

MACROCYCLIC OREXIN RECEPTOR AGONISTS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/442,247, filed January 31, 2023, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Orexin is a neuropeptide specifically produced in particular neurons located sparsely in the lateral hypothalamus and its surrounding area. Orexin consists of two subtypes, orexin A and orexin B. Both orexin A (OX-A) and orexin B (OX-B) are endogenous ligands of the orexin receptors, which are mainly present in the brain. Two orexin receptors have been cloned and characterized in mammals. They belong to the super family of G-protein coupled receptors: the orexin-1 receptor (OX or OX1R) is partially selective for OX-A and the orexin-2 receptor (OX2 or OX2R) is capable of binding OX-A as well as OX-B with similar affinity. The physiological actions in which orexins are presumed to participate are thought to be expressed via one or both of OX1 receptor and OX2 receptor as the two subtypes of orexin receptors.

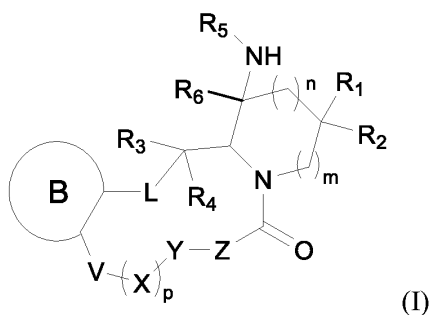
[0003] Orexins regulate states of sleep and wakefulness making the orexin system a target for potential therapeutic approaches to treat sleep disorders. Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior. Orexins have also been indicated as playing a role in arousal, emotion, energy homeostasis, reward, learning and memory.

[0004] There is a need for compounds that modulate orexin receptors, as well as compositions and methods for treating a disease or disorder that is treatable by administration of an Orexin agonist.

SUMMARY

[0005] The present disclosure is directed to compounds that are agonists of the orexin-2 receptor as well as pharmaceutical compositions thereof and uses thereof in treating a disease or disorder that is treatable by administration of an Orexin agonist.

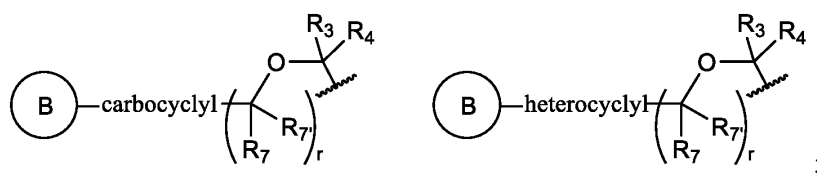
[0006] In one aspect, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

L is a linker selected from aryl, heteroaryl, $\text{-carbocyclyl-(CR}_7\text{CR}_{7'})_r\text{-O-}$, and $\text{-heterocyclyl-(CR}_7\text{CR}_{7'})_r\text{-O-}$, wherein $\text{-carbocyclyl-(CR}_7\text{CR}_{7'})_r\text{-O-}$ and $\text{-heterocyclyl-(CR}_7\text{CR}_{7'})_r\text{-O-}$ have the following orientation:



(B) is phenyl, 5- or 6-membered heteroaryl, cycloalkyl, or heterocyclyl;

V and Z are each independently -O- , $\text{-CR}_8\text{R}_9\text{-}$, or $\text{-NR}_{10}\text{-}$;

X is -O- , $\text{-CR}_{11}\text{R}_{12}\text{-}$, or $\text{-NR}_{13}\text{-}$;

Y is a bond, -O- , $\text{-CR}_8\text{R}_9\text{-}$, or $\text{-NR}_{10}\text{-}$;

R_1 and R_2 are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl, or R_1 and R_2 together with the atom to which they are attached form a carbocycle or heterocycle;

R_3 and R_4 are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl, or R_3 and R_4 together with the atom to which they are attached form a carbocycle or heterocycle;

R_5 is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, aryl, heteroaryl, alkylene-heteroaryl, or alkylene- S(O)_2 -alkyl;

R₆ is H, alkyl, cycloalkyl, heterocyclyl, alkylene-cycloalkyl, alkylene-heterocyclyl, or -CN;

R₇ and R_{7'} are each independently H, halogen, or alkyl;

R₈ and R₉ are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl, or R₈ and R₉ together with the atom to which they are attached form a carbocycle or heterocycle;

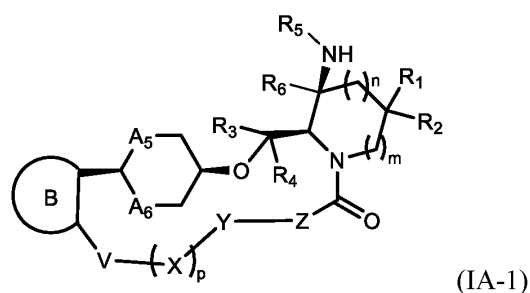
R₁₁ and R₁₂ are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl; or R₁₁ and R₁₂ together with the atom to which they are attached form a carbocycle or heterocycle;

R₁₀ and R₁₃ are each independently H, alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, -(C=O)alkyl, -(C=O)cycloalkyl, -(C=O)heterocyclyl, -(C=O)-O-alkyl, -(C=O)-O-cycloalkyl, -(C=O)-O-heterocyclyl, -(C=O)-O-heteroaryl, -S(O)₂-alkyl, -S(O)₂-cycloalkyl, or -S(O)₂-heterocyclyl;

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

r is 0 or 1.

[0007] In some embodiments, the present disclosure provides a compound of Formula (IA-1):



or a pharmaceutically acceptable salt thereof,

wherein:

ⓑ is phenyl, 5- or 6-membered heteroaryl, cycloalkyl, or heterocyclyl;

V and Z are each independently -O-, -CR₈R₉-, or -NR₁₀-;

X is -O-, -CR₁₁R₁₂-, or -NR₁₃-;

Y is a bond, -O-, -CR₈R₉-, or -NR₁₀-;

A₅ and A₆ are each independently –O– or –CH₂–;

R₁, R₂, R₃, R₄, R₈, R₉, R₁₁, and R₁₂ are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl; and/or R₁ and R₂ together with the atom to which they are attached form a carbocycle or heterocycle; and/or R₃ and R₄ together with the atom to which they are attached form a carbocycle or heterocycle; and/or R₈ and R₉ together with the atom to which they are attached form a carbocycle or heterocycle; and/or R₁₁ and R₁₂ together with the atom to which they are attached form a carbocycle or heterocycle;

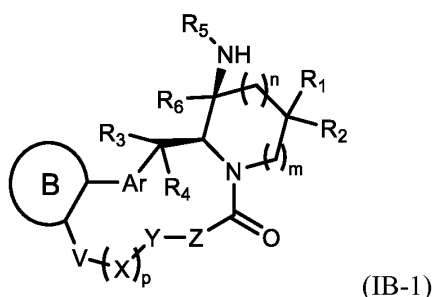
R₅ is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, aryl, heteroaryl, alkylene-heteroaryl, or alkylene–S(O)₂–alkyl;

R₆ is H, alkyl, cycloalkyl, heterocyclyl, alkylene-cycloalkyl, alkylene-heterocyclyl, or –CN;

R₁₀ and R₁₃ are each independently H, alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, –(C=O)alkyl, –(C=O)cycloalkyl, –(C=O)heterocyclyl, –(C=O)–O–alkyl, –(C=O)–O–cycloalkyl, –(C=O)–O–heterocyclyl, –(C=O)–O–heteroaryl, –S(O)₂–alkyl, –S(O)₂–cycloalkyl, or –S(O)₂–heterocyclyl; and

m, n, and p are each independently 0, 1, or 2.

[0008] In some embodiments, the present disclosure provides a compound of Formula (IB-1):



or a pharmaceutically acceptable salt thereof,

wherein:

Ar is an aryl or heteroaryl linker;

ⓑ is phenyl, 5- or 6-membered heteroaryl, cycloalkyl, or heterocyclyl;

V and Z are each independently $-O-$, $-CR_8R_9-$, or $-NR_{10}-$;

X is $-O-$, $-CR_{11}R_{12}-$, or $-NR_{13}-$;

Y is a bond, $-O-$, $-CR_8R_9-$, or $-NR_{10}-$;

R_1 , R_2 , R_3 , R_4 , R_8 , R_9 , R_{11} , and R_{12} are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl; and/or R_1 and R_2 together with the atom to which they are attached form a carbocycle or heterocycle; and/or R_3 and R_4 together with the atom to which they are attached form a carbocycle or heterocycle; and/or R_8 and R_9 together with the atom to which they are attached form a carbocycle or heterocycle; and/or R_{11} and R_{12} together with the atom to which they are attached form a carbocycle or heterocycle;

R_5 is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, aryl, heteroaryl, alkylene-heteroaryl, or alkylene- $S(O)_2$ -alkyl;

R_6 is H, alkyl, cycloalkyl, heterocyclyl, alkylene-cycloalkyl, alkylene-heterocyclyl, or $-CN$;

R_{10} and R_{13} are each independently H, alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, $-(C=O)alkyl$, $-(C=O)cycloalkyl$, $-(C=O)heterocyclyl$, $-(C=O)-O-alkyl$, $-(C=O)-O-cycloalkyl$, $-(C=O)-O-heterocyclyl$, $-(C=O)-O-heteroaryl$, $-S(O)_2-alkyl$, $-S(O)_2-cycloalkyl$, or $-S(O)_2-heterocyclyl$; and

m, n, and p are each independently 0, 1, or 2.

[0009] In some embodiments, R_1 and R_2 are each independently H, halogen, or alkyl. In some embodiments, R_1 and R_2 are each independently H or alkyl. In some embodiments, the alkyl is methyl or ethyl. In some embodiments, R_1 and R_2 are H. In some embodiments, R_1 and R_2 are H or halogen. In some embodiments, halogen is fluorine. In some embodiments, R_1 and R_2 together with the carbon atom to which they are attached form a carbocycle or heterocycle. In some embodiments, the carbocycle is a C_{3-6} cycloalkyl. In some embodiments, the heterocycle is a 3- or 6-membered heterocycle. In some embodiments, the heterocycle comprises 1 or 2 heteroatoms selected from the group consisting of N, O, and S.

[0010] In some embodiments, R_3 and R_4 are each independently H, halogen, or alkyl. In some embodiments, R_3 and R_4 are each independently H or alkyl. In some embodiments, the alkyl is

methyl or ethyl. In some embodiments, R_3 and R_4 are H. In some embodiments, R_3 and R_4 are halogen. In some embodiments, the halogen is fluorine. In some embodiments, R_3 and R_4 together with the carbon atom to which they are attached form a carbocycle or heterocycle. In some embodiments, the carbocycle is a C_{3-6} cycloalkyl. In some embodiments, the heterocycle is a 3- or 6-membered heterocycle. In some embodiments, the heterocycle comprises 1 or 2 heteroatoms selected from the group consisting of N, O, and S.

[0011] In some embodiments, R_5 is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, heteroaryl, alkylene-heteroaryl, or alkylene- $S(O)_2$ -alkyl. In some embodiments, R_5 is alkyl or haloalkyl. In some embodiments, R_5 is C_{1-5} alkyl or C_{1-5} haloalkyl. In some embodiments, R_5 is C_{1-5} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkylene-(C_{3-6} cycloalkyl), 4- to 6-membered heterocyclyl, C_{1-3} alkylene-(4- to 6-membered heterocyclyl), 5- or 6-membered heteroaryl, C_{1-3} alkylene-(5- or 6-membered heteroaryl), or C_{1-3} alkylene- $S(O)_2$ - C_{1-3} alkyl. In some embodiments, R_5 is alkyl optionally substituted with one or more halogen. In some embodiments, R_5 is alkyl optionally substituted with one or more fluorine. In some embodiments, R_5 is alkyl, C_{1-5} alkyl, or C_{1-5} haloalkyl. In some embodiments, R_5 is C_{1-3} alkylene-cycloalkyl, C_{1-3} alkylene-heterocyclyl, C_{1-3} alkylene-heteroaryl, or C_{1-3} alkylene- $S(O)_2$ -alkyl. In some embodiments, R_5 is alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-heteroaryl, or alkylene- $S(O)_2$ -alkyl, and the alkylene is a methylene or ethylene. In some embodiments, R_5 is alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-heteroaryl, or alkylene- $S(O)_2$ -alkyl, and the alkylene is a methylene.

[0012] In some embodiments, V is $-O-$ or $-CR_8R_9-$. In some embodiments, V is $-O-$ or $-NR_{10}-$. In some embodiments, V is $-O-$. In some embodiments, V is $-CR_8R_9-$. In some embodiments, R_8 and R_9 are each independently H or alkyl. In some embodiments, R_8 and R_9 together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl. In some embodiments, R_{10} is H, alkyl, $-(C=O)$ alkyl, or $-S(O)_2$ -alkyl. In some embodiments, R_{10} is H or alkyl. In some embodiments, the alkyl is methyl, ethyl, or isopropyl. In some embodiments, the alkyl is methyl.

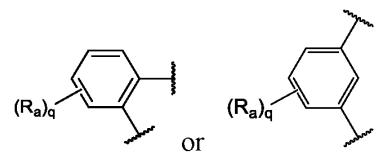
[0013] In some embodiments, Y is a bond or $-CR_8R_9-$. In some embodiments, R_8 and R_9 are each independently H or alkyl. In some embodiments, R_8 and R_9 together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl.

[0014] In some embodiments, Z is a $-\text{NR}_{10}-$ or $-\text{CR}_8\text{R}_9-$. In some embodiments, Z is $-\text{NR}_{10}-$. In some embodiments, R_8 and R_9 are each independently H or alkyl. In some embodiments, R_8 and R_9 together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl. In some embodiments, R_{10} is H, alkyl, $-(\text{C}=\text{O})\text{alkyl}$, or $-\text{S}(\text{O})_2\text{alkyl}$. In some embodiments, R_{10} is H or alkyl. In some embodiments, the alkyl is methyl, ethyl, or isopropyl. In some embodiments, the alkyl is methyl.

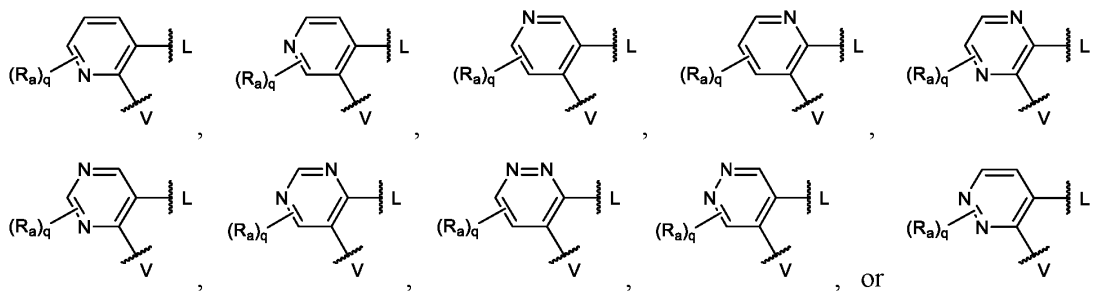
[0015] In some embodiments, X is $-\text{CR}_{11}\text{R}_{12}-$. In some embodiments, R_{11} and R_{12} are each independently H or alkyl. In some embodiments, the alkyl is methyl or ethyl. In some embodiments, R_{11} and R_{12} together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl.

[0016] In some embodiments, $\textcircled{\text{B}}$ is phenyl or 5- or 6-membered heteroaryl. In some

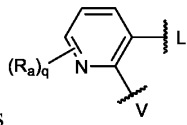
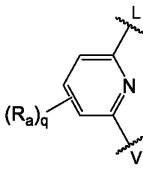
embodiments, $\textcircled{\text{B}}$ is phenyl. In some embodiments, $\textcircled{\text{B}}$ is:



wherein R_a is halogen, alkyl, $-\text{CN}$, or alkoxy; and q is 0, 1, or 2. In some embodiments, $\textcircled{\text{B}}$ is a 5- or 6-membered heteroaryl. In some embodiments, $\textcircled{\text{B}}$ is a 5-membered heteroaryl. In some embodiments, $\textcircled{\text{B}}$ is a 6-membered heteroaryl. In some embodiments, $\textcircled{\text{B}}$ is pyridinyl, pyrazinyl, pyrimidinyl, or pyridazinyl. In some embodiments, $\textcircled{\text{B}}$ is pyridinyl. In some embodiments, $\textcircled{\text{B}}$ is:



wherein R_a is halogen, alkyl, $-\text{CN}$, or alkoxy; and q is 0, 1, or 2. In some embodiments, R_a is

halogen, C₁₋₅ alkyl, or -CN. In some embodiments, (B) is  or , wherein R_a is halogen, alkyl, -CN, or alkoxy; and q is 0, 1, or 2. In some embodiments, R_a is alkyl optionally substituted with one or more fluoride. In some embodiments, R_a is alkoxy optionally substituted with one or more fluoride. In some embodiments, R_a is F, CH₃, CH₂CH₃, CH(CH₃)₂, CF₃, CHCF₂, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -OCF₃, -OCHCF₂, or -CN. In some embodiments, R_a is F, CH₃, CH₂CH₃, CH(CH₃)₂, CF₃, CHCF₂, or -CN. In some embodiments, q is 0 or 1. In some embodiments, q is 0.

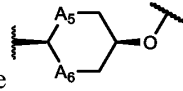
[0017] In some embodiments, m is 0 or 1. In some embodiments, m is 0.

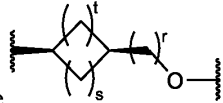
[0018] In some embodiments, n is 0 or 1. In some embodiments, n is 1.

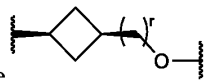
[0019] In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1.

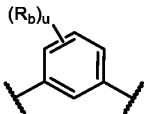
[0020] In some embodiments, r is 0. In some embodiments, r is 1.

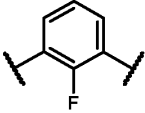
[0021] In some embodiments, L is heteroaryl, -carbocyclyl-(CR₇CR_{7'})_r-O-, or -heterocyclyl-(CR₇CR_{7'})_r-O-. In some embodiments, L is -carbocyclyl-(CH₂)_r-O- or -heterocyclyl-(CH₂)_r-O-.

In some embodiments, L has the structure , wherein A₅ and A₆ are each independently -O- or -CH₂-. In some embodiments, A₅ is -O-. In some embodiments, A₅ is -CH₂-. In some embodiments, A₆ is -O-. In some embodiments, A₆ is -CH₂-. In some

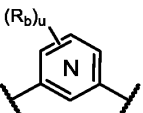
embodiments, L is a -carbocyclyl-(CH₂)_r-O-linker having the structure , wherein r is 0 or 1; s is 1 or 2; and t is 1 or 2. In some embodiments, s is 1 and t is 1. In some embodiments, s is 2 and t is 2. In some embodiments, L is a -carbocyclyl-(CH₂)_r-O-linker having

the structure , wherein r is 0 or 1.

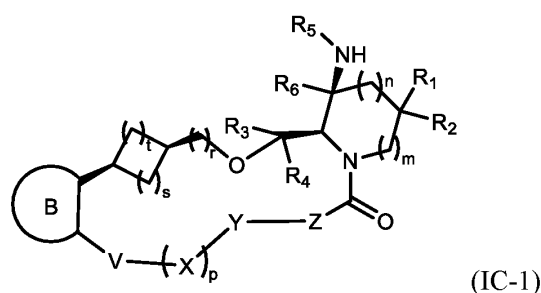
[0022] In some embodiments, L is , wherein R_b is halogen, alkyl, or alkoxy; and u is 0, 1, or 2. In some embodiments, R_b is halogen. In some embodiments, the halogen is fluoride. In some embodiments, R_b is F, CH₃, CH₂CH₃, CH(CH₃)₂, CF₃, CHCF₂, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -OCF₃, or -OCHCF₂. In some embodiments, u is 1. In some embodiments, u is 0. In

some embodiments, L is .

[0023] In some embodiments, L is a 5- or 6-membered heteroaryl linker. In some embodiments, L is a 5- or 6-membered heteroaryl linker having 1 or 2 nitrogen atoms. In some embodiments, L

is , wherein R_b is halogen, alkyl, or alkoxy; and u is 0 or 1.

[0024] In some embodiments, the present disclosure provides a compound of Formula (IC-1):



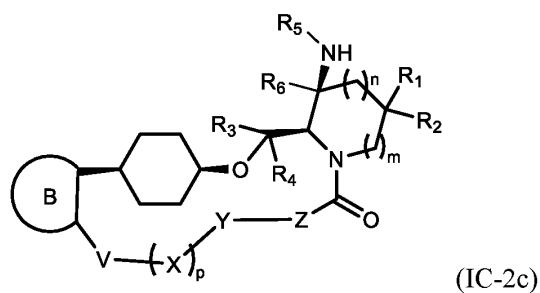
or a pharmaceutically acceptable salt thereof, wherein m, n, p, r, R₁, R₂, R₃, R₄, R₅, R₆, , V, X, Y and Z are as defined herein; s is 1 or 2; and t is 0, 1 or 2.

[0025] In some embodiments, s is 1. In some embodiments, s is 2.

[0026] In some embodiments, t is 1. In some embodiments, t is 2.

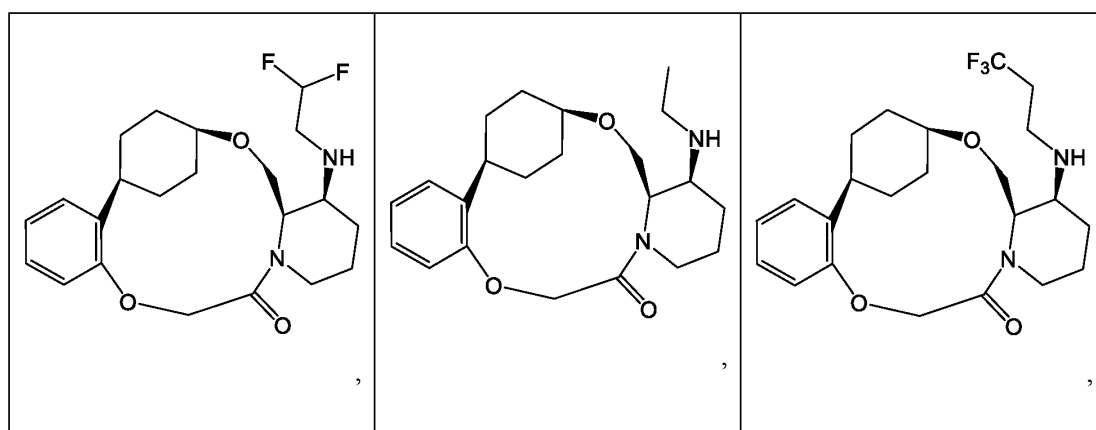
[0027] In some embodiments, s is 1 and t is 1. In some embodiments, s is 2 and t is 2.

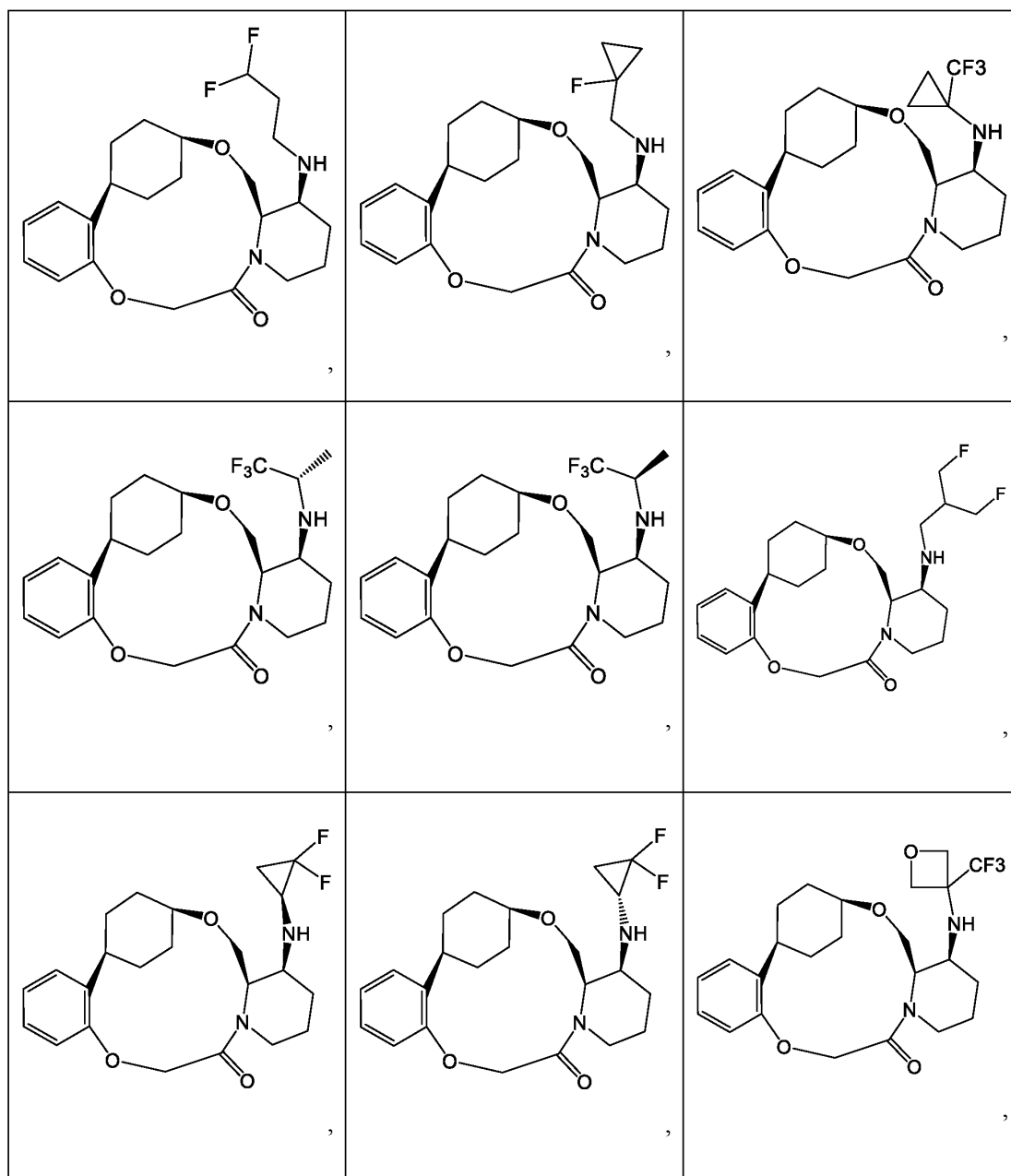
[0028] In some embodiments, the present disclosure provides a compound of Formula (ID-1):

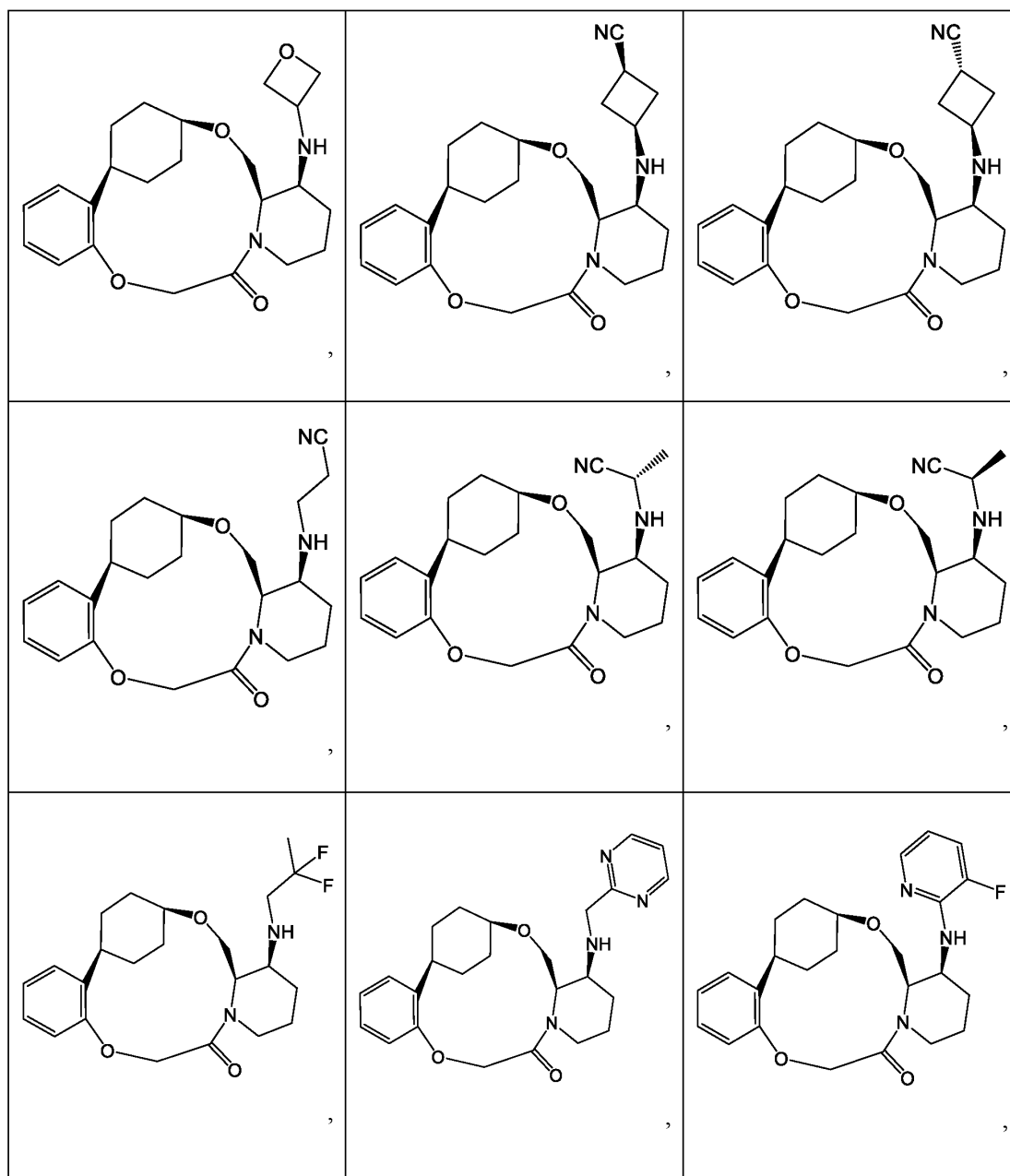


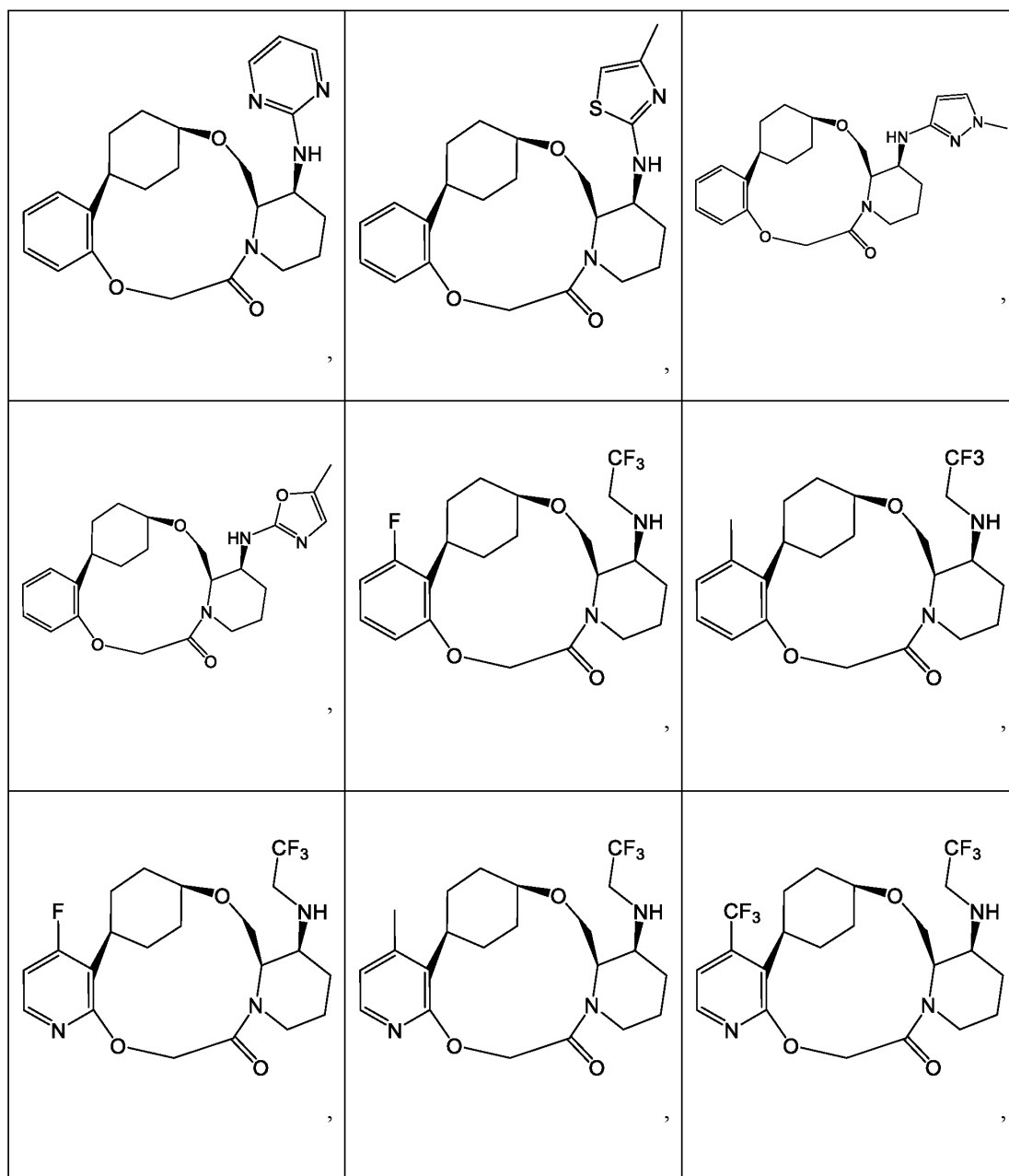
or a pharmaceutically acceptable salt thereof, wherein m, n, p, R₁, R₂, R₃, R₄, R₅, R₆, $\textcircled{\text{B}}$, V, X, Y and Z are defined herein.

