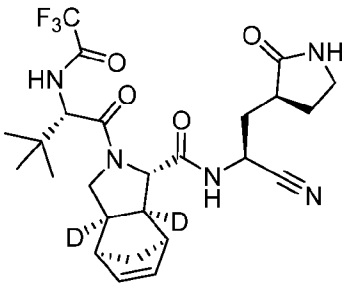
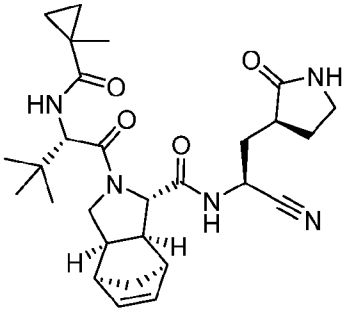
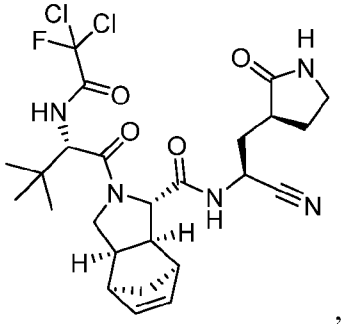
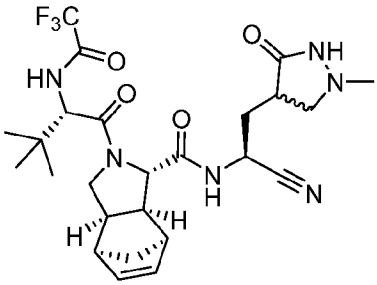
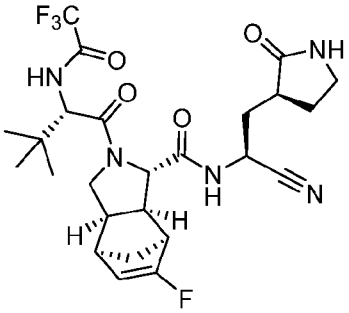
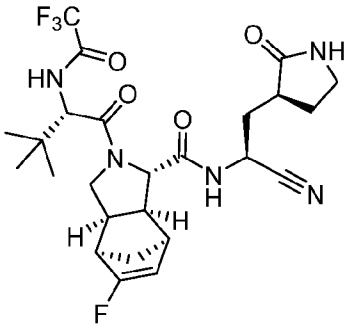
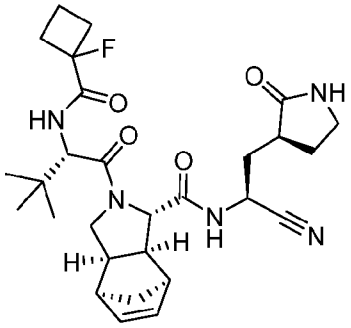
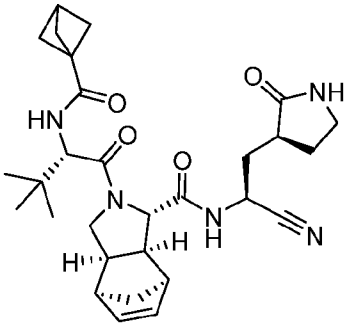
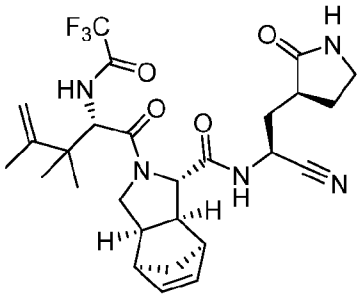
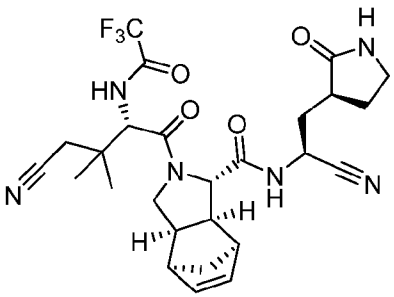

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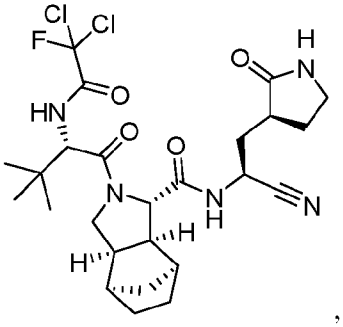
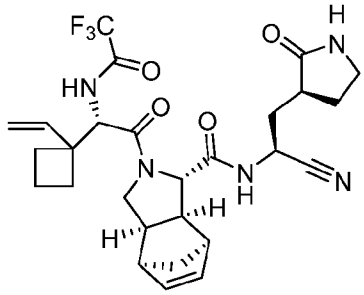
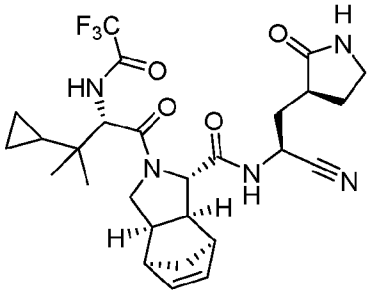
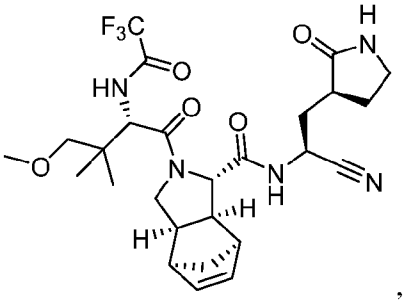
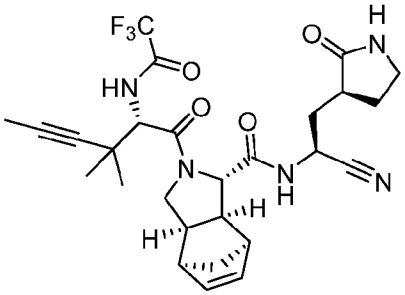
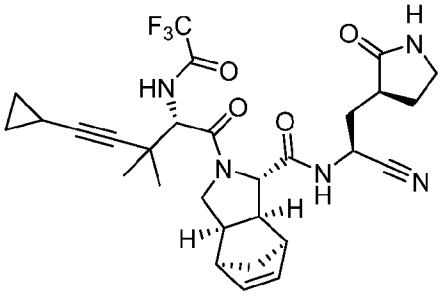
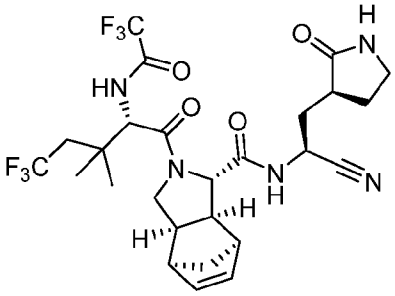
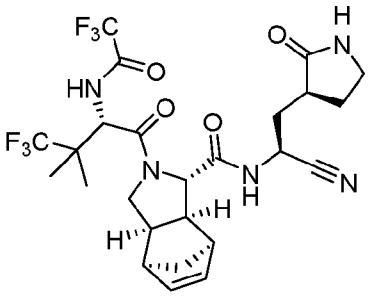
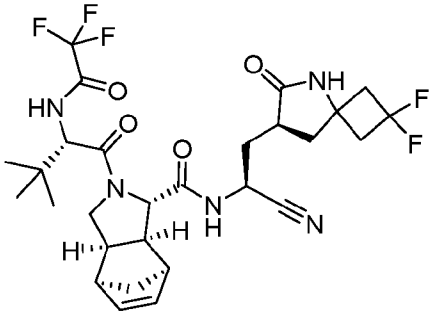

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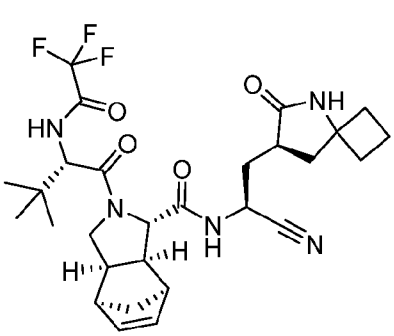
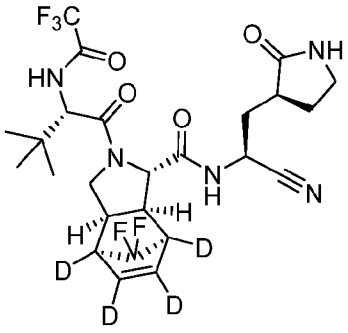
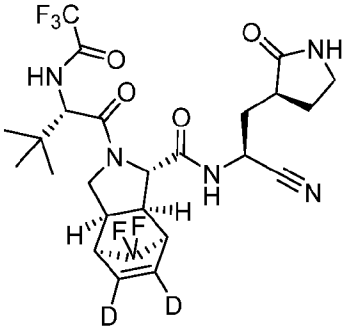
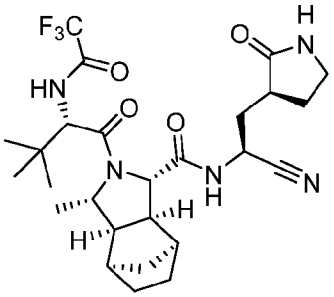
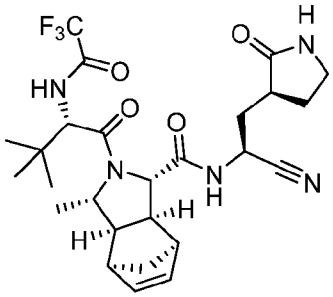
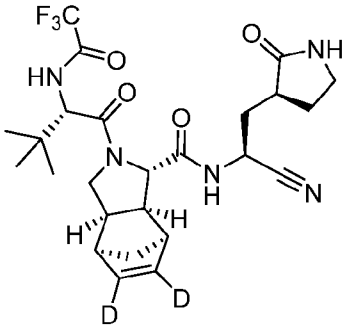

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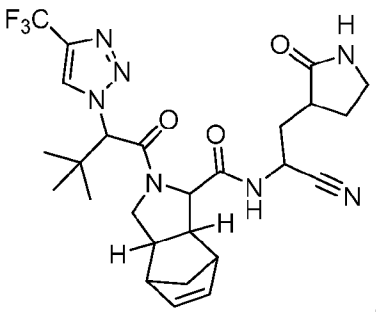
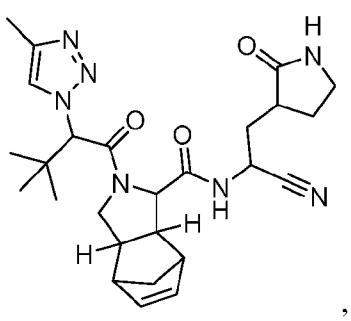
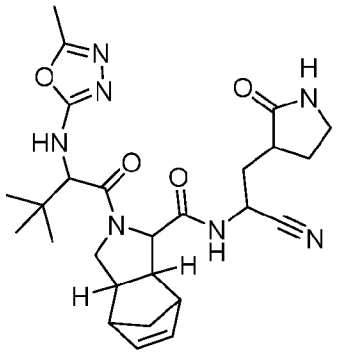
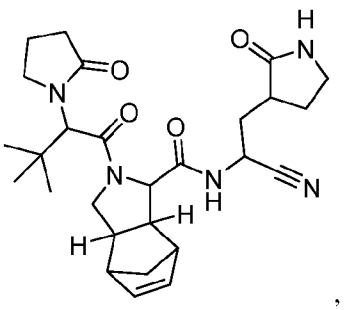
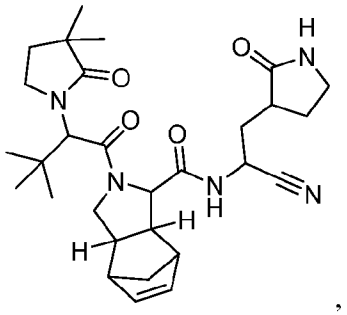
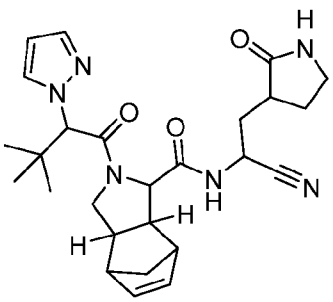

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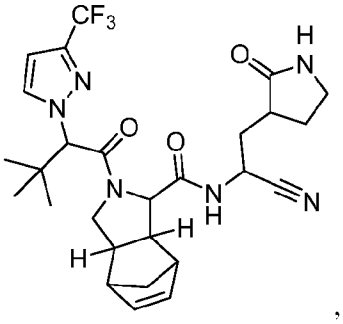
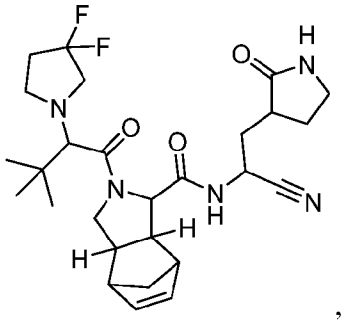
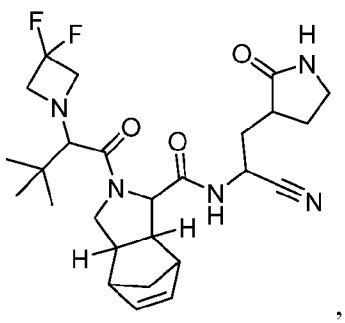
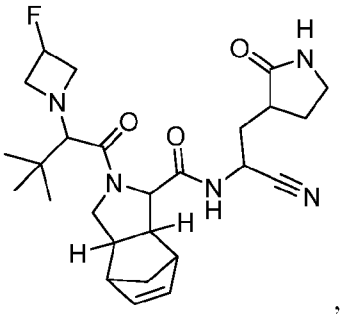
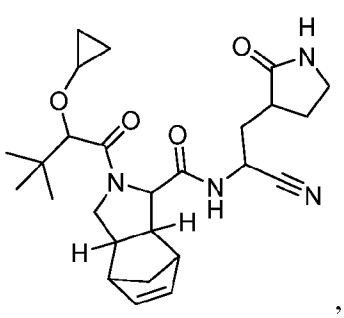
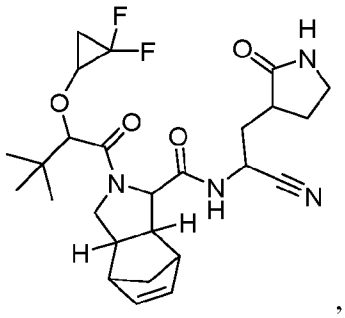
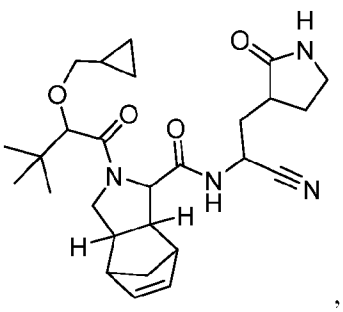
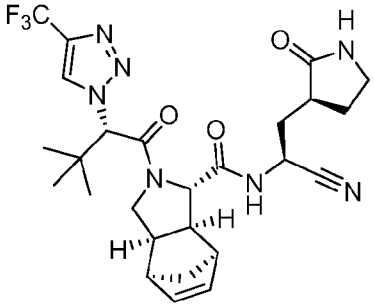
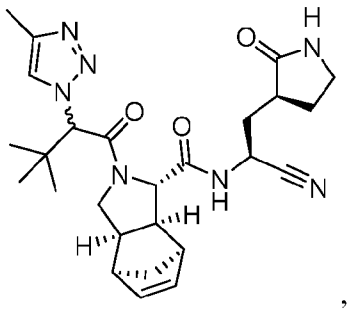
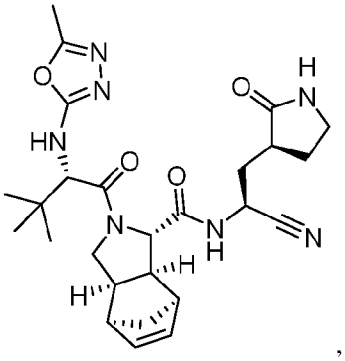
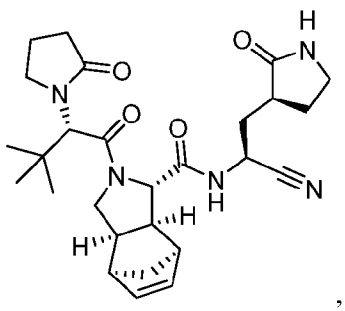
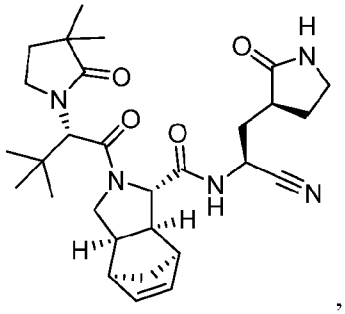

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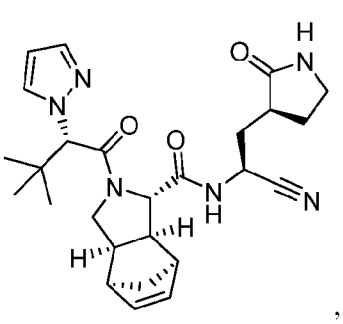
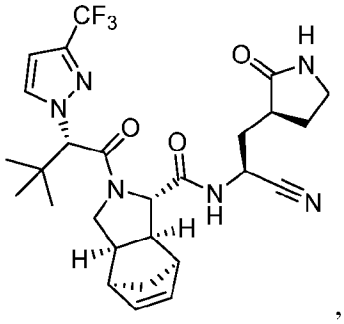
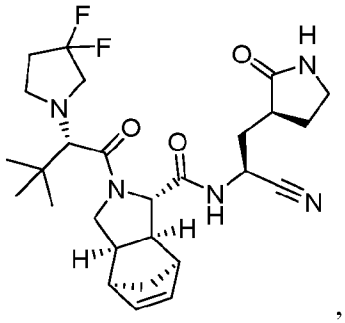
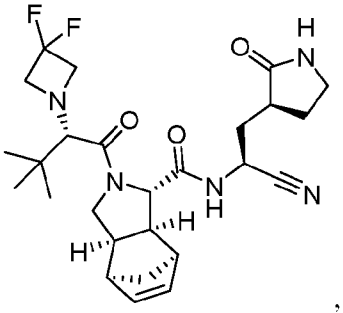
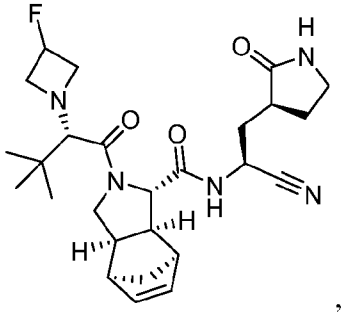
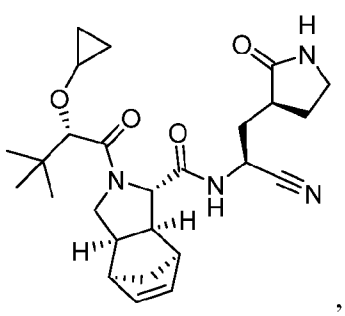
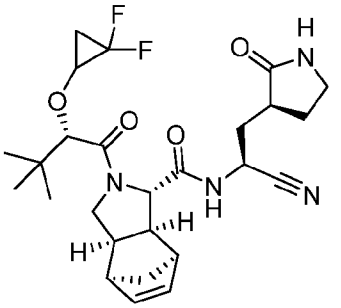
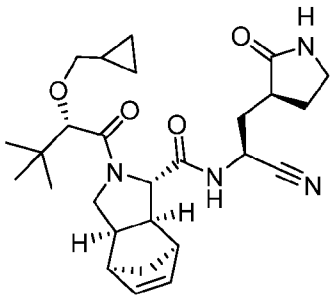

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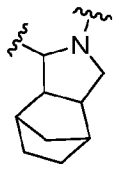
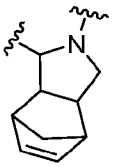

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, or a pharmaceutically acceptable salt of any of the foregoing.

[0105] Further examples of compounds of Formula (I), include the following:


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, or a pharmaceutically acceptable salt of any of the foregoing.

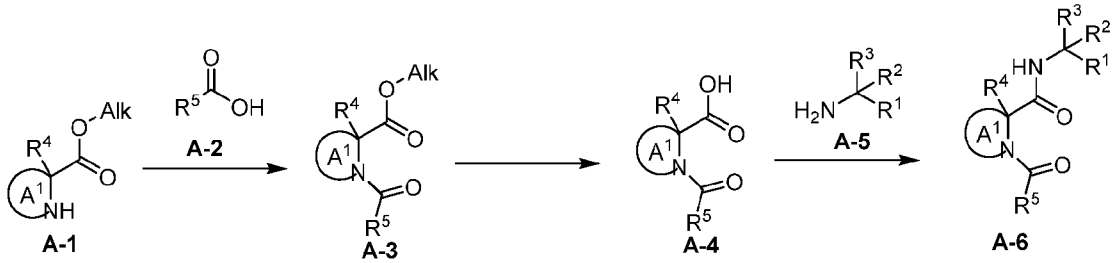
[0106] In some embodiments, Ring A^1 cannot be  . In some embodiments, Ring A^1 cannot be  .

Synthesis

[0107] Compounds of Formula (I) along with those described herein may be prepared in various ways. General synthetic routes for preparing compounds of Formula (I)

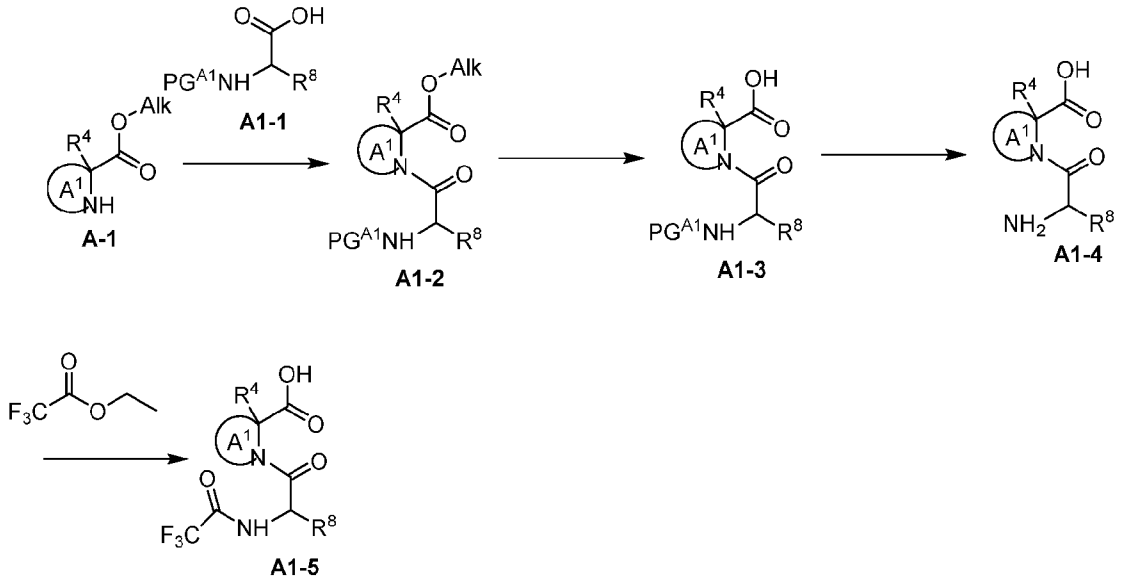
are shown and described herein along with some examples of starting materials used to synthesize compounds described herein. Additionally, for the purpose of the general synthetic routes, the structures depicted are appropriately protected, as known by one skilled in the art and the generic structures are meant to include these protecting groups. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

Scheme A



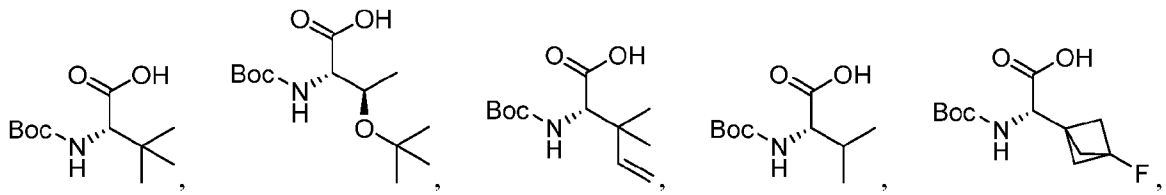
[0108] Scheme A describes the synthesis of compounds of general Formula (A-6). An amino ester of general Formula (A-1) (Alk represents alkyl) with an acid of general Formula (A-2), either by activating the carboxylic acid by converting it to an acid chloride, followed by reaction with the amino acid in the presence of a base, or by activation of the acid with a coupling reagent (such as HATU) followed by coupling with the amino ester in the presence of a base (such as DIPEA), resulting in a compound of general Formula (A-3). The ester functionality of general Formula (A-3) can be hydrolyzed, for example, under basic conditions of -OAlk is -OMe, using LiOH in MeOH, providing in a compound of general Formula (A-4). Further coupling of the carboxylic acid of general Formula (A-4) with an amine of general Formula (A-5) can provide a compound of general Formula (A-6). For the purpose of the generic synthesis, R^1 may be a latent functionality, converted to a functionality as described herein for R^1.

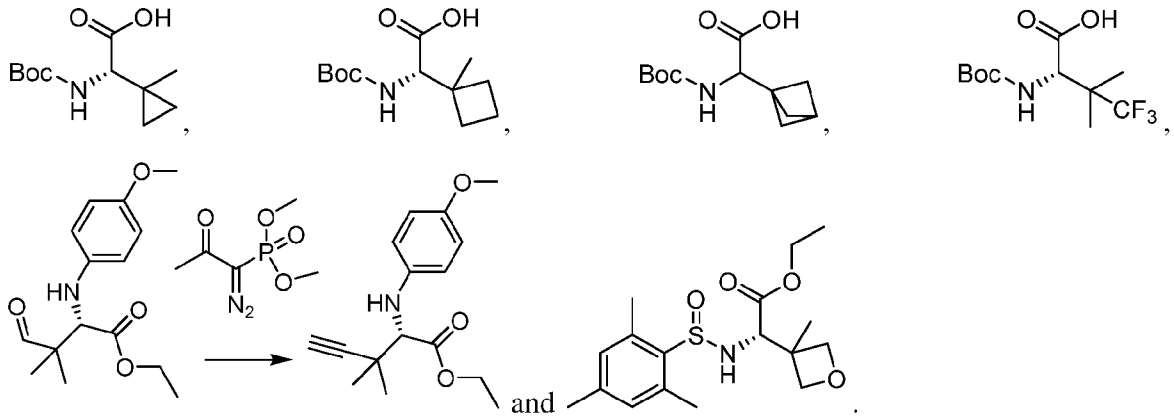
Scheme A1



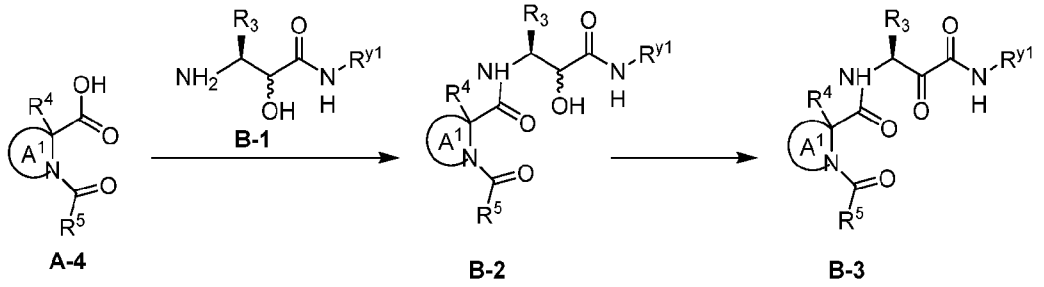
[0109] Alternatively, as described in Scheme A1, a sub-group of amino acids of general Formula (A1-5) can be prepared as described in Scheme A1. A protected (PG^{A1}) amino acid of general Formula (A1-1) can be coupled with an aminoester of general Formula (A-1) under known amide formation conditions, for example, HATU and iPr_2NEt. The ester of a compound of Formula (A1-2) can be deprotected, for example, by using LiOH in THF/H_2O, resulting in the acid of general Formula (A1-3). The protecting group PG^{A1} can be removed, for example, by treatment with TFA in case PG^{A1} being Boc, resulting in a compound of general Formula (A1-4). This compound can be converted to a compound of general Formula (A1-5), for example, by treatment with trifluoroethyl acetate in the presence of triethylamine.

[0110] General methodology for the synthesis of amino acids of general Formula (A1-1), or precursors that could be converted to an amino acid of general Formula (A1-1) by one skilled in the art, are described in the literature, and include the following examples:



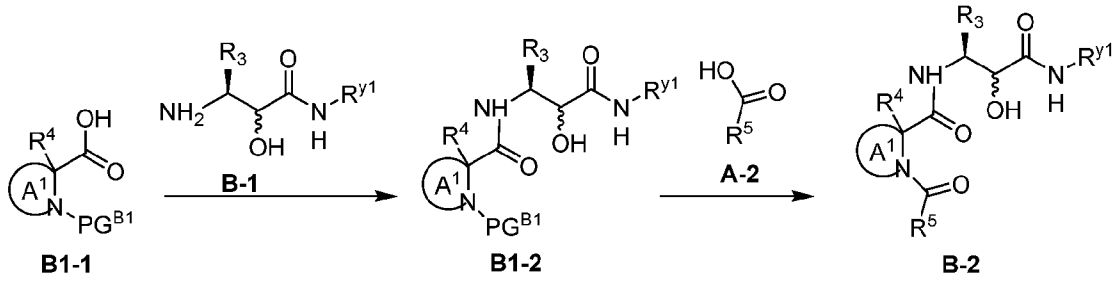


Scheme B



[0111] In Scheme B, a carboxylic acid of general Formula (A-4) can be coupled with an amino acid of general Formula (B-1), for example, under the influence of a coupling reagent (such as T3P) and a base (for example, DIPEA). The obtained compound of general Formula (B-2) can be oxidized, providing in a compound of general Formula (B-3). In Scheme B, R^{y1} can be part of the ketoamide described herein with respect to R^1.

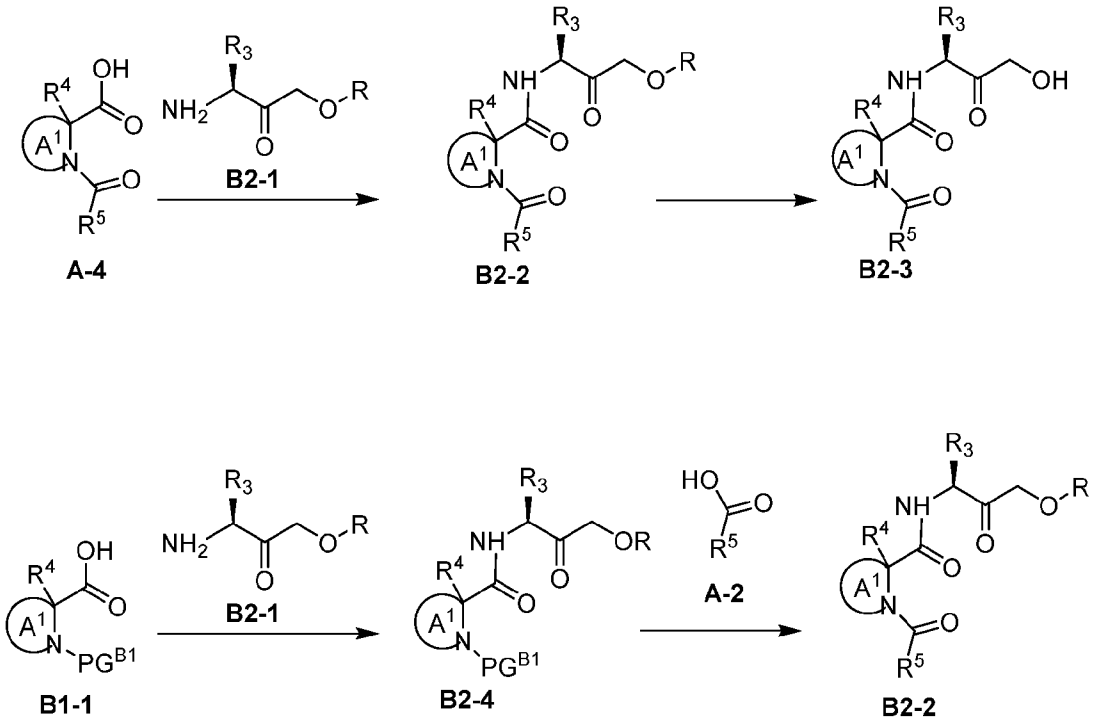
Scheme B1



[0112] Alternatively, as depicted in Scheme B1, an amino acid of general Formula (B1-1) (with PG^{B1} a protecting group of the nitrogen, for example, -Boc) can be coupled with a compound of general Formula (B-1), similar as described for the conversion

of a compound of general Formula (A-4) to a compound of general Formula (B-2). The protecting group can be removed, for example, by treatment with an acid in case of PG^{B1} being Boc, followed by coupling with a compound of general Formula (A-2), resulting in the formation of a compound of general formula (B-2).

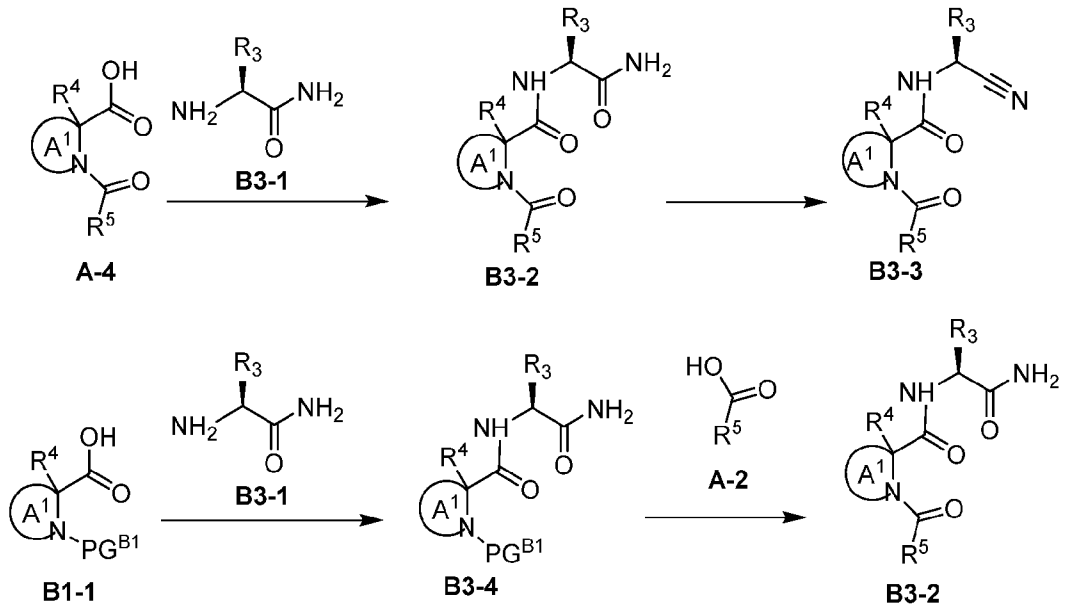
Scheme B2



[0113] As described herein, R^1 can be a substituted acyl, where the possible groups that can be present on the acyl include hydroxy, a substituted or an unsubstituted alkoxy (for example, –O–(an unsubstituted C_{1-4} alkyl) and –O–(an unsubstituted C_{3-6} cycloalkyl)), an unsubstituted C_{1-4} alkyl (such as a heteroaryl substituted with an unsubstituted C_{1-4} alkyl), a substituted or an unsubstituted phenoxy or a substituted or an unsubstituted benzyloxy). In Scheme B2, R can represent any of the aforementioned moieties that can be present on a substituted acyl for R^1. Compounds of general Formulae (B2-2) and (B2-3) can be prepared as described in Scheme B2. An amino-ketone compound of general Formula (B2-1) can be coupled to a carboxylic acid of general Formula (A-4) or (B1-1) under typical amide coupling conditions. A compound of general Formula (B2-2) can be optionally further converted in a hydroxyketone of general Formula (B2-3), for example,

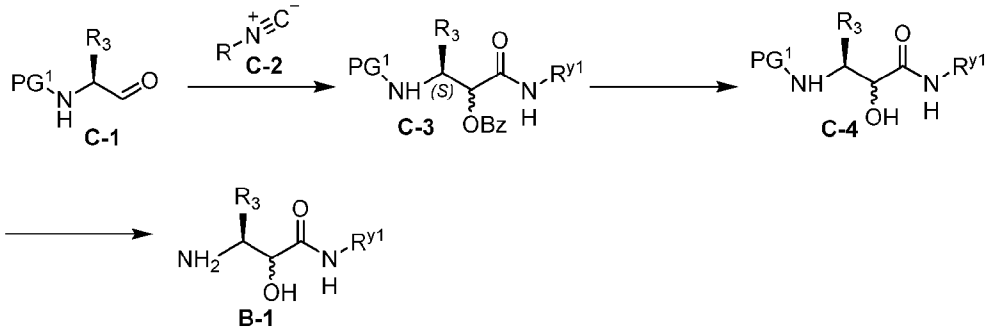
in case where R represents a benzyl group, by catalytic hydrogenolysis. The PG^{B1} of a compound of general Formula (B2-4) can be deprotected (for example in the case wherein PG^{B1} is a Boc-group, by treatment with HCl in Et_2O). The amine can then be coupled with a carboxylic acid of general Formula (A-2) under typical amide bound formation conditions, to provide a compound of general Formula (B2-2).

Scheme B3



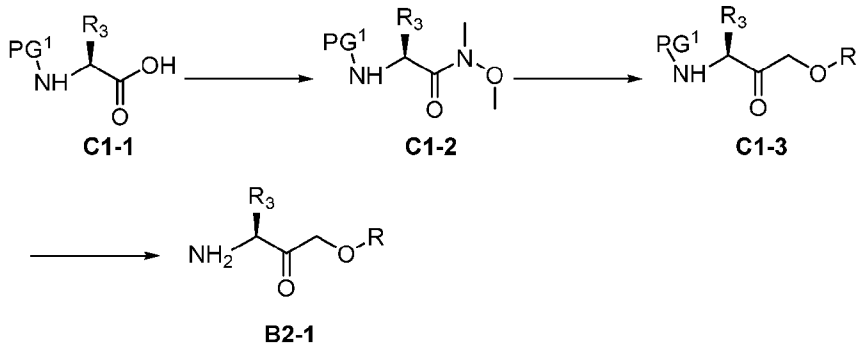
[0114] Similar as described in Scheme B2 for a compound of Formula (B2-2), using an amide of general Formula (B3-1) in place of a compound of general Formula (B2-1). a compound of general Formula (B3-2) can be obtained. Conversion of a compound of general Formula (B3-2) to a compound of general Formula B3-3 can, for example, occur under the influence of trifluoroacetic anhydride (TFAA) and pyridine in CH_2Cl_2, or by application of the Burgess reagent.

Scheme C



[0115] A compound of general Formula (B-1) can be prepared as outlined in Scheme C. An aldehyde of general Formula (C-1) (PG^1 can be a nitrogen protecting group, for example -Boc) and an isonitrile of general Formula (C-2), in the presence of a carboxylic acid (for example, benzoic acid), can be condensed in a Passerini-like reaction towards a compound of general Formula (C-3). After hydrolysis, a compound of general Formula (C-4) can be obtained. The PG^1 can be removed, for example, by treatment with HCl when PG^1 can be Boc.

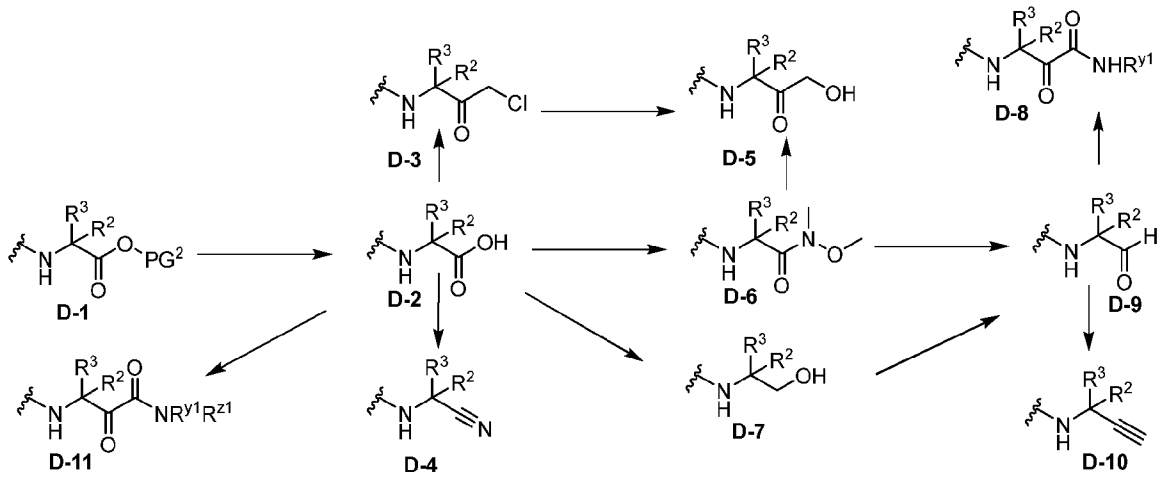
Scheme C1



[0116] An amino ketone of general Formula (B2-1), can be prepared as outline in Scheme C1. A protected amino acid of general Formula (C1-1) can be converted to its corresponding Weinreb amide under typical amide coupling conditions. Addition of an organometallic reagent to the Weinreb amide, followed by work-up, can result in a ketone of general Formula (C1-3). An example, wherein R can be benzyl, is the formation of an organometallic reagent by mixing Mg, $HgCl_2$ and benzylchloromethyl ether, followed by addition to a Weinreb amide of general Formula (C1-2), followed by work-up with saturated ammonium chloride. The protecting group (PG^1) can be removed (for example, when PG^1 is

Boc, the protecting group can be removed using HCl) resulting in the formation of an amino ketone of general Formula (B2-1). When HCl is used for the deprotection, a compound of general Formula (B2-1) can be obtained as a HCl salt. Examples of a compound of general Formula (C1-1) are (S)-2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopiperidin-3-yl)propanoic acid and (S)-2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoic acid.

Scheme D1

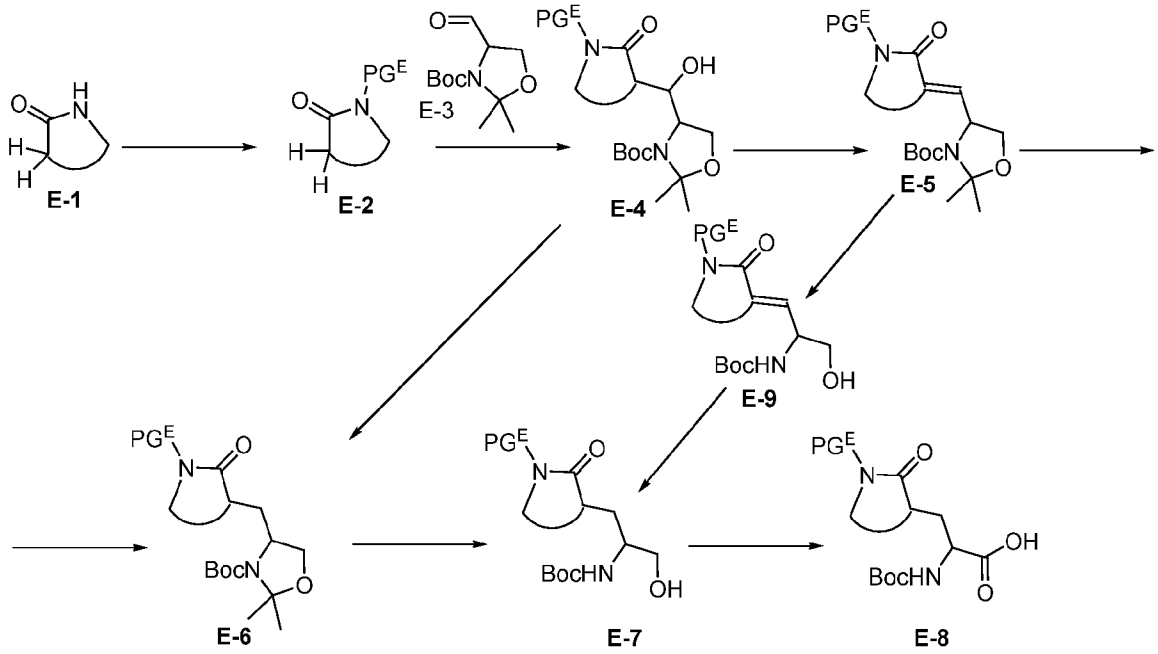


Scheme D2



[0117] Other conversions for R^1 described herein are shown in Schemes D1 and D2. In Schemes D1 and D2, PG^2 represents an appropriate protecting group, and R^{z1} and R^{y1} are part of the ketoamide described herein with respect to R^1.

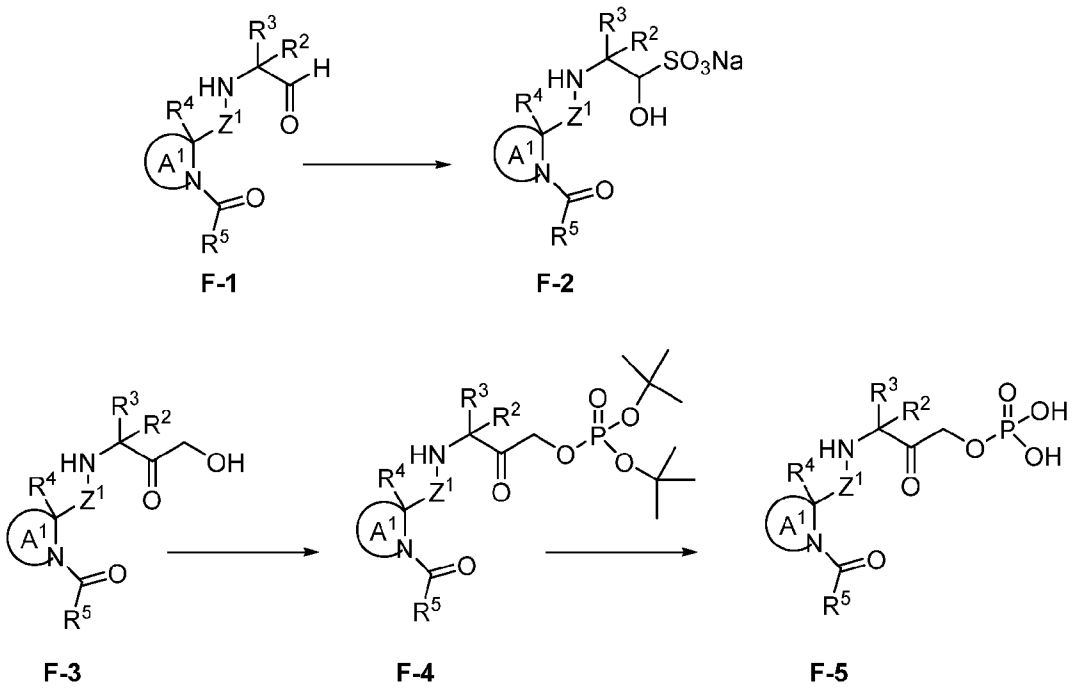
Scheme E



[0118] A method for preparing a sub-group of amino acids of general Formula (E-8) are provided in Scheme E. A lactam of general Formula (E-1) can be protected with a suitable protecting group, PG^E. An example of such a PG^E group is a Boc-group. For the purpose of the Scheme E, this protecting group can be removed at any relevant stage; and therefore, PG^E present hydrogen for any of compounds of general Formulae (E-4), (E-5), (E-6), (E-7), (E-8) and (E-9). The lactam of general Formula (E-2) can be reacted with an aldehyde of general Formula (E-3) (S or R-garner's aldehyde). The alcohol of general Formula (E-4) can be eliminated to provide an alkene compound of general Formula (E-5) (for example, by sequential conversion of the hydroxy to a corresponding mesylate, followed by elimination under basic conditions). The double bond can be reduced (for example, by hydrogenation, under influence of a homogeneous or a heterogenous catalyst, optionally diastereoselective) to provide a compound of general Formula (E-6). Removal of the acetonide in a compound of general Formula (E-6) to the Boc-protected amino alcohol of general Formula (E-7) can be followed by the oxidation to the carboxylic acid of general Formula (E-8). Alternatively, the acetonide can be deprotected in a compound of general Formula (E-5) to obtain a compound of general Formula (E-9). Reduction of the double bond of a compound of general Formula (E-9) (for example, by hydrogenation under

influence of a homogeneous or a heterogenous catalyst, optionally diastereoselective) can be used to obtain a compound of general Formula (E-7). A compound of general Formula (E-4) can be deoxygenated, for example, by a Barton-type deoxygenation, to provide a compound of general Formula (E-6).

Scheme F

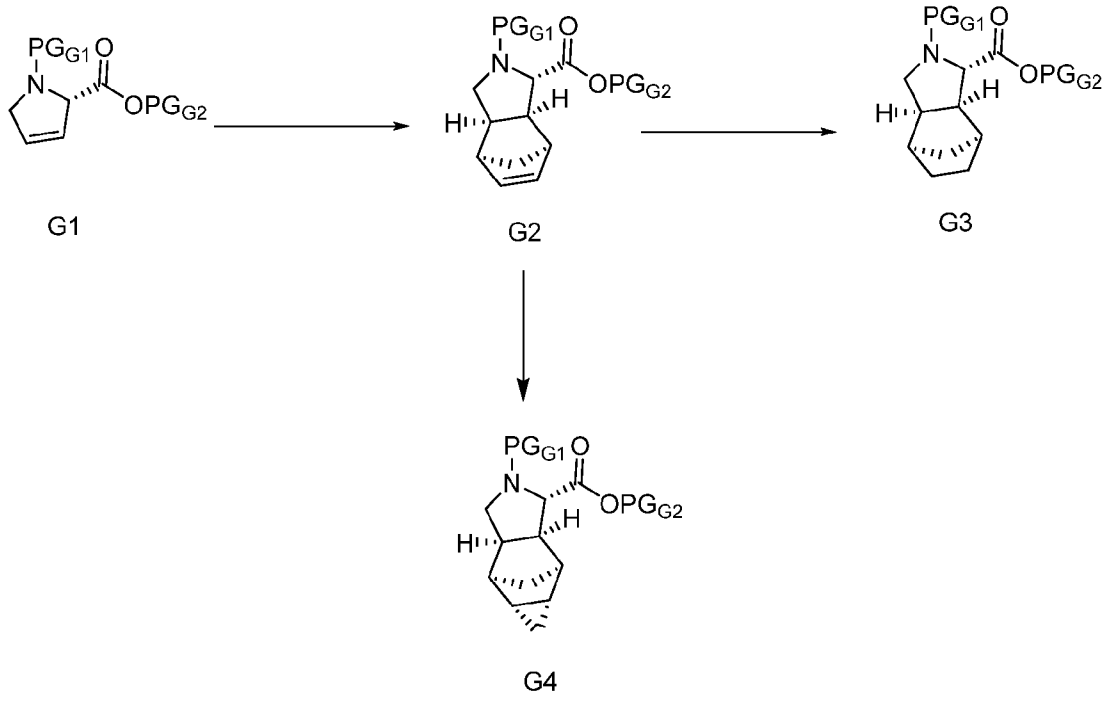


[0119] Compounds of Formula (I) can include a prodrug moieties. A method for including a prodrug moiety is depicted in Scheme F. For example an aldehyde of general Formula (F-1) can be transformed into the corresponding bisulfite adduct of general Formula (F-2), by treatment with $NaHSO_3$. A hydroxyketone of general Formula (F-3), can be transformed to the corresponding phosphate of general Formula (F-5), for example, by treatment with di-tert-butyl N,N-dipropan-2-ylphosphoramidite and tetrazole followed by oxidation with H_2O_2, that can provide a compound of general Formula (F-4). A compound of general Formula (F-4) can be deprotected (for example by treatment with TFA) to provide a compound of general Formula (F-5).

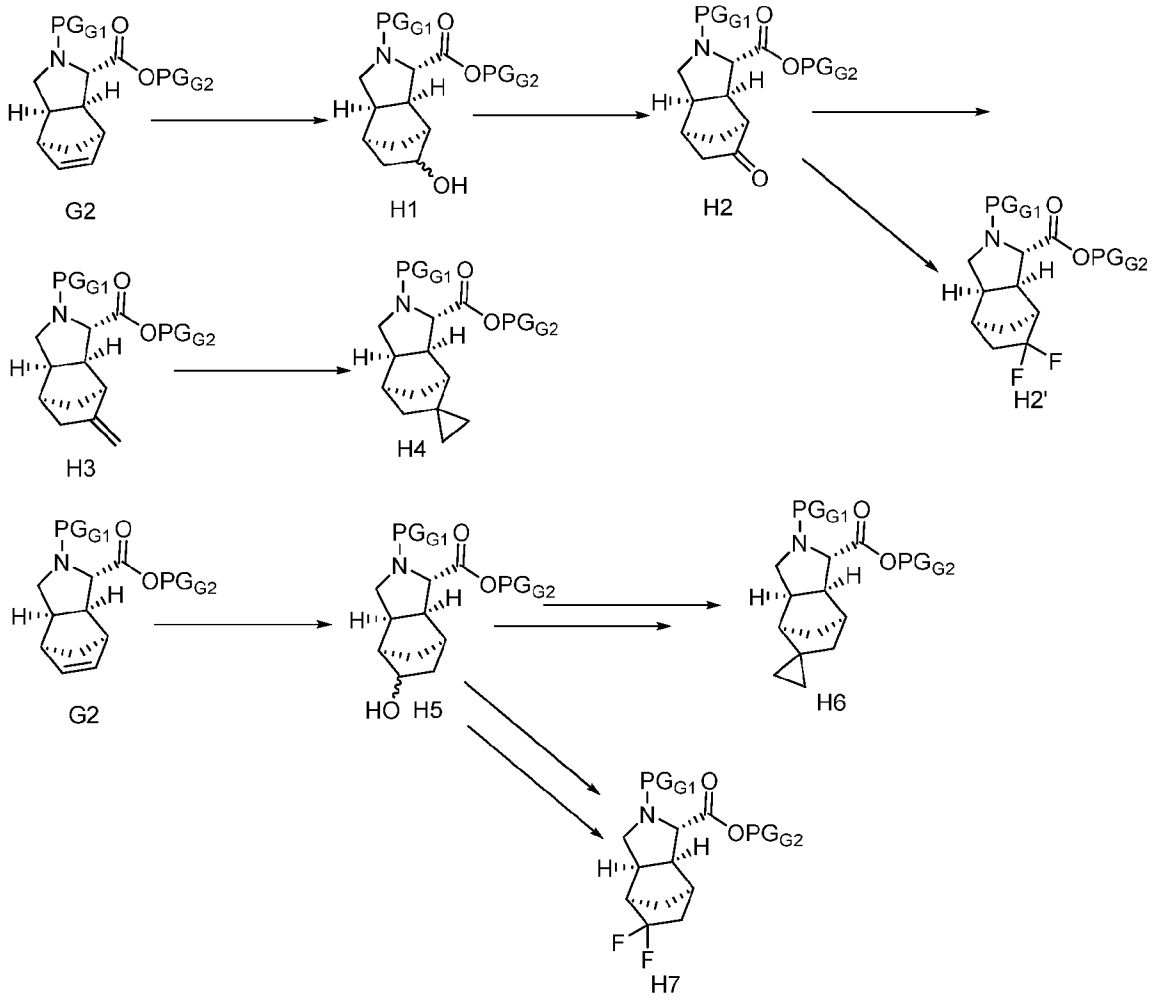
[0120] As shown in Scheme G, the synthesis of an amino ester of general Formula (G2) can be accomplished via a Diels-Alder reaction, such as described in Arakawa et al., Chemical & Pharmaceutical Bulletin (2003) 51(8), 1015-1020 (–PG_{G1} can be –Bz and

–PG_{G2} can be –CH_3). Also described herein in the synthesis of intermediates, is the use of –PG_{G1} is –Boc and –PG_{G2} is –t-Butyl or Me. A compound of general Formula (G2) can be deprotected using methods known to those skilled in the art and depending on the protecting group used for PG_{G1} and PG_{G2}. Alternatively, a compound of general Formula (G2) can be converted to a compound of general Formula (G3), by hydrogenation of the double bond, or to a compound of general Formula (G4), by cyclopropanation of the double bond. The cyclopropanation can, for example, be performed by application of a Simmons-smith cyclopropanation, by treatment with CH_2N_2 in the presence of $Pd(OAc)_2$, or other methods described known to those skilled in the art. Alternatively, deuterated intermediates can be used.

Scheme G



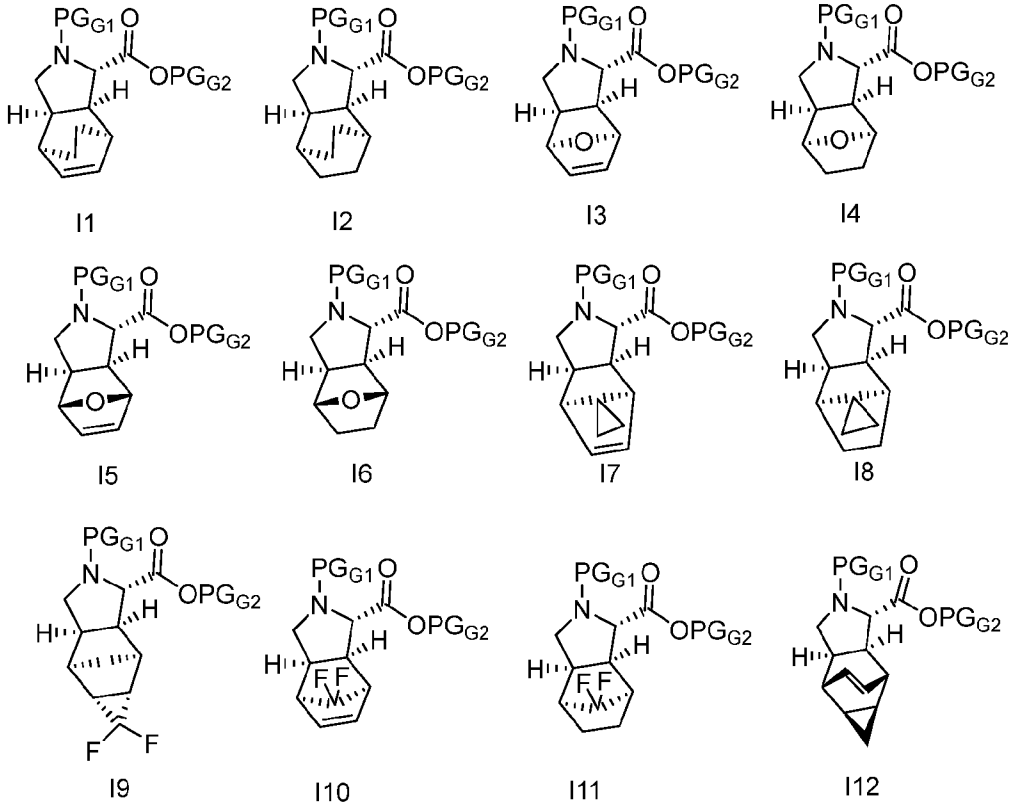
Scheme H



[0121] Other intermediates are described in Scheme H. The intermediate of general Formula (G2), can be selectively hydroxylated, for example, by hydrosilylation with trichlorosilane in the presence of a chiral Pd-catalyst, followed by $SiCl_3$/OH exchange (for example, Breuning et al, Beilstein Journal of Organic Chemistry (2009) 5(81):1-5). Oxidation of the alcohol of general Formula (H1) can provide a ketone of general Formula (H2). The ketone of general Formula (H2) can be converted to an alkene of general Formula (H3), for example, by using a Wittig or a Tebbe reagent. Transformation of the double bond towards the cyclopropyl can be done by treatment with CH_2N_2 in the presence of $Pd(OAc)_2$, or other methods described in the literature and known to those skilled in the art, and can result in a compound of general Formula (H4). A similar approach can be done with the isomer of a compound of general Formula (H1), a compound of general Formula (H5) can be

obtained by using an enantiomeric chiral Pd-catalyst. A compound of general Formula (H5) can then be converted to a compound of general Formula (H6), similar as outlined for the conversion of a compound of general Formula (H1) to a compound of general Formula (H4). Alternatively, the ketone of compound of general Formula (H2) can be converted to a compound of general Formula (H2') by fluorination, for example by application of a DAST reagent. The isomeric compound of general Formula (H7) can be obtained starting from a related isomer.

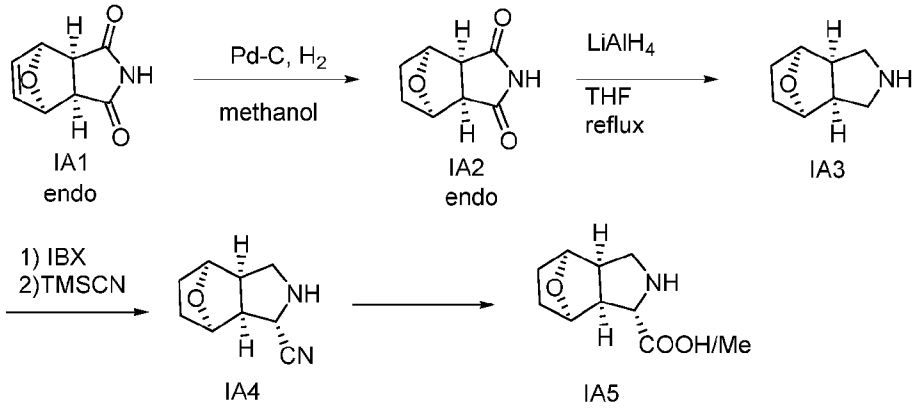
Scheme I



[0122] Other compounds of general Formulae (I1), (I2) (Johnson et al., Synthetic Communications (2011) 41(18):2769–2793), (I3), (I4), (I5), (I6), (I7), (I8), (I9), (I10), (I11) and (I12) as depicted in Scheme I can be obtained by methods described in literature (for example, de Graaff et al., Org. Biomol. Chem. (2015) 13:10108-10112; and Johnson et al., Synthetic Communications (2011) 41(18):2769-2793) and/or by applying methodologies as described herein. Compounds general Formulae (I1), (I2), (I3), (I4), (I5), (I6), (I7), (I8), (I9), (I10), (I11) and (I12) can be used to obtain compounds of Formula (I), along with

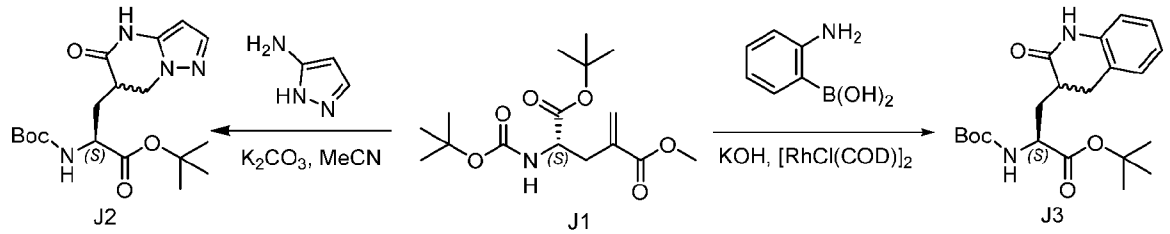
pharmaceutically acceptable salts, using similar methods as described herein.

Scheme IA



[0123] As an example, as depicted in Scheme IA, a compound of Formula (IA1) (Rulíšek et al., J. Org. Chem. (2005) 70(16):6295-6302) can be hydrogenated to a compound of Formula (IA2). After reduction of a compound of Formula (IA2), (for example, with $LiAlH_4$ (Johnson et al., Synthetic Communications (2011) 41(18):2769-2793), can result in a compound of Formula (IA3). A compound of Formula (IA3) can be oxidized using IBX (de Graaff et al., Org. Biomol. Chem. (2015) 13:10108-10112) followed by introduction of nitrile (Liu et al., Org. Process Res. Dev. (2016) 20(2):320-324) to provide a compound of Formula (IA4). The nitrile can next be converted to a carboxylic acid or ester of a compound of Formula (IA5). In the above scheme, racemic material can be obtained upon nitrile introduction from a compound of Formula (IA3) to a compound of Formula (IA4). Alternatively, achiral method can be used to provide enantioenriched compound(s).

Scheme J



[0124] An intermediate, a compound of Formula (J1) (Moody et al., J. Chem. Soc., Perkin Trans. 1 (1997) 23:3519-3530), can be used to prepare amino acids of general

Formulae (J2) and (J3) using similar procedures as described for Scheme H.

Pharmaceutical Compositions

[0125] Some embodiments described herein relate to a pharmaceutical composition, that can include an effective amount of a compound described herein (e.g., a compound, or a pharmaceutically acceptable salt thereof, as described herein) and a pharmaceutically acceptable carrier, excipient or combination thereof. A pharmaceutical composition described herein is suitable for human and/or veterinary applications.

[0126] As used herein, a "carrier" refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0127] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition that lacks pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the composition of human blood.

[0128] As used herein, an "excipient" refers to an inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. A "diluent" is a type of excipient.

[0129] Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, rectal, topical, aerosol, injection, inhalation and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0130] One may also administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into the infected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes may be targeted to and taken up selectively by the organ.

[0131] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. As described herein, compounds used in a pharmaceutical composition may be provided as salts with pharmaceutically compatible counterions.

Methods of Use

[0132] Some embodiments described herein relate to a method of treating a coronavirus infection that can include administering to a subject identified as suffering from the coronavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a coronavirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a coronavirus infection.

[0133] Some embodiments disclosed herein relate to a method of treating a coronavirus infection that can include contacting a cell infected with the coronavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a coronavirus infection. Still other embodiments described herein relate to the use of a compound, or a

pharmaceutically acceptable salt thereof, as described herein described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a coronavirus infection.

[0134] Some embodiments disclosed herein relate to a method of inhibiting replication of a coronavirus that can include contacting a cell infected with the coronavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for inhibiting replication of a coronavirus. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, for inhibiting replication of a coronavirus.

[0135] In some embodiments, the coronavirus can be an α-coronavirus or a β-coronavirus. A compound described herein may be effective against one or more variants of a coronavirus. Examples of variants include, but are not limited, to alpha-variant (B.1.1.7), beta-variant (B.1.351), gamma variant (P.1) and delta-variant (B.1.617.2). In some embodiments, the coronavirus can be selected from CoV 229E, CoV NL63, CoV OC43, CoV HKU1, Middle East Respiratory Syndrome (MERS)-CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, and SARS-CoV-2.

[0136] Some embodiments described herein relate to a method of treating a picornavirus infection that can include administering to a subject identified as suffering from the picornavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a picornavirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described

herein or a pharmaceutical composition that includes a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a picornavirus infection.

[0137] Some embodiments disclosed herein relate to a method of treating a picornavirus infection that can include contacting a cell infected with the picornavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a picornavirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a picornavirus infection.

[0138] Some embodiments disclosed herein relate to a method of inhibiting replication of a picornavirus that can include contacting a cell infected with the picornavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for inhibiting replication of a picornavirus. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, for inhibiting replication of a picornavirus.

[0139] In some embodiments, the picornavirus can be a rhinovirus, including rhinovirus A, B and/or C. In some embodiments, a compound described herein, including a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used to treat one or serotypes of a rhinovirus.

[0140] Some embodiments described herein relate to a method of treating a norovirus infection that can include administering to a subject identified as suffering from the

norovirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a norovirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a norovirus infection.

[0141] Some embodiments disclosed herein relate to a method of treating a norovirus infection that can include contacting a cell infected with the norovirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a norovirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a norovirus infection.

[0142] Some embodiments disclosed herein relate to a method of inhibiting replication of a norovirus that can include contacting a cell infected with the norovirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for inhibiting replication of a norovirus. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, for inhibiting replication of a norovirus.

[0143] Some embodiments disclosed herein relate to a method of treating a respiratory condition that is developed because of a coronavirus and/or a picornavius infection that can include administering to a subject suffering from the respiratory condition and/or contacting a cell infected with the coronavirus and/or the picornavius in a subject suffering from the respiratory condition with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a respiratory condition due to a coronavirus infection and/or a picornavius infection with an effective amount of the compound, or a pharmaceutically acceptable salt thereof. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a respiratory condition due to a coronavirus infection and/or a picornavius infection.

[0144] A subject infected with a coronavirus can be asymptotic. A coronavirus infection can manifest itself via one or more symptoms. Examples of symptoms include, but are not limited to, coughing, sore throat, runny nose, sneezing, headache, fever, shortness of breath, myalgia, abdominal pain, fatigue, difficulty breathing, persistent chest pain or pressure, difficulty waking, loss of smell and taste, muscle or joint pain, chills, nausea or vomiting, nasal congestion, diarrhea, haemoptysis, conjunctival congestion, sputum production, chest tightness and/or palpitations. A coronavirus infection can cause complications. A non-limiting list of complications include, but are not limited to, sinusitis, otitis media, pneumonia, acute respiratory distress syndrome, disseminated intravascular coagulation, pericarditis and/or kidney failure.

[0145] As with a coronavirus, a subject infected with a picornavirus can be asymptotic. Alternatively, a subject can exhibit one or more of symptoms. Examples of symptoms of a picornavirus infection include, but are not limited to, aseptic meningitis, rash, conjunctivitis, runny nose a headache a cough a fever a sore throat, chest and/or abdominal pain and paralysis. As provided herein, subjects infected with a norovirus can exhibit one or

more the symptoms including, but not limited to, nausea, non-bloody diarrhea, vomiting and abdominal pain. An example of a complication that can be attributed to a norovirus infection is dehydration, including severe dehydration.

[0146] Various indicators for determining the effectiveness of a method for treating a coronavirus, picornavirus and/or norovirus infection are also known to those skilled in the art. Examples of suitable indicators include, but are not limited to, a reduction in viral load indicated by reduction in coronavirus (or load) (e.g., reduction $<10^5$ copies/mL in serum), a reduction in plasma viral load, a reduction in viral replication, a reduction in time to seroconversion (virus undetectable in patient serum), an increase in the rate of sustained viral response to therapy a reduction of morbidity or mortality in clinical outcomes, reduction in the need for a ventilator and/or total time on a ventilator, reduction in hospitalization rates and/or reduction in time in an ICU (intensive care unit) and/or hospital.

[0147] As used herein, the terms "treat," "treating," "treatment," "therapeutic," and "therapy" do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of a disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject's overall feeling of well-being or appearance.

[0148] As used herein, a "subject" refers to an animal that is the object of treatment, observation or experiment. "Animal" includes cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. "Mammal" includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, camels, non-human primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject can be human, for example, a human subject that is 60 years old or older.

[0149] The term "effective amount" is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, an effective amount of compound can be the amount needed to alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the

disclosure provided herein. The effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0150] In some embodiments, the subject can be asymptomatic, for example, the subject can be infected with coronavirus but does not exhibit any symptoms of the viral infection. In some embodiments, the subject can be have a pre-existing condition, such as asthma, hypertension, immunocomprised subjects (such as subjects with cancer, HIV and/or genetic immune deficiencies, bone marrow transplant subjects, solid organ transplant subjects, subjects who have had stem cells for cancer treatment and/or subjects who use oral or intravenous corticosteroids or other medicines called immunosuppressants), liver disease, subjects at risk for severe illness, chronic kidney disease being treated with dialysis, chronic lung disease, diabetes, hemoglobin disorders, serious heart conditions (for example, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension), severe obesity (such as subjects with a body mass index (BMI) of 40 or above) and people who live in a nursing home or long-term care facility . Additional examples and/or further information is provided by the CDC (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html).

[0151] A compound described herein, including a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered after a subject is infected with a coronavirus. In addition and/or alternatively, a compound described herein, including a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered prophylactically.

[0152] Examples of agents that have been used to treat a coronavirus infection include Remdesivir. However, there can be drawbacks associated with compounds being used to treat a coronavirus including, but not limited to, one or more adverse side effects, the need for subcutaneous administration and/or high cost. Potential advantages of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be less adverse side effects,

delay in the onset of an adverse side effect and/or reduction in the severity of an adverse side effect.

[0153] A coronavirus infection can be treated by inhibiting certain mechanisms. In some embodiments, a compound described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be selective for a coronavirus protease. For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be selective for a coronavirus protease compared to a host protease, for example, one or more host proteases selected from Cathepsin L, Cathepsin B, Cathepsin D, Cathepsin K, Leukocyte Elastase, Chymotrypsin, Trypsin, Thrombin, Pepsin, Caspase 2, Elastase and Calpain. In some embodiments, the selectivity for a coronavirus protease over a host protease (such as those described herein) can be > 2-fold. In some embodiments, the selectivity for a coronavirus protease over a host protease (such as those described herein) can be > 10-fold. In some embodiments, the selectivity for a coronavirus protease over a host protease (such as those described herein) can be > 100-fold.

[0154] Studies have shown that the entry of SARS-CoV-2 into the target cells is a process that can be mediated by multiple proteases including cysteine cathepsins L and/or transmembrane protease serine 2 (TMPRSS2) (Shang et al., PNAS (2020) 117:11727, and Hoffmann et al., Cell (2020) 181:271-280). The cathepsin L inhibitor K117777, which lacks an inhibitory effect on the 3CLpro, can result in potent inhibition of SARS-CoV-2 in VeroE6, A549-ACE2 and/or HeLa-ACE2 (Mellott et al., bioRxiv (2020) 2020.2010.2023.347534). It has also been shown that the potent antiviral effect of K117777 is abolished when TMPRSS2 was expressed in A549-ACE2 (Steuten et al., bioRxiv (2020) 2020.2011.2021.392753). Off target activity of 3CLpro inhibitors, for example, on cathepsin L, may lead to an inaccurate assessment of the 3CLpro component of a compound's cellular potency. As an example, a compound described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can have greater selectivity for a coronavirus protease over a host protease, such as cathepsin L. The selectivity can be determined by those skilled in the art, for example, using IC_{50} and/or Ki values. In some embodiments, a compound described herein does not significantly inhibit cathepsin L (for example, $IC_{50} \geq$ 10000 nM or >3.3 μM), but inhibits a coronavirus protease (for example, SARS-Cov-2 3Clpro).

[0155] A drawback with anti-viral treatment can be the development of resistance, including cross-resistance. Resistance can be a cause for treatment failure. The term "resistance" as used herein refers to a viral strain displaying a delayed, lessened and/or null response to an anti-viral agent. In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be provided to a subject infected with a coronavirus strain that is resistant to one or more other anti-viral agents. In some embodiments, development of coronavirus resistant strains is delayed when a subject is treated with a compound, or a pharmaceutically acceptable salt thereof, as described herein compared to the development of a coronavirus resistant strain when treated with one or more other anti-viral agents.

Combination Therapies

[0156] In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be used in combination with one or more additional agent(s) for treating and/or inhibiting replication a coronavirus. Additional agents include, but are not limited to, an ACE inhibitor, an anticoagulant, an anti-inflammatory, an ARB, an ASO, a Covid-19 convalescent plasma, an entry inhibitor, an H_2 pump antagonist, an H-conducting channel, an HIV protease inhibitor, an HMG-CoA reductase inhibitor, an immune globulin, an immunosuppressant, an immunotherapeutic agent, a monoclonal antibody, a neuraminidase inhibitor, a nucleoside inhibitor, a nucleoside analog inhibitor, a polymerase inhibitor, a protease inhibitor, an siRNA, a statin, a tissue plasminogen activator, an antibiotic, an antimicrobial and a vaccine. Examples of additional agents include Ascorbic acid, Anakin, Azithromycin, Baloxavir, Baricitinib, Chloroquine Phosphate, Colchicine, a corticosteroid, Epoprostenol, Famotidine, Favipiravir, an IGIV, an interferon (for example, recombinant interferon alpha 2b, IFN-α and/or PEG-IFN-α-2a), an IVIG, Ivermectin, γ-globulin, lopinavir, Methylprednisolone, Molnupiravir (MK-4482 or EIDD-2801), Niclosamide, Nitazoxanide, Nitric oxide, Oseltamivir, Peramivir, RANTES, ribavirin, Remdesivir, Ruxolitinib, Sarilumab, Siltuximab, Sirolimus, a statin, Tacrolimus, Tocilizumab, Umifenovir, Zanamivir, Casirivimab, imdevimab, bamlanivimab, etesevimab and AT-527 (Good et al., Antimicrobial Agents and Chemotherapy (2021) 65(4):e02479-20)

[0157] In some embodiments, a compound, or a pharmaceutically acceptable salt

thereof, as described herein can be administered with one or more additional agent(s) together in a single pharmaceutical composition. In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, can be administered with one or more additional agent(s) as two or more separate pharmaceutical compositions. Further, the order of administration of a compound, or a pharmaceutically acceptable salt thereof, as described herein with one or more additional agent(s) can vary.

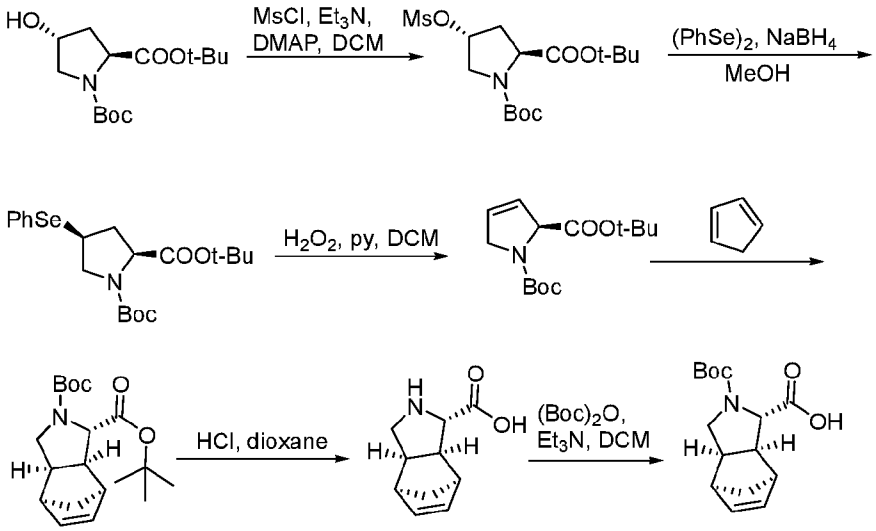
EXAMPLES

[0158] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

COMPOUNDS

[0159] Compounds of Formula (I), along with pharmaceutically acceptable salts thereof, can be prepared in various ways, including those synthetic schemes shown and described herein, are provided below. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

Synthesis of Intermediates



[0160] To a solution of 1,2-di-tert-butyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (15 g, 52.2 mmol, 1.0 eq.) in DCM (250 mL) was added triethylamine (9.51 g,

93.9 mmol, 1.8 eq.) and DMAP (1.91 g, 15.7 mmol, 0.3 eq.). MsCl (8.97 g, 78.3 mmol, 1.5 eq.) was added dropwise at 0 °C. The mixture was stirred at room temperature (rt) for 2 h, and the reaction was quenched with water (100 mL). The solution was extracted with DCM (3 x 150 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:10) to provide 1,2-di-tert-butyl (2S,4R)-4-(methanesulfonyloxy)pyrrolidine-1,2-dicarboxylate (17.8 g, 89%) as a colorless oil. LC-MS (ESI, *m/z*): 366 $[M+H]^+$.

[0161] To a solution of 1,2-di-tert-butyl (2S,4R)-4-(methanesulfonyloxy)pyrrolidine-1,2-dicarboxylate (17.8 g, 48.7 mmol, 1.0 eq.) in MeOH (400 mL) was added (phenyldiselanyl)benzene (9.12 g, 29.2 mmol, 0.6 eq.). Sodium borohydride (2.4 g, 63.3 mmol, 1.3 eq.) was added at 0 °C in several portions. The mixture was refluxed overnight and then concentrated under reduced pressure. Water (100 mL) was added, and the mixture was extracted with EA (3 x 150 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:5) to provide 1,2-di-tert-butyl (2S,4S)-4-(phenylselanyl)pyrrolidine-1,2-dicarboxylate (7.5 g, 32%) as a colorless oil. LC-MS (ESI, *m/z*): 428 $[M+H]^+$.

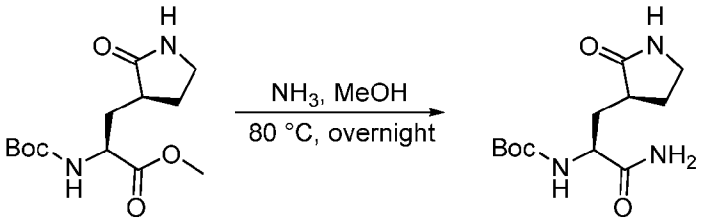
[0162] To a solution of 1,2-di-tert-butyl (2S,4S)-4-(phenylselanyl)pyrrolidine-1,2-dicarboxylate (7.5 g, 17.6 mmol, 1.0 eq.) in DCM (100 mL) was added pyridine (2.4 mL, 30.5 mmol, 1.7 eq.) and 30% aqueous H_2O_2 (5.6 mL, 71.6 mmol, 4.0 eq.). The mixture was stirred at rt for 12 h, and the reaction was quenched with water (20 mL). The solution was extracted with DCM (3 x 150 mL). The organic layers were combined, washed with 1 M citric acid (80 mL), sat. aq. Na_2SO_3 (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:9) to provide 1,2-di-tert-butyl (2S)-2,5-dihydropyrrole-1,2-dicarboxylate (2.8 g, 53%) as a colorless oil. ^1H NMR (300 MHz, DMSO-d_6) δ 6.02-6.09 (m, 1H), 5.76-5.83 (m, 1H), 4.72-4.78 (m, 1H), 4.05-4.09 (m, 2H), 1.17-1.42 (m, 18H). LC-MS (ESI, *m/z*): 270 $[M+H]^+$.

[0163] A solution of 1,2-di-tert-butyl (2S)-2,5-dihydropyrrole-1,2-dicarboxylate (2.8 g, 10.4 mmol, 1.0 eq.) in dicyclopentadiene (60 mL) was stirred at 170 °C for 48 h under

nitrogen and then resolved with DCM (200 mL). After removal of the solvent, the residue was chromatographed on a silica gel column with EA:PE (1:9) to provide the product (2.5 g, crude) as a yellow oil. The crude oil was chromatographed on a C18 column with H_2O:MeCN (2:1) to provide di-tert-butyl (1S,3aR,4S,7R,7aS)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-1,2-dicarboxylate (690 mg, 19%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.14-6.21 (m, 2H), 3.55-3.60 (m, 1H), 3.23-3.27 (m, 1H), 2.95-3.02 (m, 2H), 2.74-2.87 (m, 3H), 1.24-1.48 (m, 20H). LC-MS (ESI, *m/z*): 270 $[M+H]^+$.