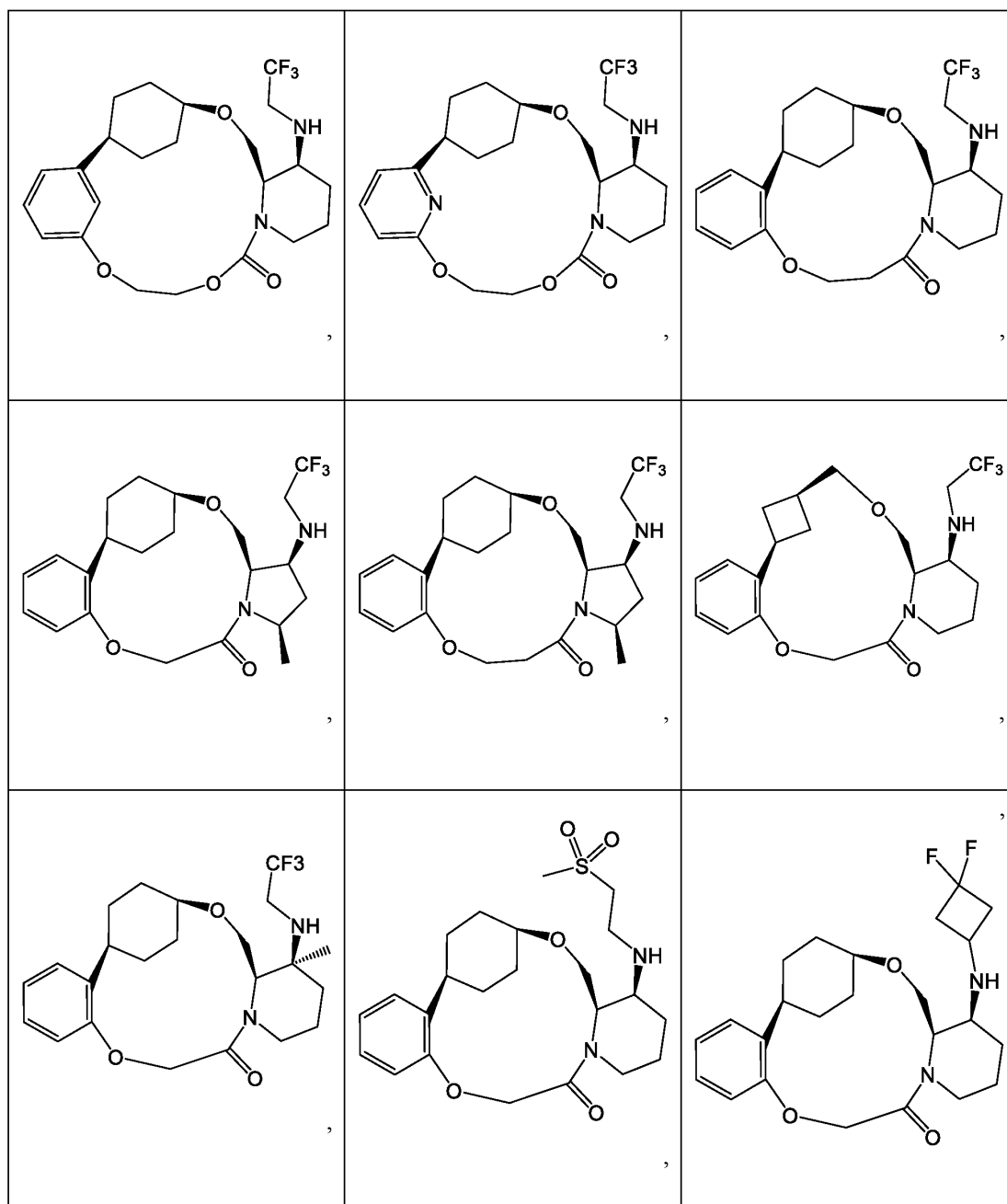
[0029] In some embodiments, the compound of the present disclosure (e.g., the compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), or Formula (IC-4)) is:

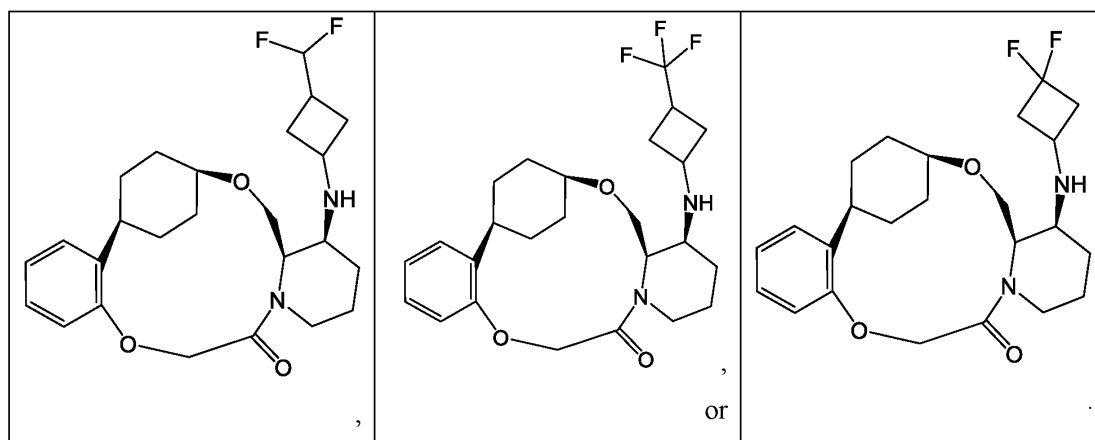












[0030] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula, (ID-4), Formula (II), or Tables 1-24) or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

DETAILED DESCRIPTION

[0031] Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference for all purposes in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications cited and this disclosure.

[0032] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0033] The term "about" when immediately preceding a numerical value means a range (e.g., plus or minus 10% of that value). For example, "about 50" can mean 45 to 55, "about 25,000" can mean 22,500 to 27,500, etc., unless the context of the disclosure indicates otherwise, or is inconsistent with such an interpretation. For example, in a list of numerical values such as "about 49, about 50, about 55, ...", "about 50" means a range extending to less than half the interval(s) between the preceding and subsequent values, e.g., more than 49.5 to less than 50.5. Furthermore, the phrases "less than about" a value or "greater than about" a value should be understood in view of the definition of the term "about" provided herein. Similarly, the term "about" when preceding a series of numerical values or a range of values (e.g., "about 10, 20, 30" or "about 10-30") refers, respectively to all values in the series, or the endpoints of the range.

[0034] The terms "administer," "administering" or "administration" as used herein refer to administering a compound or pharmaceutically acceptable salt of the compound or a composition or formulation comprising the compound or pharmaceutically acceptable salt of the compound to a patient.

[0035] The term "pharmaceutically acceptable salt" includes both acid and base addition salts. Pharmaceutically acceptable salts include those obtained by reacting the active compound functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, carbonic acid, etc. Base addition salts include but are not limited to, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris-(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e. g., lysine and arginine dicyclohexylamine and the like. Examples of metal salts include lithium, sodium, potassium, magnesium, calcium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium,

butylammonium, tetramethylammonium salts and the like. Examples of organic bases include lysine, arginine, guanidine, diethanolamine, choline and the like. Those skilled in the art will further recognize that acid addition salts may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods.

[0036] The term "treating" as used herein with regard to a patient, refers to improving at least one symptom of the patient's disorder. Treating can be improving, or at least partially ameliorating a disorder or an associated symptom of a disorder.

[0037] The terms "effective amount" and "therapeutically effective amount" are used interchangeably in this disclosure and refer to an amount of a compound, or a salt thereof, (or pharmaceutical composition containing the compound or salt) that, when administered to a patient, is capable of performing the intended result. The "effective amount" can vary depending on the active ingredient, the state, disorder, or condition to be treated and its severity, and the age, weight, physical condition and responsiveness of the mammal to be treated.

[0038] The term "therapeutically effective" applied to a dose or amount refers to that quantity of a compound or pharmaceutical formulation that is sufficient to result in a desired clinical benefit after administration to a patient in need thereof.

[0039] The term "carrier" or "vehicle" as used interchangeably herein encompasses carriers, excipients, adjuvants, and diluents or a combination of any of the foregoing, meaning a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ or portion of the body. In addition to the adjuvants, excipients and diluents known to one skilled in the art, the carrier includes nanoparticles of organic and inorganic nature.

[0040] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C₁-C₆ alkyl" is intended to encompass C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0041] "Alkyl" or "alkyl group" refers to a fully saturated, straight or branched hydrocarbon chain having from one to twelve carbon atoms, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl

comprising up to 12 carbon atoms is a C₁-C₁₂ alkyl, an alkyl comprising up to 10 carbon atoms is a C₁-C₁₀ alkyl, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl and an alkyl comprising up to 5 carbon atoms is a C₁-C₅ alkyl. A C₁-C₅ alkyl includes C₅ alkyls, C₄ alkyls, C₃ alkyls, C₂ alkyls, and C₁ alkyl (*i.e.*, methyl). A C₁-C₆ alkyl includes all moieties described above for C₁-C₅ alkyls but also includes C₆ alkyls. A C₁-C₁₀ alkyl includes all moieties described above for C₁-C₅ alkyls and C₁-C₆ alkyls, but also includes C₇, C₈, C₉ and C₁₀ alkyls. Similarly, a C₁-C₁₂ alkyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkyls. Non-limiting examples of C₁-C₁₂ alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *sec*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *t*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0042] “Alkylene” or “alkylene chain” refers to a fully saturated, straight, or branched divalent hydrocarbon chain radical, and having from one to twelve carbon atoms. Non-limiting examples of C₁-C₁₂ alkylene include methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain can be optionally substituted.

[0043] “Alkenyl” or “alkenyl group” refers to a straight or branched hydrocarbon chain having from two to twelve carbon atoms and having one or more carbon-carbon double bonds. Each alkenyl group is attached to the rest of the molecule by a single bond. Alkenyl group comprising any number of carbon atoms from 2 to 12 are included. An alkenyl group comprising up to 12 carbon atoms is a C₂-C₁₂ alkenyl, an alkenyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C₂-C₆ alkenyl and an alkenyl comprising up to 5 carbon atoms is a C₂-C₅ alkenyl. A C₂-C₅ alkenyl includes C₅ alkenyls, C₄ alkenyls, C₃ alkenyls, and C₂ alkenyls. A C₂-C₆ alkenyl includes all moieties described above for C₂-C₅ alkenyls but also includes C₆ alkenyls. A C₂-C₁₀ alkenyl includes all moieties described above for C₂-C₅ alkenyls and C₂-C₆ alkenyls, but also includes C₇, C₈, C₉ and C₁₀ alkenyls. Similarly, a C₂-C₁₂ alkenyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkenyls. Non-

limiting examples of C₂-C₁₂ alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, and 11-dodecenyl. Unless stated otherwise specifically in the specification, an alkenyl group can be optionally substituted.

[0044] “Alkenylene” or “alkenylene chain” refers to an unsaturated, straight or branched divalent hydrocarbon chain radical having one or more olefins and from two to twelve carbon atoms. Non-limiting examples of C₂-C₁₂ alkenylene include ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain can be optionally substituted.

[0045] “Alkynyl” or “alkynyl group” refers to a straight or branched hydrocarbon chain having from two to twelve carbon atoms and having one or more carbon-carbon triple bonds. Each alkynyl group is attached to the rest of the molecule by a single bond. Alkynyl group comprising any number of carbon atoms from 2 to 12 are included. An alkynyl group comprising up to 12 carbon atoms is a C₂-C₁₂ alkynyl, an alkynyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkynyl, an alkynyl group comprising up to 6 carbon atoms is a C₂-C₆ alkynyl and an alkynyl comprising up to 5 carbon atoms is a C₂-C₅ alkynyl. A C₂-C₅ alkynyl includes C₅ alkynyls, C₄ alkynyls, C₃ alkynyls, and C₂ alkynyls. A C₂-C₆ alkynyl includes all moieties described above for C₂-C₅ alkynyls but also includes C₆ alkynyls. A C₂-C₁₀ alkynyl includes all moieties described above for C₂-C₅ alkynyls and C₂-C₆ alkynyls, but also includes C₇, C₈, C₉ and C₁₀ alkynyls. Similarly, a C₂-C₁₂ alkynyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkynyls. Non-

limiting examples of C₂-C₁₂ alkenyl include ethynyl, propynyl, butynyl, pentynyl and the like. Unless stated otherwise specifically in the specification, an alkynyl group can be optionally substituted.

[0046] “Alkynylene” or “alkynylene chain” refers to an unsaturated, straight or branched divalent hydrocarbon chain radical having one or more alkynes and from two to twelve carbon atoms. Non-limiting examples of C₂-C₁₂ alkynylene include ethynylene, propynylene, *n*-butynylene, and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through any two carbons within the chain having a suitable valency. Unless stated otherwise specifically in the specification, an alkynylene chain can be optionally substituted.

[0047] “Alkoxy” refers to a group of the formula -OR_a where R_a is an alkyl, alkenyl or alkynyl as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

[0048] “Aryl” refers to a hydrocarbon ring system comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring, and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the aryl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. Aryls include, but are not limited to, aryls derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the “aryl” can be optionally substituted.

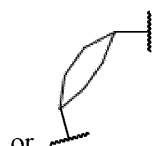
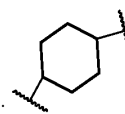
[0049] “Aralkyl” or “arylalkyl” refers to a radical of the formula -R_b-R_c where R_b is an alkylene group as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like. Unless stated otherwise specifically in the specification, an aralkyl group can be optionally substituted.

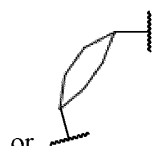
[0050] “Carbocyclyl,” “carbocyclic ring” or “carbocycle” refers to a rings structure, wherein the atoms which form the ring are each carbon, and which is attached to the rest of the molecule by a single bond. Carbocyclic rings can comprise from 3 to 20 carbon atoms in the ring. Carbocyclic

rings can include aryls and cycloalkyl, cycloalkenyl, and cycloalkynyl as defined herein. Unless stated otherwise specifically in the specification, a carbocyclyl group can be optionally substituted.

[0051] “Cycloalkyl” refers to a stable non-aromatic monocyclic or polycyclic fully saturated hydrocarbon consisting solely of carbon and hydrogen atoms, which can include fused, bridged, or spirocyclic ring systems, having from three to twenty carbon atoms (e.g., having from three to ten carbon atoms) and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

and cyclooctyl. In some embodiments, the cyclohexyl ring is depicted by the structure:



or  , wherein the stereochemistry is as provided in the compound disclosed herein. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group can be optionally substituted.

[0052] “Cycloalkenyl” refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon consisting solely of carbon and H atoms, having one or more carbon-carbon double bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkenyls include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like. Polycyclic cycloalkenyls include, for example, bicyclo[2.2.1]hept-2-enyl and the like. Unless otherwise stated specifically in the specification, a cycloalkenyl group can be optionally substituted.

[0053] “Cycloalkynyl” refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon triple bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkynyl include, for example, cycloheptynyl, cyclooctynyl, and

the like. Unless otherwise stated specifically in the specification, a cycloalkynyl group can be optionally substituted.

[0054] “Haloalkyl” refers to an alkyl, as defined above, that is substituted by one or more halo radicals, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group can be optionally substituted.

[0055] “Heterocyclyl,” “heterocyclic ring” or “heterocycle” refers to a stable saturated or unsaturated 3- to 20-membered ring which consists of two to nineteen carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and which is attached to the rest of the molecule by a single bond. Heterocyclyl or heterocyclic rings include heterocyclylalkyls, heterocyclylalkenyls, and heterocyclylalkynyls. Unless stated otherwise specifically in the specification, the heterocyclyl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused, bridged, or spirocyclic ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl can be partially or fully saturated. Examples of such heterocyclyl include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholyl, thiamorpholyl, 1-oxo-thiomorpholyl, and 1,1-dioxo-thiomorpholyl. Unless stated otherwise specifically in the specification, a heterocyclyl group can be optionally substituted.

[0056] “Heteroaryl” refers to a 5- to 20-membered ring system comprising hydrogen atoms, one to nineteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, at least one aromatic ring, and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the heteroaryl can be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl can be optionally oxidized; the nitrogen atom can be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl,

benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, carbazolyl, cinnolyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indolizyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalyl, quinolyl, quinuclidinyl, isoquinolyl, tetrahydroquinolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group can be optionally substituted.

[0057] “Heterocyclalkyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene, alkenylene, or alkynylene group as defined above and R_c is a heterocycl radical as defined above. Unless stated otherwise specifically in the specification, a heterocyclalkyl group can be optionally substituted.

[0058] The compounds disclosed herein, or their pharmaceutically acceptable salts include one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-, or by their relative stereochemistry (rel). The term “Rel” or “rel” as used herein therefore refers to a compound where the relationship between the identified stereocenters is known. Unless indicated otherwise, the present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms in cases where stereochemistry is not specifically depicted herein. Optically active compounds can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). Accordingly, in some embodiments, the compounds of the present disclosure are stereopure,

meaning that the compound exists as a single enantiomer and a single diastereomer (when more than one stereocenter is present). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0059] A “stereoisomer” refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes “enantiomers”, which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

[0060] The term “substituted” used herein means any of the groups described herein (*e.g.*, alkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, haloalkyl, heterocyclyl, and/or heteroaryl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (*e.g.*, a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, “substituted” includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_gR_h$, $-NR_gC(=O)R_h$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl,

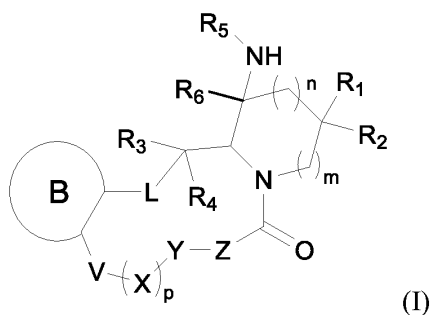
haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

[0061] As used herein, the symbol "" (hereinafter can be referred to as "a point of attachment bond") denotes a bond that is a point of attachment between two chemical entities, one of which is depicted as being attached to the point of attachment bond and the other of which is not depicted as being attached to the point of attachment bond. For example, " $XY\text{---}\text{$ " indicates that the chemical entity "XY" is bonded to another chemical entity via the point of attachment bond. Furthermore, the specific point of attachment to the non-depicted chemical entity can be specified by inference. For example, the compound $\text{CH}_3\text{---}R^3$, wherein R^3 is H or " $XY\text{---}\text{$ " infers that when R^3 is "XY", the point of attachment bond is the same bond as the bond by which R^3 is depicted as being bonded to CH_3 .

Compounds

[0062] The present disclosure provides macrocyclic compounds that are agonists of the orexin type 2 receptor as well as pharmaceutical compositions thereof and uses thereof in treating various diseases and disorders.

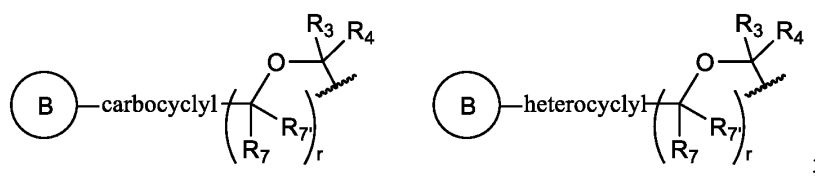
[0063] In one aspect, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

L is a linker selected from aryl, heteroaryl, $\text{-carbocyclyl-(CR}_7\text{CR}_7\text{)}_r\text{-O-}$, and $\text{-heterocyclyl-(CR}_7\text{CR}_7\text{)}_r\text{-O-}$, wherein $\text{-carbocyclyl-(CR}_7\text{CR}_7\text{)}_r\text{-O-}$ and $\text{-heterocyclyl-(CR}_7\text{CR}_7\text{)}_r\text{-O-}$ have the following orientation:



B is phenyl, 5- or 6-membered heteroaryl, cycloalkyl, or heterocyclyl;

V and Z are each independently -O- , $\text{-CR}_8\text{R}_9\text{-}$, or $\text{-NR}_{10}\text{-}$;

X is -O- , $\text{-CR}_{11}\text{R}_{12}\text{-}$, or $\text{-NR}_{13}\text{-}$;

Y is a bond, -O- , $\text{-CR}_8\text{R}_9\text{-}$, or $\text{-NR}_{10}\text{-}$;

R_1 and R_2 are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl, or R_1 and R_2 together with the atom to which they are attached form a carbocycle or heterocycle;

R_3 and R_4 are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl, or R_3 and R_4 together with the atom to which they are attached form a carbocycle or heterocycle;

R_5 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, aryl, heteroaryl, alkylene-heteroaryl, or alkylene- S(O)_2 -alkyl;

R₆ is H, alkyl, cycloalkyl, heterocyclyl, alkylene-cycloalkyl, alkylene-heterocyclyl, or -CN;

R₇ and R_{7'} are each independently H, halogen, or alkyl;

R₈ and R₉ are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl, or R₈ and R₉ together with the atom to which they are attached form a carbocycle or heterocycle;

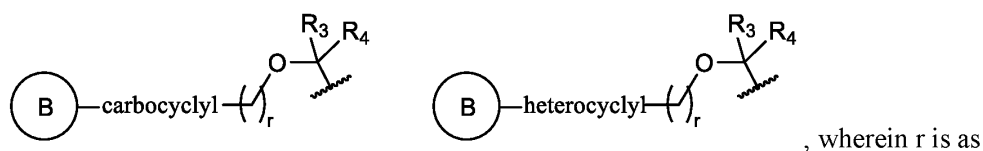
R₁₁ and R₁₂ are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl; or R₁₁ and R₁₂ together with the atom to which they are attached form a carbocycle or heterocycle;

R₁₀ and R₁₃ are each independently H, alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, -(C=O)alkyl, -(C=O)cycloalkyl, -(C=O)heterocyclyl, -(C=O)-O-alkyl, -(C=O)-O-cycloalkyl, -(C=O)-O-heterocyclyl, -(C=O)-O-heteroaryl, -S(O)₂-alkyl, -S(O)₂-cycloalkyl, or -S(O)₂-heterocyclyl;

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

r is 0 or 1.

[0064] In some embodiments, linker L is aryl, heteroaryl, -carbocyclyl-(CH₂)_r-O-, or -heterocyclyl-(CH₂)_r-O-, wherein -carbocyclyl-(CH₂)_r-O-, and -heterocyclyl-(CH₂)_r-O- have the following orientation:

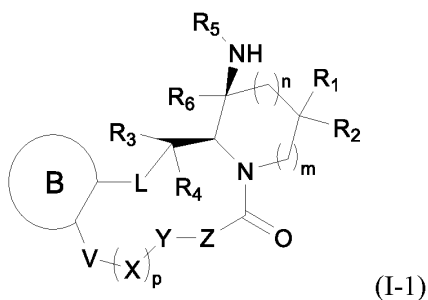


defined herein.

[0065] In some embodiments, linker L is aryl, heteroaryl, -cycloalkyl-O-, and -heterocyclyl-O-, wherein -cycloalkyl-O- and -heterocyclyl-O- have the following orientation:

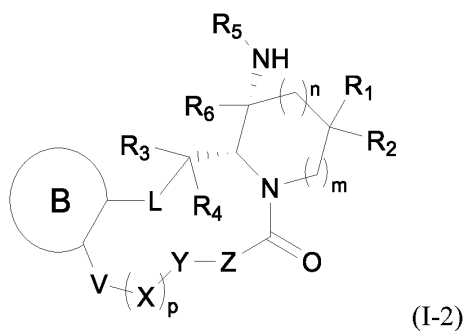


[0066] In some embodiments, the present disclosure provides a compound of Formula (I-1):



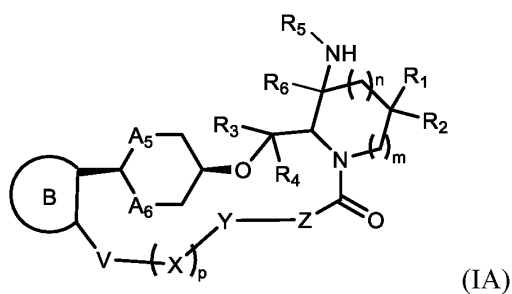
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein m, n, p, R₁, R₂, R₃, R₄, R₅, R₆, L, $\textcircled{\text{B}}$, V, X, Y and Z are as defined herein.

[0067] In some embodiments, the present disclosure provides a compound of Formula (I-2):



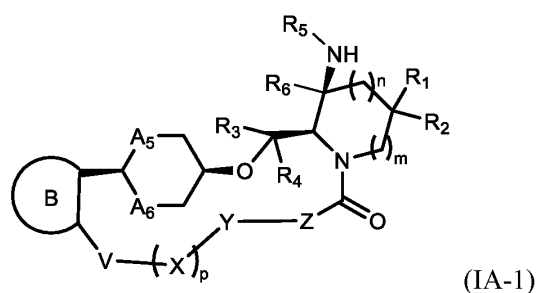
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein m, n, p, R₁, R₂, R₃, R₄, R₅, R₆, L, $\textcircled{\text{B}}$, V, X, Y and Z are as defined herein.

[0068] In some embodiments, the present disclosure provides a compound of Formula (IA):



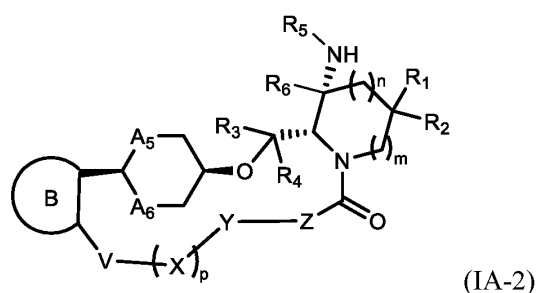
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein m, n, p, R₁, R₂, R₃, R₄, R₅, R₆, $\textcircled{\text{B}}$, V, X, Y and Z are as defined herein.

[0069] In some embodiments, the present disclosure provides a compound of Formula (IA-1):



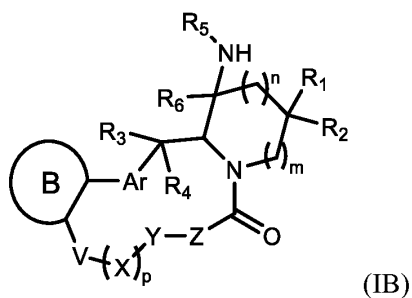
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein m, n, p, R₁, R₂, R₃, R₄, R₅, R₆, $\textcircled{\text{B}}$, V, X, Y and Z are as defined herein.

[0070] In some embodiments, the present disclosure provides a compound of Formula (IA-2):



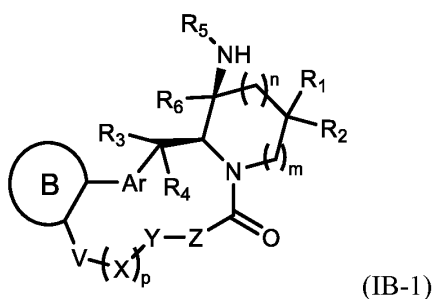
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein m, n, p, R₁, R₂, R₃, R₄, R₅, R₆, $\textcircled{\text{B}}$, V, X, Y and Z are as defined herein.

[0071] In some embodiments, the present disclosure provides a compound of Formula (IB):



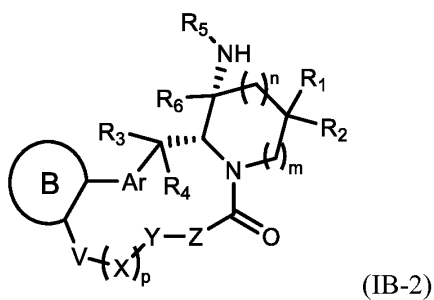
or a pharmaceutically acceptable salt thereof, wherein m, n, p, R₁, R₂, R₃, R₄, R₅, R₆, Ar, $\textcircled{\text{B}}$, V, X, Y and Z are as defined herein.

[0072] In some embodiments, the present disclosure provides a compound of Formula (IB-1):



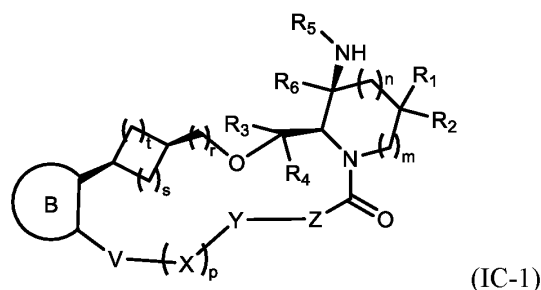
or a pharmaceutically acceptable salt thereof, wherein m, n, p, R₁, R₂, R₃, R₄, R₅, R₆, Ar, $\textcircled{\text{B}}$, V, X, Y and Z are as defined herein.

[0073] In some embodiments, the present disclosure provides a compound of Formula (IB-2):



or a pharmaceutically acceptable salt thereof, wherein m, n, p, R₁, R₂, R₃, R₄, R₅, R₆, Ar, $\textcircled{\text{B}}$, V, X, Y and Z are as defined herein.

[0074] In some embodiments, the present disclosure provides a compound of Formula (IC-1):



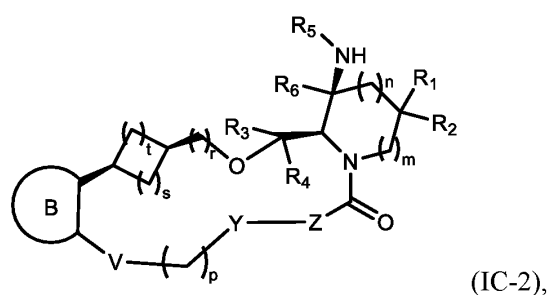
[0075] or a pharmaceutically acceptable salt thereof, wherein m, n, p, r, R₁, R₂, R₃, R₄, R₅, R₆, ^(B), V, X, Y and Z are as defined herein; s is 1 or 2; and t is 0, 1 or 2.

[0076] In some embodiments, s is 1. In some embodiments, s is 2.

[0077] In some embodiments, t is 1. In some embodiments, t is 2.

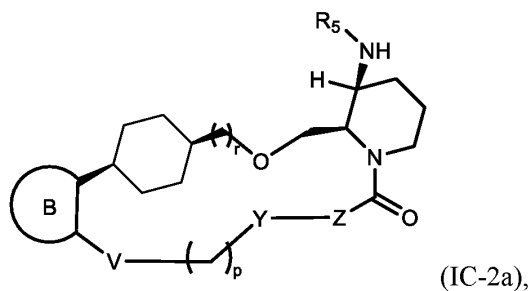
[0078] In some embodiments, s is 1 and t is 1. In some embodiments, s is 2 and t is 2. In some embodiments, s is 1 or 2 and t is 1. In some embodiments, s is 1 or 2 and t is 2. In some embodiments, s is 1 and t is 1 or 2. In some embodiments, s is 2 and t is 1 or 2.

[0079] In some embodiments, the present disclosure provides a compound of Formula (IC-2):



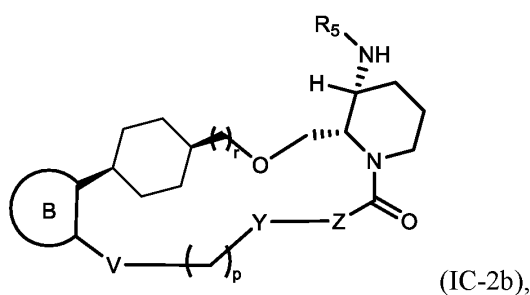
or a pharmaceutically acceptable salt thereof, wherein m, n, p, r, s, t, R₁, R₂, R₃, R₄, R₅, R₆, ^(B), V, Y and Z are as defined herein.

[0080] In some embodiments, the present disclosure provides a compound of Formula (IC-2a):



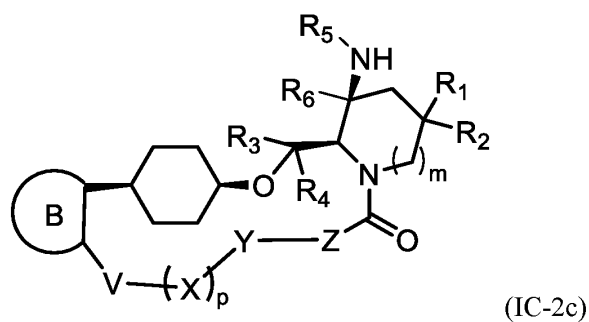
or a pharmaceutically acceptable salt thereof, wherein p , r , R_5 , $\textcircled{B}$, V , Y and Z are as defined herein.

[0081] In some embodiments, the present disclosure provides a compound of Formula (IC-2b):



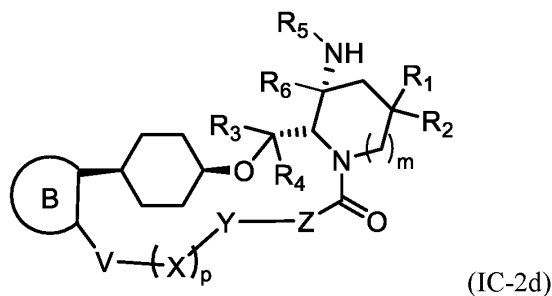
or a pharmaceutically acceptable salt thereof, wherein p , r , R_5 , $\textcircled{B}$, V , Y and Z are as defined herein.

[0082] In some embodiments, the present disclosure provides a compound of Formula (IC-2c):



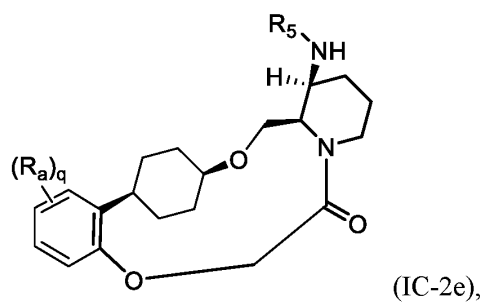
or a pharmaceutically acceptable salt thereof, wherein m , p , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , $\textcircled{B}$, V , X , Y and Z are defined herein.

[0083] In some embodiments, the present disclosure provides a compound of Formula (IC-2d):



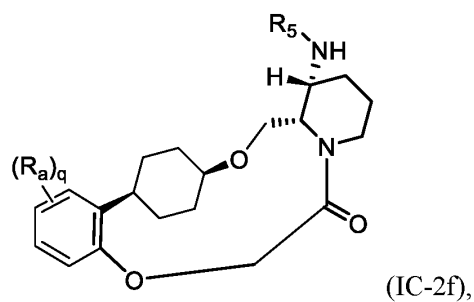
or a pharmaceutically acceptable salt thereof, wherein m , p , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , $\textcircled{B}$, V , X , Y and Z are defined herein.

[0084] In some embodiments, the present disclosure provides a compound of Formula (IC-2e):



or a pharmaceutically acceptable salt thereof, wherein q , R_a , and R_5 are as defined herein.

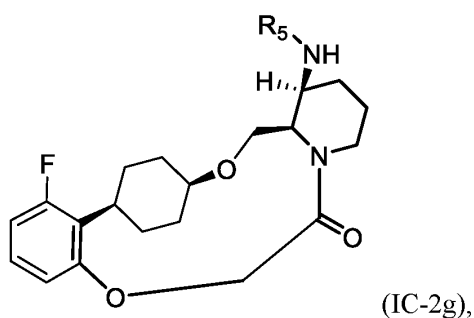
[0085] In some embodiments, the present disclosure provides a compound of Formula (IC-2f):



or a pharmaceutically acceptable salt thereof, wherein q , R_a , and R_5 are as defined herein.

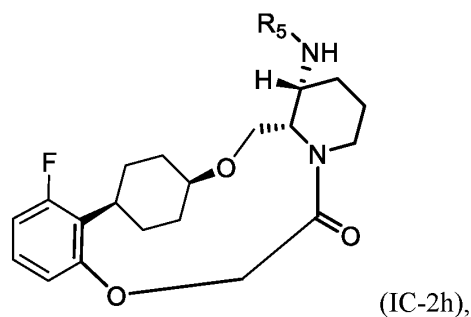
[0086] In some embodiments, R_a is H, halogen, or alkyl; and q is 1 or 2. In some embodiments, R_a is H, F, or Me and q is 0 or 1. In some embodiments, R_a is F or Me and q is 1. In some embodiments, R_a is F and q is 1.