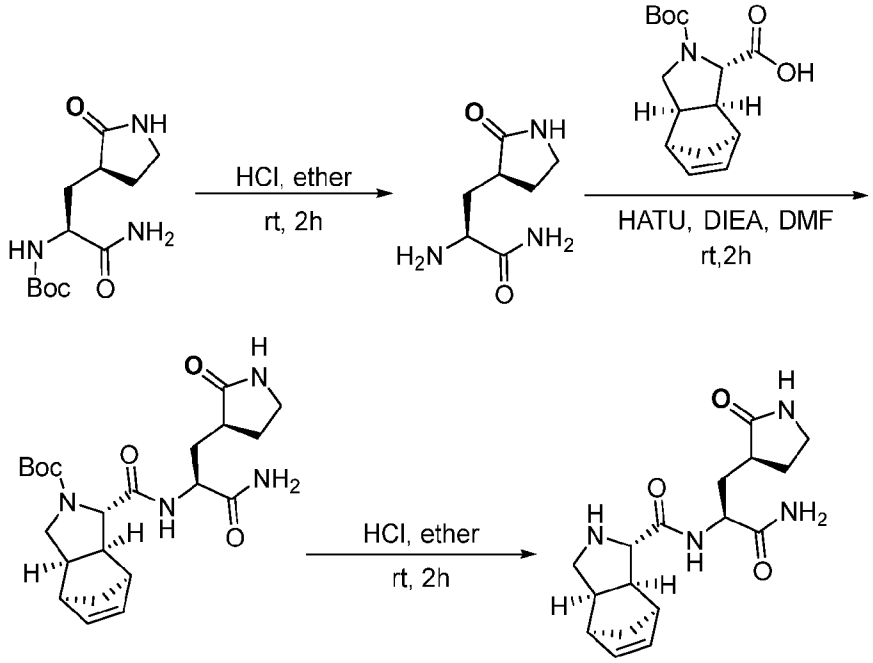
[0164] To a solution of i-tert-butyl (1S,3aR,4S,7R,7aS)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-1,2-dicarboxylate (690 mg, 2.1 mmol, 1.0 eq.) in dioxane (10 mL) was added hydrochloric acid (10 mL, 9M). The mixture was stirred at rt overnight and then concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (320 mg, crude) as a black solid. LC-MS (ESI, *m/z*): 180 $[M+H]^+$.

[0165] To a solution of (1S,3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (320 mg, 1.79 mmol, 1.0 eq.) in DCM (8 mL) was added di-tert-butyl dicarbonate (429 mg, 1.97 mmol, 1.1 eq.) and triethylamine (542 mg, 5.34 mmol, 3.0 eq.). The mixture was stirred at rt for 3 h and then concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-2-(tert-butoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (430 mg, crude) as a brown solid. LC-MS (ESI, *m/z*): 280 $[M+H]^+$.



[0166] A mixture of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (10.0 g, 34.9 mmol, 1.00 eq.) in ammonia (150 mL, 7 M in MeOH) was stirred overnight at 80 °C and concentrated under reduced pressure to afford tert-butyl N-[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamate (10.0 g, crude) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (s, 1H), 7.29 (s, 1H), 7.01 (s, 1H), 6.88-6.95 (m, 1H), 3.84-4.15 (m, 1H), 3.09-3.21 (m, 2H), 2.08-2.26 (m, 2H), 1.84-1.96 (m, 1H), 1.60-1.74 (m, 1H), 1.44-1.54 (m, 1H), 1.38 (s, 9H). LC-MS (ESI, m/z): 272

$[M+H]^+$.

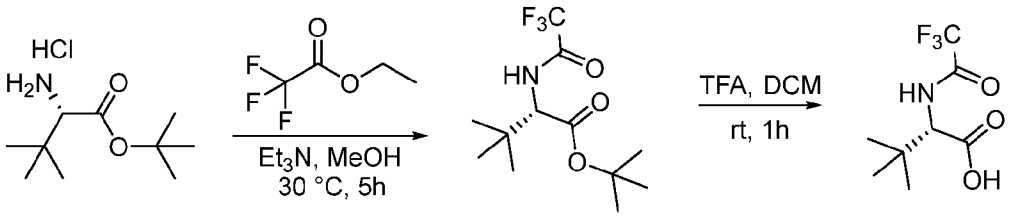


[0167] A solution of tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (710 mg, 2.62 mmol, 1.0 eq.) in hydrochloric acid in ether (12 mL, 2 mol/L) was stirred at rt for 2 h and concentrated under reduced pressure to provide (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propenamide (500 mg, crude) as a white solid. LC-MS (ESI, *m/z*): 172 $[M+H]^+$.

[0168] To a solution of (1S,3aR,4S,7R,7aS)-2-(tert-butoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (979 mg, 3.5 mmol, 1.2 eq.) in DMF (2 mL) was added N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophospate (1.44 g, 3.8 mmol, 1.3 eq.) and N,N-diisopropylethylamine (2.64 g, 20.4 mmol, 7.0 eq.). The mixture was stirred at 0 °C for 30 min and then (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide (500 mg, 2.92 mmol, 1.0 eq.) was added. The mixture was stirred at rt for 2 h, and the reaction was quenched with water (5 mL). The mixture was extracted with EA (3 x 10 mL). The organic layers were combined, washed with brine (3 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a C18 column with water:MeCN (2:1) to provide tert-butyl (1S,3aR,4S,7R,7aS)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-carboxylate

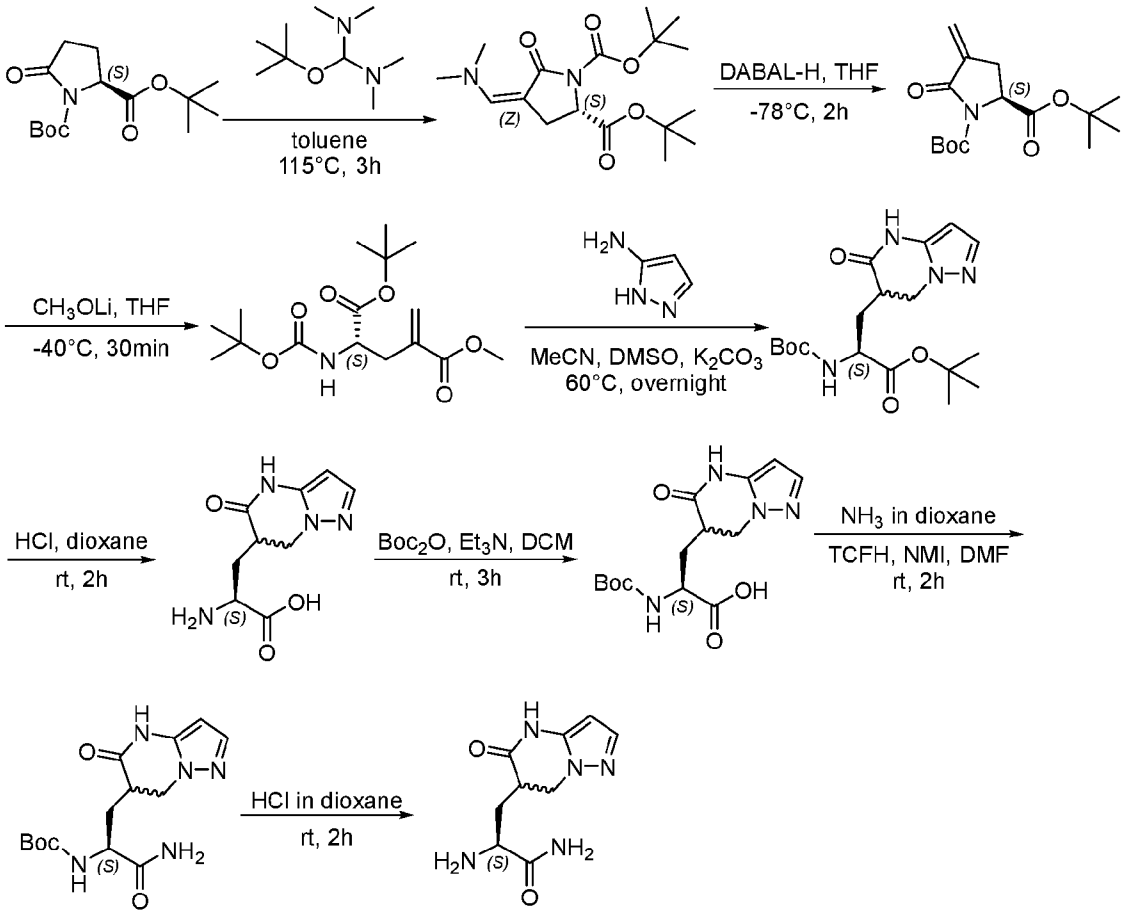
(1.05 g, 75%) as a brown yellow solid. LC-MS (ESI, *m/z*): 433 $[M+H]^+$.

[0169] A solution of tert-butyl (1S,3aR,4S,7R,7aS)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-carboxylate (300 mg, 0.69 mmol, 1.0 eq.) in hydrochloric acid in ether (5 mL, 2 mol/L) was stirred at rt for 2 h and then concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (200 mg, crude) as a white solid. LC-MS (ESI, *m/z*): 333 $[M+H]^+$.



[0170] To a stirred mixture of tert-butyl (2S)-2-amino-3,3-dimethylbutanoate hydrochloride (6.00 g, 26.8 mmol, 1.0 eq.) and trifluoroethyl acetate (7.62 g, 53.6 mmol, 2.0 eq.) in MeOH (100 mL) was added triethylamine (5.43 g, 53.7 mmol, 2.0 eq.) at 0 °C. The mixture was stirred for 5 h at 30 °C and then concentrated under reduced pressure to afford the crude product. The crude product was diluted with DCM (150 mL) and made into a slurry with 100 ~ 200 silica gel mesh (15 g), and the slurry was loaded to a column chromatography after removing the DCM. The sample was purified by column chromatography (Column size 6 x 24 cm, column volume: 600 mL, silica gel size (100 ~ 200 mesh) quantity: 330 g) and eluted with MeOH:DCM (0% ~ 10% over 30 min). The collected fractions: 0% MeOH:DCM fractions were chosen as the pure fractions. and those fractions were combined and concentrated under reduced pressure to provide tert-butyl (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoate (7.20 g, 90%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78-6.90 (m, 1H), 4.32-4.38 (m, 1H), 1.50 (s, 9H), 1.01 (s, 9H). LC-MS (ESI, *m/z*): 282 $[M-H]^-$.

[0171] To a mixture of tert-butyl (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoate (1.03 g, 3.64 mmol, 1.0 eq.) in DCM (5 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoic acid (826 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 226 $[M-H]^-$.



[0172] To a solution of 1,2-di-tert-butyl (2S)-5-oxopyrrolidine-1,2-dicarboxylate 1,2-di-tert-butyl (2S)-5-oxopyrrolidine-1,2-dicarboxylate (50 g, 175 mmol, 1.0 eq.) in toluene (500 mL) was added [tert-butoxy(dimethylamino)methyl]dimethylamine (36.7 g, 210 mmol, 1.2 eq.). The mixture was stirred at 115 °C for 3 h under nitrogen and concentrated under reduced pressure to provide di-tert-butyl (S,Z)-4-((dimethylamino)methylene)-5-oxopyrrolidine-1,2-dicarboxylate (46g, crude) as an orange oil. LC-MS (ESI, *m/z*): 341 $[M+H]^+$.

[0173] To a solution of di-tert-butyl (S,Z)-4-((dimethylamino)methylene)-5-oxopyrrolidine-1,2-dicarboxylate (46 g, 135 mmol, 1.0 eq.) in THF (900 mL) was added DIBAl-H (203 mL, 1M in toluene, 203 mmol, 1.5 eq.) dropwise at -78 °C under N_2. The mixture was stirred at -78 °C for 2 h, and was then poured into hydrochloric acid (800 mL, 2 mol/L) slowly at 0 °C. The solution was extracted with EA (3 x 600 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The

residue was chromatographed on a silica gel column with EA:PE (1:5) to provide di-tert-butyl (S)-4-methylene-5-oxopyrrolidine-1,2-dicarboxylate (16 mg, 36%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.98-6.00(m, 1H), 5.58-5.59 (m, 1H), 4.50-4.54 (m, 1H), 3.04-3.34 (m, 1H), 2.57-2.64 (m, 1H), 1.36-1.44 (m, 18H). LC-MS (ESI, *m/z*): 298 $[M+H]^+$.

[0174] To a solution of di-tert-butyl (S)-4-methylene-5-oxopyrrolidine-1,2-dicarboxylate (12 g, 40.4 mmol, 1.0 eq.) in THF (200 mL) was added methoxylithium (22 mL, 2.2M in methanol, 48.4 mmol, 1.2 eq.) at -40 °C under N_2. The mixture was stirred at -40 °C for 30 min. The reaction quenched with sat. aq. sodium chloride (100 mL). The solution was extracted with EA (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:4) to provide 1-(tert-butyl) 5-methyl (S)-2-((tert-butoxycarbonyl)amino)-4-methylenepentanedioate (12 g, 81%) as a colorless viscous oil. LC-MS (ESI, *m/z*): 330 $[M+H]^+$.

[0175] To a solution of 1-(tert-butyl) 5-methyl (S)-2-((tert-butoxycarbonyl)amino)-4-methylenepentanedioate (7 g, 21 mmol, 1.0 eq.) in MeCN (70 mL) and DMSO (70 mL) was added 2H-pyrazol-3-amine (2.1 g, 25.5 mmol, 1.2 eq.), K_2CO_3 (2.94 mg, 21 mmol, 1.0 eq.). The mixture was stirred at 60 °C overnight and then concentrated under reduced pressure. The residue was chromatographed on a C18 column with MeCN:H_2O (3:2) to provide tert-butyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanoate (1.7 g, 19%) as a brown yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.18-7.27 (m, 2H), 5.56-5.57 (m, 1H), 4.26-4.36 (m, 1H), 3.89-4.13 (m, 1H), 2.75-2.79 (m, 1H), 2.10-2.25 (m, 1H), 1.61-1.80 (m, 1H), 1.27-1.53 (m, 18H). LC-MS (ESI, *m/z*): 381 $[M+H]^+$.

[0176] To a solution of tert-butyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanoate (800 mg, 3.55 mmol, 1.0 eq.) in dioxane (8 mL) was added hydrochloric acid (8 mL, 9M). The mixture was stirred at rt for 2 h and then concentrated under reduced pressure to provide (2S)-2-amino-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanoic acid (400 mg, crude) as an off-white semi-solid. LC-MS (ESI, *m/z*): 225 $[M+H]^+$.

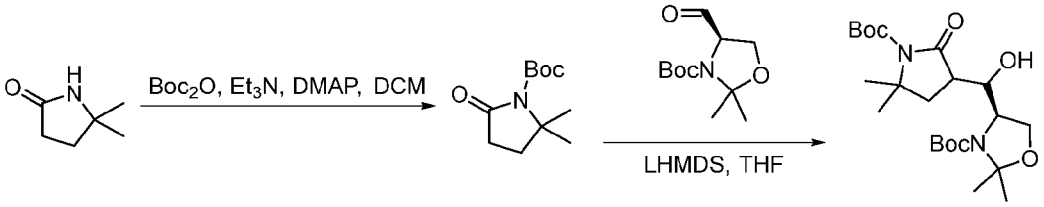
[0177] To a solution of (2S)-2-amino-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanoic acid (400 mg, 1.78 mmol, 1.0 eq.) in DCM (6 mL) was added di-

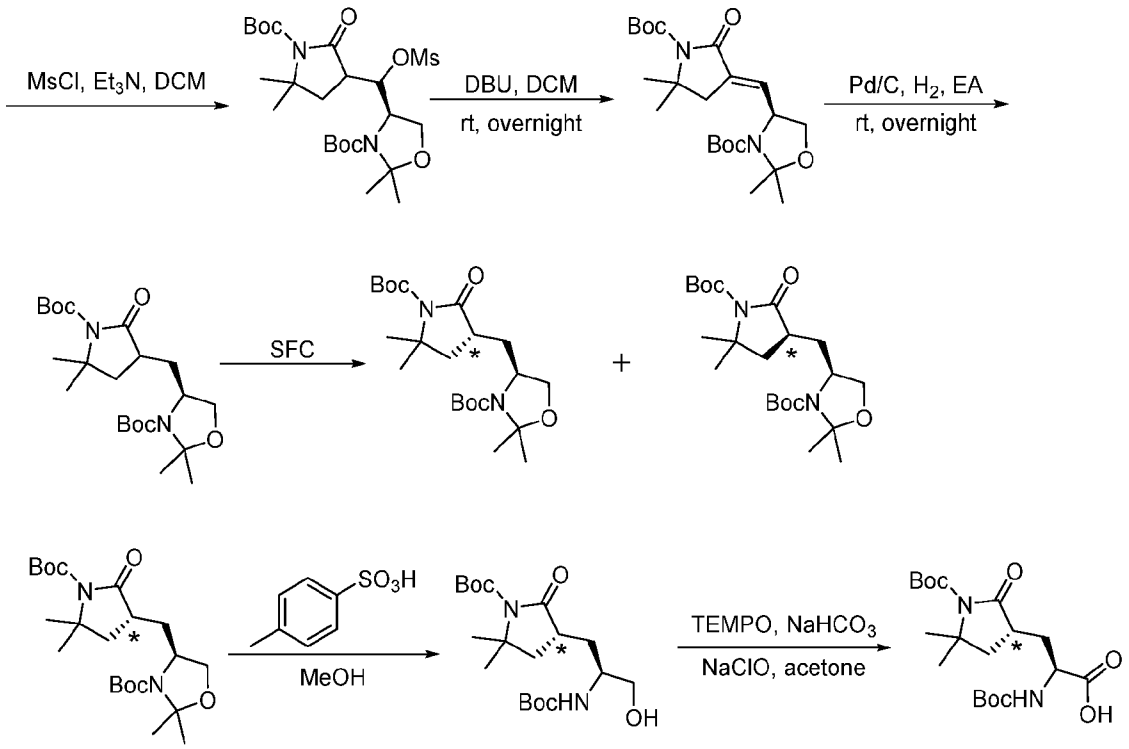
tert-butyl dicarbonate (430 mg, 1.96 mmol, 1.1 eq.) and triethylamine (180 mg, 5.36 mmol, 3.0 eq.). The mixture was stirred at rt for 3 h and then concentrated under reduced pressure to provide (2S)-2-((tert-butoxycarbonyl)amino)-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanoic acid (530 mg, crude) as a brown yellow semi-solid. LC-MS (ESI, *m/z*): 325 $[M+H]^+$.

[0178] To a solution of (2S)-2-((tert-butoxycarbonyl)amino)-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanoic acid (530 mg, 1.63 mmol, 1.0 eq.) in DMF (8 mL) was added N,N,N,N-Tetramethylchloroformamidinium hexafluorophosphate (550 mg, 1.96 mmol, 1.2 eq.), NMI (671 mg, 8.17 mmol, 5.0 eq.) and NH_3 in dioxane (40 mL, 10.0 eq., 0.4 mol/L). The mixture was stirred at rt for 2 h and then chromatographed on a C18 column with MeCN:H_2O (1:4) to provide tert-butyl ((2S)-1-amino-1-oxo-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)carbamate (280 mg, 48%) as a brown yellow oil. LC-MS (ESI, *m/z*): 324 $[M+H]^+$.

[0179] To a solution of tert-butyl ((2S)-1-amino-1-oxo-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)carbamate (280 mg, 0.87 mmol, 1.0 eq.) in hydrochloric acid (4 mL, 2 mol/L in dioxane) was stirred at rt for 2 h and then concentrated under reduced pressure to provide (2S)-2-amino-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanamide (180 mg, crude) as an off-white semi-solid. LC-MS (ESI, *m/z*): 224 $[M+H]^+$.

(S)-3-((R*)-1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((tert-butoxycarbonyl)amino)propanoic acid





The chiral center noted with "*" is tentatively assigned.

[0180] A 100 mL round-bottom flask was charged with 5,5-dimethylpyrrolidin-2-one (3.5 g, 30.9 mmol, 1.0 eq.), DCM (50 mL), di-tert-butyl dicarbonate (10.8 g, 49.5 mmol, 1.6 eq.), triethylamine (6.24 g, 61.8 mmol, 2.0 eq.) and DMAP (0.38 g, 3.09 mmol, 0.1 eq.). The solution was stirred overnight at 40 °C, and the reaction was quenched with water (150 mL). The solution was extracted with EA (5 x 300 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (13:87) to provide tert-butyl 2,2-dimethyl-5-oxopyrrolidine-1-carboxylate (4.0 g, 58%) as a white solid. LC-MS (ESI, *m/z*): 214 $[M+H]^+$.

[0181] A 100 mL round-bottom flask was charged with tert-butyl 2,2-dimethyl-5-oxopyrrolidine-1-carboxylate (3.6 g, 16.9 mmol, 1.00 eq.) and THF (50 mL). The solution was cooled to -78 °C and LiHMDS (20.2 mL, 1M in THF, 20.2 mmol, 1.2 eq.) was added. The mixture was stirred for 1 h at -78 °C, and a solution of tert-butyl (4R)-4-formyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (5.81 g, 25.3 mmol, 1.5 eq.) in THF (10 mL) was added under Ar. Stirring was continued at -78 °C for 1 h. The reaction was quenched with a sat. ammonium chloride solution (50 mL). The solution was extracted with dichloromethane

(3 x 150 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:4) to provide tert-butyl (4R)-4-{[1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl](hydroxy)methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (7.2 g, 89%) as a colorless oil. LC-MS (ESI, *m/z*): 443 $[M+H]^+$.

[0182] A 100 mL round-bottom flask was charged with tert-butyl (4R)-4-{[1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl](hydroxy)methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (1 g, 2.26 mmol, 1.00 eq.), DCM (10 mL), triethylamine (1.14 g, 11.3 mmol, 5.0 eq.) and MsCl (0.31 g, 4.52 mmol, 2.0 eq.). The mixture was stirred overnight at rt, and the reaction was quenched with water (30 mL). The solution was extracted with dichloromethane (4 x 50 mL). The organic layers were combined, washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide tert-butyl (4R)-4-{[1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl](methanesulfonyloxy)methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (960 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 521 $[M+H]^+$.

[0183] A 100 mL round-bottom flask was charged with tert-butyl (4R)-4-{[1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl](methanesulfonyloxy)methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (900 mg, 1.73 mmol, 1.0 eq.), DCM (20 mL) and DBU (1.32 g, 8.64 mmol, 5.0 eq.). The mixture was stirred overnight at rt, and the reaction was quenched with water (30 mL). The solution was extracted with dichloromethane (3 x 80 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:4) to provide tert-butyl (4S)-4-{[1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-ylidene]methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (635 mg, 82%) as a colorless oil. LC-MS (ESI, *m/z*): 425 $[M+H]^+$.

[0184] A 250 mL round-bottom flask was charged with tert-butyl (4S)-4-{[1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-ylidene]methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (4.4 g, 10.4 mmol, 1.0 eq.), EA (50 mL) and 10% palladium on activated carbon (5.51 g). The contents of the flask were placed under an atmosphere of

hydrogen (3 atm). The mixture was stirred overnight at rt. The solids were filtered off. The organic layer was concentrated under reduced pressure to provide tert-butyl (4S)-4-{[1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl]methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (4.3 g, 78%) as a colorless oil. LC-MS (ESI, *m/z*): 427 $[M+H]^+$.

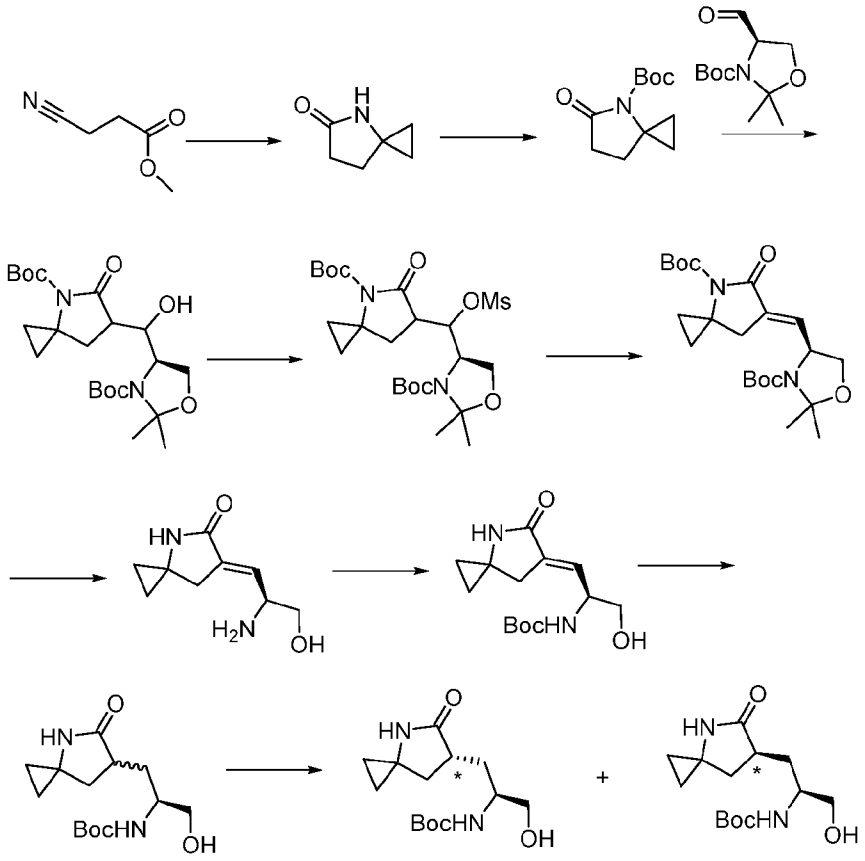
[0185] Tert-butyl (4S)-4-((1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (3.6g) was purified by prep-SFC using the following gradient conditions: Column: Lux 5um Cellulose-2, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: IPA(0.5% 2M NH_3-MeOH); Flow rate: 60 mL/min; Gradient: isocratic 10% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1 (min): 4.81; RT2(min): 6.43; Sample Solvent: MeOH--Preparative; Injection Volume: 1.5 mL; Number Of Runs: 27. Purification resulted in tert-butyl (S)-4-(((S*)-1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (990 mg) as an off-white solid (Lux Celloluse-2 4.6*50 mm, 3 μm, 35 °C. Co-Solvent : IPA (0.1%DEA), 10% to 50% in 2.0 min, hold 1.0 min at 50%): Rt: 0.969 min), and tert-butyl (S)-4-(((R*)-1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (1.6 g) as an off-white solid Lux Celloluse-2 4.6*50 mm, 3 μm, 35 °C. Co-Solvent : IPA (0.1%DEA), 10% to 50% in 2.0 min, hold 1.0 min at 50%): Rt: 1.411 min).

[0186] A 40 mL vial was charged with tert-butyl (S)-4-(((R*)-1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (1.6 g, 3.75 mmol, 1.0 eq.), para-toluene sulfonate (64.6 mg, 0.375 mmol, 0.1 eq.) and MeOH (20 mL). The mixture was stirred overnight at rt. The reaction was quenched with water (20 mL). The solution was extracted with EA (3 x 30 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide tert-butyl(S)-4-((S)-2-((tert-butoxycarbonyl)amino)-3-hydroxypropyl)-2,2-dimethyl-5-oxopyrrolidine-1-carboxylate (1.47 g, crude) as an off-white semi-solid. LC-MS (ESI, *m/z*): 387 $[M+H]^+$.

[0187] To a solution of tert-butyl (S)-4-((R*)-2-((tert-butoxycarbonyl)amino)-3-hydroxypropyl)-2,2-dimethyl-5-oxopyrrolidine-1-carboxylate (1.7 g, 4.40 mmol, 1.0 eq.) in acetone (22 mL) was added 5% sodium bicarbonate solution (22 mL, 13.1 mmol, 3.0 eq.) and 2,2,6,6-Tetramethylpiperidinooxy (0.14 g, 0.88 mmol, 0.2 eq.). Chlorosylsodium (1.15 g,

15.4 mmol, 3.5 eq.) was added dropwise at 0 °C. The mixture was stirred at rt overnight, and the reaction was quenched with water (20 mL). The solution was washed with Et2O (2 x 20 mL). The pH value of the aqueous solution was adjusted to 2 with concentrated hydrochloric acid (1 mol/L). The solution was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide (S)-3-((R*)-1-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((tert-butoxycarbonyl)amino)propanoic acid (1.2 g, 61%) as a white solid.

tert-butyl ((S)-1-hydroxy-3-((S*)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)carbamate



The absolute configuration of the chiral center noted with "*" is tentatively assigned.

[0188] To a solution of methyl 3-cyanopropanoate (10 g, 88.4 mmol, 1.0 eq.) in Et_2O (100 mL) was added $Ti(O^iPr)_4$ (5.03 g, 17.7 mmol, 0.2 eq.). EtMgBr (194 mL, 1M in THF, 194 mmol, 2.2 eq.) was then added dropwise under N_2. The mixture was stirred at rt for 2h, and the reaction was quenched with water (20 mL). The mixture was extracted with

EA (3 x 60 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with PE:MeOH (12:1) to provide 4-azaspiro[2.4]heptan-5-one (8.5 g, 69%) as a colorless oil. LC-MS (ESI, *m/z*): 112 $[M+H]^+$.

[0189] A 250 mL round-bottom flask was charged with 4-azaspiro[2.4]heptan-5-one (8.5 g, 76.5 mmol, 1.0 eq.) , DCM (100 mL), di-tert-butyl dicarbonate (26.7 g, 122 mmol, 1.6 eq.) , triethylamine (0.77 g, 7.65 mmol, 0.1 eq.) and DMAP (0.93 g, 7.65 mmol, 0.1 eq.). The solution was stirred overnight at 40 °C, and the reaction was quenched with water (70 mL). The solution was extracted with DCM (3 x 100 mL). The organic layers were combined, washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:12) to provide tert-butyl 5-oxo-4-azaspiro[2.4]heptane-4-carboxylate (11 g, 58%) as a white solid. LC-MS (ESI, *m/z*): 212 $[M+H]^+$.

[0190] A 500 mL round-bottom flask was charged with tert-butyl 5-oxo-4-azaspiro[2.4]heptane-4-carboxylate (11 g, 52.1 mmol, 1.0 eq.) and THF (150 mL). The solution was cooled to -78 °C and LiHMDS (62.5 mL, 1M in THF, 62.5 mmol, 1.2 eq.) was added. The mixture was stirred for 1 h at -78 °C and a solution of tert-butyl (4R)-4-formyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (17.9 g, 78.1 mmol, 1.5 eq.) in THF (50 mL) under Ar was added. Stirring was continued at -78 °C for 1h. The reaction was quenched with sat. ammonium chloride solution (100 mL). The solution was extracted with EA (3 x 200 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:8) to provide tert-butyl (4R)-4-((4-(tert-butoxycarbonyl)-5-oxo-4-azaspiro[2.4]heptan-6-yl)(hydroxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (19.7 g, 69%) as a colorless oil. LC-MS (ESI, *m/z*): 441 $[M+H]^+$.

[0191] A 500 mL round-bottom flask was charged with tert-butyl (4R)-4-((4-(tert-butoxycarbonyl)-5-oxo-4-azaspiro[2.4]heptan-6-yl)(hydroxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (19.7 g, 44.7 mmol, 1.0 eq.), DCM (250 mL), triethylamine (27.2 g, 268 mmol, 6.0 eq.) and MsCl (20.5 g, 179 mmol, 4.0 eq.). The mixture was stirred overnight at rt, and the reaction was quenched with water (100 mL). The

solution was extracted with DCM (4 x 150 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide tert-butyl (4R)-4-((4-(tert-butoxycarbonyl)-5-oxo-4-azaspiro[2.4]heptan-6-yl)((methylsulfonyl)oxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (22 g, crude) as an orange oil. LC-MS (ESI, *m/z*): 519 $[M+H]^+$.

[0192] A 500 mL round-bottom flask was charged with tert-butyl (4R)-4-((4-(tert-butoxycarbonyl)-5-oxo-4-azaspiro[2.4]heptan-6-yl)((methylsulfonyl)oxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (22 g, 42.4 mmol, 1.0 eq.), DCM (200 mL) and DBU (14.2 g, 93.3 mmol, 2.2 eq.). The mixture was stirred overnight at rt, and the reaction was quenched with water (80 mL). The solution was extracted with DCM (3 x 100 mL). The organic layers were combined, washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:12) to provide tert-butyl 6-{[(4S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]methylidene}-5-oxo-4-azaspiro[2.4]heptane-4-carboxylate (11.3 g,57%) as a colorless oil. LC-MS (ESI, *m/z*): 423 $[M+H]^+$.

[0193] A 250 mL vial was charged with tert-butyl 6-{[(4S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]methylidene}-5-oxo-4-azaspiro[2.4]heptane-4-carboxylate (11.3 g, 26.7 mmol, 1.0 eq.), 4-methylbenzenesulfonic acid (5.53 g, 32.1 mmol, 1.2 eq.) and MeOH (120 mL). The mixture was stirred overnight at rt, and then concentrated under reduced pressure to provide 6-[(2S)-2-amino-3-hydroxypropylidene]-4-azaspiro[2.4]heptan-5-one (5.8 g, crude) as an orange oil. LC-MS (ESI, *m/z*): 183 $[M+H]^+$.

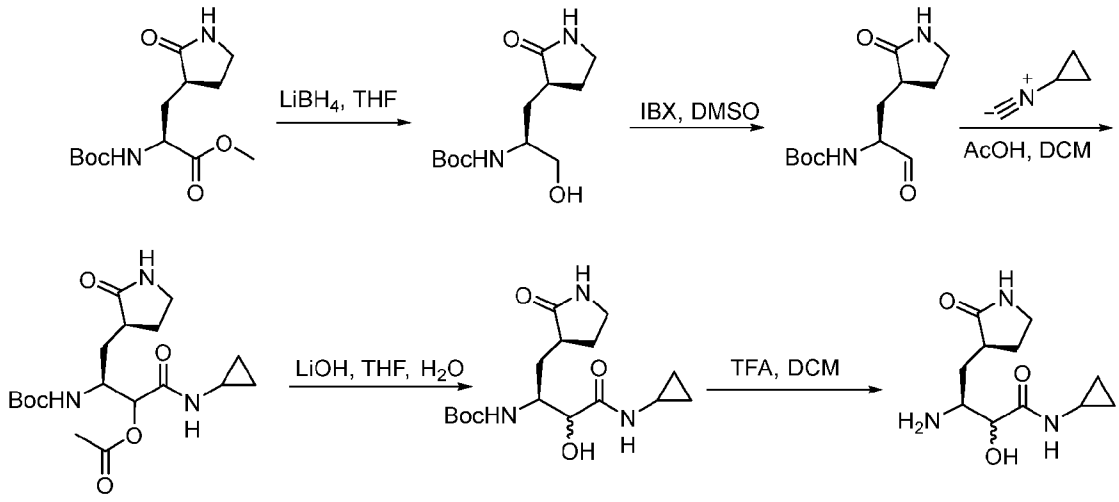
[0194] To a solution of 6-[(2S)-2-amino-3-hydroxypropylidene]-4-azaspiro[2.4]heptan-5-one (5.8 g, 31.829 mmol, 1.00 eq.) in DCM (90 mL) was added triethylamine (25.8 g, 255 mmol, 8.0 eq.) and di-tert-butyl dicarbonate (20.8 g, 95.5 mmol, 3.0 eq.). The mixture was stirred at rt overnight, and the reaction was quenched with water (30 mL). The mixture was extracted with $CDCl_3$:isopropyl alcohol = 3:1 (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with MeOH:DCM (1:25) to provide tert-butyl N-[(2S)-1-hydroxy-3-[(6E)-5-oxo-4-

azaspiro[2.4]heptan-6-ylidene]propan-2-yl]carbamate (3.9 g, 39%) as a brown yellow solid. LCMS (ESI, *m/z*): 283 $[M+H]^+$.

[0195] To a solution of tert-butyl N-[(2S)-1-hydroxy-3-[5-oxo-4-azaspiro[2.4]heptan-6-ylidene]propan-2-yl]carbamate (3.9 g, 13.8 mmol, 1.0 eq.) in THF (30 mL) and MeOH (90 mL) was added $NiCl_2 \cdot 6H_2O$ (23 g, 96.7 mmol, 7.0 eq.). $NaBH_4$ (11 g, 290 mmol, 21.0 eq.) was added in several portions at 0°C. The mixture was stirred at rt overnight, and the reaction was quenched with water (30 mL). The mixture was extracted with $CDCl_3$:isopropyl alcohol = 3:1 (3 x 60 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a C18 column with MeCN:H_2O (4:1) to provide tert-butyl N-[(2S)-1-hydroxy-3-{5-oxo-4-azaspiro[2.4]heptan-6-yl}propan-2-yl]carbamate (1.7 g, 39%) as a brown yellow solid. LCMS (ESI, *m/z*): 285 $[M+H]^+$.

[0196] Tert-butyl N-[(2S)-1-hydroxy-3-{5-oxo-4-azaspiro[2.4]heptan-6-yl}propan-2-yl]carbamate (1.7 g) was purified by SFC using the following gradient conditions: Column: NB-Lux 5um i-Cellulose-5, 2.12*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH(0.1% 2M NH_3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 25% B; Column Temperature(℃): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1 (min): 3.37; RT2(min): 4.02; Sample Solvent: MeOH--Preparative; Injection Volume: 1 mL; Number Of Runs: 40. Purification resulted in 590 mg of first eluding tert-butyl ((S)-1-hydroxy-3-((R*)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)carbamate as a brown yellow solid and 640 mg of last eluding tert-butyl ((S)-1-hydroxy-3-((S*)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)carbamate as a brown yellow solid.

(3S)-3-amino-N-cyclopropyl-2-hydroxy-4-((S)-2-oxopyrrolidin-3-yl)butanamide



[0197] To a stirred mixture of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (3.0 g, 10.5 mmol, 1.0 eq.) in tetrahydrofuran (50 mL) was added lithium borohydride (26.2 mL, 52.4 mmol, 5.0 eq.) dropwise at 0 °C. The mixture was stirred for 1 h at 0 °C and then concentrated under reduced pressure. The mixture was diluted with water (20 mL), and then extracted with isopropanol:trichloromethane (1:5, 4 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with dichloromethane:methanol (19:1) to afford tert-butyl N-[(2S)-1-hydroxy-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl]carbamate (2.6 g, crude) as a white solid. The crude product was precipitated by the addition of PE:EA (4:1, 40 mL) to afford tert-butyl N-[(2S)-1-hydroxy-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl]carbamate (2.4 g, 79%) as a white solid. LC-MS (ESI, m/z): 259 $[M+H]^+$.

[0198] To a stirred mixture of tert-butyl N-[(2S)-1-hydroxy-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl]carbamate (2.4 g, 9.29 mmol, 1.0 eq.) in dimethyl sulfoxide (40 mL) was added 2-iodoxybenzoic acid (7.80 g, 27.8 mmol, 3.0 eq.) in portions at rt. The mixture was stirred for 3 h at rt, and then basified to pH = 8 with sat. sodium bicarbonate (aq.). The mixture was diluted with water (20 mL) and extracted with EA (4 x 200 mL). The organic layers were combined, washed with brine (3 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford tert-butyl N-[(2S)-1-oxo-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl]carbamate (1.5 g, 63%) as a yellow solid.

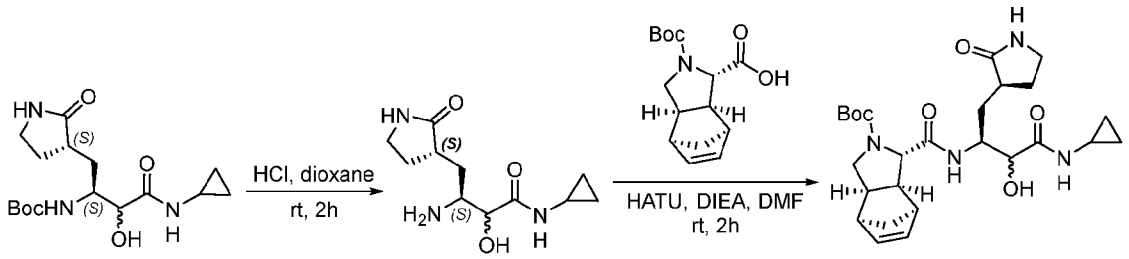
LC-MS (ESI, m/z): 257 $[M+H]^+$.

[0199] To a stirred mixture of tert-butyl N-[(2S)-1-oxo-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl]carbamate (900 mg, 3.51 mmol, 1.0 eq.) in dichloromethane (10 mL) were added isocyanocyclopropane (471 mg, 7.02 mmol, 2.0 eq.) and acetic acid (633 mg, 10.5 mmol, 3.0 eq.) dropwise at 0 °C. The mixture was stirred for 5 h at rt and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with dichloromethane:methanol (49:1) to afford (2S)-2-[(tert-butoxycarbonyl)amino]-1-(cyclopropylcarbamoyl)-3-[(3S)-2-oxopyrrolidin-3-yl]propyl acetate (820 mg, 55%) as a yellow solid. LC-MS (ESI, *m/z*): 384 $[M+H]^+$.

[0200] To a stirred mixture of (2S)-2-[(tert-butoxycarbonyl)amino]-1-(cyclopropylcarbamoyl)-3-[(3S)-2-oxopyrrolidin-3-yl]propyl acetate (810 mg, 2.11 mmol, 1.0 eq.) in tetrahydrofuran (8 mL) was added lithium hydroxide (253 mg, 10.5 mmol, 5.0 eq., in water 8 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C. The mixture was acidified to pH = 6 with hydrochloric acid (2M). The mixture was extracted with EA (4 x 60 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford tert-butyl N-[(2S)-1-(cyclopropylcarbamoyl)-1-hydroxy-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl]carbamate (680 mg, 94%) as a yellow solid. LCMS (ESI, m/z): 342 $[M+H]^+$.

[0201] To a stirred mixture of tert-butyl N-[(2S)-1-(cyclopropylcarbamoyl)-1-hydroxy-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl]carbamate (400 mg, 1.17 mmol, 1.0 eq.) in dichloromethane (6 mL) was added trifluoroacetic acid (2 mL) dropwise at rt. The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (3S)-3-amino-N-cyclopropyl-2-hydroxy-4-[(3S)-2-oxopyrrolidin-3-yl]butanamide (290 mg, crude) as a brown solid. LC-MS (ESI, m/z): 242 $[M+H]^+$.

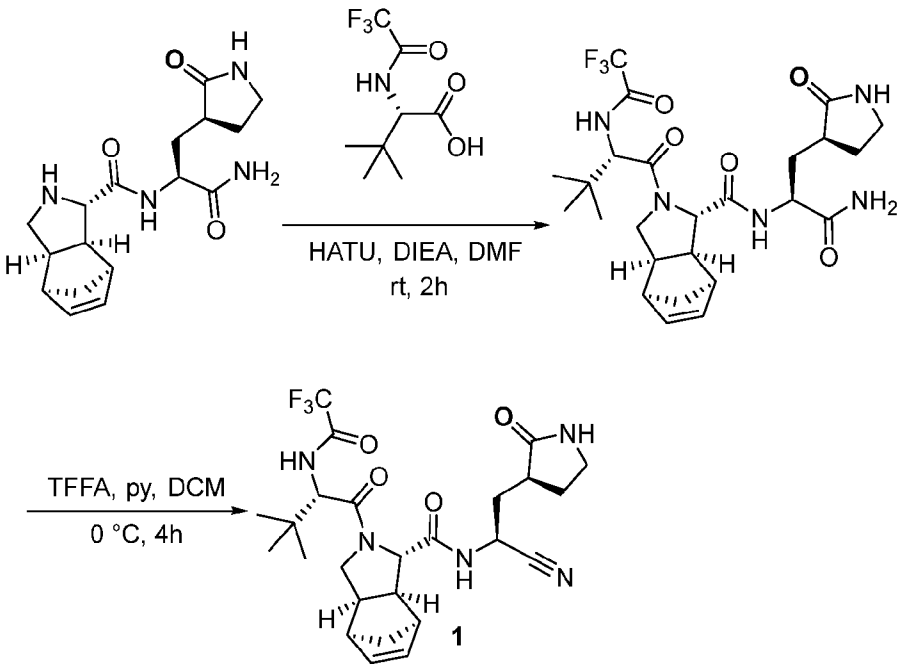
tert-butyl (1S,3aR,4S,7R,7aS)-1-(((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)carbamoyl)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-carboxylate



[0202] A solution of tert-butyl ((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)carbamate (800 mg, 2.34 mmol, 1.0 eq.) in hydrochloric acid (14 mL, 4 M in dioxane) was stirred at rt for 2 h and then concentrated under reduced pressure to provide (3S)-3-amino-N-cyclopropyl-2-hydroxy-4-((S)-2-oxopyrrolidin-3-yl)butanamide (550 mg, crude) as an off-white solid. LC-MS (ESI, *m/z*): 242 $[M+H]^+$.

[0203] To a solution of (1S,3aR,4S,7R,7aS)-2-(tert-butoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (700 mg, 2.5 mmol, 1.1 eq.) in DMF (8 mL) were added N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophospate (1.13 g, 2.96 mmol, 1.3 eq.) and N,N-diisopropylethylamine (2.06 g, 16 mmol, 7.0 eq.). The mixture was stirred at 0 °C for 30 min and (3S)-3-amino-N-cyclopropyl-2-hydroxy-4-((S)-2-oxopyrrolidin-3-yl)butanamide (550 mg, 2.28 mmol, 1.0 eq.) was added. The mixture was stirred at rt for 2 h, and the reaction was quenched with water (10 mL). The mixture was extracted with EA (3 x 20 mL). The organic layers were combined, washed with brine (3 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with MeOH:DCM (1:12) to provide tert-butyl (1S,3aR,4S,7R,7aS)-1-(((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)carbamoyl)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-carboxylate (900 mg, 70%) as a brown yellow solid. LC-MS (ESI, *m/z*): 503 $[M+H]^+$.

EXAMPLE 1
Compound 1

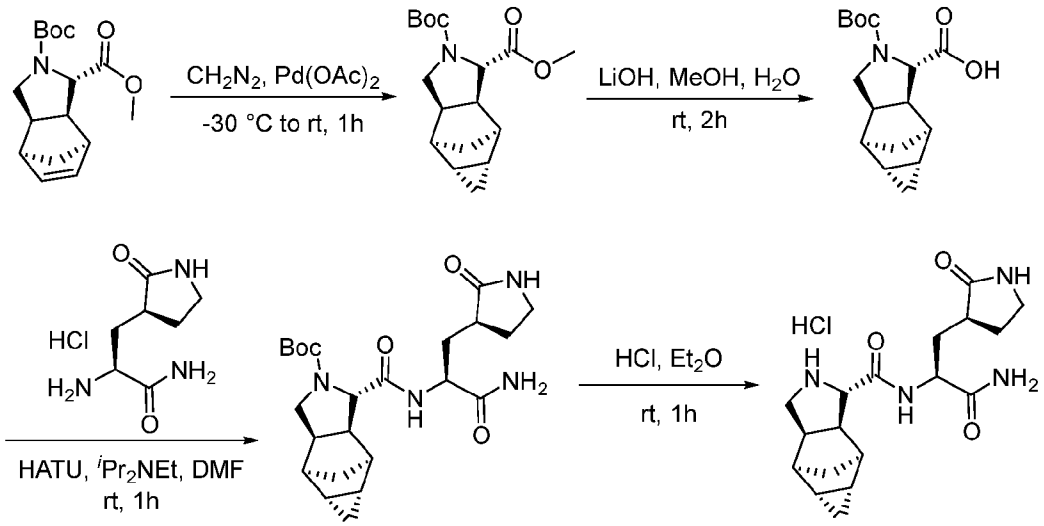


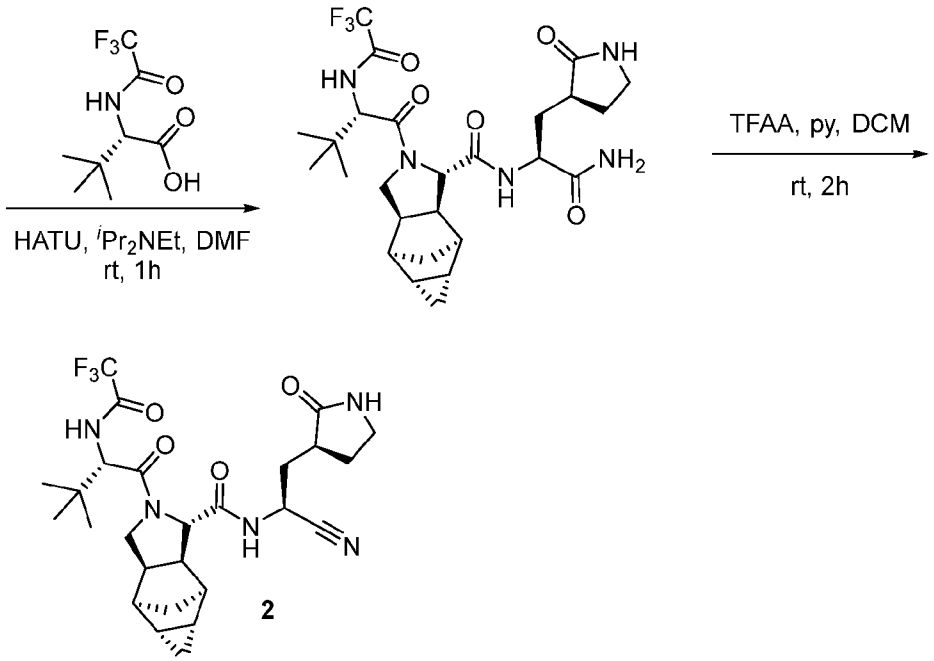
[0204] To a solution of tert-butyl (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoate (118 mg, 0.42 mmol, 1.2 eq.) in DMF (2 mL) was added N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophospate (171 mg, 0.45 mmol, 1.3 eq.) and N,N-diisopropylethylamine (313 mg, 2.42 mmol, 7.0 eq.). The mixture was stirred at 0 °C for 30 min and then (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (115 mg, 0.35 mmol, 1.0 eq.) was added. The mixture was stirred at rt for 2 h, and the reaction was quenched with water (3 mL). The mixture was extracted with EA (3 x 5 mL). The organic layers were combined, washed with brine (3 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a C18 column with water:MeCN (2:1) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (150 mg, yield 72%) as a brown yellow solid. LC-MS (ESI, *m/z*): 542 $[M+H]^+$.

[0205] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (120 mg, 0.22 mmol, 1.0

eq.) in DCM (3 mL) was added TFAA (88.4 mg, 0.42 mmol, 1.9 eq.) and pyridine (61.3mg, 0.78 mmol, 3.5 eq.). The mixture was stirred at 0 °C for 4 h, and the reaction was quenched with water (4 mL). The mixture was extracted with DCM (3 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*150 mm, 5μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 30% B to 50% B in 7 min, 50% B; Wave Length: 254 nm; RT1(min): 5.55;) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (**1**) (53.2 mg, yield 45%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 8.66-8.95 (m, 2H), 7.28-7.37 (m, 1H), 5.96-6.23 (m, 2H), 4.87-4.93 (m, 1H), 4.41-4.68 (m, 1H), 3.86-4.17 (m, 1H), 3.58-3.71 (m, 1H), 3.20-3.51 (m, 2H), 2.83-3.06 (m, 4H), 2.59-2.79 (m, 1H), 2.29-2.38 (m, 1H), 2.03-2.28 (m, 2H), 1.61-1.84 (m, 2H), 1.31-1.42 (m, 2H), 0.79-0.90 (m, 9H). LC-MS (ESI, *m/z*): 524 $[M+H]^+$.

EXAMPLE 2
Compound 2





[0206] To a solution of 4-tert-butyl 3-methyl (1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,4-dicarboxylate (300 mg, 1.02 mmol, 1.0 eq.) in Et_2O (2.5 mL) at -30°C was added diazomethane (30 mL, 30.0 eq.) and palladium(II) acetate (45.9 mg, 0.205 mmol, 0.2 eq.). The mixture was stirred for 1 h at rt and then filtered. The filter cake was washed with diethyl ether (3 x 50 mL). The filtrate was concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with ethyl acetate (EA):petroleum ether (PE) (1:8) to provide 4-tert-butyl 3-methyl (1R,2S,3S,6R,7S,8S,10R)-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3,4-dicarboxylate (200 mg, 58%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.25-4.50 (m, 1H), 3.53-3.72 (m, 4H), 3.22-3.30 (m, 1H), 2.52-2.64 (m, 2H), 2.22-2.42 (m, 2H), 1.21-1.47 (m, 9H), 1.03-1.16 (m, 1H), 0.70-0.95 (m, 3H), 0.39-0.54 (m, 1H), -0.09-0.05 (m, 1H). LC-MS (ESI, *m/z*): 208 $[M+H\text{-}Boc]^+$.

[0207] To a stirred mixture of 4-tert-butyl 3-methyl (1R,2S,3S,6R,7S,8S,10R)-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3,4-dicarboxylate (245 mg, 0.797 mmol, 1.0 eq.) in MeOH (3 mL) and H_2O (3 mL) were added lithium hydroxide (95.4 mg, 3.98 mmol, 5.0 eq.). The mixture was stirred for 2 h at rt. The mixture was acidified to pH 4 with hydrochloric acid (1M) and then extracted with ethyl acetate (3 x 10 mL). The mixture was concentrated under reduced pressure to afford (1R,2S,3S,6R,7S,8S,10R)-4-(tert-

butoxycarbonyl)-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3-carboxylic acid (200 mg, 85%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H), 4.17-4.39 (m, 1H), 3.47-3.76 (m, 1H), 3.12-3.31 (m, 1H), 2.51-2.59 (m, 2H), 2.20-2.44 (m, 2H), 1.27-1.49 (m, 9H), 1.05-1.22 (m, 1H), 0.69-0.93 (m, 3H), 0.40-0.51 (m, 1H), -0.06-0.00 (m, 1H). LC-MS (ESI, *m/z*): 238 $[M+H-56]^+$.

[0208] To a stirred mixture of (1R,2S,3S,6R,7S,8S,10R)-4-(tert-butoxycarbonyl)-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3-carboxylic acid (200 mg, 0.682 mmol, 1.0 eq.) in DMF (2 mL) was added o-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (311 mg, 0.818 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (528 mg, 4.09 mmol, 6.0 eq.) at rt. The mixture was stirred for 10 min at 0 °C and then (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (141 mg, 0.682 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% FA). The compound fraction was concentrated under reduced pressure to provide tert-butyl (1R,2S,3S,6R,7S,8S,10R)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-4-carboxylate (200 mg, 55%) as a white solid. LC-MS (ESI, *m/z*): 447 $[M+H]^+$.

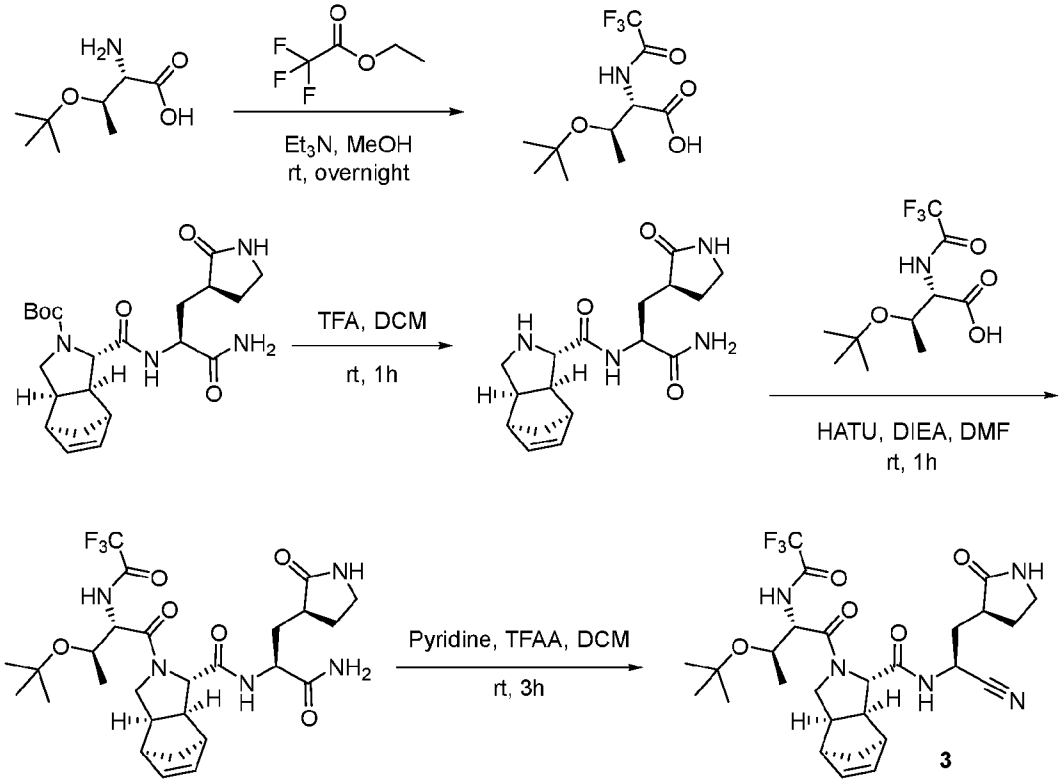
[0209] To a stirred mixture of tert-butyl (1R,2S,3S,6R,7S,8S,10R)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-4-carboxylate (200 mg, 0.448 mmol, 1.0 eq.) in DCM (1 mL) was added hydrochloric acid (3 mL, 2M in Et_2O) at rt. The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (2S)-2-[(1R,2S,3S,6R,7S,8S,10R)-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecan-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (200 mg, crude) as a white solid. LC-MS (ESI, *m/z*): 347 $[M+H]^+$.

[0210] To a stirred mixture of (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoic acid (101 mg, 0.446 mmol, 1.1 eq.) in DMF (2 mL) was added o-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (184 mg, 0.486 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (314 mg, 2.43 mmol, 6.0 eq.). The mixture was stirred for 10 min at 0 °C, and then (2S)-2-[(1R,2S,3S,6R,7S,8S,10R)-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecan-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-

yl]propanamide hydrochloride (155 mg, 0.405 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% FA). The compound fraction was concentrated under reduced pressure to provide (2S)-2-{[(1R,2S,3S,6R,7S,8S,10R)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (170 mg, 67%) as a white solid. LC-MS (ESI, *m/z*): 556 $[M+H]^+$.

[0211] To a stirred mixture of (2S)-2-{[(1R,2S,3S,6R,7S,8S,10R)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (100 mg, 0.180 mmol, 1.0 eq.) in DCM (2 mL) was added trifluoroacetic anhydride (75.6 mg, 0.360 mmol, 2.0 eq.) and pyridine (49.8 mg, 0.630 mmol, 3.5 eq.) dropwise at rt. The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with dichloromethane (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect Peptide CSH C18 19*150mm 5μm, 1; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 34% B to 48% B in 10 min, 48% B; Wave Length: 254 nm; RT1(min): 8.98) to afford (1R,2S,3S,6R,7S,8S,10R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3-carboxamide (9.6 mg, 9%) as a white solid. ^1H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.47-9.13 (m, 2H), 7.33-7.62 (m, 1H), 4.82-4.95 (m, 1H), 4.56-4.75 (m, 2H), 3.90-4.04 (m,1H), 3.57-3.70 (m, 1H), 3.08-3.20 (m, 2H), 2.59-2.72 (m, 1H), 2.24-2.45 (m, 4H), 2.05-2.20 (m, 2H), 1.60-1.84 (m, 2H), 0.91-1.11 (m, 9H), 0.85-0.91 (m, 1H), 0.75-0.84 (m, 2H), 0.56-0.65 (m, 1H), 0.38-0.51 (m, 1H), -0.30-0.00 (m,1H).

EXAMPLE 3
Compound 3



[0212] To a stirred mixture of (2S,3R)-2-amino-3-(tert-butoxy)butanoic acid (1.00 g, 5.71 mmol, 1.0 eq.) in methanol (15 mL) was added trifluoroethyl acetate (0.970 g, 6.84 mmol, 1.2 eq.) and triethylamine (1.73 g, 17.1 mmol, 3.0 eq.). The mixture was stirred for overnight at rt. The reaction was quenched with water (50 mL). The mixture was adjusted to pH 5~6 with hydrochloric acid (1 M) and then extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (2S,3R)-3-(tert-butoxy)-2-(2,2,2-trifluoroacetamido)butanoic acid (1.58 g, crude) as a light brown solid. LC-MS (ESI, m/z): 270 $[M-H]^-$.

[0213] To a stirred mixture of tert-butyl (1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-4-carboxylate (120 mg, 0.277 mmol, 1.0 eq.) in DCM (3 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (92.0 mg, crude) as a brown oil. LC-MS (ESI, *m/z*):

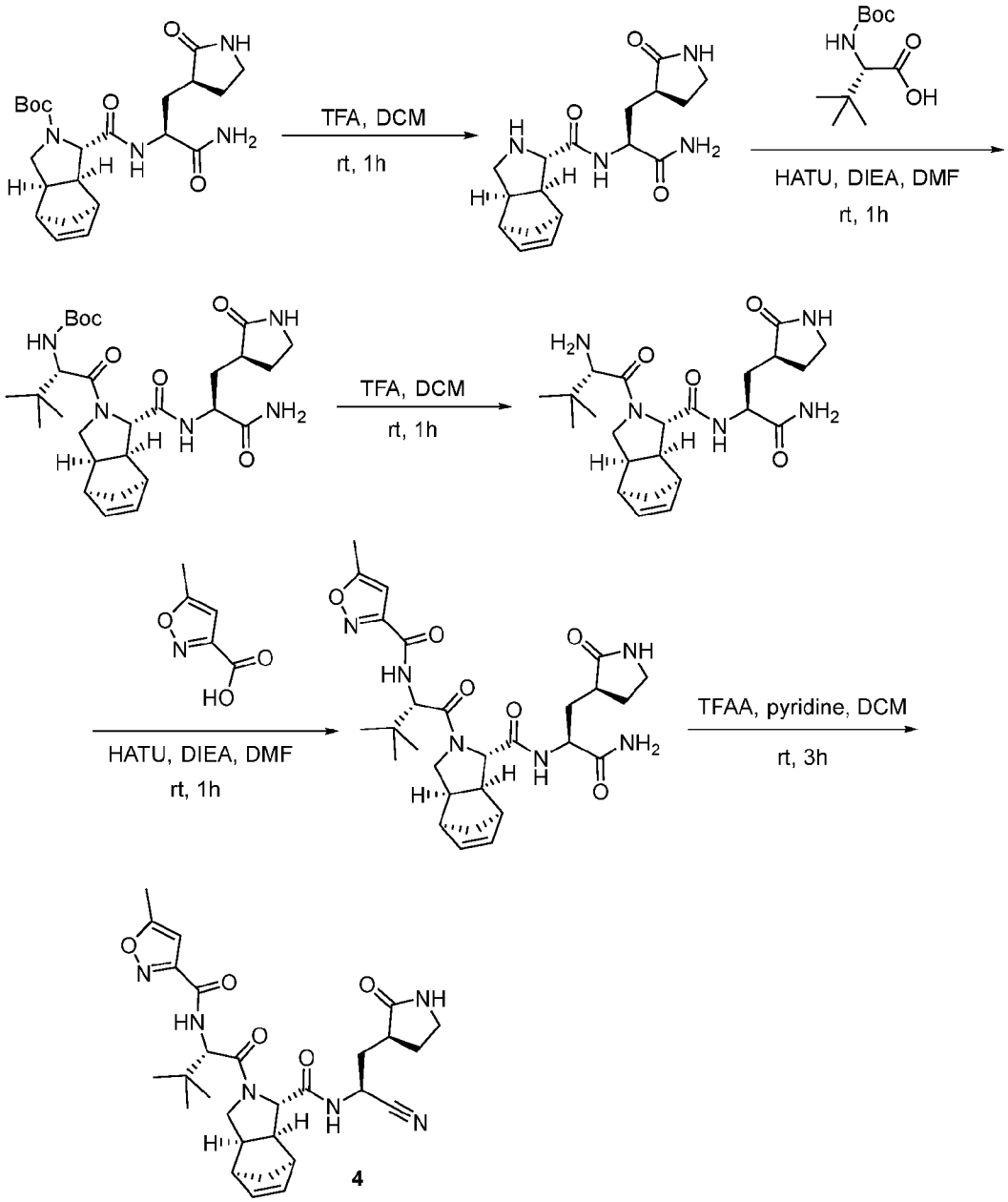
333 $[M+H]^+$.

[0214] To a stirred mixture of (2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (92.0 mg, 0.277 mmol, 1.0 eq.), (2S,3R)-3-(tert-butoxy)-2-(2,2,2-trifluoroacetamido)butanoic acid (75.1 mg, 0.277 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (126 mg, 0.332 mmol, 1.2 eq.) in DMF (4 mL) was added N-ethyl-N-isopropylpropan-2-amine (286 mg, 2.21 mmol, 8.0 eq.) at 0 °C. The mixture was stirred for 1 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (1:12) to provide the desired product. The crude product was purified by C18 column with CH_3CN:Water (0.05% TFA), the fraction was concentrated under reduced pressure to provide (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S,3R)-3-(tert-butoxy)-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (61.0 mg, crude) as a light yellow solid. LC-MS (ESI, *m/z*): 586 $[M+H]^+$.

[0215] To a stirred mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S,3R)-3-(tert-butoxy)-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (60.0 mg, 0.102 mmol, 1.0 eq.) in DCM (2 mL) were added pyridine (32.4 mg, 0.408 mmol, 4.0. eq.) and trifluoroacetic anhydride (43.1 mg, 0.204 mmol, 2.0 eq.). The mixture was stirred for 3 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by preparative HPLC (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 56% B in 10 min, 56% B; Wave Length: 254 nm; RT1(min): 8.22) to provide (1R,2S,3S,6R,7S)-4-[(2S,3R)-3-(tert-butoxy)-2-(2,2,2-trifluoroacetamido)butanoyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (1.7 mg, 2%). LC-MS (ESI, m/z): 512

$[M-56+H]^+$.

EXAMPLE 4
Compound 4



[0216] To a stirred mixture of tert-butyl (1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-4-carboxylate (500 mg, 1.15 mmol, 1.0 eq.) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to

afford (2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (380 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 333 $[M+H]^+$.

[0217] To a stirred mixture of (2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (76.0 mg, 0.229 mmol, 1.0 eq.), (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoic acid (52.9 mg, 0.229 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (104 mg, 0.275 mmol, 1.2 eq.) in DMF (2 mL) were added N-ethyl-N-isopropylpropan-2-amine (236 mg, 1.83 mmol, 8.0 eq.) at 0 °C. The mixture was stirred for 1 h at rt. The crude product was purified by C18 column with CH_3CN:Water (0.05% TFA). The compound fraction was concentrated under reduced pressure to provide tert-butyl N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (105 mg, 78%) as a white solid. LC-MS (ESI, *m/z*): 546 $[M+H]^+$.

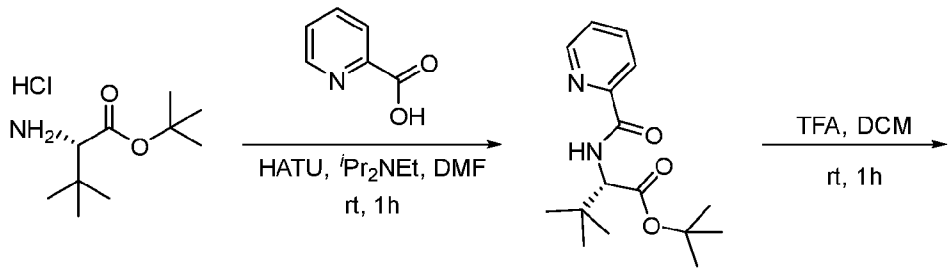
[0218] To a stirred mixture of tert-butyl N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (100 mg, 0.183 mmol, 1.0 eq.) in DCM (3 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (81.0 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 446 $[M+H]^+$.

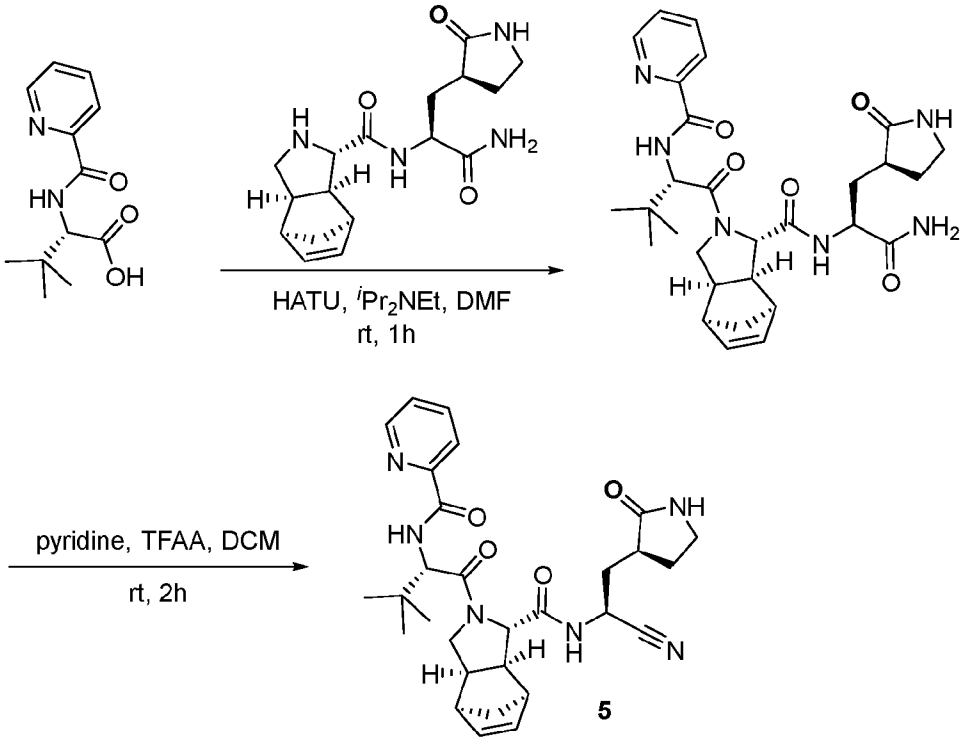
[0219] To a stirred mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (81.5 mg, 0.183 mmol, 1.0 eq.), o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (83.5 mg, 0.220 mmol, 1.2 eq.) and 5-methyl-1,2-oxazole-3-carboxylic acid (23.3 mg, 0.183 mmol, 1.0 eq.) in DMF (3 mL) were added N-ethyl-N-isopropylpropan-2-amine (189 mg, 1.46 mmol, 8.0 eq.). The mixture was stirred for 1 h at rt. The crude product was purified by C18 column with CH_3CN:Water (0.05% TFA). The compound fraction was concentrated under reduced pressure to provide

N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]-5-methyl-1,2-oxazole-3-carboxamide (74 mg, 62%) as a white solid. LC-MS (ESI, *m/z*): 554 $[M+H]^+$.

[0220] To a stirred mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]-5-methyl-1,2-oxazole-3-carboxamide (70.0 mg, 0.126 mmol, 1.0 eq.) in DCM (2 mL) were added pyridine (39.9 mg, 0.504 mmol, 4.0 eq.) and trifluoroacetic anhydride (53.0 mg, 0.252 mmol, 2.0 eq.). The mixture was stirred for 3 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 35% B to 65% B in 7 min, 65% B; Wave Length: 254 nm; RT1(min): 5) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-[(5-methyl-1,2-oxazol-3-yl)formamido]butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (7.70 mg, 11%) as a white solid. LC-MS (ESI, m/z): 537 $[M+H]^+$.

EXAMPLE 5
Compound 5





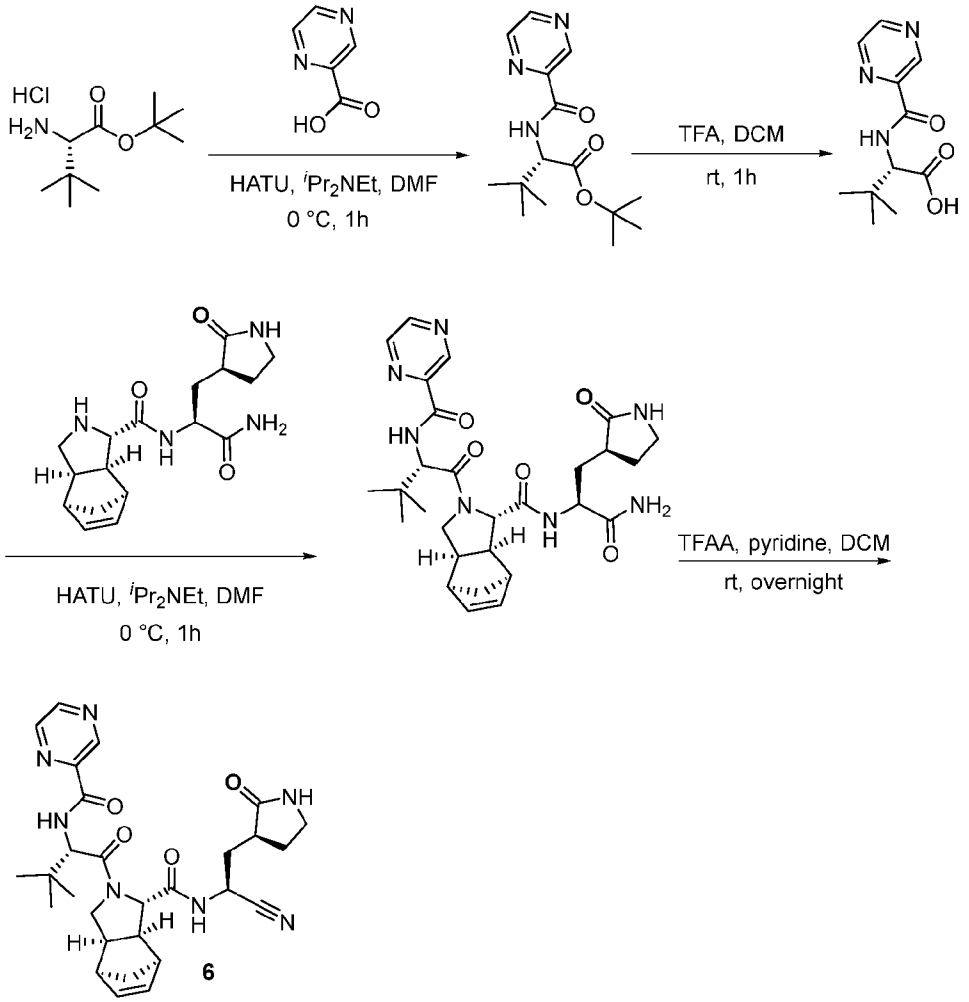
[0221] To a solution of picolinic acid (110 mg, 0.894 mmol, 1.0 eq.) in dimethylformamide (2 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (408 mg, 1.07 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (924 mg, 7.15 mmol, 8.0 eq.) 0 °C. After 0.5 h, tert-butyl (2S)-2-amino-3,3-dimethylbutanoate hydrochloride (200 mg, 0.894 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford then crude product. The crude product was purified by silica gel column chromatography to afford tert-butyl (2S)-3,3-dimethyl-2-(pyridin-2-ylformamido)butanoate (88 mg, 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67-8.73 (m, 1H), 8.40-8.50 (m, 1H), 8.00-8.10 (m, 2H), 7.62-7.69 (m, 1H), 4.26-4.33 (m, 1H), 1.44 (s, 9H), 1.00 (s, 9H). LCMS (ESI, *m/z*): 293 $[M+H]^+$.

[0222] To a solution of tert-butyl (2S)-3,3-dimethyl-2-(pyridin-2-ylformamido)butanoate (88.0 mg, 0.291 mmol, 1.0 eq.) in DCM (2 mL) was added trifluoroacetic acid (0.7 mL). The mixture was stirred for 4 h at rt and then concentrated under reduced pressure to afford the crude product. LCMS (ESI, *m/z*): 237 $[M+H]^+$.

[0223] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (100 mg, 0.301 mmol, 1 eq.) in DMF (4 mL) was added (2S)-3,3-dimethyl-2-(pyridin-2-ylformamido)butanoic acid (70.8 mg, 0.301 mmol, 1.0 eq.), o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (137.3 mg, 0.361 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (233 mg, 2.41 mmol, 8.0 eq.) stirred at 0 °C. The mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% FA). The compound fraction was concentrated under reduced pressure to afford N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]pyridine-2-carboxamide (50.0 mg, crude).

[0224] To a stirred mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]pyridine-2-carboxamide (25.0 mg, 0.045 mmol, 1.0 eq.) in DCM (2 mL) was added trifluoroacetic anhydride (8.81 mg, 0.090 mmol, 2.0 eq.) and pyridine (12.5 mg, 0.158 mmol, 3.5 eq.) dropwise at rt. The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product (25 mg) was purified by prep-HPLC with the following conditions (Column: Kinetex EVO C18, 21.2*250mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 35% B to 62% B in 7 min, 62% B; Wave Length: 254 nm; RT1(min): 5) to afford (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-(pyridin-2-ylformamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (3.2 mg, 12%) as a light yellow solid. LCMS (ESI, m/z): 533 $[M+H]^+$.

EXAMPLE 6
Compound 6



[0225] To a mixture of pyrazinoic acid (166 mg, 1.34 mmol, 1.0 eq.), o-(7-azabenzotriazol-1-yl)-N, N, N',N'-tetramethyluronium hexafluorophosphate (612 mg, 1.61 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (1.04 g, 8.05 mmol, 6.0 eq.) in N,N-dimethylformamide (3 mL) was stirred for 20 min. Tert-butyl (2S)-2-amino-3,3-dimethylbutanoate hydrochloride (300 mg, 1.34 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 1 h at rt, and the reaction quenched with water (2 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was diluted with dichloromethane (10 mL) and made into a slurry with 100 ~ 200 silica gel mesh (1 g). The slurry was loaded to a column after removing the dichloromethane. The sample was purified

by column chromatography (Column size 4 x 24 cm, column volume: 200 mL, silica gel size (100 ~ 200 mesh) and eluted with EA:PE (0% ~ 40% over 30 min). The collected fractions: 23% - 26% EA:PE fractions were chosen as the pure fractions. Those fractions were combined and concentrated under reduced pressure to provide tert-butyl (2S)-3,3-dimethyl-2-(pyrazin-2-ylformamido)butanoate (300 mg, 76%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (br, 1H), 8.91-8.95 (m, 1H), 8.75-8.82 (m, 1H), 8.29-8.33 (m, 1H), 4.31-4.34 (m, 1H), 1.45 (s, 9H), 1.01 (s, 9H). LC-MS (ESI, *m/z*): 294 $[M+H]^+$.

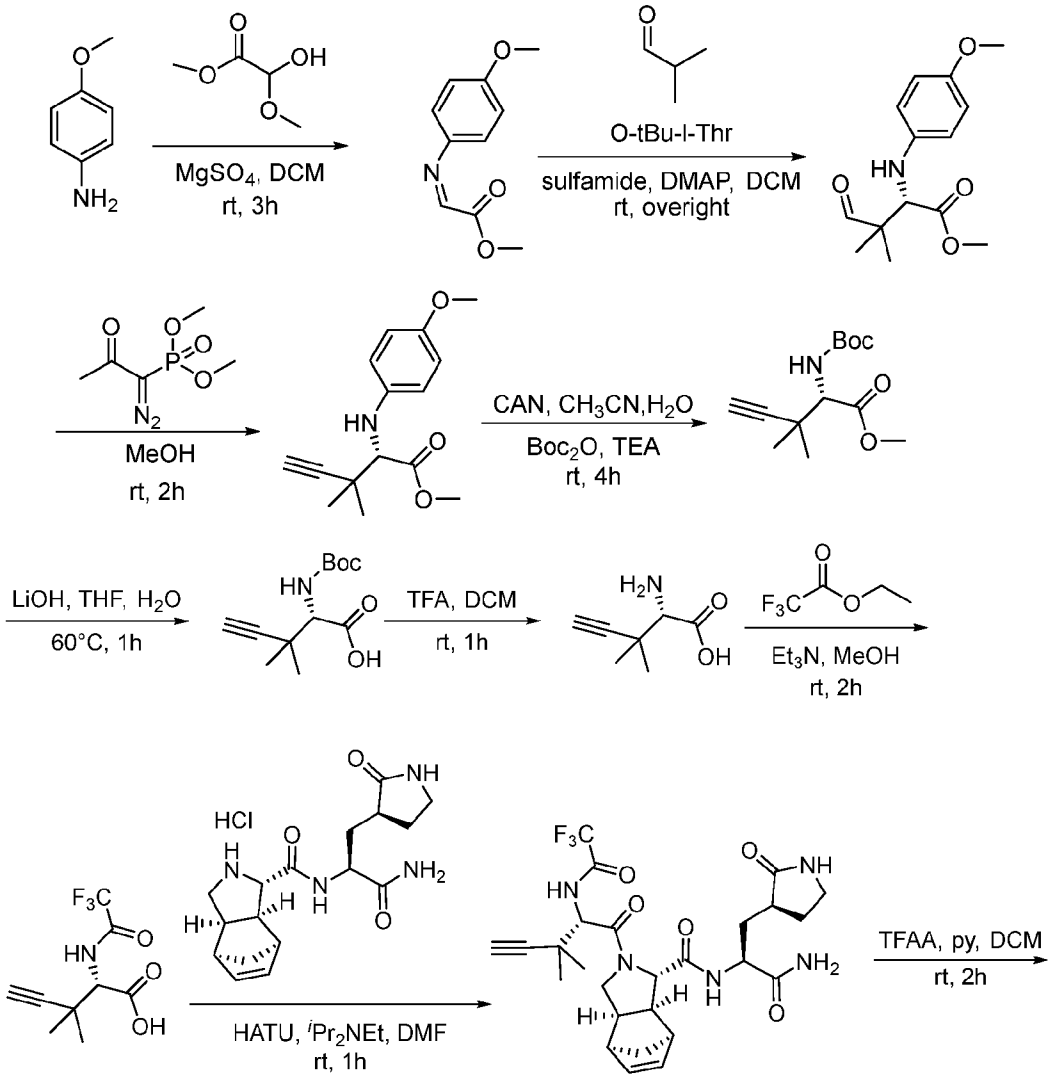
[0226] To a mixture of tert-butyl (2S)-3,3-dimethyl-2-(pyrazin-2-ylformamido)butanoate (87.9 mg, 0.300 mmol, 1.0 eq.) in dichloromethane (1 mL) was added trifluoroacetic acid (0.5 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (2S)-3,3-dimethyl-2-(pyrazin-2-ylformamido)butanoic acid (80.0 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 238 $[M+H]^+$.

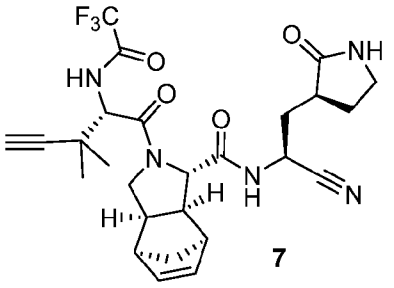
[0227] To a mixture of (2S)-3,3-dimethyl-2-(pyrazin-2-ylformamido) butanoic acid (71.1 mg, 0.30 mmol, 1.0 eq.), and (2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo [5.2.1.0^{2,6}] dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (99.6 mg, 0.30 mmol, 1.0 eq.) in DMF (3 mL) was added N-ethyl-N-isopropylpropan-2-amine (348 mg, 2.70 mmol, 9.0 eq.) at 0 °C. The mixture was stirred for 1 h at rt. The crude product was purified by C18 column with CH_3CN:Water (0.05% NH_4HCO_3). The compound fraction was concentrated under reduced pressure to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl] ethyl]-4-[(2S)-3,3-dimethyl-2-(pyrazin-2-ylformamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (70.0 mg, 43%) as a yellow solid. LC-MS (ESI, *m/z*): 552 $[M+H]^+$.