[0087] In some embodiments, the present disclosure provides a compound of Formula (IC-2g):



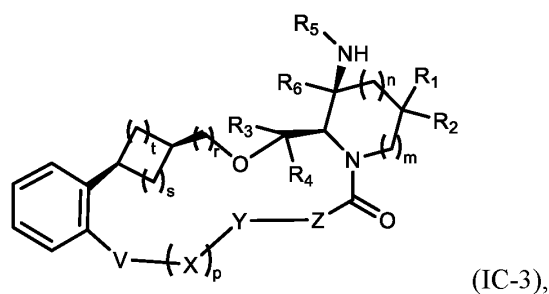
or a pharmaceutically acceptable salt thereof, wherein R_5 is as defined herein.

[0088] In some embodiments, the present disclosure provides a compound of Formula (IC-2h):



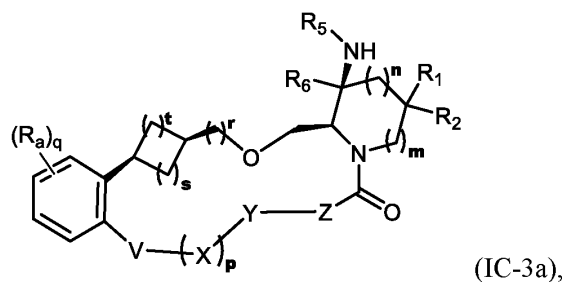
or a pharmaceutically acceptable salt thereof, wherein R_5 is as defined herein.

[0089] In some embodiments, the present disclosure provides a compound of Formula (IC-3):



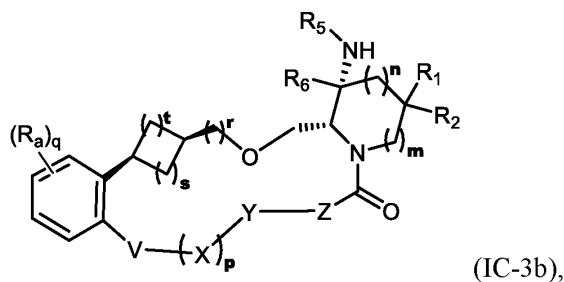
or a pharmaceutically acceptable salt thereof, wherein m, n, p, r, s, t, R₁, R₂, R₃, R₄, R₅, R₆, V, X, Y and Z are as defined herein.

[0090] In some embodiments, the present disclosure provides a compound of Formula (IC-3a):



or a pharmaceutically acceptable salt thereof, wherein m, n, p, q, r, s, t, R_a, R₁, R₂, R₃, R₄, R₅, R₆, V, X, Y and Z are as defined herein.

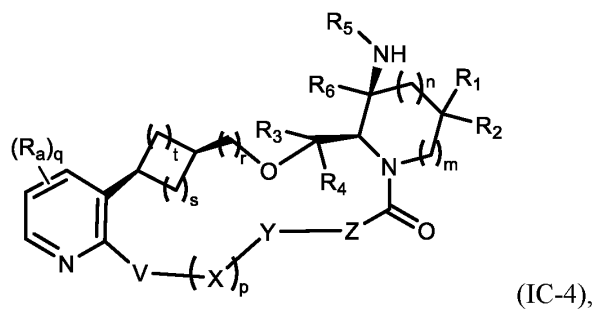
[0091] In some embodiments, the present disclosure provides a compound of Formula (IC-3b):



or a pharmaceutically acceptable salt thereof, wherein m, n, p, q, r, s, t, R_a, R₁, R₂, R₃, R₄, R₅, R₆, V, X, Y and Z are as defined herein.

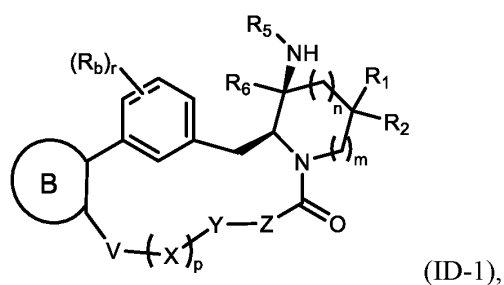
[0092] In some embodiments, R_a is H, halogen, or alkyl; and q is 1 or 2. In some embodiments, R_a is H, F, or Me and q is 0 or 1. In some embodiments, R_a is F or Me and q is 1. In some embodiments, R_a is F and q is 1.

[0093] In some embodiments, the present disclosure provides a compound of Formula (IC-4):



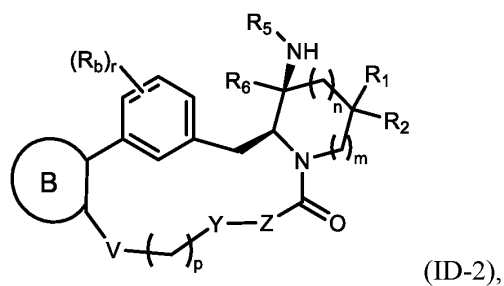
[0094] or a pharmaceutically acceptable salt thereof, wherein m, n, p, q, r, s, t, R_a , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , V, X, Y and Z are as defined herein.

[0095] In some embodiments, the present disclosure provides a compound of Formula (ID-1):



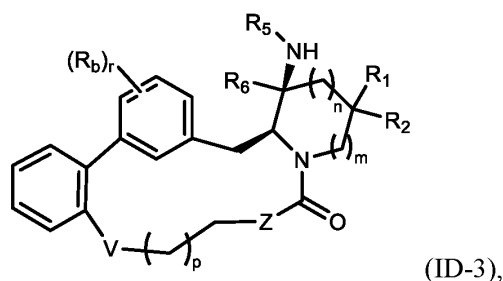
or a pharmaceutically acceptable salt thereof, wherein m, n, p, r, R_b , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , $\textcircled{B}$, V, X, Y and Z are defined herein.

[0096] In some embodiments, the present disclosure provides a compound of Formula (ID-2):



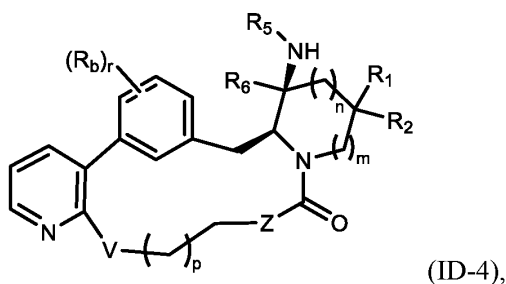
or a pharmaceutically acceptable salt thereof, wherein m, n, p, r, R_b , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , $\textcircled{B}$, V, Y and Z are defined herein.

[0097] In some embodiments, the present disclosure provides a compound of Formula (ID-3):



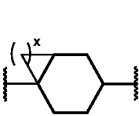
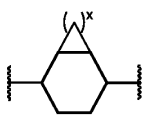
or a pharmaceutically acceptable salt thereof, wherein m, n, p, r, R_b, R₁, R₂, R₃, R₄, R₅, R₆, V, and Z are defined herein.

[0098] In some embodiments, the present disclosure provides a compound of Formula (ID-4):

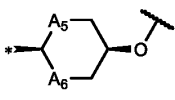


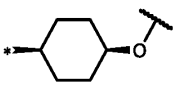
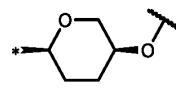
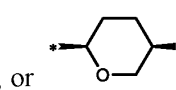
[0099] or a pharmaceutically acceptable salt thereof, wherein m, n, p, r, R_b, R₁, R₂, R₃, R₄, R₅, R₆, V, and Z are defined herein.

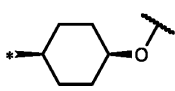
[0100] In some embodiments, linker L is aryl, -carbocyclyl-(CH₂)_r-O-, and -heterocyclyl-(CH₂)_r-O-, wherein r is 0 or 1. In some embodiments, L is -carbocyclyl-(CH₂)_r-O- or -heterocyclyl-(CH₂)_r-O-, wherein r is 0 or 1. In some embodiments, L is -carbocyclyl-(CH₂)_r-O-, wherein r is 0 or 1. In some embodiments, L is -heterocyclyl-(CH₂)_r-O-, wherein r is 0 or 1. In some embodiments, r is 0 and L is -carbocyclyl-O- or -heterocyclyl-O-. In some embodiments, the carbocyclyl is a C₃₋₆ cycloalkyl. In some embodiments, the carbocyclyl is cyclohexyl or cyclobutyl. In some embodiments, the carbocyclyl is cyclohexyl. In some embodiments, the

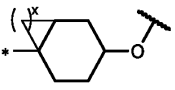
carbocyclyl is cyclobutyl. In some embodiments, the carbocyclyl is  or , wherein x is 1, 2, 3, or 4. In some embodiments, the heterocyclyl is a 4- to 6-membered

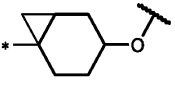
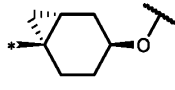
heterocyclyl. In some embodiments, the heterocycle comprises 1 or 2 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, L is a –carbocyclyl-O– or –

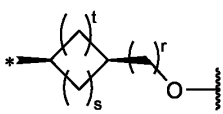
heterocyclyl-O– linker having the structure , wherein A₅ and A₆ are each independently –O– or –CH₂–. In some embodiments, A₅ is –O–. In some embodiments, A₅ is –CH₂–. In some embodiments, A₆ is –O–. In some embodiments, A₆ is –CH₂–. In some

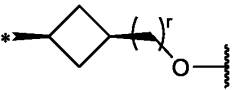
embodiments, L has the structure , , or . In some

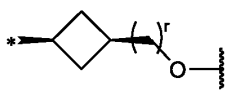
embodiments, L has the structure . In some embodiments, L has the structure

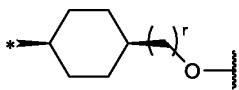
, wherein x is 1, 2, 3, or 4. In some embodiments, L has the structure

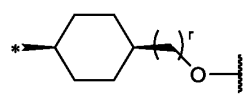
. In some embodiments, L has the structure . In some

embodiments, L is a –carbocyclyl-(CH₂)_r-O–linker having the structure , wherein r is 0 or 1; s is 1 or 2; and t is 1 or 2. In some embodiments, s is 1 and t is 1. In some embodiments, s is 2 and t is 2. In some embodiments, L is a –carbocyclyl-(CH₂)_r-O–linker having

the structure , wherein r is 0 or 1. In some embodiments, L is a –carbocyclyl-

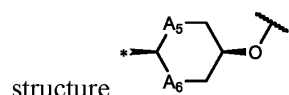
(CH₂)_r-O–linker having the structure , wherein r is 0 or 1. In some

embodiments, L is a –carbocyclyl-(CH₂)_r-O–linker having the structure , wherein r is 0 or 1. In some embodiments, L is a –carbocyclyl-(CH₂)_r-O–linker having the structure

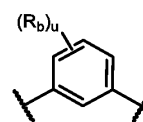


, wherein r is 0. In the above embodiments, $*$ represents the point of attachment to (B).

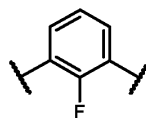
[0101] In some embodiments, L is a $-\text{carbocyclyl-O}-$ or $-\text{heterocyclyl-O}-$ linker having the



structure, wherein A_5 and A_6 are each independently $-\text{O}-$ or $-\text{CH}_2-$, and $*$ represents the point of attachment to (B). In some embodiments, A_5 is $-\text{O}-$. In some embodiments, A_5 is $-\text{CH}_2-$. In some embodiments, A_6 is $-\text{O}-$. In some embodiments, A_6 is $-\text{CH}_2-$.

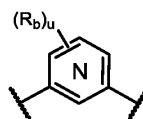


[0102] In some embodiments, L is an aryl linker having the structure, wherein R_b is halogen, alkyl, or alkoxy; and u is 0, 1, or 2. In some embodiments, R_b is halogen. In some embodiments, the halogen is fluoride. In some embodiments, u is 1. In some embodiments, u is 0.



In some embodiments, the aryl linker is

[0103] In some embodiments, L is a 5- or 6-membered heteroaryl linker. In some embodiments, L is a 5- or 6-membered heteroaryl linker having 1 or 2 nitrogen atoms. In some embodiments,



linker L is a heteroaryl linker having the structure, wherein R_b is halogen, alkyl, or alkoxy; and u is 0 or 1. In some embodiments, u is 0. In some embodiments, u is 1.

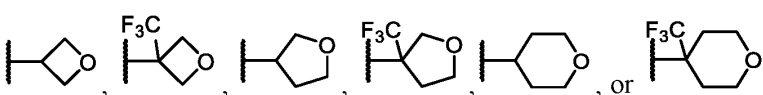
[0104] In some embodiments, R_1 , R_2 , R_3 , R_4 , R_8 , R_9 , R_{11} , and R_{12} are each independently H, halogen, alkyl, or cycloalkyl. In some embodiments, R_1 , R_2 , R_3 , R_4 , R_8 , R_9 , R_{11} , and R_{12} are each independently H, halogen, or alkyl. In some embodiments, the alkyl is a C_{1-5} alkyl. In some embodiments, the alkyl is methyl, ethyl, or isopropyl. In some embodiments, the cycloalkyl is a C_{3-6} cycloalkyl. In some embodiments, the cycloalkyl is a cyclopropyl.

[0105] In some embodiments, R₁ and R₂ are each independently H, halogen, or alkyl. In some embodiments, R₁ and R₂ are each independently H or alkyl. In some embodiments, R₁ and R₂ are alkyl. In some embodiments, the alkyl is methyl or ethyl. In some embodiments, R₁ and R₂ are H. In some embodiments, R₁ and R₂ are H or halogen. In some embodiments, halogen is fluoride. In some embodiments, R₁ and R₂ together with the carbon atom to which they are attached form a carbocycle or heterocycle. In some embodiments, the carbocycle is a C₃₋₆ cycloalkyl. In some embodiments, the carbocycle is a cyclopropyl. In some embodiments, the heterocycle is a 3- or 6-membered heterocycle. In some embodiments, the heterocycle comprises 1 or 2 heteroatoms selected from the group consisting of N, O, and S.

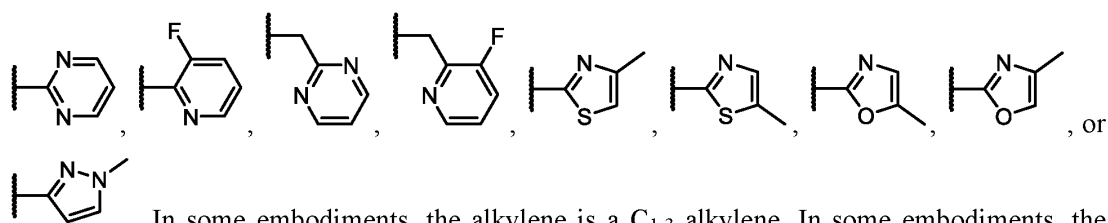
[0106] In some embodiments, R₃ and R₄ are each independently H, halogen, or alkyl. In some embodiments, R₃ and R₄ are each independently H or alkyl. In some embodiments, R₃ and R₄ are each alkyl. In some embodiments, the alkyl is methyl or ethyl. In some embodiments, R₃ and R₄ are each independently H or halogen. In some embodiments, R₃ and R₄ are H. In some embodiments, R₃ and R₄ are halogen. In some embodiments, the halogen is fluoride. In some embodiments, R₃ and R₄ together with the carbon atom to which they are attached form a carbocycle or heterocycle. In some embodiments, the carbocycle is a C₃₋₆ cycloalkyl. In some embodiments, the carbocycle is a cyclopropyl. In some embodiments, the heterocycle is a 3- or 6-membered heterocycle. In some embodiments, the heterocycle comprises 1 or 2 heteroatoms selected from the group consisting of N, O, and S.

[0107] In some embodiments, R₅ is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, aryl, heteroaryl, alkylene-heteroaryl, or alkylene-S(O)₂-alkyl. In some embodiments, R₅ is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, aryl, heteroaryl, alkylene-heteroaryl, or alkylene-S(O)₂-alkyl, each of which is optionally substituted with one or more halogen, C₁₋₅ alkyl, C₁₋₅ haloalkyl, -O-C₁₋₅ alkoxy, and/or -CN. In some embodiments, R₅ is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, heteroaryl, or alkylene-heteroaryl. In some embodiments, R₅ is C₁₋₅ alkyl, C₃₋₆ cycloalkyl, (C₁₋₃ alkylene)-C₃₋₆ cycloalkyl, 4- to 6-membered heterocyclyl, (C₁₋₃ alkylene)-(4- to 6-membered heterocyclyl), 5- to 6-membered heteroaryl, or (C₁₋₃ alkylene)-(5- to 6-membered heteroaryl). In some embodiments, R₅ is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, or alkylene-heterocyclyl. In some embodiments, R₅ is C₁₋₅ alkyl, C₃₋₆ cycloalkyl, (C₁₋₃ alkylene)-C₃₋₆ cycloalkyl, 4- to 6-membered

heterocyclyl, or (C₁₋₃ alkylene)-(4- to 6-membered heterocyclyl). In some embodiments, R₅ is cycloalkyl, heterocyclyl, or heteroaryl. In some embodiments, R₅ is cycloalkyl or heterocyclyl. In some embodiments, R₅ is heteroaryl. In some embodiments, R₅ is a C₁₋₅ alkyl, optionally substituted with one or more halogen and/or hydroxy. In some embodiments, R₅ is a C₁₋₅ alkyl or -CH₂-(C₃₋₆ cycloalkyl), each of which is optionally substituted with one or more F, CN, or CH₃. In some embodiments, R₅ is a C₁₋₅ alkyl, optionally substituted with one or more F, CN, or CH₃. In some embodiments, R₅ is a C₁₋₅ haloalkyl. In some embodiments, R₅ is a C₃₋₆ cycloalkyl, optionally substituted with one or more halogen and/or C₁₋₃ haloalkyl. In some embodiments, R₅ is cyclopropyl or cyclobutyl, each of which is optionally substituted with one or more halogen and/or C₁₋₃ haloalkyl. In some embodiments, R₅ is a cyclopropyl or cyclobutyl. In some embodiments, R₅ is a cyclopropyl or cyclobutyl, each of which is optionally substituted with one or more halogen and/or C₁₋₃ haloalkyl. In some embodiments, R₅ is a 4- to 6-membered heterocyclyl. In some embodiments, the R₅ is an oxetane, tetrahydrofuran, tetrahydropyran, morpholine, or thiomorpholine, each of which is optionally substituted with a C₁₋₃ haloalkyl. In

some embodiments, R₅ is . In

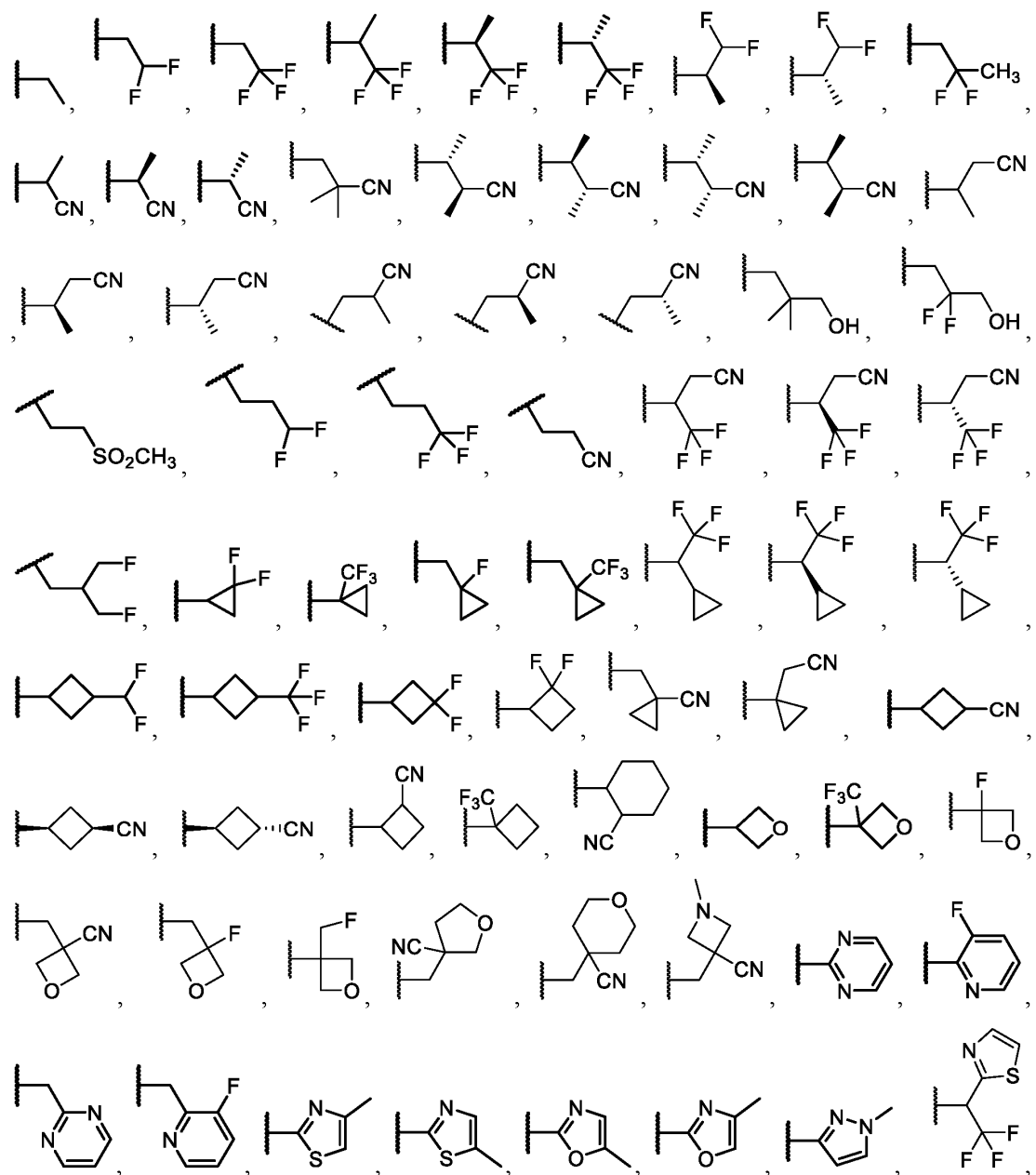
some embodiments, R₅ is phenyl. In some embodiments, R₅ is a 5- or 6-membered heteroaryl. In some embodiments, R₅ is 5- or 6-membered nitrogen-containing heteroaryl. In some embodiments, R₅ is 5-membered heteroaryl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, R₅ is heteroaryl, optionally substituted with one or more halogen and/or C₁₋₅ alkyl. In some embodiments, R₅ is heteroaryl optionally substituted with one or more F, CH₃, CH₂CH₃, CH(CH₃)₂, CF₃, CHF₂, and/or CH₂CF₃. In some embodiments, R₅ is

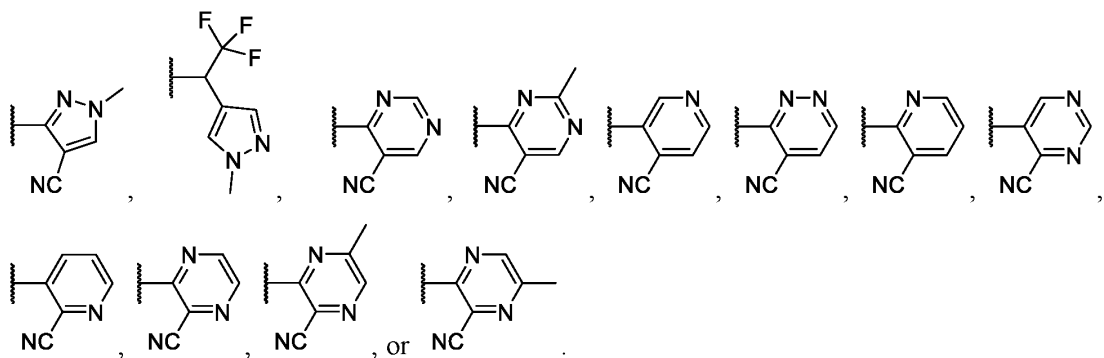


. In some embodiments, the alkylene is a C₁₋₃ alkylene. In some embodiments, the alkylene is -CH₂-. In some embodiments, R₅ is optionally substituted with one or more halogen, -OH, -O-alkyl, -CN, and/or alkyl. In some embodiments, R₅ is optionally substituted with one or more F, -OH, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -OCF₃, -OCHF₂, -OCH₂CF₃, -CN, CH₃, CH₂CH₃,

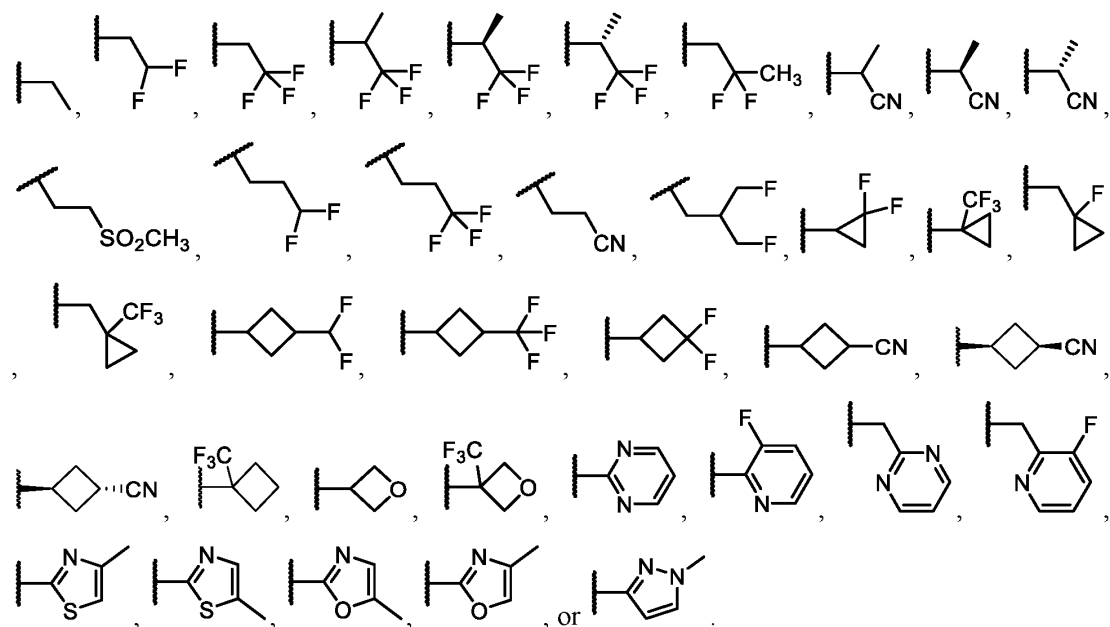
$\text{CH}(\text{CH}_3)_2$, CF_3 and/or CHF_2 . In some embodiments, R_5 is optionally substituted with one or more F, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $-\text{CN}$, CF_3 and/or CHF_2 .

[0108] In some embodiments, R_5 is:

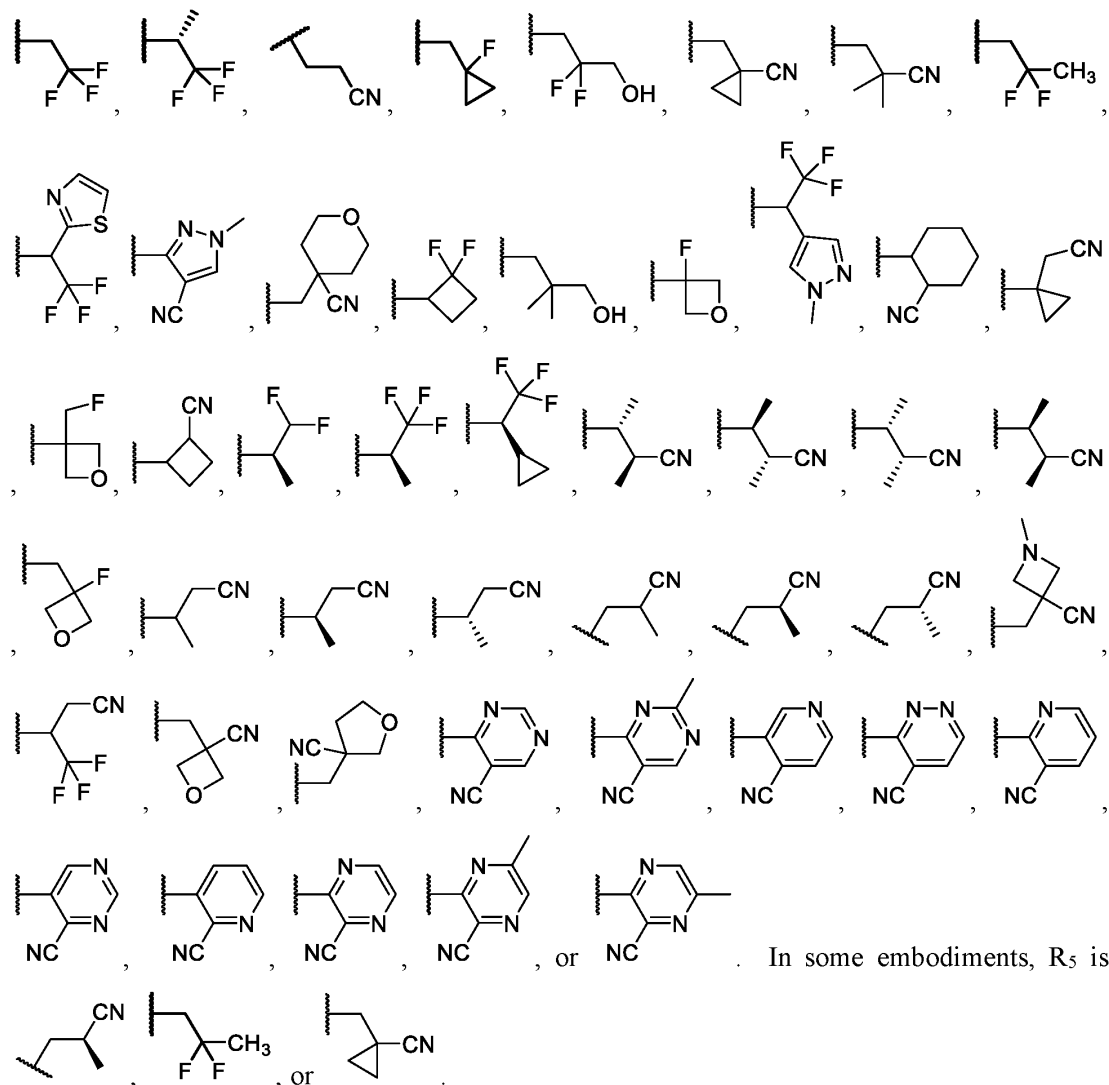




[0109] In some embodiments, R₅ is:



[0110] In some embodiments, R₅ is:



[0111] In some embodiments, R₆ is H, alkyl, cycloalkyl, heterocyclyl, or -CN. In some embodiments, R₆ is H or C₁₋₅ alkyl. In some embodiments, R₆ is H or methyl. In some embodiments, R₆ is H. In some embodiments, R₆ is methyl.

[0112] In some embodiments, R₁₀ and R₁₃ are each independently H, alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, -(C=O)alkyl, -(C=O)cycloalkyl, -(C=O)heterocyclyl, -(C=O)-O-alkyl, -(C=O)-O-cycloalkyl, -(C=O)-O-heterocyclyl, -(C=O)-

O-heteroaryl, $-\text{S}(\text{O})_2\text{-alkyl}$, $-\text{S}(\text{O})_2\text{-cycloalkyl}$, or $-\text{S}(\text{O})_2\text{-heterocyclyl}$. In some embodiments, R_{10} and R_{13} are each independently H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-(\text{C}=\text{O})\text{alkyl}$, $-(\text{C}=\text{O})\text{cycloalkyl}$, $-(\text{C}=\text{O})\text{-O-alkyl}$, $-(\text{C}=\text{O})\text{-O-cycloalkyl}$, $-\text{S}(\text{O})_2\text{-alkyl}$, or $-\text{S}(\text{O})_2\text{-cycloalkyl}$. In some embodiments, R_{10} and R_{13} are each independently H, alkyl, cycloalkyl, $-(\text{C}=\text{O})\text{alkyl}$, $-(\text{C}=\text{O})\text{cycloalkyl}$, $-(\text{C}=\text{O})\text{-O-alkyl}$, $-(\text{C}=\text{O})\text{-O-cycloalkyl}$, $-\text{S}(\text{O})_2\text{-alkyl}$, $-\text{S}(\text{O})_2\text{-cycloalkyl}$, or $-\text{S}(\text{O})_2\text{-heterocyclyl}$. In some embodiments, R_{10} and R_{13} are each independently H, alkyl, $-(\text{C}=\text{O})\text{alkyl}$, or $-\text{S}(\text{O})_2\text{-alkyl}$. In some embodiments, the alkyl is a $\text{C}_{1-5}\text{alkyl}$. In some embodiments, the alkyl is methyl, ethyl, or isopropyl. In some embodiments, the cycloalkyl is a $\text{C}_{3-6}\text{cycloalkyl}$. In some embodiments, the aryl is a phenyl. In some embodiments, the heterocyclyl is a 5- or 6-membered heterocyclyl having 1 or 2 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, the heteroaryl is a 5- or 6-membered heteroaryl having 1, 2 or 3 heteroatoms selected from the group consisting of N, O, and S.

[0113] In some embodiments, V is $-\text{O}-$ or $-\text{CR}_8\text{R}_9-$. In some embodiments, V is $-\text{O}-$ or $-\text{NR}_{10}-$. In some embodiments, V is $-\text{O}-$. In some embodiments, V is $-\text{CR}_8\text{R}_9-$. In some embodiments, R_8 and R_9 are each independently H or alkyl.

[0114] In some embodiments, X is $-\text{O}-$ or $-\text{NR}_{13}-$. In some embodiments, X is $-\text{O}-$ or $-\text{CR}_{11}\text{R}_{12}-$. In some embodiments, X is $-\text{CR}_{11}\text{R}_{12}-$ or $-\text{NR}_{13}-$. In some embodiments, X is $-\text{CR}_{11}\text{R}_{12}-$. In some embodiments, X is $-\text{CH}_2-$.

[0115] In some embodiments, Y is a bond, $-\text{CR}_8\text{R}_9-$, or $-\text{NR}_{10}-$. In some embodiments, Y is a bond, $-\text{O}-$, or $-\text{CR}_8\text{R}_9-$. In some embodiments, Y is a bond or $-\text{CR}_8\text{R}_9-$. In some embodiments, Y is a bond. In some embodiments, Y is a $-\text{CR}_8\text{R}_9-$. In some embodiments, Y is $-\text{CH}_2-$.

[0116] In some embodiments, Z is a $-\text{NR}_{10}-$ or $-\text{CR}_8\text{R}_9-$. In some embodiments, Z is $-\text{NR}_{10}-$. In some embodiments, R_8 and R_9 are each independently H or alkyl. In some embodiments, R_8 and R_9 together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl. In some embodiments, R_{10} is H, alkyl, $-(\text{C}=\text{O})\text{alkyl}$, or $-\text{S}(\text{O})_2\text{-alkyl}$. In some embodiments, R_{10} is H or alkyl. In some embodiments, the alkyl is methyl, ethyl, or isopropyl. In some embodiments, the alkyl is methyl.