[0228] To a mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]pyrazine-2-carboxamide (55.0 mg, 0.100 mmol, 1.0 eq.) in dichloromethane (1 mL) was added pyridine (31.5 mg, 0.400 mmol, 4.0 eq.) and trifluoroacetic anhydride (41.9 mg, 0.200 mmol, 2.0 eq.). The mixture was stirred for overnight at rt. The reaction was quenched with water (5 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced

pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Prep C18 OBD Column, 19*150 mm, 5μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 43% B to 53% B in 12 min, 53% B; Wave Length: 254 nm; RT1(min): 11) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-(pyrazin-2-ylformamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (3.0 mg, 5%) as an off-white solid. LC-MS (ESI, *m/z*): 534 $[M+H]^+$.

EXAMPLE 7
Compound 7





7

[0229] To a mixture of 4-methoxyaniline (5.0 g, 36.4 mmol, 1.0 eq.) and magnesium sulfate (24.4 g, 202 mmol, 5.0 eq.) in DCM (100 mL) was added methyl 2-hydroxy-2-methoxyacetate (4.88 g, 40.5 mmol, 1.0 eq.). The mixture was stirred for 3 h at rt and filtered. The filter cake was washed with dichloromethane (3 x 100 mL). The filtrate was concentrated under reduced pressure to afford methyl (2Z)-2-[(4-methoxyphenyl)imino]acetate (8 g, crude) as a brown yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.33-7.43 (m, 2H), 6.85-6.99 (m, 2H), 3.94 (s, 3H), 3.83 (s, 3H). LC-MS (ESI, *m/z*): 194 $[M+H]^+$.

[0230] To a stirred mixture of powdered molecular sieves (5 A, 4g), sulfamide (0.20 g, 2.07 mmol, 0.05 eq.) and N,N-dimethylpyridin-4-amine (0.25 g, 2.07 mmol, 0.05 eq.) in DCM (40 mL) was added methyl (2Z)-2-[(4-methoxyphenyl)imino]acetate (8.00 g, 41.4 mmol, 1.0 eq.) and isobutyraldehyde (3.58 g, 49.6 mmol, 1.2 eq.) at rt. The mixture was stirred for overnight at rt. The reaction was quenched with water (150 mL). The mixture was extracted with ethyl acetate (3 x 150 mL). The organic layers were combined, washed with brine (2 x 150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EA:PE (1:4) to provide methyl (2S)-2-[(4-methoxyphenyl)amino]-3,3-dimethyl-4-oxobutanoate (4.5 g, 36 %) as a light yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (s, 1H), 6.73 (m, 4H), 5.42 (d, J = 8.0 Hz, 1H), 4.44 (d, J = 8.0 Hz, 1H), 3.65 (s, 3H), 3.61 (s, 3H), 0.85-1.34 (m, 6H). LC-MS (ESI, *m/z*): 266 $[M+H]^+$.

[0231] To a stirred mixture of methyl (2S)-2-[(4-methoxyphenyl)amino]-3,3-dimethyl-4-oxobutanoate (4.5 g, 16.9 mmol, 1.0 eq.) and potassium carbonate (4.69 g, 33.9 mmol, 2.0 eq.) in MeOH (50 mL) was added dimethyl (1-diazo-2-oxopropyl)phosphonate (4.24 g, 22.0 mmol, 1.3 eq.) dropwise at rt under N_2. The mixture was stirred for 2 h at rt.

The reaction was quenched with water (200 mL). The mixture was extracted with ethyl acetate (3 x 200 mL). The organic layers were combined, washed with brine (2 x 200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EA:PE (1:9) to provide methyl (2S)-2-[(4-methoxyphenyl)amino]-3,3-dimethylpent-4-ynoate (1.70 g, 36 %) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.65-6.76 (m, 4H), 5.05 (d, J = 12.0 Hz, 1H), 3.92 (d, J = 12.0 Hz, 1H), 3.61-3.64 (m, 6H), 3.09 (s, 1H), 1.34 (s, 3H), 1.29 (s, 3H). LC-MS (ESI, *m/z*): 262 $[M+H]^+$.

[0232] To a stirred mixture of methyl (2S)-2-[(4-methoxyphenyl)amino]-3,3-dimethylpent-4-ynoate (1.14 g, 4.36 mmol, 1.0 eq.) in CH_3CN (9 mL) and H_2O (3 mL) were added ceric ammonium nitrate (12.0 g, 21.8 mmol, 5.0 eq.) at rt. The mixture was stirred for 2 h at rt. THF (10 mL) was added, followed by trimethylamine and di-tert-butyl dicarbonate (5.48 g, 25.1 mmol, 6.0 eq.). The mixture was stirred for 4 h at rt and then diluted with water (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EA:PE (1:9) to provide methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylpent-4-ynoate (800 mg, 63 %) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.01 (d, J = 12.0 Hz, 1H), 4.11 (d, J = 12.0 Hz, 1H), 3.65 (s, 3H), 3.06 (s, 1H), 1.39 (s, 9H), 1.21-1.23 (m, 6H). LC-MS (ESI, *m/z*): 156 $[M+H-Boc]^+$.

[0233] To a stirred mixture of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylpent-4-ynoate (800 mg, 3.13 mmol, 1.0 eq.) in THF (6 mL) and H_2O (2 mL) was added lithium hydroxide (375 mg, 15.6 mmol, 5.0 eq.) at rt . The mixture was stirred for 1 h at 60 °C. The mixture was acidified to pH 3 with hydrochloric acid (1M). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The mixture was concentrated under reduced pressure to afford (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylpent-4-ynoic acid (700 mg, 92%) as a light orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.00 (d, J = 8.0 Hz, 1H), 3.03 (s, 1H), 1.40 (s, 9H), 1.17-1.24 (m, 6H). LC-MS (ESI, *m/z*): 142 $[M-100+H]^+$.

[0234] To a stirred mixture of (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylpent-4-ynoic acid (400 mg, 1.65 mmol, 1.0 eq.) in DCM (3 mL) was added

trifluoroacetic acid (1 mL) at rt. The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (2S)-2-amino-3,3-dimethylpent-4-ynoic acid (300 mg, crude) as a brown yellow oil. LC-MS (ESI, *m/z*): 142 $[M+H]^+$.

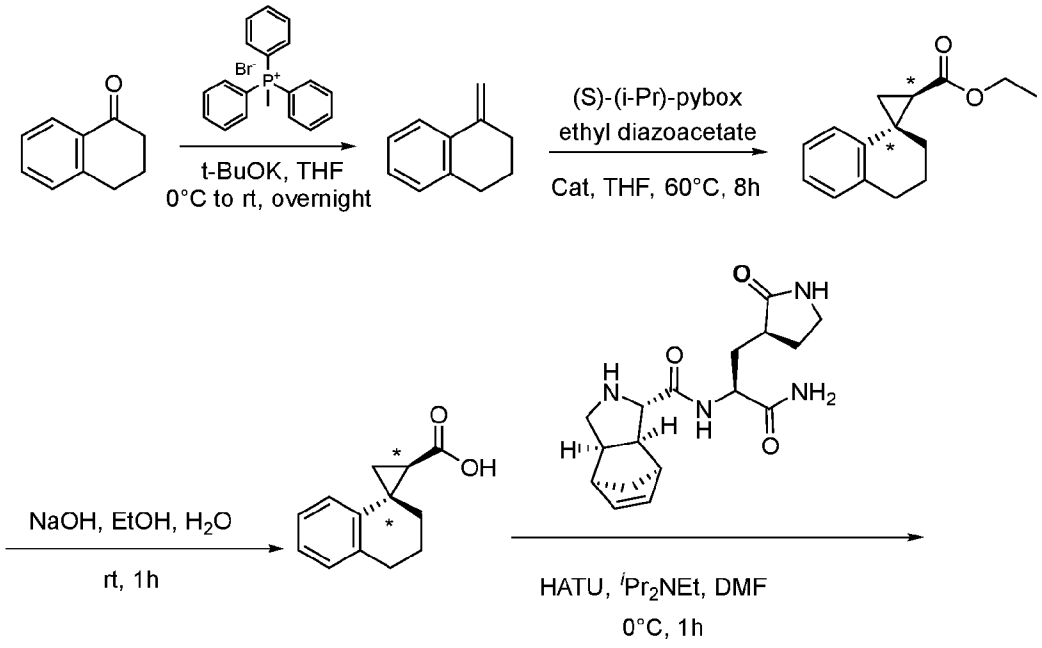
[0235] To a stirred mixture of (2S)-2-amino-3,3-dimethylpent-4-ynoic acid (234 mg, 1.65 mmol, 1.0 eq.) and triethylamine (670 mg, 6.63 mmol, 4.0 eq.) in MeOH (3 mL) was added trifluoroethyl acetate (471 mg, 3.31 mmol, 2.0 eq.). The mixture was stirred for 2 h at rt and then acidified to pH 4 with hydrochloric acid (1M). The mixture was extracted with ethyl acetate (3 x 20mL). The combined organic layers were concentrated under reduced pressure to afford (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-ynoic acid (300 mg, 76 %) as a light yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.28 (s, 1H), 9.67 (d, J = 8.0 Hz, 1H), 4.45 (d, J = 8.0 Hz, 1H), 3.09 (s, 1H), 1.25-1.41 (m, 6H). LC-MS (ESI, *m/z*): 236 $[M-H]^-$.

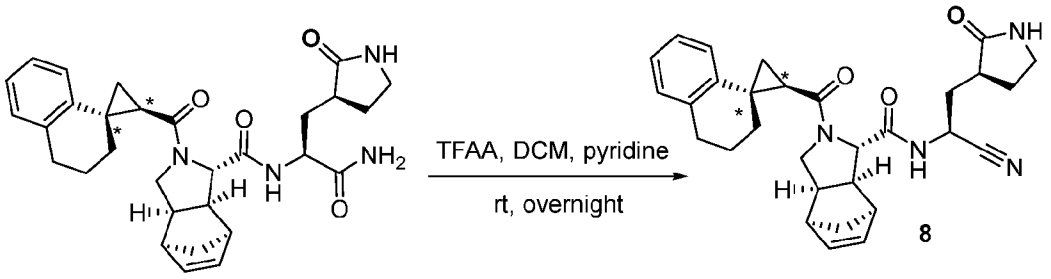
[0236] To a stirred mixture of (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-ynoic acid (71.3 mg, 0.300 mmol, 1.0 eq.) in DMF (2 mL) was added o-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (137 mg, 0.361 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (232 mg, 1.80 mmol, 6.0 eq.) at rt. The mixture was stirred for 10 min 0 °C and (2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (110 mg, 0.300 mmol, 1.0 eq.) was added. The mixture was stirred for another 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% FA). The compound fraction was concentrated under reduced pressure to provide (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-ynoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (120 mg, 51 %) as a light yellow solid. LC-MS (ESI, *m/z*): 552 $[M+H]^+$.

[0237] To a stirred mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-ynoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (120 mg, 0.218 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (60.2 mg, 0.763 mmol, 3.5 eq.) and trifluoroacetic anhydride (91.3 mg, 0.436 mmol, 2.0 eq.) at rt. The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over

anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford then crude product. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 254 nm; RT1(min): 5;) to afford (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-ynoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (14.9 mg, 12 %) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.46-9.16 (m, 2H), 7.27-7.52 (m, 1H), 5.93-6.25 (m, 2H), 4.78-4.93 (m, 1H), 4.62-4.75 (m, 1H), 3.89-4.09 (m, 1H), 3.55-3.76 (m, 1H), 3.33-3.47 (m, 1H), 3.09-3.21 (m, 2H), 2.79-3.02 (m, 4H), 2.65-2.78 (m, 1H), 2.27-2.41 (m, 1H), 1.98-2.25 (m, 2H), 1.61-1.91 (m, 2H), 1.32-1.45 (m, 2H), 1.07-1.31 (m, 6H).

EXAMPLE 8
Compound 8





Chiral centers noted with a * are tentatively assigned

[0238] To a mixture of methyltriphenylphosphanium bromide (68.4 g, 191 mmol, 1.4 eq.) in tetrahydrofuran (100 mL) was added 1-tetralone (20.0 g, 136 mmol, 1.0 eq.) at 0 °C. After stirred for 0.5 h at 0 °C, methyltriphenylphosphanium bromide (68.4 g, 191 mmol, 1.4 eq.) was added. The mixture was stirred for overnight at rt, and then filtered. The filtrate was concentrated under reduced pressure to afford the crude product. The crude product was diluted with dichloromethane (100 mL) and made into a slurry with 100~200 silica gel mesh (60 g). The mixture was loaded to a column after removing the dichloromethane. The sample was purified by column chromatography (Column size 6 x 24 cm, column volume: 600 mL, silica gel size (100 ~ 200 mesh) and eluted with petroleum ether (0 %~10% over 30 min). The collected fractions: 0% petroleum ether fractions were chosen as the pure fractions. Those fractions were combined and concentrated under reduced pressure to provide 1-methylidene-3,4-dihydro-2H-naphthalene (12.0 g, 60%) as a light yellow oil. LC-MS (ESI, *m/z*): 145 $[M+H]^+$.

[0239] To a stirred mixture of 1-methylidene-3,4-dihydro-2H-naphthalene (1.00 g, 6.930 mmol, 1.0 eq.), $[Ru(p\text{-cymene})Cl_2]_2$ (212 mg, 0.350 mmol, 0.05 eq.) and (S)-(i-Pr)-Pybox (209 mg, 0.690 mmol, 0.1 eq.) in tetrahydrofuran (80 mL) was added ethyl 2-diazoacetate (1.18 g, 10.4 mmol, 1.5 eq.) in portions over 8 h at 60 °C under nitrogen. The reaction was quenched with water (20 mL). The mixture was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The sample was purified by column chromatography (Column size 6 x 24 cm, column volume: 600 mL, silica gel size (100 ~ 200 mesh) and eluted with ethyl acetate:petroleum ether (0 %~10% over 30 min). The collected fractions: 5~8 % petroleum ether fractions were chosen as pure fractions. Those fractions were combined and concentrated under reduced pressure to provide the crude product. The crude product was

purified by TLC (Mobile phase: ethyl acetate:petroleum ether =1:40; R_f = 0.4; detection: UV) to provide ethyl (1R*,3R*)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-3-carboxylate as a light yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.01-7.13 (m, 3H), 6.81-6.86 (m, 1H), 4.02-4.19 (m, 2H), 2.80-2.84 (m, 2H), 1.76-1.93 (m, 4H), 1.52-1.71 (m, 2H), 1.34-1.43 (m, 1H), 1.16-1.24 (m, 3H). LC-MS (ESI, *m/z*): 231 $[M+H]^+$.

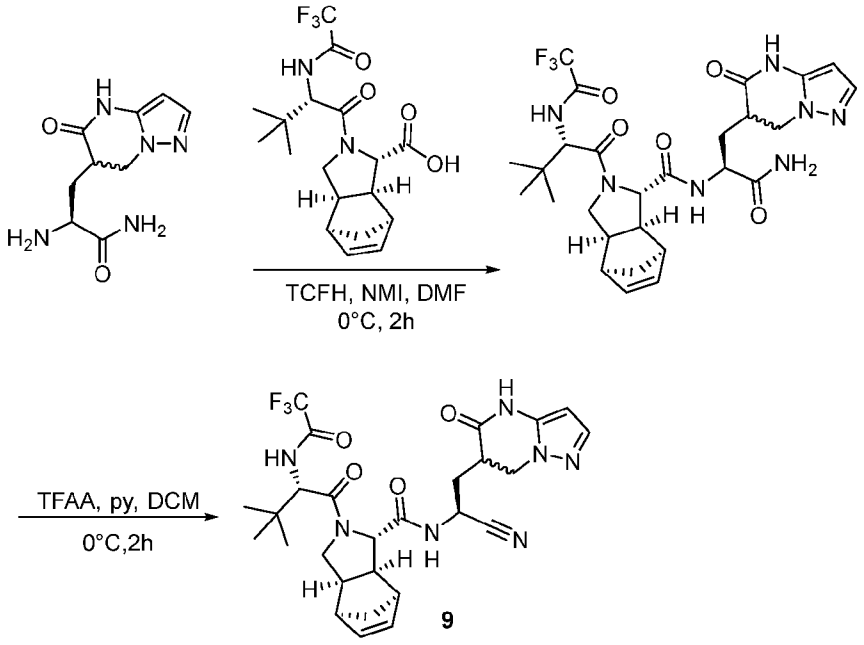
[0240] To a stirred solution of ethyl (1R,3R)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-3-carboxylate (380 mg, 1.65 mmol, 1.0 eq.) in ethanol (4 mL) were added sodium hydroxide (461 mg, 11.5 mmol, 7.0 eq., in water 4 mL). The mixture was stirred for overnight at rt. The mixture was concentrated under reduced pressure to remove the ethanol. The mixture was adjusted to pH 5 with hydrochloric acid (2 M) and then extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide (1R,3R)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-3-carboxylic acid (240 mg, 71%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.24 (br, 1H), 6.89-7.21 (m, 4H), 2.72-2.91 (m, 2H), 1.51-1.89 (m, 6H), 1.26-1.45 (m, 1H). LC-MS (ESI, *m/z*): 203 $[M+H]^+$.

[0241] To a mixture of (1R,3R)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-3-carboxylic acid (71.2 mg, 0.352 mmol, 1.0 eq.) in N,N-dimethylformamide (3 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (24.74 mg, 0.065 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (273 mg, 2.11 mmol, 6.0 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C, and then (2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (130 mg, 0.352 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 1 h rt. The crude product was purified by C18 column with CH_3CN:Water (TFA 0.05%). The compound fraction was concentrated under reduced pressure to provide (2S)-2-{[(1R,2S,3S,6R,7S)-4-{[(1R,3R)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3-yl]carbonyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propenamide (70 mg, 43%) as a yellow solid. LC-MS (ESI, m/z): 517 [M+H]+.

[0242] To a mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-{[(1S,3S)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3-yl]carbonyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-

yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (70.0 mg, 0.135 mmol, 1.0 eq.) in dichloromethane (1 mL) was added pyridine (37.5 mg, 0.473 mmol, 3.5 eq.) and trifluoroacetic anhydride (56.9 mg, 0.270 mmol, 2.0 eq.). The mixture was stirred for overnight at rt. The reaction was quenched with water (5 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 19*150 mm, 5μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 41% B to 61% B in 7 min, 61% B; Wave Length: 254 nm; RT1(min): 5.47) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-{[(1R,3R)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-3-yl]carbonyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (17 mg, 25%) as an white solid. LC-MS (ESI, *m/z*): 499 $[M+H]^+$.

EXAMPLE 9
Compound 9

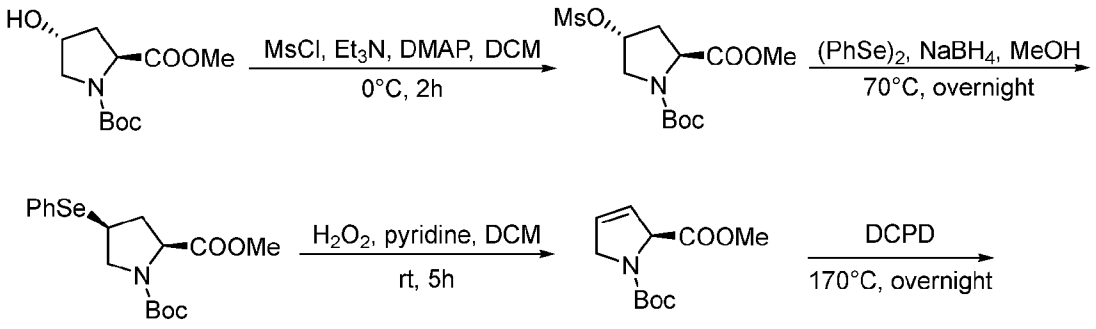


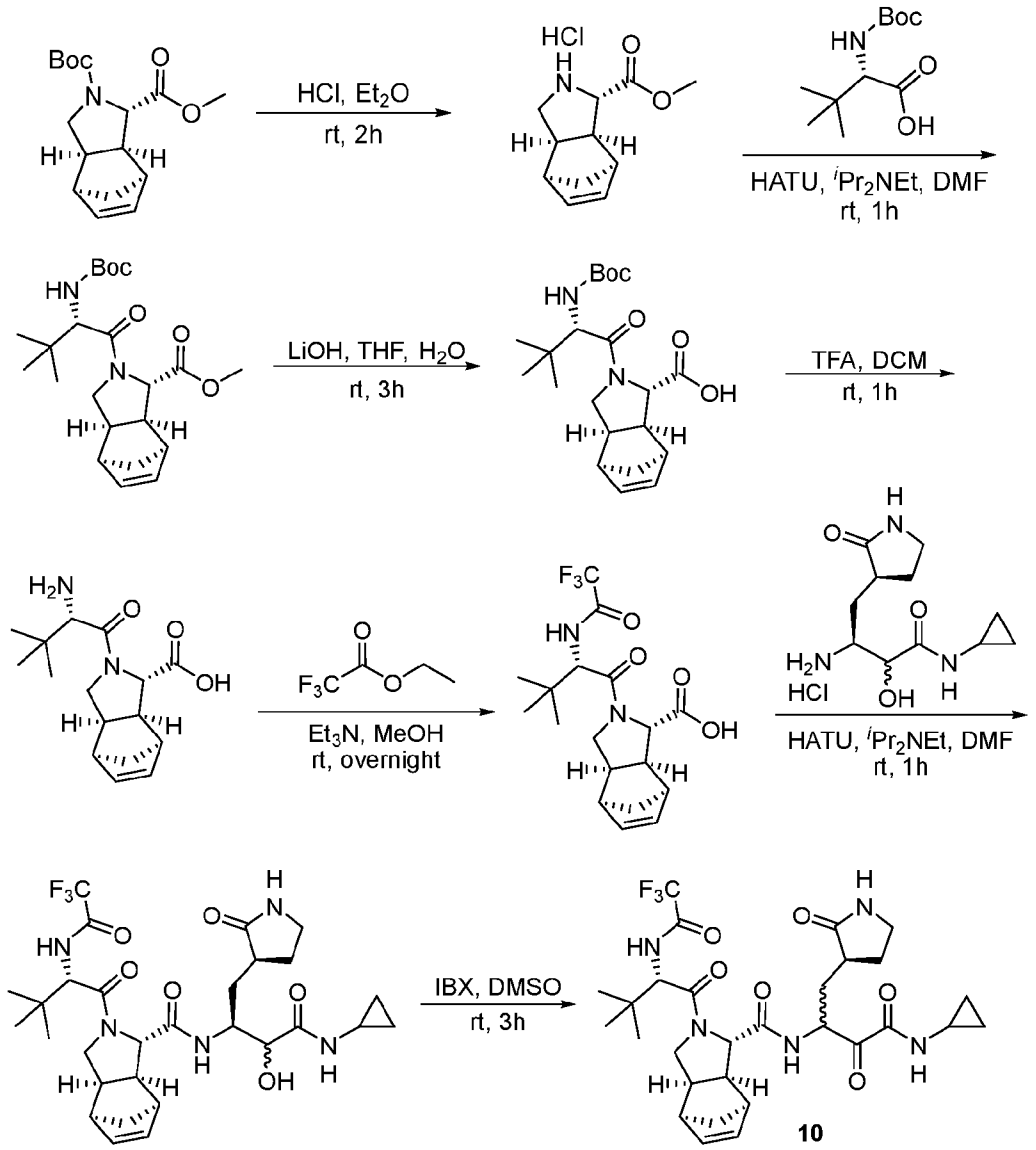
[0243] To a solution of (2S)-2-amino-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanamide(2S)-2-amino-3-{5-oxo-4H,6H,7H-pyrazolo[1,5-a]pyrimidin-6-yl}propanamide (70 mg, 0.31 mmol, 1.0 eq.) in DMF (2 mL) was added N,N,N,N-

tetramethylchloroformamidinium hexafluorophosphate (106 mg, 0.38 mmol, 1.2 eq.), NMI (180 mg, 2.2 mmol, 7.0 eq.) and (2S)-2-amino-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanamide (134 mg, 0.35 mmol, 1.1 eq.). The mixture was stirred at 0 °C for 2 h and then chromatographed on a C18 column with MeCN:H_2O (3:7) to provide (1S,3aR,4S,7R,7aS)-N-((2S)-1-amino-1-oxo-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (75 mg, 36%) as a brown yellow semi-solid. LC-MS (ESI, *m/z*): 594 $[M+H]^+$.

[0244] To a solution of (1S,3aR,4S,7R,7aS)-N-((2S)-1-amino-1-oxo-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (75 mg, 0.13 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (70 mg, 0.88 mmol, 7.0 eq.) and TFAA (106 mg, 0.5 mmol, 4.0 eq.) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction was quenched with water (2 mL). The mixture was extracted with DCM (3 x 3 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 67% B in 7 min, 67% B; Wave Length: 254 nm; RT1(min): 5.25) to provide (1S,3aR,4S,7R,7aS)-N-((1S)-1-cyano-2-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (4.5 mg, 6%) as a white solid. LC-MS (ESI, *m/z*): 576 $[M+H]^+$.

EXAMPLE 10
Compound 10





[0245] To a mixture of 1-tert-butyl 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (30.0 g, 122 mmol, 1.0 eq.), triethylamine (22.3 g, 220 mmol, 1.8 eq.) and N,N-dimethylpyridin-4-amine (4.48 g, 36.7 mmol, 0.3 eq.) in DCM (500 mL) was added dropwise methanesulfonyl chloride (21.0 g, 183 mmol, 1.5 eq.) at 0 °C. The mixture was stirred for 2 h at 0 °C. The reaction was quenched with water (500 mL). The mixture was extracted with DCM (3 x 500 mL). The organic layers were combined, washed with brine (2 x 500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EtOAc:petroleum ether (1:1) to provide 1-tert-butyl 2-methyl (2S,4R)-4-

(methanesulfonyloxy)pyrrolidine-1,2-dicarboxylate (35.0 g, 85%) as a light yellow solid. LC-MS (ESI, *m/z*): 224 $[M+H-Boc]^+$.

[0246] To a mixture of 1-tert-butyl 2-methyl (2S,4R)-4-(methanesulfonyloxy)pyrrolidine-1,2-dicarboxylate (25.0 g, 77.3 mmol, 1.0 eq.) and diphenyl diselenide (24.1 g, 77.3 mmol, 1.0 eq.) in MeOH (600 mL) was added sodium borohydride (3.80 g, 100 mmol, 1.3 eq.) at 0 °C. The mixture was stirred overnight at 70 °C and then concentrated under reduced pressure to remove the MeOH. Water (600 mL) was added, and the mixture was extracted with EtOAc (3 x 600 mL). The organic layers were combined, washed with brine (600 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EtOAc:petroleum ether (1:8) to provide 1-tert-butyl 2-methyl (2S,4S)-4-(phenylselanyl)pyrrolidine-1,2-dicarboxylate (26.8 g, 84%) as a yellow oil. LC-MS (ESI, *m/z*): 286 $[M-100+H]^+$.

[0247] To a mixture of 1-tert-butyl 2-methyl (2S,4S)-4-(phenylselanyl)pyrrolidine-1,2-dicarboxylate (26.8 g, 69.7 mmol, 1.0 eq.) and pyridine (9.38 g, 118 mmol, 1.7 eq.) in DCM (300 mL) was added hydrogen peroxide (31.6 mL, 279 mmol, 4.0 eq., 30% in water). The mixture was stirred for 5 h at rt. The reaction was quenched with water (500 mL). The mixture was extracted with DCM (3 x 400 mL). The organic layers were combined, washed with citric acid (500 mL, 1 M), saturated aqueous sodium sulfite (500 mL), washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EtOAc:petroleum ether (1:5) to provide 1-tert-butyl 2-methyl (2S)-2,5-dihydropyrrole-1,2-dicarboxylate (10.5 g, 62%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 5.91-5.04 (m, 1H), 5.67-5.79 (m, 1H), 4.92-5.09 (m, 1H), 4.17-4.35 (m, 2H), 3.71-3.79 (m, 3H), 1.42-1.52 (m, 9H). LC-MS (ESI, *m/z*): 128 $[M+H-Boc]^+$.

[0248] A mixture of 1-tert-butyl 2-methyl (2S)-2,5-dihydropyrrole-1,2-dicarboxylate (3.68 g, 16.2 mmol, 1.0 eq.) in dicyclopentadiene (40 mL) was stirred overnight at 170 °C. The mixture was diluted with DCM (500 mL) and made into a slurry with 100~200 silica gel mesh (50 g). The mixture was loaded to a column. After removed the DCM under reduced pressure, the sample was purified by column chromatography (Column size 6 x 24 cm, column volume: 600 mL, silica gel size (100 ~ 200 mesh) quantity:

330 g) and eluted with EtOAc:petroleum ether (0%~50% over 30 min). The collected fractions: 19%-25% EtOAc:petroleum ether fractions were chosen as pure fractions. Those fractions were combined and concentrated under reduced pressure to afford the crude product (2.5 g). The crude product was purified by C18 column with CH_3CN:Water (0.05% TFA). The compound fraction was concentrated under reduced pressure to provide 4-tert-butyl 3-methyl (1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,4-dicarboxylate (1.70 g, 32%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12-6.30 (m, 2H), 3.78-3.98 (m, 1H), 3.72 (s, 3H), 3.38-3.51 (m, 1H), 3.04-3.21 (m, 2H), 2.77-2.96 (m, 3H), 1.50-1.58 (m, 1H), 1.32-1.46 (m, 10H). LC-MS (ESI, *m/z*): 194 $[M+H\text{-}Boc]^+$.

[0249] A mixture of 4-tert-butyl 3-methyl (1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,4-dicarboxylate (500 mg, 1.70 mmol, 1.0 eq.) in hydrogen chloride (10 mL, 2 M in Et_2O) was stirred for 2 h at rt. The mixture was concentrated under reduced pressure to afford methyl (1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylate hydrochloride (391 mg, crude) as a yellow oil. LC-MS (ESI, m/z): 194 $[M+H]^+$.

[0250] To a mixture of methyl (1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylate hydrochloride (391 mg, 1.70 mmol, 1.0 eq.), (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoic acid (394 mg, 1.70 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (777 mg, 2.04 mmol, 1.2 eq.) in DMF (10 mL) was added N-ethyl-N-isopropylpropan-2-amine (1.32 g, 10.2mmol, 6.0 eq.) at 0 °C. The mixture was stirred for 1 h at rt. The reaction was quenched with water (20 mL). The mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EtOAc:petroleum ether (8:92) to provide methyl (1R,2S,3S,6R,7S)-4-[(2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylate (490 mg, 69%) as an off-white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03-6.27 (m, 2H), 5.11-5.26 (m, 1H), 4.18-4.36 (m, 2H), 3.72-3.78 (m, 3H), 3.54-3.70 (m, 2H), 2.97-3.14 (m, 2H), 2.86-2.94 (m, 2H), 1.49-1.54 (m, 1H), 1.41-1.48 (m, 9H), 1.33-1.39 (m, 1H), 0.92-1.00 (m, 9H). LC-MS (ESI, *m/z*): 407 $[M+H]^+$.

[0251] To a mixture of methyl (1R,2S,3S,6R,7S)-4-[(2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylate (490 mg, 1.205 mmol, 1.0 eq.) in THF (5 mL)/water (5 mL) was added lithium hydroxide (144 mg, 6.03 mmol, 5.0 eq.). The mixture was stirred for 3 h at rt. The mixture was concentrated under reduced pressure to removed then THF and the pH was adjusted to 5 with hydrochloric acid (2 M). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide (1R,2S,3S,6R,7S)-4-[(2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (465 mg, 97%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04-6.30 (m, 2H), 5.21-5.29 (m, 1H), 4.22-4.32 (m, 2H), 3.52-3.79 (m, 2H), 3.06-3.24 (m, 2H), 2.91-3.04 (m, 2H), 1.51-1.56 (m, 1H), 1.37-1.47 (m, 10H), 0.95-1.00 (m, 9H). LC-MS (ESI, *m/z*): 393 $[M+H]^+$.

[0252] To a mixture of (1R,2S,3S,6R,7S)-4-[(2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (465 mg, 1.18 mmol, 1.0 eq.) in DCM (15 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (346 mg, crude) as a dark blue semi-solid. LC-MS (ESI, *m/z*): 293 $[M+H]^+$.

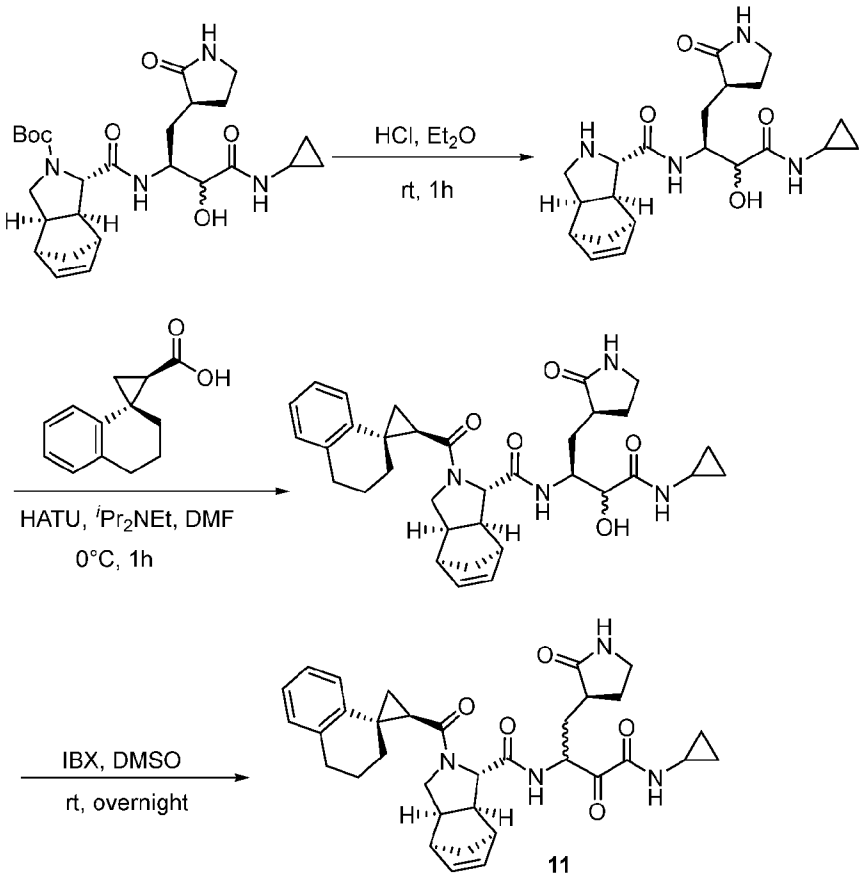
[0253] To a mixture of (1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (346 mg, 1.18 mmol, 1.0 eq.) in MeOH (10 mL) was added triethylamine (1.44 g, 14.2 mmol, 12.0 eq.) and trifluoroethyl acetate (1.01 g, 7.10 mmol, 6.0 eq.). The mixture was stirred overnight at rt and concentrated under reduced pressure to remove then MeOH. The crude product was purified by C18 column with CH_3CN:Water (0.05% TFA). The compound fraction was concentrated under reduced pressure to provide (1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (310 mg, 65%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.22-13.12 (m, 1H), 8.96-9.49 (m, 1H), 5.88-6.24 (m, 2H), 4.24-4.60 (m, 1H), 3.94-4.05 (m, 1H), 3.43-3.58 (m, 2H), 2.67-3.04 (m, 4H), 1.30-1.44 (m, 2H), 0.76-1.05 (m, 9H). LC-MS (ESI, *m/z*): 389

$[M+H]^+$.

[0254] To a mixture of (1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (102 mg, 0.263 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (120 mg, 0.316 mmol, 1.2 eq.) in DMF (2 mL) was added N-ethyl-N-isopropylpropan-2-amine (204 mg, 1.58 mmol, 6.0 eq.) at 0 °C. After stirred for 15 min at 0 °C, (3S)-3-amino-N-cyclopropyl-2-hydroxy-4-[(3S)-2-oxopyrrolidin-3-yl]butanamide hydrochloride (73.0 mg, 0.263 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford then crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (7:93) to provide (3S)-N-cyclopropyl-3-{[(1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-2-hydroxy-4-[(3S)-2-oxopyrrolidin-3-yl]butanamide (120 mg, 68%) as a light yellow solid. LC-MS (ESI, m/z): 612 $[M+H]^+$.

[0255] To a mixture of (3S)-N-cyclopropyl-3-{[(1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-2-hydroxy-4-[(3S)-2-oxopyrrolidin-3-yl]butanamide (120 mg, 0.196 mmol, 1.0 eq.) in DMSO (3 mL) was added 2-iodoxybenzoic acid (165 mg, 0.588 mmol, 3.0 eq.). The mixture was stirred for 3 h at rt. The reaction was quenched with sat. sodium bicarbonate (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (4:96) to provide N-cyclopropyl-3-{[(1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-2-oxo-4-[(3S)-2-oxopyrrolidin-3-yl]butanamide (31.8 mg, 24%) as a white solid. LC-MS (ESI, *m/z*): 610 $[M+H]^+$.

EXAMPLE 11
Compound 11



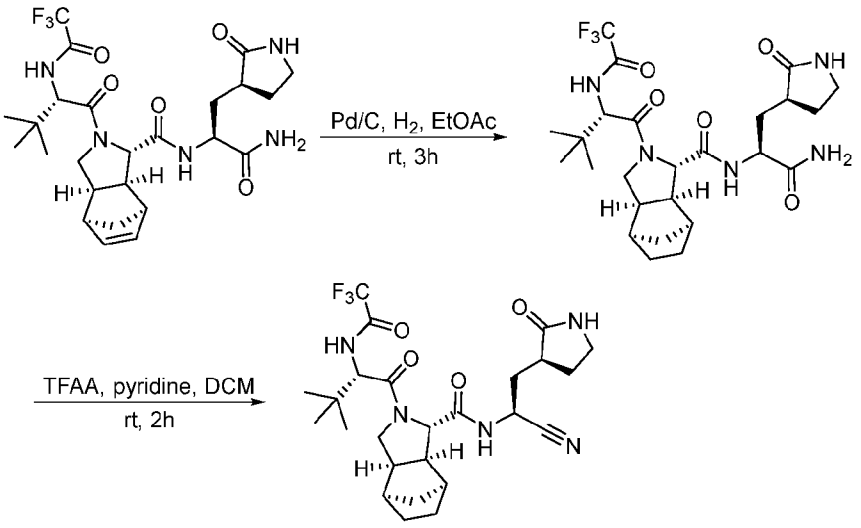
[0256] A mixture of tert-butyl (1R,2S,3S,6R,7S)-3-{[(2S)-1-(cyclopropylcarbamoyl)-1-hydroxy-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-4-carboxylate (150 mg, 0.298 mmol, 1.0 eq.) in hydrogen chloride (2 mL, 2 M in Et_2O) was stirred for 1 h at rt. The mixture was concentrated under reduced pressure to afford (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide hydrochloride (130 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 403 $[M+H]^+$.

[0257] To a mixture of (1R,3R)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-3-carboxylic acid (76.03 mg, 0.376 mmol, 1.1 eq.) in N,N-dimethylformamide (3 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(155 mg, 0.410 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (265 mg, 2.05 mmol, 6.0 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C, and then

(1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide hydrochloride (150 mg, 0.342 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 1 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The residue was purified by TLC (dichloromethane:methanol, 12:1) to afford (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((1R,2R)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (80 mg, 40%) as a yellow solid. LC-MS (ESI, m/z): 587 $[M+H]^+$.

[0258] To a stirred mixture of (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((1R,2R)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (80.0 mg, 0.136 mmol, 1.0 eq.) in DMSO (2 mL) was added 2-iodoxybenzoic acid (114 mg, 0.408 mmol, 3.0 eq.). The mixture was stirred for overnight at rt. The reaction was quenched with sat. sodium bicarbonate (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with dichloromethane:methanol (94:6) to provide (1S,3aR,4S,7R,7aS)-N-(4-(cyclopropylamino)-3,4-dioxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((1R,2R)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide as a white solid. LC-MS (ESI, *m/z*): 585 $[M+H]^+$.

EXAMPLE 12
Compound 12



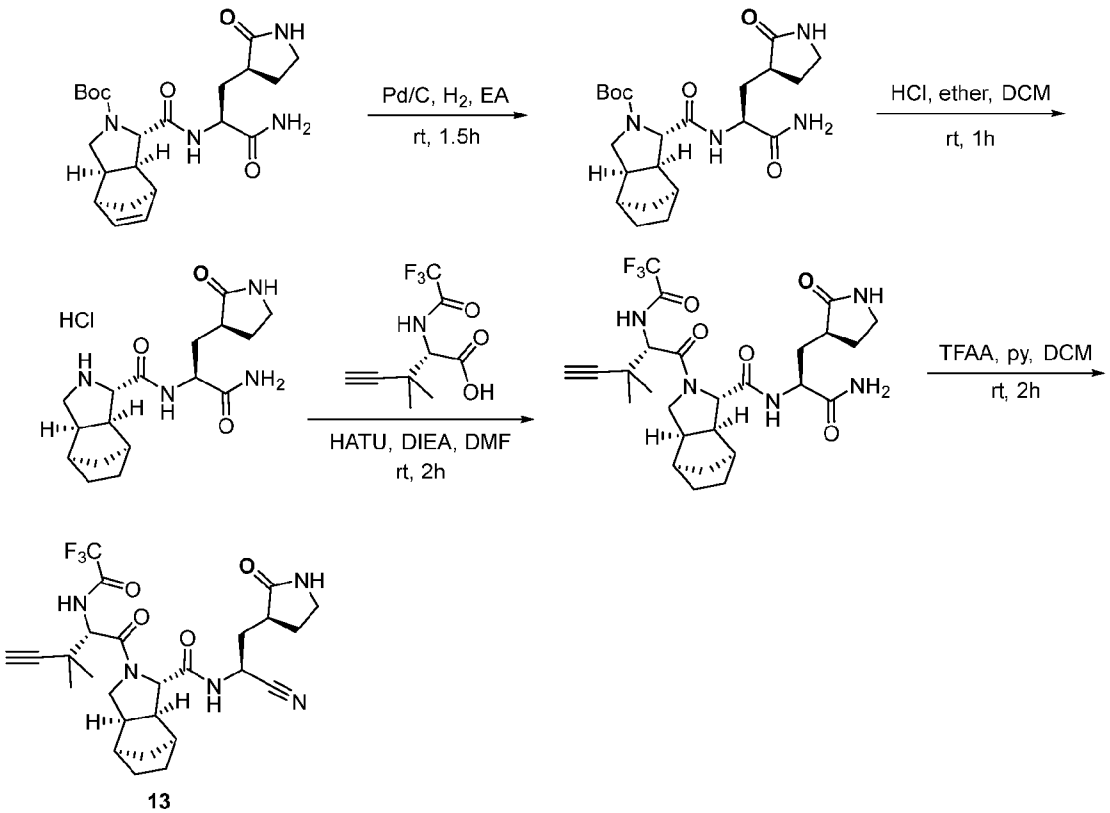
12

[0259] To a mixture of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (95.0 mg, 0.175 mmol, 1.0 eq.) in EtOAc (3 mL) was added 10% palladium on activated carbon (90.0 mg). The mixture was stirred for 3 h at rt under hydrogen. The mixture was filtered through a celite pad. The filtrate was concentrated under reduced pressure to afford (1S,3aR,4R,7S,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (75.0 mg, crude) as an off-white solid. LC-MS (ESI, *m/z*): 544 $[M+H]^+$.

[0260] To a mixture of (1S,3aR,4R,7S,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (75.0 mg, 0.138 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (76 mg, 0.966 mmol, 7.0 eq.) and trifluoroacetic anhydride (116 mg, 0.552 mmol, 4.0 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with DCM (3 x 5 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 19 x 150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase

B: ACN; Flow rate: 25 mL/min; Gradient: 36% B to 56% B in 7 min, 56% B; Wave Length: 254 nm; RT: 6.18 min) to provide (1S,3aR,4R,7S,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide(19.6 mg, 26%) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.85-9.20 (m, 1H), 8.60-8.84 (m, 1H), 7.35-7.55 (m, 1H), 4.80-4.98 (m, 1H), 4.59-4.75 (m, 1H), 4.30-4.58 (m, 1H), 3.76-3.85 (m, 1H), 3.45-3.75 (m, 1H), 3.10-3.25 (m, 2H), 2.55-2.70 (m, 1H), 2.30-2.54 (m, 3H), 2.05-2.29 (m, 3H), 1.62-1.88 (m, 2H), 1.40-1.60 (m, 2H), 1.05-1.39 (m, 4H), 0.95-1.04 (m, 9H). LC-MS (ESI, *m/z*): 526 [M+H]$^+$.

EXAMPLE 13
Compound 13



[0261] To a stirred mixture of tert-butyl (1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-4-carboxylate (250 mg, 0.578 mmol, 1.0 eq.) in ethyl acetate (3 mL) was added 10% palladium on activated carbon (120 mg) at rt. The mixture was stirred for 1.5 h under hydrogen. The

mixture was filtered, and the filter cake was washed with ethyl acetate (3 x 10 mL). The filtrate was concentrated under reduced pressure to afford tert-butyl (1S,2S,3S,6R,7R)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]decane-4-carboxylate (200 mg, 75%) as a white solid. LC-MS (ESI, m/z): 435 $[M+H]^+$.

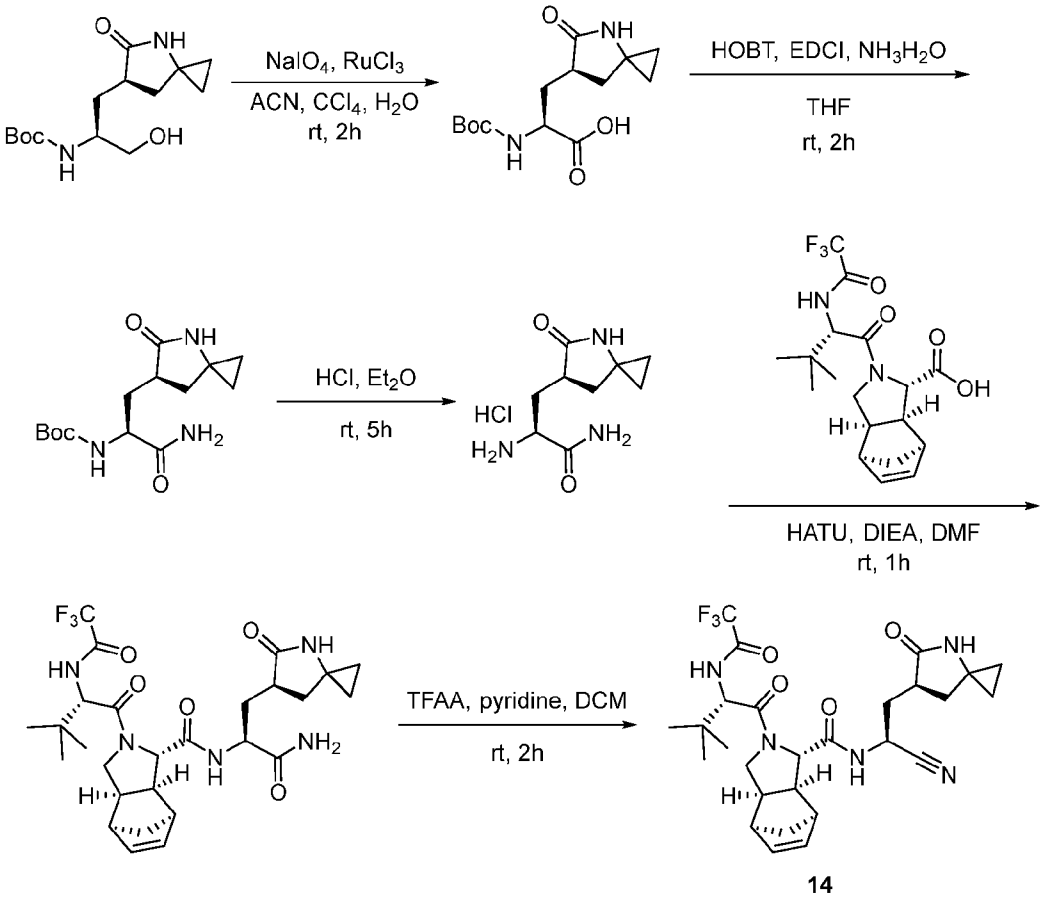
[0262] To a stirred mixture of tert-butyl (1S,2S,3S,6R,7R)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]decane-4-carboxylate (200 mg, 0.460 mmol, 1.0 eq.) in DCM (2 mL) was added hydrogen chloride (6 mL, 2M in Et_2O) at rt. The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (2S)-2-[(1S,2S,3S,6R,7R)-4-azatricyclo[5.2.1.0^{2,6}]decan-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (180 mg, crude) as a light yellow solid. LC-MS (ESI, *m/z*): 335 $[M+H]^+$.

[0263] To a stirred mixture of (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoic acid (124 mg, 0.550 mmol, 1.2 eq.) in DMF (2 mL) was added o-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (209 mg, 0.550 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (355 mg, 2.74 mmol, 6.0 eq.) at rt. The mixture was stirred for 10 min at rt, and (2S)-2-[(1S,2S,3S,6R,7R)-4-azatricyclo[5.2.1.0^{2,6}]decan-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (170 mg, 0.458 mmol, 1.0 eq.) was added. The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (1:15) to provide (2S)-2-{[(1S,2S,3S,6R,7R)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]decan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (135 mg, 54%) as a light yellow solid. LC-MS (ESI, *m/z*): 553 $[M+H]^+$.

[0264] To a stirred mixture of (2S)-2-{[(1S,2S,3S,6R,7R)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-ynoyl]-4-azatricyclo[5.2.1.0^{2,6}]decan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (135 mg, 0.244 mmol, 1.0 eq.) in DCM (2 mL) was added trifluoroacetic anhydride (102 mg, 0.488 mmol, 2.0 eq.) and

pyridine (67.5 mg, 0.854 mmol, 3.5 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with dichloromethane (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 19*150 mm, 5μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 254 nm; RT1(min): 5) to afford (1S,2S,3S,6R,7R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-ynoyl]-4-azatricyclo[5.2.1.0^{2,6}]decane-3-carboxamide (18.8 mg, 14%) as a white solid. LC-MS (ESI, *m/z*): 536 $[M+H]^+$.

EXAMPLE 14
Compound 14



14

[0265] To a solution of tert-butyl ((S)-1-hydroxy-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)carbamate (400 mg, 1.41 mmol, 1.0 eq.) in CCl_4 (6 mL) and acetonitrile (6 mL) were added sodium periodate (1.52 g, 7.13 mmol, 5.07 eq., in 9 mL water) and trichlororuthenium (35.0 mg, 0.169 mmol, 0.12 eq.) at 0 °C. The mixture was stirred for 2 h at rt and then filtered through celite. The filtrate was extracted with DCM (3 x 50 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide (S)-2-((tert-butoxycarbonyl)amino)-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoic acid (240 mg, 57%) as a white solid. LC-MS (ESI, m/z): 299 $[M+H]^+$.

[0266] To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoic acid (130 mg, 0.436 mmol, 1.0 eq.) in THF (3 mL) was added 1-hydroxybenzotriazole (177 mg, 1.31 mmol, 3.0 eq.) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (184 mg, 0.959 mmol, 2.2 eq.) stirred at 0 °C. After stirred for 1 h, ammonium hydroxide (2.6 mL) was added. The mixture was stirred for 2 h at rt and then concentrated under reduced pressure to afford the crude product. The crude product was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide tert-butyl ((S)-1-amino-1-oxo-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)carbamate (80 mg, 61%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.11-7.6 (m, 1H), 6.47-6.51 (m, 1H), 6.03 (br, 1H), 5.85 (m, 1H), 4.36-4.42 (m, 1H), 2.78-2.85 (m, 1H), 2.26-2.34 (m, 1H), 2.13-2.21 (m, 1H), 1.89-2.04 (m, 2H), 1.43-1.51 (m, 9H), 0.77-0.98 (m, 2H), 0.67-0.75 (m, 2H). LC-MS (ESI, m/z): 298 $[M+H]^+$.

[0267] A mixture of tert-butyl ((S)-1-amino-1-oxo-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)carbamate (80.0 mg, 0.269 mmol, 1.0 eq.) in hydrogen chloride (3 mL, 2 M in diethyl ether) was stirred for 5 h at rt and then concentrated under reduced pressure to afford (S)-2-amino-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanamide hydrochloride (60 mg, crude) as a yellow solid. LC-MS (ESI, *m/z*): 198 $[M+H]^+$.

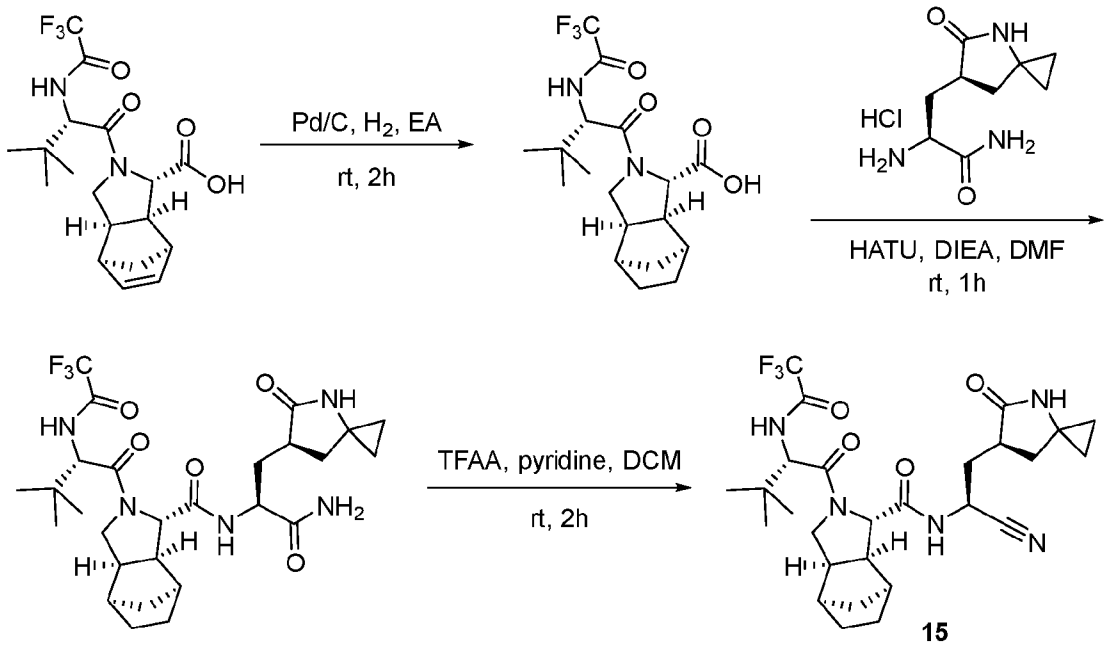
[0268] To a mixture of (1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-

trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (110 mg, 0.283 mmol, 1.1 eq.) in dimethylformamide (2 mL) were added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (117 mg, 0.308 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (199 mg, 1.54 mmol, 6.0 eq.) at 0 °C. After stirred 20 min, (S)-2-amino-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanamide hydrochloride (60.0 mg, 0.257 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The reaction was quenched with water (5 mL). The mixture was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (65 mg, 44%) as a white solid. LC-MS (ESI, *m/z*): 568 $[M+H]^+$.

[0269] To a mixture of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (60.0 mg, 0.106 mmol, 1.0 eq.) in DCM (2 mL) were added pyridine (41.8 mg, 0.530 mmol, 5.0 eq.) and trifluoroacetic anhydride (51.1 mg, 0.244 mmol, 2.3 eq.). The mixture was stirred 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with DCM (3 x 30 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 220 nm; RT1(min): 5.63;) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (27.5 mg, 47%) as a white solid. ^1H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.75-8.81 (m, 1H), 8.67-8.69 (m, 1H), 7.50-7.57 (m, 1H), 5.93-6.16 (m, 2H), 4.84-4.89 (m, 1H), 4.44-4.64 (m, 1H), 3.98-4.12 (m, 1H), 3.58-3.66 (m, 1H), 3.37-3.47 (m, 1H), 3.07-3.17 (m, 1H), 2.79-2.93 (m, 2H), 2.63-2.73 (m, 1H), 2.54-2.63 (m, 1H), 2.12-2.29 (m, 1H), 1.74-1.99 (m, 3H), 1.32-1.42 (m, 2H), 0.88-0.94 (m, 9H), 0.71-0.77 (m, 1H), 0.48-0.62 (m, 3H).

LC-MS (ESI, m/z): 550 $[M+H]^+$.

EXAMPLE 15
Compound 15



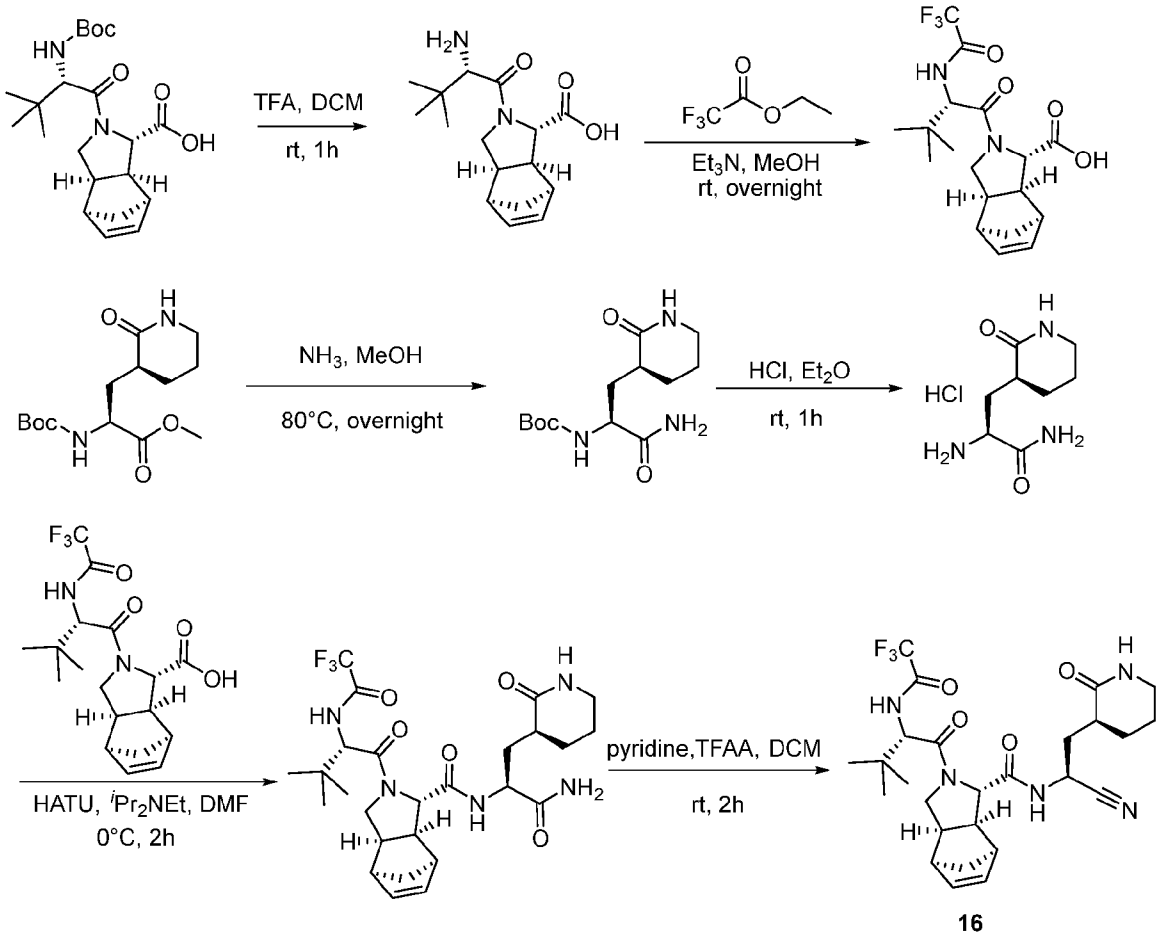
[0270] To a mixture of (1S,3aR,4S,7R,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (500 mg, 1.29 mmol, 1.0 eq.) in ethyl acetate (10 mL) was added 10% palladium on activated carbon (120 mg). The mixture was stirred for overnight at rt under hydrogen. The mixture was filtered through a celite pad and then washed with ethyl acetate (150 mL). The filtrate was concentrated under reduced pressure to afford (1S,3aR,4R,7S,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxylic acid (460 mg, crude) as an off white solid. LC-MS (ESI, *m/z*): 391 $[M+H]^+$.

[0271] To a mixture of (1S,3aR,4R,7S,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxylic acid (184 mg, 0.471 mmol, 1.1 eq.) in dimethylformamide (3 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (195 mg, 0.514 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (332 mg, 2.57 mmol, 6.0 eq.) at 0 °C. After stirred 20 min, (S)-2-amino-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanamide hydrochloride (100

mg, 0.428 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The reaction was quenched with water (5 mL). The mixture was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide (1S,3aR,4R,7S,7aS)-N-((S)-1-amino-1-oxo-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (140 mg, 57%) as a white solid. LC-MS (ESI, *m/z*): 570 $[M+H]^+$.

[0272] To a mixture of (1S,3aR,4R,7S,7aS)-N-((S)-1-amino-1-oxo-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (140 mg, 0.246 mmol, 1.0 eq.) in DCM (3 mL) was added pyridine (77.8 mg, 0.984 mmol, 4.0 eq.) and trifluoroacetic anhydride (92.9 mg, 0.443 mmol, 1.8 eq.). The mixture was stirred 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with DCM (3 x 50 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EA:PE (65%-72%) to provide (1S,3aR,4R,7S,7aS)-N-((S)-1-cyano-2-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (47.6 mg, 33%) as a white solid. ^1H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.94-8.98 (m, 1H), 8.57-8.75 (m, 1H), 7.51-7.59 (m, 1H), 4.83-4.90 (m, 1H), 4.56-4.68 (m, 1H), 4.46-4.48 (m, 1H), 3.70-3.79 (m, 1H), 3.57-3.65 (m, 1H), 2.49-2.68 (m, 2H), 2.31-2.42 (m, 2H), 2.12-2.22 (m, 2H), 1.89-2.01 (m, 2H), 1.79-1.86 (m, 1H), 1.35-1.49 (m, 2H), 1.19-1.32 (m, 3H), 1.06-1.14 (m, 1H), 0.93-0.97 (m, 9H), 0.72-0.75 (m, 1H), 0.49-0.62 (m, 3H). LC-MS (ESI, m/z): 552 $[M+H]^+$.

EXAMPLE 16
Compound 16



[0273] To a mixture of (1S,3aR,4S,7R,7aS)-2-((S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (2.00 g, 5.09 mmol, 1.0 eq.) in DCM (30 mL) was added trifluoroacetic acid (10 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford product (1S,3aR,4S,7R,7aS)-2-((S)-2-amino-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (1.40 g, crude) as a solid. LC-MS (ESI, *m/z*): 293 $[M+H]^+$.

[0274] To a stirred mixture of (1S,3aR,4S,7R,7aS)-2-((S)-2-amino-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (1.49 g, 5.09 mmol, 1.0 eq.) in MeOH (10 mL) was added triethylamine (6.19 g, 61.1 mmol, 12.0 eq.) and ethyl 2,2,2-trifluoroacetate (4.34 g, 30.5 mmol, 6.0 eq.). The mixture was stirred overnight at rt and then concentrated under reduced pressure to remove the MeOH.

The crude product was purified by C18 column with CH_3CN/Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (1.17 g, 59%) as a yellow solid. LC-MS (ESI, *m/z*): 389 $[M+H]^+$.

[0275] A mixture of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopiperidin-3-yl)propanoate (1.0 g, 3.32 mmol, 1.0 eq.) in ammonia (20 mL, 7 M in MeOH) was stirred overnight at 80 °C. The mixture was concentrated under reduced pressure to afford tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamate (1.01 g, crude) as a light brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.36-7.65 (m, 1H), 7.14-7.35 (m, 1H), 6.44-7.12 (m, 2H), 3.74-4.22 (m, 1H), 2.91-3.30 (m, 2H), 1.99-2.40 (m, 2H), 1.45-1.94 (m, 4H), 0.94-1.44 (m, 10H). LC-MS (ESI, *m/z*): 286 $[M+H]^+$.

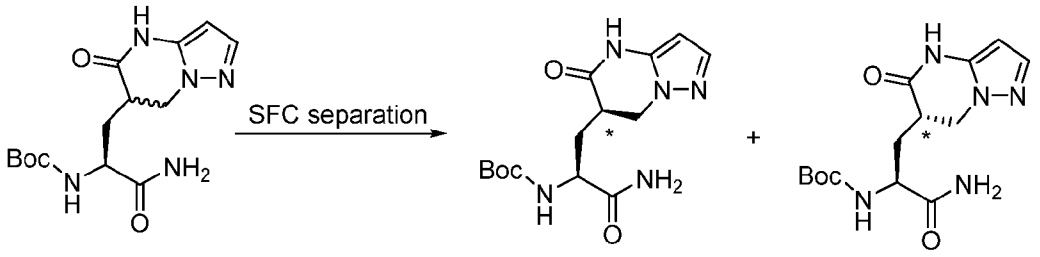
[0276] A mixture of tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamate (120 mg, 0.421 mmol, 1.0 eq.) in hydrogen chloride (3 mL, 2 M in Et_2O) was stirred for 1 h at rt. The mixture was concentrated under reduced pressure to afford (2S)-2-amino-3-[(3S)-2-oxopiperidin-3-yl]propanamide hydrochloride (80.0 mg, crude) as a yellow oil. LC-MS (ESI, m/z): 186 $[M+H]^+$.

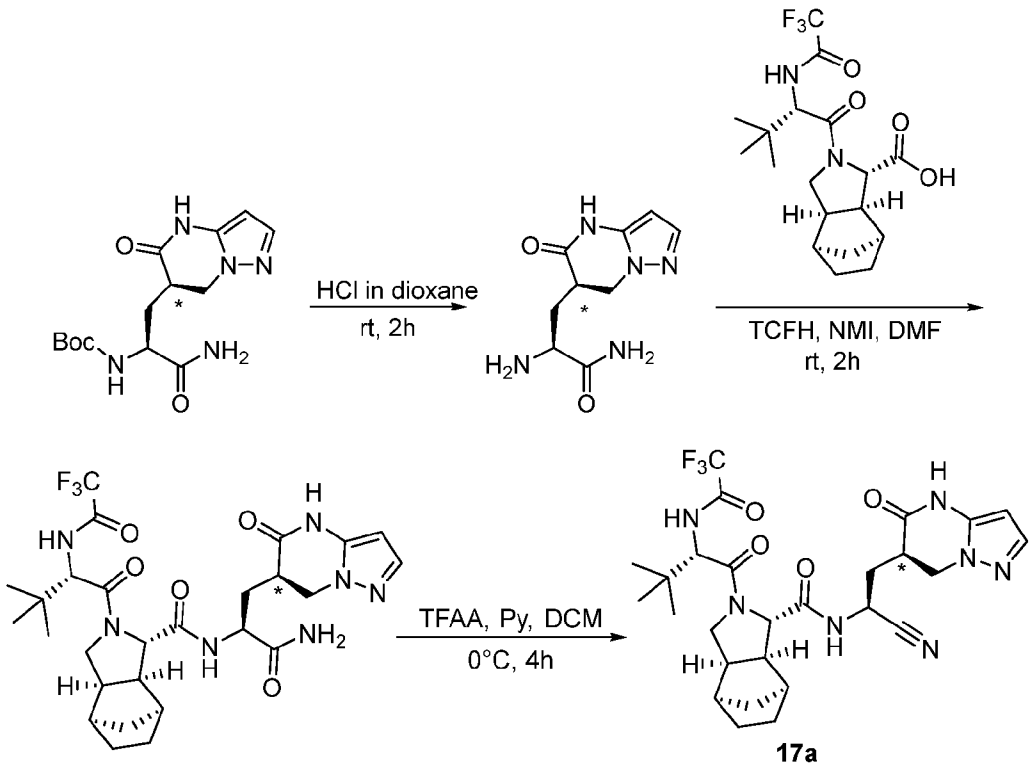
[0277] To a mixture of (1S,3aR,4S,7R,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (162 mg, 0.420 mmol, 1.0 eq.) in N,N-dimethylformamide (3 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (191 mg, 0.504 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (325 mg, 2.52 mmol, 6.0 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C, then (2S)-2-amino-3-[(3S)-2-oxopiperidin-3-yl]propanamide hydrochloride (93.0 mg, 0.420 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 2 h at rt. The reaction was quenched with water (30 mL). The mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (6:94) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-((S)-

3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (160 mg, 68%) as a light yellow solid. LC-MS (ESI, *m/z*): 556 $[M+H]^+$.

[0278] To a mixture of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (160 mg, 0.288 mmol, 1.0 eq.) in DCM (3 mL) was added pyridine (91.1 mg, 1.15 mmol, 4.0 eq.) and trifluoroacetic anhydride (120 mg, 0.576 mmol, 2.0 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 35% B to 55% B in 10 min, 55% B; Wave Length: 254 nm; RT1(min): 8.15) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (38.5 mg, 25%) as an off-white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.75-8.95 (m, 1H), 8.60-8.73 (m, 1H), 7.15-7.40 (m, 1H), 5.90-6.30 (m, 2H), 4.65-5.10 (m, 1H), 4.40-4.60 (m, 1H), 3.90-4.25 (m, 1H), 3.55-3.75 (m, 1H), 3.35-3.50 (m, 1H), 3.10-3.20 (m, 2H), 3.00-3.05 (m, 1H), 2.85-3.00 (m, 2H), 2.65-2.80 (m, 1H), 2.20-2.50 (m, 2H), 1.70-1.95 (m, 3H), 1.50-1.70 (m, 1H), 1.30-1.50 (m, 3H), 0.80-1.05 (m, 9H). LC-MS (ESI, *m/z*): 538 $[M+H]^+$.

EXAMPLE 17
Compounds 17a and 17b





17a

The chiral centers noted with "*" are tentatively assigned

[0279] Tert-butyl ((2S)-1-amino-1-oxo-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)carbamate (290 mg) was purified by SFC using the following gradient conditions: Column: OptiChiral-C9-5, 3*25 cm, 5μm; Mobile Phase A: CO_2, Mobile Phase B: IPA(0.5% 2M NH_3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 3.3; RT2(min): 5.85; Sample Solvent: MeOH-----Preparative; Injection Volume: 4.8 mL; Purification resulted in tert-butyl ((2S)-1-amino-1-oxo-3-(5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)carbamate (210 mg) as an off-white solid, which was purified by SFC using the following gradient conditions: Column: Lux 5um Cellulose-4, 3*25 cm, 5μm; Mobile Phase A: CO_2, Mobile Phase B: IPA(0.5% 2M NH_3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.87; RT2(min): 4.33; Sample Solvent: MeOH-Preparative; Injection Volume: 4.8 mL; Number Of Runs: 4. Purification resulted in a mixture of tert-butyl ((S)-1-amino-1-oxo-3-((R*)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)carbamate (80 mg) as an off-white

solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.78 (s, 1H), 7.29-7.32 (m, 2H), 6.96-7.06 (m, 2H), 5.59-5.60 (m, 1H), 4.31-4.37 (m, 1H), 3.95-4.03 (m, 2H), 2.69-2.80 (m, 1H), 2.09-2.19 (m, 1H), 1.69-1.77 (m, 1H), 1.24-1.37 (m, 9H). LC-MS (ESI, *m/z*): 324 $[M+H]^+$.

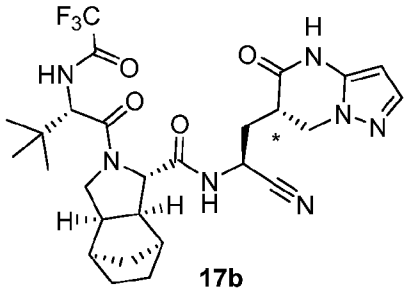
[0280] And tert-butyl ((S)-1-amino-1-oxo-3-((S)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)carbamate (90 mg) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.29-7.33 (m, 2H), 6.95-7.06 (m , 2H), 5.58-5.59 (m, 1H), 4.40-4.44 (m, 1H), 3.93-4.07 (m, 2H), 2.75-2.81 (m, 1H), 2.21-2.25 (m, 1H), 1.51-1.61 (m, 1H), 1.20-1.24 (m, 9H). LC-MS (ESI, *m/z*): 324 $[M+H]^+$.

[0281] A solution of tert-butyl ((S)-1-amino-1-oxo-3-((R*)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)carbamate (70 mg, 0.216 mmol, 1.0 eq.) in hydrochloric acid (2 mL, 4M in dioxane) was stirred at rt for 2 h and then concentrated under reduced pressure to provide (S)-2-amino-3-((R)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanamide (40 mg, crude) as a white solid. LC-MS (ESI, *m/z*): 224 $[M+H]^+$.

[0282] To a solution of (S)-2-amino-3-((R*)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propanamide (40 mg, 0.18 mmol, 1.0 eq.) in DMF (1 mL) was added (1S,3aR,4R,7S,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxylic acid (77 mg, 0.2 mmol, 1.1 eq.), N,N,N,N-tetramethylchloroformamidinium hexafluorophosphate (66 mg, 0.24 mmol, 1.3 eq.) and NMI (74 mg, 0.9 mmol, 5.0 eq.). The mixture was stirred at rt for 2 h. The residue was chromatographed on a C18 column with water:MeCN (3:1) to provide (1S,3aR,4R,7S,7aS)-N-((S)-1-amino-1-oxo-3-((R)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (50 mg, 42%) as an off-white solid. LC-MS (ESI, *m/z*): 596 $[M+H]^+$.

[0283] To a solution of (1S,3aR,4R,7S,7aS)-N-((S)-1-amino-1-oxo-3-((R*)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (50 mg, 0.08 mmol, 1.0 eq.) in DCM (3 mL) was added TFAA (35 mg, 0.17 mmol, 2.0 eq.) and pyridine (23 mg, 0.29 mmol, 3.5 eq.). The mixture was stirred at rt for 2 h. The reaction was quenched with water (3 mL). The mixture was extracted with DCM (3 x 5 mL). The organic

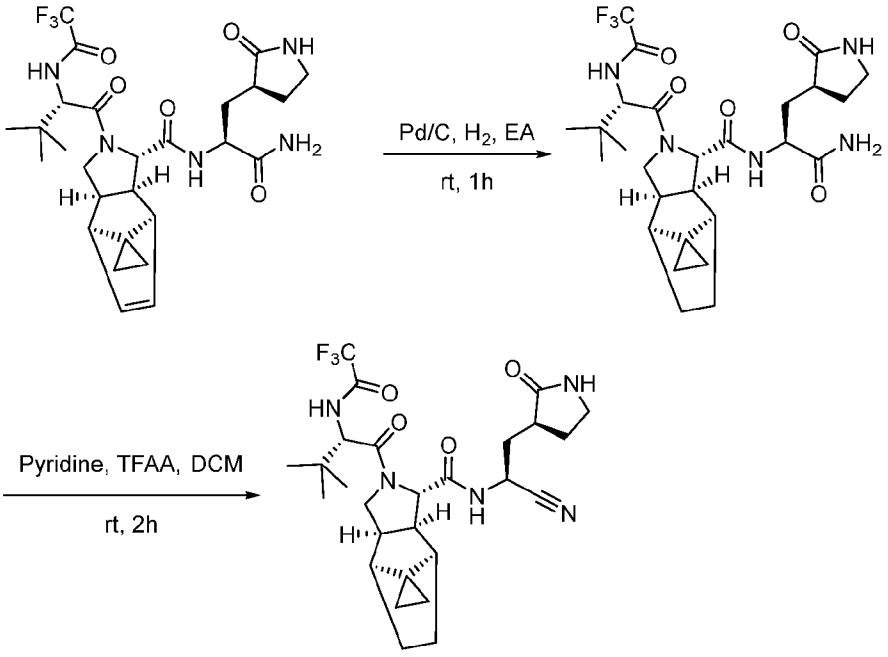
layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 52% B in 7 min, 52% B; Wave Length: 254 nm; RT1(min): 5.23) to provide (1S,3aR,4R,7S,7aS)-N-((S)-1-cyano-2-((R*)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (5.1 mg. 10%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 10.66 (br, 1H), 8.39-9.09 (m, 2H), 7.24-7.26 (m , 1H), 5.56-5.57 (m, 1H), 4.93-5.10 (m, 1H), 4.61-4.71 (m, 1H), 4.32-4.59 (m, 2H), 3.98-4.06 (m, 1H), 3.78-3.82 (m, 1H), 3.58-3.64 (m, 1H), 2.81-2.92 (m, 1H), 2.58-2.69 (m, 1H), 2.41-2.48 (m , 2H), 2.32-2.36 (m, 1H), 2.21-2.23 (m, 1H), 1.92-2.02 (m, 1H), 1.41-1.55 (m, 2H), 1.18-1.32 (m, 3H), 1.08-1.14 (m, 1H), 0.82-0.95 (m, 9H). LC-MS (ESI, *m/z*): 578 [M+H]$^+$.



17b

[0284] Compound 17b was prepared similarly as described for 17a, using tert-butyl ((S)-1-amino-1-oxo-3-((S*)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)carbamate in place of tert-butyl ((S)-1-amino-1-oxo-3-((R*)-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-6-yl)propan-2-yl)carbamate. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 10.61 (br, 1H), 8.81-8.95 (m, 1H), 8.67-8.69 (m , 1H), 7.24-7.26 (m, 1H), 5.56-5.58 (m, 1H), 5.09-5.11 (m, 1H), 4.62-4.73 (m, 1H), 4.31-4.52 (m, 2H), 3.91-4.05 (m, 1H), 3.71-3.83 (m, 1H), 3.53-3.66 (m, 1H), 2.81-2.96 (m, 1H), 2.62-2.69 (m, 1H), 2.44-2.51 (m, 2H), 2.32-2.37 (m, 1H), 2.18-2.26 (m, 1H), 1.84-2.05 (m, 1H), 1.38-1.56 (m, 2H), 1.19-1.36 (m, 3H), 1.04-1.17 (m, 1H), 0.82-1.11 (m, 9H). LC-MS (ESI, *m/z*): 578 [M+H]$^+$.

EXAMPLE 18
Compound 18



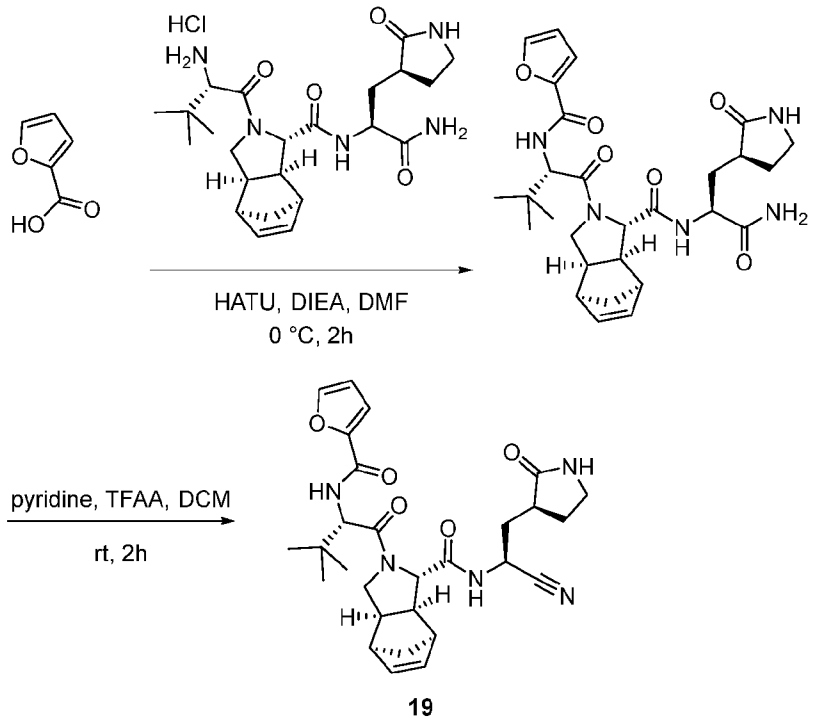
18

[0285] To a stirred mixture of (2S)-2-[(1'R,2'S,3'S,6'R,7'S)-4'-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-en-3'-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (250 mg, 0.440 mmol, 1.0 eq.) in EtOAc (4 mL) was added 10% palladium on activated carbon (100 mg). The mixture was stirred for 1 h at rt under hydrogen. The mixture was filtered through a celite pad. The filtrate was concentrated under reduced pressure to provide (2S)-2-[(1'R,2'S,3'S,6'R,7'S)-4'-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-3'-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (235 mg, 91%) as an off-white solid. LC-MS (ESI, *m/z*): 570 $[M+H]^+$.

[0286] To a stirred mixture of (2S)-2-[(1'R,2'S,3'S,6'R,7'S)-4'-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-3'-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (230 mg, 0.404 mmol, 1.0 eq.) in DCM (5 mL) was added pyridine (111 mg, 1.41 mmol, 3.5 eq.) and trifluoroacetic anhydride (152 mg, 0.727 mmol, 1.8 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (20 mL). The mixture was extracted

with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: Kinetex EVO C18, 21.2*250mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 63% B in 10 min, 63% B; Wave Length: 254 nm; RT1(min): 7.45) to provide (1'R,2'S,3'S,6'R,7'S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4'-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decane]-3'-carboxamide (44.3 mg, 19%) as a white solid. ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 8.91-9.01 (m, 1H), 8.65-8.83 (m, 1H), 7.38-7.53 (m, 1H), 4.81-4.98 (m, 1H), 4.60-4.75 (m, 1H), 4.50-4.58 (m, 1H), 3.79-3.88 (m, 1H), 3.63-3.78 (m, 1H), 3.09-3.23 (m, 2H), 2.72-2.95 (m, 1H), 2.60-2.68 (m, 1H), 2.30-2.41 (m, 1H), 2.09-2.29 (m, 2H), 1.62-1.86 (m, 2H), 1.57-1.61 (m, 1H), 1.31-1.56 (m, 4H), 1.12-1.30 (m, 1H), 0.89-1.09 (m, 9H), 0.50-0.60 (m, 2H), 0.36-0.49 (m, 2H). LC-MS (ESI, *m/z*): 552 $[M+H]^+$.

EXAMPLE 19
Compound 19

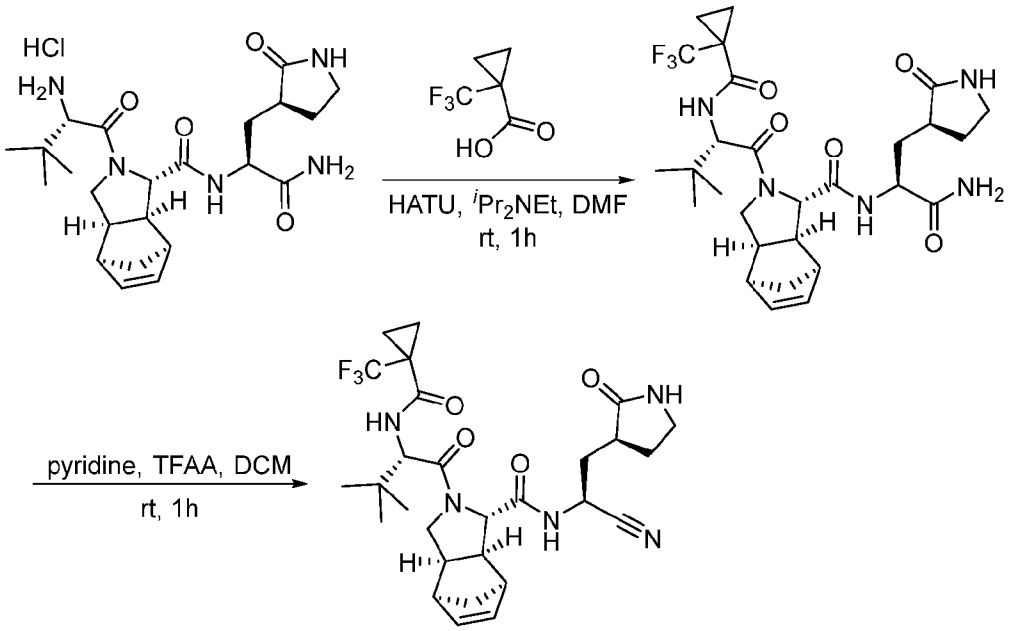


[0287] To a mixture of furan-2-carboxylic acid (30.9 mg, 0.276 mmol, 1.0 eq.) in

N, N-dimethylformamide (3 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (125 mg, 0.331 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (213 mg, 1.65 mmol, 6.0 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C, then (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-2-amino-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide hydrochloride (133 mg, 0.276 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 2 h at rt. The reaction was quenched with water (30 mL). The mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (7:93) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-2-(furan-2-carboxamido)-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (120 mg, 81%) as a light yellow solid. LC-MS (ESI, *m/z*): 540 $[M+H]^+$.

[0288] To a mixture of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-2-(furan-2-carboxamido)-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (120 mg, 0.222 mmol, 1.0 eq.) in dichloromethane (3 mL) was added pyridine (123 mg, 1.55 mmol, 7.0 eq.) and trifluoroacetic anhydride (140 mg, 0.666 mmol, 3.0 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 65% B in 7 min, 65% B; Wave Length: 254 nm; RT1(min): 6) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-2-(furan-2-carboxamido)-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (17.4 mg, 15%) as an off-white solid. LC-MS (ESI, m/z): 522 $[M+H]^+$.

EXAMPLE 20
Compound 20



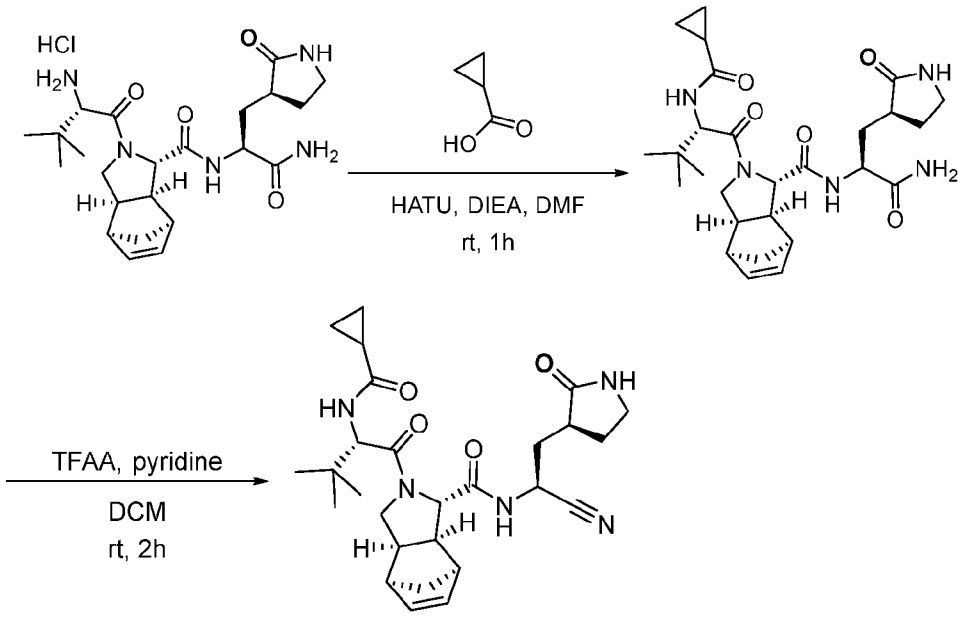
20

[0289] To a mixture of 1-(trifluoromethyl)cyclopropane-1-carboxylic acid (43.0 mg, 0.274 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (125 mg, 0.329 mmol, 1.2 eq.) in DMF (3 mL) was added N-ethyl-N-isopropylpropan-2-amine (212 mg, 1.64 mmol, 6.0 eq.) at 0 °C. After stirring for 15 min at 0 °C, (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (132 mg, 0.274 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]-1-(trifluoromethyl)cyclopropane-1-carboxamide (130 mg, 78%) as a light yellow solid. LC-MS (ESI, *m/z*): 582 $[M+H]^+$.

[0290] To a mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]-1-(trifluoromethyl)cyclopropane-1-carboxamide (130 mg, 0.224 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (71.0 mg, 0.896 mmol, 4.0 eq.) and

trifluoroacetic anhydride (85.0 mg, 0.403 mmol, 1.8 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with DCM (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 53% B in 10 min, 53% B; Wave Length: 254 nm; RT: 7.47 min) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-{[1-(trifluoromethyl)cyclopropyl]formamido}butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (55.9 mg, 44%) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.60-8.80 (m, 1H), 7.35- 7.55 (m, 1H), 6.58-7.00 (m, 1H), 5.98-6.20 (m, 2H), 4.70-4.98 (m, 1H), 4.46-4.55 (m, 1H), 4.00-4.15 (m, 1H), 3.55-3.65 (m, 1H), 3.35-3.54 (m, 1H), 3.10-3.25 (m, 2H), 3.00-3.09 (m, 1H), 2.80-2.98 (m, 2H), 2.68-2.79 (m, 1H), 2.30-2.42 (m, 1H), 2.08-2.28 (m, 2H), 1.62-1.89 (m, 2H), 1.30-1.48 (m, 3H), 1.10-1.29 (m, 3H), 0.83-0.98 (m, 9H). LC-MS (ESI, *m/z*): 564 $[M+H]^+$.

EXAMPLE 21
Compound 21



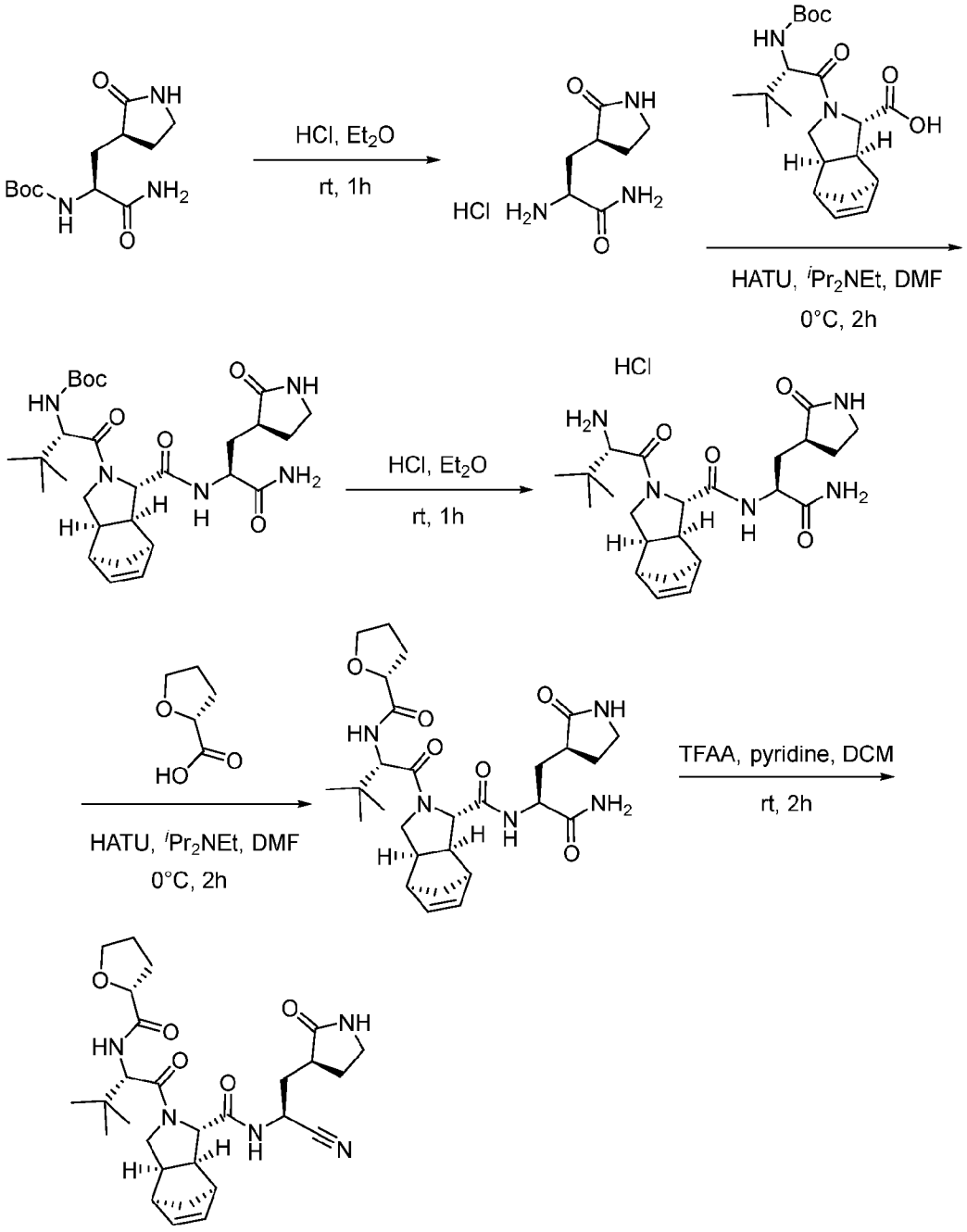
21

[0291] To a stirred mixture of cyclopropanecarboxylic acid (27.5 mg, 0.319 mmol, 1.1 eq.) in DMF (2 mL) was added o-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (132 mg, 0.348 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (225 mg, 1.74 mmol, 6.0 eq.). The mixture was stirred for 10 min at 0 °C. (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (140 mg, 0.290 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt, and then purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]cyclopropanecarboxamide (100 mg, 60%) as a white solid. LC-MS (ESI, *m/z*): 514 $[M+H]^+$.

[0292] To a stirred mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]cyclopropanecarboxamide (100 mg, 0.195 mmol, 1.0 eq.) in DCM (2 mL) was added trifluoroacetic anhydride (81.7 mg, 0.390 mmol, 2.0 eq.) and pyridine (53.9 mg, 0.682 mmol, 3.5 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 32% B to 62% B in 7 min, 62% B; Wave Length: 254 nm; RT1(min): 6) to afford (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-2-(cyclopropylformamido)-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (16.5 mg, 16%) as a white solid. ^1H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.55-8.80 (m, 1H), 7.70-7.85 (m, 1H), 7.30-7.55 (m, 1H), 5.91-6.20 (m, 2H), 4.81-4.98 (m, 1H), 4.40-4.52 (m, 1H), 3.91-4.10 (m, 1H), 3.42-3.62 (m, 2H), 3.08-3.20 (m, 2H) , 2.97-3.02 (m, 1H), 2.81-2.95 (m, 2H), 2.63-2.73 (m, 1H), 2.26-2.41 (m, 1H), 2.05-2.22 (m, 2H), 1.60-1.86 (m, 3H), 1.29-1.41 (m, 2H),

0.78-0.96 (m, 9H), 0.66-0.74 (m, 1H), 0.53-0.66 (m, 3H). LC-MS (ESI, *m/z*): 496 $[M+H]^+$.

EXAMPLE 22
Compound 22



22

[0293] A mixture of tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (1.04 g, 3.83 mmol, 1.0 eq.) in hydrogen chloride (10 mL, 2 M in

Et_2O) was stirred for 1 h at rt. The mixture was concentrated under reduced pressure to afford (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide hydrochloride (0.650 g, crude) as a yellow oil. LC-MS (ESI, *m/z*): 172 $[M+H]^+$.

[0294] To a mixture of (1S,3aR,4S,7R,7aS)-2-((S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (1.50 g, 3.82 mmol, 1.0 eq.) in N,N-dimethylformamide (15 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.74 g, 4.58 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (3.95 g, 30.5 mmol, 8.0 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C. (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide hydrochloride (650 mg, 3.82 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 2 h at rt. The reaction was quenched with water (50 mL). The mixture was extracted with EtOAc (3 x 80 mL). The organic layers were combined, washed with brine (2 x 80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (7:93) to provide tert-butyl ((S)-1-((1S,3aR,4S,7R,7aS)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindol-2-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (1.46 g, 70%) as a light yellow solid. LC-MS (ESI, *m/z*): 546 $[M+H]^+$.

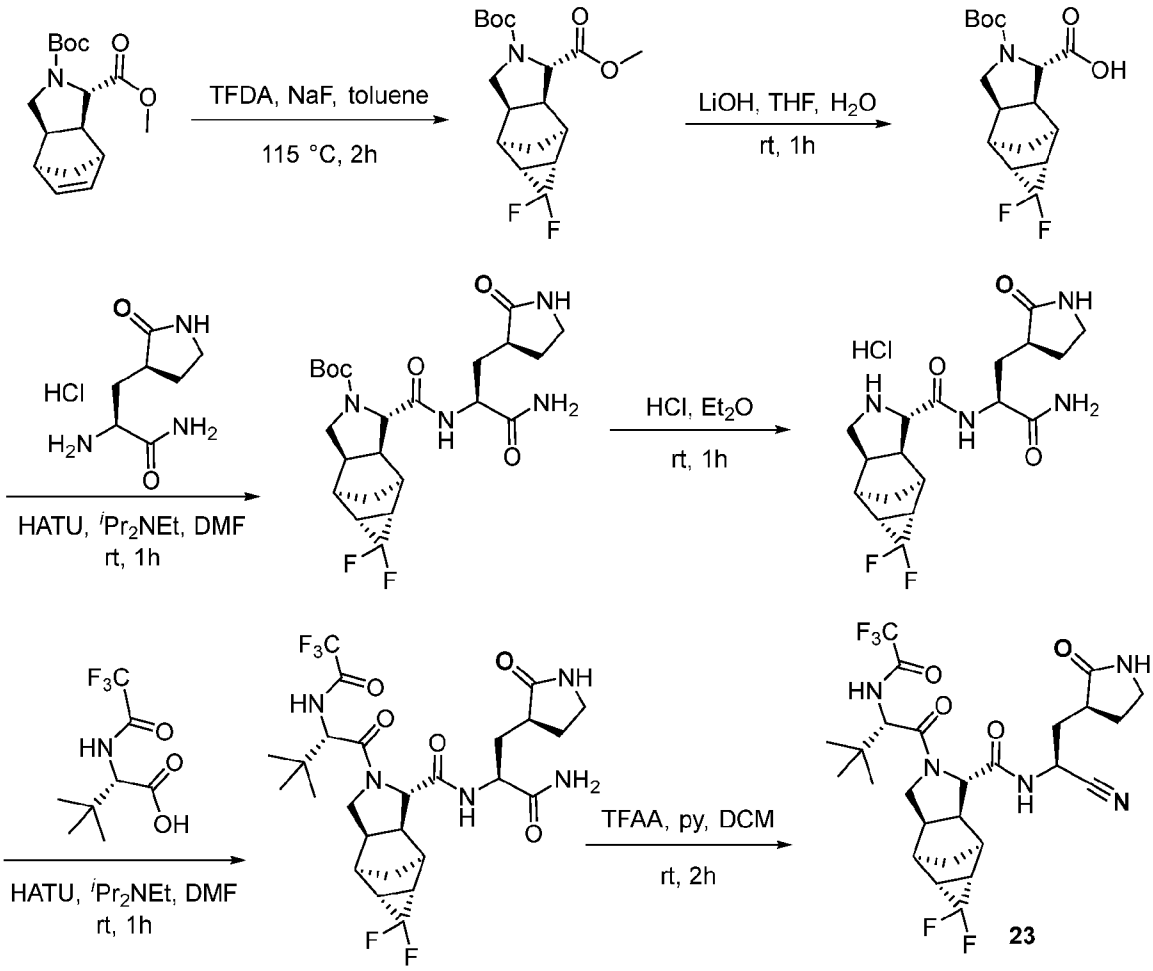
[0295] A mixture of tert-butyl ((S)-1-((1S,3aR,4S,7R,7aS)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindol-2-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (150 mg, 0.275 mmol, 1.0 eq.) in hydrogen chloride (2mL, 2 M in Et_2O) was stirred for 1 h at rt. The mixture was concentrated under reduced pressure to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-2-amino-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide hydrochloride (133 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 446 $[M+H]^+$.

[0296] To a mixture of (R)-tetrahydrofuran-2-carboxylic acid (32.0 mg, 0.276 mmol, 1.0 eq.) in N,N-dimethylformamide (3 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (125 mg, 0.331 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (213 mg, 1.65 mmol, 6.0 eq.) at 0 °C. The mixture was

stirred for 20 min at 0 °C. (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-2-amino-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide hydrochloride (133 mg, 0.276 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 2 h at 0 °C. The reaction was quenched with water (30 mL). The mixture was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-((R)-tetrahydrofuran-2-carboxamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (80 mg, 54%) as a light yellow solid. LC-MS (ESI, *m/z*): 544 $[M+H]^+$.

[0297] To a mixture of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-((R)-tetrahydrofuran-2-carboxamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (50.0 mg, 0.092 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (50.9 mg, 0.644 mmol, 7.0 eq.) and trifluoroacetic anhydride (57.9 mg, 0.276 mmol, 3.0 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 30% B to 47% B in 10 min, 47% B; Wave Length: 254 nm; RT1(min): 5.97) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-((R)-tetrahydrofuran-2-carboxamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (13.9 mg, 28%) as an off-white solid. ^1H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.60-8.90 (m, 1H), 7.35-7.60 (m, 1H), 6.80-7.20 (m, 1H), 5.80-6.20 (m, 2H), 4.65-5.00 (m, 1H), 4.30-4.50 (m, 1H), 4.15-4.30 (m, 1H), 3.95-4.05 (m, 1H), 3.70-3.90 (m, 2H), 3.50-3.65 (m, 1H), 3.30-3.55 (m, 1H), 3.10-3.25 (m, 2H), 2.90-3.05 (m, 1H), 2.65-2.80 (m, 3H), 2.25-2.45 (m, 1H), 2.05-2.25 (m, 3H), 1.65-1.95 (m, 5H), 1.30-1.50 (m, 2H), 0.65-1.10 (m, 9H). LC-MS (ESI, *m/z*): 526 $[M+H]^+$.

EXAMPLE 23
Compound 23



[0298] To a stirred mixture of 4-tert-butyl 3-methyl (1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,4-dicarboxylate (1 g, 3.40 mmol, 1.0 eq.) in toluene (4 mL) was added sodium fluoride (50.0 mg, 1.19 mmol, 0.35 eq.). Trimethylsilyl 2,2-difluoro-2-sulfoacetate (4.27 g, 17.0 mmol, 5.0 eq.) was added slowly for 2 h at 115°C under nitrogen. The reaction was quenched with water (30 mL). The mixture was extracted with ethyl acetate (3 x 30 mL)> The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide 4-tert-butyl 3-methyl (1S,2S,3S,6R,7R,8R,10S)-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3,4-dicarboxylate (180 mg, 13%) as a light

yellow oil. LC-MS (ESI, *m/z*): 288 $[M-56+H]^+$.

[0299] To a stirred mixture of 4-tert-butyl 3-methyl (1S,2S,3S,6R,7R,8R,10S)-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3,4-dicarboxylate (180 mg, 0.524 mmol, 1.0 eq.) in THF (3 mL) and H_2O (1 mL) was added lithium hydroxide (37.6 mg, 1.57 mmol, 3.0 eq.) at rt. The mixture was stirred for 1 h at rt. The mixture was acidified to pH=4 with hydrochloric acid (2M) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford (1S,2S,3S,6R,7R,8R,10S)-4-(tert-butoxycarbonyl)-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3-carboxylic acid (150 mg, crude) as a light yellow oil. LC-MS (ESI, *m/z*): 328 $[M-H]^-$.

[0300] To a stirred mixture of (1S,2S,3S,6R,7R,8R,10S)-4-(tert-butoxycarbonyl)-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3-carboxylic acid (150 mg, 0.455 mmol, 1.0 eq.) and o-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (207 mg, 0.546 mmol, 1.2 eq.) in DMF (3 mL) was added N-ethyl-N-isopropylpropan-2-amine (353 mg, 2.73 mmol, 6.0 eq.). The mixture was stirred for 10 min at 0 °C. (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (104 mg, 0.501 mmol, 1.1 eq.) was added. The mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide tert-butyl (1S,2S,3S,6R,7R,8R,10S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-4-carboxylate (160 mg, 65%) as a white solid. LC-MS (ESI, *m/z*): 483 $[M+H]^+$.

[0301] To a stirred mixture of tert-butyl (1S,2S,3S,6R,7R,8R,10S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-4-carboxylate (160 mg, 0.332 mmol, 1.0 eq.) in DCM (1 mL) were added hydrogen chloride (5 mL, 2M in Et_2O). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (2S)-2-{[(1S,2S,3S,6R,7R,8R,10S)-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (140 mg, crude) as a white solid. LC-MS (ESI, *m/z*): 383 $[M+H]^+$.

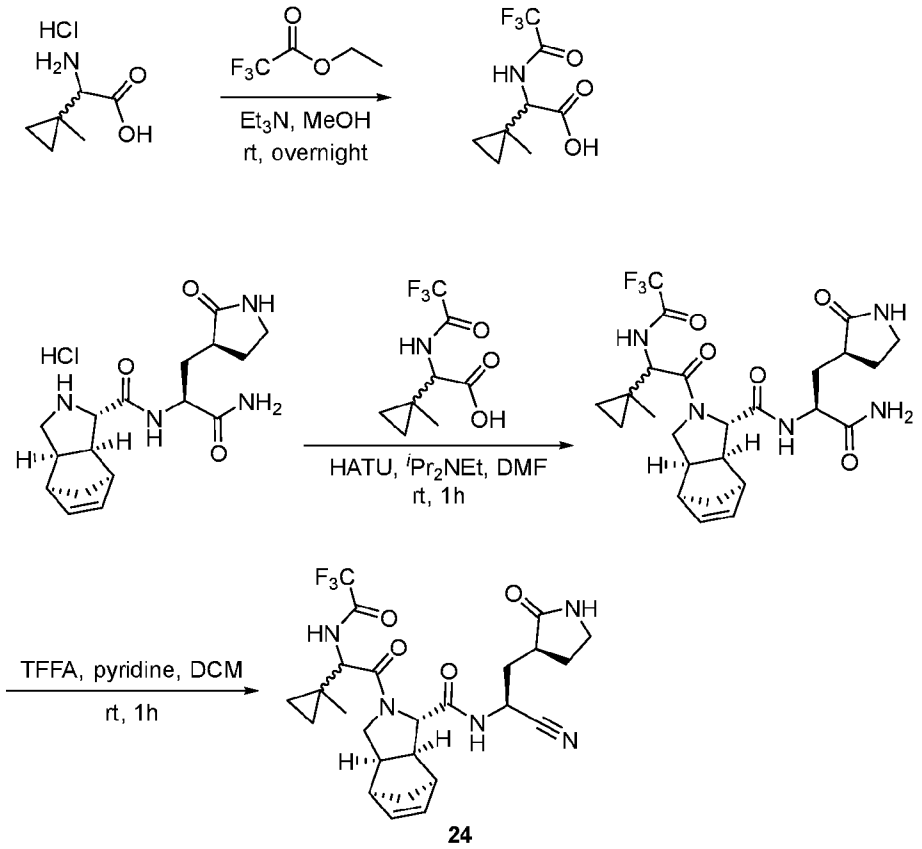
[0302] To a stirred mixture of (2S)-3,3-dimethyl-2-(2,2,2-

trifluoroacetamido)butanoic acid (83.5 mg, 0.367 mmol, 1.1 eq.) and o-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (152 mg, 0.401 mmol, 1.2 eq.) in DMF (2 mL) was added N-ethyl-N-isopropylpropan-2-amine (259 mg, 2.00 mmol, 6.0 eq.). The mixture was stirred for 10 min at 0 °C. (2S)-2-{[(1S,2S,3S,6R,7R,8R,10S)-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (140 mg, 0.334 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The crude product was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide (2S)-2-{[(1S,2S,3S,6R,7R,8R,10S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (140 mg, 63%) as a light yellow solid. LC-MS (ESI, *m/z*): 592 $[M+H]^+$.

[0303] To a stirred mixture of (2S)-2-{[(1S,2S,3S,6R,7R,8R,10S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (140 mg, 0.237 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (65.5 mg, 0.829 mmol, 3.5 eq.) and trifluoroacetic anhydride (99.4 mg, 0.474 mmol, 2.0 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with DCM (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 43% B to 73% B in 7 min, 73% B; Wave Length: 254 nm; RT1(min): 5;) to afford (1S,2S,3S,6R,7R,8R,10S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-9,9-difluoro-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3-carboxamide (30.5 mg, 21%) as a white solid. ^1H NMR (400 MHz, 80°C, DMSO-d_6) δ 8.91-9.20 (m, 1H), 8.55-8.87 (m, 1H), 7.35-7.55 (m, 1H), 4.81-4.96 (m, 1H), 4.55-4.73 (m, 2H), 3.91-4.10 (m, 1H), 3.58-3.74 (m, 1H), 3.08-3.20 (m, 2H), 2.73 -2.82 (m, 2H), 2.62-2.72 (m, 1H), 2.50-2.60 (m, 1H), 2.26-2.38 (m, 1H), 2.07-2.20 (m, 2H), 1.62-1.87 (m, 3H), 1.45-1.57 (m, 1H), 1.26-1.37 (m, 1H), 1.09-1.23

(m, 1H), 0.84-1.03 (m, 9H). LC-MS (ESI, *m/z*): 574 $[M+H]^+$.

EXAMPLE 24
Compound 24



[0304] To a mixture of amino(1-methylcyclopropyl)acetic acid hydrochloride (300 mg, 1.81 mmol, 1.0 eq.) in MeOH (5 mL) was added triethylamine (733 mg, 7.24 mmol, 4.0 eq.) and trifluoroethyl acetate (309 mg, 2.17 mmol, 1.2 eq.). The mixture was stirred overnight at rt. The mixture was concentrated under reduced pressure to afford a residue. The residue was diluted with water (10 mL). The pH was adjusted to 6 with hydrochloric acid (1 M). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide (1-methylcyclopropyl)(2,2,2-trifluoroacetamido)acetic acid (380 mg, 88%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (br, 1H), 9.76 (d, J = 7.3 Hz, 1H), 3.78 (d, J = 7.3 Hz, 1H), 1.07 (s, 3H), 0.69-0.77 (m, 1H), 0.49-0.57 (m, 1H), 0.41-0.48 (m, 1H), 0.31-0.38 (m, 1H). LC-MS (ESI, *m/z*):

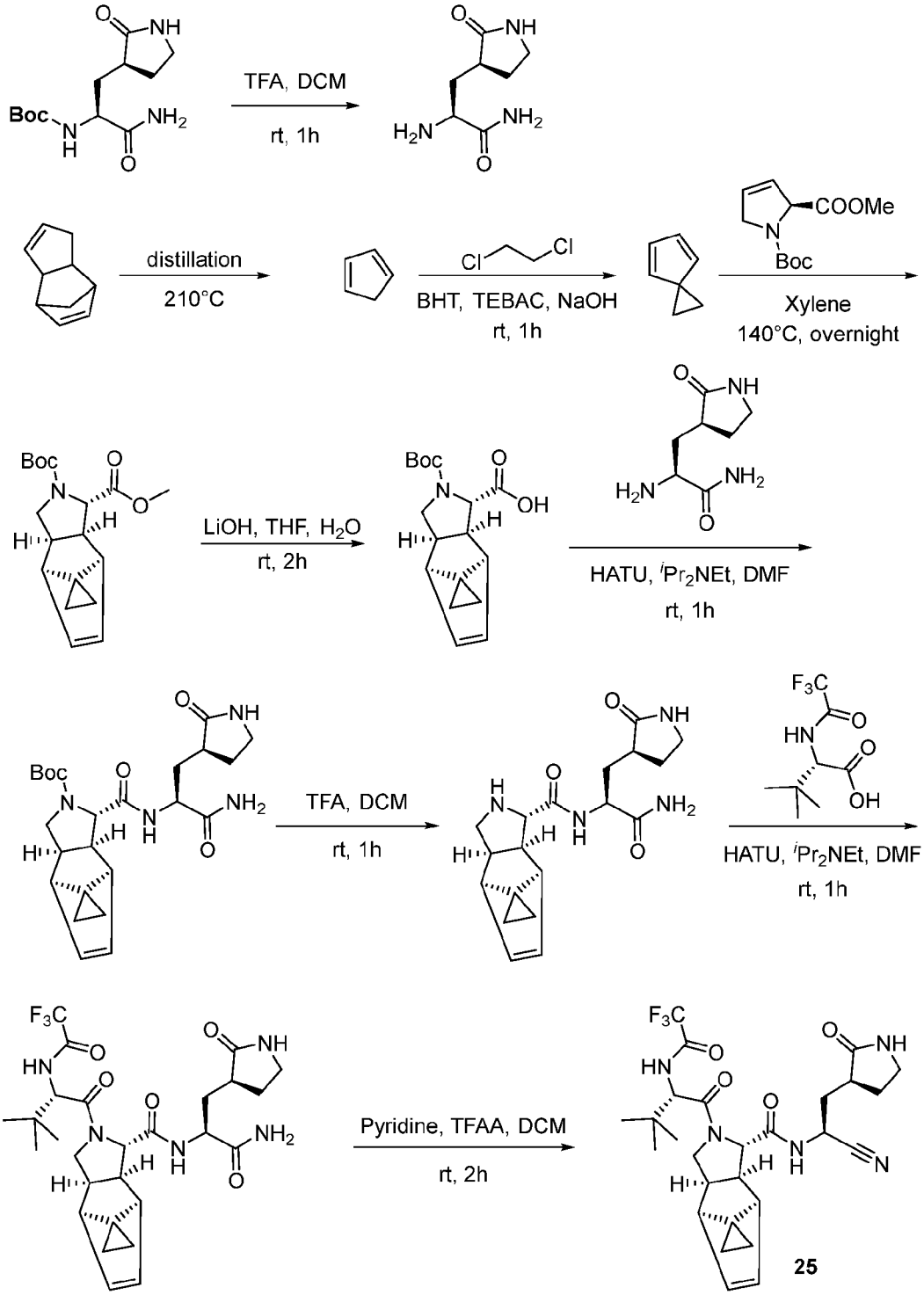
226 $[M+H]^+$.

[0305] To a mixture of (1-methylcyclopropyl)(2,2,2-trifluoroacetamido)acetic acid (78.0 mg, 0.347 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (158 mg, 0.416 mmol, 1.2 eq.) in DMF (3 mL) was added N-ethyl-N-isopropylpropan-2-amine (269 mg, 2.08 mmol, 6.0 eq.) at 0 °C. After stirred for 15 min at 0 °C, (2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (128 mg, 0.347 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide (2S)-2-{[(1R,2S,3S,6R,7S)-4-[2-(1-methylcyclopropyl)-2-(2,2,2-trifluoroacetamido)acetyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (110 mg, 50%) as an off-white solid. LC-MS (ESI, *m/z*): 540 $[M+H]^+$.

[0306] To a mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[2-(1-methylcyclopropyl)-2-(2,2,2-trifluoroacetamido)acetyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (110 mg, 0.204 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (65.0 mg, 0.816 mmol, 4.0 eq.) and trifluoroacetic anhydride (77.0 mg, 0.367 mmol, 1.8 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with DCM (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: YMC-Actus Triart C18 ExRS, 20 x 250 mm, 5 μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 38% B to 59% B in 10 min, 59% B; Wave Length: 254 nm; RT: 7.47 min) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[2-(1-methylcyclopropyl)-2-(2,2,2-trifluoroacetamido)acetyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (22.1 mg, 20%) as a white solid. ^1H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.85-9.10 (m, 1H), 8.65-8.80 (m, 1H), 7.34-7.55 (m, 1H), 6.12-6.30 (m, 1H), 5.95-6.10 (m, 1H), 4.76-4.95 (m, 1H), 4.35-4.45 (m, 1H), 3.95-4.12 (m, 1H), 3.56-3.70 (m, 1H), 3.30-3.45 (m, 1H), 3.10-3.25 (m, 2H), 2.80-3.05 (m, 3H), 2.63-2.75 (m, 1H), 2.30-2.40 (m, 1H), 1.98-2.28 (m, 2H), 1.60-1.90 (m, 2H), 1.35-1.46 (m, 2H), 0.95-1.10 (m, 3H), 0.63-0.80 (m, 2H),

0.20-0.55 (m, 2H). LC-MS (ESI, *m/z*): 522 $[M+H]^+$.

EXAMPLE 25
Compound 25



[0307] The tricyclo[5.2.1.0^{2,6}]deca-3,8-diene (110 g, 832 mmol, 1.0 eq.) was stirred at 210 °C. The cyclopentadiene was distillation at 37°C - 43°C. The fraction was collected to provide the product (46 g, 83%) as a colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.60-6.69 (m, 2H), 4.43-6.56 (m, 2H), 3.04-3.05 (m, 2H).

[0308] To a stirred mixture of cyclopentadiene (42.0 g, 635 mmol, 1.0 eq.) and ional (0.130 g, 0.572 mmol, 0.0009 eq.) in ethylene dichloride (62.8 g, 635 mmol, 1.0 eq.). After stirred for 20 min, sodium hydroxide (139 g, 3462 mmol, 5.45 eq.) and benzyltriethylazanium chloride (1.30 g, 5.72 mmol, 0.009 eq.) were added. The mixture was stirred for 1 h at rt. The reaction was quenched with water (50 mL). The mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was stirred at 130 °C. Spiro[2.4]hepta-4,6-diene was distillation at 60°C ~ 65°C under 0.7MPa. The desired fraction was collected to provide spiro[2.4]hepta-4,6-diene (10 g, 14%) as a colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.47-6.69 (m, 2H), 6.14- 6.24 (m, 2H), 1.71-1.72 (m, 4H).

[0309] To a stirred mixture of 1-tert-butyl 2-methyl (2R)-2,5-dihydropyrrole-1,2-dicarboxylate (6.00 g, 26.4 mmol, 1.0 eq.) in xylene (6 mL) was added spiro[2.4]hepta-4,6-diene (4.87 g, 52.8 mmol, 1.0 eq.). The mixture was stirred for 2 d at 140 °C and then concentrated under reduced pressure. The crude product was chromatographed on a silica gel column with ethyl acetate:petroleum ether (30:70) to provide the crude product. The crude product was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide 4'-tert-butyl 3'-methyl (1'R,2'S,3'S,6'R,7'S)-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-ene-3',4'-dicarboxylate (1.98 g, 23%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.03-6.36 (m, 2H), 3.70-3.89 (m, 1H), 3.55-3.69 (m, 3H), 3.22-3.37 (m, 1H), 2.70-3.10 (m, 3H), 2.33-2.42 (m, 1H), 2.22-2.29 (m, 1H), 1.08-1.53 (m, 9H), 0.22-0.48 (m, 4H). LC-MS (ESI, m/z): 220 $[M+H-Boc]^+$.

[0310] To a stirred mixture of 4'-tert-butyl 3'-methyl (1'R,2'S,3'S,6'R,7'S)-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-ene-3',4'-dicarboxylate (1.00 g, 3.13 mmol, 1.0 eq.) in THF (10 mL) was added lithium hydroxide (300 mg, 12.5 mmol, 4.0 eq., in water 10 mL). The mixture was stirred for 2 h at rt. The pH was adjusted to 6 with

hydrochloric acid (2 M). The mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide (1'R,2'S,3'S,6'R,7'S)-4'-(tert-butoxycarbonyl)-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-ene-3'-carboxylic acid (917 mg, 89%) as a light yellow oil. LC-MS (ESI, m/z): 250 $[M+H-56]^+$.

[0311] To a stirred mixture of (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (500 mg, 2.92 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.33 g, 3.51 mmol, 1.2 eq.) in DMF (10 mL) was added N-ethyl-N-isopropylpropan-2-amine (3.02 g, 23.4 mmol, 8.0 eq.) at 0 °C. After stirred for 20 min at 0 °C, (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (500 mg, 2.92 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The reaction was quenched with water (30 mL). The mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (1:11) to provide tert-butyl (1'R,2'S,3'S,6'R,7'S)-3'-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-ene-4'-carboxylate (758 mg, 55%) as a yellow solid. LC-MS (ESI, m/z): 359 $[M-H-Boc]^+$.

[0312] To a stirred mixture of tert-butyl (1'R,2'S,3'S,6'R,7'S)-3'-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-ene-4'-carboxylate (750 mg, 1.63 mmol, 1.0 eq.) in DCM (10 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (2S)-2-[(1'R,2'S,3'S,6'R,7'S)-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-en-3'-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (586 mg, crude) as a brown oil. LC-MS (ESI, m/z): 359 $[M+H]^+$.

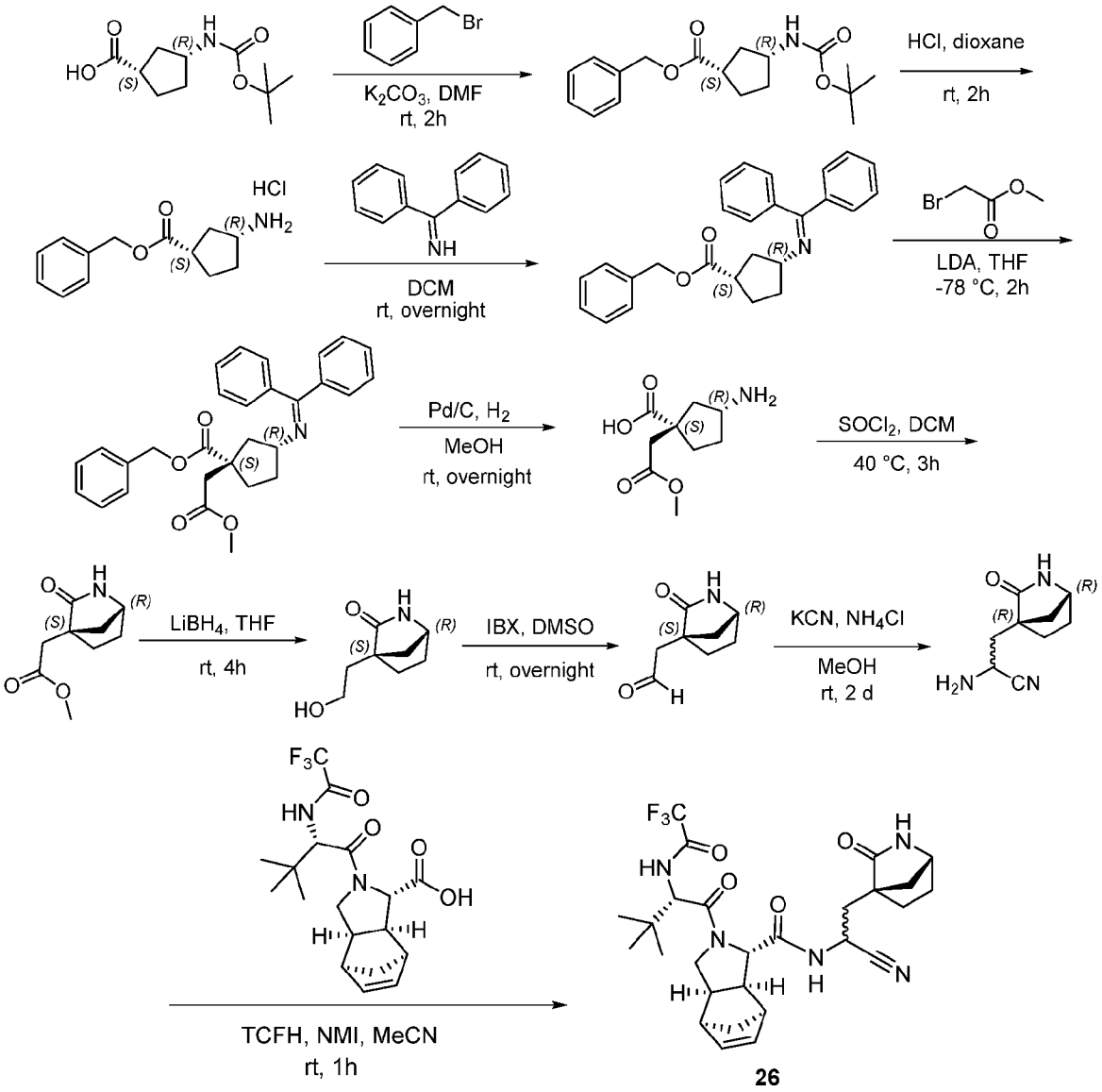
[0313] To a stirred mixture of (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoic acid (371 mg, 1.63 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (746 mg, 1.96 mmol, 1.2 eq.) in DMF (10 mL) was added N-ethyl-N-isopropylpropan-2-amine (1.69 g, 13.1 mmol, 8.0 eq.) at 0 °C. After stirred for 20 min at 0 °C, (2S)-2-[(1'R,2'S,3'S,6'R,7'S)-4'-

azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-en-3'-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (586 mg, 1.63 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The reaction was quenched with water (15 mL). The mixture was extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine (2 x 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford then crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (1:13) to provide (2S)-2-[(1'R,2'S,3'S,6'R,7'S)-4'-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-en-3'-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (667 mg, 70%) as a yellow solid. LC-MS (ESI, m/z): 568 $[M+H]^+$.

[0314] To a stirred mixture of (2S)-2-[(1'R,2'S,3'S,6'R,7'S)-4'-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-en-3'-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (150 mg, 0.264 mmol, 1.0 eq.) in DCM (4 mL) were added pyridine (73.2 mg, 0.924 mmol, 3.5 eq.) and trifluoroacetic anhydride (99.9 mg, 0.475 mmol, 1.8 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (20 mL). The mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford then crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 46% B in 10 min, 46% B to 46% B in 11 min, 46% B; Wave Length: 254 nm; RT1(min): 10.45) to provide (1'R,2'S,3'S,6'R,7'S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4'-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4'-azaspiro[cyclopropane-1,10'-tricyclo[5.2.1.0^{2,6}]decan]-8'-ene-3'-carboxamide (43.4 mg, 29%) as a white solid. ^1H NMR (400 MHz, 80°C, DMSO-d_6) δ 8.75-9.00 (m, 1H), 8.60-8.74 (m, 1H), 7.32-7.59 (m, 1H), 6.00-6.30 (m, 2H), 4.80-5.00 (m, 1H), 4.45-4.70 (m, 1H), 4.00-4.29 (m, 1H), 3.60-3.98 (m, 1H), 3.36-3.53 (m, 1H), 3.10-3.30 (m, 2H), 2.75-3.02 (m, 2H), 2.40-2.48 (m, 1H), 2.25-2.39 (m, 2H), 2.00-2.24 (m, 2H), 1.60-1.90 (m, 2H), 0.83-1.05 (m, 9H), 0.30-0.45 (m, 4H). LC-MS (ESI, m/z): 550 $[M+H]^+$.

EXAMPLE 26

Compound 26



[0315] To a mixture of (1S,3R)-3-((tert-butoxycarbonyl)amino)cyclopentane-1-carboxylic acid (35.0 g, 109 mmol, 1.0 eq.) and potassium carbonate (31.7 g, 229 mmol, 1.5 eq.) in DMF (250 mL) was added benzyl bromide (31.3 g, 183 mmol, 1.2 eq.) at rt. The mixture was stirred 2 h at rt. The mixture was filtered through a celite pad and washed with ethyl acetate (3 x 100 mL). The filtrate was quenched with water (200 mL). The mixture was extracted with ethyl acetate (3 x 500 mL). The organic layers were combined, washed with brine (2 x 300 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed

on a silica gel column with EA:PE (25%-30%) to provide benzyl (1S,3R)-3-((tert-butoxycarbonyl)amino)cyclopentane-1-carboxylate (40.0 g, 85%) as a white solid. LC-MS (ESI, *m/z*): 320 $[M+H]^+$.

[0316] To a mixture of benzyl (1S,3R)-3-((tert-butoxycarbonyl)amino)cyclopentane-1-carboxylate (40.0 g, 125 mmol, 1.0 eq.) in 1,4-dioxane (200 mL) was added hydrogen chloride (400 mL, 4 M in 1,4-dioxane) at rt. The mixture was stirred 2 h at rt and then concentrated under reduced pressure to provide benzyl (1S,3R)-3-aminocyclopentane-1-carboxylate hydrochloride (25.1 g, crude) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (br, 3H), 7.31-7.42 (m, 5H), 5.12 (s, 2H), 3.42-3.53 (m, 1H), 2.80-2.95 (m, 1H), 2.23-2.33 (m, 1H), 1.60-1.99 (m, 5H). LC-MS (ESI, *m/z*): 220 $[M+H]^+$.

[0317] To a mixture of benzyl (1S,3R)-3-aminocyclopentane-1-carboxylate hydrochloride (25.1 g, 97.8 mmol, 1.0 eq.) in DCM (400 mL) was added diphenylmethanimine (19.5 g, 108 mmol, 1.1 eq.). The mixture was stirred for overnight at rt. The mixture was filtered through a celite pad and washed with DCM (3 x 100 mL). The mixture was concentrated under reduced pressure to afford then crude product. The crude product was chromatographed on a silica gel column with EA:PE (11%-13%) to provide benzyl (1S,3R)-3-((diphenylmethylene)amino)cyclopentane-1-carboxylate (33.0 g, crude) as a yellow oil. LC-MS (ESI, *m/z*): 384 $[M+H]^+$.

[0318] To a mixture of benzyl (1S,3R)-3-((diphenylmethylene)amino)cyclopentane-1-carboxylate (33.0 g, 86.2 mmol, 1.0 eq.) in THF (400 mL) was added dropwise lithium diisopropylamide (56.1 mL, 112 mmol, 1.3 eq., 2 M in THF) at - 78 °C under nitrogen. After stirred for 1 h at -78 °C, methyl 2-bromoacetate (26.4 g, 172 mmol, 2.5 eq.) was added. The mixture was stirred for 1 h at -78 °C. The mixture was warmed to 0 °C and stirred for 2 h at 0 °C under nitrogen. The reaction was quenched with water (200 mL). The mixture was extracted with ethyl acetate (3 x 300 mL). The organic layers were combined, washed with brine (2 x 200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EA:PE (12%-15%) to provide benzyl (1S,3R)-3-((diphenylmethylene)amino)-1-(2-methoxy-2-oxoethyl)cyclopentane-1-carboxylate (10.7 g, crude) as a yellow oil. LC-MS (ESI, *m/z*): 456

$[M+H]^+$.

[0319] To a mixture of benzyl (1S,3R)-3-((diphenylmethylene)amino)-1-(2-methoxy-2-oxoethyl)cyclopentane-1-carboxylate (10.7 g, 23.5 mmol, 1.0 eq.) in MeOH (150 mL) was added 10% palladium on activated carbon (3.5 g). The mixture was stirred overnight at rt under hydrogen and then filtered. The filter cake was washed with MeOH (3 x 150 mL). The filtrate was concentrated under reduced pressure to afford (1S,3R)-3-amino-1-(2-methoxy-2-oxoethyl)cyclopentane-1-carboxylic acid (4.5 g, crude) as a yellow solid. LC-MS (ESI, *m/z*):202 $[M+H]^+$.

[0320] To a mixture of (1S,3R)-3-amino-1-(2-methoxy-2-oxoethyl)cyclopentane-1-carboxylic acid (4.5 g, 22.4 mmol, 1.0 eq.) in DCM (50 mL) was added thionyl chloride (4.26 g, 35.8 mmol, 1.6 eq.). The mixture was stirred 3 h at 40 °C. The reaction was quenched with water (20 mL). The mixture was extracted with DCM (3 x 100 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EA :PE (70%-85%) to provide methyl 2-((1R,4S)-3-oxo-2-azabicyclo[2.2.1]heptan-4-yl)acetate (400 mg, 9%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (br, 1H), 3.89-3.90 (m, 1H), 3.71 (s, 3H), 2.86-2.91 (m, 1H), 2.68-2.72 (m, 1H), 2.05-2.09 (m, 1H), 1.92-1.99 (m, 1H), 1.82-1.88 (m, 1H), 1.65-1.73 (m, 1H), 1.60-1.63 (m, 1H), 1.51-1.59 (m, 1H). LC-MS (ESI, *m/z*): 184 $[M+H]^+$.

[0321] To a mixture of methyl 2-((1R,4S)-3-oxo-2-azabicyclo[2.2.1]heptan-4-yl)acetate (400 mg, 2.18 mmol, 1.0 eq.) in THF (5 mL) was added lithium borohydride (4.4 mL, 8.73 mmol, 4.0 eq., 2 M in THF) at 0 °C. The mixture was stirred for 4 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with ethyl acetate (6 x 50 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH :DCM (2%-4%) to provide (1R,4S)-4-(2-hydroxyethyl)-2-azabicyclo[2.2.1]heptan-3-one (240 mg, 70%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (br, 1H), 3.92 (s, 1H), 3.75-3.86 (m, 2H), 3.11 (br, 1H), 2.06-2.14 (m, 1H), 1.92-2.03 (m, 3H), 1.65-1.77 (m, 3H), 1.41-1.44 (m, 1H). LC-MS (ESI, *m/z*): 156 $[M+H]^+$.

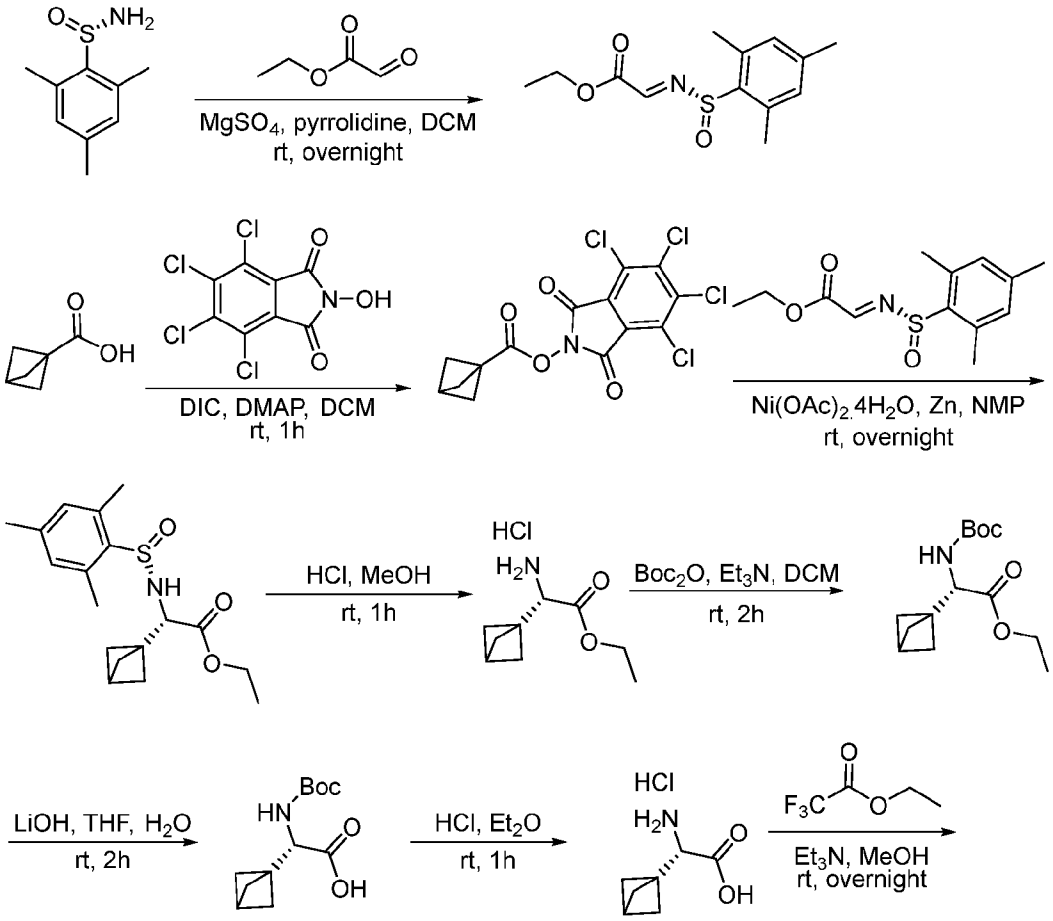
[0322] To a mixture of (1R,4S)-4-(2-hydroxyethyl)-2-azabicyclo[2.2.1]heptan-3-one (120 mg, 0.773 mmol, 1.0 eq.) in DMSO (2 mL) was added 2-iodoxybenzoic acid (650 mg, 2.31 mmol, 3.0 eq.). The mixture was stirred for overnight at rt. The reaction was quenched with saturated aqueous sodium bicarbonate (10 mL). The mixture was extracted with ethyl acetate (5 x 30 mL). The organic layers were combined, washed with brine (2 x 20 mL), saturated aqueous sodium bicarbonate (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2-((1R,4S)-3-oxo-2-azabicyclo[2.2.1]heptan-4-yl)acetaldehyde (80.0 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 154 $[M+H]^+$.

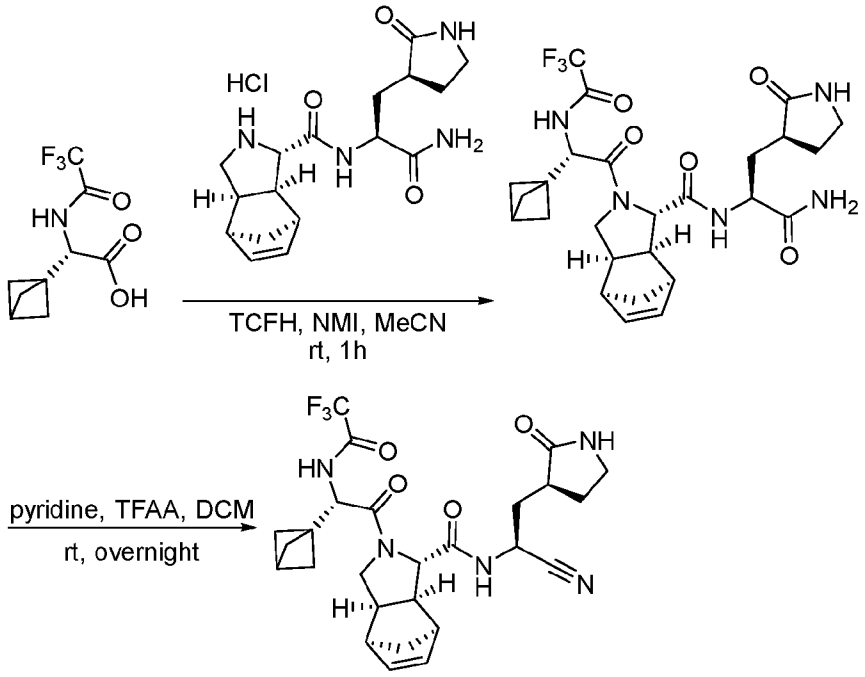
[0323] To a solution of 2-((1R,4S)-3-oxo-2-azabicyclo[2.2.1]heptan-4-yl)acetaldehyde (80.0 mg, 0.522 mmol, 1.0 eq.) in CH_3OH (2 mL) was added ammonium chloride (83.8 mg, 1.57 mmol, 3.0 eq.). After stirred 2 h at rt, zyankali (44.1 mg, 0.679 mmol, 1.3 eq.) was added. The mixture was stirred for 2 d at rt. The mixture was filtered through a celite pad and washed with CH_3OH (3 x 20 mL) and DCM (3 x 20 mL). The filtrate was concentrated under reduced pressure to afford 2-amino-3-((1R,4R)-3-oxo-2-azabicyclo[2.2.1]heptan-4-yl)propanenitrile (80.0 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 180 $[M+H]^+$.

[0324] To a mixture of 2-amino-3-((1R,4R)-3-oxo-2-azabicyclo[2.2.1]heptan-4-yl)propanenitrile (80.0 mg, 0.446 mmol, 1.0 eq.), (1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (191 mg, 0.491 mmol, 1.1 eq.) and N,N,N,N-tetramethylchloroformamidinium hexafluorophosphate (150 mg, 0.535 mmol, 1.2 eq.) in acetonitrile (3 mL) was added 1-methyl-1H-imidazole (367 mg, 4.46 mmol, 10.0 eq.) at 0 °C. The mixture was stirred for 1 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with ethyl acetate:petroleum ether (78%-85%) to provide the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 35% B to 55% B in 10 min, 55% B; Wave Length: 220 nm;

RT1(min): 8.48;) to provide (1S,3aR,4S,7R,7aS)-N-(1-cyano-2-((1R,4S)-3-oxo-2-azabicyclo[2.2.1]heptan-4-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (17.4 mg, 7%) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.53-8.94 (m, 2H), 7.47 (s, 1H), 5.93-6.16 (m, 2H), 4.71-4.88 (m, 1H), 4.46 (s, 1H), 3.99-4.15 (m, 1H), 3.66-3.77 (m, 1H), 3.56-3.67 (m, 1H), 3.40-3.44 (m, 1H), 2.97-3.02 (m, 1H), 2.78-2.95 (m, 2H), 2.63-2.75 (m, 1H), 2.05-2.29 (m, 2H), 1.60-1.85 (m, 3H), 1.21-1.51 (m, 5H), 0.85-0.96 (m, 9H). LC-MS (ESI, m/z): 550 $[M+H]^+$.

EXAMPLE 27
Compound 27





27

[0325] To a mixture of (S)-2,4,6-trimethylbenzenesulfinamide (400 mg, 2.18 mmol, 1.0 eq.) and magnesium sulfate (1.31 g, 10.9 mmol, 5.0 eq.) in DCM (12 mL) was added pyrrolidine (16.0 mg, 0.218 mmol, 0.1 eq.) and ethyl glyoxylate (1.34 g, 6.55 mmol, 3.0 eq., 50% in toluene). The mixture was stirred overnight at rt and then filtered. The filtrate was concentrated under reduced pressure to afford ethyl 2-{[(S)-2,4,6-trimethylbenzenesulfinyl]imino}acetate (584 mg, crude) as a light yellow oil. LC-MS (ESI, *m/z*): 268 $[M+H]^+$.

[0326] To a mixture of bicyclo[1.1.1]pentane-1-carboxylic acid (300 mg, 2.68 mmol, 1.0 eq.), 4,5,6,7-tetrachloro-2-hydroxyisoindole-1,3-dione (805 mg, 2.68 mmol, 1.0 eq.) and N,N-dimethylpyridin-4-amine (33.0 mg, 0.268 mmol, 0.1 eq.) in DCM (20 mL) was added N,N'-diisopropylcarbodiimide (371 mg, 2.94 mmol, 1.1 eq.). The mixture was stirred for 1 h at rt. The mixture was chromatographed on a silica gel column with EtOAc:petroleum ether (15:85) to provide 4,5,6,7-tetrachloro-1,3-dioxoisoindol-2-yl bicyclo[1.1.1]pentane-1-carboxylate (540 mg, 47%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (s, 1H), 2.30 (m, 6H).

[0327] To a mixture of 4,5,6,7-tetrachloro-1,3-dioxoisoindol-2-yl bicyclo[1.1.1]pentane-1-carboxylate (540 mg, 1.38 mmol, 1.0 eq.), ethyl 2-{[(S)-2,4,6-trimethylbenzenesulfinyl]imino}acetate (585 mg, 2.19 mmol, 1.6 eq.) and Nickel(II) acetate

tetrahydrate (85.0 mg, 0.342 mmol, 0.25 eq.) in 1-methyl-2-pyrrolidinone (10 mL) was added zinc (268 mg, 4.10 mmol, 3.0 eq.). The mixture was stirred overnight at rt under nitrogen. The reaction was quenched with water (30 mL). The mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by TLC (Mobile phase: EtOAc:petroleum ether =1:5; Rf = 0.5; detection: UV) to provide ethyl (2S)-2-{bicyclo[1.1.1]pentan-1-yl}-2-{[(S)-2,4,6-trimethylbenzenesulfinyl]amino}acetate (200 mg, 35%) as a light yellow oil. LC-MS (ESI, *m/z*): 336 $[M+H]^+$.

[0328] To a mixture of ethyl (2S)-2-{bicyclo[1.1.1]pentan-1-yl}-2-{[(S)-2,4,6-trimethylbenzenesulfinyl]amino}acetate (200 mg, 0.596 mmol, 1 eq.) in MeOH (2 mL) was added hydrogen chloride (0.60 mL, 2.38 mmol, 4.0 eq., 4 M in EtOH). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford ethyl (2S)-2-amino-2-{bicyclo[1.1.1]pentan-1-yl}acetate hydrochloride (120 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 170 $[M+H]^+$.

[0329] To a mixture of ethyl (2S)-2-amino-2-{bicyclo[1.1.1]pentan-1-yl}acetate hydrochloride (120 mg, 0.583 mmol, 1.0 eq.) in DCM (3 mL) was added triethylamine (295 mg, 2.91 mmol, 5.0 eq.) and di-tert-butyl dicarbonate (153 mg, 0.700 mmol, 1.2 eq.). The mixture was stirred for 2 h at rt and then concentrated under reduced pressure to remove the DCM. The residue was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide ethyl (2S)-2-{bicyclo[1.1.1]pentan-1-yl}-2-[(tert-butoxycarbonyl)amino]acetate (120 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 214 $[M-56+H]^+$.

[0330] To a mixture of ethyl (2S)-2-{bicyclo[1.1.1]pentan-1-yl}-2-[(tert-butoxycarbonyl)amino]acetate (120 mg, 0.446 mmol, 1.0 eq.) in THF (1.5 mL):water (1.5 mL) was added lithium hydroxide (54.0 mg, 2.23 mmol, 5.0 eq.). The mixture was stirred for 2 h at rt and then concentrated under reduced pressure to remove the THF. The pH was adjusted to 6 with hydrochloric acid (1 M). The mixture was extracted with EtOAc (3 x 3 mL). The organic layers were combined, washed with brine (2 x 2 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (S)-bicyclo[1.1.1]pentan-1-yl[(tert-butoxycarbonyl)amino]acetic acid (100 mg, crude) as a

yellow oil. LC-MS (ESI, *m/z*): 186 $[M-56+H]^+$.

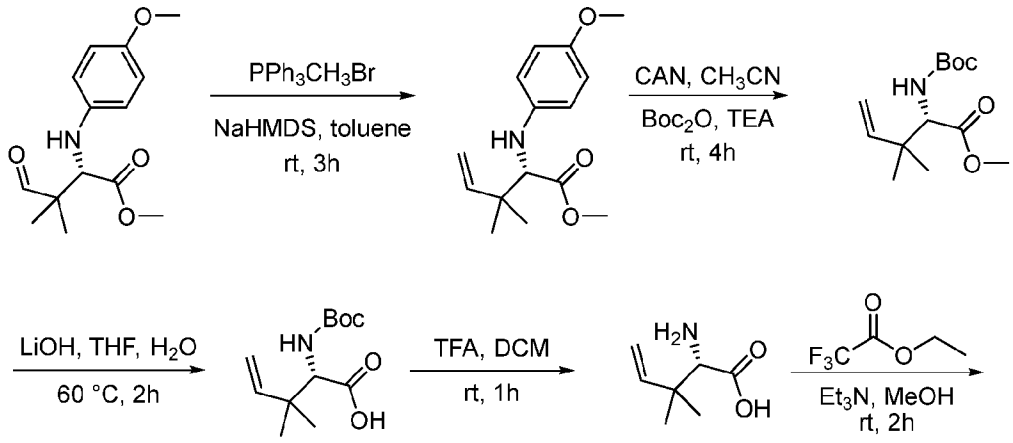
[0331] A mixture of (S)-bicyclo[1.1.1]pentan-1-yl[(tert-butoxycarbonyl)amino]acetic acid (100 mg, 0.414 mmol, 1.0 eq.) in hydrogen chloride (2 mL, 2 M in Et_2O) was stirred for 1 h at rt. The mixture was concentrated under reduced pressure to afford (S)-amino(bicyclo[1.1.1]pentan-1-yl)acetic acid hydrochloride (73 mg, crude) as an off-white solid. LC-MS (ESI, *m/z*): 142 $[M+H]^+$.

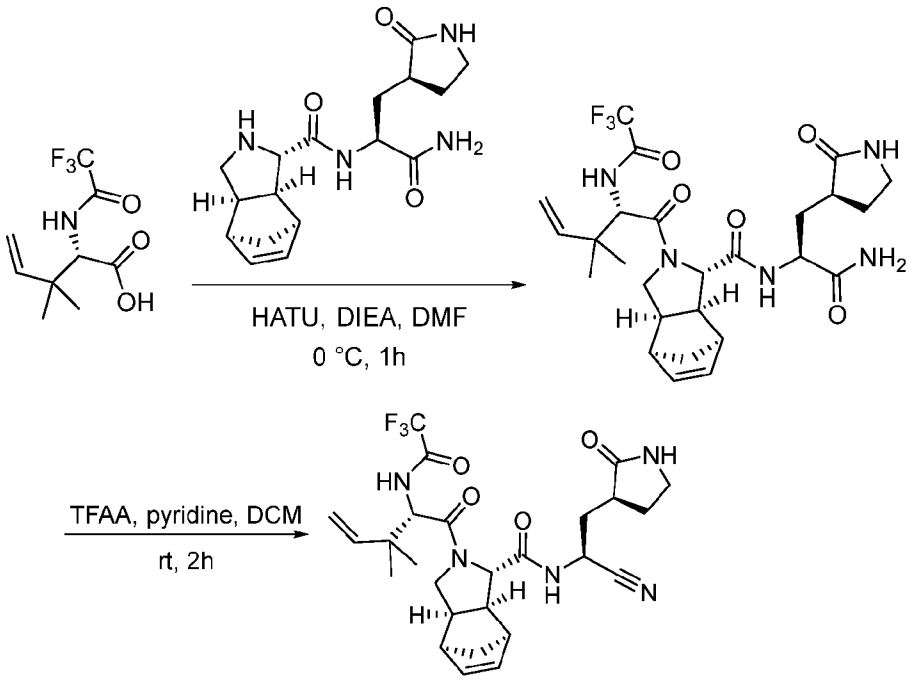
[0332] To a mixture of (S)-amino(bicyclo[1.1.1]pentan-1-yl)acetic acid hydrochloride (73 mg, 0.411 mmol, 1.0 eq.) in MeOH (2 mL) was added triethylamine (166 mg, 1.64 mmol, 4.0 eq.) and trifluoroethyl acetate (117 mg, 0.822 mmol, 2.0 eq.). The mixture was stirred overnight at rt, and then concentrated under reduced pressure to remove the MeOH. The mixture was diluted with water (5 mL) and the pH was adjusted to 6 with hydrochloric acid (1 M). The mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide (S)-bicyclo[1.1.1]pentan-1-yl(2,2,2-trifluoroacetamido)acetic acid (40 mg, 37%) as a yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.65-6.87 (m, 1H), 4.70-4.77 (m, 1H), 2.61 (s, 1H), 1.79-1.94 (m, 6H). LC-MS (ESI, *m/z*): 236 $[M-H]^-$.

[0333] To a mixture of (2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (62.0 mg, 0.168 mmol, 1.0 eq.), (S)-bicyclo[1.1.1]pentan-1-yl(2,2,2-trifluoroacetamido)acetic acid (40.0 mg, 0.168 mmol, 1.0 eq.) and N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate (61.0 mg, 0.218 mmol, 1.3 eq.) in MeCN (2 mL) was added N-methylimidazole (138 mg, 1.68 mmol, 10.0 eq.). The mixture was stirred for 1 h at rt and then purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-{bicyclo[1.1.1]pentan-1-yl}-2-(2,2,2-trifluoroacetamido)acetyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (60.0 mg, 54%) as a yellow solid. LC-MS (ESI, *m/z*): 552 $[M+H]^+$.

[0334] To a mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-{bicyclo[1.1.1]pentan-1-yl}-2-(2,2,2-trifluoroacetamido)acetyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (60.0 mg, 0.109 mmol, 1.0 eq.) in DCM (1 mL) were added pyridine (35.0 mg, 0.436 mmol, 4.0 eq.) and trifluoroacetic anhydride (41.0 mg, 0.196 mmol, 1.8 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with DCM (3 x 5 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19 x 250 mm, 10 μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 38% B to 68% B in 7 min, 68% B; Wave Length: 220 nm; RT: 5.28 min) to provide (1R,2S,3S,6R,7S)-4-[(2S)-2-{bicyclo[1.1.1]pentan-1-yl}-2-(2,2,2-trifluoroacetamido)acetyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (6.2 mg, 10%) as a white solid. LC-MS (ESI, *m/z*): 534 $[M+H]^+$.

EXAMPLE 28
Compound 28





28

[0335] To a solution of methyl (S)-2-((4-methoxyphenyl)amino)-3,3-dimethyl-4-oxobutanoate (5.17 g, 18.6 mmol, 1.1 eq.) in toluene was added sodium bis(trimethylsilyl)amide (3.42 g, 18.6 mmol, 1.1 eq.) at 0°C. The mixture was stirred for 30 min at rt. After cooling to 0°C, a solution of methyl (2S)-2-[(4-methoxyphenyl)amino]-3,3-dimethyl-4-oxobutanoate (4.50 g, 16.9 mmol, 1.0 eq.) in toluene (50 mL) was added. The mixture was stirred for 30 min at 0°C and then poured into ice-cold water (50 mL). The mixture was extracted with ethyl acetate (3 x 80 mL). The organic phases were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with ethyl acetate:petroleum ether (6:94) to provide the crude product. The crude product was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide methyl (S)-2-((4-methoxyphenyl)amino)-3,3-dimethylpent-4-enoate (600 mg, crude) as a brown oil. ^1H NMR (400 MHz, DMSO-d_6) δ 6.26 -7.33 (m, 4H), 5.64-6.16 (m, 1H), 4.76-5.27 (m, 2H), 3.72-3.87 (m, 1H), 3.37 -3.71 (m, 6H), 0.47-1.43 (m, 6H). LC-MS (ESI, *m/z*): 264 $[M+H]^+$.

[0336] To a stirred mixture of methyl (S)-2-((4-methoxyphenyl)amino)-3,3-dimethylpent-4-enoate (0.460 g, 1.75 mmol, 1.0 eq.) in CH_3CN (2.4 mL) and H_2O (0.8 mL)

were added ceric ammonium nitrate (4.80 g, 8.73 mmol, 5.0 eq.) at rt. The mixture was stirred for 2 h at rt and THF (2.5 mL), trimethylamine (basified to pH=8), di-tert-butyl dicarbonate (2.28 g, 10.4 mmol, 6.0 eq.) were added. The mixture was stirred for 2 h at rt. The reaction was quenched with water (30 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with ethyl acetate:petroleum ether (10:90) to provide methyl (S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylpent-4-enoate (195 mg, 43%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75-7.25 (m, 1H), 5.52-6.16 (m, 1H), 4.68-5.20 (m, 2H), 3.80-4.10 (m, 1H), 3.43-3.70 (m, 3H), 1.13-1.73 (m, 9H), 0.64-1.10 (m, 6H). LC-MS (ESI, *m/z*): 202 $[M-56+H]^+$.

[0337] To a stirred mixture of methyl (S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylpent-4-enoate (195 mg, 0.758 mmol, 1.0 eq.) in THF (3 mL) and H_2O (1 mL) was added lithium hydroxide (90.7 mg, 3.79 mmol, 5.0 eq.) at rt. The mixture was stirred for 2 h at 60 °C and then acidified to pH=3 with hydrochloric acid (1M). The mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylpent-4-enoic acid (160 mg, 86%, crude) as a light orange solid. LC-MS (ESI, *m/z*): 188 $[M-56+H]^+$.

[0338] To a stirred mixture of (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylpent-4-enoic acid (160 mg, 0.658 mmol, 1.0 eq.) in DCM (3 mL) was added trifluoroacetic acid (1 mL) at rt. The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to (2S)-2-amino-3,3-dimethylpent-4-enoic acid (200.0 mg, crude) as a brown yellow oil. LC-MS (ESI, *m/z*): 144 $[M+H]^+$.

[0339] To a stirred mixture of (2S)-2-amino-3,3-dimethylpent-4-enoic acid (200 mg, 1.39 mmol, 1.0 eq.) and triethylamine (565 mg, 5.58 mmol, 4.0 eq.) in MeOH (3 mL) was added trifluoroethyl acetate (396 mg, 2.79 mmol, 2.0 eq.). The mixture was stirred for 2 h at rt and then acidified to pH=4 with hydrochloric acid (1M). The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were concentrated under reduced pressure to afford (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-enoic acid

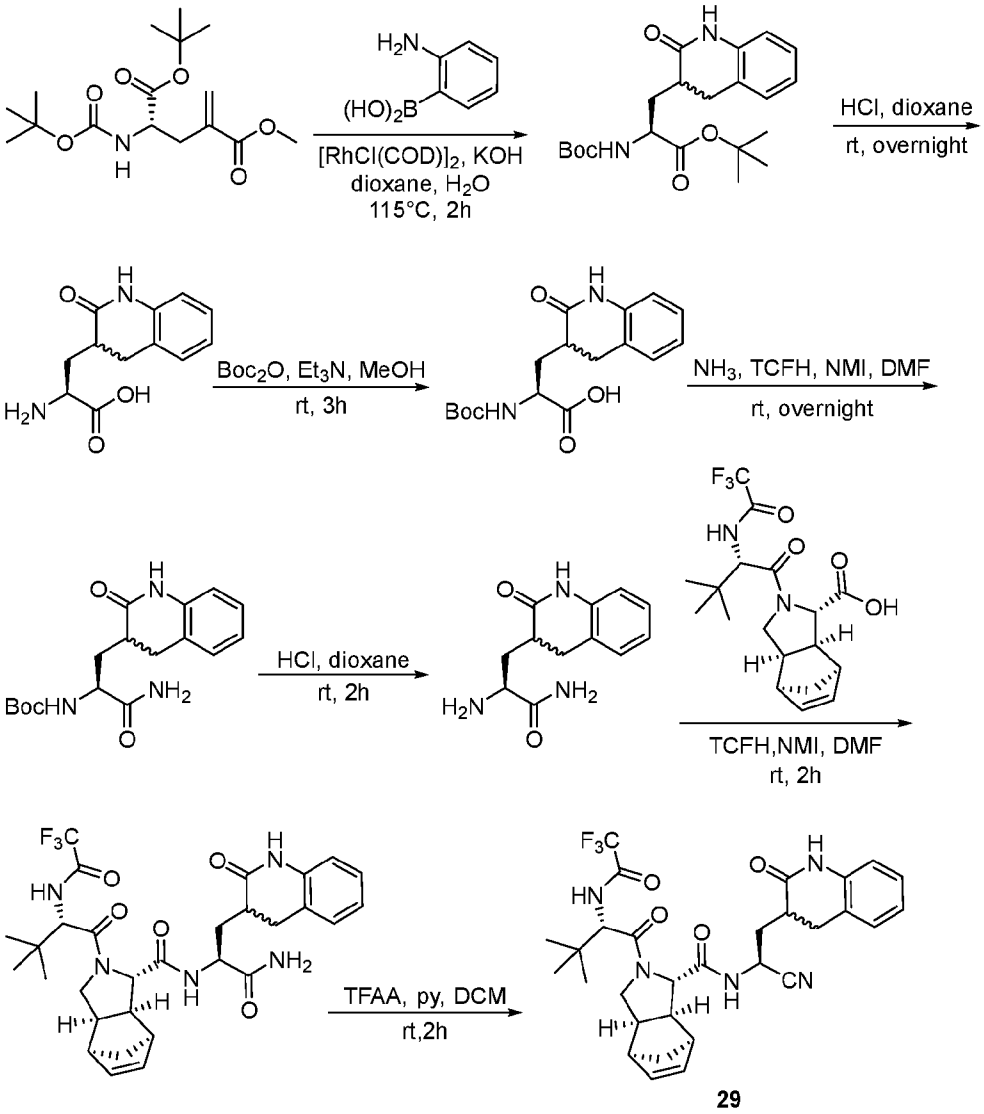
(100 mg, 29%) as a light yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19-9.65 (m, 1H), 5.76-6.11 (m, 1H), 4.69-5.29 (m, 2H), 4.13-4.51 (m, 1H), 1.08-1.26 (m, 6H). LC-MS (ESI, *m/z*): 240 $[M+H]^+$.

[0340] To a mixture of(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-enoic acid (107 mg, 0.451 mmol, 1.0 eq.) in N,N-dimethylformamide (2mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (205 mg, 0.541 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (349 mg, 2.70 mmol, 6.0 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C, and then(2S)-2-[(1R,2S,3S,6R,7S)-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (150 mg, 0.451 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 2 h at rt. The reaction was quenched with water (20 mL). The mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The reaction mixture was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-enoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (100 mg, 40%) as a light yellow solid. LC-MS (ESI, *m/z*): 554 $[M+H]^+$.

[0341] To a mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-enoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (100 mg, 0.181 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (57.1 mg, 0.724 mmol, 4.0 eq.) and trifluoroacetic anhydride (68.2 mg, 0.326 mmol, 1.8 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 30% B to 47% B in 10 min, 47% B; Wave Length: 254 nm; RT1(min): 5.97) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)pent-4-enoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-

carboxamide (9.3 mg, 10%) as an white solid. ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 8.40-9.00 (m, 2H), 7.30-7.62 (m, 1H), 5.75-6.30 (m, 3H), 4.80-5.10 (m, 3H), 4.45-4.75 (m, 1H), 3.85-4.40 (m, 1H), 3.60-3.80 (m, 1H), 3.30-3.58 (m, 1H), 3.10-3.28 (m, 3H), 2.55-3.00 (m, 3H), 2.00-2.45 (m, 3H), 1.60-1.95 (m, 2H), 1.15-1.50 (m, 2H), 0.80-1.10 (m, 6H). LC-MS (ESI, *m/z*): 536 $[M+H]^+$.

EXAMPLE 29
Compound 29



[0342] To a solution of 1-(tert-butyl) 5-methyl (S)-2-((tert-butoxycarbonyl)amino)-4-methylenepentanedioate (2 g, 6.07 mmol, 1.0 eq.) in dioxane (30

mL) was added 2-aminophenylboronic acid (1.66 g, 12.1 mmol, 2.0 eq.), Chloro(1,5-cyclooctadiene)rhodium(I) dimer (89.8 mg, 0.18 mmol, 0.03 eq.), potassium hydroxide solution (0.6 mL, 1.52 mmol, 0.25 eq.), was stirred at 115 °C for 2 h under N_2. The reaction was quenched with water (20 mL). The mixture was extracted with EA (3 x 30 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with ethyl acetate:petroleum ether (1:4) to provide tert-butyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propanoate (1.5 g, 57%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 7.01-7.24 (m, 3H), 6.82-6.92 (m, 2H), 3.86-4.12(m, 1H), 2.86-2.95 (m, 1H), 2.59-2.71 (m, 1H), 2.38-2.49 (m, 1H), 2.07-2.18 (m, 1H), 1.54-1.69 (m, 1H), 1.35-1.44 (m, 18H). LC-MS (ESI, *m/z*): 391 $[M+H]^+$.

[0343] To a solution of tert-butyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propanoate (1.3 g, 3.33 mmol, 1.0 eq.) in dioxane (15 mL) was added hydrochloric acid (15 mL, 9 mol/L in dioxane). The mixture was stirred at rt overnight and then concentrated under reduced pressure to provide (2S)-2-amino-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propanoic acid (700 mg, crude) as a white solid. LC-MS (ESI, *m/z*): 235 $[M+H]^+$.

[0344] To a solution of (2S)-2-amino-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propanoic acid (700 mg, 2.99 mmol, 1.0 eq.) in MeOH (10 mL) was added di-tert-butyl dicarbonate (717 mg, 3.29 mmol, 1.1 eq.) and triethylamine (907 mg, 8.96 mmol, 3.0 eq.). The mixture was stirred at rt for 3 h and then concentrated under reduced pressure to provide (2S)-2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propanoic acid (800 mg, crude) as an off-white solid. LC-MS (ESI, *m/z*): 335 $[M+H]^+$.

[0345] To a solution of (2S)-2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propanoic acid (800 mg, 2.39 mmol, 1.0 eq.) in DMF (10 mL) was added N,N,N,N-tetramethylchloroformamidinium hexafluorophosphate (4.03 g, 14.4 mmol, 6.0 eq.), NMI (4.91 g, 59.8 mmol, 25.0 eq.), NH_3 (120 mL, 0.4 mol/L in dioxane, 47.8 mmol, 20.0 eq.). The mixture was stirred at rt overnight and then chromatographed on a C18 column with MeCN:H_2O (1:4) to provide tert-butyl ((2S)-1-amino-1-oxo-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propan-2-yl)carbamate (600 mg, 68%) as a brown yellow solid. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 10.12-10.14 (m, 1H), 7.12-7.24 (m, 3H), 6.84-7.01 (m, 4H), 4.01-4.11 (m, 1H), 2.88-3.18 (m, 1H), 2.63-2.72 (m, 1H), 2.41-2.45 (m, 1H), 2.05-2.18 (m, 1H), 1.49-1.67 (m, 1H), 1.36-1.48 (m, 9H). LC-MS (ESI, *m/z*): 334 $[M+H]^+$.

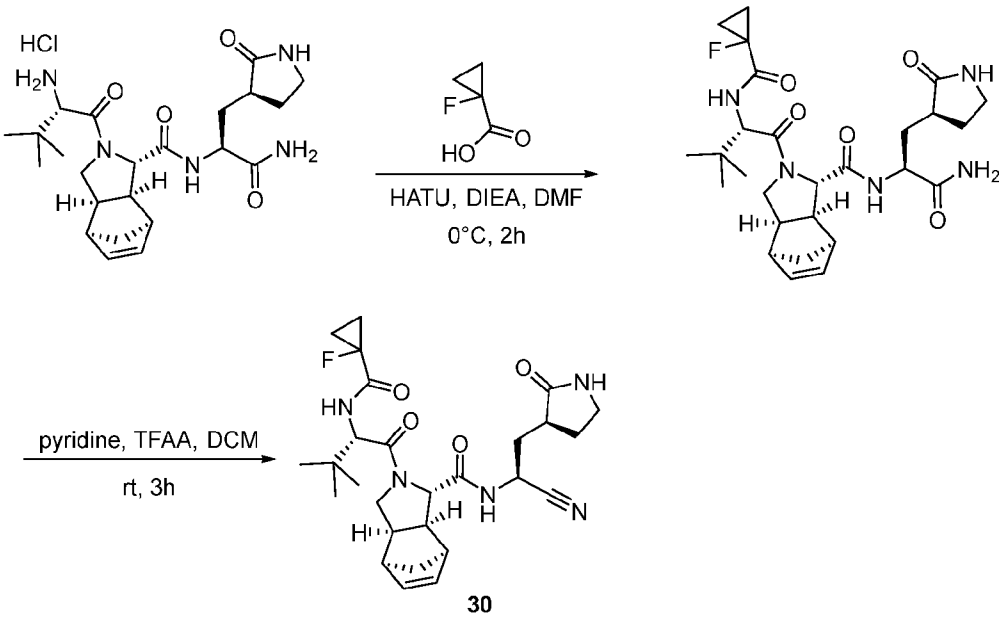
[0346] A solution of tert-butyl ((2S)-1-amino-1-oxo-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propan-2-yl)carbamate (150 mg, 0.450 mmol, 1 eq.) in hydrochloric acid (3 mL, 4M in dioxane) was stirred at rt for 2 h and then concentrated under reduced pressure to provide (2S)-2-amino-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propenamide (100 mg, crude) as an off-white solid. LC-MS (ESI, *m/z*): 234 $[M+H]^+$.