[0117] In some embodiments, $\text{V}(\text{X})_p\text{-Y-Z}$ is $-\text{O}(\text{CH}_2)_p\text{-CH}_2\text{-CH}_2-$ or $-\text{O}(\text{CH}_2)_p\text{-CH}_2-$, wherein p is 0 or 1. In some embodiments, $\text{V}(\text{X})_p\text{-Y-Z}$ is $-\text{O}(\text{CH}_2)_p\text{-CH}_2\text{-O}-$, wherein p is 1. In some

embodiments, $V-(X)_p-Y-Z$ is $-O-CH_2-CH_2-O-$. In some embodiments, $V-(X)_p-Y-Z$ is $-O-CH_2-O-$. In some embodiments, $V-(X)_p-Y-Z$ is $-O-CH_2-$. In some embodiments, $V-(X)_p-Y-Z$ is $-O-CH_2-CH_2-$.

[0118] In some embodiments, $V-(X)_p-Y-Z$ does not comprise an $-O-O-$ or $-N-N-$ bond.

[0119] In some embodiments, R_8 and R_9 are each independently H, halogen, or alkyl. In some embodiments, R_8 and R_9 are each independently H or alkyl. In some embodiments, R_8 and R_9 are alkyl. In some embodiments, the alkyl is methyl or ethyl. In some embodiments, R_8 and R_9 are each independently H or halogen. In some embodiments, R_8 and R_9 are H. In some embodiments, R_8 and R_9 are halogen. In some embodiments, the halogen is fluoride. In some embodiments, R_8 and R_9 together with the carbon atom to which they are attached form a carbocycle or heterocycle. In some embodiments, the carbocycle is a C_{3-6} cycloalkyl. In some embodiments, the carbocycle is a cyclopropyl. In some embodiments, the heterocycle is a 3- or 6-membered heterocycle. In some embodiments, the heterocycle comprises 1 or 2 heteroatoms selected from the group consisting of N, O, and S.

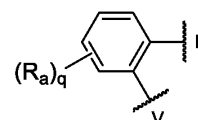
[0120] In some embodiments, R_{10} is H, alkyl, cycloalkyl, $-(C=O)-O-$ alkyl, $-S(O)_2-$ alkyl. In some embodiments, R_{10} is H, alkyl, cycloalkyl, $-(C=O)-O-$ alkyl, or $-S(O)_2-$ alkyl. In some embodiments, R_{10} is H, alkyl, $-(C=O)-O-$ alkyl, or $-S(O)_2-$ alkyl. In some embodiments, R_{10} is H, alkyl, or cycloalkyl. In some embodiments, R_{10} is H or alkyl. In some embodiments, R_{10} is alkyl. In some embodiments, the alkyl is a C_{1-5} alkyl. In some embodiments, the alkyl is methyl, ethyl, or isopropyl. In some embodiments, the alkyl is methyl. In some embodiments, the cycloalkyl is a C_{3-6} cycloalkyl.

[0121] In some embodiments, R_{11} and R_{12} are each independently H, halogen, or alkyl. In some embodiments, R_{11} and R_{12} are each independently H or alkyl. In some embodiments, R_{11} and R_{12} are alkyl. In some embodiments, the alkyl is methyl or ethyl. In some embodiments, R_{11} and R_{12} are each independently H or halogen. In some embodiments, R_{11} and R_{12} are H. In some embodiments, R_{11} and R_{12} are halogen. In some embodiments, the halogen is fluoride. In some embodiments, R_{11} and R_{12} together with the carbon atom to which they are attached form a carbocycle or heterocycle. In some embodiments, the carbocycle is a C_{3-6} cycloalkyl. In some embodiments, the carbocycle is a cyclopropyl. In some embodiments, the heterocycle is a 3- or 6-

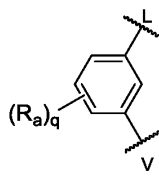
membered heterocycle. In some embodiments, the heterocycle comprises 1 or 2 heteroatoms selected from the group consisting of N, O, and S.

[0122] In some embodiments, $\textcircled{\text{B}}$ is phenyl or 5- or 6-membered heteroaryl.

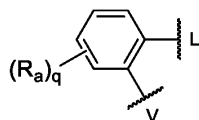
[0123] In some embodiments, $\textcircled{\text{B}}$ is phenyl. In some embodiments, $\textcircled{\text{B}}$ is:



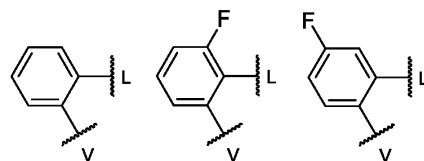
or



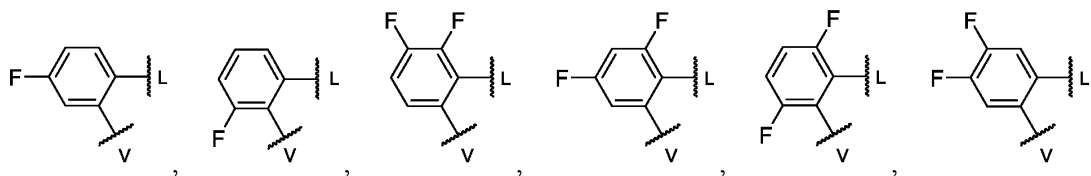
, wherein R_a is each independently halogen, alkyl, -CN, or alkoxy; and q is 0, 1, or

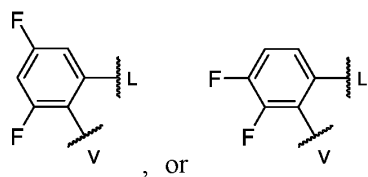


2. In some embodiments, $\textcircled{\text{B}}$ is: , wherein R_a is each independently halogen, alkyl, -CN, or alkoxy; and q is 0, 1, or 2. In some embodiments, R_a is each independently halogen or C_{1-5} alkyl optionally substituted with one or more fluoride. In some embodiments, R_a is each independently F, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, CF_3 , $CHCF_2$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-OCHCF_2$, or -CN. In some embodiments, R_a is each independently F, CH_3 , CH_2CH_3 , CF_3 , CHF_2 , $-OCH_3$, $-OCF_3$, or $-OCHF_2$. In some embodiments, R_a is each independently F, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, CF_3 , $CHCF_2$, or -CN. In some embodiments, R_a is each independently F or CH_3 . In some embodiments, each R_a is F. In some embodiments, q is 0 or 1. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 2.

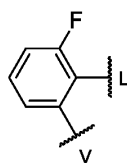


In some embodiments, when $\textcircled{\text{B}}$ is phenyl, the phenyl is:

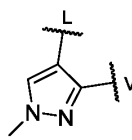




. In some embodiments, when (B) is phenyl, the phenyl is:

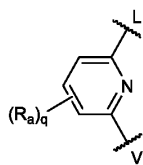
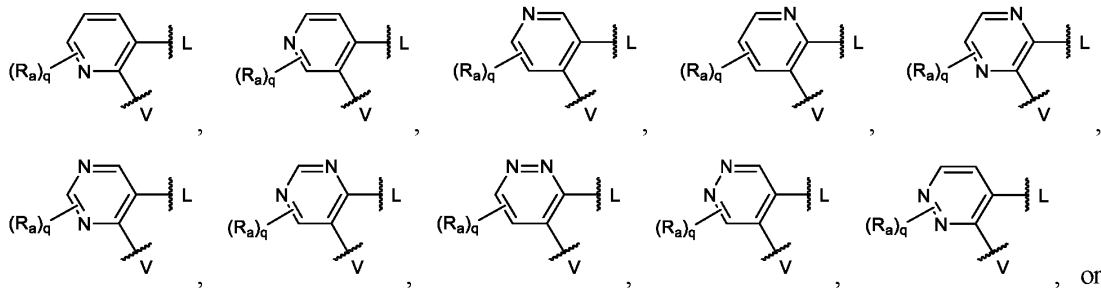


[0124] In some embodiments, (B) is a 5-membered heteroaryl. In some embodiments, (B) is 5-membered heteroaryl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O,

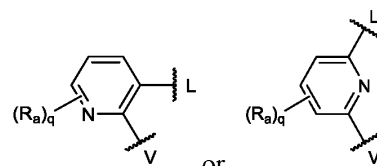


and S. In some embodiments, the 5-membered heteroaryl is

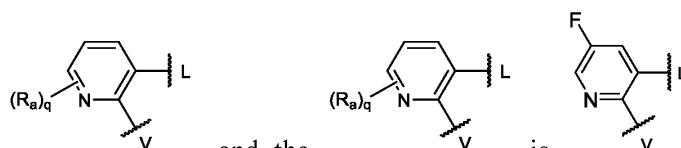
(B) is a 6-membered heteroaryl. In some embodiments, (B) is a 6-membered heteroaryl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, (B) is a 6-membered heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyrimidinyl, or pyridazinyl. In some embodiments, the 6-membered heteroaryl is:



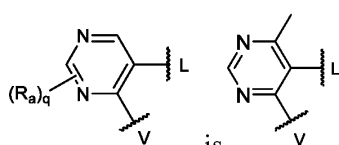
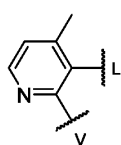
, wherein R_a is each independently halogen, alkyl, -CN, or alkoxy; and q is 0, 1, or 2.



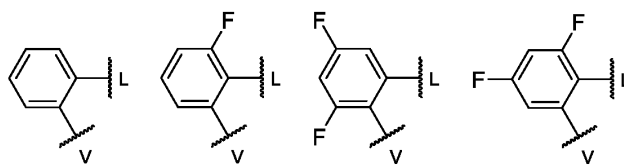
In some embodiments, the 6-membered heteroaryl is: or , wherein R_a is each independently halogen, alkyl, -CN, or alkoxy; and q is 0, 1, or 2. In some embodiments,



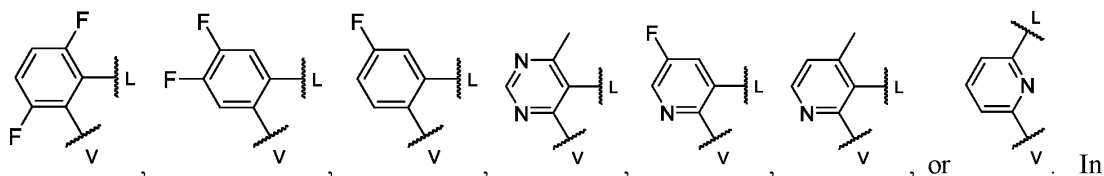
the 6-membered heteroaryl is , and the is or

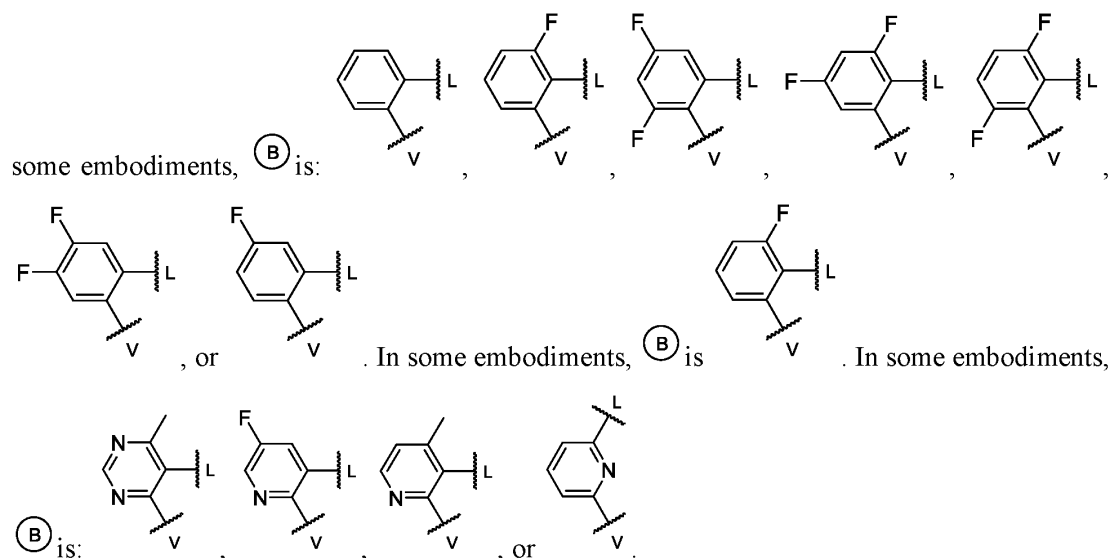


. In some embodiments, is . In some embodiments, R_a is each independently halogen or alkyl. In some embodiments, R_a is each independently halogen or C_{1-5} alkyl. In some embodiments, R_a is each independently F, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, CF_3 , $CHCF_2$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-OCHCF_2$, or -CN. In some embodiments, R_a is each independently F, CH_3 , CH_2CH_3 , CF_3 , CHF_2 , $-OCH_3$, $-OCF_3$, or $-OCHF_2$. In some embodiments, R_a is each independently F, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, CF_3 , $CHCF_2$, or -CN. In some embodiments, R_a is each independently F or CH_3 . In some embodiments, each R_a is F. In some embodiments, each R_a is CH_3 . In some embodiments, q is 0 or 1. In some embodiments, q is 0. In some embodiments, q is 1.



[0125] In some embodiments, (B) is:





[0126] In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1.

[0127] In some embodiments, n is 0 or 1. In some embodiments, n is 1.

[0128] In some embodiments, the sum of m and n is from 1 to 3. In some embodiments, the sum of m and n is 1 or 2. In some embodiments, m is 0 and n is 1 or 2. In some embodiments, m is 1 and n is 0, 1, or 2. In some embodiments, n is 0 and m is 1 or 2. In some embodiments, n is 1 and m is 0, 1, or 2. In some embodiments, m is 0 and n is 1; n is 0 and m is 1; or m is 1 and n is 1. In some embodiments, m is 1 and n is 1. In some embodiments, m is 0 and n is 1. In some embodiments, n is 0 and m is 1.

[0129] In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1.

[0130] In some embodiments, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{O}-$, $-\text{CH}_2-$, or $-\text{N}(\text{alkyl})-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

[0131] In some embodiments, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{O}-$, $-\text{CH}_2-$, $-\text{CH}(\text{Me})-$, or $-\text{N}(\text{alkyl})-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

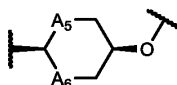
[0132] In some embodiments, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$ or $-\text{O}-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

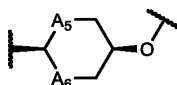
[0133] In some embodiments, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$, m is 0 or 1, n is 1, and p is 0 or 1.

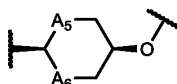
[0134] In some embodiments, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond, Z is $-\text{CH}_2-$, m is 0 or 1, n is 1, and p is 0.

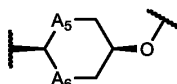
[0135] In some embodiments, L is $-\text{carbocyclyl-O}-$ or $-\text{heterocyclyl-O}-$, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{O}-$, $-\text{CH}_2-$, $-\text{CH}(\text{Me})-$, or $-\text{N}(\text{alkyl})-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

[0136] In some embodiments, L is $-\text{carbocyclyl-O}-$ or $-\text{heterocyclyl-O}-$, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$ or $-\text{O}-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

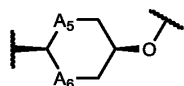


[0137] In some embodiments, L is , wherein A_5 and A_6 are each independently $-\text{CH}_2-$ or $-\text{O}-$, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{O}-$, $-\text{CH}_2-$, $-\text{CH}(\text{Me})-$, or $-\text{N}(\text{alkyl})-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.



[0138] In some embodiments, L is , wherein A_5 and A_6 are each independently $-\text{CH}_2-$ or $-\text{O}-$, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$ or $-\text{O}-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

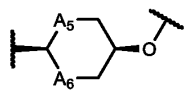
[0139] In some embodiments, $\textcircled{\text{B}}$ is phenyl or heteroaryl having 1 or 2 N atoms, L is



, wherein A_5 and A_6 are each independently $-\text{CH}_2-$ or $-\text{O}-$, R_1 and R_2 are each

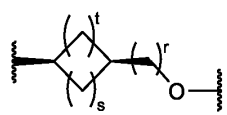
independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{O}-$, $-\text{CH}_2-$, $-\text{CH}(\text{Me})-$, or $-\text{N}(\text{alkyl})-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

[0140] In some embodiments, $\textcircled{\text{B}}$ is phenyl or heteroaryl having 1 or 2 N atoms, L is



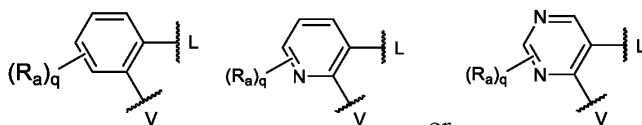
, wherein A_5 and A_6 are each independently $-\text{CH}_2-$ or $-\text{O}-$, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$ or $-\text{O}-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

[0141] In some embodiments, $\textcircled{\text{B}}$ is phenyl or heteroaryl having 1 or 2 N atoms, L is



, wherein r is 0 or 1, s is 1, and t is 1, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$ or $-\text{O}-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

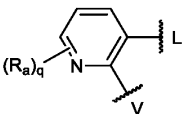
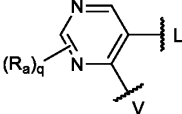
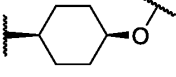
[0142] In some embodiments, $\textcircled{\text{B}}$ is

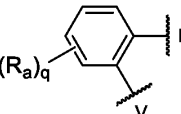
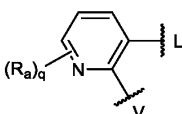
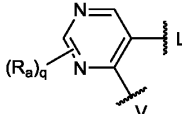
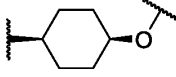


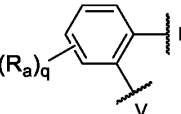
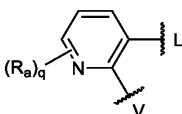
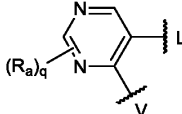
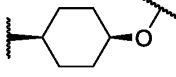
wherein R_a and q are as defined herein, L is , R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$ or $-\text{O}-$, m is 0 or 1, n is 1, and p is 0. In some embodiments, m is 1.

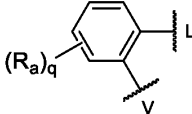
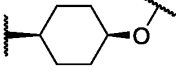
[0143] In some embodiments, $\textcircled{\text{B}}$ is , wherein R_a and q are as defined herein, L

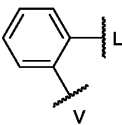
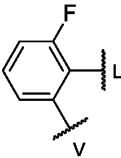
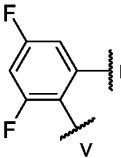
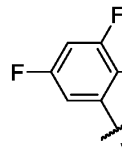
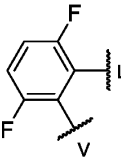
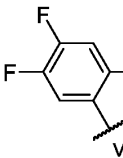
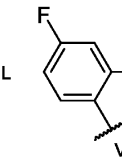
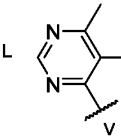
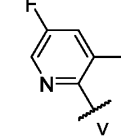
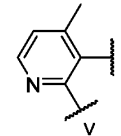
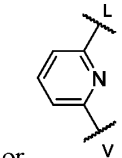
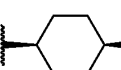
is , R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$ or $-\text{O}-$, m is 0 or 1, n is 1, and p is 0. In some embodiments, m is 1.

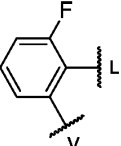
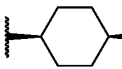
[0144] In some embodiments, $\textcircled{\text{B}}$ is  or , wherein R_a and q are as defined herein, L is , R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$ or $-\text{O}-$, m is 0 or 1, n is 1, and p is 0. In some embodiments, m is 1.

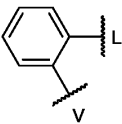
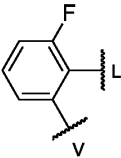
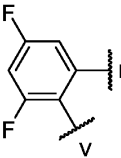
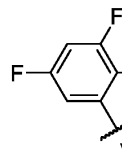
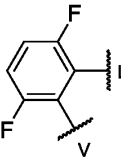
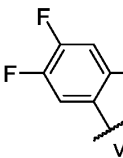
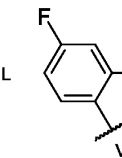
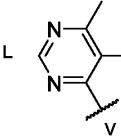
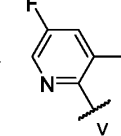
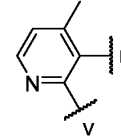
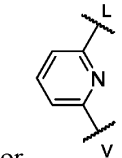
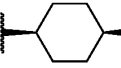
[0145] In some embodiments, $\textcircled{\text{B}}$ is , , or , wherein R_a and q are as defined herein, L is , R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$, m is 1, n is 1, and p is 0 or 1.

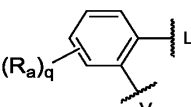
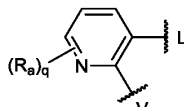
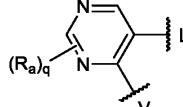
[0146] In some embodiments, $\textcircled{\text{B}}$ is , , or , wherein R_a and q are as defined herein, L is , R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, R_5 is as defined herein, R_6 is H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$, m is 0 or 1, n is 1, and p is 0 or 1.

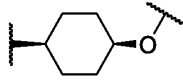
[0147] In some embodiments, $\textcircled{\text{B}}$ is , wherein R_a and q are as defined herein, L is , R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, R_5 is as defined herein, R_6 is H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond, Z is $-\text{CH}_2-$, m is 1, n is 1, and p is 0.

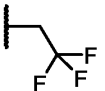
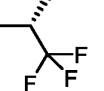
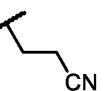
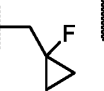
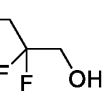
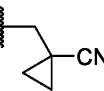
[0148] In some embodiments, (B) is , , , , , , , , , , or , L is , R₁ and R₂ are each independently H or alkyl, R₃ and R₄ are H, R₅ is as defined herein, R₆ is H, X is -CH₂-, V is -O-, Y is a bond, Z is -CH₂-, m is 1, n is 1, and p is 0.

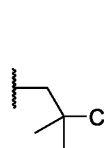
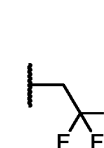
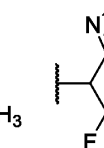
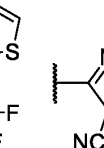
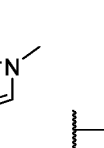
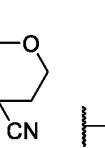
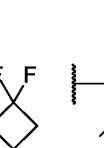
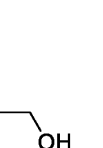
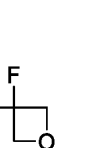
[0149] In some embodiments, (B) is , L is , R₁ and R₂ are each independently H or alkyl, R₃ and R₄ are H, R₅ is as defined herein, R₆ is H, X is -CH₂-, V is -O-, Y is a bond, Z is -CH₂-, m is 1, n is 1, and p is 0.

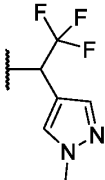
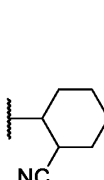
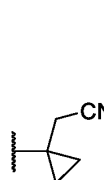
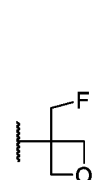
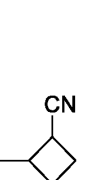
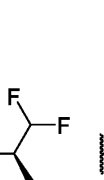
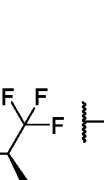
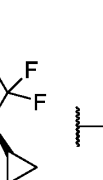
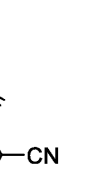
[0150] In some embodiments, (B) is , , , , , , , , , , or , L is , R₁ and R₂ are each independently H or alkyl, R₃ and R₄ are H, R₅ is as defined herein, R₆ is H, X is -CH₂-, V is -O-, Y is a bond, Z is -CH₂-, m is 1, n is 1, and p is 0.

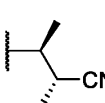
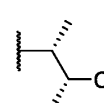
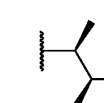
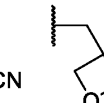
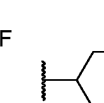
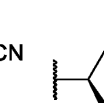
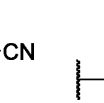
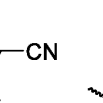
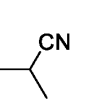
[0151] In some embodiments, (B) is , , or ,

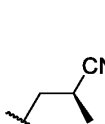
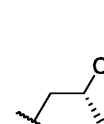
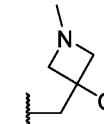
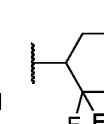
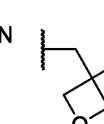
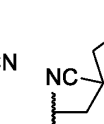
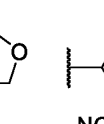
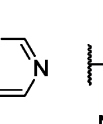
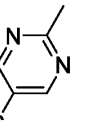
wherein R_a and q are as defined herein, L is , R_1 and R_2 are each independently H

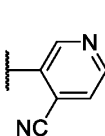
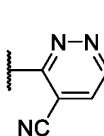
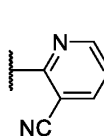
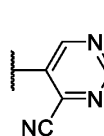
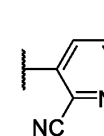
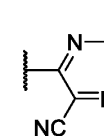
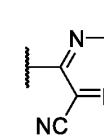
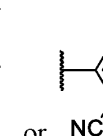
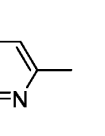
or alkyl, R_3 and R_4 are H, R_5 is , , , , , ,

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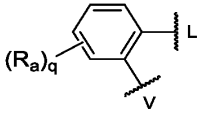
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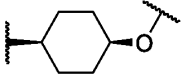
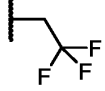
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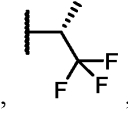
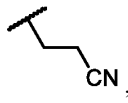
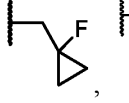
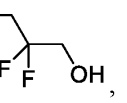
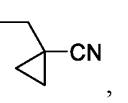
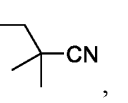
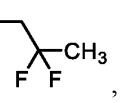
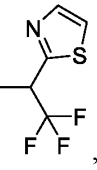
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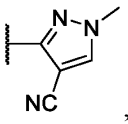
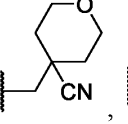
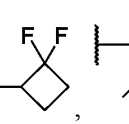
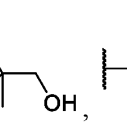
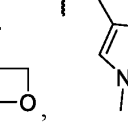
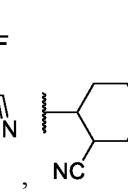
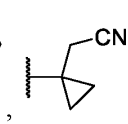
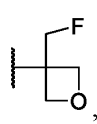
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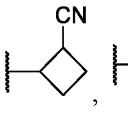
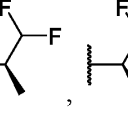
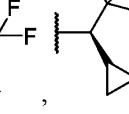
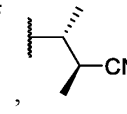
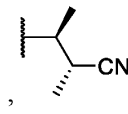
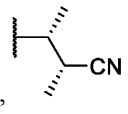
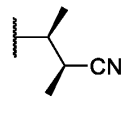
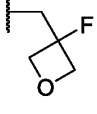
R_6 is H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$, m is 0 or 1, n is 1, and p is 0 or 1.

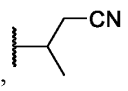
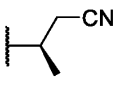
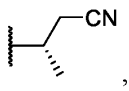
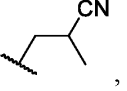
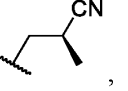
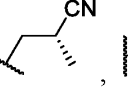
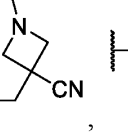
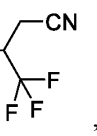
[0152] In some embodiments, $\textcircled{\text{B}}$ is , wherein R_a and q are as defined herein,

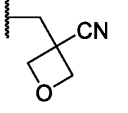
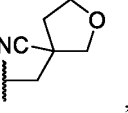
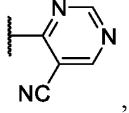
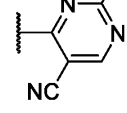
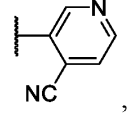
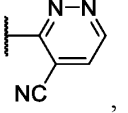
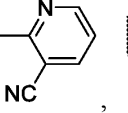
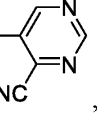
L is , R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, R_5 is ,

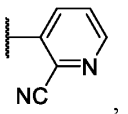
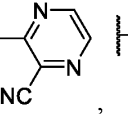
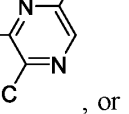
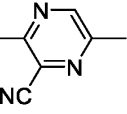
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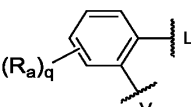
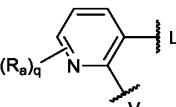
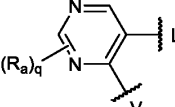
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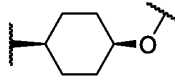
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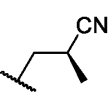
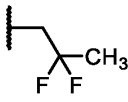
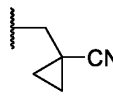
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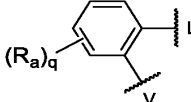
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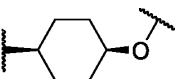
, , , or , R_6 is H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$, m is 0 or 1, n is 1, and p is 0 or 1.

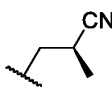
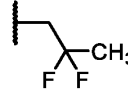
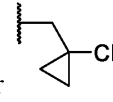
[0153] In some embodiments, (B) is , , or ,

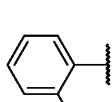
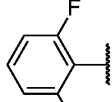
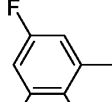
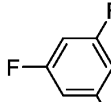
wherein R_a and q are as defined herein, L is , R_1 and R_2 are each independently H

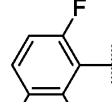
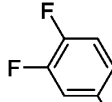
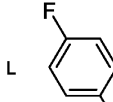
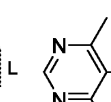
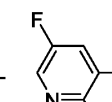
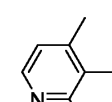
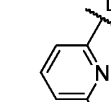
or alkyl, R_3 and R_4 are H, R_5 is , , or , R_6 is H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$, m is 0 or 1, n is 1, and p is 0 or 1.

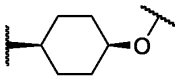
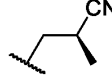
[0154] In some embodiments, (B) is , wherein R_a and q are as defined herein,

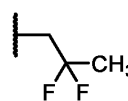
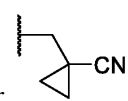
L is , R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, R_5 is

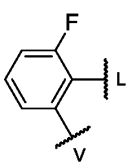
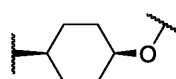
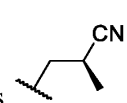
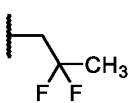
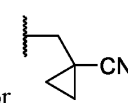
, , or , R_6 is H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{CH}_2-$, m is 0 or 1, n is 1, and p is 0 or 1.

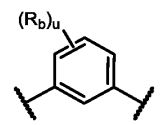
[0155] In some embodiments, (B) is , , , or ,

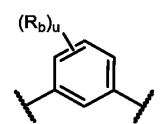
, , , , , , or , L is

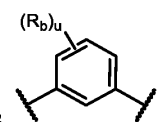
, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, R_5 is ,

, or , R_6 is H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond, Z is $-\text{CH}_2-$, m is 1, n is 1, and p is 0.

[0156] In some embodiments, $\textcircled{\text{B}}$ is , L is , R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, R_5 is , , or , R_6 is H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond, Z is $-\text{CH}_2-$, m is 1, n is 1, and p is 0.

[0157] In some embodiments, $\textcircled{\text{B}}$ is phenyl or heteroaryl having 1 or 2 N atoms, L is , wherein R_b is halogen, alkyl, or alkoxy, and u is 0, 1, or 2, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{O}-$, $-\text{CH}_2-$, $-\text{CH}(\text{Me})-$, or $-\text{N}(\text{alkyl})-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

[0158] In some embodiments, $\textcircled{\text{B}}$ is phenyl or heteroaryl having 1 or 2 N atoms, L is , wherein R_b is halogen, alkyl, or alkoxy, and u is 0, 1, or 2, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is $-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{O}-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

[0159] In some embodiments, $\textcircled{\text{B}}$ is phenyl, L is , wherein R_b is halogen, alkyl, or alkoxy, and u is 0, 1, or 2, R_1 and R_2 are each independently H or alkyl, R_3 and R_4 are H, X is

$-\text{CH}_2-$, V is $-\text{O}-$, Y is a bond or $-\text{CH}_2-$, Z is $-\text{O}-$, $-\text{CH}_2-$, $-\text{CH}(\text{Me})-$, or $-\text{N}(\text{alkyl})-$, m is 0 or 1, n is 0 or 1, and p is 0 or 1.

[0160] In some embodiments, the compounds disclosed herein are a racemic mixture. In some embodiments, the compounds disclosed herein are enriched in one enantiomer. In some embodiments, the compounds disclosed herein are enriched in one enantiomer and substantially free of the opposite enantiomer. In some embodiments, the compounds disclosed herein have an enantiomeric excess of about or greater than about 55%, about or greater than about 60%, about or greater than about 65%, about or greater than about 70%, about or greater than about 75%, about or greater than about 80%, about or greater than about 85%, about or greater than about 90%, about or greater than about 91%, about or greater than about 92%, about or greater than about 93%, about or greater than about 94%, about or greater than about 95%, about or greater than about 96%, about or greater than about 97%, about or greater than about 98%, about or greater than about 98.5%, about or greater than about 99%, about or greater than about 99.5%, or more, including all subranges and values therebetween. In some embodiments, the compounds of the present disclosure are provided as a mixture of diastereomers. In some embodiments, a diastereomer of a compound of the present disclosure is provided substantially free of other possible diastereomer(s). The present disclosure includes tautomers of any compounds described herein.