[0347] To a solution of (2S)-2-amino-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propanamide (100 mg, 0.43 mmol, 1.0 eq.) in DMF (3 mL) were added (1S,3aR,4S,7R,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (183 mg, 0.47 mmol, 1.1 eq.), N,N,N,N-tetramethylchloroformamidinium hexafluorophosphate (156 mg, 0.56 mmol, 1.3 eq.) and NMI (176 mg, 2.15 mmol, 5.0 eq.). The mixture was stirred at rt for 2 h and then chromatographed on a C18 column with water:MeCN (3:1) to provide (1S,3aR,4S,7R,7aS)-N-((2S)-1-amino-1-oxo-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (200 mg, 70%) as an off-white solid. LC-MS (ESI, *m/z*): 604 $[M+H]^+$.

[0348] To a solution of (1S,3aR,4S,7R,7aS)-N-((2S)-1-amino-1-oxo-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (90 mg, 0.15 mmol, 1.0 eq.) in DCM (30 mL) was added pyridine (71 mg, 0.89 mmol, 6.0 eq.) and TFAA (94 mg, 0.45 mmol, 3.0 eq.). The mixture was stirred at rt for 2 h. The reaction was quenched with water (3 mL). The mixture was extracted with DCM (3 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 75% B in 7 min, 75% B; Wave Length: 254 nm; RT1(min): 5.88) to provide (1S,3aR,4S,7R,7aS)-N-((1S)-1-cyano-2-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-

trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (24.7 mg, 28%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 9.86-10.07 (m, 1H), 8.29-8.84 (m, 2H), 6.81-7.24 (m, 4H), 5.98-6.18 (m, 2H), 4.90-5.13 (m, 1H), 4.39-4.52 (m, 1H), 3.98-4.18 (m, 1H), 3.17-3.68 (m, 2H), 3.01-3.03 (m, 1H), 2.88-2.98 (m, 3H), 2.68-2.81 (m, 2H), 2.50-2.52 (m, 1H), 2.29-2.43 (m, 1H), 1.82-1.97 (m, 1H), 1.38-1.47 (m, 2H), 0.51-1.04 (m, 9H). LC-MS (ESI, *m/z*): 586 $[M+H]^+$.

EXAMPLE 30
Compound 30



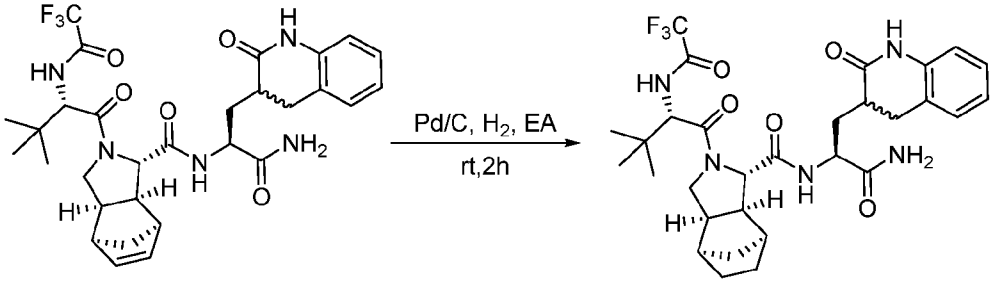
30

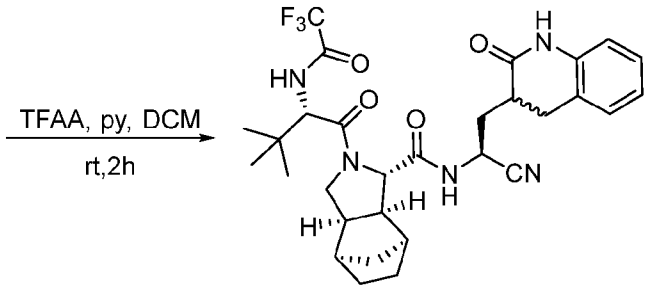
[0349] To a mixture of 1-fluorocyclopropane-1-carboxylic acid (25.9 mg, 0.249 mmol, 1.0 eq.) in N,N-dimethylformamide (3 mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (113 mg, 0.299 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (193 mg, 1.49 mmol, 6.0 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C, and then (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (120 mg, 0.249 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 2 h at rt and then purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-

yl]-1-fluorocyclopropane-1-carboxamide (70.0 mg, 52%) as a light yellow solid. LC-MS (ESI, *m/z*): 532 $[M+H]^+$.

[0350] To a mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]-1-fluorocyclopropane-1-carboxamide (70.0 mg, 0.132 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (41.7 mg, 0.528 mmol, 4.0 eq.) and trifluoroacetic anhydride (49.8 mg, 0.238 mmol, 1.8 eq.). The mixture was stirred for 3 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 38% B to 68% B in 7 min, 68% B; Wave Length: 254 nm; RT1(min): 4.48) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-2-[(1-fluorocyclopropyl)formamido]-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (29.2 mg, 42%) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.60-8.90 (m, 1H), 7.30-7.60 (m, 1H), 6.90-7.20 (m, 1H), 5.90-6.40 (m, 2H), 4.80-5.00 (m, 1H), 4.40-4.65 (m, 1H), 4.00-4.25 (m, 1H), 3.55-3.80 (m, 1H), 3.35-3.55 (m, 1H), 3.10-3.25 (m, 2H), 2.90-3.00 (m, 2H), 3.70-2.90 (m, 1H), 2.30-2.45 (m, 1H), 2.05-2.30 (m, 2H), 1.60-1.95 (m, 2H), 1.30-1.60 (m, 3H), 1.00-1.30 (m, 4H), 0.70-1.00 (m, 9H). LC-MS (ESI, m/z): 514 $[M+H]^+$.

EXAMPLE 31
Compound 31





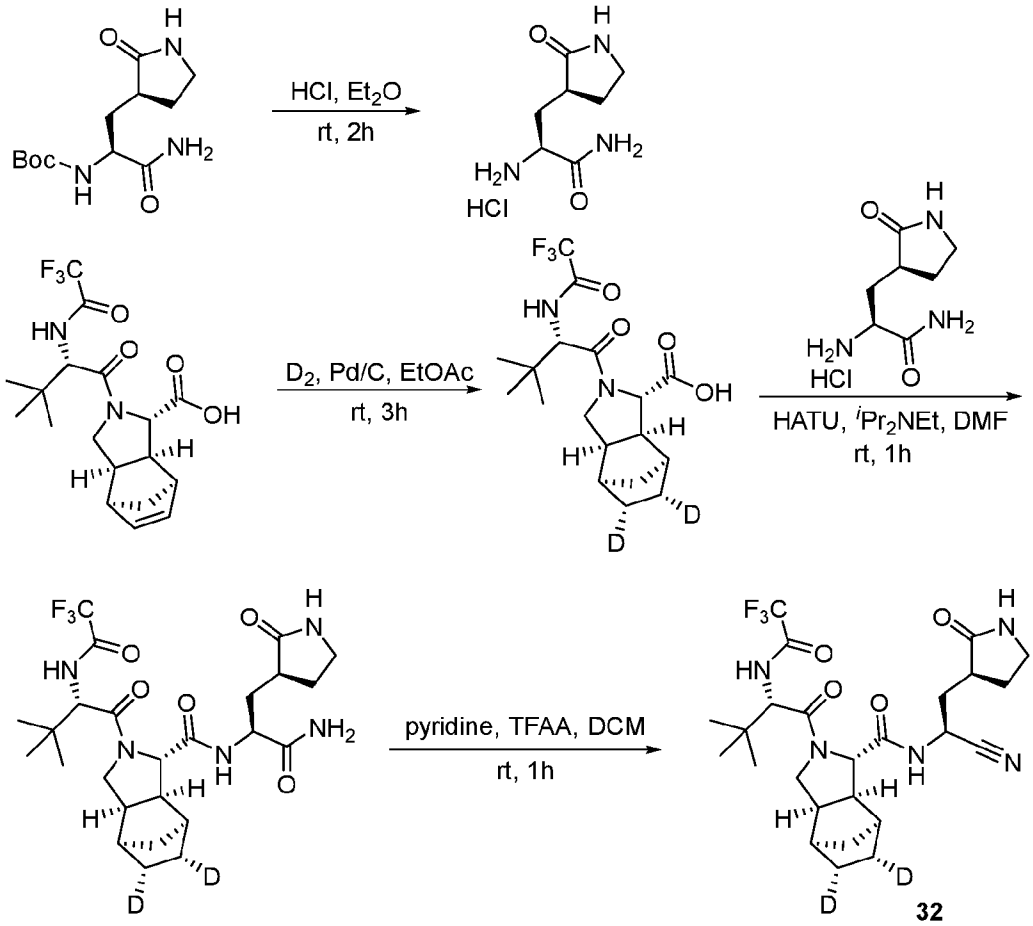
31

[0351] A 50 mL round-bottom flask was charged with (1S,3aR,4S,7R,7aS)-N-((2S)-1-amino-1-oxo-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (100 mg, 0.17 mmol, 1.0 eq.), ethyl acetate (5 mL), 10% palladium on activated carbon (50 mg). The contents of the flask were placed under an atmosphere of hydrogen (3 atm). The mixture was stirred at rt for 2 h. The solids were filtered out. The organic layer was concentrated under reduced pressure to provide (1S,3aR,4R,7S,7aS)-N-((2S)-1-amino-1-oxo-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (50 mg, 45%) as a white solid. LC-MS (ESI, *m/z*): 606 $[M+H]^+$.

[0352] To a solution of (1S,3aR,4R,7S,7aS)-N-((2S)-1-amino-1-oxo-3-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (45 mg, 0.07 mmol, 1.0 eq.) in DCM (2 mL) was added TFAA (31 mg, 0.15 mmol, 2.0 eq.) and pyridine (24 mg, 0.3 mmol, 4.0 eq.). The mixture was stirred at rt for 2 h. The reaction was quenched with water (3 mL). The mixture was extracted with DCM (3 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 48% B to 78% B in 7 min, 78% B; Wave Length: 254 nm; RT1(min): 5.67) to provide (1S,3aR,4R,7S,7aS)-N-((1S)-1-cyano-2-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxamide (24.1 mg, 55%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 9.96-10.00 (m, 1H), 8.83-

9.01 (m, 1H), 8.64-8.66 (m , 1H), 7.10-7.16 (m, 2H), 6.84-6.90 (m, 2H), 4.93-5.08 (m, 1H), 4.61-4.72 (m, 1H), 4.46-4.56 (m, 1H), 3.75-3.81 (m, 1H), 3.58-3.64 (m, 1H), 2.93-3.07 (m, 1H), 2.51-2.80 (m, 3H), 2.30-2.48 (m , 3H), 2.10-2.22 (m, 1H), 1.82-1.94 (m, 1H), 1.37-1.55 (m, 2H), 1.19-1.34 (m, 3H), 1.03-1.17 (m, 1H), 0.85-0.99 (m, 9H). LC-MS (ESI, *m/z*): 588 $[M+H]^+$.

EXAMPLE 32
Compound 32



[0353] To a mixture of (1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (200 mg, 0.515 mmol, 1.0 eq.) in EtOAc (5 mL) was added 10% palladium on activated carbon (80 mg). The mixture was stirred for 3 h at rt under deuterium. The mixture was filtered. The filtrate was concentrated under reduced pressure to provide (1S,3aR,4R,5S,6R,7S,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-

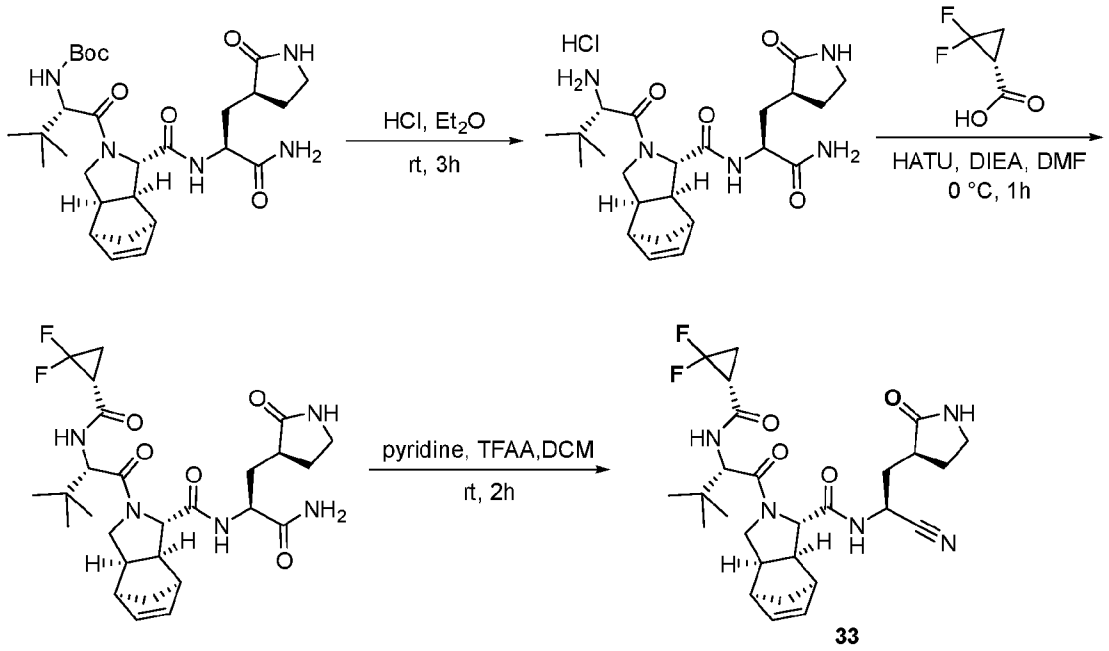
methanoisoindole-1-carboxylic-5,6-d_2 acid (190 mg, 91%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (br, 1H), 9.14-9.61 (m, 1H), 4.69-4.84 (m, 1H), 4.41-4.59 (m, 1H), 3.76-3.88 (m, 1H), 3.43-3.67 (m, 1H), 2.53-2.82 (m, 2H), 2.26-2.41 (m, 1H), 2.13-2.24 (m, 1H), 1.35-1.54 (m, 2H), 1.15-1.31 (m, 2H), 0.93-1.06 (m, 9H). LC-MS (ESI, *m/z*): 393 $[M+H]^+$.

[0354] To a mixture of (1S,3aR,4R,5S,6R,7S,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-1-carboxylic-5,6-d_2 acid (144 mg, 0.366 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (167 mg, 0.439 mmol, 1.2 eq.) in DMF (3 mL) was added N-ethyl-N-isopropylpropan-2-amine (284 mg, 2.20 mmol, 6.0 eq.) at 0 °C. After stirred for 15 min at 0 °C, (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (76.0 mg, 0.366 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide (1S,3aR,4R,5S,6R,7S,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-5,6-d_2-1-carboxamide (160 mg, 75%) as a light yellow solid. LC-MS (ESI, *m/z*): 546 $[M+H]^+$.

[0355] To a mixture of (1S,3aR,4R,5S,6R,7S,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-5,6-d_2-1-carboxamide (160 mg, 0.293 mmol, 1.0 eq.) in DCM (5 mL) was added pyridine (139 mg, 1.76 mmol, 6.0 eq.) and trifluoroacetic anhydride (136 mg, 0.645 mmol, 2.2 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (20 mL). The mixture was extracted with DCM (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford then crude product. The crude product was purified by prep-HPLC (Column: XBridge Prep Phenyl OBD Column, 19 x 250 mm, 5μm; Mobile Phase A: Water (0.05%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 42% B to 72% B in 7 min, 72% B; Wave Length: 254 nm; RT: 5 min) to provide (1S,3aR,4R,5S,6R,7S,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-methanoisoindole-5,6-d^2-1-carboxamide

(45.4 mg, 28%) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.85-9.10 (m, 1H), 8.56-8.80 (m, 1H), 7.32-7.60 (m, 1H), 4.80-4.95 (m, 1H), 4.60-4.75 (m, 1H), 4.45-4.58 (m, 1H), 3.75-3.88 (m, 1H), 3.55-3.73 (m, 1H), 3.10-3.22 (m, 2H), 2.50-2.70 (m, 1H), 2.25-2.48 (m, 3H), 2.06-2.24 (m, 3H), 1.60-1.90 (m, 2H), 1.35-1.58 (m, 2H), 1.20-1.34 (m, 1H), 1.05-1.19 (m, 1H), 0.78-1.04 (m, 9H). LC-MS (ESI, *m/z*): 528 $[M+H]^+$.

EXAMPLE 33
Compound 33

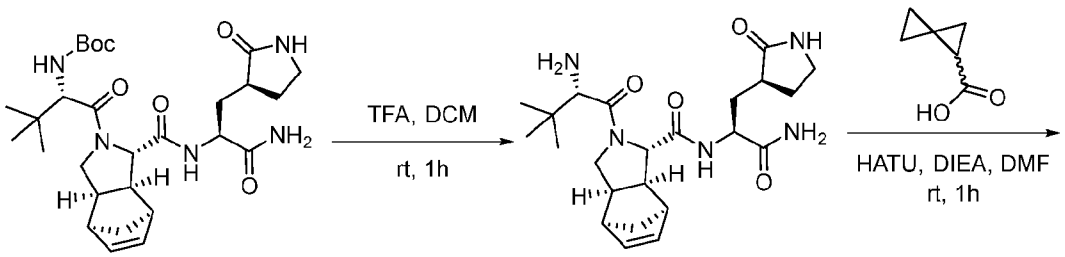


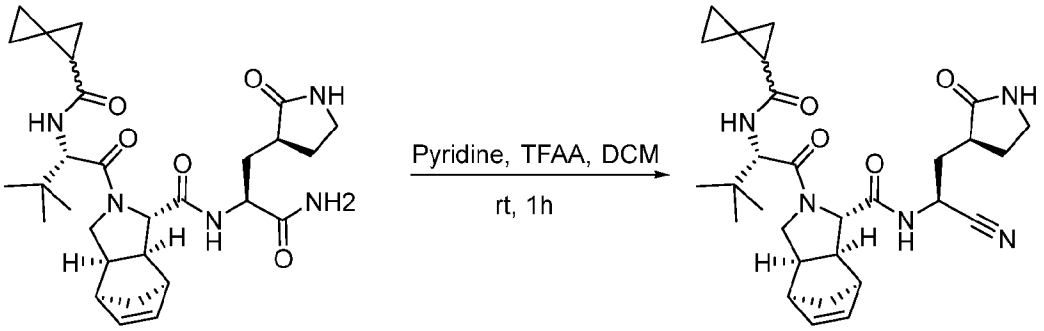
[0356] To a mixture of (R)-2,2-difluorocyclopropane-1-carboxylic acid (49.1 mg, 0.403 mmol, 1.0 eq.) in N,N-dimethylformamide (3mL) was added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (183 mg, 0.484 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (312 mg, 2.41 mmol, 6.0 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C, then (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (194 mg, 0.403 mmol, 1.0 eq.) was added at 0 °C for 2 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-2-((R)-2,2-difluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-

hexahydro-1H-4,7-methanoisoindole-1-carboxamide (160 mg, 72%) as a light yellow solid. LC-MS (ESI, *m/z*): 550 $[M+H]^+$.

[0357] To a mixture of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-2-((R)-2,2-difluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (160 mg, 0.291 mmol, 1.0 eq.) in DCM (2 mL) was added pyridine (92.1 mg, 1.16 mmol, 4.0 eq.) and trifluoroacetic anhydride (110 mg, 0.524 mmol, 1.8 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Prep OBD C18 Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 38% B to 68% B in 7 min, 68% B; Wave Length: 254 nm; RT1(min): 4.95) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-2-((R)-2,2-difluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (47.0 mg, 30%) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.55-8.75 (m, 1H), 8.05-8.30 (m, 1H), 7.30-7.60 (m, 1H), 5.80-6.30 (m, 2H), 4.80-5.00 (m, 1H), 4.40-4.60 (m, 1H), 3.90-4.15 (m, 1H), 3.45-3.75 (m, 2H), 3.05-3.30 (m, 2H), 2.95-3.00 (m, 1H), 2.85-2.95 (m, 3H), 2.60-2.85 (m, 1H), 2.30-2.50 (m, 1H), 2.05-2.30 (m, 2H), 1.80-2.00 (m, 1H), 1.60-1.80 (m, 3H), 1.30-1.50 (m, 2H), 0.80-1.00 (m, 9H). LC-MS (ESI, m/z): 532 $[M+H]^+$.

EXAMPLE 34
Compound 34





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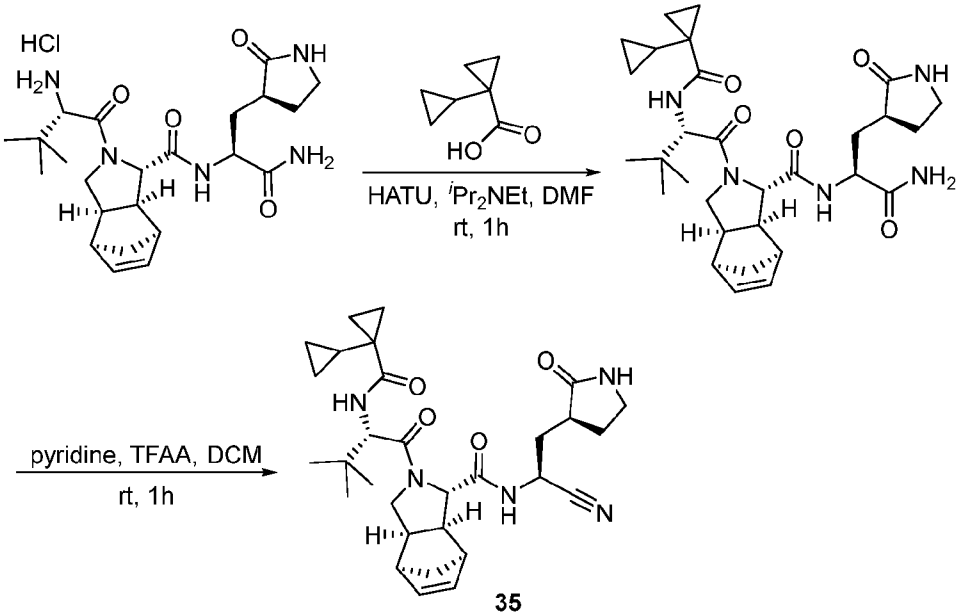
[0358] To a stirred mixture of tert-butyl N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (220 mg, 0.403 mmol, 1.0 eq.) in DCM (6 mL) were added trifluoroacetic acid (2 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (179 mg, crude) as a brown oil. LC-MS (ESI, *m/z*): 379 $[M+H]^+$.

[0359] To a stirred mixture of spiro[2.2]pentane-1-carboxylic acid (47.3 mg, 0.422 mmol, 1.05 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (183 mg, 0.482 mmol, 1.2 eq.) in DMF (5 mL) were added N-ethyl-N-isopropylpropan-2-amine (415 mg, 3.21 mmol, 8.0 eq.) at 0 °C. After stirred for 20 min at 0 °C, (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (179 mg, 0.402 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The crude product was purified by C18 column with CH_3CN:Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]spiro[2.2]pentane-1-carboxamide (145 mg, 65%) as a yellow solid. LC-MS (ESI, *m/z*): 540 $[M+H]^+$

[0360] To a stirred mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]spiro[2.2]pentane-1-carboxamide (120 mg, 0.222 mmol, 1.0 eq.) in DCM (4 mL) was added pyridine (66.8 mg, 0.844 mmol, 3.8 eq.) and

trifluoroacetic anhydride (38.8 mg, 0.400 mmol, 1.8 eq.) . The mixture was stirred for 1 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford then crude product. The crude product was purified by prep-HPLC (Column: XBridge Prep OBD C18 Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 38% B to 68% B in 7 min, 68% B; Wave Length: 254 nm; RT1(min): 4.78) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-{spiro[2.2]pentan-1-ylformamido}butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (34.8 mg, 29%) as a white solid. ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 8.50-8.83 (m, 1H), 7.28-7.70 (m, 2H), 5.84-6.25 (m, 2H), 4.65-5.00 (m, 1H), 4.25-4.64 (m, 1H), 3.81-4.24 (m, 1H), 3.40-3.80 (m, 2H), 3.10-3.39 (m, 2H), 2.97-3.05 (m, 1H), 2.80-2.96 (m, 2H), 2.62-2.79 (m, 1H), 2.44-2.23 (m, 1H), 2.00-2.43 (m, 3H), 1.61-1.90 (m, 2H), 1.34-1.50 (m, 2H), 1.00-1.33 (m, 2H), 0.70-0.99 (m, 12H), 0.47-0.69 (m, 1H). LC-MS (ESI, *m/z*): 522 $[M+H]^+$.

EXAMPLE 35
Compound 35



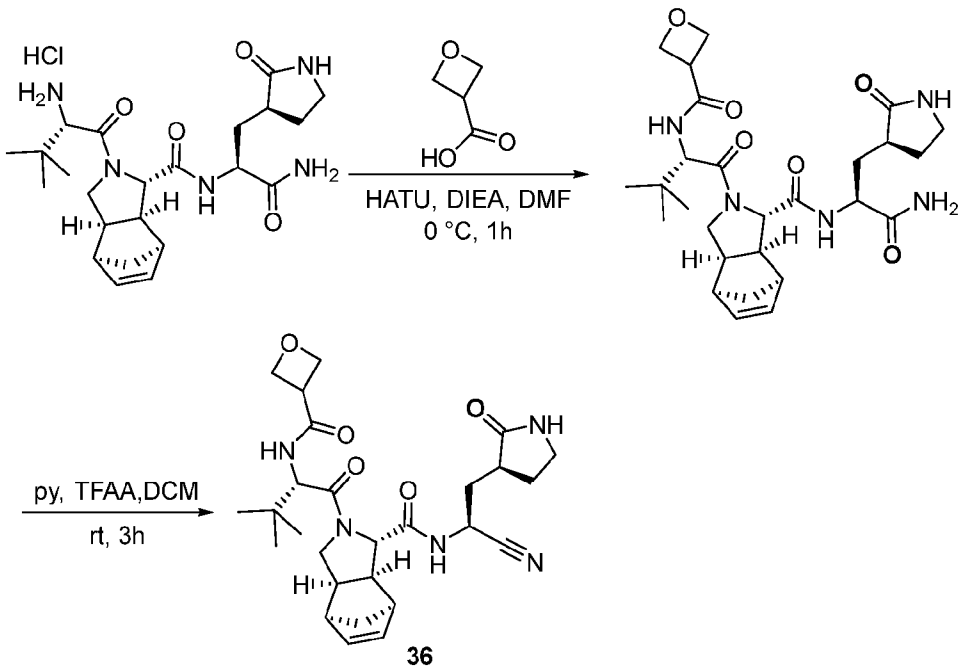
35

[0361] To a mixture of [1,1'-bi(cyclopropane)]-1-carboxylic acid (47.0 mg, 0.367 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

hexafluorophosphate (168 mg, 0.440 mmol, 1.2 eq.) in DMF (3 mL) was added N-ethyl-N-isopropylpropan-2-amine (285 mg, 2.20 mmol, 6.0 eq.) at 0 °C. After stirred for 15 min at 0 °C, (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (177 mg, 0.367 mmol, 1.0 eq.) was added. The resulting was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN :Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]-[1,1'-bi(cyclopropane)]-1-carboxamide (180 mg, 81%) as an off-white solid. LC-MS (ESI, *m/z*): 554 $[M+H]^+$.

[0362] To a mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]-[1,1'-bi(cyclopropane)]-1-carboxamide (180 mg, 0.325 mmol, 1.0 eq.) in DCM (5 mL) were added pyridine (103 mg, 1.30 mmol, 4.0 eq.) and trifluoroacetic anhydride (123 mg, 0.585 mmol, 1.8 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (20 mL). The mixture was extracted with DCM (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Prep OBD C18 Column, 19 x 250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 254 nm; RT: 5.32 min) to provide (1R,2S,3S,6R,7S)-4-[(2S)-2-{[1,1'-bi(cyclopropane)]-1-ylformamido}-3,3-dimethylbutanoyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (62.4 mg, 35%) as a white solid. ^1H NMR (400 MHz, 80°C, DMSO-d_6) δ 8.60-8.85 (m, 1H), 7.32-7.60 (m, 1H), 6.84-7.13 (m, 1H), 5.90-6.20 (m, 2H), 4.60-4.98 (m, 1H), 4.40-4.53 (m, 1H), 3.96-4.20 (m, 1H), 3.55-3.77 (m, 1H), 3.38-3.54 (m, 1H), 3.10-3.25 (m, 2H), 3.00-3.05 (m, 1H), 2.78-2.99 (m, 2H), 2.60-2.77 (m, 1H), 2.30-2.42 (m, 1H), 2.05-2.29 (m, 2H), 1.63-1.89 (m, 2H), 1.30-1.45 (m, 2H), 1.15-1.29 (m, 1H), 0.85-1.10 (m, 10H), 0.70-0.84 (m, 1H), 0.32-0.65 (m, 4H), 0.05-0.20 (m, 2H). LC-MS (ESI, *m/z*): 536 $[M+H]^+$.

EXAMPLE 36
Compound 36



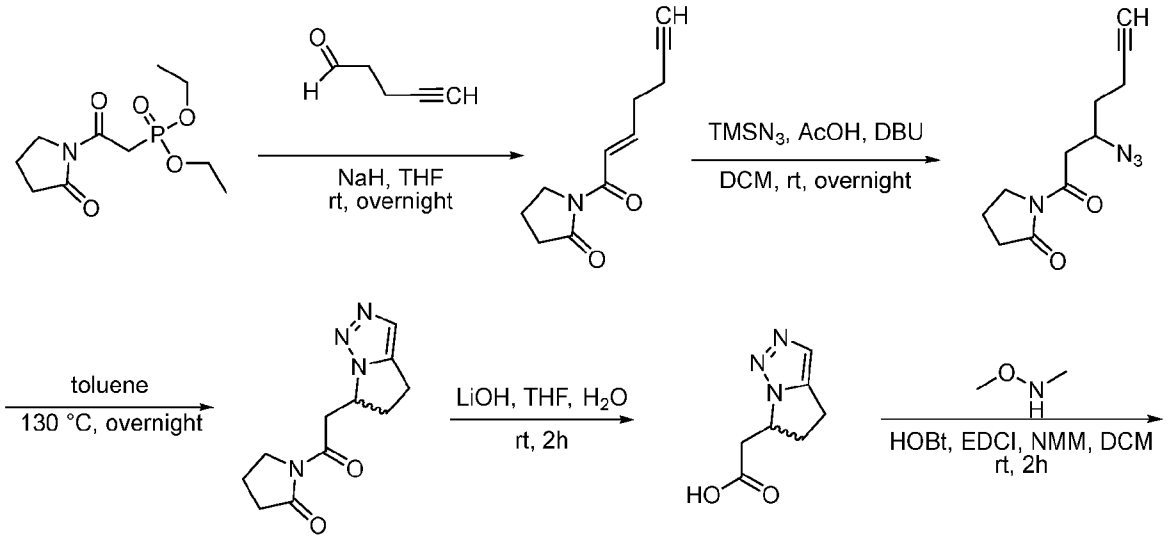
36

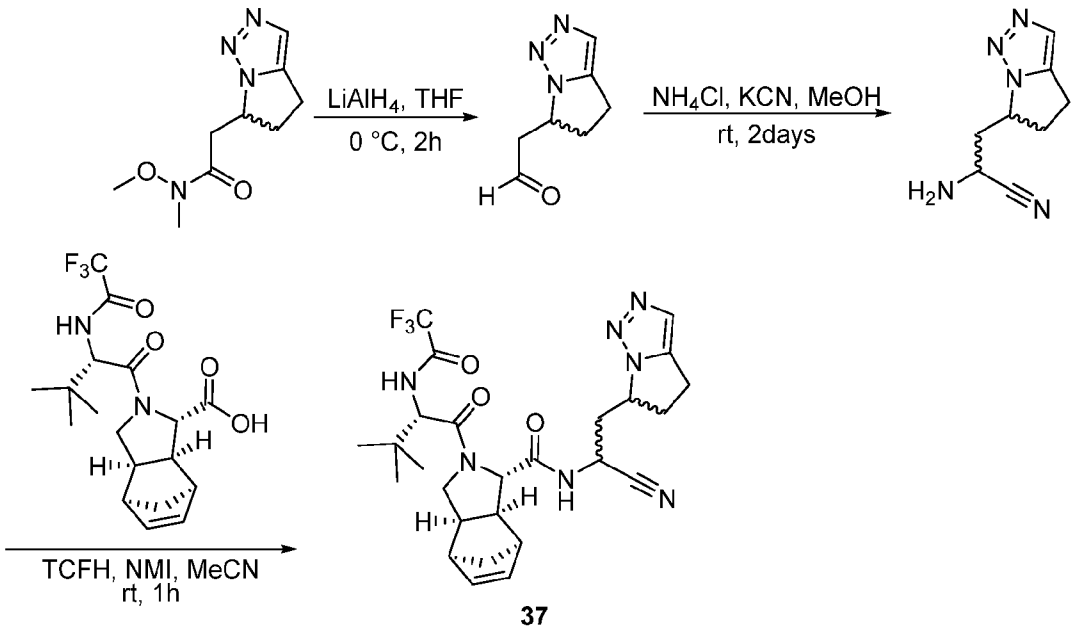
[0363] To a stirred mixture of oxetane-3-carboxylic acid (40.7 mg, 0.399 mmol, 1.1 eq.), o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (165 mg, 0.436 mmol, 1.2 eq.) in DMF (4 mL) was added N-ethyl-N-isopropylpropan-2-amine (281 mg, 2.17 mmol, 6.0 eq.). The mixture was stirred for 10 min at 0°C, and (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (175 mg, 0.363 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]oxetane-3-carboxamide (170 mg, 83 %) as an off-white solid. LC-MS (ESI, *m/z*): 530 $[M+H]^+$.

[0364] To a stirred mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]oxetane-3-carboxamide (170 mg, 0.321 mmol, 1.0 eq.) in DCM (3 mL) was added pyridine (101 mg, 1.28 mmol, 4.0 eq.) and trifluoroacetic

anhydride (155 mg, 0.738 mmol, 2.3 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 30% B to 60% B in 7 min, 60% B; Wave Length: 254 nm; RT1(min): 6) to afford (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-(oxetan-3-ylformamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (54.2 mg, 32 %) as a white solid. ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 8.57-8.65 (m, 1H), 7.58-7.65 (m, 1H), 7.30-7.55 (m, 1H), 6.09-6.14 (m, 1H), 5.90-5.96 (m, 1H), 4.83-4.92 (m, 1H), 4.53-4.75 (m, 3H), 4.44-4.52 (m, 2H), 3.92-4.20 (m, 1H), 3.75-3.92 (m, 1H), 3.58-3.67 (m, 1H), 3.50-3.58 (m, 1H), 3.07-3.21 (m, 2H), 2.97-3.02 (m, 1H), 2.83-2.97 (m, 2H), 2.64-2.83 (m, 1H), 2.26-2.40 (m, 1H), 2.04-2.19 (m, 2H), 1.60-1.81 (m, 2H), 1.33-1.42 (m, 2H), 0.80-0.90 (m, 9H). LC-MS (ESI, *m/z*): 512 $[M+H]^+$.

EXAMPLE 37
Compound 37





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[0365] To a mixture of diethyl 2-oxo-2-(2-oxopyrrolidin-1-yl)ethylphosphonate (Gansauer et al., Ang. Chem. Int. Ed. (2009) 48(47), 8882-8885, S8882/1-S8882/32; 5.29 g, 20.1 mmol, 1.1 eq.) in THF (50 mL) was added sodium hydride (804 mg, 20.1 mmol, 1.1 eq., 60% in mineral oil) at 0 °C. After stirred for 20 min at 0 °C, a mixture of pent-4-ynal (1.50 g, 18.3 mmol, 1.0 eq.) in DCM (5 mL) was added. The mixture was stirred overnight at rt. The reaction was quenched with saturated aqueous ammonium chloride (100 mL). The mixture was extracted with DCM (3 x 100 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was diluted with DCM (60 mL) and made into a slurry with 100~200 silica gel mesh (3 g). The slurry was loaded onto a column after removing the DCM. The sample was purified by column chromatography (Column size 5 x 24 cm, column volume: 300 mL, silica gel size (100 ~ 200 mesh) quantity: 120 g) and eluted with EtOAc/petroleum ether (0 % ~ 50 % over 30 min). The collected fractions: 33 %-35 % EtOAc/petroleum ether fractions were chosen as the pure fractions. Those fractions were combined and concentrated under reduced pressure to provide 1-[(2E)-hept-2-en-6-ynoyl]pyrrolidin-2-one (2.00 g, 55%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ 7.28-7.37 (m, 1H), 7.06-7.19 (m, 1H), 3.80-3.91 (m, 2H), 2.57-2.67 (m, 2H), 2.45-2.56 (m, 2H), 2.32-2.42 (m, 2H), 1.95-2.14 (m, 3H). LC-MS (ESI, *m/z*): 192 $[M+H]^+$.

[0366] To a mixture of trimethylsilyl azide (6.02 g, 52.3 mmol, 5.0 eq.) in DCM (50 mL) was added acetic acid (3.14 g, 52.3 mmol, 5.0 eq.). The mixture was stirred for 20 min at rt, and 1-[(2E)-hept-2-en-6-ynoyl]pyrrolidin-2-one (2.00 g, 10.5 mmol, 1.0 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (318 mg, 2.09 mmol, 0.2 eq.) in DCM (50 mL) were added. The mixture was stirred overnight at rt. The reaction quenched with saturated aqueous sodium bicarbonate (100 mL). The mixture was extracted with DCM (3 x 100 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was diluted with DCM (60 mL) and made into a slurry with 100 ~ 200 silica gel mesh (5 g). The slurry was loaded to a column after removing the DCM. The sample was purified by column chromatography (Column size 5 x 24 cm, column volume: 300 mL, silica gel size (100~200 mesh) quantity: 120 g) and eluted with EtOAc/petroleum ether (0%~50% over 30 min). The collected fractions: 33%-35% EtOAc/petroleum ether fractions were chosen as the pure fractions. Those fractions were combined and concentrated under reduced pressure to provide 1-(3-azidohept-6-ynoyl)pyrrolidin-2-one (2.4 g, 96%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ 4.05-4.22 (m, 1H), 3.78-3.96 (m, 2H), 3.15-3.28 (m, 1H), 2.98-3.10 (m, 1H), 2.55-2.66 (m, 2H), 2.31-2.46 (m, 2H), 1.93-2.17 (m, 3H), 1.64-1.85 (m, 2H). LC-MS (ESI, *m/z*): 235 $[M+H]^+$.

[0367] A solution of 1-(3-azidohept-6-ynoyl)pyrrolidin-2-one (2.40 g, 10.2 mmol, 1.0 $CDCl_3$) in toluene (20 mL) was stirred overnight at 130 °C. The mixture was concentrated under reduced pressure to afford the crude product. The crude product was diluted with DCM (50 mL) and made into a slurry with 100~200 silica gel mesh (5 g). The slurry was loaded to a column after removing the DCM. The sample was purified by column chromatography (Column size 5 x 24 cm, column volume: 300 mL, silica gel size (100 ~ 200 mesh) quantity: 120 g) and eluted with MeOH:DCM (0%~5% over 20 min). The collected fractions: 2%-3% MeOH:DCM fractions were chosen as the pure fractions. Those fractions were combined and concentrated under reduced pressure to provide 1-(2-{4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-yl}acetyl)pyrrolidin-2-one (2.20 g, 73%) as a brown semi solid. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ 7.38 (s, 1H), 5.00-5.11 (m, 1H), 3.78-3.91 (m, 3H), 3.28-3.40 (m, 1H), 3.04-3.17 (m, 1H), 2.87-2.99 (m, 2H), 2.57-2.64 (m, 2H), 2.44-2.55 (m, 1H), 2.02-2.13 (m, 2H). LC-MS (ESI, *m/z*): 235 $[M+H]^+$.

[0368] To a mixture of 1-(2-{4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-yl}acetyl)pyrrolidin-2-one (1.00 g, 4.27 mmol, 1.0 eq.) in THF (5 mL):water (5 mL) was added lithium hydroxide (307 mg, 12.8 mmol, 3.0 eq.). The mixture was stirred for 2 h at rt. The mixture was concentrated under reduced pressure to remove the THF and adjusted to pH = 6 with HCl (2 M). The mixture was extracted with EtOAc (5 x 20 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-ylacetic acid (600 mg, crude) as a yellow semi-solid. LC-MS (ESI, *m/z*): 168 $[M+H]^+$.

[0369] To a mixture of 4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-ylacetic acid (600 mg, 3.59 mmol, 1.0 eq.) in DCM (15 mL) were added N,O-dimethylhydroxylamine hydrochloride (350 mg, 3.59 mmol, 1.0 eq.), 1-hydroxybenzotriazole (485 mg, 3.59 mmol, 1.0 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (757 mg, 3.95 mmol, 1.1 eq.) and N-methylmorphline (1.09 g, 10.77 mmol, 3.0 eq.) at rt. The mixture was stirred for 2 h at rt. The reaction was quenched with water (30 mL). The mixture was extracted with DCM (4 x 30 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was diluted with DCM (30 mL) and made into a slurry with 100~200 silica gel mesh (3 g). The slurry was loaded to a column after removing the DCM. The sample was purified by column chromatography (Column size 5 x 24 cm, column volume: 300 mL, silica gel size (100 ~ 200 mesh) quantity: 120 g) and eluted with MeOH:DCM (0%~10% over 20 min). The collected fractions: 3% MeOH:DCM fractions were chosen as the pure fractions. Those fractions were combined and concentrated under reduced pressure to provide N-methoxy-N-methyl-2-{4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-yl}acetamide (340 mg, 40%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ 7.43 (s, 1H), 4.91-5.05 (m, 1H), 3.70 (s, 3H), 3.46-3.56 (m, 1H), 3.22 (s, 3H), 3.08-3.20 (m, 1H), 2.80-2.98 (m, 3H), 2.45-2.59 (m, 1H). LC-MS (ESI, *m/z*): 211 $[M+H]^+$.

[0370] To a mixture of N-methoxy-N-methyl-2-{4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-yl}acetamide (300 mg, 1.43 mmol, 1.0 eq.) in THF (6 mL) was added dropwise lithium aluminum hydride (0.68 mL, 1.71 mmol, 1.2 eq., 2.5 M in THF) at 0 °C under nitrogen. The mixture was stirred for 2 h at 0 °C. The reaction was quenched with

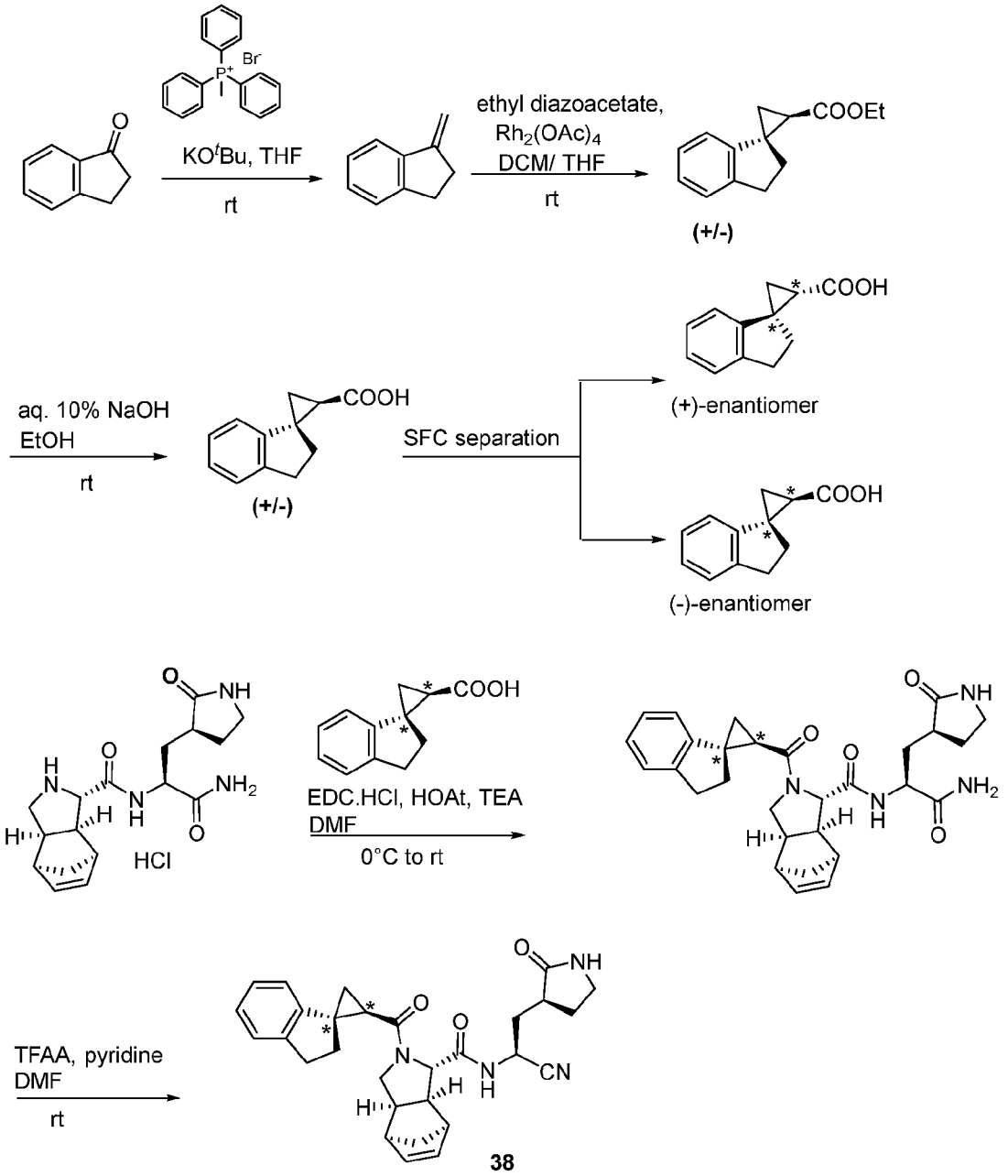
saturated aqueous ammonium chloride (20 mL). The mixture was extracted with chloroform:isopropyl alcohol (5/1, 4 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2-{4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-yl}acetaldehyde (216 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 152 $[M+H]^+$.

[0371] To a mixture of 2-{4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-yl}acetaldehyde (216 mg, 1.43 mmol, 1.0 eq.) in MeOH (5 mL) was added ammonium chloride (153 mg, 2.86 mmol, 2.0 eq.). After being stirred for 2 h at rt, potassium cyanide (140 mg, 2.14 mmol, 1.5 eq.) was added. The mixture was stirred for 2 days at rt, and then filtered. The filtrate was concentrated under reduced pressure to remove the MeOH. The residue was diluted with DCM (5 mL) and filtered. The filtrate was concentrated under reduced pressure to provid 2-amino-3-{4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-yl}propanenitrile (190 mg, crude) as a yellow oil. LC-MS (ESI, *m/z*): 178 $[M+H]^+$.

[0372] To a mixture of (1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (416 mg, 1.07 mmol, 1.0 eq.), 2-amino-3-{4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-yl}propanenitrile (190 mg, 1.07 mmol, 1.0 eq.) and N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate (391 mg, 1.39 mmol, 1.3 eq.) in acetonitrile (10 mL) was added N-methylimidazole (880 mg, 10.7 mmol, 10.0 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (30 mL). The mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to remove then EtOAc. The residue was chromatographed on a silica gel column with MeOH:DCM (8/92) to afford the crude product. The crude product was purified by preparative HPLC (Column: Xselect CSH C18 OBD Column 30 x 150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 8 min, 45% B; Wave Length: 254/220 nm; RT: 6.7 min) to provide (1R,2S,3S,6R,7S)-N-(1-cyano-2-{4H,5H,6H-pyrrolo[1,2-c][1,2,3]triazol-6-yl}ethyl)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (56.0 mg, 9%) as a white solid. LC-MS (ESI, *m/z*): 548 $[M+H]^+$.

EXAMPLE 38

Compound 38



The chiral centers noted with "*" are tentatively assigned.

[0373] To a suspension of 2,3-dihydro-1H-inden-1-one (4.0 g, 30.3 mmol, 1 eq.) and methyltriphenylphosphonium bromide (16.2 g, 45.4 mmol, 2 eq.) in THF (52 mL) was added dropwise a solution of tBuOK (6.8 g, 60.5 mmol, 2 eq.) in THF (27 mL) over a period

of 2 h. The reaction mixture was stirred at rt for 3 h and was concentrated under reduced pressure. The residue was taken up in hexane. The mixture was filtered through a silica-gel plug and rinsed with hexane to get 1-methylene-2,3-dihydro-1H-indene (2.8 g, 71%) as a colorless liquid.

[0374] To a solution of 1-methylene-2,3-dihydro-1H-indene (2 g, 15.4 mmol, 1 eq.) and $Rh_2(OAc)_4$ (69 mg, 0.153 mmol, 0.01 eq.) in DCM (6 mL) was added a solution of ethyl diazoacetate (4.05 mL, 38.4 mmol, 2.5 eq.) in THF (4 mL) over a period of 1 h. The reaction mixture was stirred at rt for 1 h and was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of EA (0 to 2%) in PE and by prep-HPLC (Column: KROMOSIL-C18, 25×150mm 7um; Mobile Phase A: 10 mM NH_4HCO_3 in water, Mobile Phase B: ACN; Flow rate:22 mL/min; Isocratic eluent: 70%B) to afford trans ethyl 2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylate (650 mg, 19%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18-7.24 (m, 1H), 7.11-7.17 (m, 2H), 6.85-6.92 (m, 1H), 4.10 (q, 2H), 2.85-3.02 (m, 2H), 2.13 (t, 2H), 2.03 (t, 1H), 1.45-1.52 (m, 2H), 1.18 (t, 3H). LC-MS (ESI, *m/z*): 217 $[M+H]^+$.

[0375] 250 mg of cis ethyl 2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylate was also obtained.

[0376] To a solution of trans ethyl 2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylate (350 mg, 1.62 mmol, 1 eq.) in EtOH (3.7 mL) was added 10% NaOH aqueous solution (2.7 mL, 6.17 mmol, 4 eq.). The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 5 mL). The aqueous phase was acidified with 1M HCl and extracted with EA (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford trans 2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (300 mg, 98%) as a white solid.

[0377] trans 2',3'-Dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (450 mg) was purified by prep-SFC using the following conditions: Column: Chiralpak AD-H, 4.6*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH; Flow rate: 60 g/min; Gradient: isocratic 15% B; Column Temperature: 30°C; Back Pressure: 100 bar. Purification resulted in (1S*,2S*)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (210 mg) and (1R*,2R*)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (180

mg).

[0378] (1S*,2S*)-2',3'-Dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (brs, 1H), 7.18-7.25 (m, 1H), 7.10-7.17 (m, 2H), 6.82-6.88 (m, 1H), 2.88-3.20 (m, 2H), 2.08-2.22 (m, 2H), 1.88-1.95 (m, 1H), 1.38-1.48 (m, 2H). $[\alpha]^{25}_D$: +444.3° (c 0.1, MeOH). SFC: Chiralpak IG, 4.6*150 mm, 5 µm, 30 °C, co-Solvent : MeOH, hold 7 min at 10%, Rt: 2.21 min.

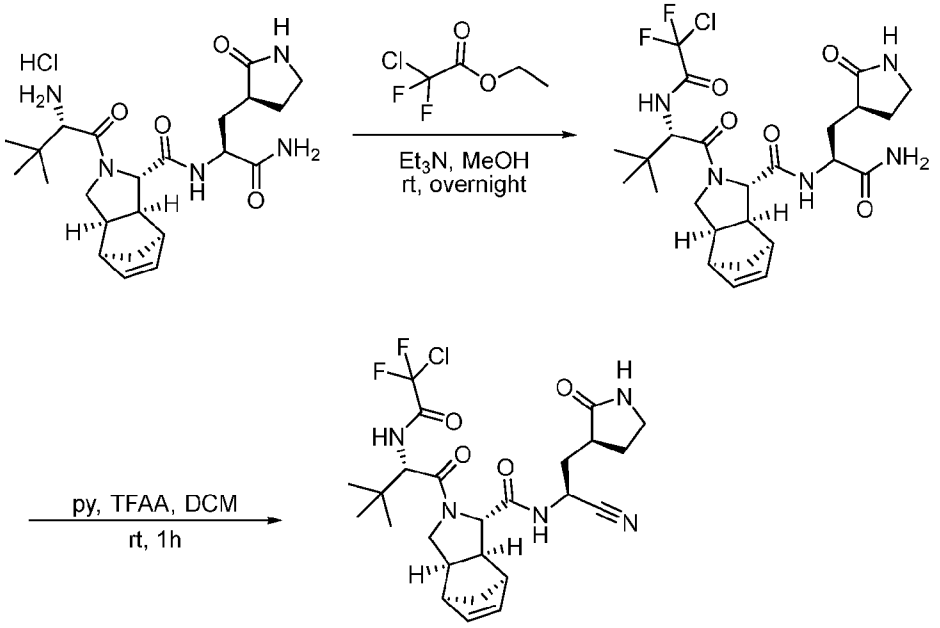
[0379] (1R*,2R*)-2',3'-Dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.10 (brs, 1H), 7.18-7.24 (m, 1H), 7.10-7.17 (m, 2H), 6.82-6.87 (m, 1H), 2.90-3.00 (m, 2H), 2.10-2.22 (m, 2H), 1.90-1.94 (m, 1H), 1.38-1.45 (m, 2H). $[\alpha]^{25}_D$: -335.9° (c 0.1, MeOH). SFC: Chiralpak IG, 4.6*150 mm, 5 µm, 30 °C, co-Solvent : MeOH, hold 7 min at 10%, Rt: 2.89 min.

[0380] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide hydrochloride (120 mg, 0.325 mmol, 1.0 eq.) in DMF (1.0 mL) cooled at 0 °C were added (1R*,2R*)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (61 mg, 0.324 mmol, 1.0 eq.), EDC•HCl (122 mg, 0.637 mmol, 2.0 eq.), HOAt (43 mg, 0.320 mmol, 1.0 eq.) and NEt_3 (0.170 mL, 1.28 mmol, 3.0 eq.). The reaction mixture was stirred at rt for 16 h. The mixture was diluted with water (5 mL) and extracted with EA (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (12 g column) using a gradient of MeOH (1 to 10%) in DCM to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((1R*,2R*)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (100 mg, 61%) as a white solid. LC-MS (ESI, *m/z*): 503 $[M+H]^+$.

[0381] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((1R*,2R*)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (80 mg, 0.159 mmol, 1.0 eq.) in DMF (0.8 mL) were added pyridine (0.038 mL, 0.470 mmol, 3.0 eq.) and TFAA (0.040 mL; 0.318 mmol, 2.0 eq.). The reaction mixture was stirred at rt for 1 h. The mixture was diluted with water (10 mL) and extracted with EA (3x 10 mL). The organic

phases were combined, washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on C18 gel (12 g column) using 0.01% ammonium bicarbonate/ACN and by flash chromatography on silica gel (12 g column) using a gradient of MeOH (1 to 10%) in DCM to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((1R*,2R*)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (25 mg, 35%) as a white solid. ^{1}H NMR (400 MHz, 360K, DMSO-d_6) δ 8.25-8.55 (m, 1H), 7.00-7.42 (m, 4H), 6.70-6.88 (m, 1H), 5.85-6.22 (m, 2H), 4.25-4.95 (m, 1H), 3.98-4.12 (m, 1H), 3.31-3.67 (m, 1H), 3.00-3.22 (m, 4H), 2.70-2.95 (m, 5H), 2.30-2.42 (m, 1H), 1.94-2.22 (m, 4H), 1.68-1.90 (m, 2H), 1.20-1.55 (m, 5H). LCMS (ESI, m/z): 485 $[M+H]^+$.

EXAMPLE 39
Compound 39



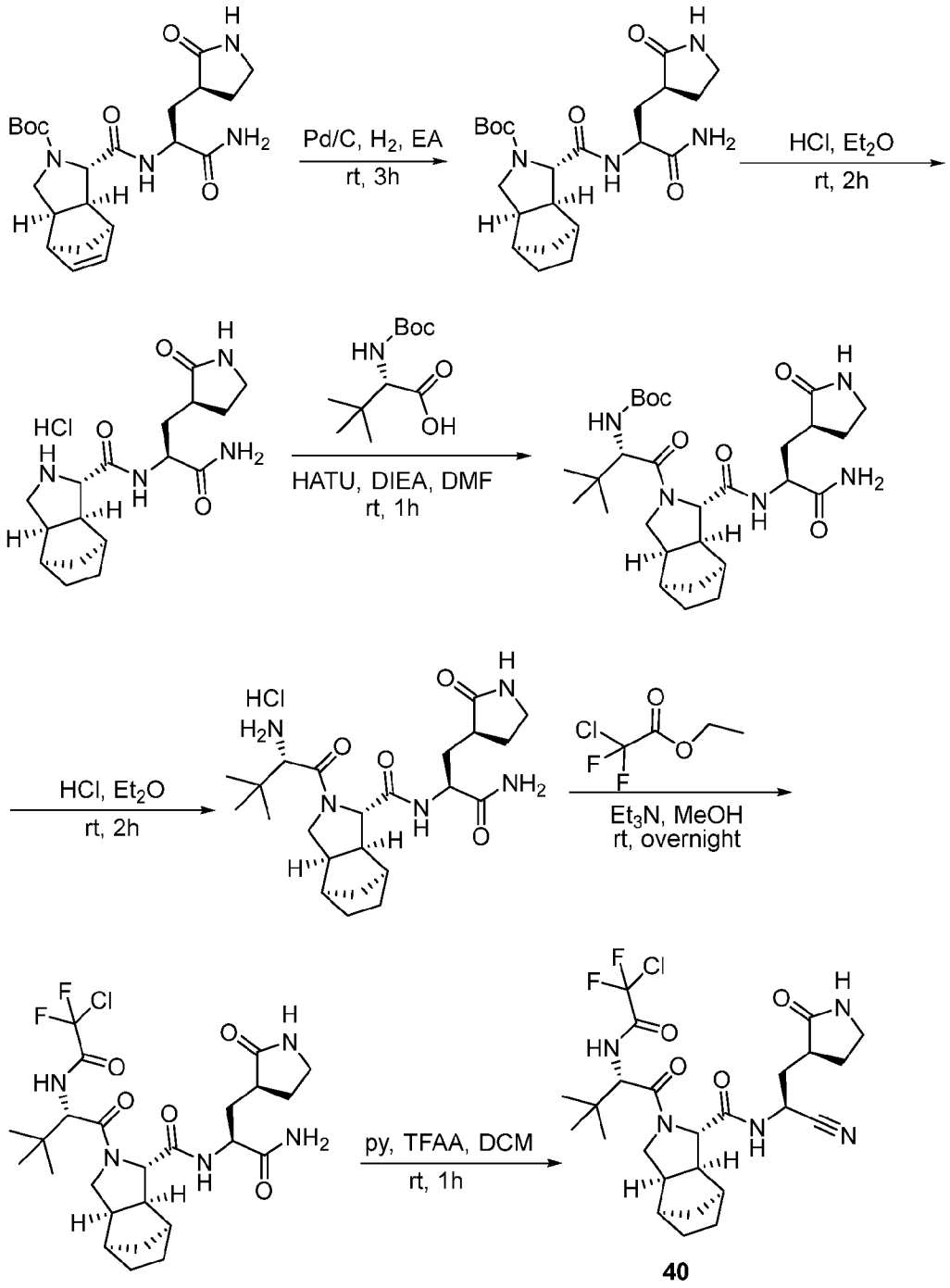
39

[0382] To a mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (177 mg, 0.367 mmol, 1.0 eq.) in MeOH (5 mL) was added triethylamine (446 mg, 4.40 mmol, 12.0 eq.) and ethyl 2-chloro-2,2-difluoroacetate (582 mg, 3.67 mmol, 10.0 eq.). The mixture was stirred overnight at rt, and

then concentrated under reduced pressure to remove the MeOH. The mixture was diluted with water (20 mL) and the pH was adjusted to 6 with hydrochloric acid (1 M). The mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-(2-chloro-2,2-difluoroacetamido)-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (180 mg, 80%) as a light yellow solid. LC-MS (ESI, *m/z*): 558 $[M+H]^+$.

[0383] To a mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-(2-chloro-2,2-difluoroacetamido)-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (180 mg, 0.323 mmol, 1.0 eq.) in DCM (3 mL) was added pyridine (102 mg, 1.29 mmol, 4.0 eq.) and trifluoroacetic anhydride (122 mg, 0.581 mmol, 1.8 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (20 mL). The mixture was extracted with DCM (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19 x 250 mm, 10μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 254 nm; RT: 5.4 min;) to provide (1R,2S,3S,6R,7S)-4-[(2S)-2-(2-chloro-2,2-difluoroacetamido)-3,3-dimethylbutanoyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (41.2 mg, 23%) as a white solid. ^1H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.65-8.90 (m, 1H), 8.40-8.64 (m, 1H), 7.30-7.62 (m, 1H), 5.95-6.25 (m, 2H), 4.83-5.01 (m, 1H), 4.40-4.75 (m, 1H), 3.95-4.20 (m, 1H), 3.56-3.75 (m, 1H), 3.32-3.55 (m, 1H), 3.06-3.30 (m, 2H), 3.01-3.05 (m, 1H), 2.80-3.00 (m, 2H), 2.60-2.79 (m, 1H), 2.21-2.40 (m, 1H), 2.00-2.20 (m, 2H), 1.60-1.95 (m, 2H), 1.30-1.48 (m, 2H), 0.72-1.10 (m, 9H). LC-MS (ESI, *m/z*): 540 $[M+H]^+$.

EXAMPLE 40
Compound 40



[0384] To a mixture of tert-butyl (1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-4-carboxylate (250 mg, 0.578 mmol, 1.0 eq.) in EtOAc (5 mL) was added 10% palladium on

activated carbon (120 mg). The mixture was stirred for 3 h at rt under hydrogen and then filtered. The filtrate was concentrated under reduced pressure to provide tert-butyl (1S,2S,3S,6R,7R)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]decane-4-carboxylate (200 mg, 75%) as an off-white solid. LC-MS (ESI, *m/z*): 435 $[M+H]^+$.

[0385] A mixture of tert-butyl (1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-4-carboxylate (200 mg, 0.462 mmol, 1.0 eq.) in hydrogen chloride (5 mL, 2M in Et_2O) was stirred for 2 h at rt. The mixture was concentrated under reduced pressure to afford (2S)-2-[(1S,2S,3S,6R,7R)-4-azatricyclo[5.2.1.0^{2,6}]decan-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (170 mg, crude) as an off-white solid. LC-MS (ESI, *m/z*): 335 $[M+H]^+$.

[0386] To a mixture of (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoic acid (106 mg, 0.458 mmol, 1.0 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (209 mg, 0.550 mmol, 1.2 eq.) in DMF (3 mL) was added N-ethyl-N-isopropylpropan-2-amine (355 mg, 2.75 mmol, 6.0 eq.) at 0 °C. After stirred for 15 min at 0 °C, (2S)-2-[(1S,2S,3S,6R,7R)-4-azatricyclo[5.2.1.0^{2,6}]decan-3-ylformamido]-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (170 mg, 0.458 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water(0.05% TFA). The desired fraction was concentrated under reduced pressure to provide tert-butyl N-[(2S)-1-[(1S,2S,3S,6R,7R)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]decan-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (155 mg, 59%) as a light yellow solid. LC-MS (ESI, *m/z*): 548 $[M+H]^+$.

[0387] A mixture of tert-butyl N-[(2S)-1-[(1S,2S,3S,6R,7R)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]decan-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (155 mg, 0.283 mmol, 1.0 eq.) in hydrogen chloride (5 mL, 2 M in Et_2O) was stirred for 2 h at rt. The mixture was concentrated under reduced pressure to afford (2S)-2-{[(1S,2S,3S,6R,7R)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]decan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (137 mg, crude) as an off-white solid.

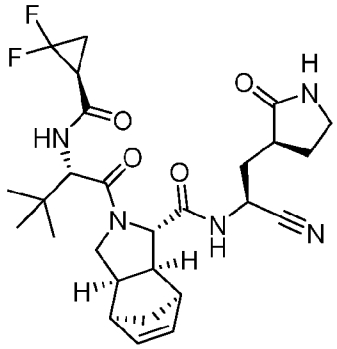
LC-MS (ESI, *m/z*): 448 $[M+H]^+$.

[0388] To a mixture of (2S)-2-{[(1S,2S,3S,6R,7R)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]decan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (137 mg, 0.283 mmol, 1.0 eq.) in MeOH (3 mL) was added triethylamine (344 mg, 3.40 mmol, 12.0 eq.) and ethyl 2-chloro-2,2-difluoroacetate (449 mg, 2.83 mmol, 10.0 eq.). The mixture was stirred overnight at rt. The mixture was concentrated under reduced pressure to remove MeOH. The mixture was diluted with water (20 mL) and the pH was adjusted to 6 with hydrochloric acid (1 M). The mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide (2S)-2-{[(1S,2S,3S,6R,7R)-4-[(2S)-2-(2-chloro-2,2-difluoroacetamido)-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]decan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (100 mg, 57%) as a yellow solid. LC-MS (ESI, *m/z*): 560 $[M+H]^+$.

[0389] To a mixture of (2S)-2-{[(1S,2S,3S,6R,7R)-4-[(2S)-2-(2-chloro-2,2-difluoroacetamido)-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]decan-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (100 mg, 0.179 mmol, 1.0 eq.) in DCM (3 mL) was added pyridine (56.0 mg, 0.716 mmol, 4.0 eq.) and trifluoroacetic anhydride (68.0 mg, 0.322 mmol, 1.8 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with DCM (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19 x 250 mm, 10 μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 254 nm; RT: 5.43 min) to provide (1S,2S,3S,6R,7R)-4-[(2S)-2-(2-chloro-2,2-difluoroacetamido)-3,3-dimethylbutanoyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-azatricyclo[5.2.1.0^{2,6}]decane-3-carboxamide (25.2 mg, 25%) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.55-8.80 (m, 2H), 7.35-7.60 (m, 1H), 4.80-4.95 (m, 1H), 4.60-4.75 (m, 1H), 4.40-4.55 (m, 1H), 3.75-3.90 (m, 1H), 3.50-3.74 (m, 1H), 3.10-3.40 (m, 2H), 2.60-2.73 (m, 1H), 2.36-2.44 (m, 1H), 2.26-2.35 (m, 2H), 2.17-2.22 (m, 1H),

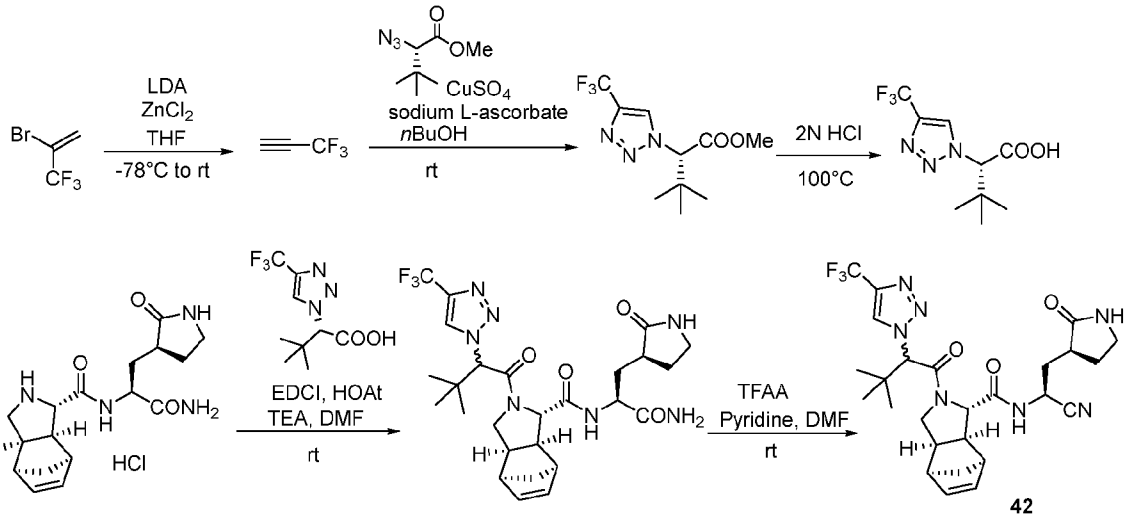
2.00-2.16 (m, 2H), 1.61-1.89 (m, 2H), 1.40-1.60 (m, 2H), 1.20-1.38 (m, 3H), 1.05-1.19 (m, 1H), 0.76-1.04 (m, 9H). LC-MS (ESI, *m/z*): 542 $[M+H]^+$.

EXAMPLE 41
Compound 41



[0390] Compound 41 was prepared similarly as described for compound 33, using (S)-2,2-difluorocyclopropane-1-carboxylic acid in place of (R)-2,2-difluorocyclopropane-1-carboxylic acid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.55-8.80 (m, 1H), 7.80-8.20 (m, 1H), 7.30-7.60 (m, 1H), 5.85-6.30 (m, 2H), 4.70-5.00 (m, 1H), 4.40-4.60 (m, 1H), 3.90-4.25 (m, 1H), 3.30-3.70 (m, 2H), 3.10-3.25 (m, 2H), 2.95-3.05 (m, 1H), 2.85-2.95 (m, 2H), 2.60-2.85 (m, 2H), 2.30-2.50 (m, 1H), 2.05-2.30 (m, 2H), 1.60-2.00 (m, 4H), 1.30-1.50 (m, 2H), 0.80-1.00 (m, 9H). LC-MS (ESI, m/z): 532 $[M+H]^+$.

EXAMPLE 42
Compound 42



[0391] To a solution of diisopropylamine (3.0 g, 37.7 mmol, 2.2 eq.) in THF (30 mL) cooled to -78°C were added 1.6M *n*BuLi in hexanes (23 mL, 37.7 mmol, 2.2 eq.) and 2-bromo-3,3,3-trifluoroprop-1-ene (3.0 g, 17.1 mmol, 1.0 eq.). The mixture was stirred at -78°C for 30 min and 0.5M $ZnCl_2$ in THF (37 mL, 18.5 mmol, 1.1 eq.). The mixture was warmed to rt over 1 h. The solution of 3,3,3-trifluoroprop-1-yne in THF was used as such directly in the next step.

[0392] To a mixture of methyl (*S*)-2-azido-3,3-dimethylbutanoate (1.5 g, 8.77 mmol, 1.0 eq.) and a solution of 3,3,3-trifluoroprop-1-yne in THF (17.1 mmol, 2.0 eq.) in *n*-BuOH (13.5 mL) and water (1.5 mL) were added copper sulfate (69 mg, 0.043 mmol, 0.05 eq.) and sodium ascorbate (260 mg, 1.31 mmol, 0.15 eq.). The mixture was stirred at rt overnight. Water (50 mL) was added. The resulting precipitate was filtered and washed with water and diethyl ether. The phases of the filtrate were separated. The organic phase was washed with water (3 x 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of EA (5 to 10%) in hexane to afford methyl (S)-3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoate (600 mg, 21%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 5.37 (s, 1H), 3.83 (s, 3H), 1.03 (s, 9H).

[0393] A mixture of (S)-3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoate (600 mg, 2.26 mmol, 1.0 eq.) and 2M HCl (4.0 mL, 8.00 mmol) was heated at 100°C for 48 h. After cooling to rt, the mixture was extracted with EtOAc (2 x 50 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with 5% diethyl ether in pentane to afford (S)-3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoic acid (0.720 g, 83%) as a white solid.

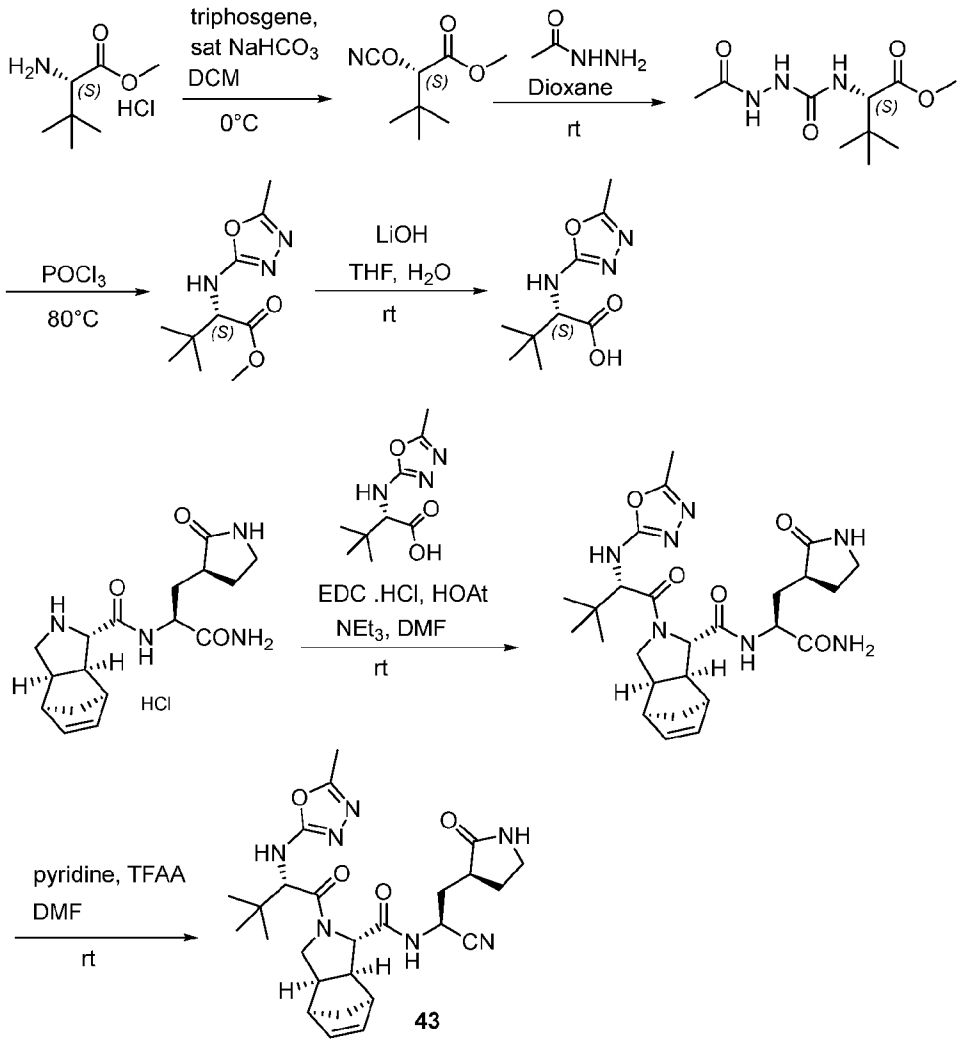
[0394] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide hydrochloride (100 mg, 0.271 mmol, 1.0 eq.) in DMF (1.0 mL) cooled at 0 °C were added (S)-3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoic acid (82 mg, 0.326 mmol, 1.2 eq.), EDC•HCl (104 mg, 0.543 mmol, 2.0 eq.), HOAt (37 mg, 0.271 mmol, 1.0 eq.) and NEt_3 (0.151 mL, 1.09 mmol, 4.0 eq.). The mixture was stirred at rt for 16 h. The mixture was diluted with water (5 mL) and extracted with EA (3 x 10 mL). The

organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (12 g column) using a gradient of MeOH (1 to 10%) in DCM to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (100 mg, 60%) as a white solid. LC-MS (ESI, m/z): 566 $[M+H]^+$.

[0395] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (70 mg, 0.123 mmol, 1.0 eq.) in DMF (0.7 mL) were added pyridine (0.030 mL, 0.371 mmol, 3.0 eq.) and TFAA (0.034 mL; 0.247 mmol, 2.0 eq.). The mixture was stirred at rt for 1 h. The mixture was diluted with water (10 mL) and extracted with EA (3 x 10 mL). The organic phases were combined, washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: X-SELECT-C18, 19×150mm 5um; Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: ACN; Flow rate: 17 mL/min; gradient: 20% B to 70% B in 8 min) to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (33 mg, 47%) as a white solid. ^1H NMR (400 MHz, 362K, DMSO-d_6) δ 8.42-8.76 (m, 2H), 7.34 (m, 1H), 6.16-6.30 (m, 1H), 5.61-5.83 (m, 1H), 5.44 (m, 1H), 4.90-5.01 (m, 1H), 4.01 (m, 1H), 3.75 (m, 1H), 3.40-3.53 (m, 1H), 3.07-3.24 (m, 4H), 2.87 (m, 1H), 2.73-2.85 (m, 1H), 2.37 (m, 1H), 2.03-2.19 (m, 2H), 1.55-1.84 (m, 2H), 1.35-1.44 (m, 2H), 0.94 (s, 9H). LCMS (ESI, m/z): 546 $[M-H]^-$.

EXAMPLE 43

Compound 43



[0396] To a solution of methyl (S)-2-amino-3,3-dimethylbutanoate hydrochloride (1.0 g, 6.90 mmol, 1.0 eq.) in a mixture of sat. $NaHCO_3$ (43 mL) and DCM (22 mL) cooled at 0 °C was added triphosgene (818 mg, 2.76 mmol, 0.4 eq.). The mixture was stirred at 0 °C for 2 h. The mixture was diluted with DCM (10 mL) and washed with brine (10 mL). The phases were separated. The organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford methyl (S)-2-isocyanato-3,3-dimethylbutanoate as a pale yellow liquid, which was used in the next step without further purification.

[0397] To a solution of methyl (S)-2-isocyanato-3,3-dimethylbutanoate (6.90 mmol, 1.0 eq.) in dioxane (10 mL) was added acetohydrazide (649 mg, 8.77 mmol, 1.5 eq.).

The mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (24 g column) using a gradient of EA (40 to 60%) in PE to afford methyl (S)-2-(2-acetylhydrazine-1-carboxamido)-3,3-dimethylbutanoate (1.0 g, 59% over two steps) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.56 (s, 1H), 7.86 (s, 1H), 6.54 (d, 1H), 4.02 (d, 1H), 3.63 (s, 3H), 1.80 (s, 3H), 0.90 (s, 9H).

[0398] A solution of methyl (S)-2-(2-acetylhydrazine-1-carboxamido)-3,3-dimethylbutanoate (1.0 g, 4.08 mmol, 1.0 eq.) in $POCl_3$ (4 mL) was heated at 80°C for 2 h. After cooling to rt, the mixture was poured into ice/water (20 mL), basified with $NaHCO_3$ until pH=8 and extracted with EA (2 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (24 g column) using a gradient of EA (20 to 40%) in PE to afford methyl (S)-3,3-dimethyl-2-((5-methyl-1,3,4-oxadiazol-2-yl)amino)butanoate (800 mg, 90%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, 1H), 3.91 (d, 1H), 3.63 (s, 3H), 2.29 (s, 3H), 0.98 (s, 9H).

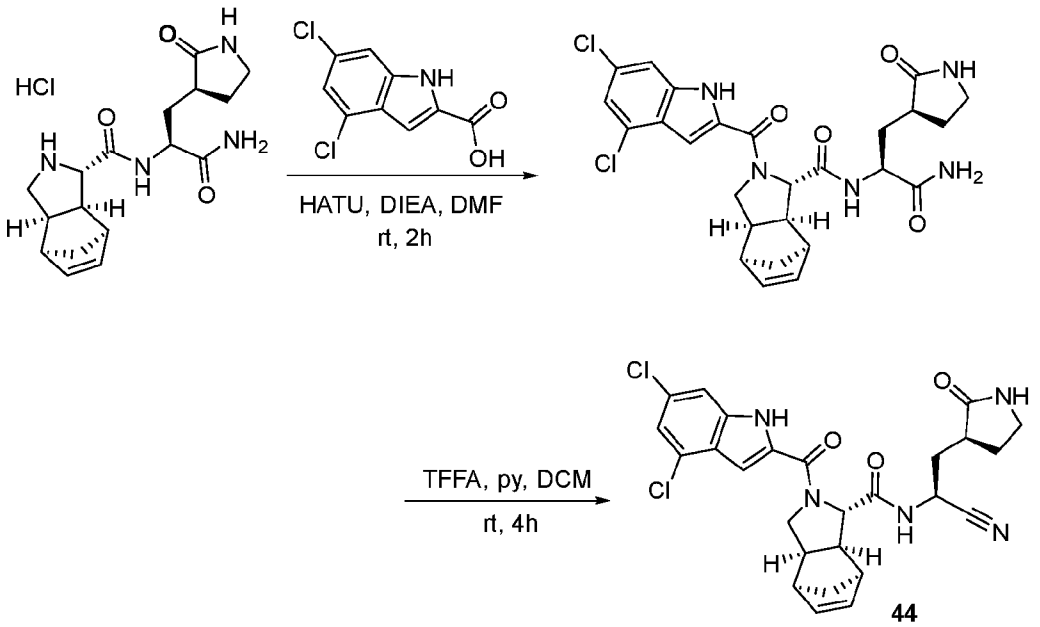
[0399] To a solution of methyl (S)-3,3-dimethyl-2-((5-methyl-1,3,4-oxadiazol-2-yl)amino)butanoate (200 mg, 0.881 mmol, 1.0 eq.) in THF (1 mL) and water (1 mL) was added LiOH (42 mg, 1.76 mmol, 2.0 eq.). The mixture was stirred at rt for 2 h. The mixture was diluted with water (5 mL), acidified with sat. citric acid and extracted with EA (2 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (S)-3,3-dimethyl-2-((5-methyl-1,3,4-oxadiazol-2-yl)amino)butanoic acid (170 mg, 91%) as an off-white solid. LC-MS (ESI, *m/z*): 214 $[M+H]^+$.

[0400] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide hydrochloride (100 mg, 0.272 mmol, 1.0 eq.) in DMF (1.0 mL) cooled at 0 °C were added (S)-3,3-dimethyl-2-((5-methyl-1,3,4-oxadiazol-2-yl)amino)butanoic acid (70 mg, 0.326 mmol, 1.2 eq.), EDC•HCl (103 mg, 0.544 mmol, 2.0 eq.), HOAt (37 mg, 0.272 mmol, 1.0 eq.) and NEt_3 (0.110 mL, 0.816 mmol, 3.0 eq.). The mixture was stirred at rt for 16 h. The mixture was diluted with water (5 mL) and extracted with EA (2 x 5 mL). The organic phases were combined, washed with brine (2 x 5 mL), dried over Na_2SO_4, filtered and

concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (12 g column) using a gradient of MeOH (1 to 10%) in DCM to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-((5-methyl-1,3,4-oxadiazol-2-yl)amino)butanoyl)-2,3,3a,4,7,7a-hexa hydro-1H-4,7-methanoisoindole-1-carboxamide (70 mg, 49%) as an off-white solid. LC-MS (ESI, *m/z*): 528 $[M+H]^+$.

[0401] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-((5-methyl-1,3,4-oxadiazol-2-yl)amino)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (70 mg, 0.132 mmol, 1.0 eq.) in DMF (0.7 mL) were added pyridine (0.030 mL, 0.398 mmol, 3.0 eq.) and TFAA (0.030 mL; 0.260 mmol, 2.0 eq.). The mixture was stirred at rt for 30 min. The mixture was diluted with water (5 mL) and extracted with EA (2 x 10 mL). The organic phases were combined, washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: X-SELECT-C18, 19×150mm 5um; Mobile Phase A: 10mM Ammonium bicarbonate, Mobile Phase B: ACN; Flow rate: 17 mL/min; gradient: 10% B to 60% B in 8 min) to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-((5-methyl-1,3,4-oxadiazol-2-yl)amino)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (35 mg, 52%) as a white solid. ^{1}H NMR (500 MHz, 363K, DMSO-d_6) δ 8.60 (br. s., 1H), 7.32 (s, 1H), 6.93 (br. s., 1H), 6.08 (m, 1H), 5.91 (m, 1H), 4.90 (m, 1H), 4.12 (s, 1H), 3.98 (m, 1H), 3.66 (m, 2H), 3.08-3.20 (m, 3H), 2.88 (m, 2H), 2.71 (m, 1H), 2.36 (m, 1H), 2.28 (s, 3H), 2.15 (m, 2H), 1.69-1.79 (m, 2H), 1.39 (s, 2H), 0.94 (s, 9H). LCMS (ESI, m/z): 508 $[M-H]^-$.

EXAMPLE 44
Compound 44

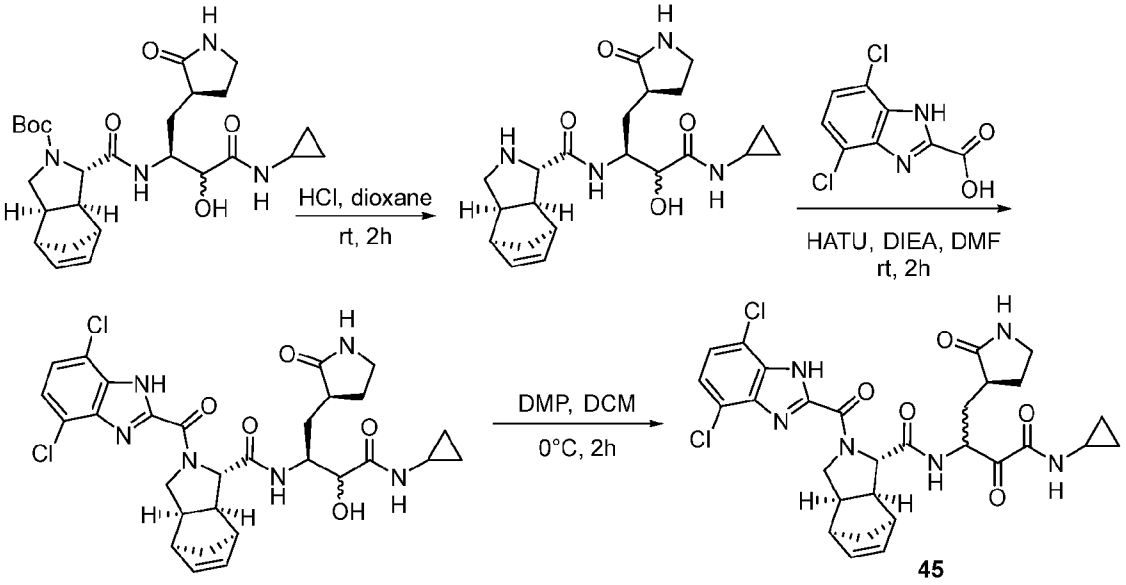


[0402] To a solution of 4,6-dichloro-1H-indole-2-carboxylic acid (83 mg, 0.36 mmol, 1.2 eq.) in DMF (2 mL) were added N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophospate (149 mg, 0.39 mmol, 1.3 eq.) and N,N-diisopropylethylamine (272 mg, 2.1 mmol, 7.0 eq.). The mixture was stirred at 0 °C for 30 min and (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (100 mg, 0.30 mmol, 1.0 eq.) was added. The mixture was stirred at rt for 2 h. The reaction was quenched with water (3 mL). The mixture was extracted with EA (3 x 5 mL). The organic layers were combined, washed with brine (3 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a C18 column with water:McCN (2:1) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4,6-dichloro-1H-indole-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (70 mg, 40%) as a brown yellow solid. LC-MS (ESI, *m/z*): 544 $[M+H]^+$.

[0403] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4,6-dichloro-1H-indole-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (70 mg, 0.13 mmol, 1.0 eq.) in DCM (1

mL) were added TFAA (37.8 mg, 0.18 mmol, 1.4 eq.) and pyridine (35.6 mg, 0.45 mmol, 3.5 eq.). The mixture was stirred at rt for 4 h. The reaction was quenched with water (2 mL). The mixture was extracted with DCM (3 x 3 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Pre-HPLC (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 254 nm; RT1(min): 5.2;) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4,6-dichloro-1H-indole-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (18.3 mg, 27%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 11.78 (br, 1H), 8.72-9.00 (m, 1H), 7.44-7.52 (m, 2H), 7.34 (s, 1H), 6.59-6.90 (m, 1H), 6.05-6.25 (m, 2H), 4.80-5.05 (m, 1H), 4.30-4.61 (m, 1H), 3.85-4.05 (m, 1H), 3.63-3.65 (m, 1H), 3.01-3.10 (m, 3H), 2.79-2.96 (m, 3H), 2.01-2.50 (m, 3H), 1.56-1.96 (m, 2H), 1.44 (s, 2H). LC-MS (ESI, *m/z*): 526 [M+H]$^+$.

EXAMPLE 45
Compound 45



[0404] A solution of tert-butyl (1S,3aR,4S,7R,7aS)-1-(((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)carbamoyl)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-carboxylate (400 mg, 0.8 mmol, 1.0

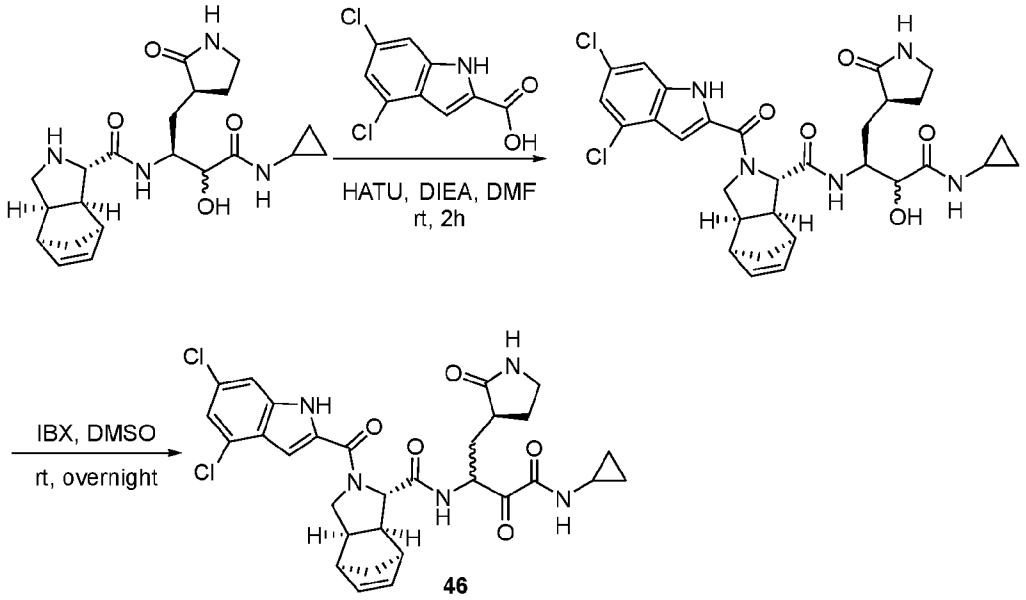
eq.) in hydrochloric acid (8 mL, 4M in dioxane) was stirred at rt for 2 h and then concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (300 mg, crude) as an off-white solid. LC-MS (ESI, *m/z*): 403 $[M+H]^+$.

[0405] To a solution of 4,7-dichloro-1H-benzo[d]imidazole-2-carboxylic acid (63 mg, 0.27 mmol, 1.1 eq.) in DMF (2 mL) were added N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophospate (123 mg, 0.32 mmol, 1.3 eq.) and N,N-diisopropylethylamine (225 mg, 1.74 mmol, 7.0 eq.). The mixture was stirred at 0 °C for 30 min and (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (100 mg, 0.25 mmol, 1.0 eq.) was added. The mixture was stirred at rt for 2 h. The reaction was quenched with water (3 mL). The mixture was extracted with EA (3 x 5 mL). The organic layers were combined, washed with brine (3 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with MeOH:DCM (1:12) to provide (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-(4,7-dichloro-1H-benzo[d]imidazole-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (80 mg, 47%) as a white solid. LC-MS (ESI, *m/z*): 615 $[M+H]^+$.

[0406] To a solution of (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-(4,7-dichloro-1H-benzo[d]imidazole-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (80 mg, 0.13 mmol, 1.0 eq.) in DCM (2 mL) was added DMP (165 mg, 0.39 mmol, 3.0 eq.) at 0 °C under N_2. The mixture was stirred at 0 °C for 2 h. The reaction was quenched with sodium thiosulfate solution (2 mL) and sodium bicarbonate solution (2 mL). The mixture was extracted with DCM (3 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC to provide (1S,3aR,4S,7R,7aS)-N-(4-(cyclopropylamino)-3,4-dioxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-(4,7-dichloro-1H-benzo[d]imidazole-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (30.4 mg, 38%)

as a white solid. LC-MS (ESI, *m/z*): 613 $[M+H]^+$.

EXAMPLE 46
Compound 46

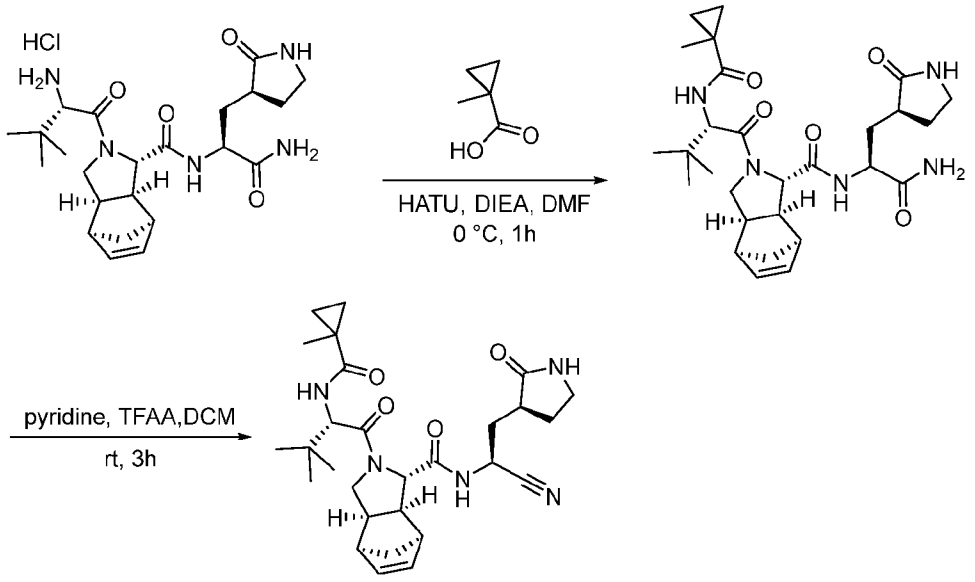


[0407] To a solution of 4,6-dichloro-1H-indole-2-carboxylic acid (126 mg, 0.55 mmol, 1.1 eq.) in DMF (3 mL) were added N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophospate (246 mg, 0.65 mmol, 1.3 eq.) and N,N-diisopropylethylamine (450 mg, 3.48 mmol, 7.0 eq.). The mixture was stirred at 0° C for 30 min and (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (200 mg, 0.5 mmol, 1.0 eq.) was added. The mixture was stirred at rt for 2 h. The reaction was quenched with water (3 mL). The mixture was extracted with EA (3 x 5 mL). The organic layers were combined, washed with brine (3 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with MeOH:DCM (1:12) to provide (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-(4,6-dichloro-1H-indole-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (70 mg, 20%) as a white solid. LC-MS (ESI, *m/z*): 614 $[M+H]^+$.

[0408] To a solution of (1S,3aR,4S,7R,7aS)-N-((2S)-4-(cyclopropylamino)-3-

hydroxy-4-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-(4,6-dichloro-1H-indole-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (70 mg, 0.11 mmol, 1.0 eq.) in DMSO (3 mL) was added IBX (96 mg, 0.34 mmol, 3.0 eq.). The mixture was stirred at rt overnight. The reaction was quenched with water (3 mL). The mixture was extracted with EA (3 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC to provide (1S,3aR,4S,7R,7aS)-N-(4-(cyclopropylamino)-3,4-dioxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-(4,6-dichloro-1H-indole-2-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (26.5 mg, 37%) as a white solid. LC-MS (ESI, m/z): 612 $[M+H]^+$.

EXAMPLE 47
Compound 47



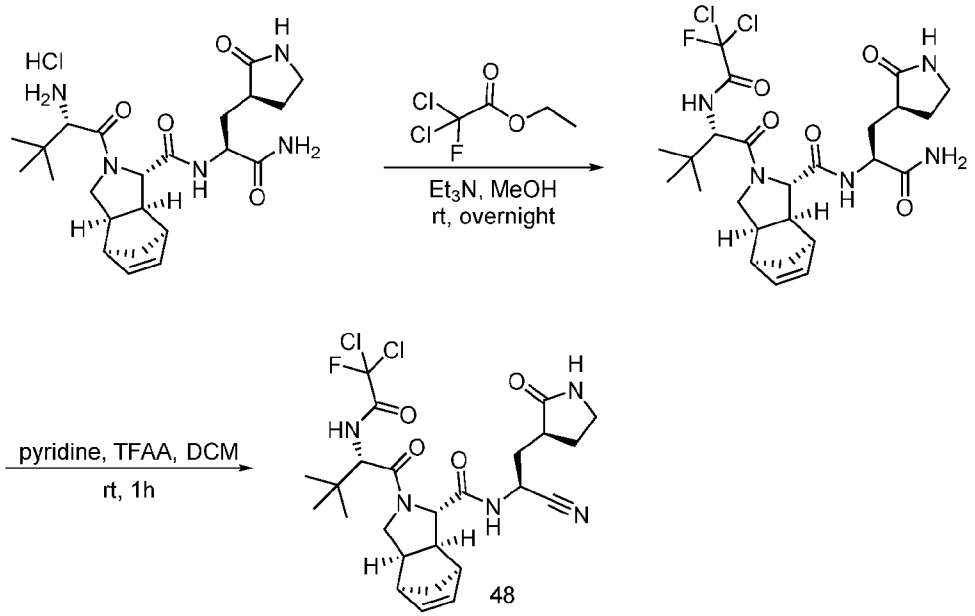
47

[0409] To a mixture of 1-methylcyclopropane-1-carboxylic acid (36.3 mg, 0.363 mmol, 1.1 eq.) in N,N-dimethylformamide (3mL) were added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (163 mg, 0.429 mmol, 1.3 eq.) and N-ethyl-N-isopropylpropan-2-amine (341 mg, 2.64 mmol, 8.0 eq.) at 0 °C. The mixture was stirred for 20 min at 0 °C, and then (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (140 mg, 0.314 mmol, 1.0 eq.) was added at 0 °C. The

mixture was stirred for 1 h at rt. The mixture was purified by C18 column with CH_3CN:Water (0.05% FA). The desired fraction was concentrated under reduced pressure to provide N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]-1-methylcyclopropane-1-carboxamide (160 mg, 91%) as a light yellow solid. LC-MS (ESI, *m/z*): 528 $[M+H]^+$.

[0410] To a mixture of N-[(2S)-1-[(1R,2S,3S,6R,7S)-3-{[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl]-3,3-dimethyl-1-oxobutan-2-yl]-1-methylcyclopropane-1-carboxamide (160 mg, 0.303 mmol, 1.0 eq.) in DCM (2 mL) were added pyridine (95.6 mg, 1.21 mmol, 4.0 eq.) and trifluoroacetic anhydride (114 mg, 0.545 mmol, 1.8 eq.). The mixture was stirred for 3 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 37% B to 67% B in 7 min, 67% B; Wave Length: 254 nm; RT1(min): 5.15) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-3,3-dimethyl-2-[(1-methylcyclopropyl)formamido]butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (27.9 mg, 16%) as a white solid. ^1H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.55-8.85 (m, 1H), 7.30-7.60 (m, 1H), 6.35-6.60 (m, 1H), 5.90-6.30 (m, 2H), 4.60-5.00 (m, 1H), 4.40-4.55 (m, 1H), 3.95-4.20 (m, 1H), 3.55-3.70 (m, 1H), 3.35-3.55 (m, 1H), 3.15-3.30 (m, 1H), 3.05-3.15 (m, 2H), 2.80-3.00 (m, 2H), 2.60-2.80 (m, 1H), 2.25-2.45 (m, 1H), 2.05-2.25 (m, 2H), 1.60-1.95 (m, 2H), 1.35-1.50 (m, 2H), 1.15-1.35 (m, 3H), 0.75-1.10 (m, 11H), 0.40-0.75 (m, 2H). LC-MS (ESI, m/z): 510 $[M+H]^+$.

EXAMPLE 48
Compound 48

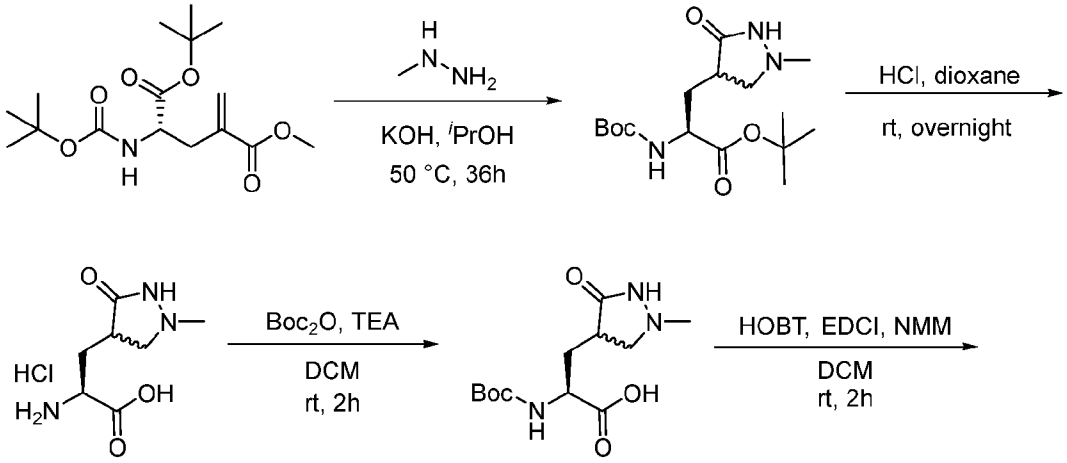


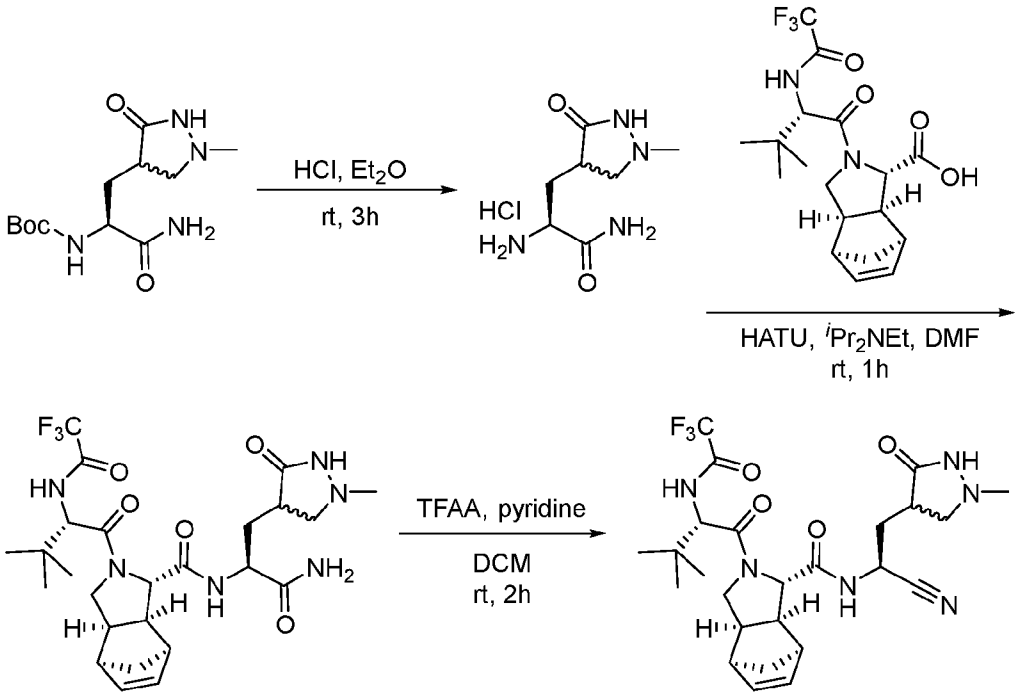
[0411] To a mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide hydrochloride (177 mg, 0.367 mmol, 1.0 eq.) in MeOH (3 mL) was added triethylamine (446 mg, 4.40 mmol, 12.0 eq.) and ethyl 2,2-dichloro-2-fluoroacetate (643 mg, 3.67 mmol, 10.0 eq.). The mixture was stirred overnight at rt. The mixture was concentrated under reduced pressure to remove MeOH. The mixture was diluted with water (10 mL) and adjusted to pH = 6 with hydrochloric acid (1 M). The resulting mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was triturated with Et_2O (5 mL) to provide (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-(2,2-dichloro-2-fluoroacetamido)-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (75.0 mg, 33%) as an off-white solid. LC-MS (ESI, *m/z*): 574[M+H]$^+$.

[0412] To a mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-2-(2,2-dichloro-2-fluoroacetamido)-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (75.0 mg, 0.131 mmol, 1.0 eq.) in DCM (1 mL) were added pyridine (41.0 mg, 0.524 mmol, 4.0 eq.) and trifluoroacetic

anhydride (49.0 mg, 0.236 mmol, 1.8 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (5 mL). The mixture was extracted with DCM (3 x 5 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: Kinetex EVO C18, 21.2 x 250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 254 nm; RT: 5.55 min) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-[(2S)-2-(2,2-dichloro-2-fluoroacetamido)-3,3-dimethylbutanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (28.3 mg, 37%) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 8.60-8.90 (m, 1H), 7.90-8.20 (m, 1H), 7.30-7.62 (m, 1H), 5.90-6.25 (m, 2H), 4.65-5.00 (m, 1H), 4.40-4.52 (m, 1H), 3.95-4.23 (m, 1H), 3.56-3.75 (m, 1H), 3.35-3.55 (m, 1H), 3.08-3.30 (m, 2H), 2.98-3.05 (m, 1H), 2.78-2.97 (m, 2H), 2.63-2.77 (m, 1H), 2.30-2.45 (m, 1H), 2.05-2.29 (m, 2H), 1.62-1.93 (m, 2H), 1.30-1.50 (m, 2H), 0.73-1.15 (m, 9H). LC-MS (ESI, *m/z*): 556 $[M+H]^+$.

EXAMPLE 49
Compound 49





49

[0413] To a mixture of 1-(tert-butyl) 5-methyl (S)-2-((tert-butoxycarbonyl)amino)-4-methylenepentanedioate (5.0 g, 15.2 mmol, 1.0 eq.) in ^{i}PrOH (50 mL) were added methyl hydrazine (3.50 g, 75.9 mmol, 5.0 eq.) and potassium hydroxide (42.6 mg, 0.759 mmol, 0.05 eq.) at rt. The mixture was stirred for 36 h at 50 °C and then concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with EA:PE (90%-100%) to provide the crude product. The crude product was separated by prep-achiral-SFC-HPLC column (Column: GreenSep Basic, 3*15 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH (0.1% 2M NH_3-MeOH); Flow rate: 75 mL/min; Gradient: isocratic 13% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 1.56; RT2(min): 3.85; Sample Solvent: MeOH--HPLC; Injection Volume: 1.5 mL;) to provide tert-butyl (S)-2-((tert-butoxycarbonyl)amino)-3-(-1-methyl-3-oxopyrazolidin-4-yl)propanoate (1.75 g, 33%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 - 5.58 (m, 1H), 4.13 - 4.25 (m, 1H), 3.40 - 3.65 (m, 1H), 2.85 - 2.99 (m, 2H), 2.66 - 2.67 (m, 3H), 2.02 - 2.38 (m, 1H), 1.75 - 1.93 (m, 1H), 1.46 - 1.51 (m, 18H). LC-MS (ESI, m/z): 344 $[M+H]^+$.

[0414] To a solution of tert-butyl (S)-2-((tert-butoxycarbonyl)amino)-3-(1-methyl-3-oxopyrazolidin-4-yl)propanoate (800 mg, 2.33 mmol, 1.0 eq.) in 1,4-dioxane (8

mL) was added hydrogen chloride (8 mL, 9 M in H_2O). The reaction mixture was stirred for overnight at room temperature and concentrated under reduced pressure to afford the crude product (S)-2-amino-3-(1-methyl-3-oxopyrazolidin-4-yl)propanoic acid hydrochloride (500 mg, crude) as a yellow solid. LC-MS (ESI, m/z): 188 $[M+H]^+$.

[0415] To a solution of (S)-2-amino-3-(1-methyl-3-oxopyrazolidin-4-yl)propanoic acid hydrochloride (500 mg, 2.23 mmol, 1.0 eq.) in DCM (10 mL) were added di-tert-butyl dicarbonate (537 mg, 2.46 mmol, 1.1 eq.) and triethylamine (679 mg, 6.71 mmol, 3.0 eq.). The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was concentrated under reduced pressure to remove DCM and adjusted to pH = 6 with HCl (1 M). The mixture was extracted with $CHCl_3$:^{i}PrOH (4:1) (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (S)-2-((tert-butoxycarbonyl)amino)-3-(1-methyl-3-oxopyrazolidin-4-yl)propanoic acid (400 mg, crude) as a yellow solid. LC-MS (ESI, *m/z*): 288 $[M+H]^+$.

[0416] To a mixture of (S)-2-((tert-butoxycarbonyl)amino)-3-((R)-1-methyl-3-oxopyrazolidin-4-yl)propanoic acid (400 mg, 1.39 mmol, 1.0 eq.) in DCM (8 mL) was added 1-hydroxybenzotriazole (225 mg, 1.67 mmol, 1.2 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (294 mg, 1.53 mmol, 1.1 eq.), ammonia (0.04 mL, 0.280 mmol, 2.0 eq., 7 M in MeOH) and N-methylmorphline (422 mg, 4.18 mmol, 3.0 eq.) stirred at 0 °C. The mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with $CHCl_3$:^{i}PrOH (4:1) (5 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (12%) to provide tert-butyl ((S)-1-amino-3-(1-methyl-3-oxopyrazolidin-4-yl)-1-oxopropan-2-yl)carbamate (110 mg, crude) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87-6.99 (m, 2H), 5.85-5.99 (m, 2H), 4.36-4.42 (m, 1H), 3.38-3.56 (m, 1H), 2.84-3.14 (m, 2H), 2.64-2.68 (m, 3H), 1.94-2.16 (m, 2H), 1.45-1.48 (m, 9H). LC-MS (ESI, *m/z*): 287$[M+H]^+$.

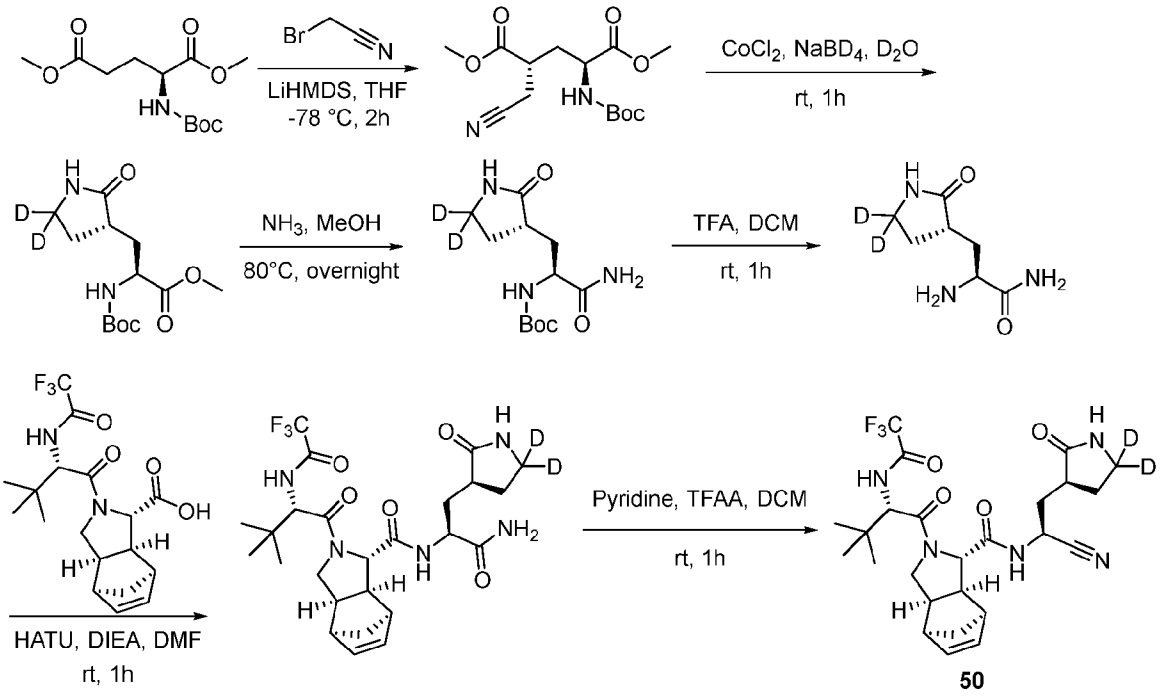
[0417] A mixture of tert-butyl ((S)-1-amino-3-(1-methyl-3-oxopyrazolidin-4-yl)-1-oxopropan-2-yl)carbamate (110 mg, 0.384 mmol, 1.0 eq.) in hydrogen chloride (3 mL, 2 M in diethyl ether) was stirred for 3 h at rt and then concentrated under reduced pressure to

afford (S)-2-amino-3-((R)-1-methyl-3-oxopyrazolidin-4-yl)propanamide hydrochloride (70 mg, crude) as a yellow solid. LC-MS (ESI, *m/z*): 187 $[M+H]^+$.

[0418] To a mixture of (1S,2S,3S,6R,7R)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]decane-3-carboxylic acid (129 mg, 0.330 mmol, 1.1 eq.) in dimethylformamide (3 mL) were added o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (137 mg, 0.360 mmol, 1.2 eq.) and N-ethyl-N-isopropylpropan-2-amine (232 mg, 1.80 mmol, 6.0 eq.) at 0 °C. After stirred 20 min, (S)-2-amino-3-(1-methyl-3-oxopyrazolidin-4-yl)propanamide hydrochloride (70 mg, 0.300 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The reaction was quenched with water (5 mL). The mixture was purified by C18 column with CH_3CN/Water (0.05% TFA). The fraction was concentrated under reduced pressure to provide the desired product (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-3-(1-methyl-3-oxopyrazolidin-4-yl)-1-oxopropan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (50.0 mg, 29%) as a white solid. LC-MS (ESI, m/z): 557 $[M+H]^+$.

[0419] To a mixture of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-3-(1-methyl-3-oxopyrazolidin-4-yl)-1-oxopropan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (50.0 mg, 0.090 mmol, 1.0 eq.) in DCM (2 mL) were added pyridine (28.4 mg, 0.360 mmol, 4.0 eq.) and trifluoroacetic anhydride (32.1 mg, 0.153 mmol, 1.7 eq.). The mixture was stirred 2 h at rt. The reaction was quenched with water (10 mL). The mixture was extracted with DCM (3 x 50 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 39% B to 69% B in 7 min, 69% B; Wave Length: 254 nm; RT1(min): 5.18;) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-(1-methyl-3-oxopyrazolidin-4-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (12.6 mg, 25%) as an off-white solid. LC-MS (ESI, m/z): 539 $[M+H]^+$.

EXAMPLE 50
Compound 50



[0420] To a mixture of 1,5-dimethyl (2S)-2-[(tert-butoxycarbonyl)amino]pentanedioate (60.0 g, 217 mmol, 1.0 eq.) in THF (500 mL) was added lithium bis(trimethylsilyl)amide (80.2 g, 479 mmol, 2.2 eq.) at - 78 °C under nitrogen atmosphere. After stirred for 1h at - 78 °C, 2-bromoacetonitrile (28.7 g, 239 mmol, 1.1 eq.) was added. The mixture was stirred for 2h at - 78 °C under nitrogen. The reaction was quenched with methanol (200 mL) and hydrochloric acid (300 mL, 2M). The mixture was extracted with ethyl acetate (3 x 250 mL). The organic layers were combined, washed with brine (2 x 250 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with ethyl acetate:petroleum ether (1:1) to provide 1,5-dimethyl (2S,4R)-2-[(tert-butoxycarbonyl)amino]-4-(cyanomethyl)pentanedioate (41.4 g, 57%) as a yellow oil. LC-MS (ESI, *m/z*): 315 $[M+H]^+$.

[0421] To a stirred mixture of 1,5-dimethyl (2S,4R)-2-[(tert-butoxycarbonyl)amino]-4-(cyanomethyl)pentanedioate (1.50 g, 4.77 mmol, 1.0 eq.) and cobalt(II) chloride (1.24 g, 9.54 mmol, 2.0 eq.) in D_2O (15 mL) was added sodium borodeuteride (2.00 g, 47.7 mmol, 10 eq.). The mixture was stirred for 1 h at rt. The

reaction was quenched with water (30 mL). The mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (1:20) to provide methyl (S)-2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl-5,5-d2)propanoate (190 mg, 13%) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53-7.73 (m, 1H), 7.28-7.49 (m, 1H), 3.96-4.11 (m, 1H), 3.54-3.71 (m, 3H), 2.20-2.32 (m, 1H), 2.07-2.18 (m, 1H), 1.91-2.06 (m, 1H), 1.50-1.70 (m, 2H), 1.30-1.44 (m, 9H). LC-MS (ESI, *m/z*): 189 $[M\text{-}Boc+H]^+$.

[0422] Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl-5,5-d2)propanoate (190 mg, 0.659 mmol, 1.0 eq.) was stirred with NH_3 in MeOH (10 mL, 7 M NH_3 in MeOH). The mixture was stirred overnight at 80°C and then concentrated under reduced pressure to afford tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl-5,5-d2)propan-2-yl)carbamate (140 mg, crude) as a brown oil. LC-MS (ESI, *m/z*): 274 $[M+H]^+$.

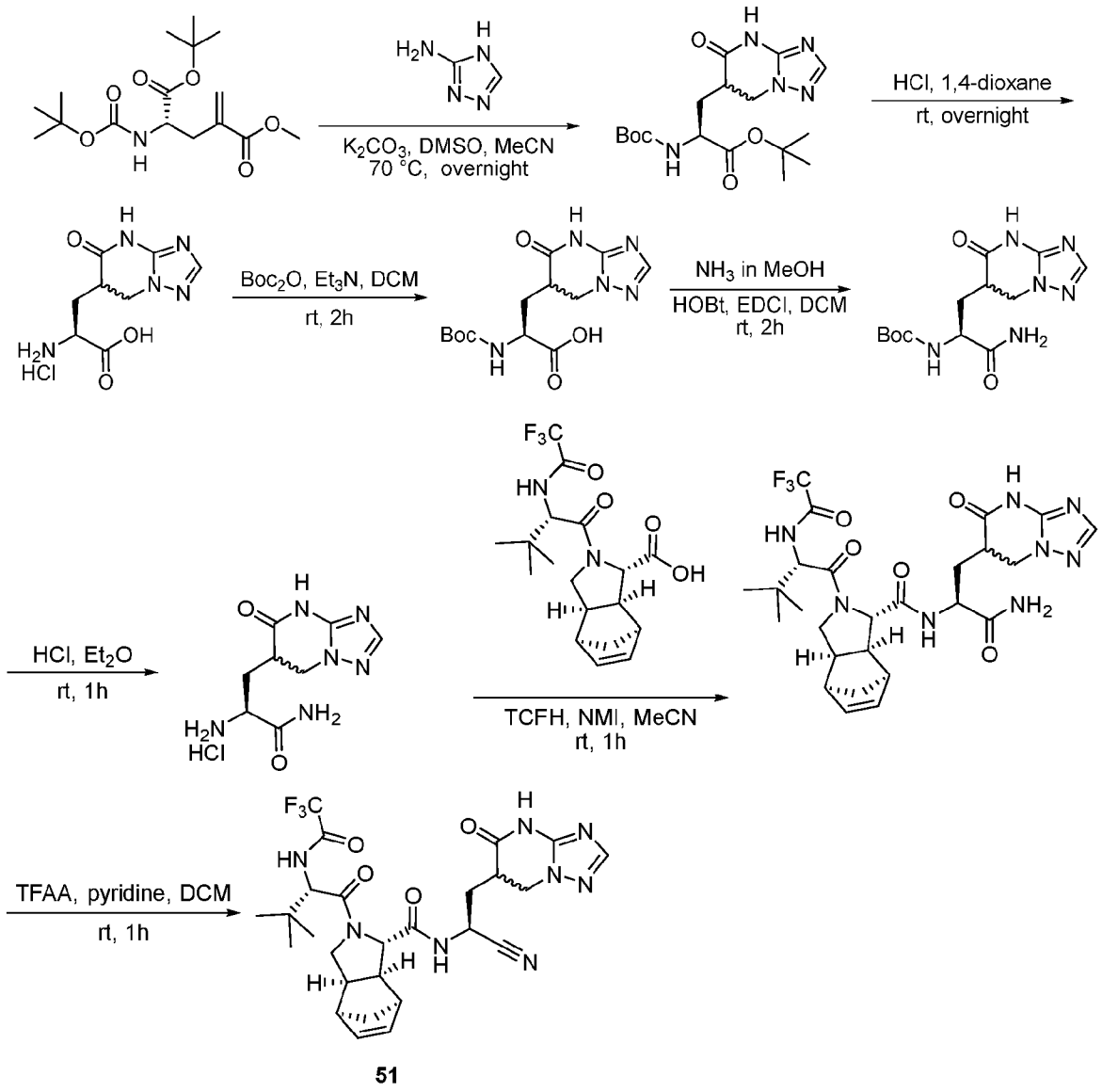
[0423] To a stirred mixture of tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl-5,5-d2)propan-2-yl)carbamate (140 mg, 0.512 mmol, 1.0 eq.) in DCM (4 mL) was added trifluoroacetic acid (1.5 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to afford (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl-5,5-d2)propanamide (88 mg, crude) as a brown oil. LC-MS (ESI, *m/z*): 174 $[M+H]^+$.

[0424] To a stirred mixture of (1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (217 mg, 0.559 mmol, 1.1 eq.) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (231 mg, 0.610 mmol, 1.2 eq.) in DMF (3 mL) was added N-ethyl-N-isopropylpropan-2-amine (525 mg, 4.06 mmol, 8.0 eq.) at 0°C. After stirred for 20 min at 0 °C, (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl-5,5-d2)propanamide (88.0 mg, 0.508 mmol, 1.0 eq.) was added. The mixture was stirred for 1 h at rt. The reaction quenched with water (15 mL). The mixture was extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine (2 x 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (9:91) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl-5,5-d2)propan-2-yl)-

2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (170 mg, 61%) as a white solid. LC-MS (ESI, *m/z*): 544 $[M+H]^+$.

[0425] To a stirred mixture of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl-5,5-d2)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (170 mg, 0.313 mmol, 1.0 eq.) in DCM (4 mL) were added pyridine (98.9 mg, 1.25 mmol, 4.0 eq.) and trifluoroacetic anhydride (111 mg, 0.532 mmol, 1.7 eq.). The mixture was stirred for 1 h at rt. The reaction was quenched with water (15 mL). The mixture was extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine (2 x 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 75% B in 7 min, 75% B; Wave Length: 254 nm; RT1 (min): 5.42) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl-5,5-d2)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (58.6 mg, 35%) as a white solid. ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 8.73-9.09 (m, 1H), 8.30-8.72 (m, 1H), 7.29-7.62 (m, 1H), 5.91-6.29 (m, 2H), 4.80-5.01 (m, 1H), 4.40-4.75 (m, 1H), 3.92-4.25 (m, 1H), 3.56-3.79 (m, 1H), 3.30-3.55 (m, 1H), 3.00-3.05 (m, 1H), 2.89-2.99 (m, 2H), 2.60-2.88 (m, 1H), 2.30-2.40 (m, 1H), 2.00-2.29 (m, 2H), 1.60-1.93 (m, 2H), 1.19-1.53 (m, 2H), 0.70-1.15 (m, 9H). LC-MS (ESI, *m/z*): 526 $[M+H]^+$.

EXAMPLE 51
Compound 51



51

[0426] To a mixture of 1-tert-butyl 5-methyl (2S)-2-[(tert-butoxycarbonyl)amino]-4-methylidenepentanedioate (1.00 g, 3.04 mmol, 1 eq.) in DMSO (5 mL)/MeCN (5 mL) were added 2-amino-1,3,4-triazole (383 mg, 4.55 mmol, 1.5 eq.) and potassium carbonate (634 mg, 4.55 mmol, 1.5 eq.). The mixture was stirred overnight at 70 °C. The reaction was quenched with water (50 mL). The mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column

with EtOAc:petroleum ether (7:3) to provide tert-butyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanoate (620 mg, 49 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42-11.53 (m, 1H), 7.67-7.75 (m, 1H), 7.19-7.32 (m, 1H), 4.30-4.42 (m, 1H), 3.88-4.14 (m, 2H), 2.88-3.04 (m, 1H), 2.18-2.29 (m, 1H), 1.52-1.88 (m, 1H), 1.31-1.48 (m, 18H). LC-MS (ESI, *m/z*): 382 $[M+H]^+$.

[0427] To a mixture of tert-butyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanoate (900 mg, 2.36 mmol, 1.0 eq.) in 1,4-dioxane (15 mL) was added hydrochloric acid (15 mL, 9 M). The mixture was stirred overnight at rt. The mixture was concentrated under reduced pressure to afford (2S)-2-amino-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanoic acid hydrochloride (616 mg, crude) as an off-white solid. LC-MS (ESI, *m/z*): 226 $[M+H]^+$.

[0428] To mixture of (2S)-2-amino-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanoic acid hydrochloride (616 mg, 2.35 mmol, 1.0 eq.) in DCM (10 mL) were added triethylamine (1.43 g, 14.1 mmol, 6.0 eq.) and di-tert-butyl dicarbonate (1.03 g, 4.71 mmol, 2.0 eq.). The mixture was stirred for 2 h at rt and then concentrated under reduced pressure to remove DCM. The residue was diluted with water (30 mL) and adjusted to pH = 6 with hydrochloric acid (1 M). The mixture was extracted with IPA:chloroform (1:4, 3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (2S)-2-[(tert-butoxycarbonyl)amino]-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanoic acid (768 mg, crude) as an off-white solid. LC-MS (ESI, *m/z*): 270 $[M-56+H]^+$.

[0429] To a mixture of (2S)-2-[(tert-butoxycarbonyl)amino]-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanoic acid (384 mg, 1.18 mmol, 1.0 eq.) in DCM (5 mL) were added 1-hydroxybenzotriazole (191 mg, 1.42 mmol, 1.2 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (249 mg, 1.30 mmol, 1.1 eq.) and ammonia (1.69 mL, 11.8 mmol, 10.0 eq., 7 M in MeOH). The mixture was stirred for 2 h at rt. The reaction was quenched with water (20 mL). The mixture was extracted with IPA:chloroform (1:4, 3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was chromatographed on a silica gel column with MeOH:DCM (11:89) to provide tert-butyl N-[(1S)-1-carbamoyl-2-{5-oxo-

4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}ethyl]carbamate (60.0 mg, 14%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41-11.51 (m, 1H), 7.69-7.75 (m, 1H), 7.29-7.40 (m, 1H), 7.09 (s, 1H), 6.94-7.02 (m, 1H), 4.31-4.50 (m, 1H), 3.94-4.06 (m, 2H), 2.82-2.98 (m, 1H), 2.09-2.34 (m, 1H), 1.53-1.79 (m, 1H), 1.27-1.48 (m, 9H). LC-MS (ESI, *m/z*): 269 $[M-56+H]^+$.

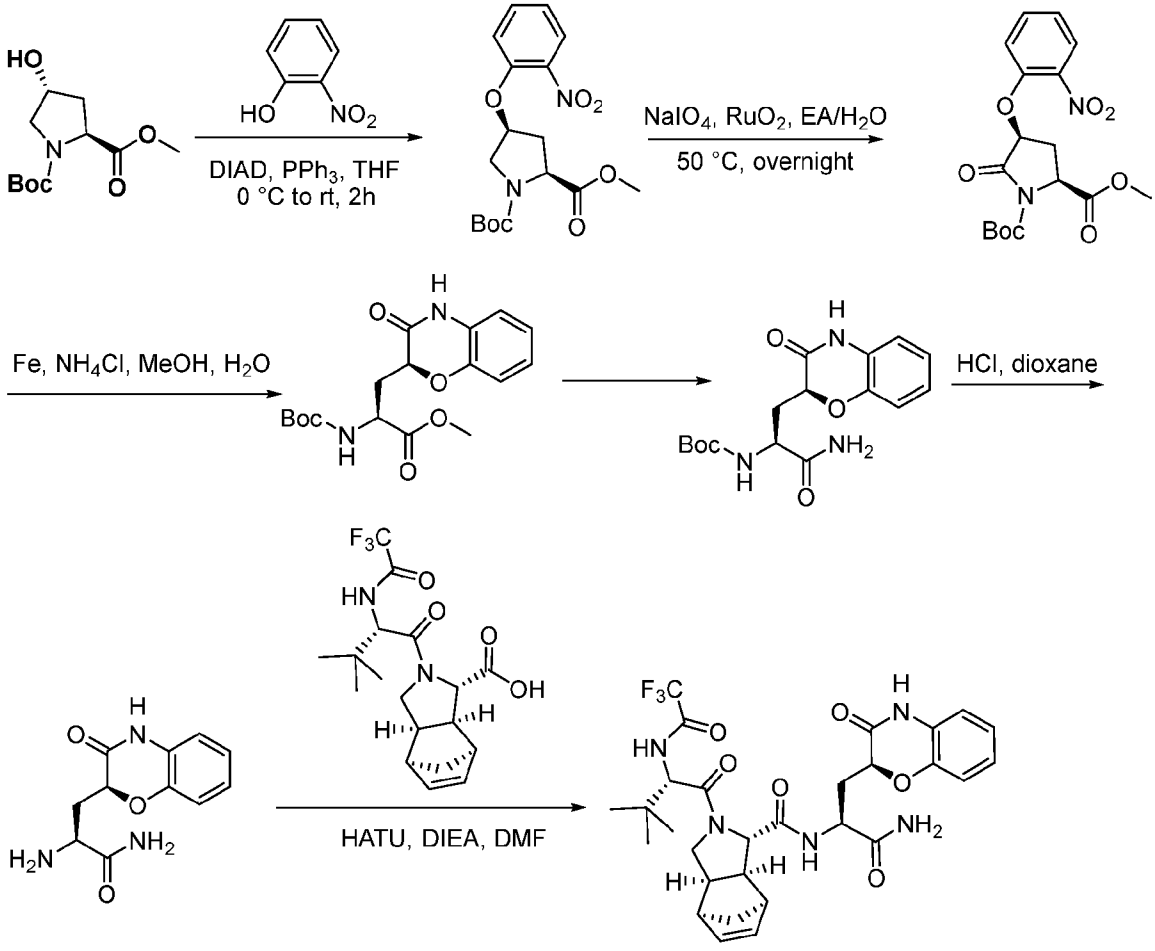
[0430] A mixture of tert-butyl N-[(1S)-1-carbamoyl-2-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}ethyl]carbamate (60.0 mg, 0.185 mmol, 1.0 eq.) in hydrogen chloride (3 mL, 2 M in Et_2O) was stirred for 1 h at rt. The mixture was concentrated under reduced pressure to afford (2S)-2-amino-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanamide hydrochloride (48.0 mg, crude) as a white solid. LC-MS (ESI, *m/z*): 225 $[M+H]^+$.

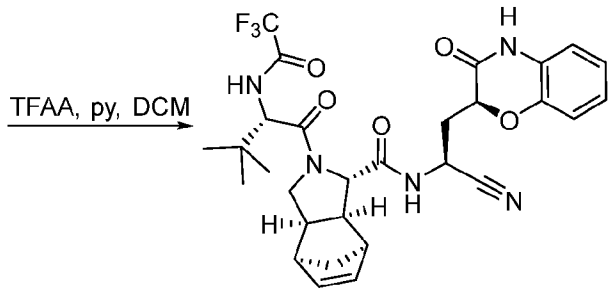
[0431] To a mixture of (2S)-2-amino-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanamide hydrochloride (48.0 mg, 0.184 mmol, 1.0 eq.), (1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxylic acid (72.0 mg, 0.184 mmol, 1.0 eq.) and N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate (67.0 mg, 0.239 mmol, 1.3 eq.) in MeCN (3 mL) was added N-methylimidazole (151 mg, 1.84 mmol, 10.0 eq.). The mixture was stirred for 1 h at rt. The crude product was purified by C18 column with CH_3CN/Water (0.05% TFA). The desired fraction was concentrated under reduced pressure to provide (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanamide (80.0 mg, 68%) as an off-white solid.

[0432] To a mixture of (2S)-2-{[(1R,2S,3S,6R,7S)-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]formamido}-3-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}propanamide (80.0 mg, 0.135 mmol, 1.0 eq.) in DCM (2 mL) were added pyridine (43.0 mg, 0.540 mmol, 4.0 eq.) and trifluoroacetic anhydride (42.0 mg, 0.203 mmol, 1.5 eq.). The mixture was stirred for 1 h at rt. The mixture was quenched with water (10 mL). The mixture was extracted with DCM (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product. The

crude product was purified by prep-HPLC (Column: XBridge Prep Phenyl OBD Column, 19 x 250 mm, 5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 37% B to 67% B in 7 min, 67% B; Wave Length: 254 nm; RT: 5 min) to provide (1R,2S,3S,6R,7S)-N-[(1S)-1-cyano-2-{5-oxo-4H,6H,7H-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl}ethyl]-4-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3-carboxamide (23.5 mg, 30 %) as a white solid. LC-MS (ESI, *m/z*): 577[M+H]$^+$.

EXAMPLE 52
Compound 52

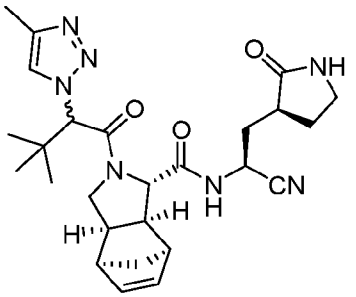




52

[0433] Compound 52 was prepared according to the synthetic scheme described above. LC-MS (ESI, *m/z*): [M+H]+=588.

EXAMPLE 53
Compound 53



53

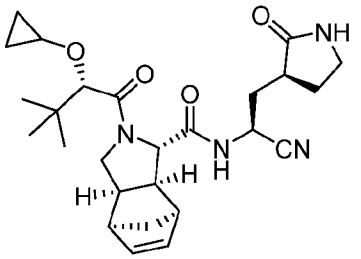
[0434] Compound 53 was prepared similarly as described for Compound 42 using methyl (S)-3,3-dimethyl-2-(4-methyl-1H-1,2,3-triazol-1-yl)butanoate in place of methyl (S)-3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoate. ^{1}H NMR (500 MHz, 365K, DMSO-d_6) δ 8.62-8.78 (m, 1H), 7.74 (m, 1H), 7.36 (br. s., 1H), 6.21 (m, 1H), 5.83 (m, 1H), 5.51 (m, 1H), 5.20 (s, 1H), 4.92 (m, 1H), 3.97 (m, 1H), 3.74 (m, 1H), 3.07-3.24 (m, 4H), 2.89-3.09 (m, 1H), 2.83 (m, 1H), 2.73 (m, 1H), 2.33-2.42 (m, 1H), 2.10-2.29 (m, 4H), 1.67-1.88 (m, 2H), 1.31-1.35 (m, 2H), 0.91-0.95 (s, 9H). LCMS (ESI, m/z): 492 [M-H]$^-$.

[0435] Methyl (S)-3,3-dimethyl-2-(4-methyl-1H-1,2,3-triazol-1-yl)butanoate: To a solution of 4-methylbenzenesulfonohydrazide (1.57 g, 8.46 mmol, 1.0 eq.) in DMSO (4.0 mL) was added 1,1-dimethoxypropan-2-one (1.0 g, 8.46 mmol, 1.0 eq.). The mixture was stirred at rt for 1 h and then diluted with water (100 mL). The mixture was stirred vigorously for 10 min. The precipitate was filtered and dried under high vacuum to afford N'-(1,1-dimethoxypropan-2-ylidene)-4-methylbenzenesulfonohydrazide (800 mg, 41%) as a white

solid.

[0436] A solution of N'-(1,1-dimethoxypropan-2-ylidene)-4-methylbenzenesulfonohydrazide (0.800 g, 2.89 mmol, 1.0 eq.), methyl (S)-2-amino-3,3-dimethylbutanoate (0.400 g, 2.79 mmol, 1.0 eq.) and NEt_3 (0.428 mL, 3.07 mmol, 1.1 eq.) in MeOH (16 mL) was heated at 75 °C for 18 h. After cooling to rt, the mixture was diluted with water (80 mL) and extracted with EA (3 x 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using 15% EA in PE as eluent to afford methyl (S)-3,3-dimethyl-2-(4-methyl-1H-1,2,3-triazol-1-yl)butanoate (0.500 g, 84%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.78 (s, 1H), 5.25 (s, 1H), 3.78 (s, 3H), 2.37 (s, 3H), 1.02 (s, 9H).

EXAMPLE 54
Compound 54



54

[0437] Compound 54 was prepared similarly as described for Compound 42 using (S)-2-cyclopropoxy-3,3-dimethylbutanoic acid in place of (S)-3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoic acid. ^{1}H NMR (500 MHz, 362K, DMSO-d_6) δ 8.63 (d, 1H), 7.33 (m, 1H), 6.17 (m, 1H), 6.10 (m, 1H), 4.90 (m, 1H), 4.07 (m, 1H), 3.72 (s, 1H), 3.62 (m, 1H), 3.49 (m, 1H), 3.12 (m, 2H), 3.07 (m, 2H), 2.93-3.00 (m, 2H), 2.70 (m, 1H), 2.40 (m, 1H), 2.12-2.18 (m, 2H), 1.68-1.77 (m, 2H), 1.43 (m, 2H), 0.82 (s, 9H), 0.33-0.57 (m, 4H). LCMS (ESI, m/z): 467 $[M-H]^-$.

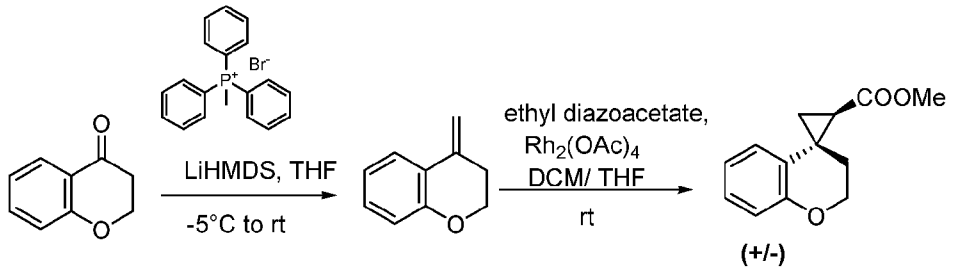
[0438] (S)-2-Cyclopropoxy-3,3-dimethylbutanoic acid: A mixture of methyl (S)-2-hydroxy-3,3-dimethylbutanoate (2.0 g, 13.7 mmol, 1.0 eq.), chloro-1,5-cyclooctadiene iridium(I) dimer (453 mg, 0.674 mmol, 0.05 eq.), sodium carbonate (870 mg, 8.21 mmol, 0.6 eq.) and vinyl acetate (5 mL, 54.8 mmol, 4.0 eq.) in toluene (20 mL) was heated at 100 °C

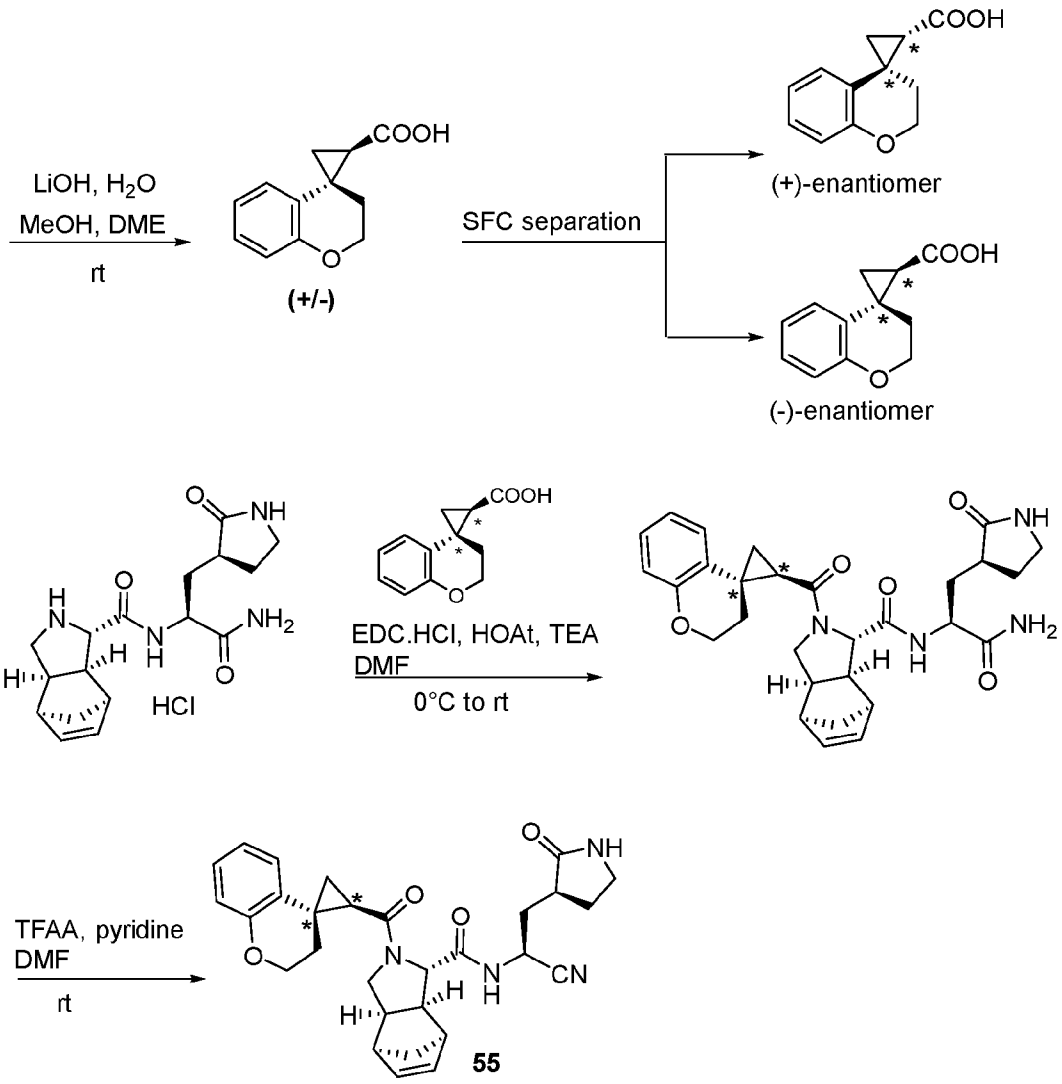
for 3 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of EA (5 to 10%) in PE to afford methyl (S)-3,3-dimethyl-2-(vinyloxy)butanoate (900 mg, 40%) as a pale yellow liquid.

[0439] To a solution of methyl (S)-3,3-dimethyl-2-(vinyloxy)butanoate (1.0 g, 5.81 mmol, 1.0 eq.) in DCM (10 mL) cooled at 0 °C were added 1M diethyl zinc solution in THF (14.53 mL, 14.53 mmol, 2.5 eq.) followed by diiodomethane (2.3 mL, 29.1 mmol, 5.0 eq.). The mixture was stirred at rt for 16 h. The reaction was quenched by the addition of cold water (20 mL). The mixture was extracted with DCM (3 x 20 mL). The organic phases were combined, washed with water (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of EA (15 to 20%) in PE to afford methyl (S)-2-cyclopropoxy-3,3-dimethylbutanoate (700 mg, 65%) as a pale yellow liquid.

[0440] To a solution of methyl (S)-2-cyclopropoxy-3,3-dimethylbutanoate (400 mg, 2.15 mmol, 1.0 eq.) in THF (1.3 mL), MeOH (1.3 mL) and water (1.3 mL) cooled at 0 °C was added LiOH (180 mg, 4.30 mmol, 1.5 eq.). The mixture was stirred at rt for 16 h and then concentrated under reduced pressure. The residues were taken up with water, acidified with sat. citric acid solution and extracted with 10% MeOH/DCM (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (S)-2-cyclopropoxy-3,3-dimethylbutanoic acid (70 mg, 97%) as a pale yellow liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (br. s., 1H), 3.46 (s, 1H), 3.26 (m, 1H), 0.87 (s, 9H), 0.57 (m, 1H), 0.31-0.50 (m, 3H).

EXAMPLE 55
Compound 55





The chiral centers noted with "*" are tentatively assigned.

[0441] To a suspension of methyltriphenylphosphonium bromide (14.5 g, 40.5 mmol, 1.2 eq.) in THF (50 mL) cooled at 0 °C was added 1M LiHMDS in THF (40.5 mL, 40.5 mmol, 1.2 eq.). The mixture was stirred at rt for 1 h. After cooling to -5 °C, a solution of chroman-4-one (5.0 g, 33.8 mmol, 1.0 eq.) in THF (10 mL) added dropwise. The mixture was stirred at rt for 1.5 h. The reaction mass was quenched with addition of sat. NH_4Cl (100 mL). The aqueous phase was extracted with EA (3 x 50 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of EA (20 to 25%) in PE to afford 4-methylenechromane (3.1 g, 63%) as a colourless liquid.

[0442] To a solution of 4-methylenechromane (2.1 g, 14.4 mmol, 1.0 eq.),

$Rh_2(OAc)_4$ (64 mg, 0.142 mmol, 0.01 eq.) in DCM (8.8 mL) was added a solution of ethyl diazoacetate (3.8 mL, 35.9 mmol, 2.5 eq.) in THF (4.2 mL) over a period of 1 h. The mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of EA (3 to 5%) in PE and by prep-HPLC (Column: X-SELECT-C18 19×250mm, 5um; Mobile Phase A: 10 mM NH_4HCO_3 in water, Mobile Phase B: ACN; Flow rate: 17 mL/min; gradient: 20% B to 70% B in 8 min) to afford trans ethyl spiro[chromane-4,1'-cyclopropane]-2'-carboxylate (800 mg, 24%) as a colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-7.14 (m, 1H), 6.81-6.89 (m, 2H), 6.75-6.78 (m, 1H), 4.20-4.28 (m, 1H), 3.98-4.15 (m, 3H), 1.98-2.12 (m, 3H), 1.65-1.72 (m, 1H), 1.44 (t, 1H), 1.18 (t, 3H). LC-MS (ESI, m/z): 233 $[M+H]^+$. (cis ethyl spiro[chromane-4,1'-cyclopropane]-2'-carboxylate (500 mg) was also obtained.)

[0443] To a solution of trans ethyl spiro[chromane-4,1'-cyclopropane]-2'-carboxylate (800 mg, 3.44 mmol, 1.0 eq.) in MeOH (3.5 mL), DME (3.5 mL) and water (1.4 mL) cooled at 0 °C was added LiOH (289 mg, 6.89 mmol, 2.0 eq.). The mixture was stirred at rt for 16 h. 10% citric acid (15 mL) was added. The mixture was extracted with EA (4 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford trans spiro[chromane-4,1'-cyclopropane]-2'-carboxylic acid (690 mg, 98%) as a white solid.

[0444] trans Spiro[chromane-4,1'-cyclopropane]-2'-carboxylic acid (690 mg) was purified by prep-SFC using the following conditions: Column: Chiralcel OJ-H, 30*250 mm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH; Flow rate: 90 g/min; Gradient: isocratic 20% B; Column Temperature: 30°C; Back Pressure: 100 bar. Purification resulted in (2'S*,4R*)-spiro[chromane-4,1'-cyclopropane]-2'-carboxylic acid (270 mg) and (2'R*,4S*)-spiro[chromane-4,1'-cyclopropane]-2'-carboxylic acid (280 mg).

[0445] (2'S*,4R*)-Spiro[chromane-4,1'-cyclopropane]-2'-carboxylic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.41 (br. s., 1H), 7.05-7.12 (m, 1H), 6.82-6.87 (m, 2H), 6.76 (d, 1H), 4.28-4.30 (m, 1H), 4.00-4.08 (m, 1H), 1.98-2.08 (m, 3H), 1.60-1.65 (m, 1H), 1.39 (t, 1H). $[\alpha]^{25}_D$: +311.7° (c 0.1, MeOH). SFC: Chiralcel OJ-H, 4.6*250 mm, 3 μm, 30 °C, co-Solvent : MeOH, hold 5 min at 20%, Rt: 1.29 min.

[0446] (2'R*,4S*)-Spiro[chromane-4,1'-cyclopropane]-2'-carboxylic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (br. s., 1H), 7.05-7.12 (m, 1H), 6.82-6.87 (m, 2H), 6.76

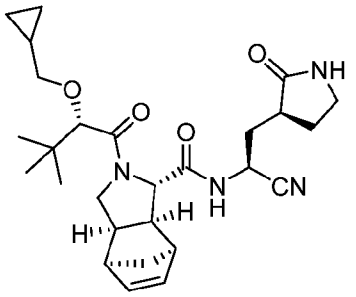
(d, 1H), 4.28-4.30 (m, 1H), 4.00-4.08 (m, 1H), 1.98-2.08 (m, 3H), 1.60-1.65 (m, 1H), 1.39 (t, 1H). $[\alpha]^{25}_{D}$: -321.8° (c 0.1, MeOH). SFC: Chiralcel OJ-H, 4.6*250 mm, 3 µm, 30 °C, co-Solvent : MeOH, hold 5 min at 20%, Rt: 1.76 min.

[0447] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide hydrochloride (120 mg, 0.325 mmol, 1.0 eq.) in DMF (1.2 mL) cooled at 0 °C were added (2'R*,4S*)-spiro[chromane-4,1'-cyclopropane]-2'-carboxylic acid (65 mg, 0.318 mmol, 1.0 eq.), EDC•HCl (122 mg, 0.637 mmol, 2.0 eq.), HOAt (43 mg, 0.320 mmol, 1.0 eq.) and NEt_3 (0.170 mL, 1.28 mmol, 3.0 eq.). The mixture was stirred at rt for 16 h. The mixture was diluted with water (5 mL) and extracted with EA (3 x 5 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (1 to 10%) in DCM to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((2'R*,4S*)-spiro[chromane-4,1'-cyclopropane]-2'-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (110 mg, 65%) as an off-white solid. LC-MS (ESI, *m/z*): 519 $[M+H]^+$.

[0448] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((2'R*,4S*)-spiro[chromane-4,1'-cyclopropane]-2'-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (90 mg, 0.174 mmol, 1.0 eq.) in DMF (0.9 mL) were added pyridine (0.042 mL, 0.521 mmol, 3.0 eq.) and TFAA (0.040 mL; 0.390 mmol, 2.2 eq.). The mixture was stirred at rt for 1 h. The mixture was diluted with water (10 mL) and extracted with EA (3 x 10 mL). The organic phases were combined, washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (1 to 10%) in DCM and by flash chromatography on C18 gel using a gradient of ACN (30 to 40%) in water to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((2'R*,4S*)-spiro[chromane-4,1'-cyclopropane]-2'-carbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (30 mg, 34%) as a white solid. ^{1}H NMR (500 MHz, 365K, DMSO-d_6) δ 8.52 (br. s., 1H), 7.29-7.46 (m, 1H), 6.95-7.10 (m, 1H), 6.62-6.88 (m, 3H), 6.25-6.00 (m, 2H), 4.35-4.92 (m, 1H), 4.17 (m, 1H), 3.91-4.12 (m, 2H), 3.75 (m, 1H), 3.10-3.40 (m, 4H), 2.70-2.95 (m, 3H), 2.38 (m, 1H),

1.90-2.22 (m, 4H), 1.68-1.86 (m, 3H), 1.40 (m, 4H). LCMS (ESI, m/z): 501 $[M+H]^+$.

EXAMPLE 56
COMPOUND 56



56

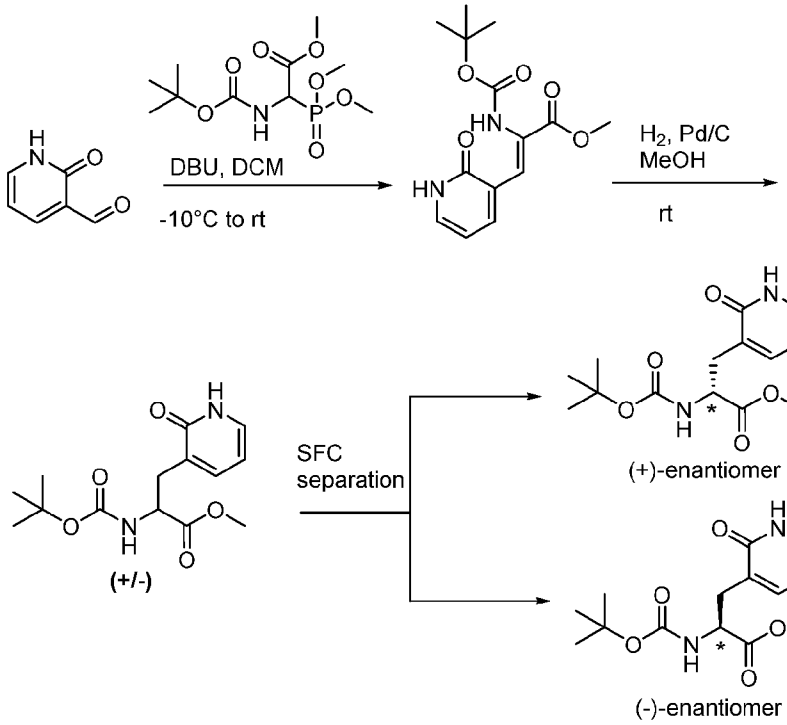
[0449] Compound 56 was prepared similarly as described for Compound 42 using (S)-2-(cyclopropylmethoxy)-3,3-dimethylbutanoic acid in place of (S)-3,3-dimethyl-2-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)butanoic acid. ^{1}H NMR (500 MHz, 363K, DMSO-d_6) δ 8.63 (br. s., 1H), 7.34-7.50 (m, 1H), 6.05-6.18 (m, 2H), 4.91 (m, 1H), 4.00-4.12 (m, 1H), 3.67 (s, 1H), 3.59 (m, 1H), 3.47 (m, 1H), 3.05-3.25 (m, 5H), 2.90-3.00 (m, 2H), 2.71 (m, 1H), 2.40 (m, 1H), 2.17 (m, 2H), 1.68-1.84 (m, 2H), 1.43 (m, 2H), 1.00 (m, 1H), 0.90 (m, 9H), 0.40-0.50 (m, 2H), 0.10-0.22 (m, 2H). LCMS (ESI, m/z): 483 $[M+H]^+$.

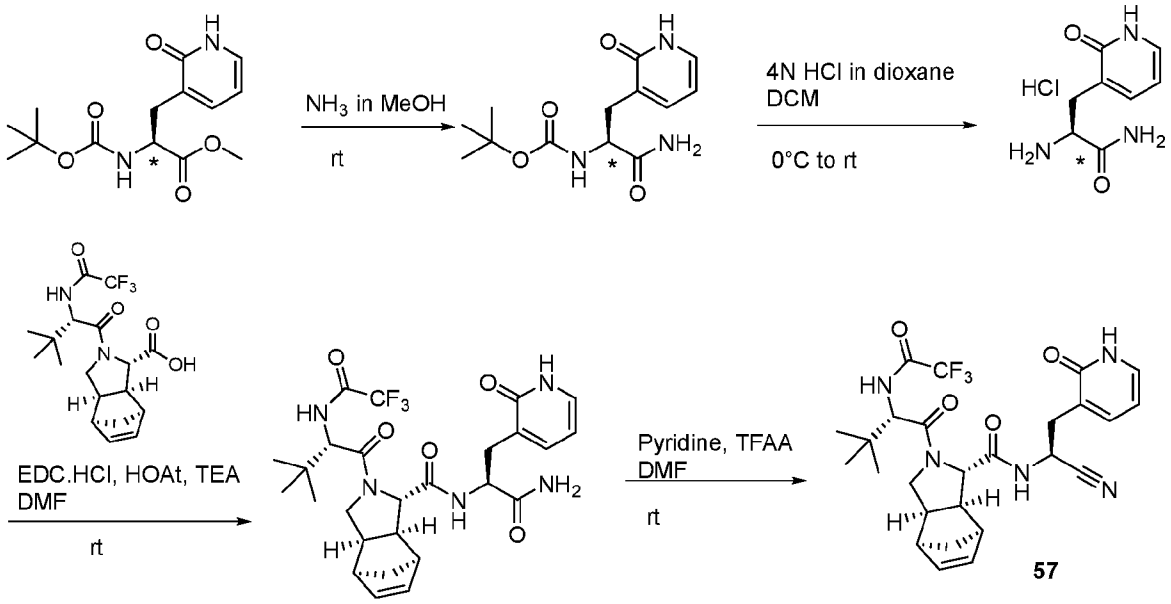
[0450] (S)-2-(Cyclopropylmethoxy)-3,3-dimethylbutanoic acid: To a solution of methyl (S)-2-hydroxy-3,3-dimethylbutanoate (100 mg, 0.684 mmol, 1.0 eq.) and (bromomethyl)cyclopropane (0.140 mL, 1.37 mmol, 2.0 eq.) in DMF (1 mL) cooled at 0 °C was added portion wise NaH (30 mg, 0.750 mmol, 1.1 eq.). The mixture was stirred at 0 °C for 6 h. The reaction was quenched by addition of cold water (5 mL). The mixture was extracted with Et_2O (3 x 10 mL). The organic phases were combined, washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of Et_2O (5 to 10%) in pentane to afford methyl (S)-2-(cyclopropylmethoxy)-3,3-dimethylbutanoate (30 mg, 22%) as a colourless liquid.

[0451] To a solution of methyl (S)-2-(cyclopropylmethoxy)-3,3-dimethylbutanoate (350 mg 1.75 mmol, 1.0 eq.) in THF (1.5 mL), MeOH (1.5 mL), and water (0.4 mL) cooled at 0 °C was added LiOH (221 mg, 5.25 mmol, 3.0 eq.). The mixture stirred at rt for 8 h. The mixture was diluted with EA (3 mL) and water (2 mL), and then

acidified with 1N HCl. The phases were separated. The aqueous phase was extracted with EA (2 x 5 mL). The organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (S)-2-(cyclopropylmethoxy)-3,3-dimethylbutanoic acid (100 mg, 36%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.43 (br. s., 1H), 3.45 (s, 1H), 3.26-3.35 (m, 1H), 3.09-3.15 (m, 1H), 0.95-1.02 (m, 1H), 0.92 (s, 9H), 0.40-0.50 (m, 2 H), 0.12-0.22 (m, 2H).

EXAMPLE 57
COMPOUND 57





[0452] To a solution of methyl 2-((tert-butoxycarbonyl)amino)-2-(dimethoxyphosphoryl)acetate 1 (1.5 g, 12.2 mmol, 1.0 eq.) in DCM (20 mL) cooled at -10 °C was added DBU (2.2 mL, 14.6 mmol, 1.2 eq.). The mixture was stirred at -10 °C for 30 min. 2-Oxo-1,2-dihydropyridine-3-carbaldehyde (4.34 g, 14.6 mmol, 1.2 eq.) was added, and the mixture was stirred at rt for 16 h. The mixture was diluted with water (20 mL) and extracted with EA (2 x 20 mL). The organic phases were combined, washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (1 to 10%) in DCM to afford methyl 2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2-dihydropyridin-3-yl)acrylate (1.5 g, 42%) as an off-white solid.

[0453] To a solution of methyl 2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2-dihydropyridin-3-yl)acrylate (1.5 g, 5.10 mmol, 1.0 eq.) in MeOH (15 mL) was added 10% Pd/C (1.0 g). The mixture was stirred for 3 h under hydrogen bladder pressure and then filtered through celite bed. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (1 to 10%) in DCM to afford methyl 2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (1.4 g, 91%) as a white solid.

[0454] Methyl 2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (1.2 g) was purified by prep-SFC using the following conditions: Column: Chiralpak-IG, 25*200 mm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH; Flow rate:

100 g/min; Gradient: isocratic 15% B; Column Temperature: 30°C; Back Pressure: 110 bar. Purification resulted in methyl (R*)-2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (500 mg) and methyl (S*)-2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (480 mg).

[0455] Methyl (R*)-2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.64 (s, 1H), 7.22-7.31 (m, 3H), 6.12 (t, 1H), 4.24-4.29 (m, 1H), 3.58 (s, 3H), 2.87 (dd, 1H), 2.54-2.60 (m, 1H), 1.20-1.37 (m, 9H). $[\alpha]^{25}_D$: +70.2° (c 0.1, MeOH). SFC: Chiralpak-IG, 4.6*150 mm, 3 μm, 30 °C, co-Solvent : 0.5% DEA in MeOH, hold 12 min at 20%, Rt: 1.74 min.

[0456] Methyl (S*)-2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 7.22-7.31 (m, 3H), 6.12 (t, 1H), 4.24-4.29 (m, 1H), 3.58 (s, 3H), 2.87 (dd, 1H), 2.58 (dd, 1H), 1.23-1.33 (m, 9H). $[\alpha]^{25}_D$: -97.9° (c 0.1, MeOH). SFC: Chiralpak-IG, 4.6*150 mm, 3 μm, 30 °C, co-Solvent : 0.5% DEA in MeOH, hold 12 min at 20%, Rt: 3.73 min.

[0457] A solution of methyl (S*)-2-((tert-butoxycarbonyl)amino)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (300 mg, 1.01 mmol, 1.0 eq.) in 7M NH_3 in MeOH (10 mL) was stirred at rt for 32 h in a sealed tube. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (1 to 10%) in DCM to afford tert-butyl (S*)-(1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)carbamate (260 mg, 91%) as a white solid.

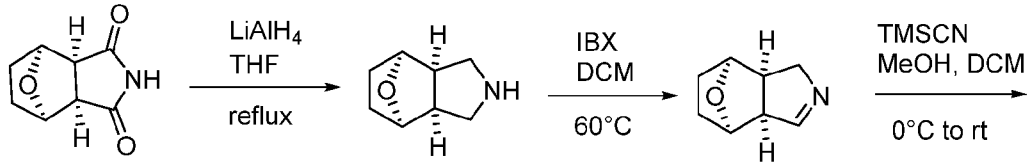
[0458] To a solution of tert-butyl (S*)-(1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)carbamate (260 mg, 0.925 mmol, 1.0 eq.) in DCM (3 mL) cooled at 0 °C was added 4N HCl in dioxane (0.920 mL, 3.70 mmol, 4.0 eq.). The mixture was stirred at rt for 2 h and then concentrated under reduced pressure to afford (S*)-2-amino-3-(2-oxo-1,2-dihydropyridin-3-yl)propanamide hydrochloride (150 mg, 89%) as a white solid.

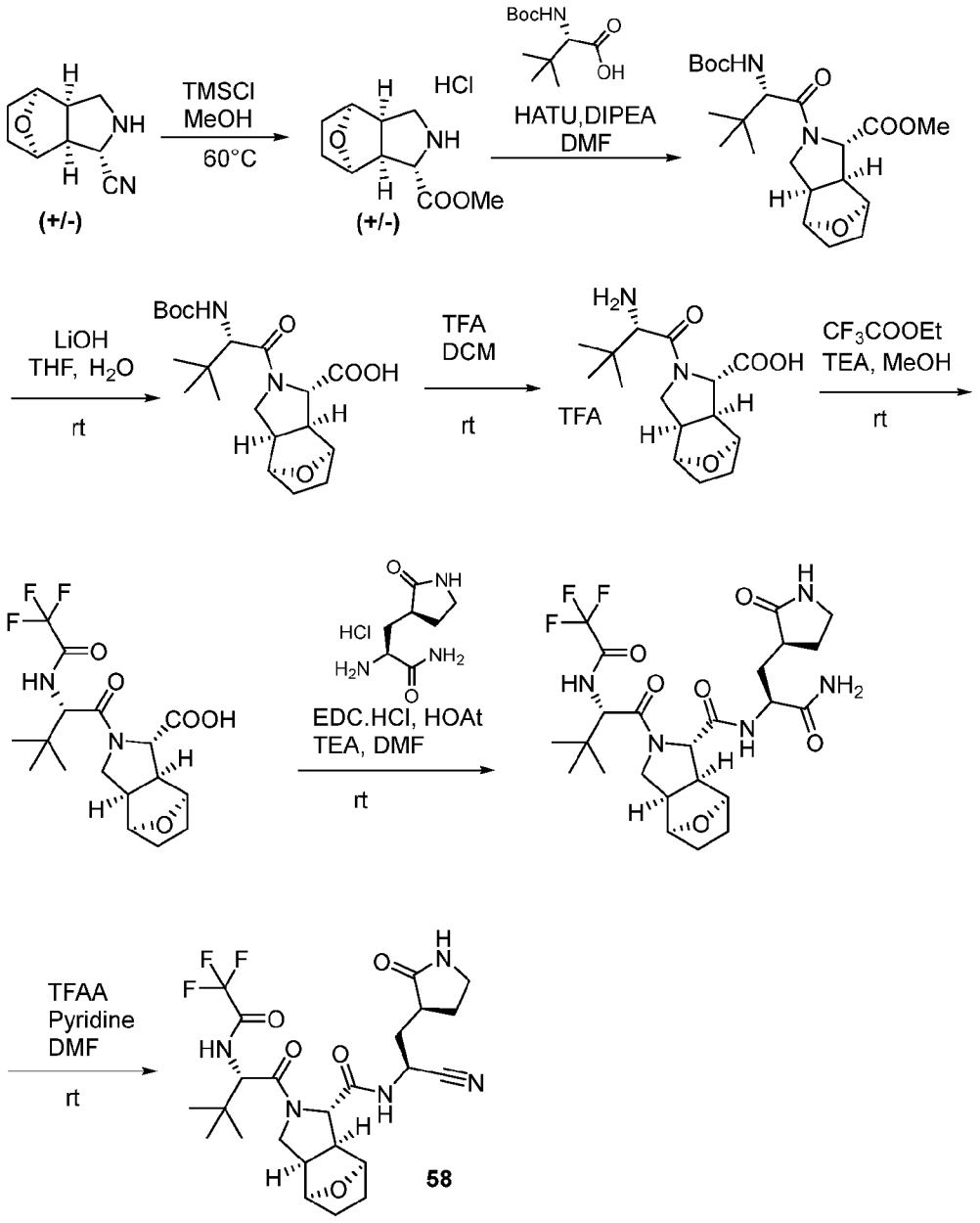
[0459] To a solution of (1S,3aR,4S,7R,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxylic acid (150 mg, 0.386 mmol, 1.0 eq.) in DMF (1.5 mL) cooled at 0 °C were added (S*)-2-amino-3-(2-oxo-1,2-dihydropyridin-3-yl)propanamide hydrochloride (100 mg, 0.463 mmol, 1.2 eq.), EDC•HCl (147 mg, 0.772 mmol, 2.0 eq.), HOAt (52 mg, 0.386 mmol, 1.0

eq.) and NEt_3 (0.16 mL, 1.15 mmol, 3.0 eq.). The mixture was stirred at rt for 16 h. The mixture was diluted with water (10 mL) and extracted with EA (2 x 10 mL). The organic phases were combined, washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on C18 gel using 0.01% FA in ACN to afford (1S,3aR,4S,7R,7aS)-N-((S*)-1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (150 mg, 70%) as a white solid. LC-MS (ESI, m/z): 552 $[M+H]^+$.