[0161] In some embodiments, provided herein is one or more compounds selected from Table 1 or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

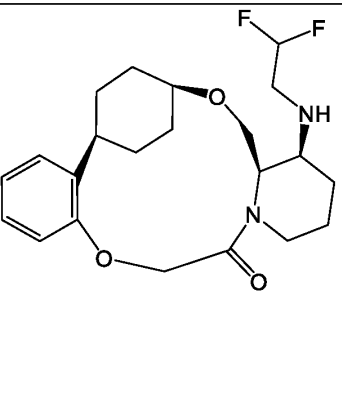
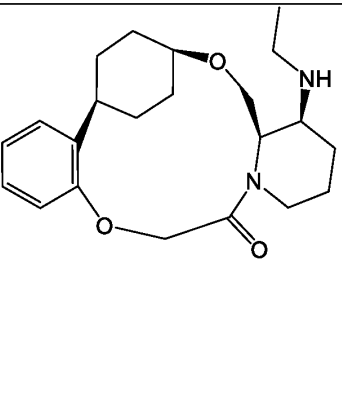
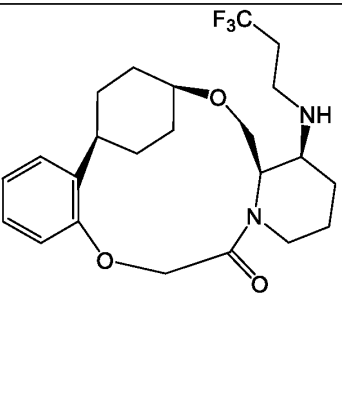
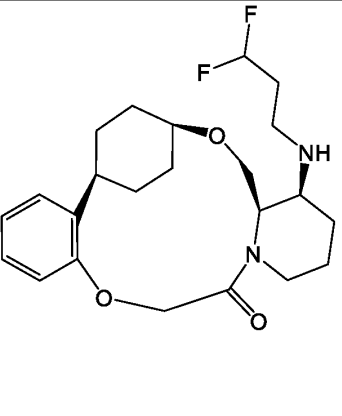
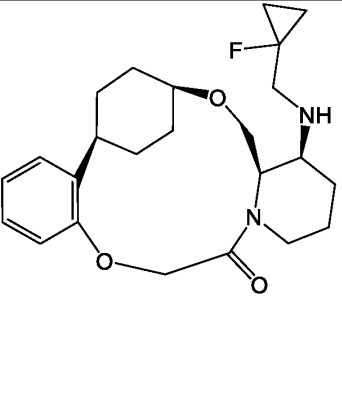
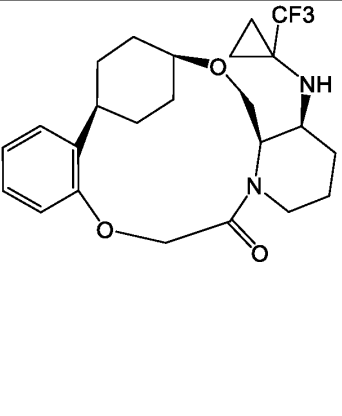
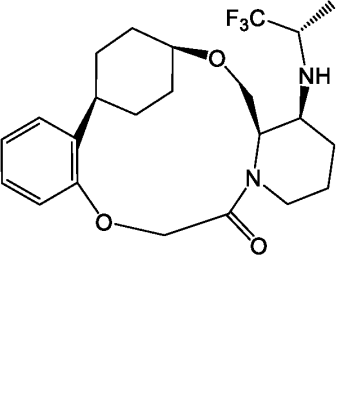
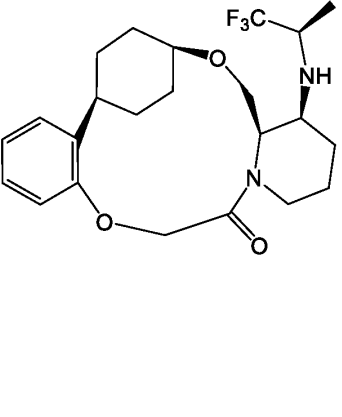
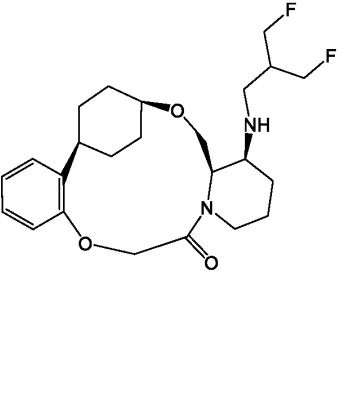
[0162] In some embodiments, provided herein is one or more compounds selected from Table 1 or a pharmaceutically acceptable salt thereof, or an enantiomer thereof.

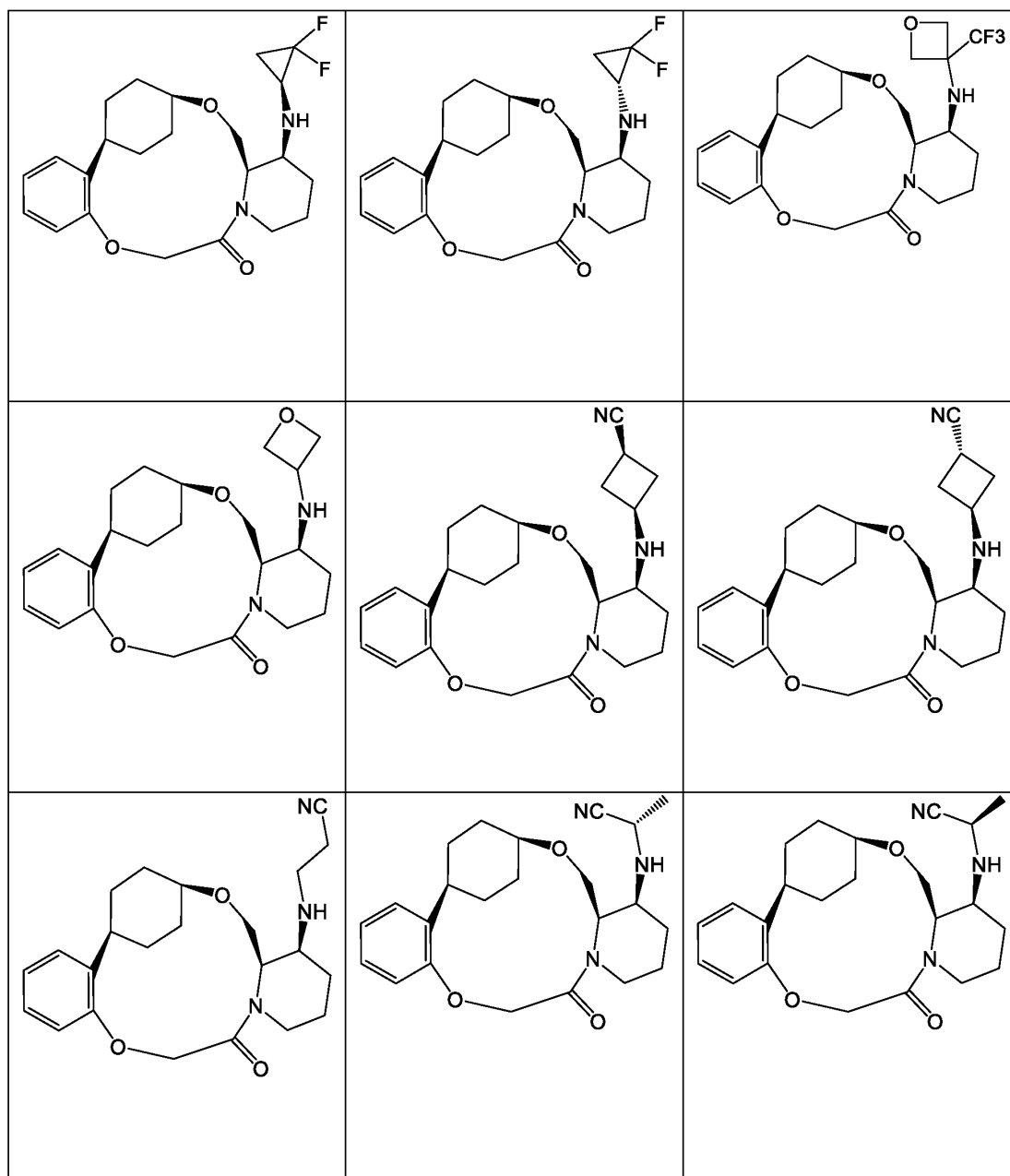
[0163] In some embodiments, provided herein is one or more compounds selected from Table 1 or a pharmaceutically acceptable salt thereof, or a diastereomer, or mixture of diastereomers thereof.

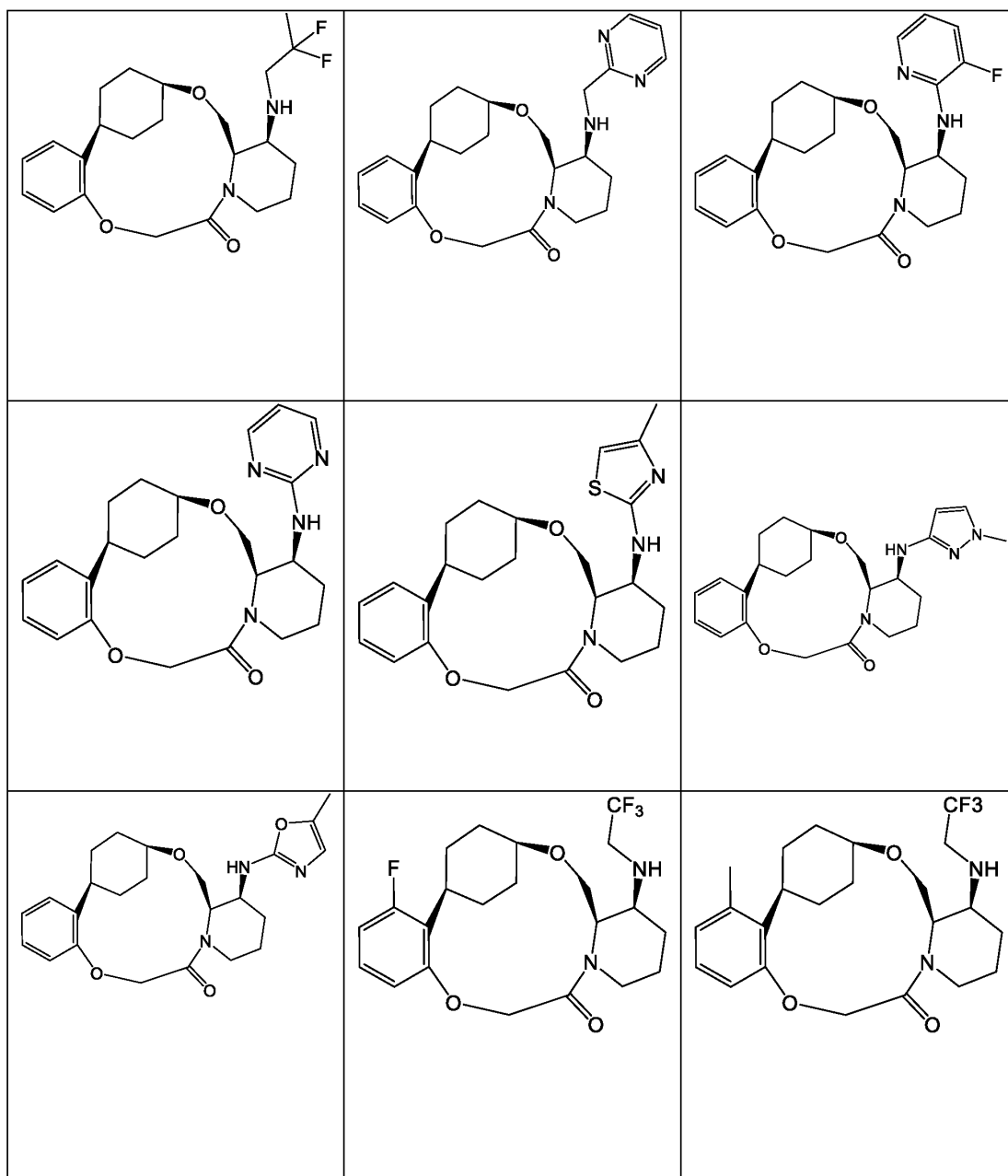
[0164] In some embodiments, provided herein is one or more compounds selected from Table 1.

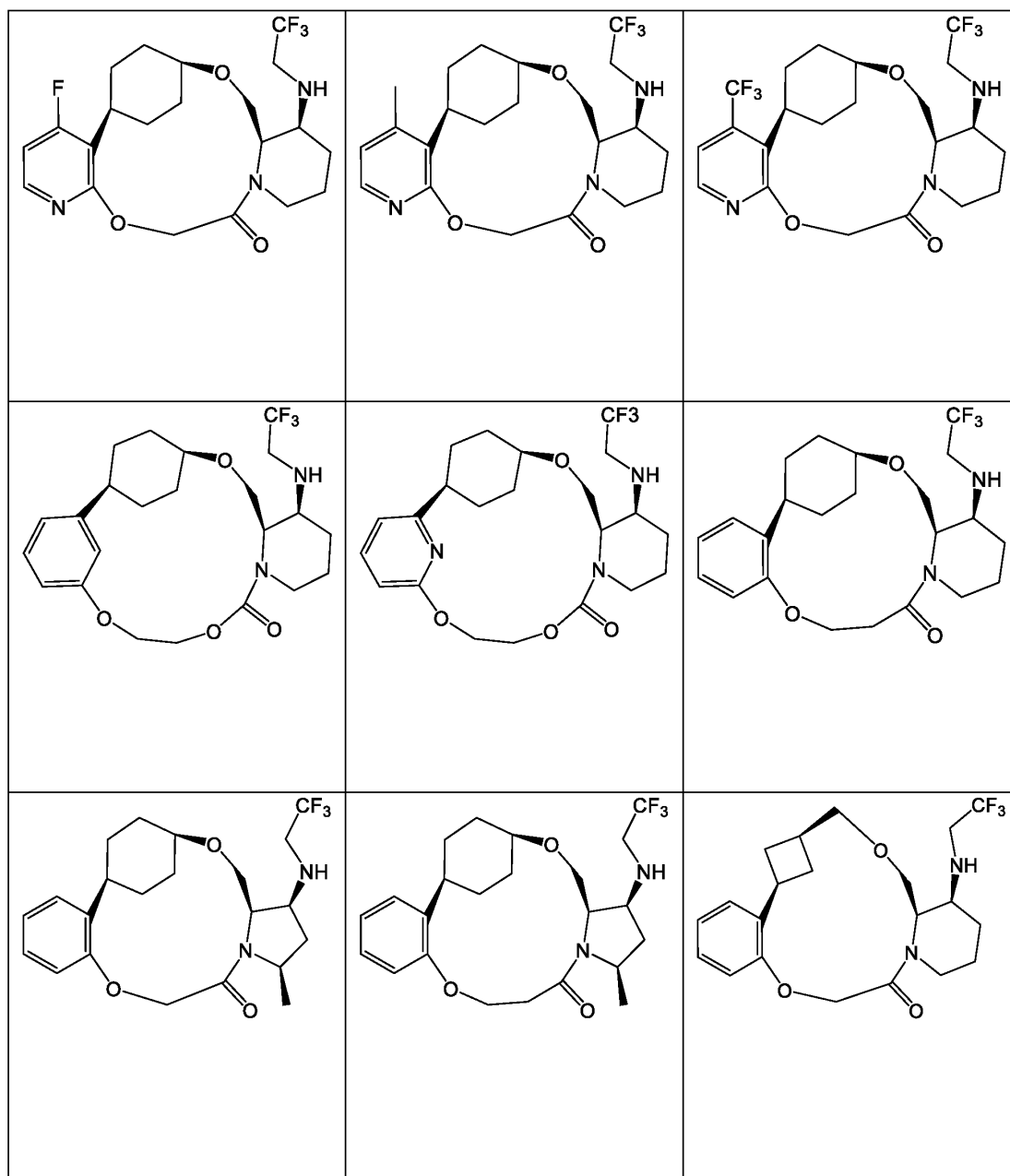
[0165] In some embodiments, provided herein is one or more pharmaceutically acceptable salts of a compound selected from Table 1.

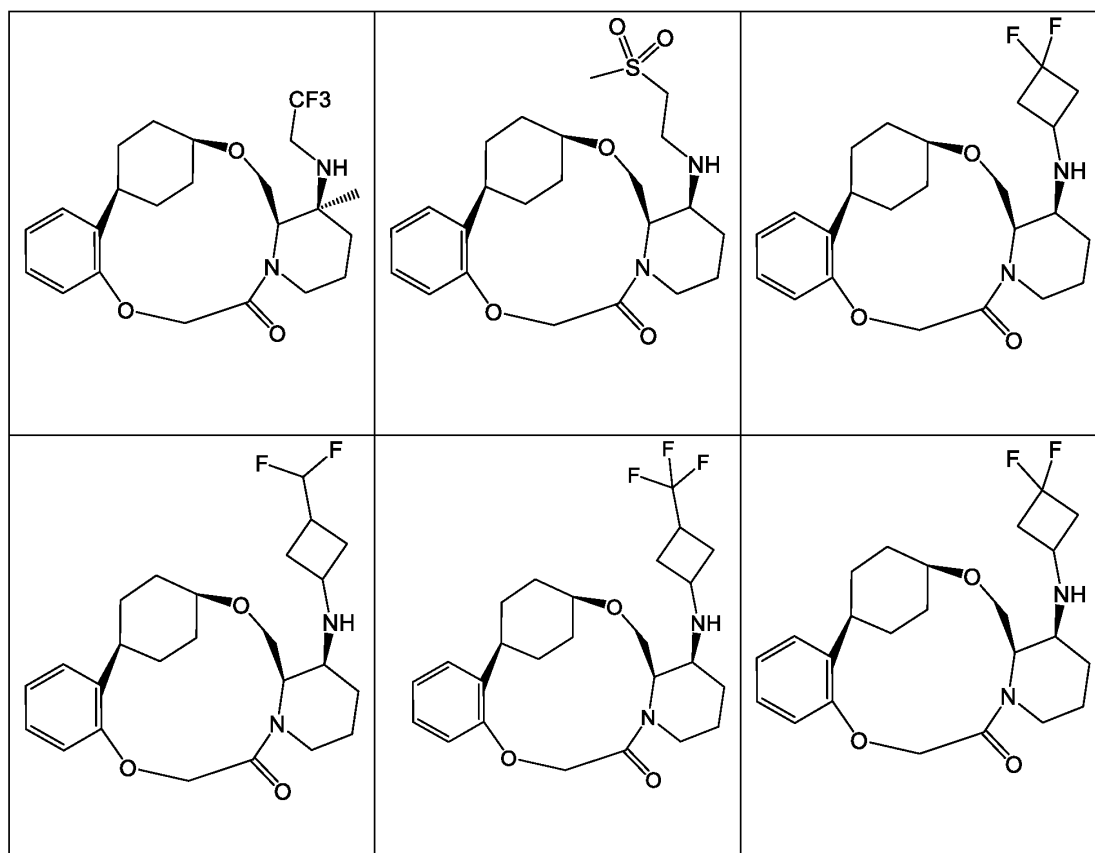
Table 1. Compounds of the Disclosure

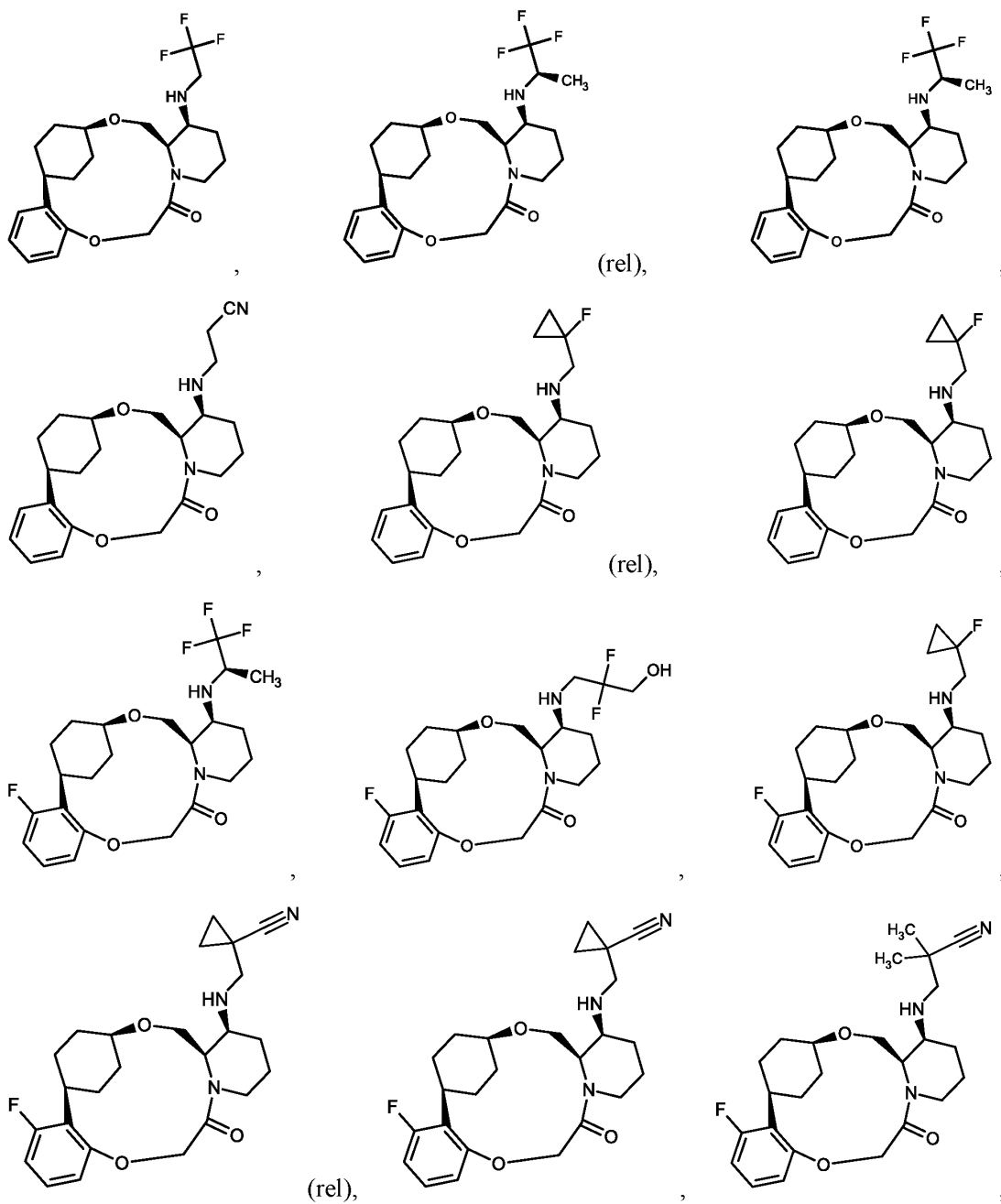


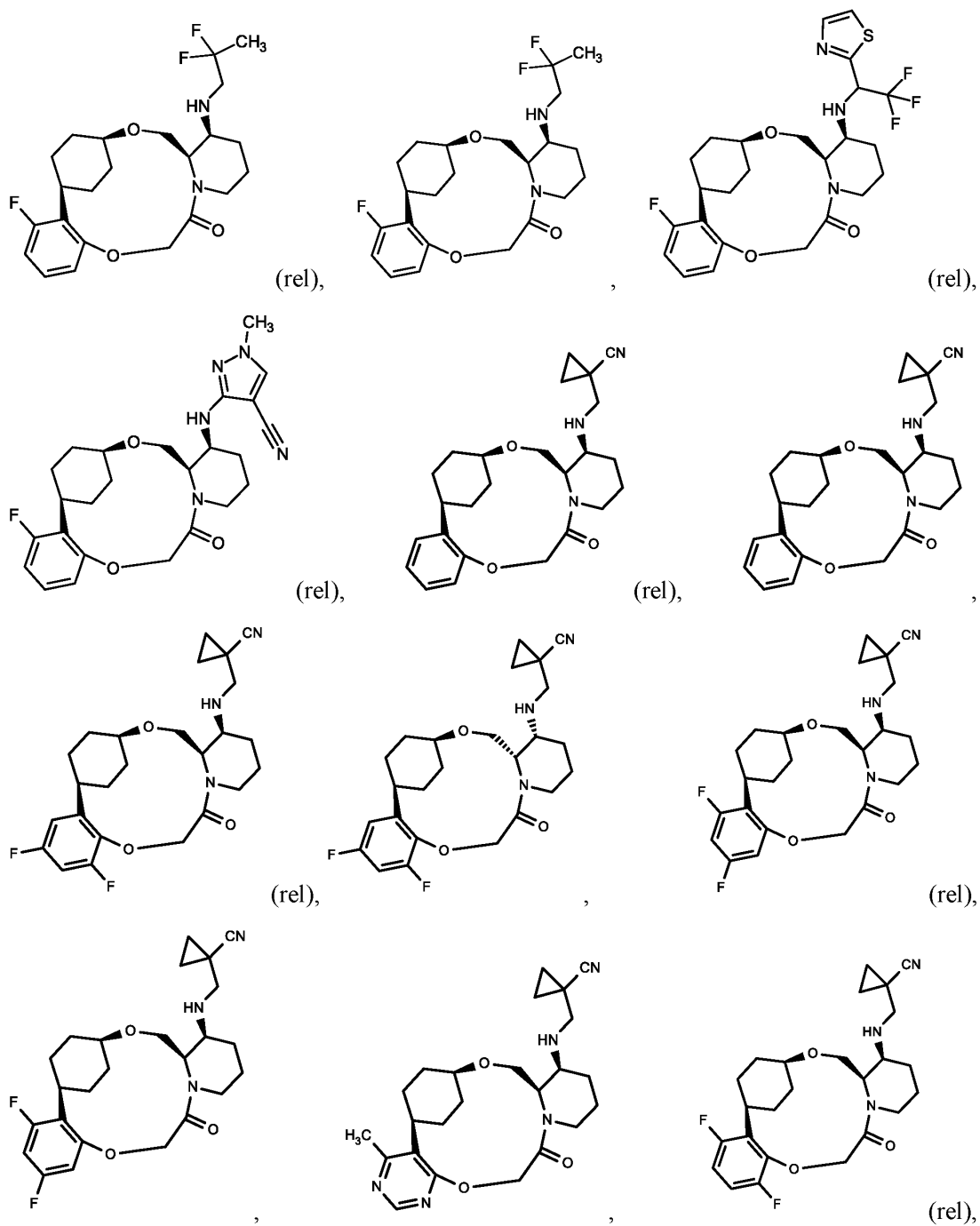


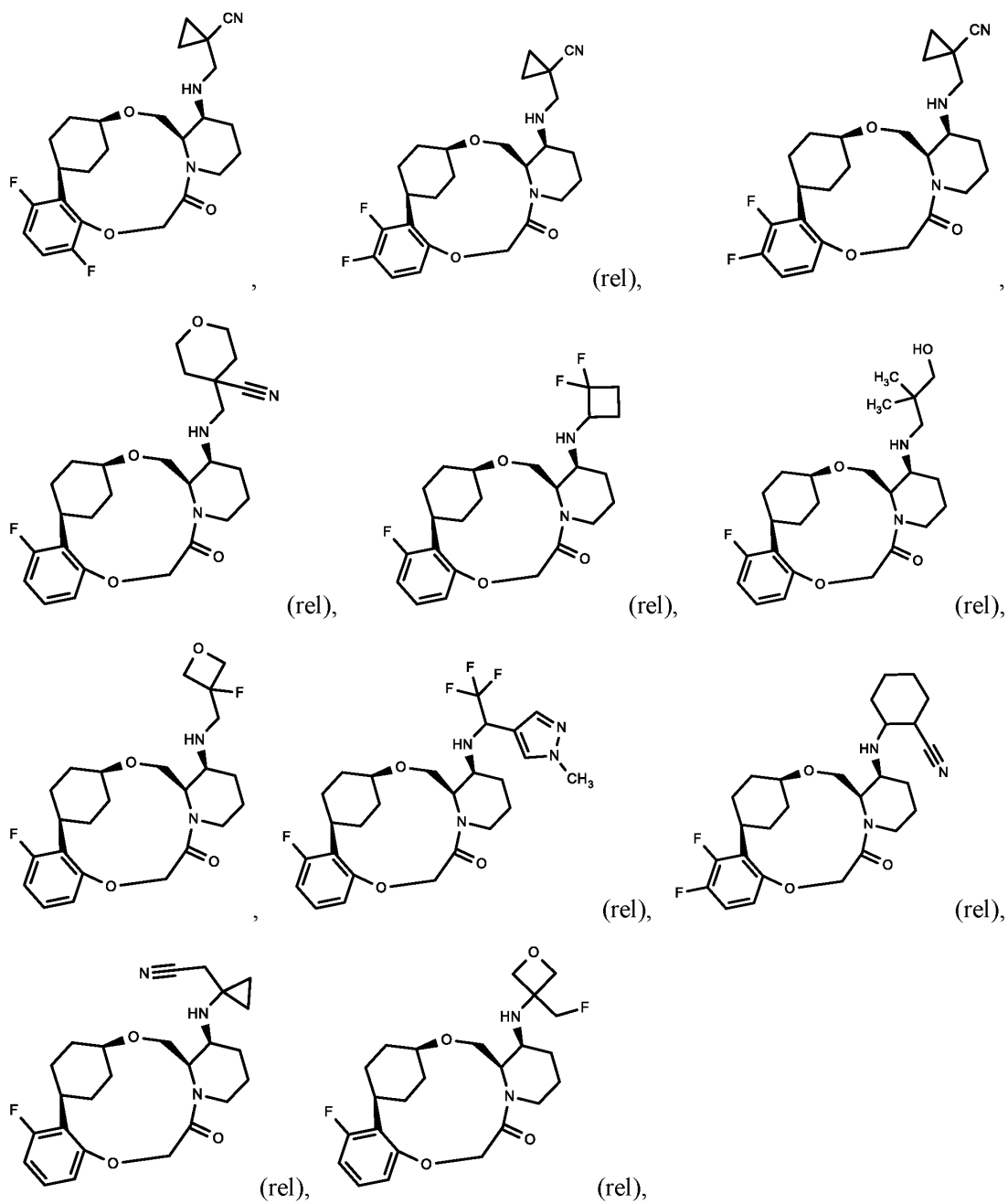


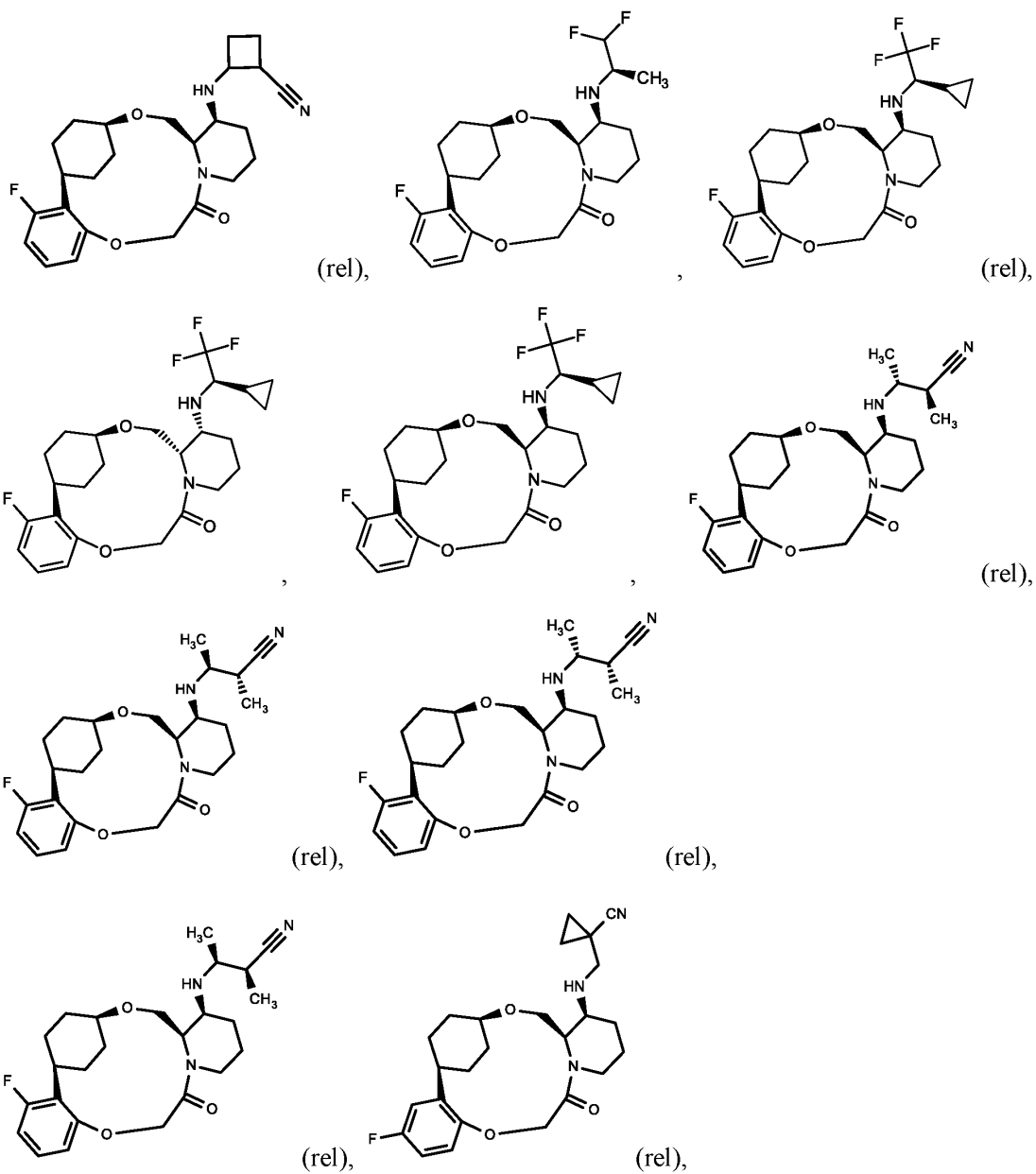


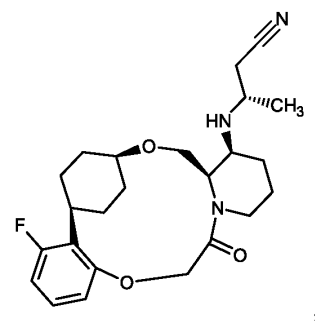
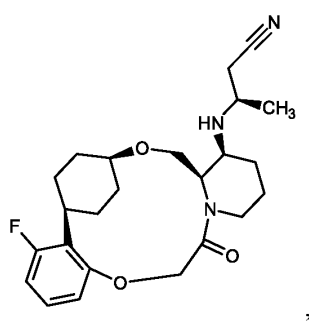
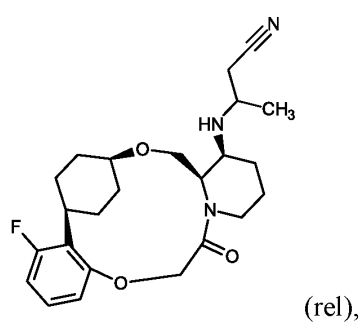
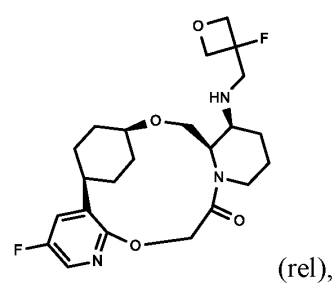
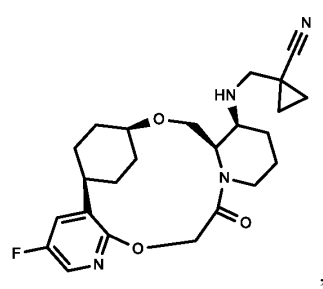
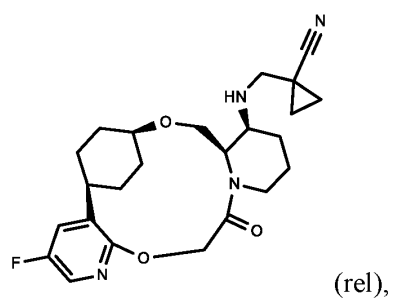
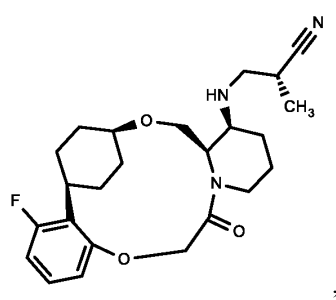
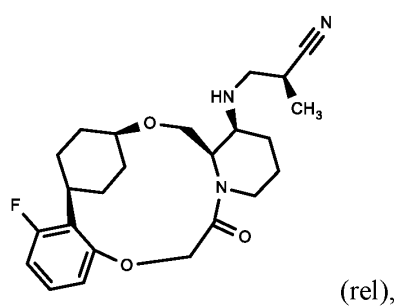
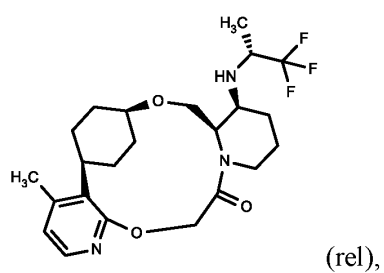
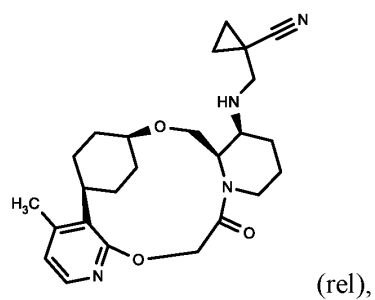
[0166] In some embodiments, the present disclosure provides a compound, e.g., a compound of Formula (I), having the structure:

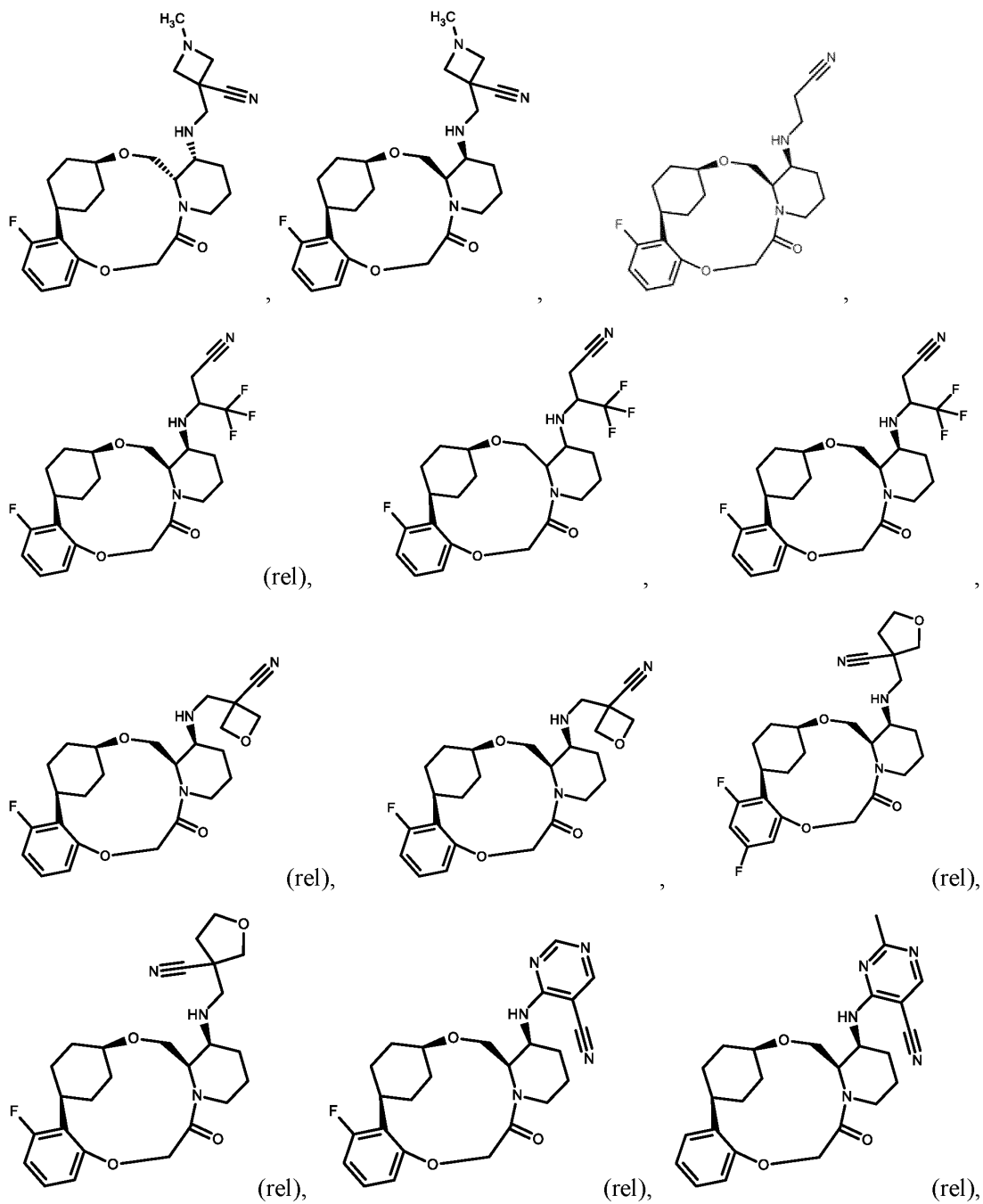


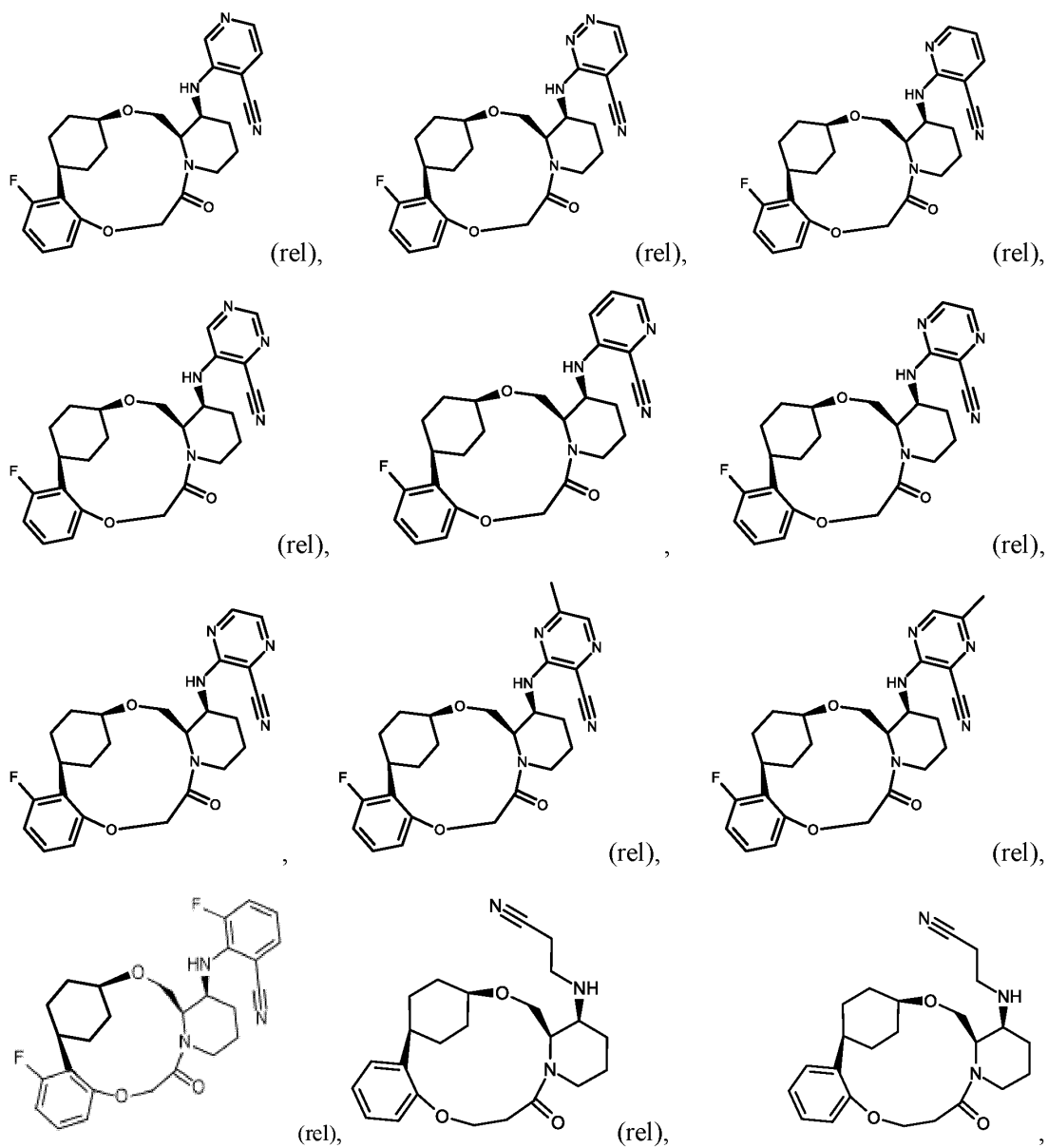


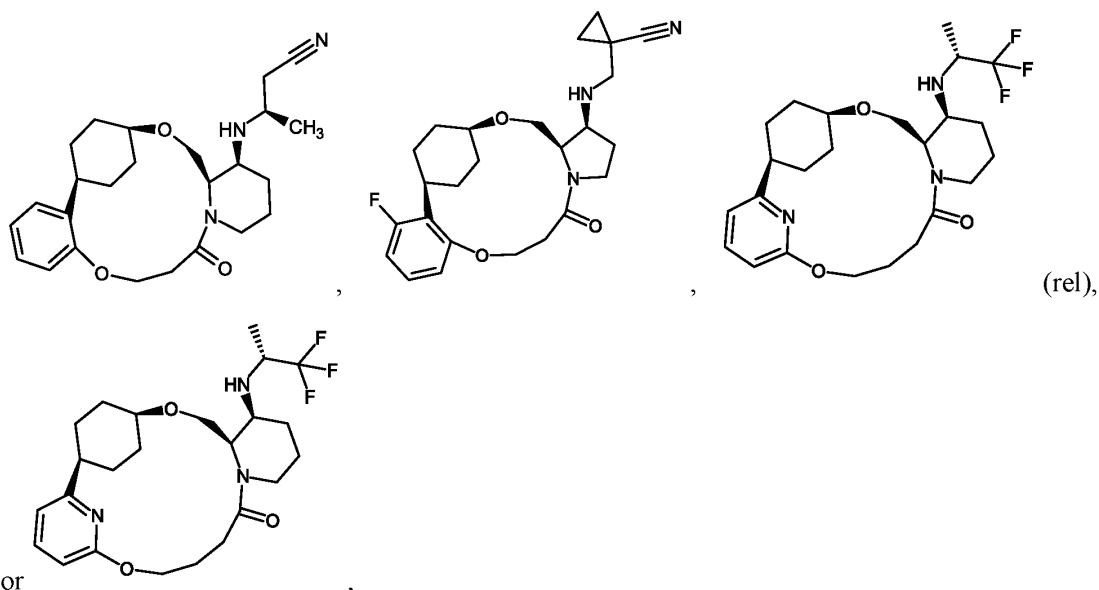








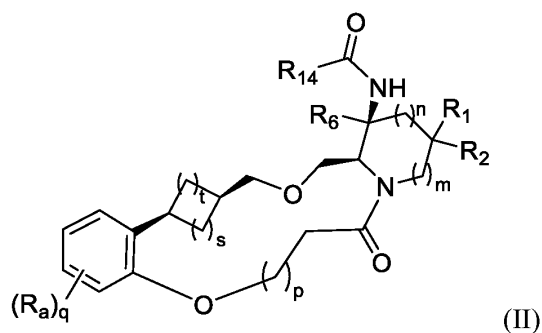




or a pharmaceutically acceptable salt thereof.

[0167] In some embodiments, the compound of the present disclosure is a compound provided in Tables 3-24. In some embodiments, the compound of the present disclosure is a compound provided in Tables 3-24 that has “A” ($EC_{50} < 100$ nM) or “B” activity (EC_{50} between 100 nM and 1,000 nM). In some embodiments, the compound of the present disclosure is a compound provided in Tables 3-24 that has “A” activity.

[0168] In some embodiments, the present disclosure provides a compound of Formula (II):



or a pharmaceutically acceptable salt thereof,

wherein:

R₁, R₂, R₃, R₄, R₆, R_a, m, n, and p are as defined herein:

R₁₄ is C₁₋₅ haloalkyl; and

s and t are each independently 1 or 2.

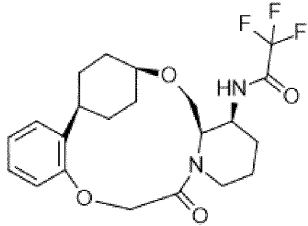
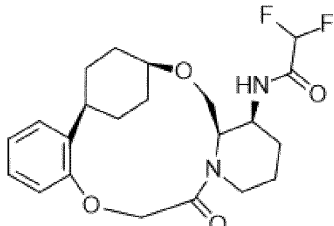
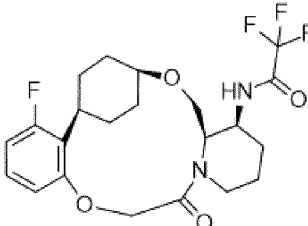
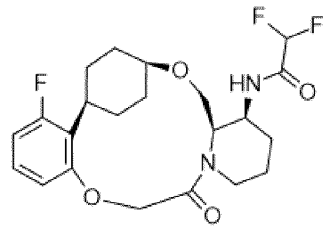
[0169] In some embodiments, R₁₄ is CF₃ or CHF₂.

[0170] In some embodiments, R_a is F.

[0171] In some embodiments, R₁ and R₂ are each H; R₆ is H or CH₃; R₁₄ is CF₃ or CHF₂; R_a is F; m and n are each 1; p is 0 or 1; q is 0 or 1; and s and t are each 2. In some embodiments, R₁ and R₂ are each H; R₆ is H; R₁₄ is CF₃ or CHF₂; R_a is F; m and n are each 1; p is 0; q is 0 or 1; and s and t are each 2.

[0172] In some embodiments, the compound of Formula (II) is a compound having a structure provided in Table 2 or a pharmaceutically acceptable salt thereof.

Table 2. Compounds of the Disclosure

[0173] In some embodiments, the compound of present disclosure, e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB),

Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), or Formula (II), excludes the compounds disclosed in WO2021/108628 and WO2022/232025.

Compositions

[0174] The present disclosure provides pharmaceutical compositions for modulating orexin receptor (e.g., orexin type 2 receptor) in a subject. In some embodiments, a pharmaceutical composition comprises a compound of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24) or a pharmaceutically acceptable salt thereof.

[0175] In some embodiments of the present disclosure, a pharmaceutical composition comprises a therapeutically effective amounts of one or more compounds of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24) or a pharmaceutically acceptable salt thereof.

[0176] In some embodiments, a pharmaceutical composition, as described herein, comprises a compound selected from Table 1, or a pharmaceutically acceptable salt thereof or stereoisomer thereof. In some embodiments, a pharmaceutical composition, as described herein, comprises a compound selected from Table 2, or a pharmaceutically acceptable salt thereof or stereoisomer thereof. In some embodiments, a pharmaceutical composition, as described herein, comprises a compound selected from any one of Tables 1-24, or a pharmaceutically acceptable salt thereof.

[0177] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24), or a pharmaceutically acceptable salt thereof; and one or more pharmaceutically acceptable carriers.

[0178] In some embodiments of the present disclosure, a pharmaceutical composition comprising one or more compounds of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or adjuvant is provided. The pharmaceutically acceptable excipients and adjuvants are added to the composition or formulation for a variety of purposes. In some embodiments, a pharmaceutical composition comprising one or more compounds disclosed herein, or a pharmaceutically acceptable salt thereof, further comprise a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutically acceptable carrier includes a pharmaceutically acceptable excipient, binder, and/or diluent. In some embodiments, suitable pharmaceutically acceptable carriers include, but are not limited to, inert solid fillers or diluents and sterile aqueous or organic solutions. In some embodiments, suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, and the like.

[0179] For the purposes of this disclosure, the compounds of the present disclosure can be formulated for administration by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous,

intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters.

[0180] Generally, the compounds of the present disclosure are administered in a therapeutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound -administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Methods of Use

[0181] The compounds of the present disclosure find use in any number of methods. For example, in some embodiments the compounds are useful in methods for modulating an orexin receptor, e.g., orexin type 2 receptor. Accordingly, in some embodiments, the present disclosure provides the use of any one of the foregoing compounds of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24 or a pharmaceutically acceptable salt thereof, for modulating orexin receptor (e.g., orexin type 2 receptor) activity. For example, in some embodiments, modulating orexin receptor (e.g., orexin type 2 receptor) activity is in a mammalian cell. Modulating orexin receptor (e.g., orexin type 2 receptor) activity can be in a subject in need thereof (e.g., a mammalian subject, such as a human) and for treatment of any of the described conditions or diseases.

[0182] In some embodiments, the modulating orexin receptor (e.g., orexin type 2 receptor) activity is binding. In some embodiments, the modulating orexin receptor (e.g., orexin type 2 receptor) activity is agonizing or stimulating the orexin receptor.

[0183] In some embodiments, the present disclosure provides methods of treating a disease or disorder that is treatable by administration of an Orexin agonist, the method comprising administering a therapeutically effective amount of one or more compounds of the present disclosure (e.g., compounds of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula

(IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24) to a subject in need thereof.

[0184] In some embodiments, the present disclosure provides methods of treating a disease or disorder that is treatable by administration of an Orexin agonist, the method comprising administering a composition comprising a therapeutically effective amount of one or more compounds of the present disclosure (e.g., compounds of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24) to a subject in need thereof.

[0185] In some embodiments, the compounds of the present disclosure are used for treating, preventing, ameliorating, controlling or reducing the risk of a variety of disorders associated with orexin receptors, including one or more of the following conditions or diseases: narcolepsy, narcolepsy syndrome accompanied by narcolepsy-like symptoms, cataplexy in narcolepsy, excessive daytime sleepiness (EDS) in narcolepsy, hypersomnia, idiopathic hypersomnia, repeatability hypersomnia, intrinsic hypersomnia, hypersomnia accompanied by daytime hypersomnia, interrupted sleep, sleep apnea, hypersomnia associated with sleep apnea, nocturnal myoclonus, disturbances of consciousness, such as coma, REM sleep interruptions, jet-lag, excessive daytime sleepiness, shift workers' sleep disturbances, dyssomnias, sleep disorders, sleep disturbances, hypersomnia associated with depression, emotional/mood disorders, drug use, Alzheimer's disease or cognitive impairment, Parkinson's disease, Guillain-Barre syndrome, Kleine Levin syndrome, and sleep disorders which accompany aging, muscular dystrophies, immune-mediated diseases; Alzheimer's sundowning; conditions associated with circadian rhythmicity as well as mental and physical disorders associated with travel across time zones and with rotating shift-work schedules; fibromyalgia; cardiac failure; diseases related to bone loss; sepsis; syndromes which are manifested by non-restorative sleep and muscle pain or sleep apnea

which is associated with respiratory disturbances during sleep; conditions which result from a diminished quality of sleep; and other diseases related to general orexin system dysfunction. In some embodiments, compounds of the present disclosure are useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanied by narcolepsy-like symptoms, hypersomnia syndrome accompanied by daytime hypersomnia (e.g., Parkinson's disease, Guillain-Barre syndrome and Kleine Levin syndrome), Alzheimer's disease obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, sepsis, disturbance of consciousness such as coma and the like, side effects and complications due to anesthesia, and the like, or anesthetic antagonist.

[0186] In some embodiments, a compound of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula, (ID-4), Formula (II), or Tables 1-24), a pharmaceutically acceptable salt thereof, or a composition thereof is used to treat diseases or disorders or symptoms associated with excessive sleepiness in a subject in need thereof. In some embodiments, the excessive sleepiness is caused by any one of the following: insufficient quality or quantity of night time sleep; misalignments of the body's circadian pacemaker with the environment (e.g., caused by requirement to remain awake at night for employment such as shift work or personal obligations such as caretaker for sick, young or old family members), such as jet lag, shift work and other circadian rhythm sleep disorders; another underlying sleep disorder, such as narcolepsy (e.g., narcolepsy type 1, narcolepsy type 2, probable narcolepsy), sleep apnea (e.g., obstructive sleep apnea, obstructive sleep apnea with use of continuous positive airway pressure), idiopathic hypersomnia, idiopathic excessive sleepiness, and restless legs syndrome; disorders, such as clinical depression or atypical depression; tumors; head trauma; anemia; kidney failure; hypothyroidism; injury to the central nervous system; drug abuse; genetic vitamin deficiency, such as biotin deficiency; and particular classes of prescription and over the counter medication.

[0187] In some embodiments, a compound of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24), a pharmaceutically acceptable salt thereof, or a composition thereof is used to treat any one of the following: shift work disorder; shift work sleep disorder; and jet lag syndrome. In some embodiments, the methods and uses herein are used to treat any one of the following: narcolepsy type 1, narcolepsy type 2, probable narcolepsy, idiopathic hypersomnia, idiopathic excessive sleepiness, hypersomnia, hypersomnolence, sleep apnea syndrome (e.g., obstructive sleep apnea, obstructive sleep apnea with use of continuous positive airway pressure); or disturbance of consciousness such as coma and the like; and narcolepsy syndrome accompanied by narcolepsy-like symptoms; hypersomnolence or hypersomnia syndrome accompanied by daytime hypersomnia (e.g., Parkinson's disease, Guillain-Barre syndrome and Kleine Levin syndrome); excessive daytime sleepiness in Parkinson's disease, Prader-Willi Syndrome, depressions (depression, atypical depression, major depressive disorder, treatment resistant depression), ADHD, sleep apnea syndrome (e.g., obstructive sleep apnea, obstructive sleep apnea with use of continuous positive airway pressure) and other disorders of vigilance; residual excessive daytime sleepiness in sleep apnea syndrome (e.g., obstructive sleep apnea, obstructive sleep apnea with use of continuous positive airway pressure); and the like. Narcolepsy (e.g., narcolepsy type 1, narcolepsy type 2, probable narcolepsy) may be diagnosed by diagnostic criteria generally used in the field, e.g., The third edition of the International Classification of Sleep Disorders (ICSD-3) and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). In some embodiments, the excessive sleepiness is excessive daytime sleepiness or excessive sleepiness during working hours, or excessive sleepiness or reduced quantity of sleep which is caused by requirement to remain awake at night for employment (e.g., shift work) or personal obligations (e.g., caretaker for sick, young or old family members). In some embodiments, the subject suffers from the diseases or disorders or symptoms associated with excessive sleepiness. In some embodiments, the subject is sleep-deprived subject, subject with excessive sleepiness, subject with

disruptive regular sleep cycle, or subject with a need to decrease sleepiness. In some embodiments, the present disclosure provides methods for decreasing or treating excessive sleepiness. In some embodiments, the excessive sleepiness is caused by narcolepsy type 1, narcolepsy type 2 or idiopathic hypersomnia. In some embodiments, the excessive sleepiness is caused by obstructive sleep apnea despite the use of continuous positive airway pressure (CPAP). In some embodiments, methods for increasing wakefulness in a subject in need thereof is provided. In some embodiments, the orexin level in the subject is not compromised or partially compromised.

[0188] In some embodiments of the present disclosure, a method for the treatment of a sleep disorder (e.g., as disclosed herein) in a subject in need thereof is provided, comprising administering a compound of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24), a pharmaceutically acceptable salt thereof, or a composition thereof, to the subject. In some embodiments, a compound of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-3), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24), or a pharmaceutically acceptable salt thereof, is used to treat a subject with a sleep disorder, to treat a sleep disorder, or to treat the symptoms of a sleep disorder.

[0189] In some embodiments of the present disclosure, a method for the treatment of narcolepsy in a subject in need thereof is provided, comprising administering a compound of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), or Tables 1-24), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some

embodiments, a compound of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24), or a pharmaceutically acceptable salt thereof, is used to treat a subject with narcolepsy, to treat narcolepsy, or to treat the symptoms of narcolepsy.

[0190] In some embodiments of the present disclosure, a method for the treatment of idiopathic hypersomnia (IH) in a subject in need thereof is provided, comprising administering a compound of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some embodiments, a compound of the present disclosure (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (IA), Formula (IA-1), Formula (IA-2), Formula (IB), Formula (IB-1), Formula (IB-2), Formula (IC-1), Formula (IC-2), Formula (IC-2a), Formula (IC-2b), Formula (IC-2c), Formula (IC-2d), Formula (IC-2e), Formula (IC-2f), Formula (IC-2g), Formula (IC-2h), Formula (IC-3), Formula (IC-3a), Formula (IC-3b), Formula (IC-4), Formula (ID-1), Formula (ID-2), Formula (ID-3), Formula (ID-4), Formula (II), or Tables 1-24), or a pharmaceutically acceptable salt thereof, is used to treat a subject with IH, to treat IH, or to treat the symptoms of IH.

EXAMPLES

[0191] The disclosure, now being generally described, will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present disclosure and are not intended to limit the disclosure.

[0192] The compounds of the present disclosure can be synthesized using the methods as hereinafter described below, together with synthetic methods known in the art of synthetic organic chemistry or variations thereon as appreciated by those skilled in the art.

[0193] Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene and Wuts, *Protective Groups in Organic Synthesis*, 44th. Ed., Wiley & Sons, 2006, as well as in Jerry March, *Advanced Organic Chemistry*, 4th edition, John Wiley & Sons, publisher, New York, 1992 which are incorporated herein by reference in their entirety.

[0194] Abbreviations

ABNO	9-azabicyclo[3.3.1]nonane N-oxyl radical
AcOH	acetic acid
cHex	cyclohexane
CPME	cyclopentyl methylether
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	<i>N,N'</i> -diisopropylethylamine
DMA	<i>N,N'</i> -dimethylacetamide
DMPU	<i>N, N'</i> -dimethylpropyleneurea
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
IPA	isopropyl alcohol
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
LDA	lithium diisopropylamide
MTBE	methyl-tertbutyl ether
NMO	<i>N</i> -methylmorpholine- <i>N</i> -Oxide
TBAI	tetrabutylammonium iodide

TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran

General Synthesis

[0195] The compounds of the present disclosure can be synthesized using the following methods. General reaction conditions are given, and reaction products can be purified by generally known methods including silica gel chromatography using various organic solvents such as hexane, dichloromethane, ethyl acetate, methanol and the like or preparative reverse phase high pressure liquid chromatography.

[0196] Analytical conditions:

Method A:

- Column: Waters UPLC® BEH™ C18, Part No. 186002352, 2.1 x 100mm, 1.7µm
- Column Temperature: 40 °C
- Mobile Phase A: 2mM ammonium bicarbonate, buffered to pH 10
- Mobile Phase B: Acetonitrile
- Injection volume: 1 µL
- Gradient program: Flow rate 0.6 mL/minutes

<u>Time</u>	<u>A%</u>	<u>B%</u>
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0.00	95.00	5.00
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5.30	0	100
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5.80	0	100
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5.82	95.00	5.00
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<u>7.00</u>	<u>95.00</u>	<u>5.00</u>
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- UV 215 nm, PDA spectrum 200 – 400 nm, step: 1 nm
- MSD Scan Positive: 100-1000 ; Scan Positive Negative: 150-850; Scan Neg:100-1000

Method B:

- Column: Phenomenex, Kinetex-XB C18, Part No.00D-4498-AN, 2.1 mm x 100 mm, 1.7 µm

- Column temperature: 40 °C
- Mobile Phase A: 0.1% Formic acid in water
- Mobile Phase B: 0.1% Formic acid in acetonitrile
- Injection volume: 1 µL
- Gradient program: Flow rate 0.6 mL/minutes

<u>Time</u>	<u>A%</u>	<u>B%</u>
0.00	95	5
5.30	0	100
5.80	0	100
5.82	95	5
<u>7.00</u>	<u>95</u>	<u>5</u>

- UV 215 nm, PDA spectrum 200 – 400 nm, step: 1 nm
- MSD Scan Positive: 100-1000 ; Scan Positive Negative: 150-850

Method C:

- Column: Acquity UPLC CSH C18 (5.0 mm x 2.1 mm I.d. 1.7 µm) column
- Column Temperature: 40 °C
- Mobile Phase A: 0.1% Formic acid in water
- Mobile Phase B: 0.1% Formic acid in acetonitrile
- Gradient program: Flow rate 1 mL/minute

<u>Time</u>	<u>A%</u>	<u>B%</u>
0.00	97.00	3.00
1.50	0.10	99.90
1.90	0.10	99.90
<u>2.00</u>	<u>97.0</u>	<u>3.00</u>

Method D:

- Column: Kintex EVO C18 (1.7 µm, 2.1x50mm) column
- Column Temperature: 40 °C
- Mobile Phase A: 10 mM ammonium bicarbonate aq. solution adjusted to pH 10 with NH₃
- Mobile Phase B: Acetonitrile
- Gradient program: Flow rate 1 mL/minute

<u>Time</u>	<u>A%</u>	<u>B%</u>
0.00	97.00	3.00
1.50	0.10	99.90
1.90	0.10	99.90
2.00	97.0	3.00

[0197] IP-1 ACCUMULATION ASSAY

[0198] The accumulation of Inositol-1 Monophosphate (IP-1) was measured using IP-One HTRF® Terbium cryptate based assay (Cisbio) with human recombinant OX1 (hOX1) and OX2 (hOX2) receptors expressed in CHO cells (DiscoverX) according to the manufacturer's instructions for cells tested in suspension.

[0199] hOX1-CHO and hOX2-CHO cells were seeded into white 384-well plates at a density of 20,000 cells/well in Hank's Balanced Salt Solution (HBSS) containing 20 mM HEPES pH 7.4, 50 mM, LiCl and 0.1% and Bovine Serum Albumin (BSA).

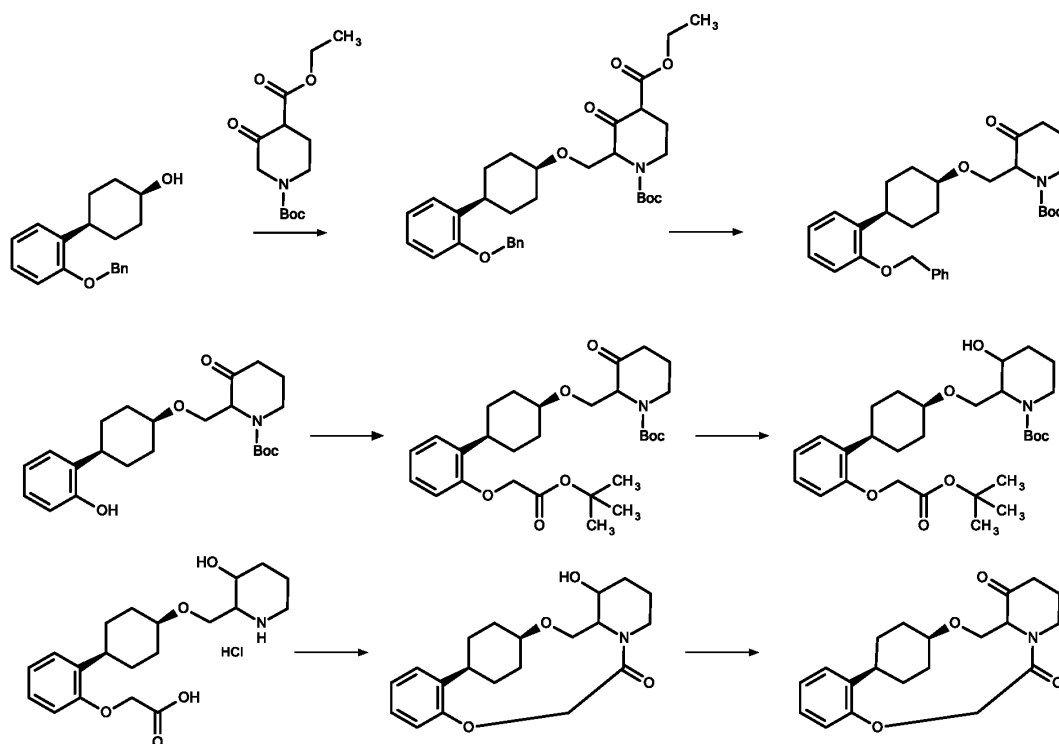
[0200] Compounds of the invention were tested in 11 point concentration response curves (CRC) serially diluted in neat DMSO at 200-fold concentrations and added by Echo acoustic liquid handling (Labcyte) to the cells (0.5% DMSO final in the assay). After 60 minutes of incubation at 37 °C detection reagents, IP1-d2 tracer and anti-IP1-cryptate were diluted in lysis buffer according to the manufacturer's descriptions and added to the cells.

[0201] Following 60 minutes incubation at room temperature, time-resolved fluorescence (HTRF) was measured at 615 nm and 665 nm by Envision Multilabel reader (Perkin Elmer) and the HTRF ratio ($A_{665}/A_{615} \times 10^4$) was calculated.

[0202] The IP-1 accumulation response was expressed as percentage of the maximal OX-A response.

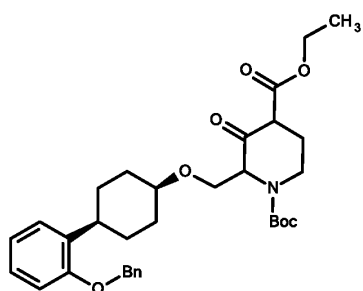
[0203] Curve fitting and EC₅₀ estimations were carried out using a four-parameter logistic model using XLfit Software. Mean data of EC₅₀ are calculated from at least two independent experiments performed in duplicate.

[0204] EC₅₀: Category A corresponds to compounds displaying an EC₅₀<100nM, Category B between 100nM and 1,000nM, Category C between 1,000nM and 10,000nM and Category D above 10,000 nM



[0205] SYNTHESIS OF INTERMEDIATE 1

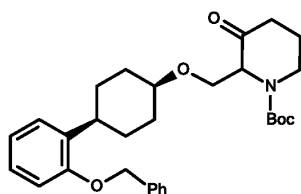
[0206] 1-tert-butyl-4-ethyl-3-oxo-2-({[(1s,4s)-4-[2-(benzyloxy)phenyl]cyclohexyl]-oxy}methyl)-piperidine-1,4-dicarboxylate



[0207] In a flask, a 2.4M solution of *n*BuLi in heptane (79 mL, 0.191 mol) was added to a stirred solution of *N*-(propan-2-yl)propan-2-amine (26 mL, 0.188 mol) in anhydrous THF (90 mL) at -78 °C. The reaction was held at this temperature for 40 minutes. This freshly prepared LDA solution was transferred to an addition funnel and added over 0.5 h to a stirred solution of 1-tert-butyl-4-ethyl-3-oxopiperidine-1,4-dicarboxylate (24.00 g, 86.7 mmol) and DMPU (42 mL, 0.345 mol) in anhydrous THF (60 mL) at -78 °C, ensuring the reaction temperature did not rise above -70 °C. The solution was held at this temperature for 20 minutes. The oil containing 1-benzyloxy-2-[4-(chloromethoxy)cyclohexyl]benzene (28.65 g, 86.6 mmol, prepared as described in WO2022233872A1) was dissolved in anhydrous THF (90 mL) and added to the reaction mixture over 20 minutes, ensuring the reaction temperature did not rise above -70 °C. The reaction mixture was stirred at -78 °C for 1 h, warmed to room temperature and stirred for 2 h. The reaction was quenched with sat. aq. NH₄Cl. The crude mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 300 mL). The combined extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using a silica cartridge (0 - 50% EtOAc in heptane) to afford the title compound (15 g, 26.55 mmol, 30% yield) as a pale-yellow oil. [M+Na]⁺ *m/z* = 588.3

[0208] SYNTHESIS OF INTERMEDIATE 2

[0209] tert-butyl-3-oxo-2-({[(1*s*,4*s*)-4-[2-(benzyloxy)phenyl]cyclohexyl]-oxy}methyl)piperidine-1-carboxylate



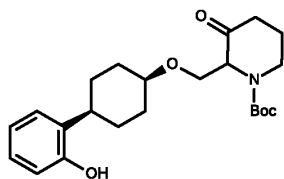
[0210] To a solution of Intermediate 1 (15 g, 26.55 mmol) in DMSO (95 mL) was added sodium chloride (2.26 g, 38.6 mmol) and water (9.5 mL) and the reaction mixture was heated to 125 °C for 2.5 h. The reaction mixture was cooled to room temperature, diluted with water (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water (2 x 200 mL) and brine (200 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to afford the crude material. The latter was purified by column chromatography using a silica cartridge (0-50% EtOAc

in heptane) to afford the title compound (7.03 g, 14.25 mmol, 54% yield) as an orange oil.