[0460] To a solution of (1S,3aR,4S,7R,7aS)-N-((S*)-1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (150 mg, 0.272 mmol, 1.0 eq.) in DMF (1.5 mL) were added pyridine (0.060 mL, 0.816 mmol, 3.0 eq.) and TFAA (0.070 mL, 0.544 mmol, 2.0 eq.). The mixture was stirred at rt for 1 h. The mixture was diluted with water (5 mL) and extracted with EA (2 x 5 mL). The organic phases were combined, washed with brine (2 x 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: KROMOSIL-C18, 25×150mm, 7um; Mobile Phase A: 10 mM Ammonium bicarbonate in water, Mobile Phase B: ACN; Flow rate: 22 mL/min; gradient: 20% B to 70% B in 8 min) to afford (1S,3aR,4S,7R,7aS)-N-((S*)-1-cyano-2-(2-oxo-1,2-dihydropyridin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (60 mg, 41%) as a white solid. ^1H NMR (400 MHz, 363K, DMSO-d_6) δ 10.5 (br. s., 1H), 8.73 (br. s., 1H), 7.38 (d, 1H), 7.30 (d, 1H), 6.14 (t, 1H), 5.99 (m, 2H), 4.97 (m, 1H), 4.46 (m, 1H), 4.01-4.10 (m, 1H), 3.65 (m, 1H), 3.43 (m, 1H), 2.82-3.10 (m, 6H), 2.65 (m, 1H), 1.37 (m, 2H), 0.94 (s, 9H). LCMS (ESI, m/z): 532 $[M-H]^-$.

EXAMPLE 58
COMPOUND 58





[0461] To a solution of (3aR,4R,7S,7aS)-hexahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (260 mg, 1.55 mmol, 1.0 eq.) in THF (5 mL) cooled at 0 °C was added 2M $LiAlH_4$ in THF (3.1 mL, 6.20 mmol, 4 eq.). The mixture was stirred at reflux for 16 h. After cooling to rt, the reaction was quenched with sat. Na_2SO_4 (10 mL). The mixture was filtered through celite, and the solids were washed with THF (10 mL). The filtrate was concentrated under reduced pressure to afford quantitatively (3aR,4S,7R,7aS)-octahydro-1H-4,7-epoxyisoindole as a pale yellow viscous liquid.

[0462] To a solution of (3aR,4S,7R,7aS)-octahydro-1H-4,7-epoxyisoindole (1.8

g, 12.9 mmol, 1.0 eq.) in DCM (20 mL) was added IBX (3.6 g, 12.9 mmol, 1.0 eq.). The mixture was stirred in sealed tube at 60 °C for 1 h. After cooling to rt, the mixture was washed with sat. sodium dithionate (10 mL). The phases were separated. The organic phase was washed with sat. sodium carbonate (70 mL) and brine (30 mL). The aqueous phases were extracted with DCM (3 x 50 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (2 to 5%) in DCM to afford (3aS,4R,7S,7aR)-3a,4,5,6,7,7a-hexahydro-1H-4,7-epoxyisoindole (1.2 g, 68%) as a pale yellow oil.

[0463] To a solution of (3aS,4R,7S,7aR)-3a,4,5,6,7,7a-hexahydro-1H-4,7-epoxyisoindole (1.2 g, 8.75 mmol, 1.0 eq.) in DCM (12 mL) and MeOH (1.2 mL) cooled at 0 °C was added TMSCN (2.7 mL, 21.9 mmol, 2.5 eq.). The mixture was stirred at rt for 16 h and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (1 to 3%) in DCM to afford (+/-)-(1S,3aR,4S,7R,7aS)-octahydro-1H-4,7-epoxyisoindole-1-carbonitrile (800 mg, 56%) as an off-white solid.

[0464] To a solution of (+/-)-((1S,3aR,4S,7R,7aS)-octahydro-1H-4,7-epoxyisoindole-1-carbonitrile (300 mg, 1.82 mmol, 1.0 eq.) in MeOH (3 mL) cooled at 0 °C was added TMSCl (0.600 mL, 5.48 mmol, 3.0 eq.). The mixture was stirred at 60 °C for 6 h. The mixture was concentrated under reduced pressure to afford quantitatively (+/-)-methyl (1S,3aR,4S,7R,7aS)-octahydro-1H-4,7-epoxyisoindole-1-carboxylate hydrochloride as a pale yellow solid.

[0465] To a solution of (+/-)-methyl (1S,3aR,4S,7R,7aS)-octahydro-1H-4,7-epoxyisoindole-1-carboxylate hydrochloride (360 mg, 1.82 mmol, 1.0 eq.) in DMF (3.6 mL) cooled at 0°C were added (S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (506 mg, 2.19 mmol, 1.2 eq.), HATU (1.05 g, 2.73 mmol, 1.5 eq.) and DIPEA (1.0 mL, 5.46 mmol, 3.0 eq.). The mixture was stirred at rt for 5 h. The mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 10 mL). The organic phases were combined, washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of EA (30 to 60%) in PE to afford methyl (1S,3aR,4S,7R,7aS)-2-((S)-2-((tert-butoxycarbonyl)amino)-3,3-

dimethylbutanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxylate (350 mg, 50%) as a colourless viscous liquid.

[0466] To a solution of methyl (1S,3aR,4S,7R,7aS)-2-((S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxylate (350 mg, 0.853 mmol, 1.0 eq.) in THF (3 mL) and water (3 mL) cooled at 0 °C was added LiOH (53 mg, 1.28 mmol, 1.5 eq.). The mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was taken up with 1N HCl and extracted with EA (2 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (1S,3aR,4S,7R,7aS)-2-((S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxylic acid (280 mg, 82%) as an off-white solid.

[0467] To a solution of (1S,3aR,4S,7R,7aS)-2-((S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxylic acid (250 mg, 0.631 mmol, 1.0 eq.) in DCM (3 mL) cooled at 0°C was added TFA (0.350 mL, 3.15 mmol, 5.0 eq.). The mixture was at rt stirred for 2 h and then concentrated under reduced pressure to afford (1S,3aR,4S,7R,7aS)-2-((S)-2-amino-3,3-dimethylbutanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxylic under its acid trifluoroacetic acid salt (250 mg) as an oil.

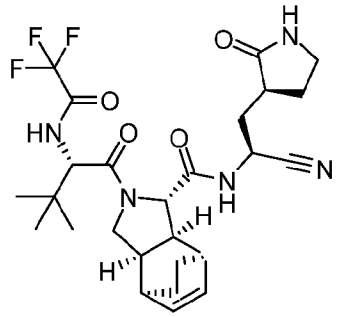
[0468] To a solution of (1S,3aR,4S,7R,7aS)-2-((S)-2-amino-3,3-dimethylbutanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxylic acid under its trifluoroacetic acid salt (250 mg, 0.844 mmol, 1.0 eq.) in MeOH (2.5 mL) were added ethyl 2,2,2-trifluoroacetate (0.300 mL, 4.22 mmol, 5.0 eq.) and NEt_3 (0.600 mL, 4.22 mmol, 5.0 eq.). The mixture was stirred at rt for 32 h and then concentrated under reduced pressure. The residue was purified by flash chromatography on C18 gel using 0.01% TFA in ACN to afford (1S,3aR,4S,7R,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxylic acid (90 mg, 36% over 2 steps) as a white solid.

[0469] To a solution of (1S,3aR,4S,7R,7aS)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxylic acid (90 mg, 0.229 mmol, 1.0 eq.) in DMF (1 mL) at 0 °C were added (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide hydrochloride (60 mg, 0.276 mmol, 1.2 eq.), EDC•HCl (88

mg, 0.646 mmol, 2.8 eq.), HOAt (31 mg, 0.228 mmol, 1.0 eq.) and TEA (0.1 mL, 0.717 mmol, 3.1 eq.). The mixture was stirred at rt for 16 h. The mixture was diluted with water (10 mL) and extracted with EA (2 x 10 mL). The organic phases were combined, washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on C18 gel using 0.01% FA in ACN to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxamide (75 mg, 60%) as a white solid.

[0470] To a stirred solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxamide (70 mg, 0.128 mmol, 1.0 eq.) in DMF (0.7 mL) were added pyridine (0.036 mL, 0.256 mmol, 3.0 eq.) and TFAA (0.03 mL, 0.384 mmol, 2.0 eq.). The mixture was stirred at rt for 2 h. The mixture was diluted with water (5 mL) and extracted with EA (2 x 5 mL). The organic phases were combined, washed with brine (2 x 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: X-SELECT-C18, 19×250mm, 5um; Mobile Phase A: 10mM Ammonium bicarbonate in water, Mobile Phase B: ACN; Flow rate: 17 mL/min; gradient: 10% B to 60% B in 8 min) to afford (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)octahydro-1H-4,7-epoxyisoindole-1-carboxamide (25 mg, 40%) as a white solid. ^{1}H NMR (500 MHz, 363K, DMSO-d_6) δ 8.60-8.90 (m, 2H), 7.30 -7.40 (m, 1H), 4.89 (m, 1H), 4.46-4.66 (m, 4H), 3.55-3.85 (m, 2H), 3.08-3.16 (m, 2H), 2.70-2.81 (m, 1H), 2.59 (m, 1H), 2.35 (m, 1H), 2.05-2.22 (m, 2H), 1.69-1.82 (m, 2H), 1.31-1.61 (m, 4H), 0.97 (m, 9H). LCMS (ESI, m/z): 528 $[M+H]^+$.

EXAMPLE 59
COMPOUND 59



59

[0471] Compound 59 was prepared similarly as described for Compound 58 using (+/-)-methyl (1S,3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-ethanoisoindole-1-carboxylate hydrochloride in place of (+/-)-methyl (1S,3aR,4S,7R,7aS)-octahydro-1H-4,7-epoxyisoindole-1-carboxylate hydrochloride. ^{1}H NMR (500 MHz, 363K, DMSO-d_6) δ 8.40-8.79 (m, 2H), 7.32-7.44 (m, 1H), 6.09-6.23 (m, 2H), 4.91 (m, 1H), 4.51-4.70 (m, 1H), 3.99-4.10 (m, 1H), 3.80 (m, 1H), 3.30-3.60 (m, 1H), 3.06-3.21 (m, 2H), 2.80 (m, 1H), 2.57-2.69 (m, 2H), 2.00-2.45 (m, 4H), 1.68-1.80 (m, 2H), 1.40-1.51 (m, 2H), 1.06-1.20 (m, 2H), 0.88-1.00 (m, 9H). LCMS (ESI, m/z): 538 $[M+H]^+$.

[0472] (+/-)-Methyl (1S,3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-ethanoisoindole-1-carboxylate hydrochloride: To a solution of (3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-ethanoisoindole (1.1 g, 7.37 mmol, 1.0 eq.) in DCM (35 mL) was added IBX (2.06 g, 7.37 mmol, 1.0 eq.). The mixture was stirred in sealed tube at 60 °C for 1 h. After cooling to rt, the mixture was washed with sat. sodium dithionate (40 mL). The phases were separated. The organic phase was washed with sat. sodium carbonate (70 mL) and brine (30 mL). The aqueous phases were extracted with DCM (3 x 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (1 to 5%) in DCM to afford (3aS,4R,7S,7aR)-3a,4,7,7a-tetrahydro-1H-4,7-ethanoisoindole (780 mg, 71%) as a white oil.

[0473] To a solution of (3aS,4R,7S,7aR)-3a,4,7,7a-tetrahydro-1H-4,7-ethanoisoindole (780 mg, 5.31 mmol, 1.0 eq.) in DCM (8 mL) and MeOH (0.6 mL) cooled at 0 °C was added TMSCN (1.8 mL, 13.3 mmol, 2.5 eq.). The mixture was stirred at 0-10 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was

purified by flash chromatography on silica gel using a gradient of MeOH (1 to 5%) in DCM to afford (+/-)-(1S,3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-ethanoisoindole-1-carbonitrile (550 mg, 59%) as a brown oil.

[0474] A solution of (+/-)-(1S,3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-ethanoisoindole-1-carbonitrile (550 mg, 3.16 mmol, 1.0 eq.) in 4N HCl in MeOH (5.5 mL) was stirred for 6 h at 60 °C. The mixture was concentrated under reduced pressure to afford (+/-)-methyl (1S,3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-ethanoisoindole-1-carboxylate hydrochloride (580 mg, 88%) as a yellow oil.

EXAMPLE 60
LC-MS Methods

Compound No.	Rt (min)	$[M+H]^+$ or $[M-H]^-$	LCMS Method
1	1.119	$[M+H]^+$=524	48
2	1.234	$[M+H]^+$=538	48
3	1.244	$[M+H-56]^+$=512	48
4	1.633	$[M+H]^+$=537	57
5	1.071	$[M+H]^+$=533	48
6	1.062	$[M+H]^+$=534	23
7	1.153	$[M+H]^+$=534	23
8	1.291	$[M+H]^+$=499	48
9	0.820, 0.856	$[M+H]^+$=576	41
10	1.035, 1.096	$[M+H]^+$=610	48
11	1.167, 1.236	$[M+H]^+$=585	48
12	1.503	$[M+H]^+$=526	59
13	1.195	$[M+H]^+$=536	48
14	0.997	$[M+H]^+$=550	11
15	1.016	$[M+H]^+$=552	11
16	0.959	$[M+H]^+$=538	11
17a	1.456	$[M+H]^+$=578	62
17b	1.451	$[M+H]^+$=578	62
18	1.632	$[M+H]^+$=552	59
19	1.330	$[M+H]^+$=522	27
20	0.955	$[M+H]^+$=564	11
21	1.282	$[M+H]^+$=496	27
22	0.826	$[M+H]^+$=526	27
23	1.426	$[M+H]^+$=574	61
24	1.378	$[M+H]^+$=522	58
25	0.937	$[M+H]^+$=550	60
26	0.917	$[M+H]^+$=550	60
27	0.937, 0.947	$[M+H]^+$=534	11

Compound No.	Rt (min)	$[M+H]^+$ or $[M-H]^-$	LCMS Method
28	0.966	$[M+H]^+$=536	11
29	1.063, 1.073	$[M+H]^+$=586	11
30	0.893	$[M+H]^+$=514	11
31	1.385, 1.428	$[M+H]^+$=588	37
32	0.966	$[M+H]^+$=528	11
33	0.893	$[M+H]^+$=532	11
34	0.928	$[M+H]^+$=522	11
35	0.944	$[M+H]^+$=536	11
36	0.770	$[M+H]^+$=512	11
37	0.955, 0.970	$[M+H]^+$=548	11
38	2.092	$[M+H]^+$= 485	A
39	0.965	$[M+H]^+$=540	11
40	0.989	$[M+H]^+$=542	11
41	0.997, 1.026	$[M+H]^+$=532	64
42	2.187	$[M-H]^{--}$= 546	A
43	1.940	$[M-H]^-$ = 508	A
44	1.402	[M+H]+=526	48
45	0.924	[M+H]+=613	47
46	1.212, 1.331	[M+H]+=612	48
47	0.893	[M+H]+=510	11
48	0.982	[M+H]+=556	11
49	0.907	[M+H]+=539	11
50	1.441	[M+H]+=526	58
51	1.104, 1.128	[M+H]+=577	64
52	1.078	[M+H]+=588	11
53	1.992	$[M-H]^-$= 492	A
54	2.159	$[M-H]^-$= 497	A
55	2.103	$[M+H]^+$ = 501	A
56	2.221	$[M+H]^+$ = 483	A
57	2.128	$[M-H]^-$= 532	A
58	2.016	$[M+H]^+$= 528	A
59	2.191	$[M+H]^+$= 538	A

Final compounds can be obtained in some cases as a mixture with a corresponding stereoisomer. Retention times of the main isomers are depicted in the table above.

Description of LC-MS methods

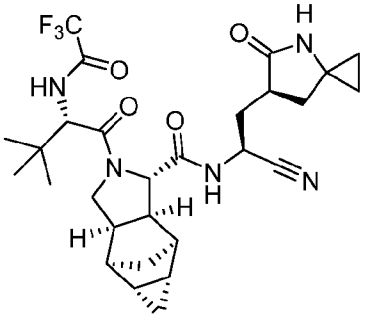
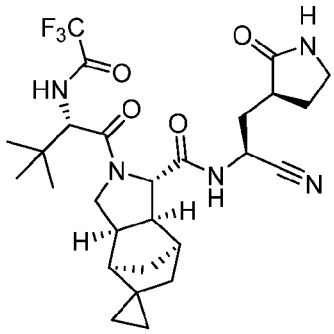
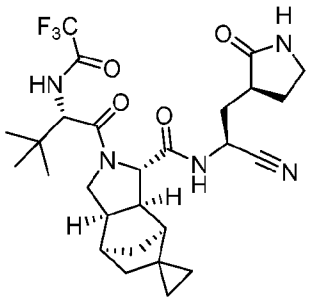
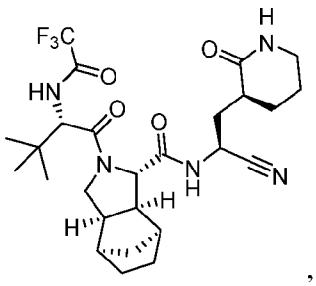
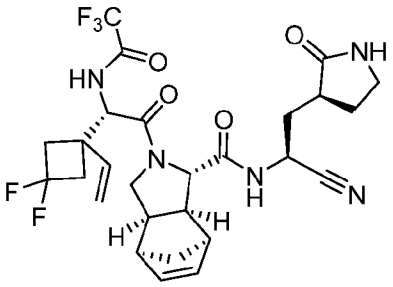
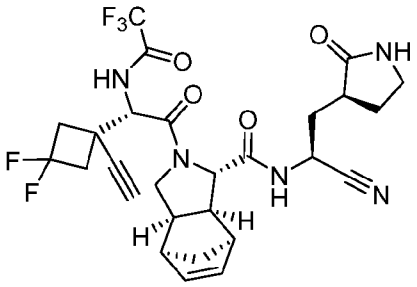
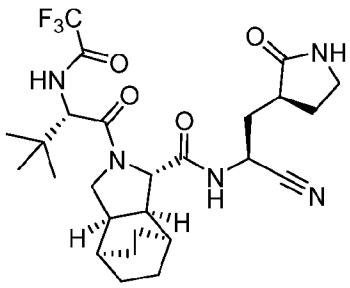
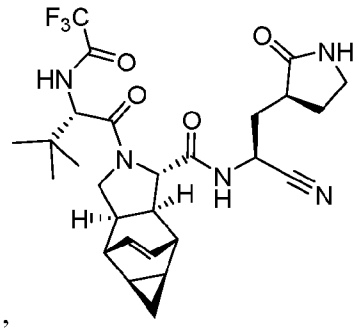
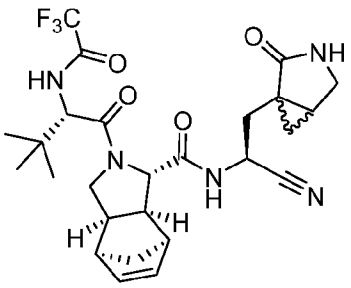
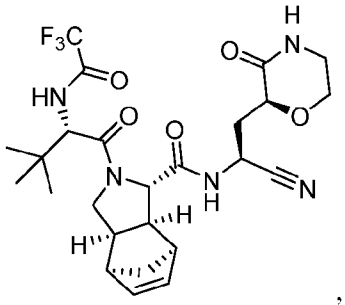
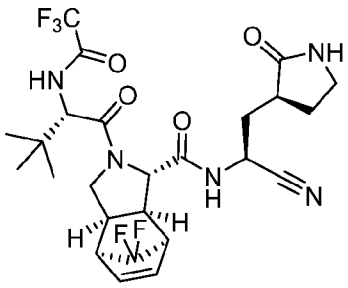
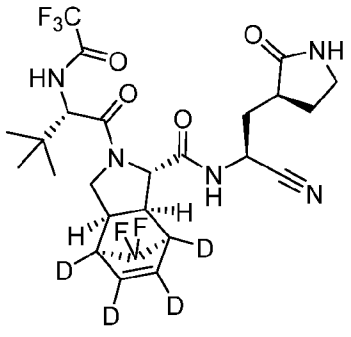
LC Method	Instrument	Column	Mobile Phase	Gradient	Flow	Col T	Run Time
11	Shimadzu LCMS-2020	HALO 2.0µm C18 90A (2.0µm, 3.0*30mm)	A:Water/0.1% FA B:Acetonitrile /0.1%FA	From 95% A to 0% A in 1.09min, held for 0.6min, to 95% A in 0.05 min, held for 0.10min	1.5mL /min	40	1.85 min
23	Shimadzu LCMS-2020	Shim-pack Scepter SP-C18 (3µm, 3.0*33mm)	A: Water/6.5 mM NH_4HCO_3 + Ammonia Hydroxide (pH=10) B: Acetonitrile	From 90% A to 5% A in 1.19min, held for 0.6min, to 90% A in 0.02 min, held for 0.18min	1.2 mL/ min	40	2 min
27	Shimadzu LCMS-2020	HALO 2.0µm C18 90A (2.0µm, 3.0*30mm)	A :Water/0.1%F A B:ACN/0.1% FA	From 95% A to 35% A in 1.69min, to 0% A in0.6 min, held for 0.5min, to 95% A in 0.03 min, held for 0.17min	1.5mL /min	40	3 min
41	Shimadzu LCMS-2020	HALO C18 (2.0µm, 3.0*30mm)	A :Water+0.05 %TFA B: ACN+0.05% TFA	From 95% A to 0% A in 1.19min, held for 0.5min, to 95% A in 0.05 min, held for 0.25min	1.5 mL/ min	40	2 min
47	Shimadzu LCMS-2020	Shim-pack Scepter SP-C18 (3µm, 3.0*33mm)	A:Water/6.5 mMNH_4HCO_3+Ammonia Hydroxide(pH =10) B:Acetonitrile	From 80% A to 5% A in 1.99min, held for 0.7min, to 90% A in 0.05 min, held for 0.25min	1.2 mL/m in	40	3 min

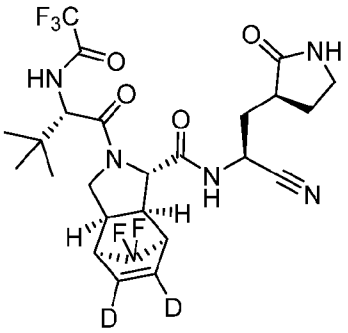
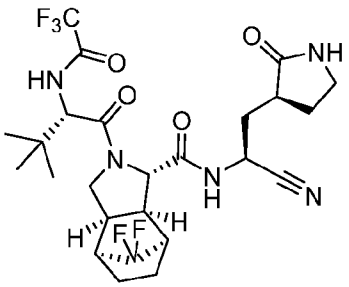
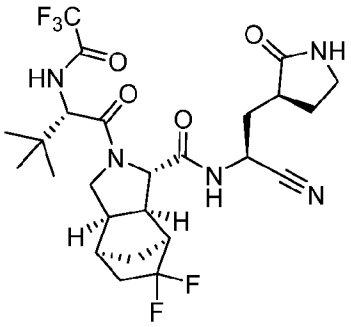
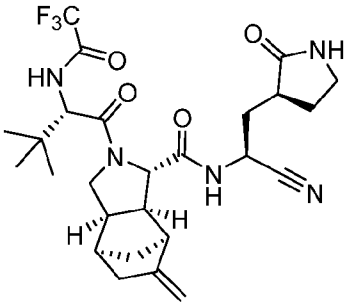
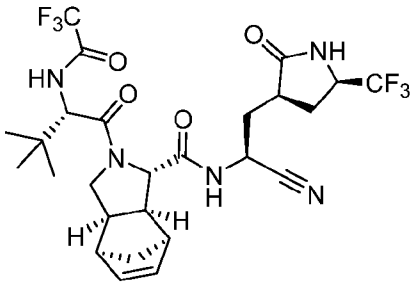
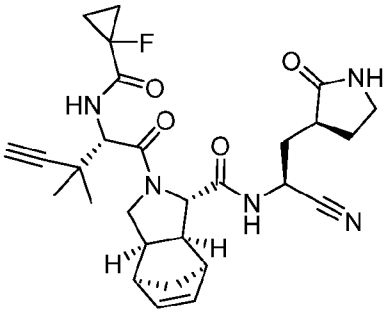
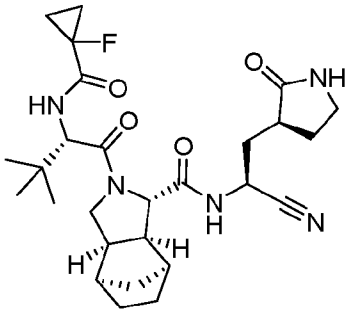
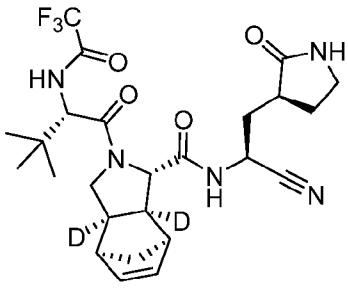
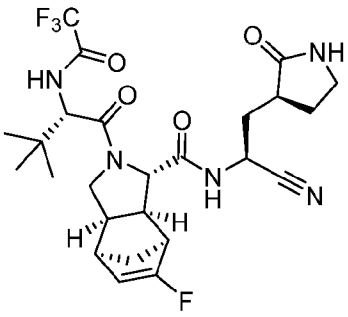
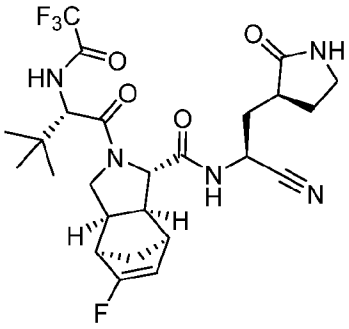
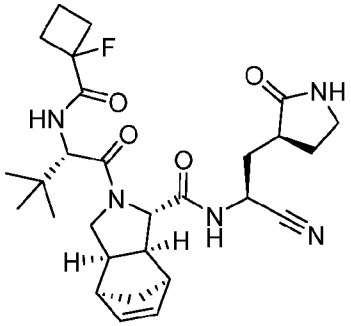
LC Method	Instrument	Column	Mobile Phase	Gradient	Flow	Col T	Run Time
48	Shimadzu LCMS-2020	Shim-pack Scepter SP-C18 (3µm, 3.0*33mm)	A: Water/6.5 mM NH_4HCO_3 + Ammonia Hydroxide (pH=10) B: Acetonitrile	From 70% A to 5% A in 1.99min, held for 0.7min, to 90% A in 0.05 min, held for 0.25min	1.2 mL/ min	40	3 min
57	Shimadzu LCMS-2020	Shim-Pack C18 (3µm, 3.0*33mm)	A: Water/6.5 mM NH_4HCO_3 + Ammonia Hydroxide (pH=10) B: Acetonitrile	From 90% A to 30% A in 1.69min, to 5% A in 0.6 min, held for 0.5min, to 90% A in 0.03 min, held for 0.17min	1.2 mL/ min	40	3 min
58	Shimadzu LCMS-2020	HALO 2.0µm C18 90A (2.0µm, 3.0*30mm)	A :Water/0.1%FA B:ACN/0.1% FA	From 95% A to 30% A in 1.69min, to 0% A in0.6 min, held for 0.5min, to 95% A in 0.03 min, held for 0.17min	1.5mL /min	40	3 min
59	Shimadzu LCMS-2020	HALO C18 (2.0µm, 3.0*30mm)	A: Watcr+0.05% TFA B: ACN+0.05% TFA	From 95% A to 35% A in 1.69min, to 5% A in 0.6 min, held for 0.5min, to 95% A in 0.03 min, held for 0.17min	1.5 mL/ min	40	3 min
60	Shimadzu LCMS-2020	HALO 90A C18 (2.0µm, 3.0*30mm)	A :Water+0.05 %TFA B:ACN+0.05 %TFA	From 95% A to 0% A in 1.19min, held for 0.6min, to 95% A in 0.05 min, held for 0.15min	1.2mL /min	40	1.9 min

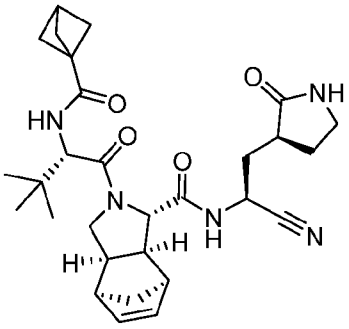
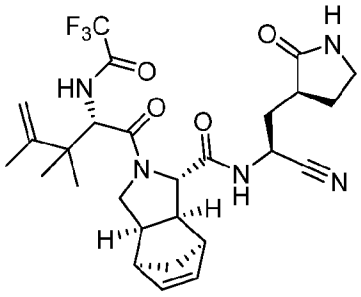
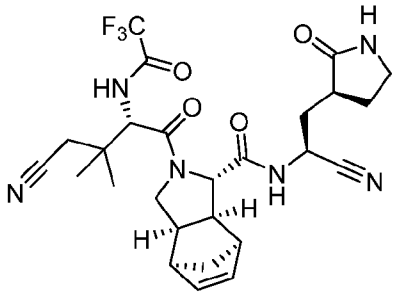
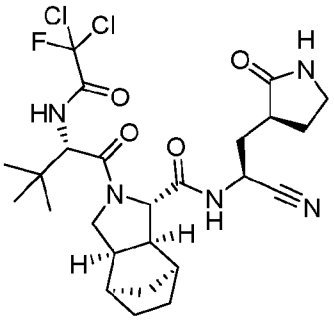
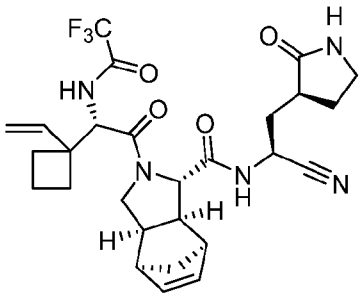
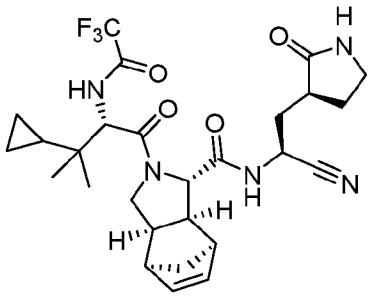
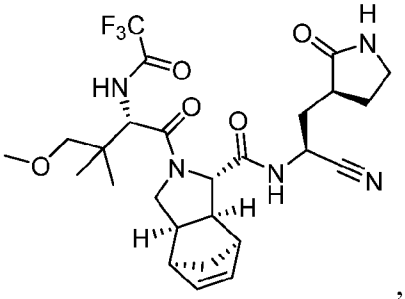
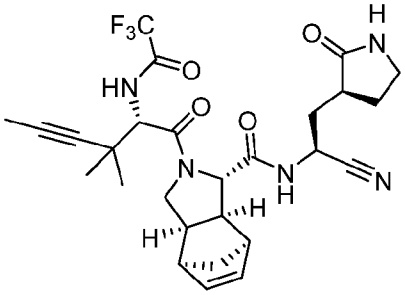
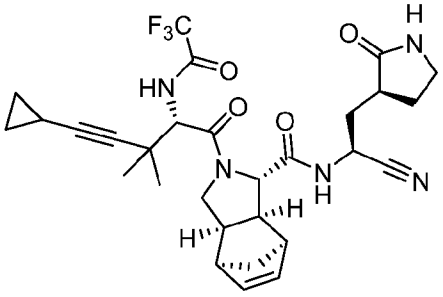
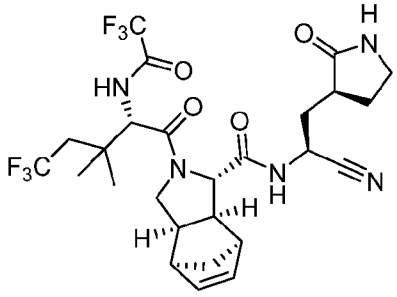
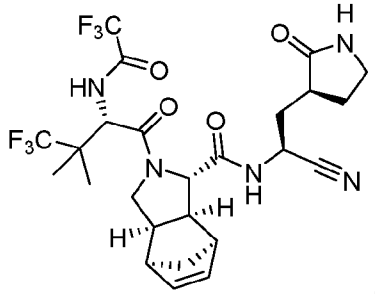
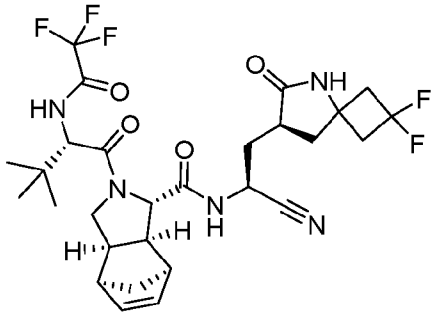
LC Method	Instrument	Column	Mobile Phase	Gradient	Flow	Col T	Run Time
61	Shimadzu LCMS-2020	HALO 2.0µm C18 90A (2.0µm, 3.0*30mm)	A :Water/0.1%FA B:ACN/0.1% FA	From 95% A to 0% A in 2.19min, held for 0.5min, to 95% A in 0.05 min, held for 0.45min	1.5mL /min	40	3.2 min
62	Shimadzu LCMS-2020	HALO 2.0µm C18 90A (2.0µm, 3.0*30mm)	A :Water/0.1%FA B:ACN/0.1% FA	From 95% A to 5% A in 2.19min, held for 0.6min, to 95% A in 0.05 min, held for 0.25min	1.5mL /min	40	3 min
A	Agilent 6150 SQ Mass Spectrometer coupled to an Agilent 1290 Infinity LC System	Acquity UPLC BEH C18 (1.7 µm, 2.1*50 mm)	A: 0.1% FA in Water, B: 0.1% FA in Acetonitrile	98% A held for 0.2 min, to 2% A in 1.3 min, held for 1.8 min, to 98% A in 0.1 min, held for 0.4 min	0.6 mL/ min	70	3.8 min
64	Shimadzu LCMS-2020	HALO 2.0µm C18 90A (2.0µm, 3.0*30mm)	A :Water/0.1%FA B:ACN/0.1% FA	From 80% A to 30% A in 1.69min, to 100% A in 0.6min, held for 0.5min, to 95% A in 0.03 min, held for 0.17min	1.5mL /min	40	3 min

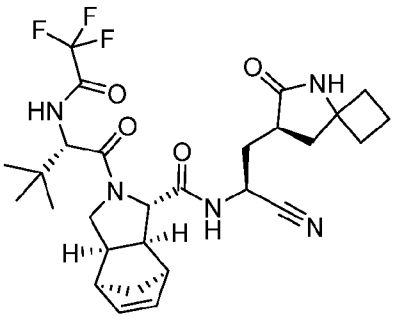
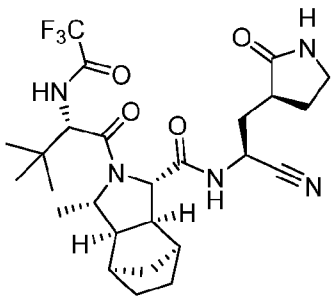
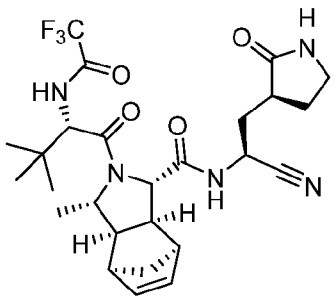
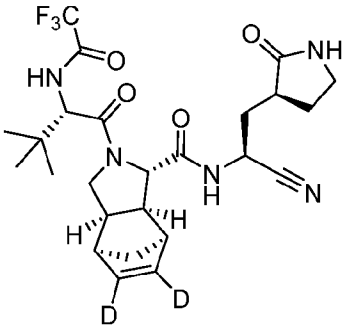
EXAMPLE 61
Additional Compounds

[0475] Additional compounds of Formula (I) can be prepared using similar materials and methods described herein, such as those described herein.


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and

, including pharmaceutically acceptable salts thereof.

EXAMPLE A

SARS-Cov-2 3CLpro and HRV3C Duplex assay

[0476] Protease assays were performed in 384-well low volume polypropylene microtiter plates at ambient temperature. For the duplex assay, 3CLpro and HRV3C was added using a Multidrop Combi (Thermo Scientific; Waltham, MA) and preincubated for 30 mins with small molecules. The reactions were initiated by the addition of the two peptide substrates. The reactions were incubated for 30 mins and quenched by the addition of 0.5% formic acid (final) with subsequent neutralization using 1% sodium bicarbonate (final). Internal standard peptides were added in 20 mM Hepes pH 8.0 for quantitation of the protease products. For SAMDI-MS analysis, 2 μL of each reaction mixture was transferred using a 384-channel automated liquid handler to SAMDI biochip arrays functionalized with a neutravidin-presenting self-assembled monolayer. The SAMDI arrays were incubated for 1 h in a humidified chamber to allow the specific immobilization of the biotinylated peptide substrates, cleaved products and internal standards. The samples were purified by washing the SAMDI arrays with deionized ultrafiltered water and dried with compressed air. A matrix comprising alpha-cyano cinnamic acid in 80% acetonitrile:20% aqueous ammonium citrate was applied in an automated format by dispensing 50 nL to each spot in the array.

SAMDI-MS was performed using reflector-positive mode on an AB Sciex TOF-TOF 5800 System (AB Sciex, Framingham, MA) with 400 shots/spot analyzed in a random raster sampling. For data analysis, area under the curves (peaks) (AUCs) for the product and internal standard were calculated using the TOF/TOF Series Explorer (AB Sciex), and the amount of product formed was calculated using the equation (AUC product/AUC internal standard). The amount of product generated was calculated using the ratio of product area under the curve (AUC) divided by the AUC of the internal standard. Negative controls were pre-quenched with 0.5% formic acid final. Assay robustness was determined by Z-Factor. The IC_{50}s were determined by fitting the curves using a four-parameter equation in Graphpad Prism 8.

[0477] Table 1 indicates related IC_{50} values for the tested compounds where 'A' indicates an EC_{50} < 20 nM, 'B' indicates an IC_{50} of ≥20 nM and < 200 nM, 'C' indicates an IC_{50} ≥ 200 nM and < 2000 nM, 'D' indicates an IC_{50} ≥ 2000 nM and < 20000 nM and 'E' indicates an IC_{50} ≥ 20000 nM and < 100000 nM. As shown by the data in Table 1, compounds described herein (including pharmaceutically acceptable salts thereof) can effectively inhibit and be used to treat a coronavirus and rhinovirus.

Table 1

Compound	SARS-Cov-2	HRV
1	A	>10 μM
2	B	>10 μM
3	A	>10 μM
4	B	>10 μM
5	C	>10 μM
6	B	>10 μM
7	A	>10 μM
8	B	>10 μM
9	A	>10 μM
10	A	B
11	A	C
12	A	>10 μM
13	B	>10 μM
14	A	>10 μM
15	A	>10 μM
16	A	>10 μM
17a	A	>10 μM

Compound	SARS-Cov-2	HRV
17b	A	>10 μM
18	A	>10 μM
19	B	>10 μM
20	A	>10 μM
21	A	>10 μM
22	C	>10 μM
23	B	>10 μM
24	B	>10 μM
25	A	>10 μM
26	B	>10 μM
27	A	>10 μM
28	A	>10 μM
29	A	>10 μM
30	A	>10 μM
31	A	>10 μM
32	A	>10 μM

Compound	SARS-Cov-2	HRV
33	A	>10 μM
34	A	>10 μM
35	B	>10 μM
36	A	>10 μM
37	B	>10 μM
38	B	>10 μM
39	A	>10 μM
40	A	>10 μM
41	A	>10 μM
42	B	>10 μM
43	>10 μM	>10 μM
44	B	>10 μM

Compound	SARS-Cov-2	HRV
45	B	D
46	A	C
47	B	>10 μM
48	A	>10 μM
49	A	>10 μM
50	A	>10 μM
51	A	>10 μM
53	B	>10 μM
54	C	>10 μM
55	B	>10 μM
56	C	>10 μM
57	B	>10 μM

EXAMPLE B
CORONAVIRUS ASSAY

OC43 Coronavirus Assay in HeLa cells

[0478] The human beta-coronavirus OC43 was purchased from ATCC (Manassas, VA) and propagated using HCT-8 human colorectal epithelial cells (ATCC). HeLa human cervical epithelial cells (ATCC) were used as susceptible host cell lines and were cultured using EMEM media, supplemented with 10% fetal bovine serum (FBS), 1% (v/v) penicillin/streptomycin (P/S), 1% (v/v) HEPES and 1% (v/v) cellgro glutagro™ supplement (all Corning, Manassas, VA) at 37 °C. For the OC43 antiviral assay, 1.5 x 10^4 HeLa cells per well were plated in 100 μL complete media in white 96-well plates with clear bottoms at 37 °C for up to 24 h to facilitate attachment and allow cells to recover from seeding stresses. Next day, the cell culture medium was removed. Serially diluted compounds in 100 μL assay media (EMEM, 2% FBS, 1% P/S, 1% cellgro glutagro™ supplement, 1% HEPES) were added to the cells and incubated for 4 H at 37 °C in a humidified 5% CO_2 incubator. 100 μL of OC43 virus stock was diluted to a concentration known to produce optimal cytopathic effect, inducing 80-90% reduction in cell viability. 96-well plates were incubated for 6 (HeLa) days at 33 °C; each plate contains uninfected control wells as well as virus-infected wells that were not treated with compound. Cytotoxicity plates without the addition of OC43 virus were carried out in parallel. At the end of the incubation period, 100 μL cell culture supernatant was replaced with 100 μL cell-titer-glo reagent (Promega, Madison, WI) and incubated for at least 10 min at rt prior to measuring

luminescence. Luminescence was measured on a Perkin Elmer (Waltham, MA) Envision plate reader. Antiviral % inhibition was calculated as follows: [(Compound treated cells infected sample) − (no compound infected control)]/[(Uninfected control) − (no compound infected control)]*100; Using GraphPad (San Diego, CA) prism software version 8.3.1, the antiviral dose-response plot was generated as a sigmoidal fit, log(inhibitor) vs response-variable slope (four parameters) model and the EC_{50} was calculated which is the predicted compound concentration corresponding to a 50% inhibition of the viral cytopathic effect.

[0479] Table 2 indicates related EC_{50} and CC_{50} values for the tested compounds 'A' indicates an EC_{50} < 100 nM, 'B' indicates an EC_{50} of ≥100 nM and < 1000 nM, 'C' indicates an EC_{50} ≥ 1000 nM and < 10000 nM and 'D' indicates an EC_{50} ≥ 10000 nM and < 100000 nM. For CC_{50}, the values are reported in micromolar (μm), 'A' indicates a CC_{50} ≥ 10000 nM and 'B' indicates a CC_{50} ≥ 1 μm and <10 μm.

Table 2

Compound	EC_{50}	CC_{50}
1	A	>100
2	B	>100
3	A	>100
4	A	>100
5	B	>100
6	A	>100
7	A	>100
8	B	>100
9	A	>100
10	B	A
11	B	>100
12	A	>100
13	B	>100
14	A	>100
16	A	>100
17a	A	>100
17b	B	>100
18	A	>100
19	A	>100
20	A	>100
21	A	>100
22	C	>100
23	C	>100

Compound	EC_{50}	CC_{50}
24	A	>100
25	A	>100
26	B	>100
27	A	>100
28	A	>100
29	A	A
30	A	>100
31	B	>100
32	A	>100
33	A	>100
34	A	>100
35	B	>100
36	B	>100
37	>10 μM	>100
38	C	>100
39	A	>100
40	A	>100
41	A	>100
42	B	>100
43	B	>100
44	B	B
45	C	>100
46	B	A

Compound	EC_{50}	CC_{50}
47	B	>100
48	A	>100
49	B	>100
53	C	A

Compound	EC_{50}	CC_{50}
54	>10 μM	>100
55	C	>100
56	>10 μM	>100
57	B	>100

SARS-CoV-2 infection model in VeroE6 cells

[0480] The SARS-CoV-2 antiviral assay is derived from the previously established SARS-CoV assay (PMID: 15961169). In this assay, fluorescence of Vero E6-eGFP cells declines after infection with SARS-CoV-2 due to the cytopathogenic effect of the virus. In the presence of an antiviral compound, the cytopathogenicity is inhibited and the fluorescent signal rescued. On day -1, the test compounds were serially diluted in assay medium (DMEM supplemented with 2% v/v FCS). The plates were incubated (37 °C, 5% CO_2 and 95% relative humidity) overnight. On day 0, the diluted compounds were mixed with Vero E6-eGFP cells (25,000 cells/well), SARS-CoV-2-GHB-03021/2020 (20 $TCID_{50}$/well) and the MDR1-inhibitor CP-100356 (final concentration 0.5 μM) in 96-well blackview plates (Greiner Bio-One, Vilvoorde, Belgium). The plates were incubated in a humidified incubator at 37 °C and 5% CO_2. At 4 days p.i., the wells were examined for eGFP expression using an argon laser-scanning microscope. The microscope settings were excitation at 488 nm and emission at 510 nm and the fluorescence images of the wells were converted into signal values. The results were expressed as EC_{50} values defined as the concentration of compound achieving 50% rescue from the virus-reduced eGFP signals as compared to the untreated virus-infected control cells. Toxicity of compounds in the absence of virus was evaluated in a standard MTS-assay as described previously (PMID: 22575574).

[0481] Table 3 indicates related EC_{50} and CC_{50} values for the tested compounds 'A' indicates an $EC_{50} < 100$ nM, 'B' indicates an EC_{50} of ≥ 100 nM, < 1000 nM, 'C' indicates an $EC_{50} \geq 1000$ nM and < 10000 nM and 'D' indicates an $EC_{50} \geq 10000$ nM and < 50000 nM. For CC_{50}, the values are reported in micromolar (μm). 'A' indicates a $CC_{50} \geq 10$ μm. 'B' indicates a $CC_{50} \geq 1$ μm and <10 μm.

Table 3

Compound	VeroE6+CP (EC_{50})	VeroE6+CP (CC_{50})
1	A	>50
2	A	>50
3	A	>50
4	B	>50
5	C	>50
6	C	>50
7	A	>50
8	B	>50
9	A	>50
10	B	>50
11	B	>50
12	A	>50
13	A	>50
16	A	>50
17a	A	>50
17b	B	>50
18	A	>50
19	B	>50
20	A	>50
21	A	>50
22	C	>50
23	B	>50
24	B	>50
25	B	>50
26	B	>50
27	A	> 10
28	A	> 10
29	A	> 10

Compound	VeroE6+CP (EC_{50})	VeroE6+CP (CC_{50})
30	A	> 10
31	B	>50
32	A	>50
33	A	>50
34	A	>50
35	B	>50
36	B	>50
37	C	>50
38	B	>50
39	A	>50
40	A	>50
41	A	>50
42	B	>50
43	B	>50
44	C	A
45	C	>100
46	B	A
47	B	>50
48	A	>50
49	B	>50
53	B	>50
54	C	>50
55	B	>50
56	C	>50
57	B	>50
58	D	>50
59	A	>50

[0482] Tables 2 and 3 demonstrate that compounds described herein (including pharmaceutically acceptable salts thereof) can effectively inhibit and treat a coronavirus.

EXAMPLE C
PICORNAVIRUS & NOROVIRUS ASSAYS

[0483] Compounds of Formula (I), including pharmaceutically acceptable salts thereof, are tested following a protocol similar to the protocol described in one of the following articles: Kim et al., Journal of Virology (2012) 86(21):11754-11762, Zhang et al,

JACS (2020) (https://dx.doi.org/10.1021/acs.jmedchem.9b01828), and U.S. Patent No. 9,603,864.

[0484] The protocols of Kim et al., and Zhang et al., can be used to test for activity against a coronavirus.

EXAMPLE D

[0485] For the cathepsin L assay, 10 pM of human cathepsin L (R&D Systems; Minneapolis, MN) was preincubated for 30 mins with test compounds. Reactions were initiated by the addition of a peptide substrate Z-FR-AMC (final concentration 2 μM, Anaspec; Fremont, CA). Fluorescence was measured at 2-minute intervals for 30 mins using a 355/460 excitation/emission filter module on an Envision plate reader (Perkin Elmer; Waltham, MA). The IC_{50} values were calculated for each assay by fitting the curves using a four-parameter equation in GraphPad Prism.

[0486] Table 4 indicates related IC_{50} values for the tested compounds where 'A' indicates an $IC_{50} \geq 10000$ nM, 'B' indicates an IC_{50} of ≥ 1000 nM and < 10000 nM, 'C' indicates an $IC_{50} \geq 100$ nM and < 1000 nM, 'D' indicates an $IC_{50} < 100$ nM.

Table 4

Compound	Cathepsin L IC_{50}
1	A
2	A
3	A
4	A
5	A
6	A
7	A
8	A
9	A
10	A
11	A
12	A
13	A
14	A
15	A
16	A
17a	A

Compound	Cathepsin L IC_{50}
17b	A
18	A
19	A
20	A
21	A
22	A
23	A
24	A
25	A
26	A
27	A
28	A
29	A
30	A
31	A
32	A
33	A

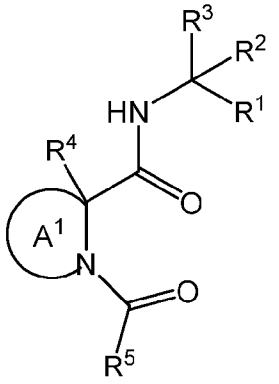
Compound	Cathepsin L IC_{50}
34	A
35	A
36	A
37	A
38	A
39	A
40	A
41	A
42	A
43	A
44	A
45	A

Compound	Cathepsin L IC_{50}
46	A
47	A
48	A
49	A
50	A
51	A
53	A
54	A
55	A
56	A
57	A

[0487] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the present disclosure.

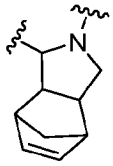
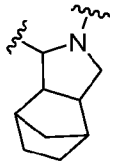
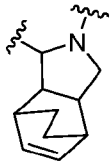
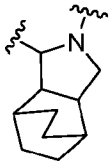
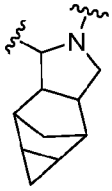
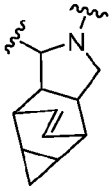
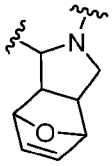
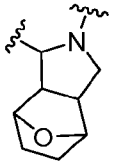
WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein:

Ring A^1 is  ,  ,  ,  ,  ,  ,  and  , and wherein Ring A^1 is optionally substituted with one or more moieties independently selected from the group consisting of deuterium, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl;

R^1 is selected from the group consisting of cyano, an unsubstituted or a substituted C_{2-5} alkynyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted ketoamide, –CH(OH)-($S(=O)_2$-O^-), –CH(OH)(($P=O)(OR^6)_2$) and –$C(=O)CH_2$-O-(($P=O)(OR^7)_2$);

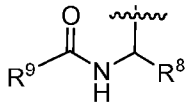
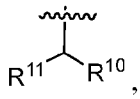
each R^6 and each R^7 are independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl);

R^2 is hydrogen, deuterium or halogen;

R^3 is an unsubstituted or a substituted monocyclic nitrogen-containing

heterocyclyl(C_{1-4} alkyl), an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl), an unsubstituted or a substituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl);

R^4 is hydrogen, deuterium or halogen;

R^5 is  ,  , a substituted monocyclic C_{3-6} cycloalkyl or a substituted 4- to 6-membered monocyclic heterocyclyl;

R^8 and R^{10} are independently selected from the group consisting of an unsubstituted or a substituted C_{2-6} alkyl, an unsubstituted or a substituted C_{2-6} alkenyl, an unsubstituted or a substituted C_{2-6} alkynyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted bicyclic C_{5-8} cycloalkyl and an unsubstituted or a substituted monocyclic 4- to 6-membered heterocyclyl,

wherein when the C_{2-6} alkyl is substituted, the C_{2-6} alkyl is substituted 1, 2, 3 or 4 times with a substituent independently selected from the group consisting of halogen, cyano, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl and an unsubstituted C_{1-4} alkoxy;

wherein when the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted, the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted 1, 2, 3 or 4 times with a substituent independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl and an unsubstituted C_{1-4} alkoxy; and

R^9 is selected from the group consisting of an unsubstituted C_{1-6} alkyl, an unsubstituted C_{1-6} haloalkyl, a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted bicyclic C_{5-6} cycloalkyl, an unsubstituted or a substituted monocyclic heteroaryl and an unsubstituted or a substituted monocyclic heterocyclyl, wherein the substituted monocyclic C_{3-6} cycloalkyl is substituted 1, 2, 3 or 4 times with a substituent independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted

C_{1-4} haloalkyl and an unsubstituted monocyclic C_{3-6} cycloalkyl; and

R^{11} is an optionally substituted monocyclic 4- to 6-membered heterocyclyl, $-(NH)_m-$ an optionally substituted 5- to 6-membered monocyclic heteroaryl, –O–an optionally substituted C_{1-6} alkyl, –O–an optionally substituted C_{3-8} cycloalkyl and –O–an optionally substituted C_{3-8} cycloalkyl(C_{1-4} alkyl), wherein m is 0 or 1.

2. The compound of Claim 1, wherein R^1 is an unsubstituted or a substituted ketoamide.

3. The compound of Claim 1, wherein R^1 is an unsubstituted or a substituted acyl.

4. The compound of Claim 1, wherein R^1 is $-CH(OH)-(S(=O)_2-O^-)$.

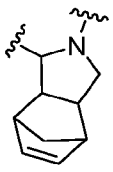
5. The compound of Claim 1, wherein R^1 is $-CH(OH)((P=O)(OR^6)_2)$, wherein each R^6 are independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl).

6. The compound of Claim 1, wherein R^1 is $-C(=O)CH_2-O-((P=O)(OR^7)_2)$, wherein each R^7 are independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl).

7. The compound of Claim 1, wherein R^1 is cyano.

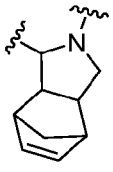
8. The compound of Claim 1, wherein R^1 is an unsubstituted or a substituted C_{2-5} alkynyl.

9. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted



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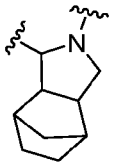
10. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted

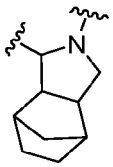


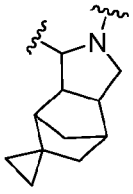
substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an

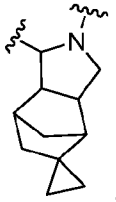
unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl.

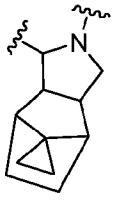
11. The compound of Claim 10, wherein Ring A^1 is  .

12. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted  .

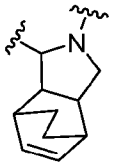
13. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted  substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl.

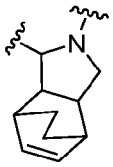
14. The compound of Claim 13, wherein Ring A^1 is  .

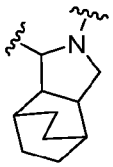
15. The compound of Claim 13, wherein Ring A^1 is  .

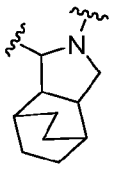
16. The compound of Claim 13, wherein Ring A^1 is  .

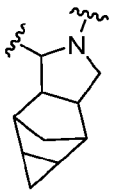
17. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted



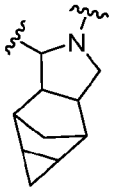
18. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted  substituted with one or more moieties independently selected from the group consisting of deuterium, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl.

19. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted 

20. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted  substituted with one or more moieties independently selected from the group consisting of deuterium, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl.

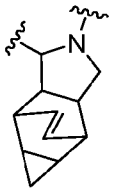
21. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted 

22. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted



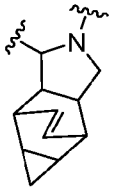
substituted with one or more moieties independently selected from the group consisting of deuterium, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl.

23. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted



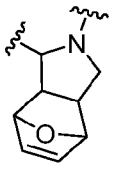
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24. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted



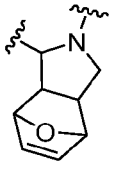
substituted with one or more moieties independently selected from the group consisting of deuterium, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl.

25. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted



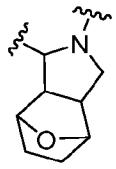
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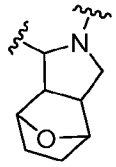
26. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted

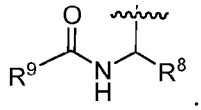


substituted with one or more moieties independently selected from the group consisting of deuterium, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic

cycloalkyl.

27. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted  .

28. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted  substituted with one or more moieties independently selected from the group consisting of deuterium, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl.

29. The compound of any one of Claims 1-28, wherein R^5 is  .

30. The compound of Claim 29, wherein R^8 is an unsubstituted C_{2-6} alkyl,

31. The compound of Claim 29, wherein R^8 is a substituted C_{2-6} alkyl.

32. The compound of Claim 29, wherein R^8 is an unsubstituted C_{2-6} alkenyl.

33. The compound of Claim 29, wherein R^8 is a substituted C_{2-6} alkenyl.

34. The compound of Claim 29, wherein R^8 is an unsubstituted C_{2-6} alkynyl.

35. The compound of Claim 29, wherein R^8 is a substituted C_{2-6} alkynyl.

36. The compound of Claim 29, wherein R^8 is an unsubstituted monocyclic C_{3-6} cycloalkyl.

37. The compound of Claim 29, wherein R^8 is a substituted monocyclic C_{3-6} cycloalkyl.

38. The compound of Claim 29, wherein R^8 is an unsubstituted bicyclic C_{5-8} cycloalkyl.

39. The compound of Claim 29, wherein R^8 is a substituted bicyclic C_{5-8} cycloalkyl.

40. The compound of Claim 29, wherein R^8 is an unsubstituted monocyclic 4- to 6-membered heterocyclyl.

41. The compound of Claim 29, wherein R^8 is a substituted monocyclic 4- to 6-membered heterocyclyl.

42. The compound of any one of Claims 29-41, wherein R^9 is an unsubstituted C_{1-6} alkyl.

43. The compound of any one of Claims 29-41, wherein R^9 is an unsubstituted C_{1-6} haloalkyl.

44. The compound of any one of Claims 29-41, wherein R^9 is an unsubstituted or substituted monocyclic C_{3-6} cycloalkyl.

45. The compound of any one of Claims 29-41, wherein R^9 is an unsubstituted or a substituted bicyclic C_{5-6} cycloalkyl.

46. The compound of any one of Claims 29-41, wherein R^9 is an unsubstituted or a substituted monocyclic heteroaryl or an unsubstituted or a substituted monocyclic heterocyclyl.

47. The compound of any one of Claims 1-28, wherein R^5 is  .

48. The compound of Claim 47, wherein R^{10} is an unsubstituted C_{2-6} alkyl,

49. The compound of Claim 47, wherein R^{10} is a substituted C_{2-6} alkyl.

50. The compound of Claim 47, wherein R^{10} is an unsubstituted C_{2-6} alkenyl.

51. The compound of Claim 47, wherein R^{10} is a substituted C_{2-6} alkenyl.

52. The compound of Claim 47, wherein R^{10} is an unsubstituted C_{2-6} alkynyl.

53. The compound of Claim 47, wherein R^{10} is a substituted C_{2-6} alkynyl.

54. The compound of Claim 47, wherein R^{10} is an unsubstituted monocyclic C_{3-6} cycloalkyl.

55. The compound of Claim 47, wherein R^{10} is a substituted monocyclic C_{3-6} cycloalkyl.

56. The compound of Claim 47, wherein R^{10} is an unsubstituted bicyclic C_{5-8} cycloalkyl.

57. The compound of Claim 47, wherein R^{10} is a substituted bicyclic C_{5-8} cycloalkyl.

58. The compound of Claim 47, wherein R^{10} is an unsubstituted monocyclic 4- to 6-membered heterocyclyl.

59. The compound of Claim 47, wherein R^{10} is a substituted monocyclic 4- to 6-membered heterocyclyl.

60. The compound of any one of Claims 47-59, wherein R^{11} is –an optionally substituted 5- to 6-membered monocyclic heteroaryl.

61. The compound of any one of Claims 47-59, wherein R^{11} is –(NH)–an optionally substituted 5- to 6-membered monocyclic heteroaryl.

62. The compound of any one of Claims 47-59, wherein R^{11} is an optionally substituted monocyclic heterocyclyl.

63. The compound of any one of Claims 47-59, wherein R^{11} is –O–an optionally substituted alkyl.

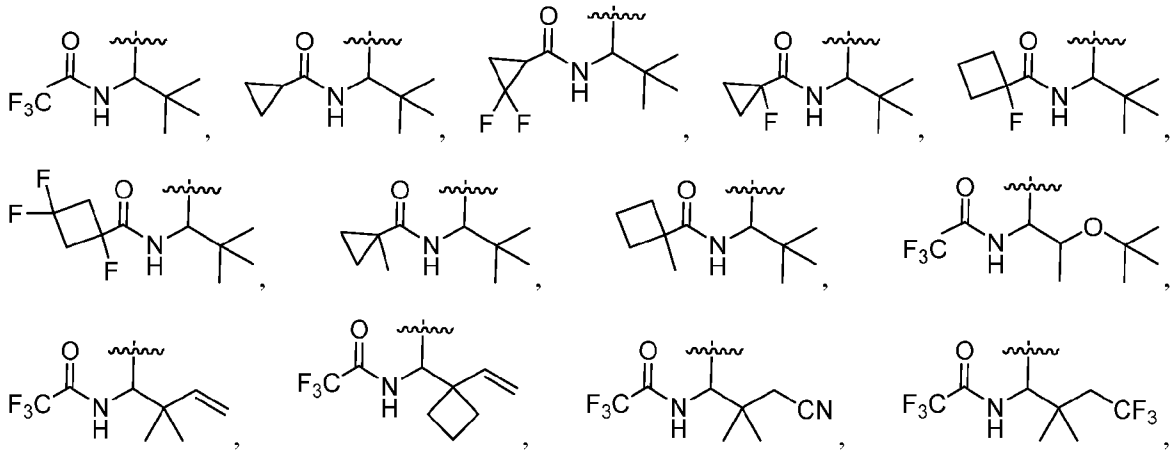
64. The compound of any one of Claims 47-59, wherein R^{11} is –O–an optionally substituted cycloalkyl.

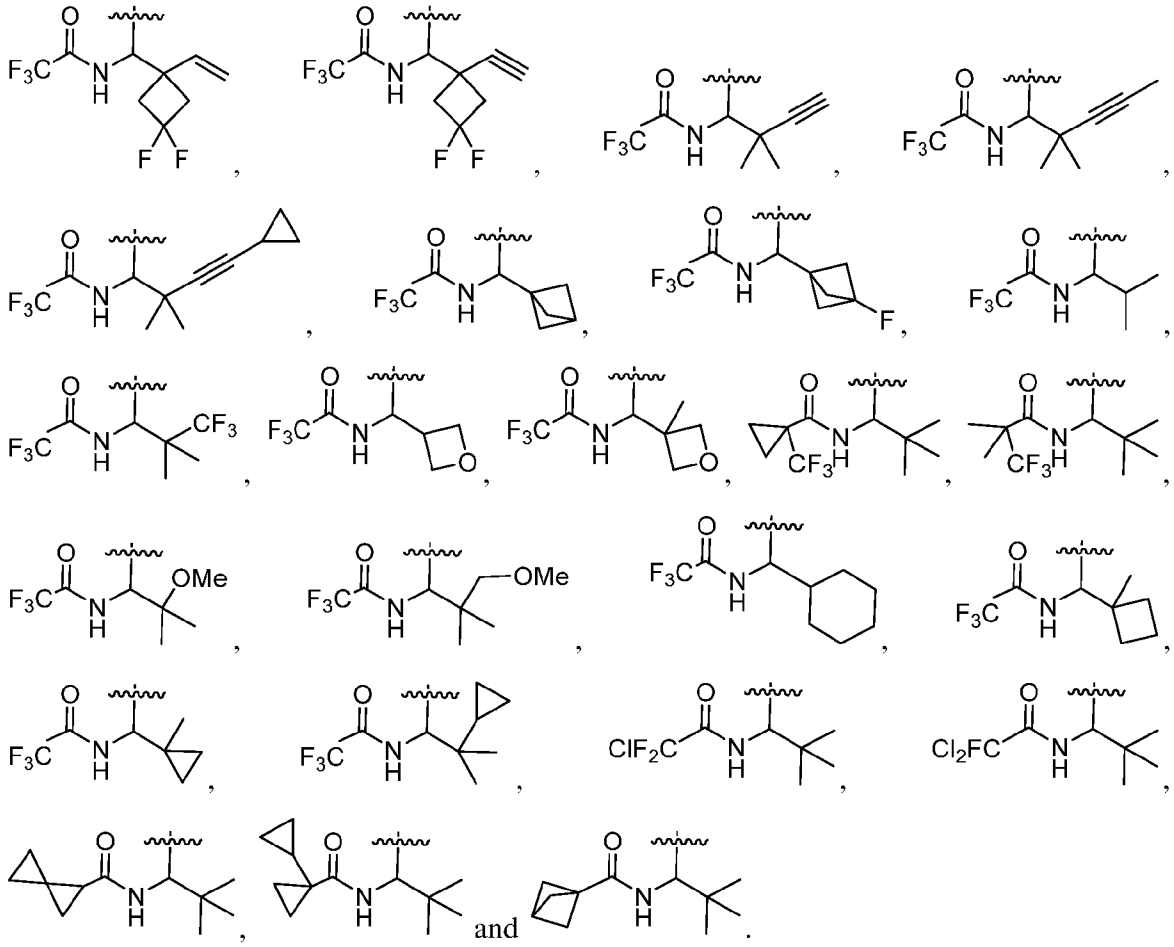
65. The compound of any one of Claims 47-59, wherein R^{11} is –O–an optionally substituted cycloalkyl(C_{1-4} alkyl).

66. The compound of any one of Claims 1-28, wherein R^5 is a substituted monocyclic C_{3-6} cycloalkyl.

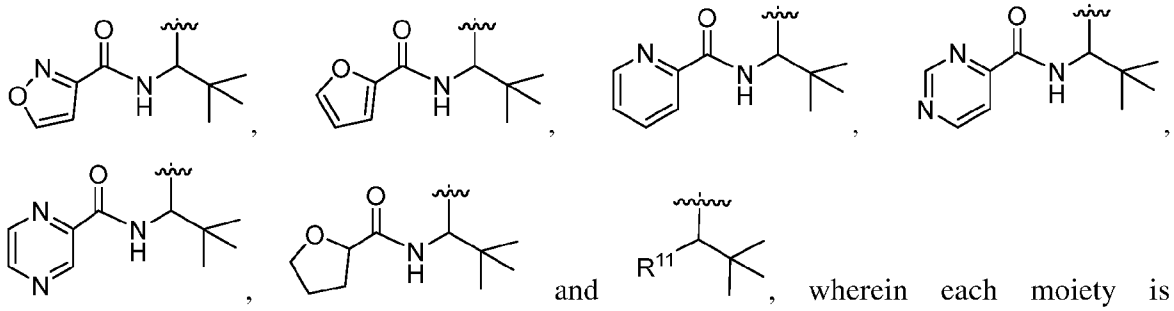
67. The compound of any one of Claims 1-28, wherein R^5 is a substituted 4- to 6-membered monocyclic heterocyclyl.

68. The compound of any one of Claims 1-28, wherein R^5 is selected from the group consisting of:





69. The compound of any one of Claims 1-28, wherein R^5 is selected from the group consisting of:



unsubstituted or substituted.

70. The compound of any one of Claims 1-69, wherein R^3 is an unsubstituted monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl).

71. The compound of any one of Claims 1-69, wherein R^3 is a substituted monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl).

72. The compound of Claim 70 or 71, wherein the monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) is a 5-membered monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl).

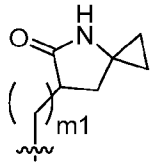
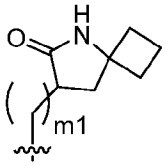
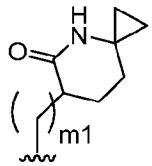
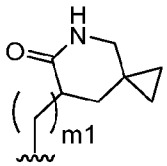
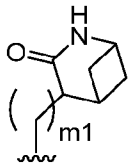
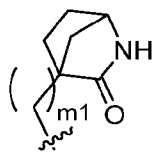
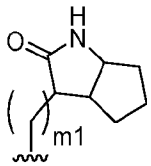
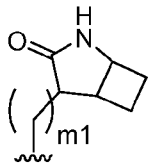
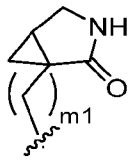
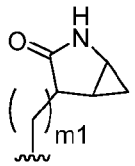
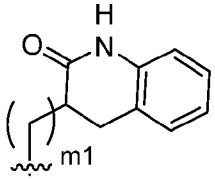
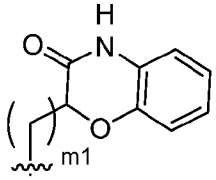
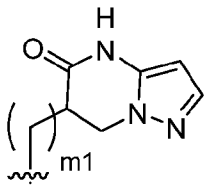
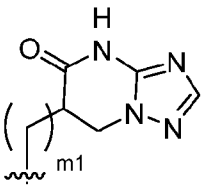
73. The compound of Claim 70 or 71, wherein the monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) is a 6-membered monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl).

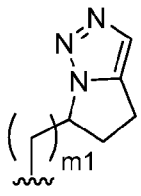
74. The compound of Claim 70 or 71, wherein the monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) is azepan-2-one(C_{1-4} alkyl), imidazolidin-2-one(C_{1-4} alkyl), tetrahydropyrimidin-2-one(C_{1-4} alkyl), pyrrolidin-2-one(C_{1-4} alkyl), piperidin-2-one(C_{1-4} alkyl), pyrazolidin-3-one(C_{1-4} alkyl) or morpholin-3-one(C_{1-4} alkyl).

75. The compound of any one of Claims 1-69, wherein R^3 is an unsubstituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl).

76. The compound of any one of Claims 1-69, wherein R^3 is a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl).

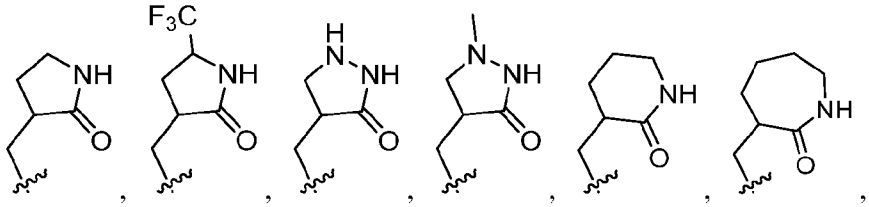
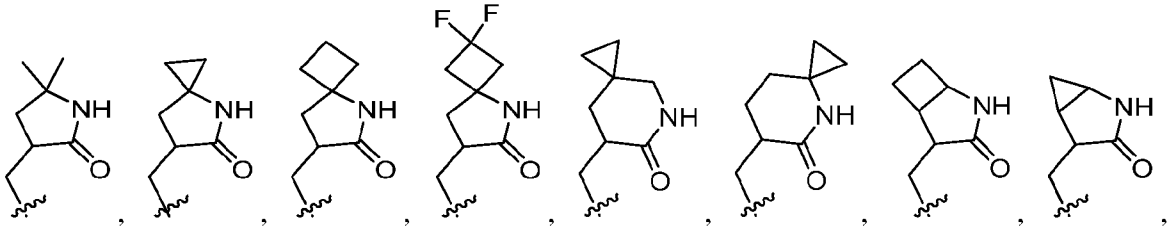
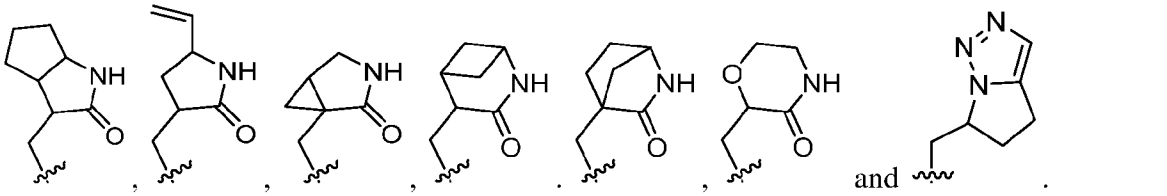
77. The compound of Claim 75 or 76, wherein the bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) is a 9-membered or 10-membered bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl).

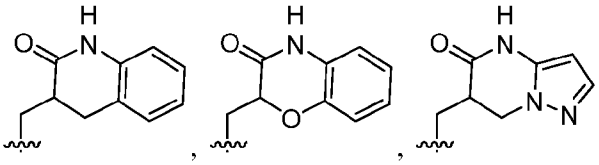
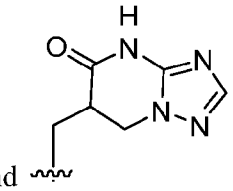
78. The compound of Claim 75 or 76, wherein R^3 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or

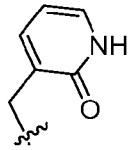

, wherein each m1 is independently 1, 2, 3 or 4.

79. The compound of any one of Claims 1-69, wherein R^3 is an unsubstituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl).

80. The compound of any one of Claims 1-69, wherein R^3 is a substituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl).

81. The compound of any one of Claims 1-69, wherein R^3 is selected from the group consisting of:  ,  ,  , and .

82. The compound of any one of Claims 1-69, wherein R^3 is selected from the group consisting of:  , and  .

83. The compound of any one of Claims 1-69, wherein R^3 is  .

84. The compound of any one of Claims 1-83, wherein R^2 is hydrogen.

85. The compound of any one of Claims 1-83, wherein R^2 is deuterium.

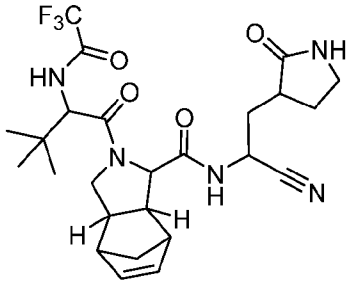
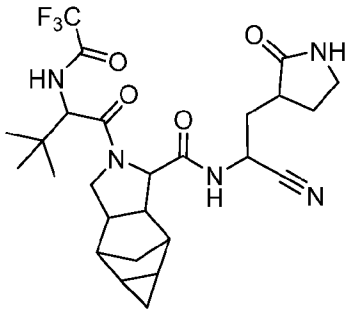
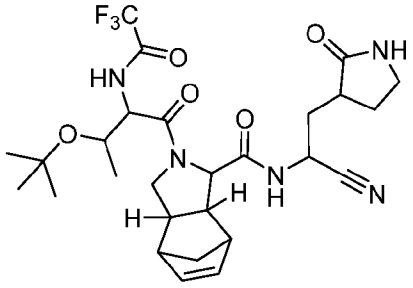
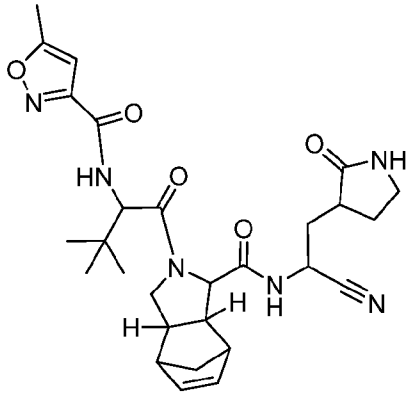
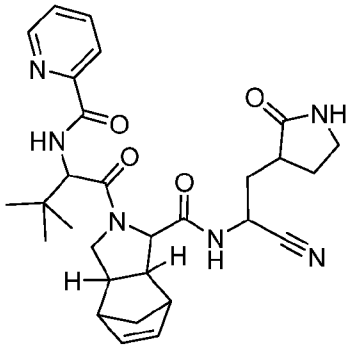
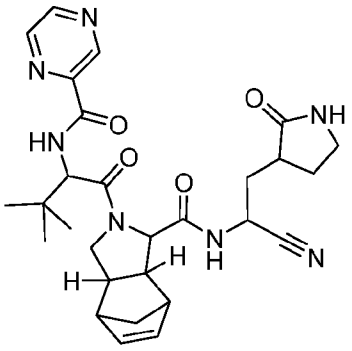
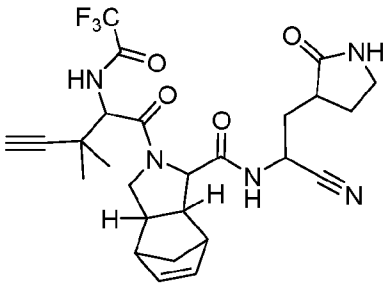
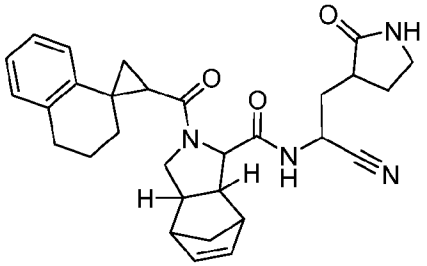
86. The compound of any one of Claims 1-83, wherein R^2 is halogen.

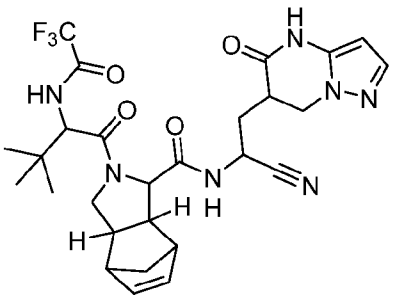
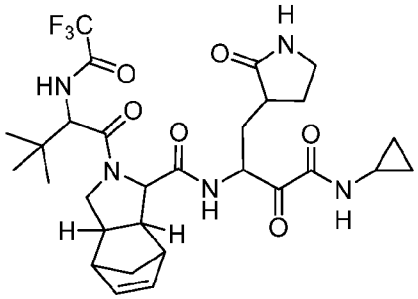
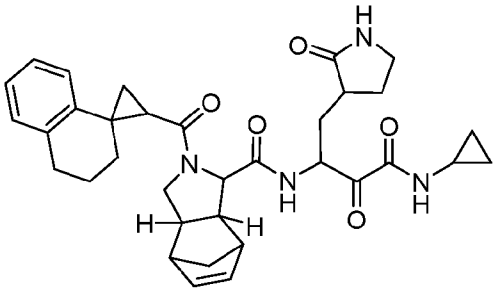
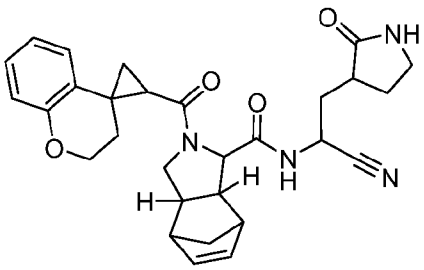
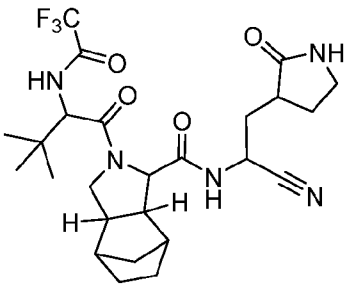
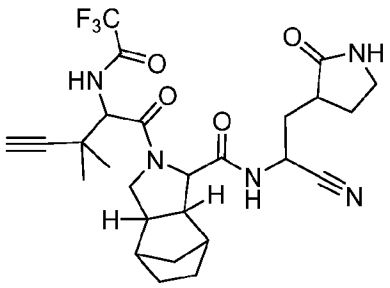
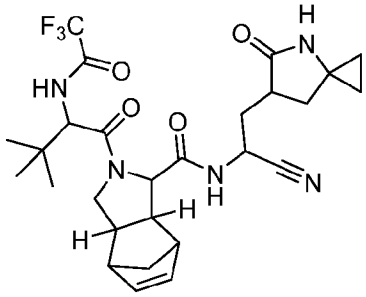
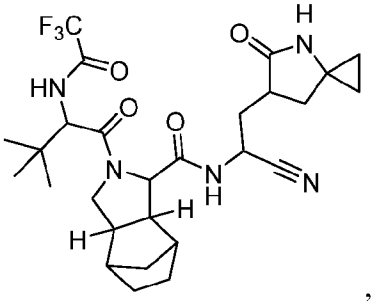
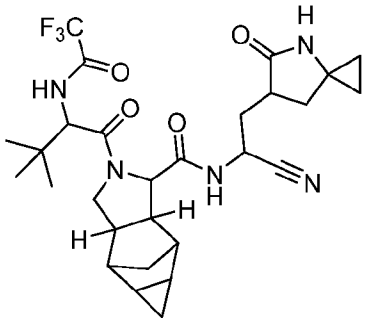
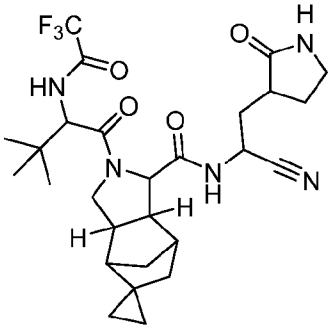
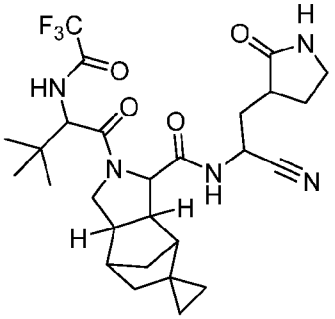
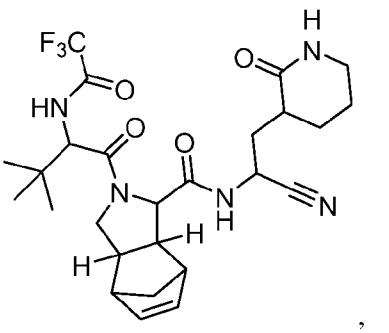
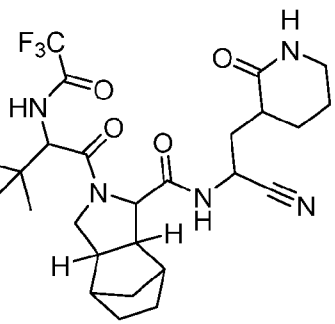
87. The compound of any one of Claims 1-86, wherein R^4 is hydrogen.