$[M+Na]^+$ m/z = 516.3

[0211] SYNTHESIS OF INTERMEDIATE 3

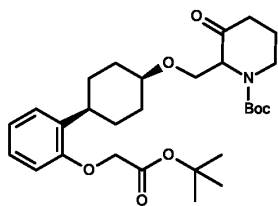
[0212] tert-butyl-3-oxo-2-({[(1s,4s)-4-(2-hydroxyphenyl)cyclohexyl]-oxy}methyl)piperidine-1-carboxylate



[0213] Intermediate 2 (17.4 g, 35.3 mmol) was dissolved in EtOH (300 mL) and the reaction vessel was evacuated and backfilled with $N_{2(g)}$ 3 times. 10% wt. Pd/C (3.57 g, 3.36 mmol) was added and the reaction vessel was evacuated and backfilled with $H_{2(g)}$ 3 times. The reaction was stirred for 18 h and then filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated *in vacuo* to afford the title compound (13.9 g, 34.46 mmol, 97% yield) as a yellow oil. $[M+Na]^+$ m/z = 426.3

[0214] SYNTHESIS OF INTERMEDIATE 4

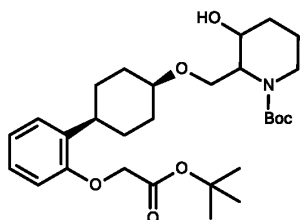
[0215] tert-butyl-3-oxo-2-({[(1s,4s)-4-(2-hydroxyphenyl)cyclohexyl]oxy}methyl)-piperidine-1-carboxylate



[0216] To a solution of Intermediate 3 (11.80 g, 29.2 mmol) and tert-butyl bromoacetate (5.0 mL, 33.6 mmol) in acetone (152 mL) was added potassium carbonate (12.18 g, 88.1 mmol) and the mixture was stirred at room temperature overnight. The solids were filtered off and the filtrate was concentrated *in vacuo* to afford the title compound (15.50 g, quant. yield) as a colorless oil. $[M+Na]^+$ m/z = 540.3

[0217] SYNTHESIS OF INTERMEDIATE 5

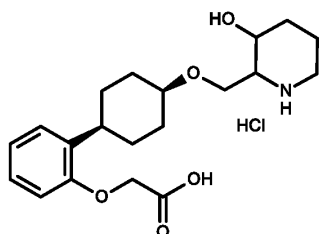
[0218] tert-butyl-3-hydroxy-2-({[(1s,4s)-4-{2-[2-(tert-butoxy)-2-oxoethoxy]phenyl}cyclohexyl]oxy}methyl)piperidine-1-carboxylate



[0219] Sodium borohydride (1.07 g, 28.3 mmol) was added portion wise to a stirred solution of Intermediate 4 (15.50 g, 28.4 mmol) in anhydrous DCM (118 mL) and MeOH (118 mL) at 0 °C and the mixture was stirred for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was re-suspended in water (300 mL) and extracted with DCM (3 x 200 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to afford the title compound (14.7 g, quant. yield) as a white solid. $[M+H]^+$ m/z = 542.3

[0220] SYNTHESIS OF INTERMEDIATE 6

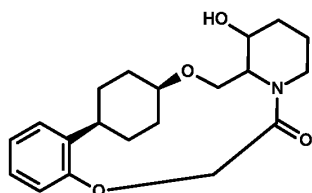
[0221] 2-{2-[(1s,4s)-4-[(3-hydroxypiperidin-2-yl)methoxy]cyclohexyl]phenoxy}acetic acid hydrochloride



[0222] A 4M solution of HCl in 1,4-dioxane (69 mL, 0.277 mol) was added to Intermediate 5 (14.70 g, 27.7 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was concentrated *in vacuo* to afford the title compound (11.5 g, quant. yield) as a white solid. $[M+H]^+$ m/z = 362.3

[0223] SYNTHESIS OF INTERMEDIATE 7

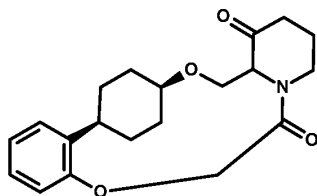
[0224] (1s,19s)-15-hydroxy-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-triene-10-one



[0225] To a stirred solution of HATU (15.00 g, 39.4 mmol) and DIPEA (23 mL, 0.132 mol) in MeCN (1240 mL) was added Intermediate 6 (10.50 g, 26.3 mmol) in anhydrous DMF (124 mL) over 2 h using a syringe pump. The resulting solution was stirred for 1 h, then it was concentrated *in vacuo* to afford the crude material. The mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography using a silica cartridge (0-40% 3:1 EtOAc/EtOH in heptane) to afford the title compound (5.9 g, 17.0 mmol, 65% yield) as a white solid. [M+H]⁺ m/z = 346.28

[0226] SYNTHESIS OF INTERMEDIATE 8

[0227] (1s,19s)-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-triene-10,15-dione

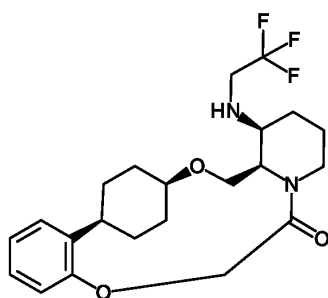


[0228] To a solution of Intermediate 7 (5.90 g, 15.9 mmol) in anhydrous DCM (130.64 mL) at 0 °C was added Dess-Martin periodinane (8.76 g, 20.6 mmol). The mixture was stirred at room temperature for 1 h. The mixture was diluted with DCM (200 mL), then washed with saturated aqueous. NaHCO₃ (100 mL), 1 M aq. Na₂S₂O₃ (100 mL), and 1M aq. Na₂CO₃ (100 mL). The organic phase was dried by passing through a hydrophobic filter and concentrated *in vacuo* to give the crude product. The crude material was purified by column chromatography using a silica

cartridge (0-100% 3:1 EtOAc/EtOH in heptane) to afford the title compound (4.1 g, 11.94 mmol, 75% yield) as a pale-yellow solid. $[M+H]^+$ $m/z = 344.2$

[0229] Example 1

[0230] Rel-(1s,15S,16R,19s)-15-[(2,2,2-trifluoroethyl)amino]-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricos-2(7),3,5-trien-10-one



[0231] Method A: A solution of 2,2,2-trifluoroethanamine (8.6 mg, 0.0865 mmol) and Intermediate 8 (25 mg, 0.0721 mmol) in anhydrous THF (1 mL) was heated to 70 °C for 16 h. The reaction mixture was cooled to room temperature, then sodium triacetoxyborohydride (31 mg, 0.144 mmol) was added and the mixture was stirred for 2 h. The reaction was quenched with water (2 mL) and extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to afford the crude material. The crude material was purified by column chromatography using a C18 cartridge (10-100% MeCN + 0.1% NH₃ in H₂O + 0.1% NH₃) to afford the title compound (1.8 mg, 0.004 mmol, 6% yield) as a white solid.

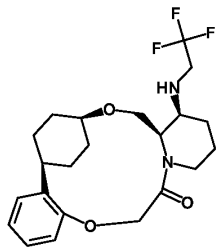
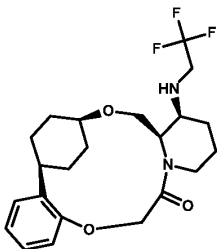
[0232] Method B: A solution of 2,2,2-trifluoroethanamine (125 mg, 1.26 mmol), Ti(OEt)₄ (191 mg, 0.839 mmol) and Intermediate 8 (150 mg, 0.420 mmol) in anhydrous THF (5 mL) was heated to 70 °C for 16 h. The reaction mixture was cooled to room temperature, then sodium borohydride (254 mg, 6.71 mmol) was added and the mixture was stirred for 3h. The reaction was quenched with water (15 mL) and diluted with EtOAc (15 mL). The mixture was filtered through a pad of Celite and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to afford the crude material.

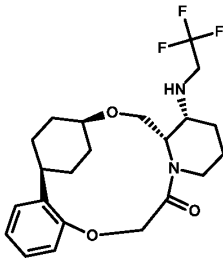
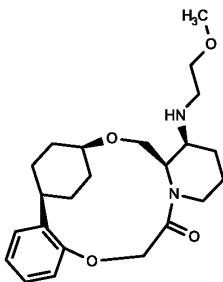
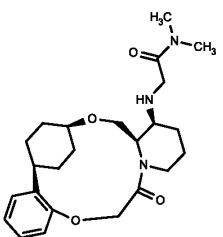
The crude material was purified by column chromatography using a C18 cartridge (10-100% MeCN + 0.1% NH₃ in H₂O + 0.1% NH₃) to afford the title compound (108 mg, 0.253 mmol, 60% yield) as a white solid.

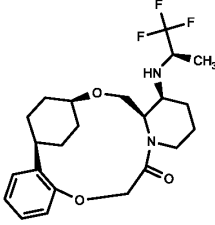
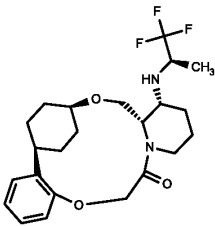
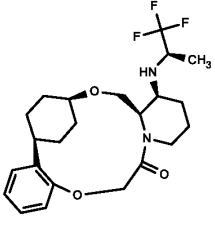
[0233] The examples below were prepared following procedures described for Example 1 using the appropriate reagents.

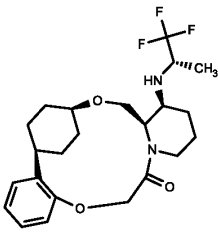
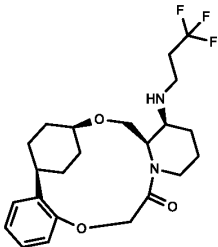
[0234] Stereoisomers were separated by chiral purification using appropriate chiral columns and combination of solvent mixtures; Chiralpak columns (AD-H, IC, OJ-H); solvent mixture of n-Hexane / EtOH, n-Hexane / (EtOH + 0.1% iPrNH₂), n-Hexane / (EtOH/MeOH 1:1 + 0.1% iPrNH₂).

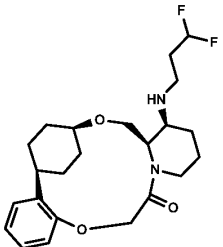
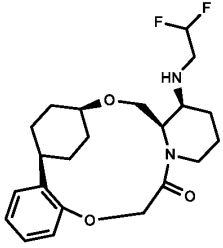
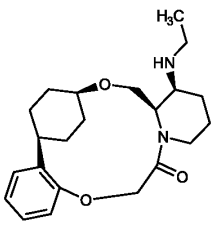
Table 3. Prepared Compounds and the Biological Activity Thereof

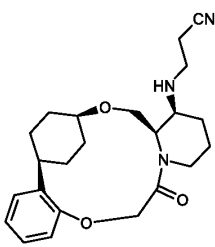
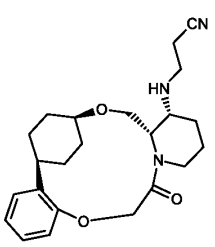
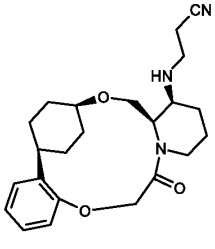
Cmpd	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
1		Rel-(1s,15S,16R,19s)-15-[(2,2,2-trifluoroethyl)amino]-8,18-dioxa-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]triosa-2(7),3,5-trien-10-one	[M+H] ⁺ 427.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.16 (td, J = 7.7, 1.8 Hz, 1H), 7.09 (dd, J = 7.5, 1.7 Hz, 1H), 6.89 (td, J = 7.4, 1.2 Hz, 1H), 6.74 (dd, J = 8.1, 1.2 Hz, 1H), 5.24 (dt, J = 10.2, 4.6 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.29 (d, J = 10.4 Hz, 1H), 3.82 (dd, J = 11.0, 9.1 Hz, 1H), 3.67 (d, J = 16.3 Hz, 2H), 3.54 – 3.41 (m, 2H), 3.30 (qd, J = 9.3, 2.0 Hz, 2H), 3.03 (dt, J = 9.4, 4.6 Hz, 1H), 2.75 – 2.49 (m, 2H), 2.27 (qd, J = 14.2, 5.6 Hz, 1H), 2.08 (d, J = 16.9 Hz, 1H), 1.93 – 1.79 (m, 3H), 1.66 – 1.22 (m, 6H).	B
2		(1s,15S,16R,19s)-15-[(2,2,2-trifluoroethyl)amino]-8,18-dioxa-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]triosa-2(7),3,5-trien-10-one	[M+H] ⁺ 427.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.15 (td, J = 7.7, 1.8 Hz, 1H), 7.09 (dd, J = 7.4, 1.7 Hz, 1H), 6.89 (td, J = 7.4, 1.2 Hz, 1H), 6.74 (dd, J = 8.1, 1.2 Hz, 1H), 5.24 (dt, J = 10.2, 4.7 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.29 (d, J = 10.4 Hz, 1H), 3.90 – 3.73 (m, 1H), 3.73 – 3.62 (m, 2H), 3.54 – 3.41 (m, 2H), 3.30 (qd, J = 9.3, 1.9 Hz, 2H), 3.03 (dt, J = 11.7, 4.5 Hz, 1H), 2.77 – 2.49 (m, 2H), 2.27 (qd, J = 14.2, 5.7 Hz, 1H), 2.07 (ddq, J = 14.1, 4.3, 2.3	A

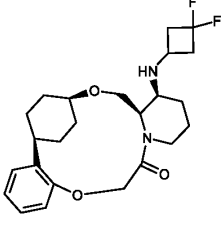
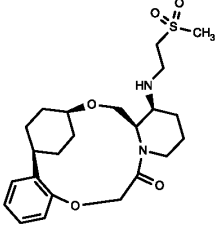
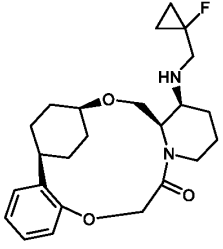
				Hz, 1H), 1.95 – 1.78 (m, 3H), 1.61 – 1.22 (m, 6H).	
3		(1s,15R,16S,19s)-15-[(2,2,2-trifluoroethyl)amino]-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trien-10-one	[M+H] ⁺ 427.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.15 (td, J = 7.7, 1.8 Hz, 1H), 7.09 (dd, J = 7.5, 1.7 Hz, 1H), 6.89 (td, J = 7.4, 1.1 Hz, 1H), 6.74 (dd, J = 8.1, 1.2 Hz, 1H), 5.24 (dt, J = 10.2, 4.7 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.29 (d, J = 10.4 Hz, 1H), 3.89 – 3.75 (m, 1H), 3.73 – 3.62 (m, 2H), 3.54 – 3.42 (m, 2H), 3.30 (qd, J = 9.2, 1.9 Hz, 2H), 3.03 (dt, J = 11.6, 4.6 Hz, 1H), 2.76 – 2.49 (m, 2H), 2.27 (qd, J = 14.3, 5.7 Hz, 1H), 2.19 – 2.02 (m, 1H), 1.93 – 1.79 (m, 3H), 1.66 – 1.22 (m, 6H).	D
4		Rel-(1s,15S,16R,19s)-15-[(2-methoxyethyl)amino]-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trien-10-one	[M+H] ⁺ 403.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.15 (td, J = 7.7, 1.7 Hz, 1H), 7.08 (dd, J = 7.5, 1.7 Hz, 1H), 6.94 – 6.79 (m, 1H), 6.74 (dd, J = 8.1, 1.2 Hz, 1H), 5.27 (dt, J = 10.9, 4.6 Hz, 1H), 5.10 (d, J = 10.3 Hz, 1H), 4.28 (d, J = 10.3 Hz, 1H), 3.89 – 3.73 (m, 1H), 3.73 – 3.61 (m, 2H), 3.61 – 3.38 (m, 4H), 3.36 (s, 3H), 2.98 – 2.80 (m, 3H), 2.69 (qd, J = 12.8, 4.4 Hz, 1H), 2.63 – 2.48 (m, 1H), 2.36 – 2.20 (m, 1H), 2.12 – 2.02 (m, 1H), 1.93 – 1.84 (m, 1H), 1.84 – 1.75 (m, 2H), 1.65 – 1.24 (m, 6H).	D
5		Rel-2-[(1s,15S,16R,19s)-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trien-15-yl]amino}acetamide	[M+H] ⁺ 430.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.16 (td, J = 7.7, 1.8 Hz, 1H), 7.09 (dd, J = 7.4, 1.8 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 6.82 – 6.71 (m, 1H), 5.33 – 5.13 (m, 1H), 5.10 (dd, J = 10.4, 2.2 Hz, 1H), 4.28 (dd, J = 10.3, 3.3 Hz, 1H), 4.09 – 3.80 (m, 1H), 3.74 – 3.41 (m, 3H), 3.06 – 2.87 (m, 6H), 2.61 (ddt, J = 40.4, 12.3, 6.5 Hz, 2H), 2.35 – 1.99 (m, 2H), 1.97 – 1.22 (m, 13H).	D

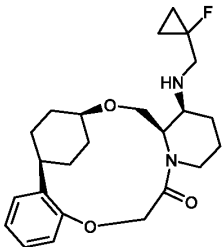
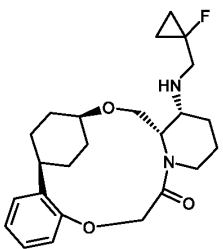
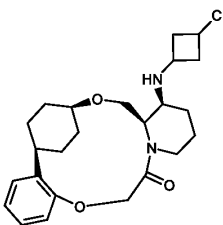
6		Rel- (1s,15S,16R,19s) -15-{[(2R)-1,1,1- trifluoropropan- 2-yl]amino}- 8,18-dioxa-11- azatetracyclo[17. 2.2.0 ^{2,7,0^{11,16}}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 441.3	¹ H NMR (500 MHz, CDCl ₃) δ 7.15 (td, J = 7.7, 1.8 Hz, 1H), 7.08 (dd, J = 7.1, 1.6 Hz, 1H), 6.88 (td, J = 7.4, 1.1 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 5.27 – 5.14 (m, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.28 (dd, J = 10.3, 2.1 Hz, 1H), 3.88 – 3.77 (m, 1H), 3.72 – 3.62 (m, 2H), 3.60 – 3.32 (m, 3H), 3.19 – 3.02 (m, 1H), 2.74 – 2.61 (m, 1H), 2.60 – 2.50 (m, 1H), 2.33 – 2.19 (m, 1H), 2.11 – 2.01 (m, 1H), 1.92 – 1.86 (m, 1H), 1.83 – 1.78 (m, 1H), 1.76 – 1.64 (m, 2H), 1.63 – 1.52 (m, 2H), 1.49 – 1.45 (m, 1H), 1.44 – 1.38 (m, 1H), 1.36 – 1.30 (m, 2H), 1.29 – 1.23 (m, 3H).	A
7		(1s,15S,16R,19s) -15-{[(2R)-1,1,1- trifluoropropan- 2-yl]amino}- 8,18-dioxa-11- azatetracyclo[17. 2.2.0 ^{2,7,0^{11,16}}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 441.3	¹ H NMR (500 MHz, CDCl ₃) δ 7.16 (td, J = 7.7, 1.7 Hz, 1H), 7.09 (dd, J = 7.4, 1.6 Hz, 1H), 6.90 (td, J = 7.4, 1.1 Hz, 1H), 6.75 (dd, J = 8.0, 0.9 Hz, 1H), 5.23 (dt, J = 10.1, 4.7 Hz, 1H), 5.11 (d, J = 10.4 Hz, 1H), 4.29 (d, J = 10.4 Hz, 1H), 3.84 (dd, J = 10.8, 9.2 Hz, 1H), 3.70 (br s, 1H), 3.66 (br dd, J = 13.8, 3.4 Hz, 1H), 3.50 (dd, J = 9.1, 4.0 Hz, 1H), 3.48 – 3.42 (m, 1H), 3.41 – 3.33 (m, 1H), 3.15 (dt, J = 12.2, 4.3 Hz, 1H), 2.69 (qd, J = 13.0, 4.5 Hz, 1H), 2.56 (tt, J = 12.4, 5.2 Hz, 1H), 2.28 (qd, J = 12.9, 4.0 Hz, 1H), 2.09 (br d, J = 14.0 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.86 – 1.77 (m, 2H), 1.65 – 1.58 (m, 1H), 1.53 – 1.30 (m, 5H), 1.25 (d, J = 6.7 Hz, 3H), 0.94 (br s, 1H).	D
8		(1s,15R,16S,19s) -15-{[(2R)-1,1,1- trifluoropropan- 2-yl]amino}- 8,18-dioxa-11- azatetracyclo[17. 2.2.0 ^{2,7,0^{11,16}}]tric	[M+H] ⁺ 441.3	¹ H NMR (500 MHz, CDCl ₃) δ 7.16 (td, J = 7.7, 1.7 Hz, 1H), 7.10 (dd, J = 7.5, 1.6 Hz, 1H), 6.90 (td, J = 7.4, 1.1 Hz, 1H), 6.75 (dd, J = 8.1, 0.8 Hz, 1H), 5.19 (br dt, J = 10.7, 4.7 Hz, 1H), 5.11 (d, J = 10.4 Hz, 1H), 4.30 (d, J = 10.3 Hz, 1H), 3.82 (dd, J = 10.7, 9.3 Hz, 1H), 3.73 – 3.64 (m, 2H), 3.59 (dd, J = 9.1, 4.1 Hz, 1H), 3.48 (td, J = 13.1, 2.8 Hz, 1H), 3.44 – 3.33 (m, 1H), 3.07 (dt, J = 11.3, 4.8 Hz, 1H),	A

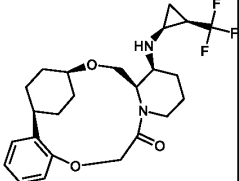
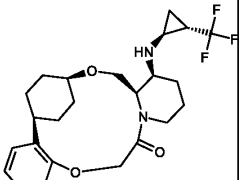
		osa-2(7),3,5-trien-10-one		2.69 (qd, J = 12.9, 4.5 Hz, 1H), 2.56 (tt, J = 12.2, 5.2 Hz, 1H), 2.28 (qd, J = 12.7, 3.8 Hz, 1H), 2.08 (br d, J = 14.1 Hz, 1H), 1.94 – 1.87 (m, 1H), 1.87 – 1.81 (m, 1H), 1.79 – 1.72 (m, 1H), 1.67 – 1.59 (m, 1H), 1.55 – 1.31 (m, 5H), 1.29 (d, J = 6.6 Hz, 3H), 0.80 (br s, 1H).	
9		Rel- (1s,15S,16R,19s) -15-[(2S)-1,1,1-trifluoropropan-2-yl]amino}-8,18-dioxa-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trienosa-2(7),3,5-trien-10-one	[M+H] ⁺ 441.3	¹ H NMR (500 MHz, CDCl ₃) δ 7.17 (td, J = 7.7, 1.8 Hz, 1H), 7.11 (dd, J = 7.5, 1.8 Hz, 1H), 6.91 (td, J = 7.5, 1.2 Hz, 1H), 6.76 (dd, J = 8.0, 1.1 Hz, 1H), 5.28 – 5.16 (m, 1H), 5.12 (d, J = 10.4 Hz, 1H), 4.30 (dd, J = 10.4, 2.1 Hz, 1H), 3.89 – 3.79 (m, 1H), 3.76 – 3.63 (m, 2H), 3.63 – 3.32 (m, 3H), 3.21 – 3.00 (m, 1H), 2.76 – 2.63 (m, 1H), 2.62 – 2.51 (m, 1H), 2.34 – 2.20 (m, 1H), 2.16 – 2.06 (m, 1H), 1.98 – 1.88 (m, 1H), 1.86 – 1.74 (m, 2H), 1.65 – 1.60 (m, 2H), 1.59 – 1.54 (m, 1H), 1.52 – 1.46 (m, 1H), 1.45 – 1.40 (m, 1H), 1.38 – 1.32 (m, 2H), 1.28 (dd, J = 20.7, 6.8 Hz, 3H).	B
10		Rel- (1s,15S,16R,19s) -15-[(3,3,3-trifluoropropyl)amino]-8,18-dioxa-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trienosa-2(7),3,5-trien-10-one	[M+H] ⁺ 441.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.16 (td, J = 7.7, 1.7 Hz, 1H), 7.09 (dd, J = 7.5, 1.7 Hz, 1H), 6.89 (td, J = 7.4, 1.1 Hz, 1H), 6.74 (dd, J = 8.1, 1.1 Hz, 1H), 5.26 (dt, J = 10.4, 4.7 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.29 (d, J = 10.4 Hz, 1H), 3.89 – 3.79 (m, 1H), 3.72 – 3.63 (m, 2H), 3.52 – 3.41 (m, 2H), 3.11 – 2.94 (m, 3H), 2.75 – 2.49 (m, 2H), 2.45 – 2.19 (m, 3H), 2.12 – 2.04 (m, 1H), 1.93 – 1.79 (m, 3H), 1.70 – 1.23 (m, 6H).	C

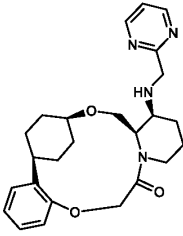
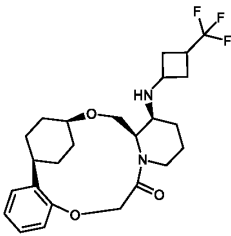
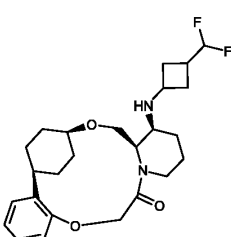
11		Rel- (1s,15S,16R,19s) -15-[(3,3- difluoropropyl)amino]-8,18- dioxo-11- azatetracyclo[17. 2.2.0 ^{2,7} .0 ^{11,16}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 423.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.09 (td, J = 7.7, 1.7 Hz, 1H), 7.02 (dd, J = 7.5, 1.7 Hz, 1H), 6.82 (td, J = 7.4, 1.2 Hz, 1H), 6.67 (dd, J = 8.2, 1.2 Hz, 1H), 6.07 – 5.73 (m, 1H), 5.25 – 5.18 (m, 1H), 5.03 (d, J = 10.4 Hz, 1H), 4.22 (d, J = 10.4 Hz, 1H), 3.84 – 3.72 (m, 1H), 3.66 – 3.57 (m, 2H), 3.46 – 3.35 (m, 2H), 3.02 – 2.82 (m, 2H), 2.67 – 2.42 (m, 2H), 2.26 – 1.96 (m, 2H), 1.90 – 1.73 (m, 2H), 1.67 – 1.16 (m, 10H).	C
12		Rel- (1s,15S,16R,19s) -15-[(2,2- difluoroethyl)amino]-8,18-dioxo- 11- azatetracyclo[17. 2.2.0 ^{2,7} .0 ^{11,16}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 409.2	¹ H NMR (400 MHz, CDCl ₃) δ 7.16 (td, J = 7.7, 1.7 Hz, 1H), 7.09 (dd, J = 7.4, 1.8 Hz, 1H), 6.89 (td, J = 7.4, 1.2 Hz, 1H), 6.74 (dd, J = 8.1, 1.2 Hz, 1H), 5.88 (t, J = 56.2 Hz, 1H), 5.26 (dt, J = 10.3, 4.6 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.29 (d, J = 10.4 Hz, 1H), 3.88 – 3.79 (m, 1H), 3.72 – 3.63 (m, 2H), 3.55 – 3.41 (m, 2H), 3.23 – 2.94 (m, 2H), 2.75 – 2.49 (m, 2H), 2.34 – 2.19 (m, 1H), 2.12 – 2.04 (m, 1H), 1.93 – 1.79 (m, 3H), 1.69 – 1.22 (m, 7H).	B
13		Rel- (1s,15S,16R,19s) -15- (ethylamino)- 8,18-dioxo-11- azatetracyclo[17. 2.2.0 ^{2,7} .0 ^{11,16}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 373.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.15 (td, J = 7.9, 1.7 Hz, 1H), 7.08 (dd, J = 7.4, 1.5 Hz, 1H), 6.88 (t, J = 7.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 5.26 (dt, J = 10.2, 4.6 Hz, 1H), 5.10 (d, J = 10.3 Hz, 1H), 4.28 (d, J = 10.3 Hz, 1H), 3.89 – 3.78 (m, 1H), 3.72 – 3.62 (m, 2H), 3.54 – 3.40 (m, 2H), 3.00 – 2.91 (m, 1H), 2.85 – 2.50 (m, 5H), 2.35 – 2.21 (m, 1H), 2.13 – 2.03 (m, 1H), 1.93 – 1.84 (m, 1H), 1.84 – 1.75 (m, 2H), 1.63 – 1.53 (m, 3H), 1.40 – 1.22 (m, 3H), 1.13 (t, J = 7.1 Hz, 3H).	C

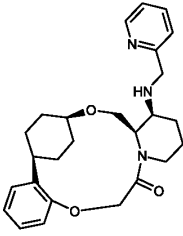
14		Rel-3- {[(1s,15S,16R,19 s)-10-oxo-8,18- dioxo-11- azatetracyclo[17. 2.2.0 ² , ⁷ .0 ¹¹ , ¹⁶]tric osa-2(7),3,5- trien-15- yl]amino}propan enitrile	[M+H] ⁺ 398.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.18 (td, J = 7.8, 1.7 Hz, 1H), 7.11 (dd, J = 7.4, 1.6 Hz, 1H), 6.91 (td, J = 7.4, 0.9 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.26 (dt, J = 10.1, 4.6 Hz, 1H), 5.12 (d, J = 10.4 Hz, 1H), 4.30 (d, J = 10.4 Hz, 1H), 3.85 (dd, J = 10.8, 9.4 Hz, 1H), 3.70 (d, J = 15.7 Hz, 2H), 3.56 – 3.43 (m, 2H), 3.14 – 2.92 (m, 3H), 2.70 (qd, J = 13.5, 5.1 Hz, 1H), 2.60 – 2.46 (m, 2H), 2.37 – 2.15 (m, 1H), 2.10 (d, J = 14.1 Hz, 1H), 1.96 – 1.78 (m, 3H), 1.70 – 1.25 (m, 8H).	B
15		3- {[(1s,15R,16S,19 s)-10-oxo-8,18- dioxo-11- azatetracyclo[17. 2.2.0 ² , ⁷ .0 ¹¹ , ¹⁶]tric osa-2(7),3,5- trien-15- yl]amino}propan enitrile	[M+H] ⁺ 498.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.17 (td, J=7.7, 1.4 Hz, 1 H), 7.06 - 7.12 (m, 1 H), 6.86 - 6.95 (m, 1 H), 6.75 (d, J=8.0 Hz, 1 H), 5.25 (dt, J=9.9, 4.4 Hz, 1 H), 5.11 (d, J=10.4 Hz, 1 H), 4.29 (d, J=10.4 Hz, 1 H), 3.85 (t, J=10.1 Hz, 1 H), 3.71 (br s, 1 H), 3.63 - 3.73 (m, 1 H), 3.52 (dd, J=9.2, 3.9 Hz, 1 H), 3.42 - 3.52 (m, 1 H), 3.02 - 3.15 (m, 2 H), 2.99 (dt, J=10.4, 4.8 Hz, 1 H), 2.60 - 2.75 (m, 1 H), 2.47 - 2.62 (m, 3 H), 2.21 - 2.35 (m, 1 H), 2.04 - 2.15 (m, 1 H), 1.80 - 1.94 (m, 3 H), 1.44 - 1.64 (m, 3 H), 1.25 - 1.44 (m, 3 H).	D
16		3- {[(1s,15S,16R,19 s)-10-oxo-8,18- dioxo-11- azatetracyclo[17. 2.2.0 ² , ⁷ .0 ¹¹ , ¹⁶]tric osa-2(7),3,5- trien-15- yl]amino}propan enitrile	[M+H] ⁺ 498.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.17 (td, J=7.7, 1.4 Hz, 1 H), 7.06 - 7.12 (m, 1 H), 6.86 - 6.95 (m, 1 H), 6.75 (d, J=8.0 Hz, 1 H), 5.25 (dt, J=9.9, 4.4 Hz, 1 H), 5.11 (d, J=10.4 Hz, 1 H), 4.29 (d, J=10.4 Hz, 1 H), 3.85 (t, J=10.1 Hz, 1 H), 3.71 (br s, 1 H), 3.63 - 3.73 (m, 1 H), 3.52 (dd, J=9.2, 3.9 Hz, 1 H), 3.42 - 3.52 (m, 1 H), 3.02 - 3.15 (m, 2 H), 2.99 (dt, J=10.4, 4.8 Hz, 1 H), 2.60 - 2.75 (m, 1 H), 2.47 - 2.62 (m, 3 H), 2.21 - 2.35 (m, 1 H), 2.04 - 2.15 (m, 1 H), 1.80 - 1.94 (m, 3 H), 1.44 - 1.64 (m, 3 H), 1.25 - 1.44 (m, 3 H).	A