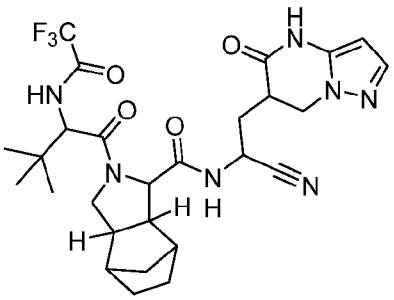
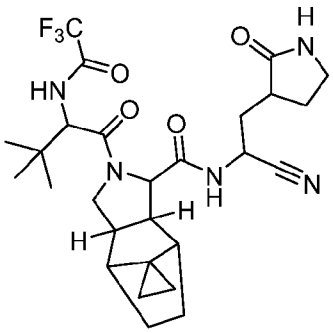
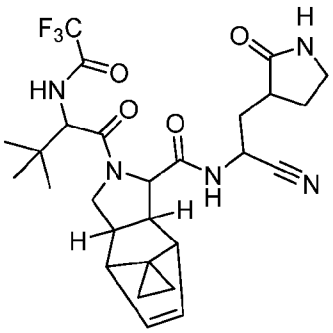
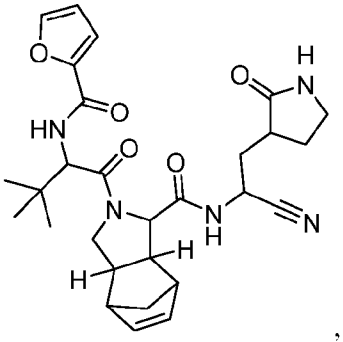
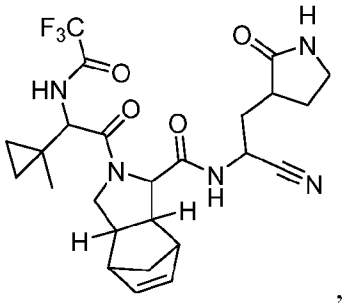
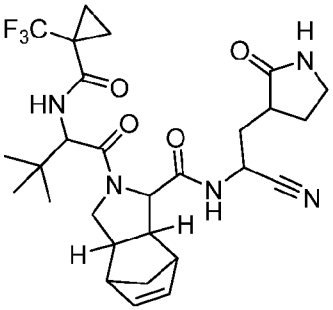
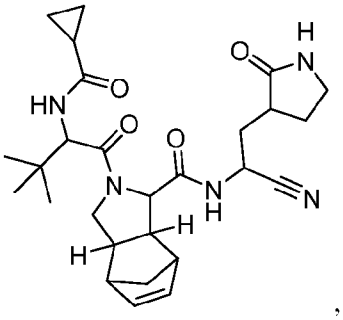
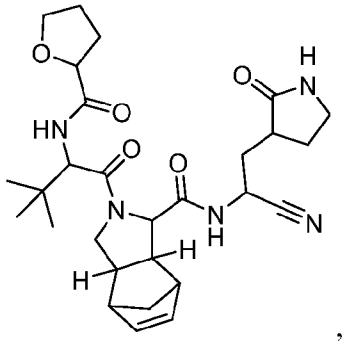
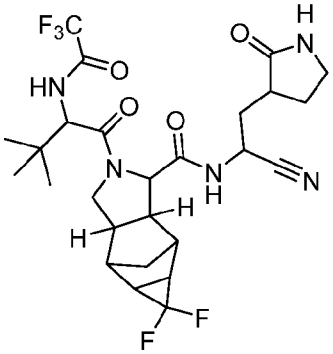
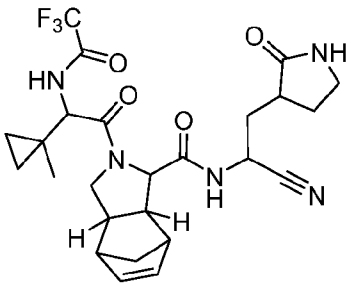
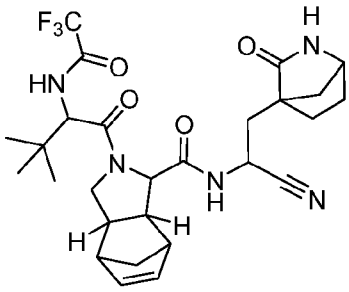
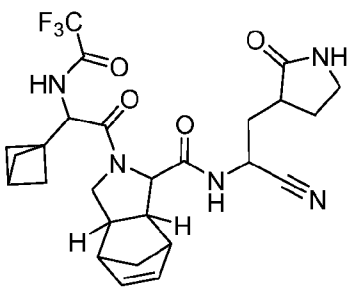
88. The compound of any one of Claims 1-86, wherein R^4 is deuterium.

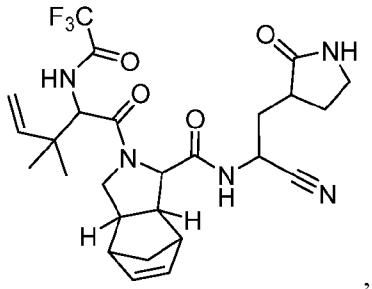
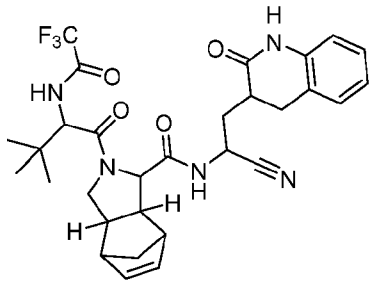
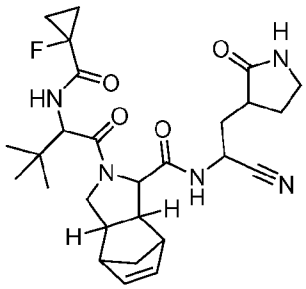
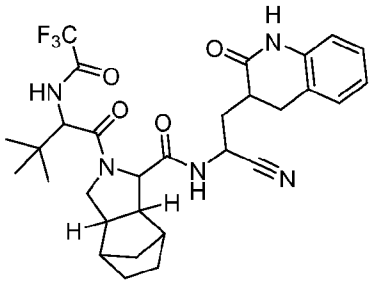
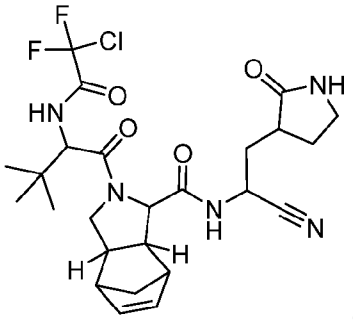
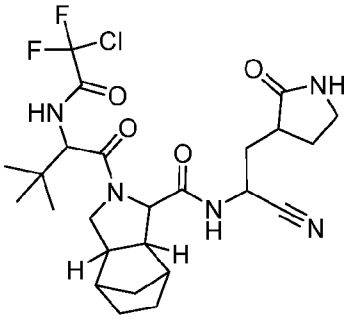
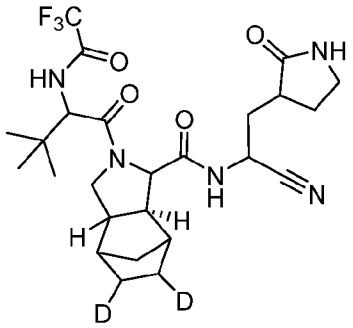
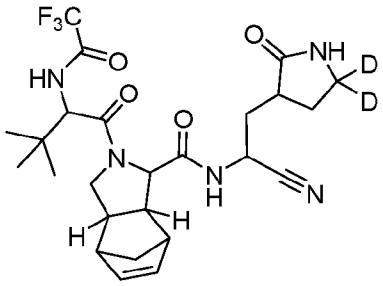
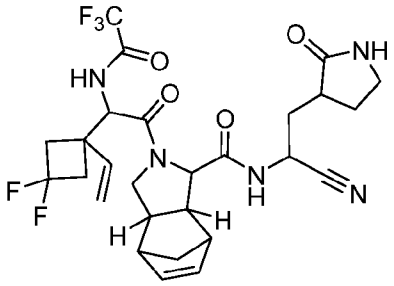
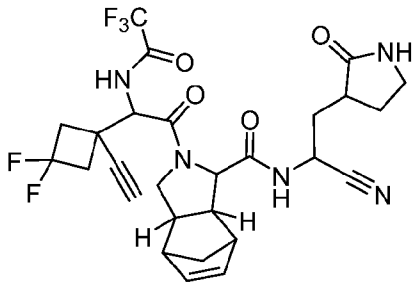
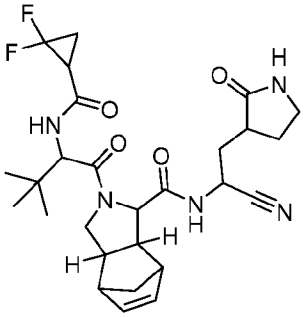
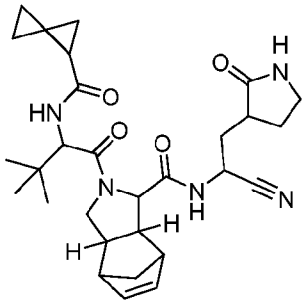
89. The compound of any one of Claims 1-86, wherein R^4 is halogen.

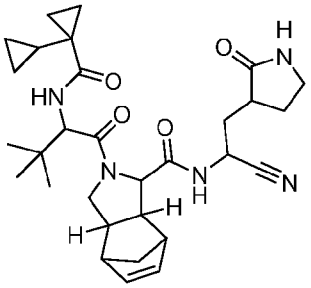
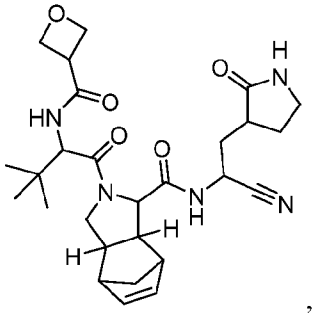
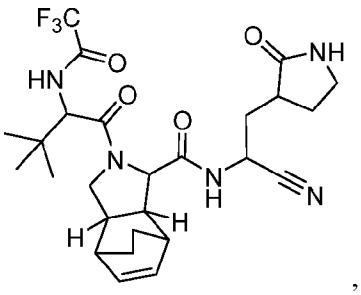
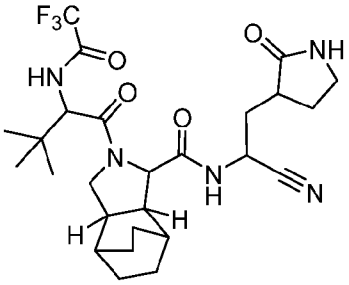
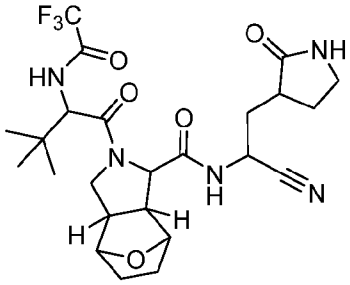
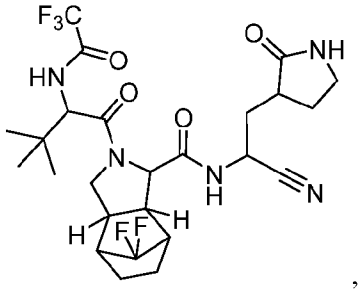
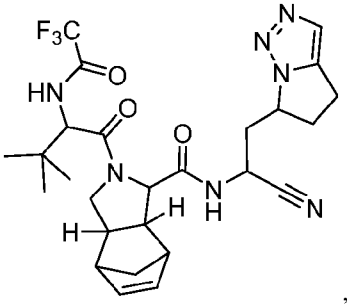
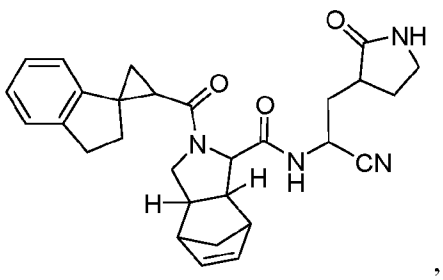
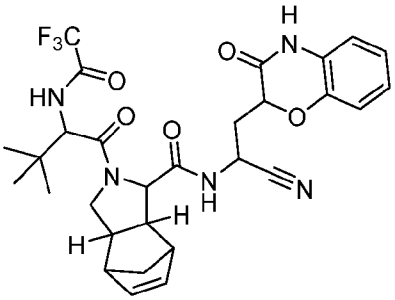
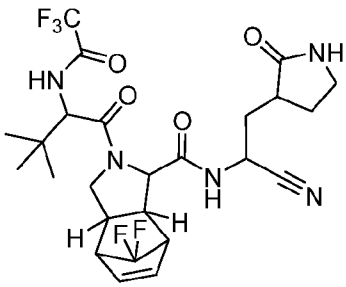
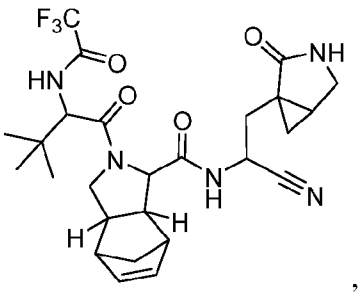
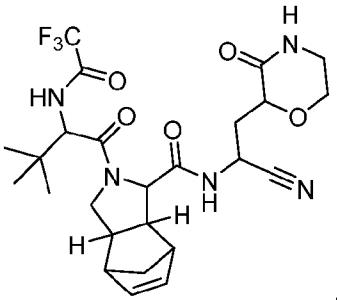
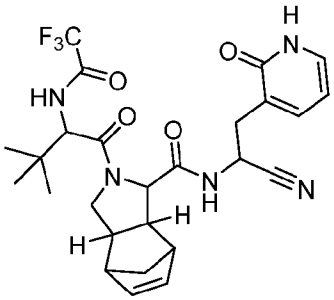
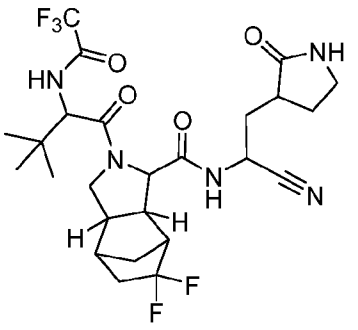
90. The compound of Claim 1, wherein the compound is selected from the group consisting of:

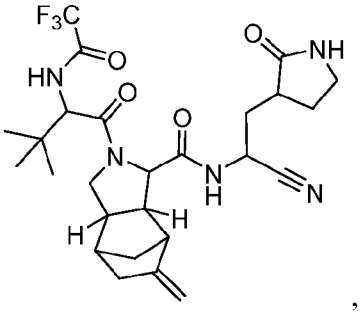
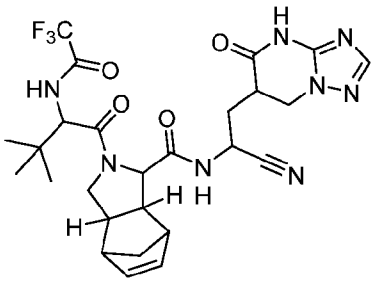
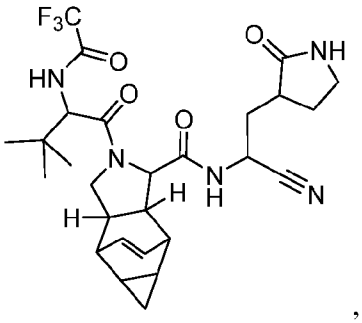
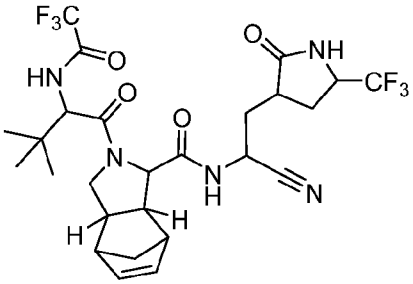
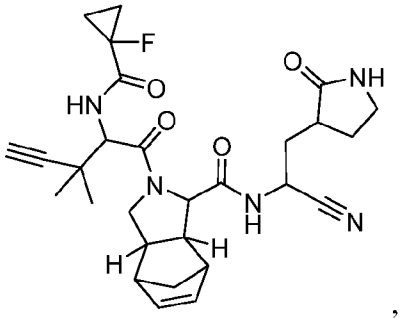
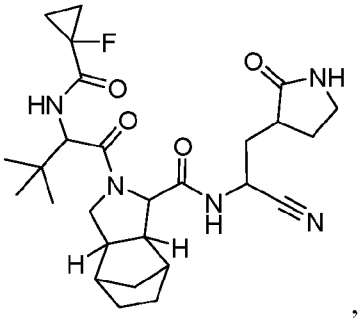
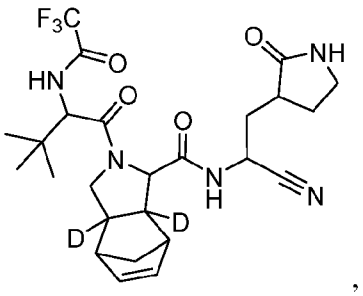
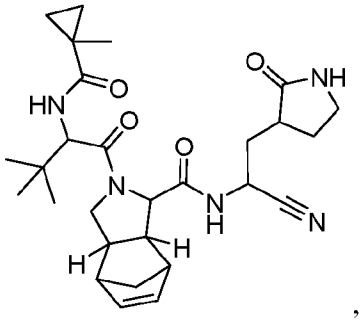
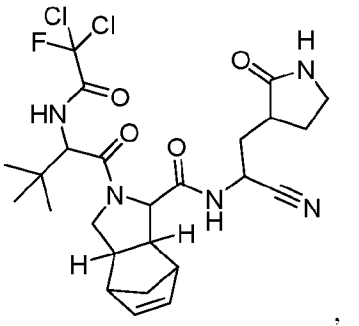
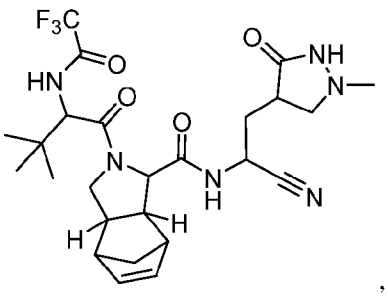
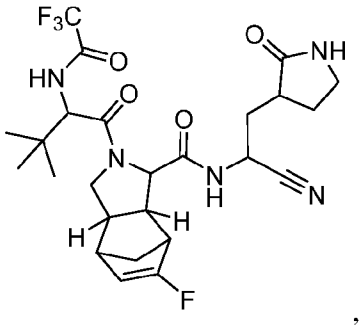

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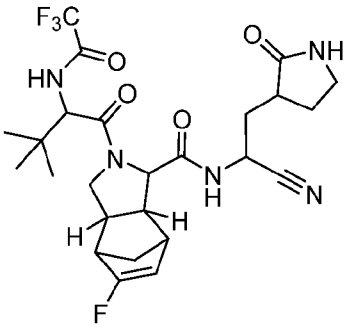
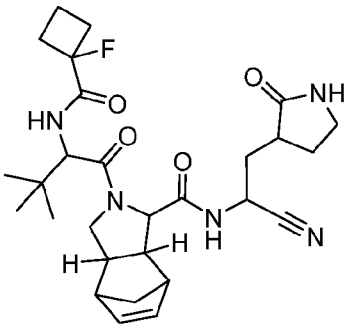
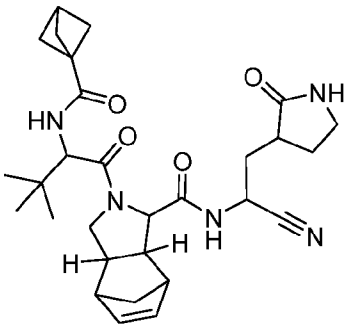
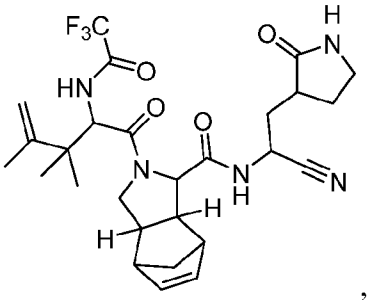
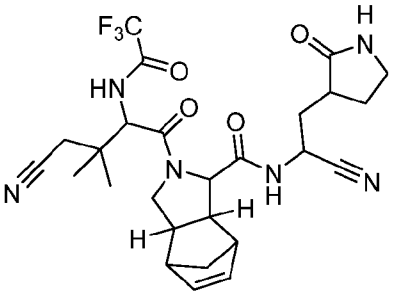
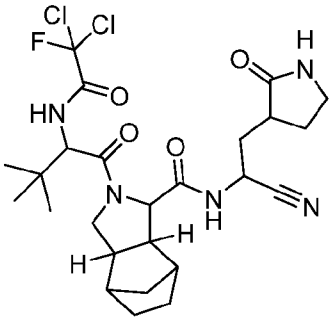
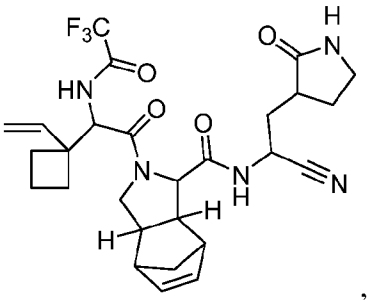
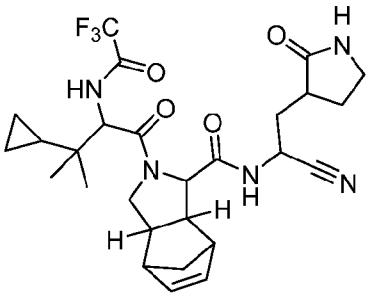
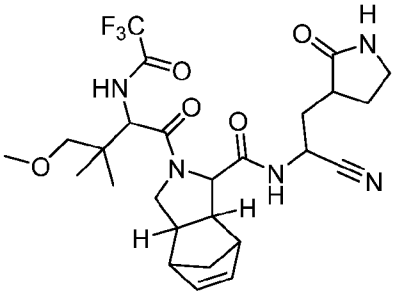
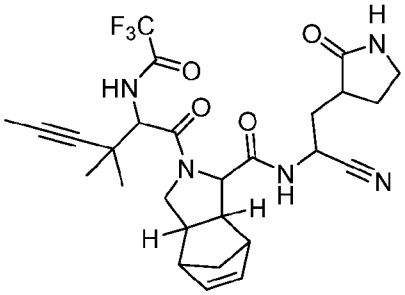
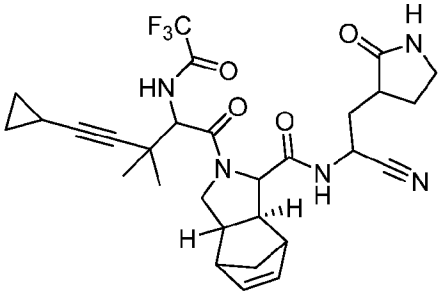
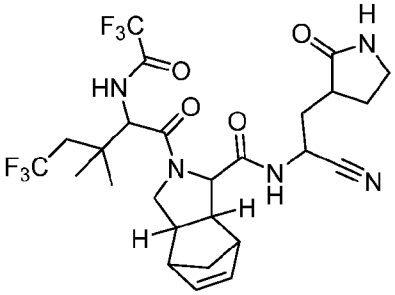

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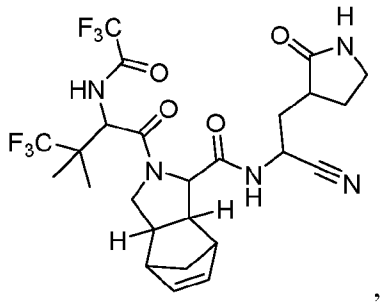
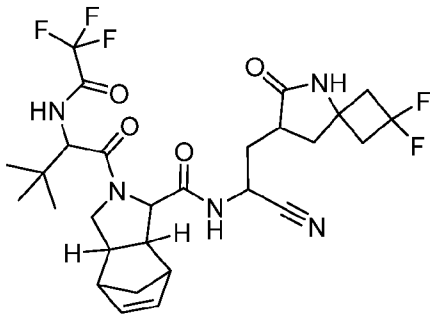
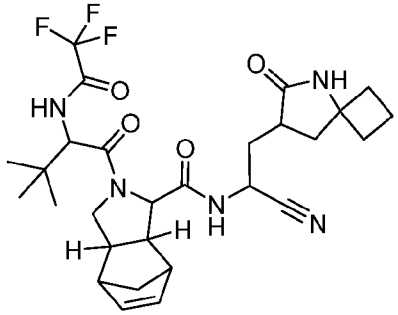
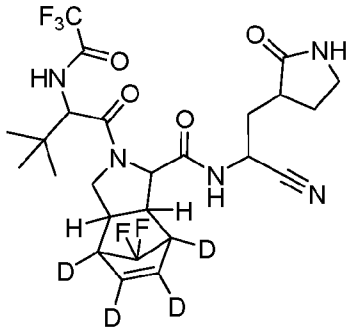
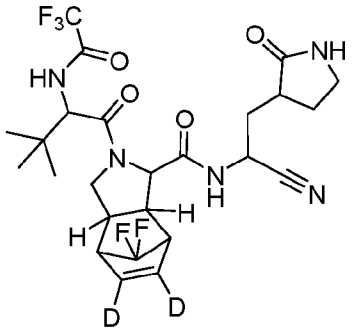
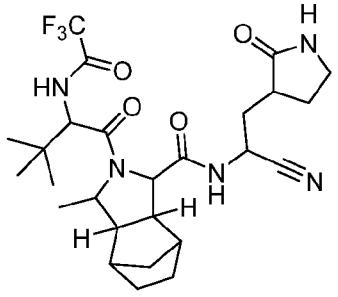
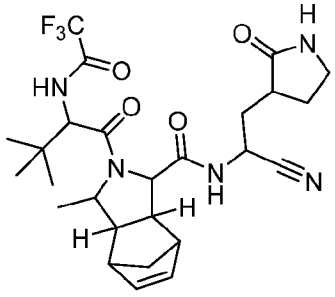
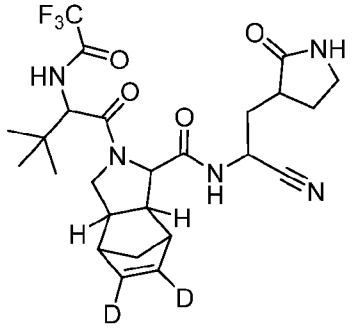

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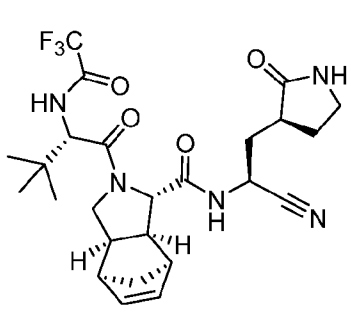
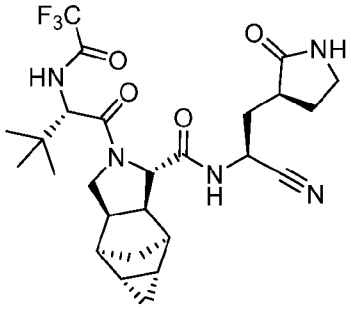
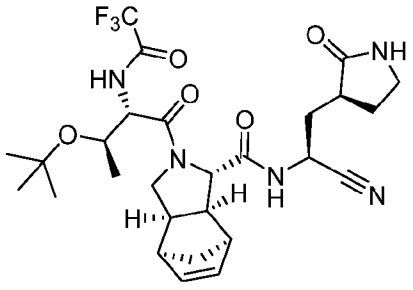
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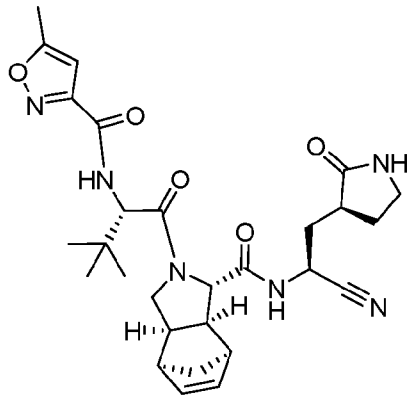
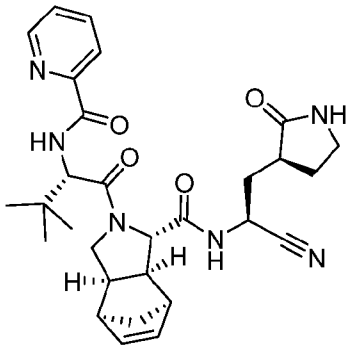
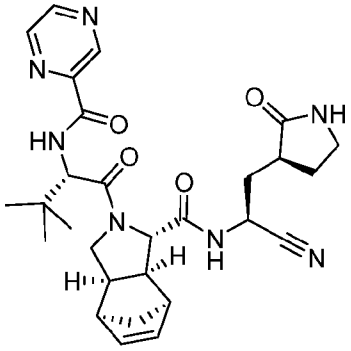
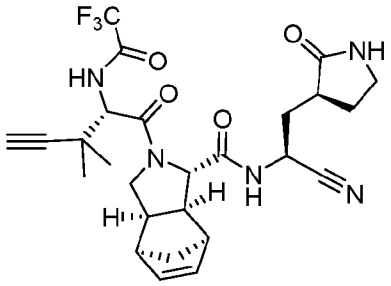
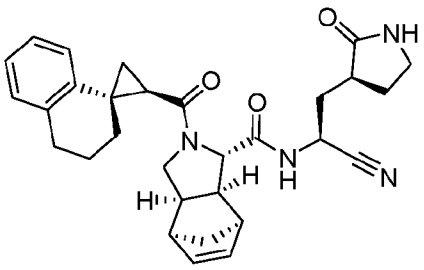
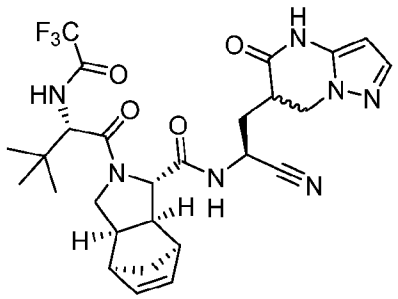
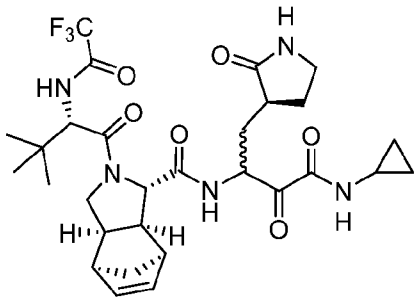
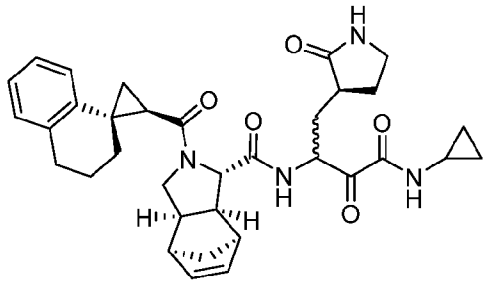
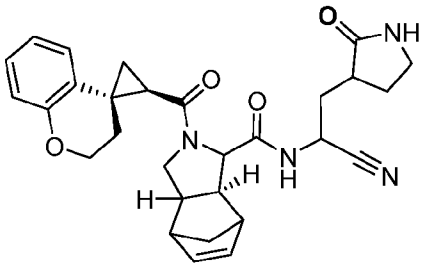
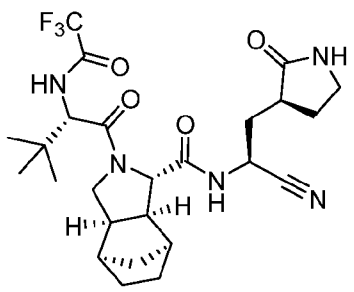
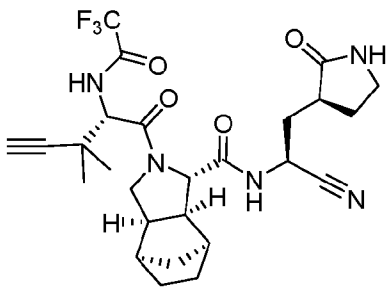
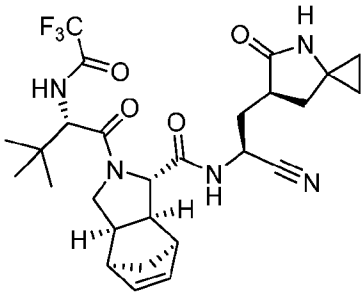
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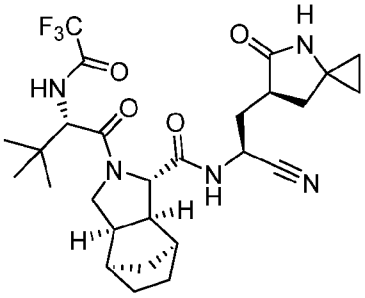
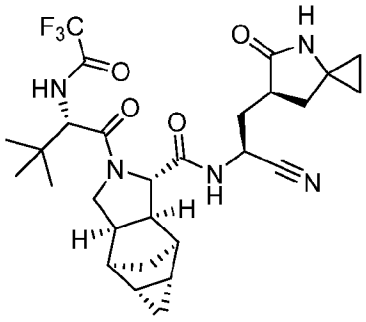
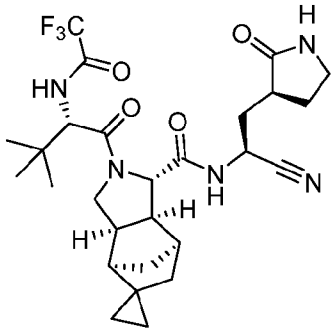
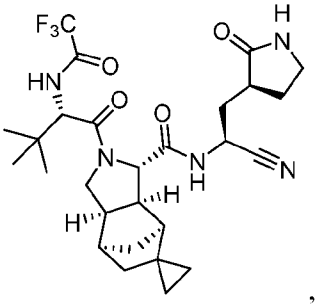
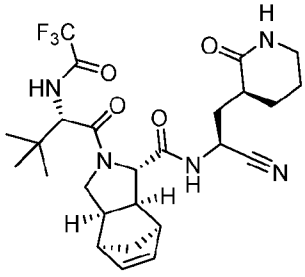
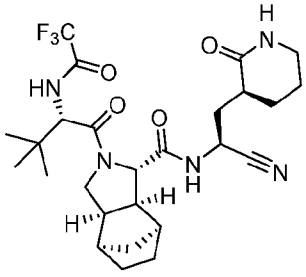
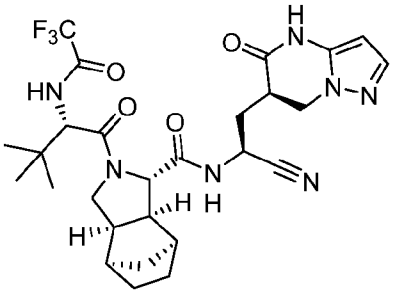
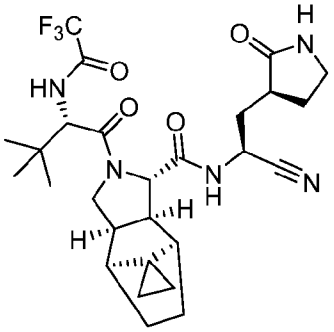
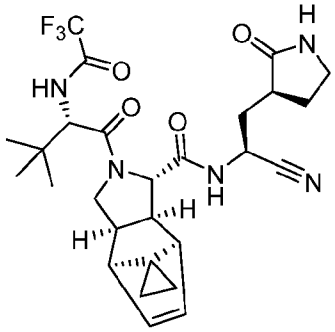
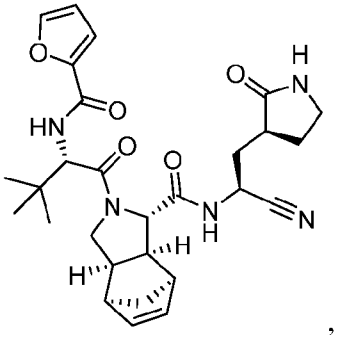
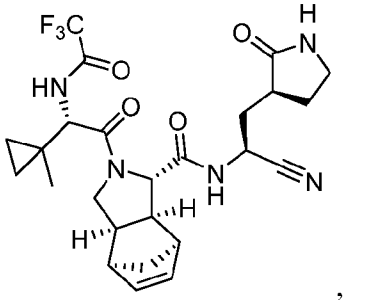
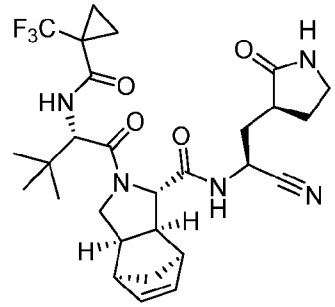

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and

, or a pharmaceutically acceptable salt of any of the foregoing.

91. The compound of Claim 1, wherein the compound is selected from the group consisting of:


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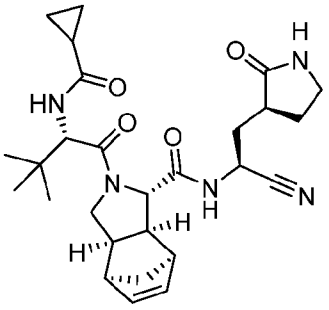
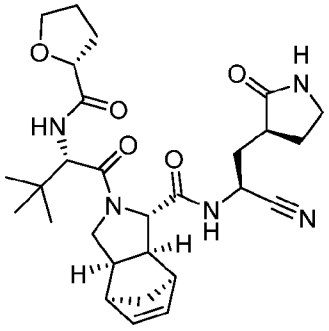
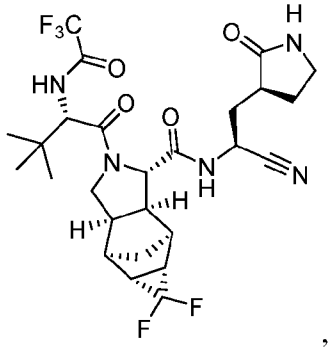
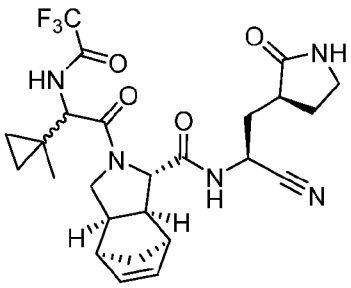
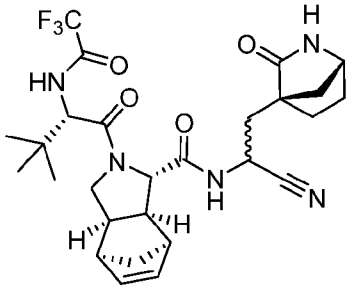
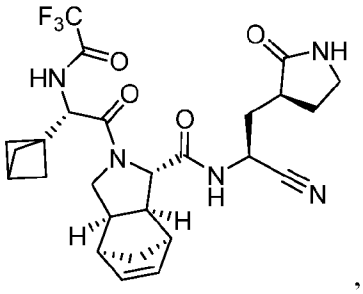
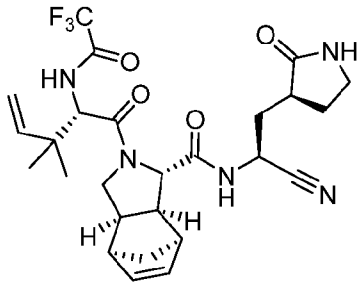
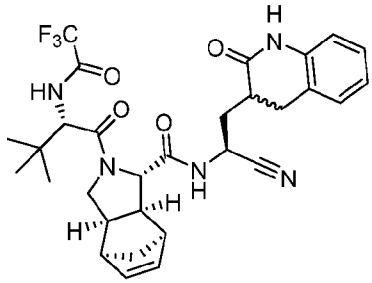
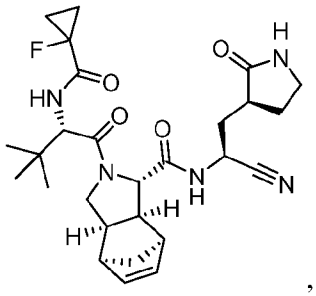
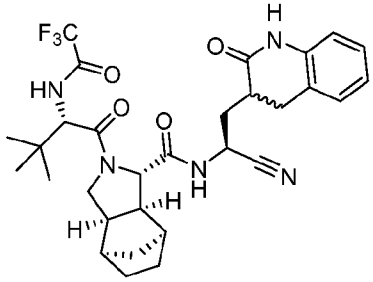
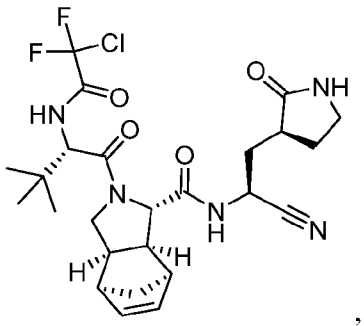
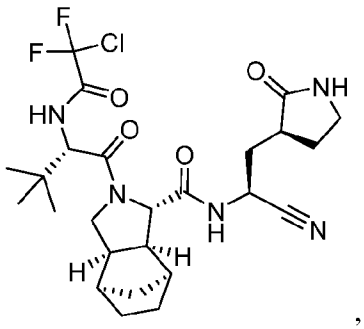

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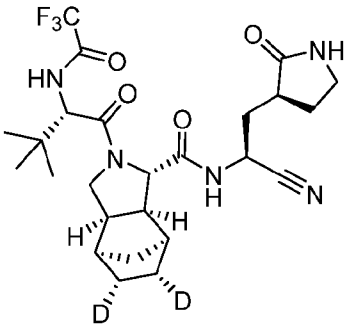
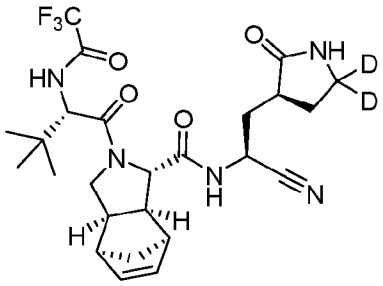
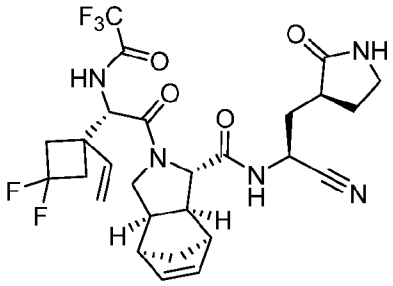
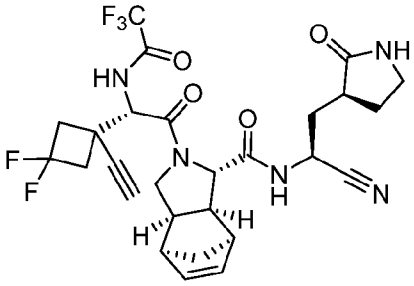
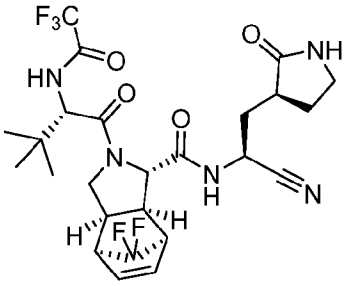
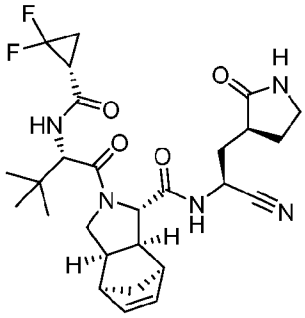
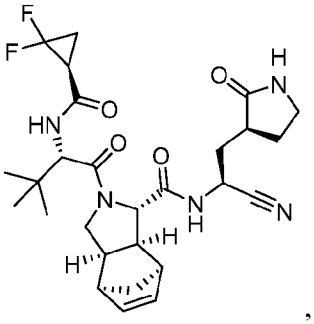
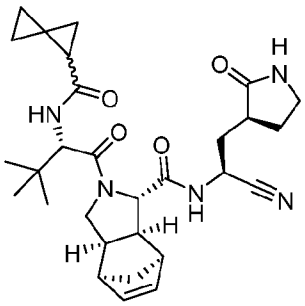
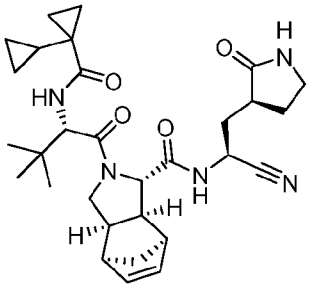
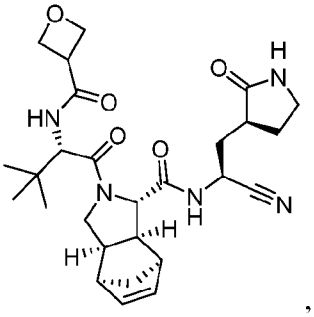
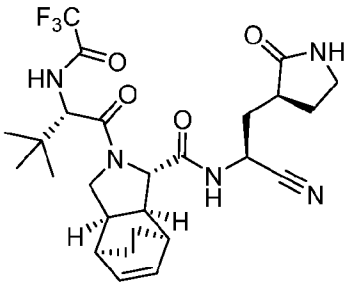
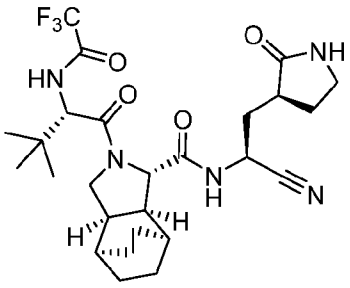
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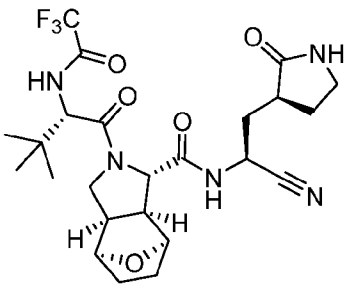
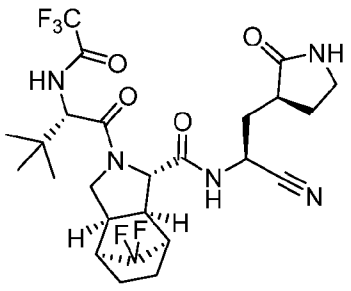
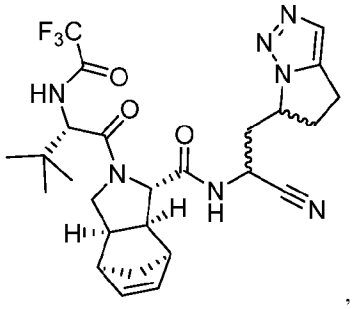
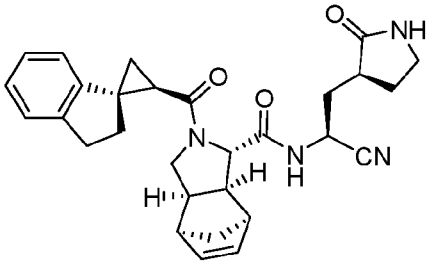
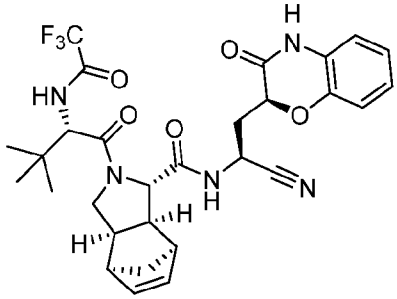
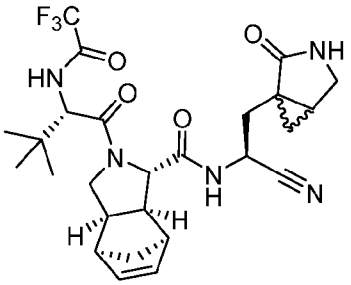
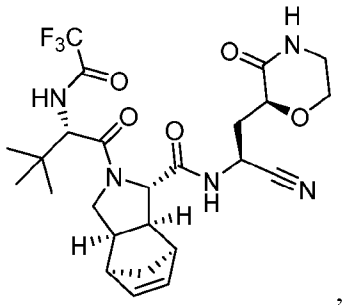
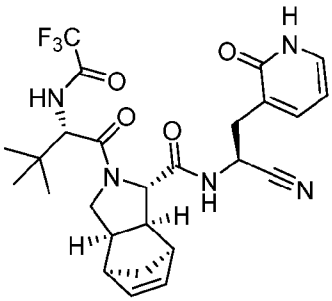
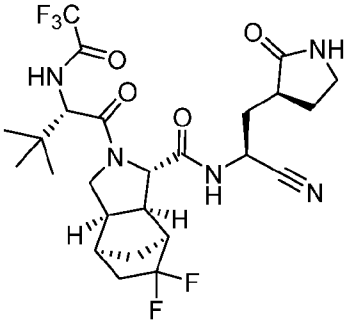
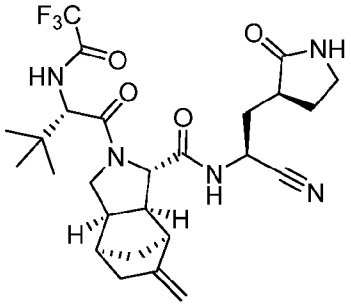
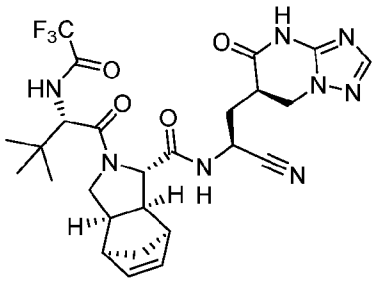
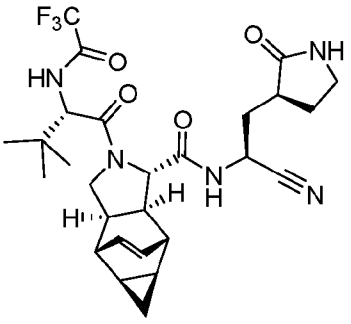
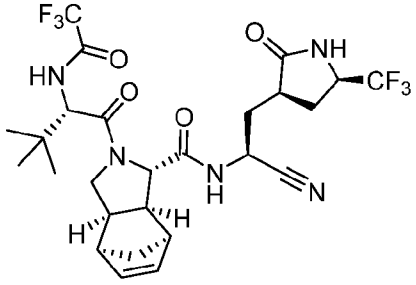

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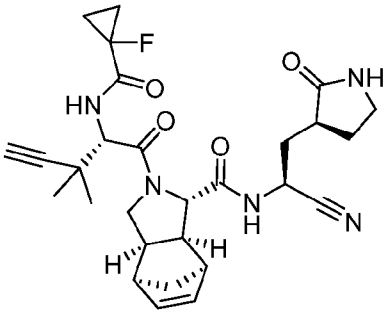
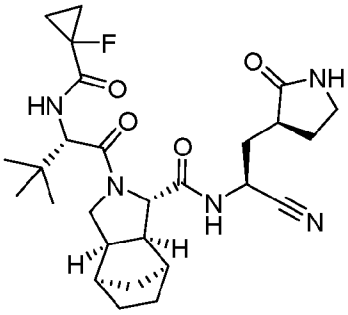
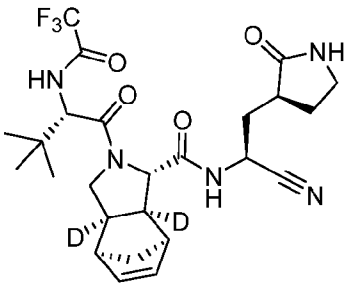
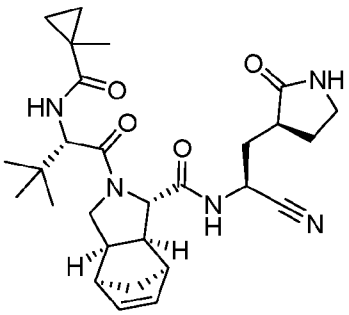
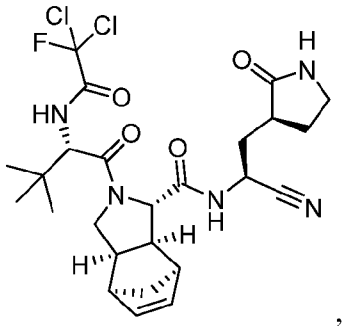
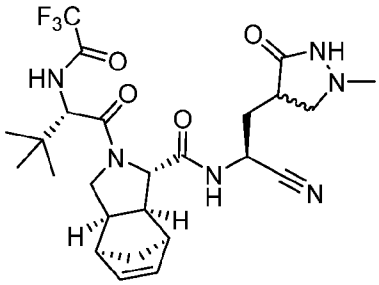
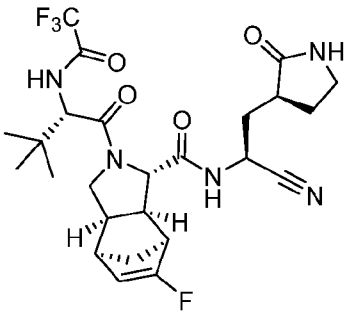
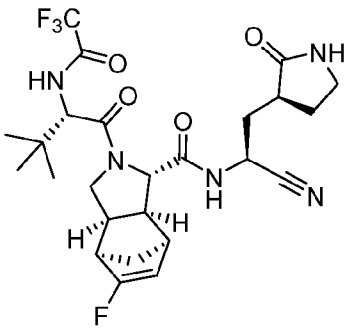
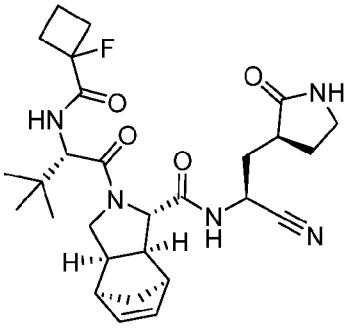
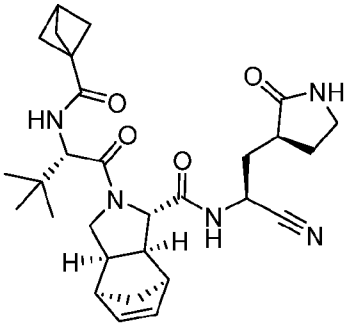
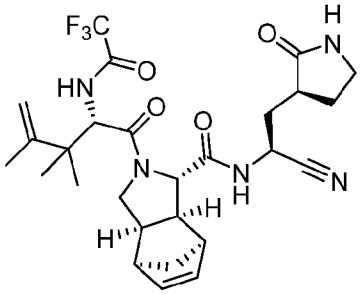
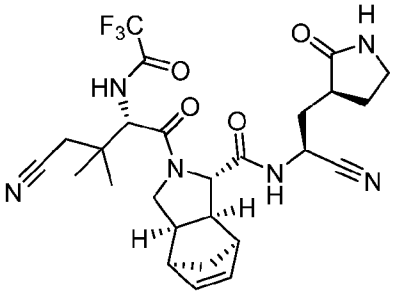
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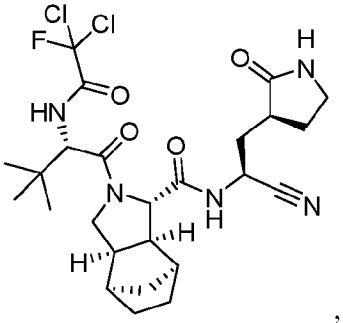
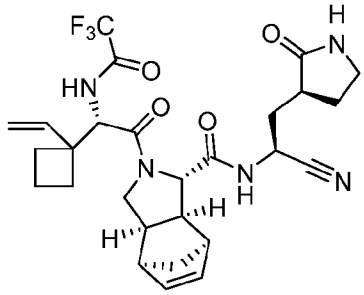
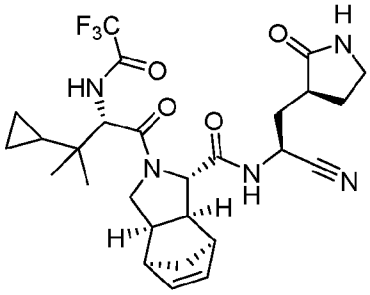
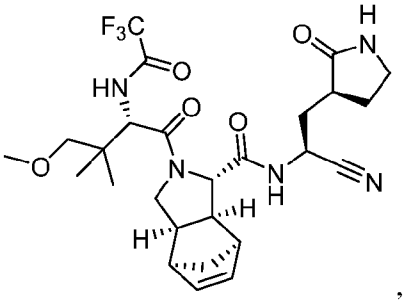
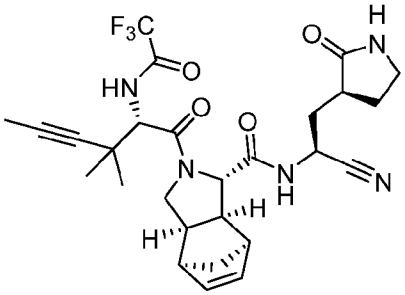
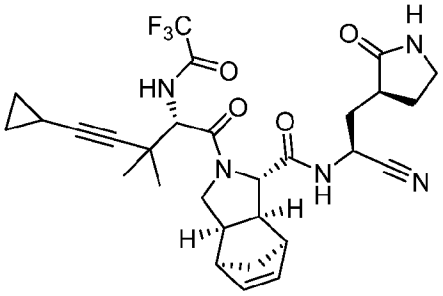
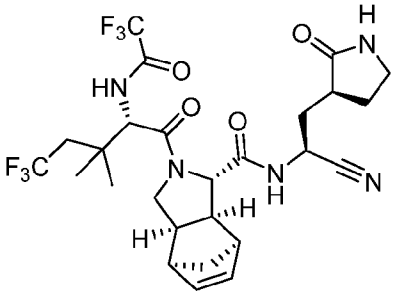
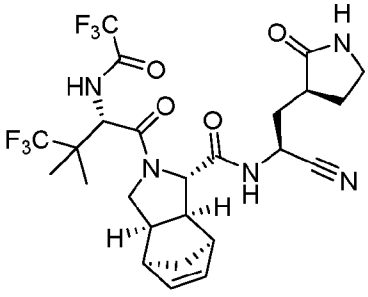
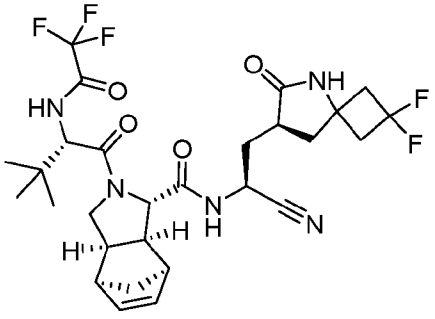

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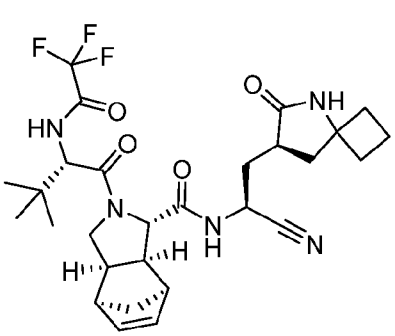
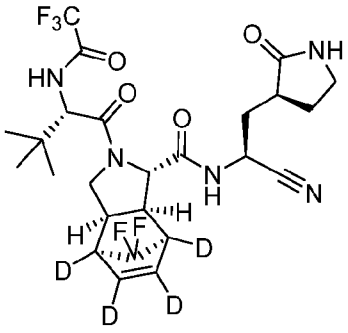
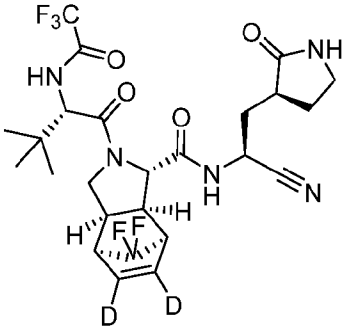
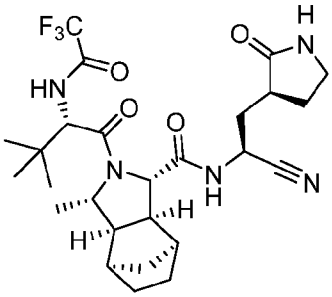
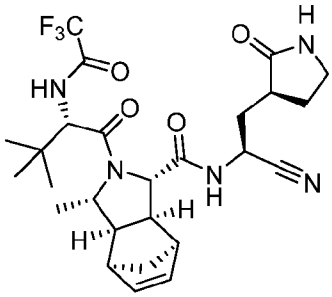
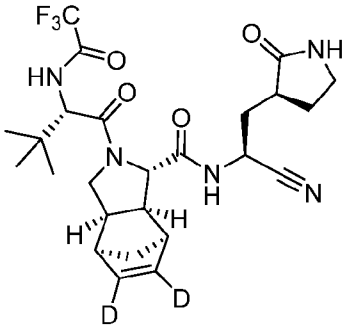

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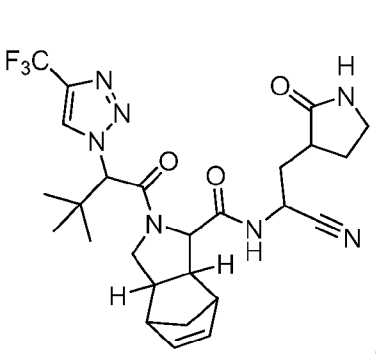
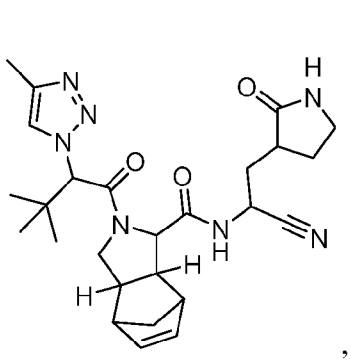
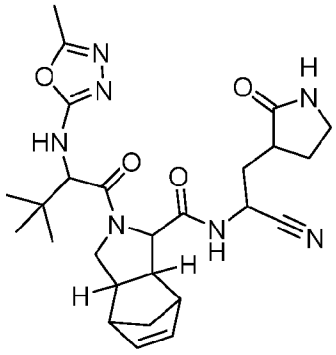
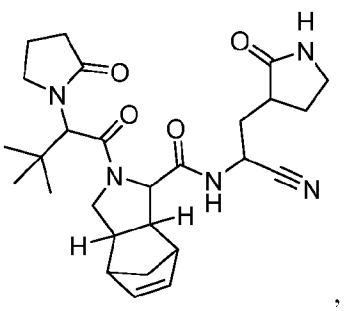
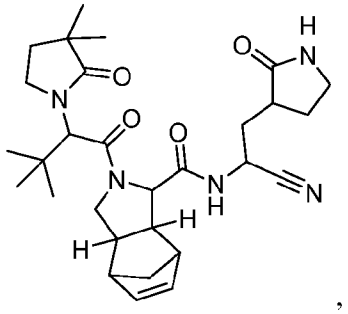
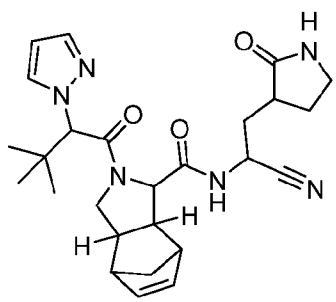
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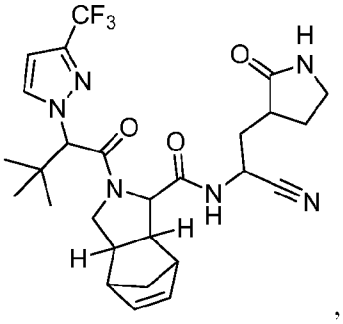
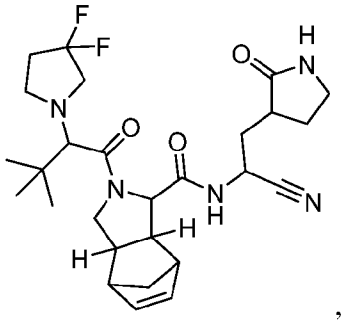
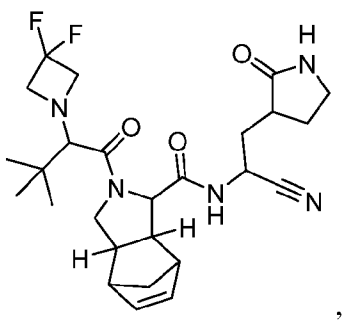
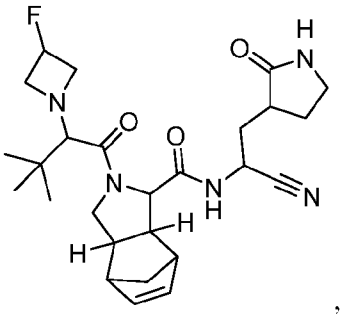
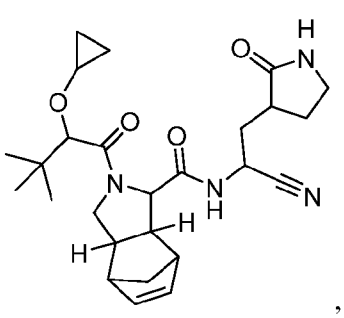
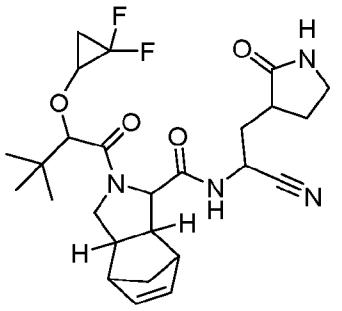
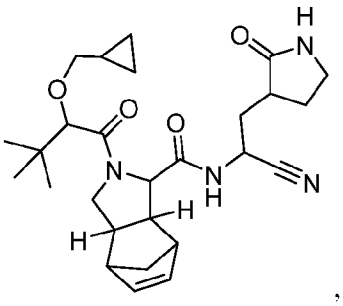
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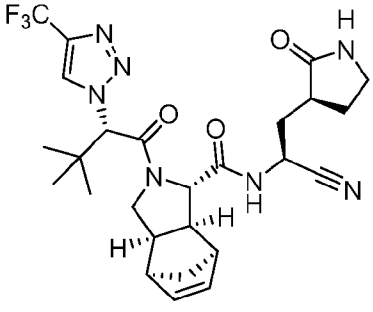
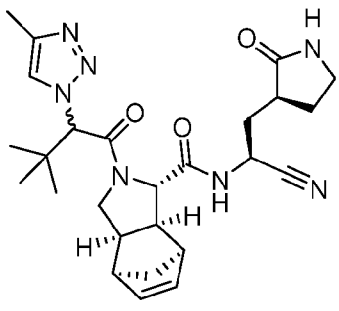
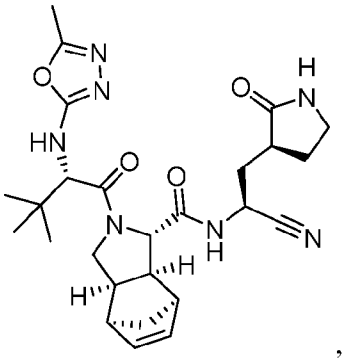

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and

, or a pharmaceutically acceptable salt of any of the foregoing.

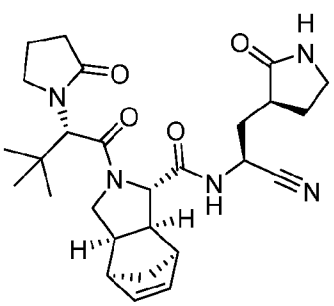
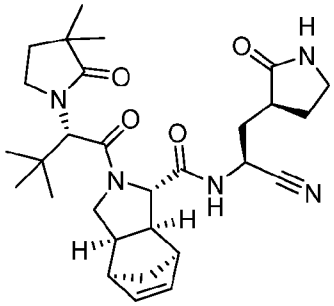
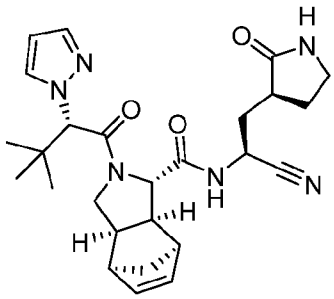
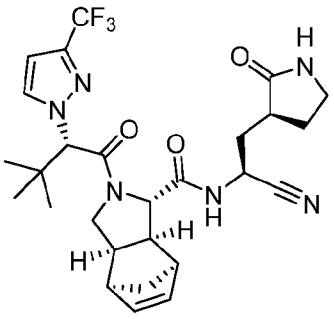
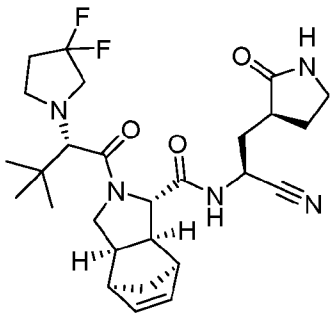
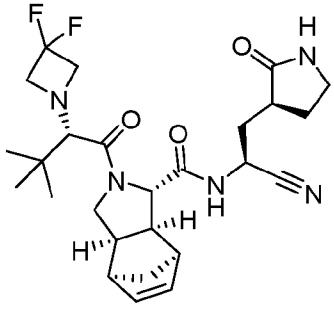
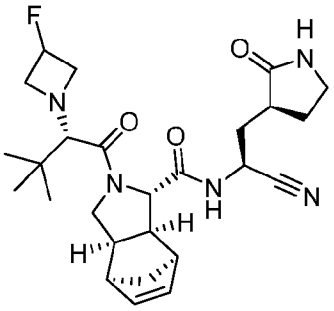
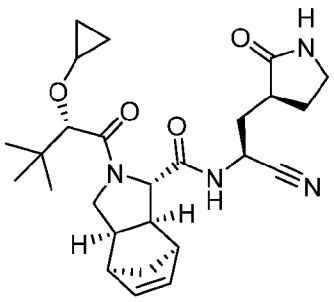
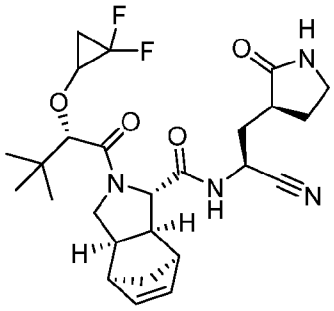
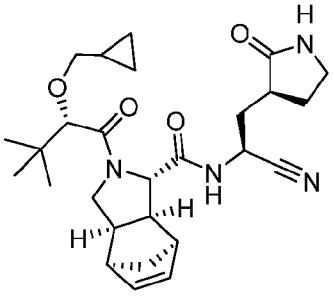
92. The compound of Claim 1, wherein the compound is selected from the group consisting of:


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, or a pharmaceutically acceptable salt of any of the foregoing.

93. The compound of Claim 1, wherein the compound is selected from the group consisting of:


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and

, or a pharmaceutically acceptable salt of any of the foregoing.

94. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof, and excipient.

95. Use of the compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a coronavirus infection.

96. The use of Claim 95, wherein the use further comprises the use of an

additional agent selected from the group consisting of an ACE inhibitor, an anticoagulant, an anti-inflammatory, an ARB, an ASO, a Covid-19 convalescent plasma, an entry inhibitor, an H_2 pump antagonist, an H-conducting channel, an HIV protease inhibitor, an HMG-CoA reductase inhibitor, an immune globulin, an immunosuppressant, an immunotherapeutic agent, a neuraminidase inhibitor, a nucleoside inhibitor, a nucleoside analog inhibitor, a polymerase inhibitor, a protease inhibitor, an siRNA, a statin, a tissue plasminogen activator, an antibiotic, an antimicrobial and a vaccine.

97. The use of Claim 96, wherein the additional agent selected from the group consisting of Ascorbic acid, Anakinra, Azithromycin, Baloxavir, Baricitinib, Chloroquine Phosphate, Colchicine, a corticosteroid, Epoprostenol, Famotidine, Favipiravir, an IGIV, an interferon, an IVIG, Ivermectin, γ-globulin, lopinavir, Methylprednisolone, Niclosamide, Molnupiravir (MK-4482 or EIDD-2801), Nitazoxanide, Nitric oxide, Oseltamivir, Peramivir, RANTES, ribavirin, Remdesivir, Ruxolitinib, Sarilumab, Siltuximab, Sirolimus, a statin, Tacrolimus, Tocilizumab, Umifenovir, Zanamivir, Casirivimab, imdevimab, bamlanivimab, etesevimab and AT-527.

98. The use of any one of Claims 93-97, wherein the coronavirus is β-coronavirus.

99. The use of any one of Claims 93-97, wherein the coronavirus is coronavirus selected from the group consisting of CoV 229E, CoV NL63, CoV OC43, CoV HKU1, Middle East Respiratory Syndrome (MERS)-CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, and SARS-CoV-2.

100. Use of the compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a picornavirus infection.

101. The use of Claim 100, wherein the picornavirus infection is a rhinovirus infection.

102. Use of the compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a norovirus infection.

103. A compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof, for use in treating a coronavirus infection.

104. The compound of Claim 103, wherein the compound is used in combination with an additional agents selected from the group consisting of an ACE inhibitor, an anticoagulant, an anti-inflammatory, an ARB, an ASO, a Covid-19 convalescent plasma, an entry inhibitor, an H_2 pump antagonist, an H-conducting channel, an HIV protease inhibitor, an HMG-CoA reductase inhibitor, an immune globulin, an immunosuppressant, an immunotherapeutic agent, a neuraminidase inhibitor, a nucleoside inhibitor, a nucleoside analog inhibitor, a polymerase inhibitor, a protease inhibitor, an siRNA, a statin, a tissue plasminogen activator, an antibiotic, an antimicrobial and a vaccine.

105. The compound of Claim 104, wherein the additional agent is selected from the group consisting of Ascorbic acid, Anakinra, Azithromycin, Baloxavir, Baricitinib, Chloroquine Phosphate, Colchicine, a corticosteroid, Epoprostenol, Famotidine, Favipiravir, an IGIV, an interferon, an IVIG, Ivermectin, γ-globulin, lopinavir, Methylprednisolone, Molnupiravir (MK-4482 or EIDD-2801), Niclosamide, Nitazoxanide, Nitric oxide, Oseltamivir, Peramivir, RANTES, ribavirin, Remdesivir, Ruxolitinib, Sarilumab, Siltuximab, Sirolimus, a statin, Tacrolimus, Tocilizumab, Umifenovir, Zanamivir, Casirivimab, imdevimab, bamlanivimab, etesevimab and AT-527.

106. The compound of any one of Claims 103-105, wherein the coronavirus is β-coronavirus.

107. The compound of any one of Claims 103-105, wherein the coronavirus is coronavirus selected from the group consisting of CoV 229E, CoV NL63, CoV OC43, CoV HKU1, Middle East Respiratory Syndrome (MERS)-CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, and SARS-CoV-2.

108. A compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof, for use in treating a picornavirus infection.

109. The compound of Claim 108, wherein the picornavirus infection is a rhinovirus infection.

110. A compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof, for use in treating a norovirus infection.

111. A method for treating a coronavirus infection in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof.

112. The method of Claim 111, further comprising administering an additional agent selected from the group consisting of an ACE inhibitor, an anticoagulant, an anti-inflammatory, an ARB, an ASO, a Covid-19 convalescent plasma, an entry inhibitor, an H_2 pump antagonist, an H-conducting channel, an HIV protease inhibitor, an HMG-CoA reductase inhibitor, an immune globulin, an immunosuppressant, an immunotherapeutic agent, a neuraminidase inhibitor, a nucleoside inhibitor, a nucleoside analog inhibitor, a polymerase inhibitor, a protease inhibitor, an siRNA, a statin, a tissue plasminogen activator, an antibiotic, an antimicrobial and a vaccine.

113. The method of Claim 112, wherein the additional agent selected from the group consisting of Ascorbic acid, Anakinra, Azithromycin, Baloxavir, Baricitinib, Chloroquine Phosphate, Colchicine, a corticosteroid, Epoprostenol, Famotidine, Favipiravir, an IGIV, an interferon, an IVIG, Ivermectin, γ-globulin, lopinavir, Methylprednisolone, Molnupiravir (MK-4482 or EIDD-2801), Niclosamide, Nitazoxanide, Nitric oxide, Oseltamivir, Peramivir, RANTES, ribavirin, Remdesivir, Ruxolitinib, Sarilumab, Siltuximab, Sirolimus, a statin, Tacrolimus, Tocilizumab, Umifenovir, Zanamivir, Casirivimab, imdevimab, bamlanivimab, etesevimab and AT-527.

114. The method of any one of Claims 111-113, wherein the coronavirus is β-coronavirus.

115. The method of any one of Claims 111-113, wherein the coronavirus is coronavirus selected from the group consisting of CoV 229E, CoV NL63, CoV OC43, CoV HKU1, Middle East Respiratory Syndrome (MERS)-CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, and SARS-CoV-2.

116. A method for treating a picornavirus infection in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof.

117. The method of Claim 116, wherein the picornavirus infection is a rhinovirus infection.

118. A method for treating a norovirus infection in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof.

119. The use of any one of Claims 95-102, the compound of any one of Claims

103-110, or the method of any one of Claims 111-118, wherein the subject is a human.

120. The use, compound or method of Claim 119, wherein the subject is 60 years old or older.

121. The use, compound or method of Claim 119, wherein the subject is a non-human primate.

122. The use, compound or method of Claim 119, wherein the subject is a cat.

123. The use, compound or method of Claim 119, wherein the subject is a camel.

124. The use of any one of Claims 95-102, the compound of any one of Claims 103-110, or the method of any one of Claims 111-118, wherein the coronavirus causes one or more symptoms selected from the group consisting of coughing, sore throat, runny nose, sneezing, headache, fever, shortness of breath, myalgia, abdominal pain, fatigue, difficulty breathing, persistent chest pain or pressure, difficulty waking, loss of smell and taste, muscle or joint pain, chills, nausea or vomiting, nasal congestion, diarrhea, haemoptysis, conjunctival congestion, sputum production, chest tightness and palpitations.

125. The use of any one of Claims 95-102, the compound of any one of Claims 103-110, or the method of any one of Claims 111-118, wherein the coronavirus causes a complication selected from the group consisting of sinusitis, otitis media, pneumonia, acute respiratory distress syndrome, disseminated intravascular coagulation, pericarditis and kidney failure.

126. The use of any one of Claims 95-102, the compound of any one of Claims 103-110, or the method of any one of Claims 111-118, wherein the compound is administered intravenously, subcutaneously, orally or via inhalation.

127. The use of Claim 97, the compound of Claim 105, or the method of Claim 113, wherein the interferon is selected from the group consisting of recombinant interferon alpha 2b, IFN-α and PEG-IFN-α-2a.

128. A method for inhibiting a coronavirus protease comprising contacting a cell infected with a coronavirus with an effective amount of a compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof, wherein the compound of any one of Claims 1-93, or a pharmaceutically acceptable salt thereof, selectively inhibits the coronavirus protease compared to a host protease.

129. The method of Claim 128, wherein the compound of formula (I) selectively

inhibits the coronavirus protease over the host protease that is selected from the group consisting of Cathepsin L, Cathepsin B, Cathepsin D, Cathepsin K, Leukocyte Elastase, Chymotrypsin, Trypsin, Thrombin, Pepsin, Caspase 2, Elastase and Calpain.

130. The method of Claim 128 or 129, wherein the host protease is selected from Cathepsin L and Cathepsin B.

131. The method of any one of Claims 128-130, wherein the selectively is > 2-fold.

ABSTRACT

Provided herein are compounds of Formula (I), or pharmaceutically acceptable salts thereof, pharmaceutical compositions that include a compound described herein (including pharmaceutically acceptable salts of a compound described herein) and methods of synthesizing the same. Also provided herein are methods of treating diseases and/or conditions with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

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PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
63/265,479	**12/15/2021 06:47:21 PM ET**	**ALIG.072PR4**

Title of Invention

ANTI-VIRAL COMPOUNDS

Application Information

APPLICATION TYPE	Utility - Provisional Application under 35 USC 111(b)	PATENT #	-
CONFIRMATION #	9701	FILED BY	Evelyn Salcido
PATENT CENTER #	60446461	FILING DATE	-
CUSTOMER #	20995	FIRST NAMED INVENTOR	Koen Vandyck
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kimberly Miller

Documents

TOTAL DOCUMENTS: 4

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
2021-12-15 ADS - ALIG.072PR4.PDF		10	Application Data Sheet	1227 KB
App_ALIG_072PR4.pdf		288	-	3003 KB
App_ALIG_072PR4-SPEC.pdf	(1-253)	253	Specification	2591 KB
App_ALIG_072PR4-CLM.pdf	(254-287)	34	Claims	449 KB
App_ALIG_072PR4-ABST.pdf	(288-288)	1	Abstract	12 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2021-12-15 ADS - ALIG.072PR4.PDF	A5B27BCAD907476708361AA0DC0FC2CBB0BBB5B12F0580A5BCDAAA8F29D604ACC078C86DF84BA13C3E21D663E96B32C6477C517CED62CFE77C8676AD127A080D
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App_ALIG_072PR4-CLM.pdf	694A14E1E705FD4F201A35295AAEECCA808BF0E32AA4433BEC9EA3B2AE78328815640EBE17A92AB9716384A111792669FDD5B5453BFA6B8E31CA497D5E46C9EA
App_ALIG_072PR4-ABST.pdf	9830666F2C6CD47F99037C80A855F2099869F7B5466C900C12A14A99A8AA7C85F31DD799A82122486ADDC9E9669E6F2F160FC27851F59F9BB6F5FB44398AB781

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ALIG.072PR4
	Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
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Residence Information (Select One) US Residency ● Non US Residency Active US Military Service

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ALIG.072PR4
	Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS	

Prefix	Given Name	Middle Name	Family Name	Suffix
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Inventor 4 Remove

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Prefix	Given Name	Middle Name	Family Name	Suffix
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Residence Information (Select One) ● US Residency ○ Non US Residency Active US Military Service

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Inventor 5 Remove

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Postal Code	94080	Country i	US

Inventor 6 Remove

Legal Name

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ALIG.072PR4
	Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS	

Prefix	Given Name	Middle Name	Family Name	Suffix
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Residence Information (Select One) ○ US Residency ◉ Non US Residency Active US Military Service

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Inventor 7 Remove

Legal Name

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	Arnaud	Didier Marie	Marchand	

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Mailing Address of Inventor:

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Address 2	Gaston Geenslaan 2

City	Leuven	State/Province	
Postal Code	3001	**Country** [i]	BE

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	20995		
Email Address	efiling@knobbe.com	Add Email	Remove Email

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ALIG.072PR4
	Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS	

Application Information:

Title of the Invention	ANTI-VIRAL COMPOUNDS		
Attorney Docket Number	ALIG.072PR4	**Small Entity Status Claimed**	☐
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	20995		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ALIG.072PR4
	Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ALIG.072PR4
	Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ALIG.072PR4
	Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Aligos Therapeutics, Inc.		
Mailing Address Information For Applicant:			
Address 1	1 Corporate Drive		
Address 2	2nd Floor		
City	South San Francisco	**State/Province**	CA
Country	US	Postal Code	94080
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ALIG.072PR4
	Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS	

Applicant 2 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Katholieke Universiteit Leuven		
Mailing Address Information For Applicant:			
Address 1	KU Leuven R&D		
Address 2	Waaistraat 6, box 5105		
City	Leuven	**State/Province**	
Country	BE	Postal Code	3000
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	ALIG.072PR4
	Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country [i]		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Kimberly J. Miller/			Date (YYYY-MM-DD)	2021-12-15
First Name	Kimberly J.	Last Name	Miller	Registration Number	61749

Additional Signature may be generated within this form by selecting the Add button. Add

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.