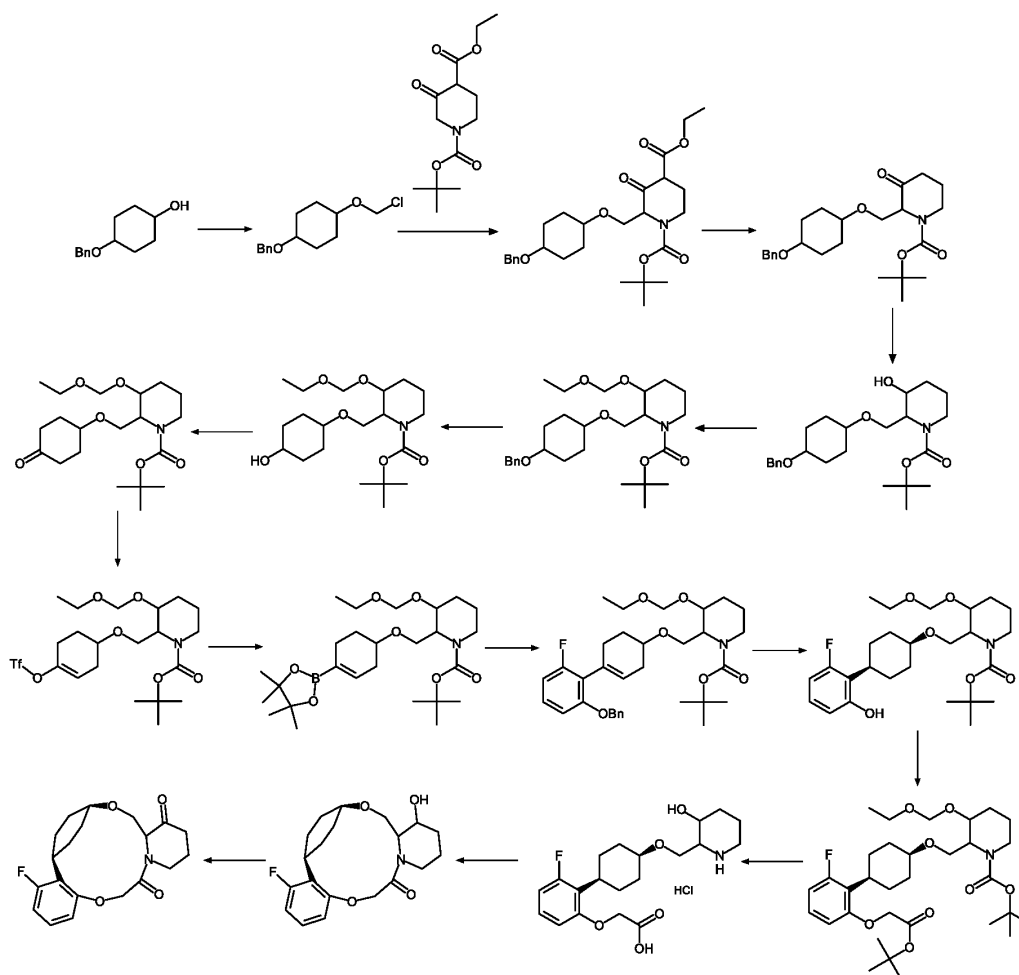
17		Rel- (1s,15S,16R,19s) -15-[(3,3- difluorocyclobut yl)amino]-8,18- dioxo-11- azatetracyclo[17. 2.2.0 ^{2,7} .0 ^{11,16}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 435.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.08 (t, J = 7.7 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 6.81 (t, J = 7.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.12 (s, 1H), 5.02 (d, J = 10.5 Hz, 1H), 4.20 (d, J = 10.4 Hz, 1H), 3.78 (s, 2H), 3.60 (d, J = 17.7 Hz, 2H), 3.42 (s, 3H), 2.95 – 2.41 (m, 7H), 2.17 (d, J = 14.8 Hz, 2H), 2.00 (d, J = 14.8 Hz, 1H), 1.78 (s, 2H), 1.40 – 1.11 (m, 6H).	B
18		Rel- (1s,15S,16R,19s) -15-[(2- methanesulfonyl ethyl)amino]- 8,18-dioxo-11- azatetracyclo[17. 2.2.0 ^{2,7} .0 ^{11,16}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 451.2	¹ H NMR (400 MHz, CDCl ₃) δ 7.16 (td, J = 7.8, 1.7 Hz, 1H), 7.08 (dd, J = 7.4, 1.6 Hz, 1H), 6.89 (td, J = 7.4, 1.0 Hz, 1H), 6.74 (d, J = 7.3 Hz, 1H), 5.27 (dq, J = 10.0, 4.8 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.28 (d, J = 10.4 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.68 (d, J = 13.7 Hz, 2H), 3.52 – 3.42 (m, 2H), 3.28 (dq, J = 21.0, 10.6 Hz, 4H), 3.00 (s, 4H), 2.61 (dddd, J = 39.7, 17.1, 12.3, 6.7 Hz, 2H), 2.32 – 2.16 (m, 1H), 2.07 (d, J = 14.4 Hz, 1H), 1.92 – 1.79 (m, 3H), 1.54 – 1.19 (m, 7H).	C
19		Rel- (1s,15S,16R,19s) -15-[(1- fluorocyclopropy l)methyl]amino}- 8,18-dioxo-11- azatetracyclo[17. 2.2.0 ^{2,7} .0 ^{11,16}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 417.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.15 (td, J = 7.8, 1.7 Hz, 1H), 7.09 (dd, J = 7.4, 1.6 Hz, 1H), 6.89 (td, J = 7.4, 0.9 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 5.28 (dd, J = 10.6, 5.0 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.28 (d, J = 10.4 Hz, 1H), 3.93 – 3.83 (m, 1H), 3.75 – 3.62 (m, 2H), 3.57 – 3.42 (m, 2H), 3.21 – 3.00 (m, 3H), 2.76 – 2.49 (m, 3H), 2.37 – 2.18 (m, 1H), 2.14 – 2.04 (m, 1H), 1.95 – 1.78 (m, 3H), 1.46 – 1.23 (m, 5H), 1.18 – 0.98 (m, 2H), 0.92 – 0.56 (m, 3H).	A

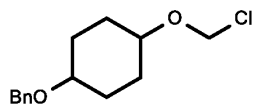
20		(1s,15S,16R,19s) -15-{{(1-fluorocyclopropyl)methyl}amino} -8,18-dioxa-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 417.3	¹ H NMR (500 MHz, MeOD) δ 7.14 (td, J=7.8, 1.6 Hz, 1 H), 7.07 (dd, J=7.4, 1.6 Hz, 1 H), 6.81 - 6.88 (m, 2 H), 5.29 (d, J=10.6 Hz, 1 H), 5.23 (dt, J=11.4, 4.4 Hz, 1 H), 4.11 (d, J=10.6 Hz, 1 H), 3.94 (dd, J=11.1, 9.3 Hz, 1 H), 3.75 - 3.83 (m, 1 H), 3.69 (br s, 1 H), 3.50 (td, J=13.2, 2.8 Hz, 1 H), 3.45 (dd, J=9.3, 3.8 Hz, 1 H), 2.97 - 3.13 (m, 2 H), 2.97 - 3.04 (m, 1 H), 2.74 (qd, J=13.0, 4.5 Hz, 1 H), 2.51 - 2.61 (m, 1 H), 2.31 (qd, J=13.0, 4.3 Hz, 1 H), 2.13 - 2.21 (m, 1 H), 1.75 - 1.94 (m, 2 H), 1.75 - 1.83 (m, 1 H), 1.51 - 1.68 (m, 2 H), 1.44 - 1.50 (m, 1 H), 1.41 - 1.48 (m, 1 H), 1.31 - 1.40 (m, 1 H), 1.23 - 1.30 (m, 1 H), 0.97 - 1.08 (m, 2 H), 0.62 - 0.83 (m, 2 H).	A
21		(1s,15R,16S,19s) -15-{{(1-fluorocyclopropyl)methyl}amino} -8,18-dioxa-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one		¹ H NMR (500 MHz, MeOD) δ 7.14 (td, J=7.8, 1.6 Hz, 1 H), 7.07 (dd, J=7.4, 1.6 Hz, 1 H), 6.81 - 6.88 (m, 2 H), 5.29 (d, J=10.6 Hz, 1 H), 5.23 (dt, J=11.4, 4.4 Hz, 1 H), 4.11 (d, J=10.6 Hz, 1 H), 3.94 (dd, J=11.1, 9.3 Hz, 1 H), 3.75 - 3.83 (m, 1 H), 3.69 (br s, 1 H), 3.50 (td, J=13.2, 2.8 Hz, 1 H), 3.45 (dd, J=9.3, 3.8 Hz, 1 H), 2.97 - 3.13 (m, 2 H), 2.97 - 3.04 (m, 1 H), 2.74 (qd, J=13.0, 4.5 Hz, 1 H), 2.51 - 2.61 (m, 1 H), 2.31 (qd, J=13.0, 4.3 Hz, 1 H), 2.13 - 2.21 (m, 1 H), 1.75 - 1.94 (m, 2 H), 1.75 - 1.83 (m, 1 H), 1.51 - 1.68 (m, 2 H), 1.44 - 1.50 (m, 1 H), 1.41 - 1.48 (m, 1 H), 1.31 - 1.40 (m, 1 H), 1.23 - 1.30 (m, 1 H), 0.97 - 1.08 (m, 2 H), 0.62 - 0.83 (m, 2 H).	C
22		Rel-3- {{(1s,15S,16R,19s)-10-oxo-8,18-dioxa-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-	[M+H] ⁺ 424.4	¹ H NMR (500 MHz, DMSO) δ 7.14 (td, J = 7.8, 1.7 Hz, 1H), 7.09 - 7.05 (m, 1H), 6.85 - 6.79 (m, 2H), 5.31 - 5.24 (m, 1H), 4.94 - 4.86 (m, 1H), 3.94 (d, J = 10.4 Hz, 1H), 3.82 - 3.72 (m, 1H), 3.69 - 3.49 (m, 3H), 3.38 - 3.35 (m, 1H), 3.30 - 3.25 (m, 1H), 3.23 - 3.13 (m, 1H), 2.72 - 2.58 (m, 2H), 2.45 - 2.33 (m, 2H), 2.32 - 2.17 (m, 2H), 2.17 - 2.03 (m, 3H), 1.74 -	C

		yl]amino}cyclobutane-1-carbonitrile		1.61 (m, 3H), 1.49 – 1.18 (m, 6H), 1.18 – 1.09 (m, 1H).	
23		Rel- (1s,15S,16R,19s) -15-([rel- (1S,2R)-2-(trifluoromethyl) cyclopropyl]amino)-8,18-dioxabenzotetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trien-2(7),3,5-trien-10-one	[M+H] ⁺ 453.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.22 – 7.15 (m, 1H), 7.14 – 7.08 (m, 1H), 6.91 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.42 – 5.21 (m, 1H), 5.13 (d, J = 10.3 Hz, 1H), 4.31 (dd, J = 10.4, 1.9 Hz, 1H), 3.92 – 3.79 (m, 1H), 3.69 (d, J = 15.1 Hz, 2H), 3.63 – 3.42 (m, 2H), 3.13 – 3.00 (m, 1H), 2.75 – 2.52 (m, 3H), 2.38 – 2.23 (m, 1H), 2.19 – 2.07 (m, 1H), 1.99 – 1.74 (m, 4H), 1.54 – 1.27 (m, 7H), 1.1 – 0.9 (m, 2H).	B
24		Rel- (1s,15S,16R,19s) -15-([rel(1S,2S)-2-(trifluoromethyl) cyclopropyl]amino)-8,18-dioxabenzotetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trien-2(7),3,5-trien-10-one	[M+H] ⁺ 453.2	¹ H NMR (400 MHz, CDCl ₃) δ 7.18 (td, J = 7.8, 1.7 Hz, 1H), 7.11 (dd, J = 7.4, 1.6 Hz, 1H), 6.91 (td, J = 7.4, 0.9 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 5.24 (ddt, J = 14.8, 10.2, 4.6 Hz, 1H), 5.13 (d, J = 10.4 Hz, 1H), 4.30 (dd, J = 10.4, 1.0 Hz, 1H), 3.82 (q, J = 9.4 Hz, 1H), 3.73 – 3.64 (m, 2H), 3.55 – 3.40 (m, 2H), 3.06 (ddt, J = 22.0, 12.1, 4.7 Hz, 1H), 2.79 – 2.43 (m, 3H), 2.29 (qd, J = 14.1, 5.5 Hz, 1H), 2.17 – 1.78 (m, 4H), 1.66 – 1.46 (m, 3H), 1.38 (dtt, J = 30.7, 18.2, 6.3 Hz, 5H), 1.11 – 0.98 (m, 1H), 0.93 (ddt, J = 20.0, 9.7, 5.0 Hz, 1H).	C

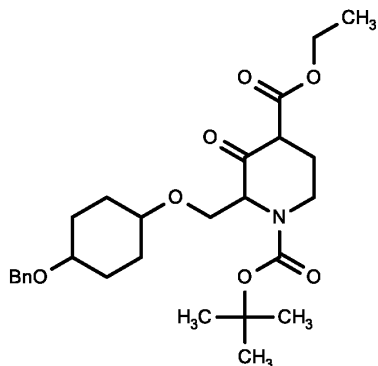
25		Rel- (1s,15S,16R,19s) -15- {[(pyrimidin-2-yl)methyl]amino }-8,18-dioxa-11- azatetracyclo[17. 2.2.0 ^{2,7.0^{11,16}}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 437.3	¹ H NMR (500 MHz, CDCl ₃) δ 8.84 – 8.59 (m, 1H), 7.25 – 7.21 (m, 1H), 7.19 – 7.10 (m, 2H), 7.10 – 7.02 (m, 1H), 6.95 – 6.80 (m, 1H), 6.72 (q, J = 8.0 Hz, 1H), 5.46 – 5.27 (m, 1H), 5.09 (q, J = 10.4 Hz, 1H), 4.39 – 4.06 (m, 2H), 4.08 – 3.82 (m, 1H), 3.84 – 3.32 (m, 4H), 3.10 – 2.91 (m, 1H), 2.91 – 2.41 (m, 2H), 2.39 – 2.17 (m, 1H), 2.15 – 1.62 (m, 6H), 1.52 – 1.09 (m, 5H).	D
26		Rel- (1s,15S,16R,19s) -15-{[3- (trifluoromethyl) cyclobutyl]amin o}-8,18-dioxa- 11- azatetracyclo[17. 2.2.0 ^{2,7.0^{11,16}}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 467.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.15 (t, J = 7.7 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 5.19 (s, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.28 (d, J = 10.4 Hz, 1H), 3.94 – 3.61 (m, 4H), 3.50 (d, J = 13.0 Hz, 2H), 3.08 – 2.76 (m, 3H), 2.73 – 2.46 (m, 4H), 2.25 (s, 3H), 2.14 – 2.01 (m, 2H), 1.88 (d, J = 13.3 Hz, 3H), 1.44 – 1.21 (m, 5H).	C
27		Rel- (1s,15S,16R,19s) -15-{[3- (difluoromethyl) cyclobutyl]amin o}-8,18-dioxa- 11- azatetracyclo[17. 2.2.0 ^{2,7.0^{11,16}}]tric osa-2(7),3,5- trien-10-one	[M+H] ⁺ 449.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.16 (t, J = 7.0 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.78 – 6.71 (m, 1H), 5.91 (s, 1H), 5.25 (s, 1H), 5.15 – 5.05 (m, 1H), 4.29 (d, J = 10.5 Hz, 1H), 4.03 – 3.44 (m, 7H), 2.57 (m, 7H), 2.31 – 2.04 (m, 4H), 1.87 (s, 2H), 1.45 – 1.20 (m, 5H).	C

28		Rel-(1s,15S,16R,19s)-15-{[(pyridin-2-yl)methyl]amino}-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]trienosa-2(7),3,5-trien-10-one	[M+H]⁺ 436.3	¹H NMR (400 MHz, CDCl₃) δ 8.49 (d, J = 4.2 Hz, 1H), 7.60 (td, J = 7.7, 1.7 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.16 – 6.98 (m, 4H), 6.81 (td, J = 7.4, 1.0 Hz, 1H), 6.66 (d, J = 7.3 Hz, 1H), 5.31 (dt, J = 10.1, 4.5 Hz, 1H), 5.02 (d, J = 10.4 Hz, 1H), 4.21 (d, J = 10.4 Hz, 1H), 4.03 (s, 2H), 3.90 – 3.82 (m, 1H), 3.68 – 3.54 (m, 3H), 3.42 (td, J = 13.4, 2.6 Hz, 1H), 3.02 – 2.94 (m, 1H), 2.69 – 2.41 (m, 3H), 2.24 – 2.13 (m, 1H), 2.07 – 1.99 (m, 1H), 1.91 – 1.75 (m, 4H), 1.34 – 1.20 (m, 4H).	C
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[0235] SYNTHESIS OF INTERMEDIATE 9**[0236]** ({[4-(chloromethoxy)cyclohexyl]oxy}methyl)benzene

[0237] In a 10L reactor 4-benzyloxycyclohexanol (924 g, 4479 mmol) was dissolved in DCM (5 L) at 20 °C, then paraformaldehyde (135 g, 4479 mmol) was added in one portion. The suspension was stirred at 20 °C for 1 h, then chloro(trimethyl)silane (1137 mL, 8958 mmol) was added dropwise over 2 h. The reaction mixture was stirred for 3 h at 20 °C, then it was filtered to remove small particulates in suspension and the filtrate was evaporated *in vacuo* at 22 °C to afford the title compound (1115 g, 4375 mmol, 97% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 1.06 - 2.07 (m, 8 H) 3.15 - 4.03 (m, 2 H) 4.33 - 4.52 (m, 2 H) 4.53 - 4.95 (m, 2 H) 7.18 - 7.45 (m, 5 H).

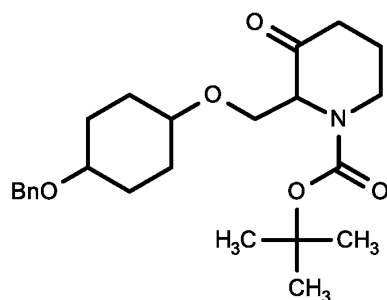
[0238] SYNTHESIS OF INTERMEDIATE 10**[0239]** 1-tert-butyl 4-ethyl 2-({[4-(benzyloxy)cyclohexyl]oxy}methyl)-3-oxopiperidine-1,4-dicarboxylate

[0240] A 10 L jacketed reactor was charged with dry MeTHF (3935 mL) followed by sodium hydride (89.16 g, 2229 mmol). The suspension was cooled to -15 °C, then a solution of 1-tert-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (465.2 g, 1714.7 mmol) in dry MeTHF (1093 mL) was added dropwise over 2 h maintaining the internal temperature below -10 °C. The mixture was stirred for 30 minutes, then a 2.5M solution of n-BuLi in hexane (891.6 mL, 2229 mmol) was

added dropwise over 2 h, maintaining the internal temperature below -10 °C. The mixture was stirred for 30 minutes. A solution of Intermediate 9 (550 g, 1714 mmol) in dry MeTHF (1093 mL) was added dropwise over 1 h, maintaining the internal temperature below -10 °C. The mixture was then stirred at 0 °C for 16 h. A 10% aqueous solution of KHSO₄ (3.3 L) was added and the mixture was stirred for 30 minutes. The phases were separated and the organic layer was washed with water (2 L) and 13% aqueous NaCl solution (2 L) and concentrated *in vacuo*. The product was purified using a silica gel pad (2000 g, 0-20% EtOAc in cHex) to afford the title compound (530 g, 1082 mmol, 63% yield) as a yellow oil. $[M+Na]^+$ $m/z = 512.7$

[0241] SYNTHESIS OF INTERMEDIATE 11

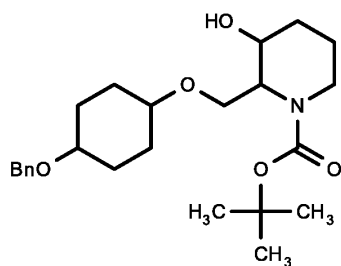
[0242] tert-butyl 2-({[4-(benzyloxy)cyclohexyl]oxy}methyl)-3-oxopiperidine-1-carboxylate



[0243] A Vapourtec flow setup was equipped with a 25 mL high temperature high-pressure Stainless-steel reactor and a set of backpressure regulators (450 psi, idle pressure of ca. 34 bar). A solution of Intermediate 10 (530 g, 1083 mmol) in a mixture of acetone (3180 mL) and water (265 mL) was pumped through the reactor set at a temperature of 205 °C with a residence time of 7 minutes (flow = 3.75 mL/min). The collected reaction mixture was concentrated *in vacuo* to remove most of the volatiles, then the residue was dissolved in EtOAc (1 L). The obtained organic phase was sequentially washed with 5% aqueous KHSO₄ solution (200 mL) and brine (50 mL), water (500 mL) and brine (50 mL), saturated aqueous KHCO₃ solution (200 mL), and brine (100 mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound (486 g, quant. yield) as a brown oil. $[M+Na]^+$ $m/z = 440.6$

[0244] SYNTHESIS OF INTERMEDIATE 12

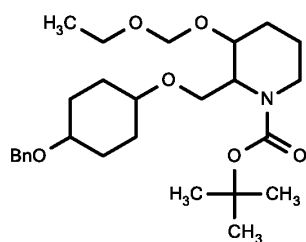
[0245] tert-butyl 2-({[4-(benzyloxy)cyclohexyl]oxy}methyl)-3-hydroxypiperidine-1-carboxylate



[0246] A 4 L round-bottomed flask was charged with a solution of Intermediate 11 (257 g, 616 mmol) in MeOH (1.2 L). The mixture was cooled to 0 °C and sodium borohydride (9.5 g, 251 mmol) was added portionwise and subsequently the mixture was stirred and allowed to warm to room temperature over 2 h. The mixture was cooled with an ice/water bath and quenched by dropwise addition of water (500 mL), stirred for 10 minutes and then allowed to warm to room temperature. The mixture was concentrated *in vacuo* to remove most of the MeOH. The aqueous residue was diluted with additional water (500 mL) and extracted with MTBE (800+300 mL). The combined organic phases were washed with water (600 mL) and brine (300 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford a yellow oil that was purified by column chromatography using a silica cartridge (cHex/EtOAc from 0% to 50%) to afford the title compound (110g, 262 mmol, 56% yield) as a pale-yellow oil. [M+Na]⁺ m/z = 442.8

[0247] SYNTHESIS OF INTERMEDIATE 13

[0248] tert-butyl 2-({[4-(benzyloxy)cyclohexyl]oxy}methyl)-3-(ethoxymethoxy)piperidine-1-carboxylate

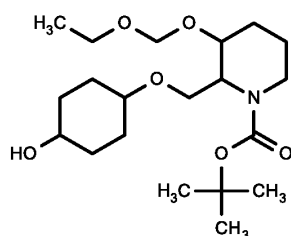


[0249] To a solution of Intermediate 12 (110g, 265 mmol) in DCM (500 mL) under a nitrogen atmosphere, were added TBAI (9.8g, 12.9 mmol) and DIPEA (136 mL, 781 mmol). A solution of ethoxy chloromethane (99.7g, 526 mmol) in DCM (100 mL) was added dropwise and the final

mixture was then heated under reflux for 2 h. The reaction mixture was cooled to 10 °C, then saturated aqueous NH₄Cl solution (300 mL) was added, followed by aqueous 1M NaOH solution (200 mL). The mixture was stirred for 10 minutes, then the layers were separated. The organic phase was sequentially washed with 10% vol. aqueous AcOH solution (600 mL), water (600 mL) and saturated aqueous KHCO₃ solution (600 mL), dried over Na₂SO₄ and evaporated *in vacuo* to afford the title compound (138g, quant. yield) as a yellow oil. [M-Boc+2H]⁺ m/z = 378.6

[0250] SYNTHESIS OF INTERMEDIATE 14

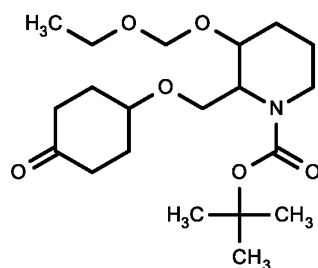
[0251] tert-butyl 3-(ethoxymethoxy)-2-{[(4-hydroxycyclohexyl)oxy]methyl}piperidine-1-carboxylate



[0252] A round-bottomed flask was charged with a solution of Intermediate 13 (13 g, 27.22 mmol) and EtOH (70 mL). Pd/C 5% wt. wet matrix (1.26 g, 0.59 mmol) was added, then the reactor was filled with H_{2(g)} (1 bar). The mixture was vigorously stirred at room temperature for 4 h. The suspension was filtered through a pad of Celite, then the filtrate was concentrated *in vacuo*. The colorless residue was co-evaporated with *n*-heptane (3 x 40 mL) *in vacuo* to afford the title compound (60.5 g, 156 mmol, 69% yield) as a colorless oil. [M-Boc+2H]⁺ m/z = 288.6

[0253] SYNTHESIS OF INTERMEDIATE 15

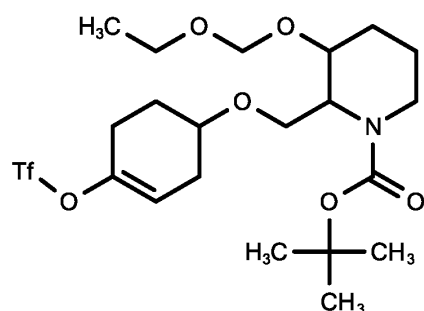
[0254] tert-butyl 3-(ethoxymethoxy)-2-{[(4-oxocyclohexyl)oxy]methyl}piperidine-1-carboxylate



[0255] To a solution of Intermediate 14 (9.7 g, 25 mmol) in MeCN (60 mL) were added Cu(MeCN)₄OTf (0.23 g, 0.62 mmol), 4,4'-dimethoxy-2,2'-bipyridine (0.135 g, 0.62 mmol), ABNO (0.018 g, 0.125 mmol) and *N*-methylimidazole (0.21 g, 2.50 mmol). The mixture was stirred while air was bubbled through the solution. After 1 h the mixture was concentrated *in vacuo*. The residue was dissolved in MTBE (60 mL) and washed with 4% wt. aqueous NH₄OH solution (40 mL), 5% wt. aqueous KHSO₄ solution (40 mL) and brine (30 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated *in vacuo*. The product was purified by column chromatography using a silica cartridge (0% to 30% EtOAc in cHex) to afford the title compound (7 g, 18.2 mmol, 72% yield) as a light-yellow oil. [M-Boc+2H]⁺ m/z = 286.6

[0256] SYNTHESIS OF INTERMEDIATE 16

[0257] tert-butyl 3-(ethoxymethoxy)-2-({[4-(trifluoromethanesulfonyloxy)cyclohex-3-en-1-yl]oxy}methyl)piperidine-1-carboxylate

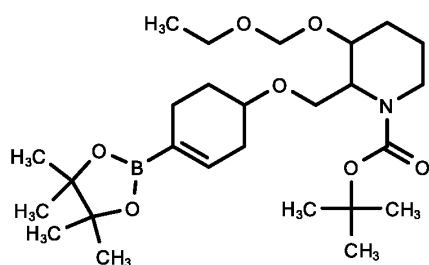


[0258] In a 250 mL round-bottomed flask, Intermediate 15 (5.0 g, 12.97 mmol) was dissolved in THF (40 mL) then 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (4.63 g, 12.97 mmol) was added. The mixture was cooled to -20 °C and then a 1 M solution of lithium bis(trimethylsilyl)amide in THF (14.27 mL, 14.27 mmol) was added dropwise, maintaining the internal temperature below -15 °C. The obtained suspension was stirred at this temperature for 30 minutes, then gradually warmed to room temperature and stirred at this temperature for 1 h. The mixture was quenched with saturated aqueous NH₄Cl solution (40 mL) and stirred for 10 minutes, then the layers were separated. The organic layer was concentrated *in vacuo* and redissolved in MTBE (50 mL), while the aqueous phase was extracted with MTBE (30

mL). The combined organic fractions were washed with saturated aqueous KHCO_3 solution (60 mL) and brine (40 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford the title compound (8.3 g, quant. yield) as a yellow oil. $[\text{M-Boc}+2\text{H}]^+ \text{ m/z} = 418.6$

[0259] SYNTHESIS OF INTERMEDIATE 17

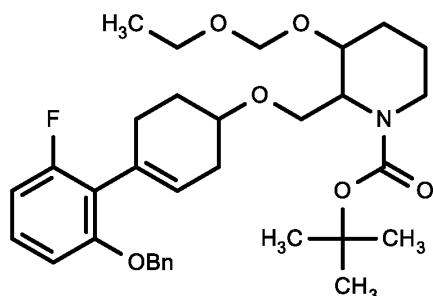
[0260] tert-butyl 3-(ethoxymethoxy)-2-({[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]oxy}methyl)piperidine-1-carboxylate



[0261] In a round-bottomed flask Intermediate 16 (15.42 g, 29.79 mmol), bis(pinacolato)diboron (8.32 g, 32.77 mmol), potassium acetate (8.77 g, 89.37 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (1.09 g, 1.49 mmol) were suspended in anhydrous CPME (298 mL). The suspension was degassed by several vacuum/ $\text{N}_{2(g)}$ cycles and then by bubbling $\text{N}_{2(g)}$ through the mixture for 10 minutes. The mixture was stirred at 105 °C for 16 h, then it was cooled to room temperature and saturated aqueous NaHCO_3 solution was added. The mixture was extracted three times with EtOAc. The combined organic layers were dried by filtering through a hydrophobic frit (Phase Separator) and concentrated *in vacuo*. The product was purified by column chromatography using a silica cartridge (0-20% EtOAc in cHex) to afford the title compound (7.3 g, 14.73 mmol, 49% yield) as a yellow oil. $[\text{M}+\text{H}]^+ \text{ m/z} = 496.3$

[0262] SYNTHESIS OF INTERMEDIATE 18

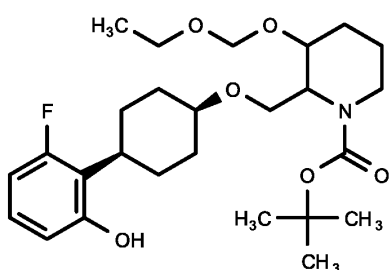
[0263] tert-butyl 2-[(4-[2-(benzyloxy)-6-fluorophenyl]cyclohex-3-en-1-yl]oxy)methyl]-3-(ethoxymethoxy)piperidine-1-carboxylate



[0264] Pd(PPh₃)₂Cl₂ (1.27 g, 1.82 mmol) was added to a mixture of Intermediate 17 (15 g, 30.27 mmol), 1-benzyloxy-2-bromo-3-fluoro-benzene (9.36 g, 33.3 mmol) and potassium carbonate (20.92 g, 151.37 mmol) in water (130 mL) and 1,2-dimethoxyethane (130 mL). The suspension was degassed by bubbling N₂(g) through the mixture for 10 minutes, then it was stirred at 80 °C overnight. The mixture was diluted with EtOAc and washed with water. The organic layer was dried (Na₂SO₄) and evaporated *in vacuo*. The product was purified by column chromatography using a silica cartridge (0-20% EtOAc in cHex) to afford the title compound (11.7 g, 20.54 mmol, 68% yield) as a yellow oil. [M+H]⁺ m/z = 570.3

[0265] SYNTHESIS OF INTERMEDIATE 19

[0266] tert-butyl 3-(ethoxymethoxy)-2-({[(1s,4s)-4-(2-fluoro-6-hydroxyphenyl)cyclohexyl]-oxy}methyl)piperidine-1-carboxylate

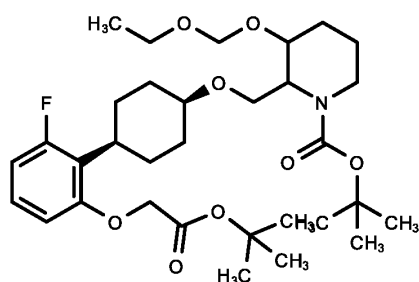


[0267] 10% wt. Pd/C wet matrix 50% (6.0 g, 2.82 mmol) was added to a solution of Intermediate 18 (23.6 g, 49.21 mmol) in ethanol (250 mL). The mixture was set under a H₂(g) atmosphere (7 atm) and stirred at room temperature overnight. The mixture was filtered over Celite and

concentrated *in vacuo* to afford the title compound (21.5 g, 44.64 mmol, 91% yield) as a colorless gum. $[M-Boc+2H]^+$ $m/z = 382.5$

[0268] SYNTHESIS OF INTERMEDIATE 20

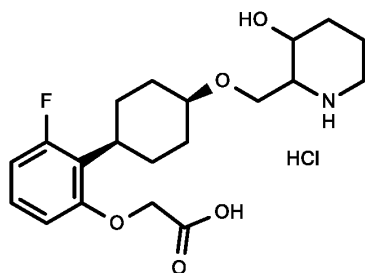
[0269] tert-butyl 3-(ethoxymethoxy)-2-({[(1s,4s)-4-{2-[2-(tert-butoxy)-2-oxoethoxy]-6-fluorophenyl}cyclohexyl]oxy}methyl)piperidine-1-carboxylate



[0270] To a mixture of Intermediate 19 (75.0 g, 155.73 mmol) and potassium carbonate (47.35 g, 342.61 mmol) in MeCN (400 mL), 2-bromoacetic acid tert-butyl ester (22.52 mL, 155.73 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes, then it was heated to 70 °C for 30 minutes. The reaction mixture was cooled to room temperature, filtered, and concentrated *in vacuo*. The residue was dissolved in EtOAc (300 mL) and washed with saturated aqueous NH_4Cl solution (200 mL) and N aqueous NaOH solution (100 mL). The aqueous phase was extracted with EtOAc (150 mL), then the combined organic fractions were washed with saturated aqueous NH_4Cl solution (300 mL), and brine (150 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The product was purified by column chromatography using a silica cartridge (0-20% EtOAc in cHex) to afford the title compound (57 g, 95.68 mmol, 61% yield) as a colorless oil. $[M+Na]^+$ $m/z = 618.5$

[0271] SYNTHESIS OF INTERMEDIATE 21

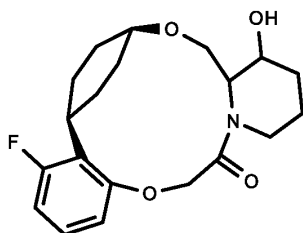
[0272] 2-{3-fluoro-2-[(1s,4s)-4-[(3-hydroxypiperidin-2-yl)methoxy]cyclohexyl]phenoxy}acetic acid hydrochloride



[0273] Intermediate 20 (6.66 g, 11.18 mmol) was dissolved in 1,4-dioxane (40 mL) and a 4 M solution of HCl in 1,4-dioxane (39.13 mL, 156.54 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was evaporated *in vacuo* and then co-evaporated twice with toluene to afford the title compound (5.2 g, quant. yield) as a white solid. $[M+H]^+$ $m/z = 382.2$

[0274] SYNTHESIS OF INTERMEDIATE 22

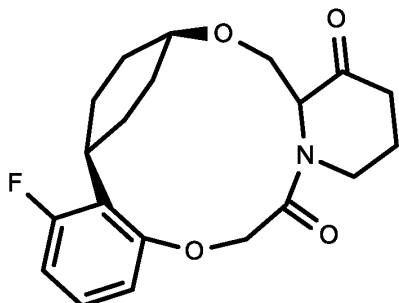
[0275] (1s,19s)-3-fluoro-15-hydroxy-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricos-2(7),3,5-trien-10-one



[0276] To a solution of HATU (10.92 g, 28.72 mmol) and DIPEA (16.67 mL, 95.72 mmol) in MeCN (4.786 L) under nitrogen, a solution of Intermediate 21 (8.0 g, 19.14 mmol) in DMA (125 mL) was added dropwise at room temperature through a peristaltic pump over a period of 22 h. After an additional 60 minutes the reaction mixture was concentrated *in vacuo*. The crude mixture was taken up with Et₂O, washed 5 times with water, then once 1M aqueous HCl solution and saturated aqueous NaHCO₃ solution, and finally with brine. The organic phase was filtered through a hydrophobic frit (Phase Separator) and concentrated *in vacuo* to afford the title compound (6 g, 16.51 mmol, 86% yield) as an orange solid. $[M+H]^+$ $m/z = 364.2$

[0277] SYNTHESIS OF INTERMEDIATE 23

[0278] (1s,19s)-3-fluoro-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-triene-10,15-dione



[0279] To a solution of Intermediate 22 (2.0 g, 5.5 mmol) in DCM (50 mL) at 0 °C was added Dess-Martin periodinane (2.57 g, 6.05 mmol). The mixture was stirred at room temperature for 2 h. Water was added and the mixture was stirred overnight, then it was filtered over a Gooch filter to remove the precipitate and the filtrate was diluted with DCM. The separated aqueous phase was extracted with DCM. The combined organic phases were evaporated *in vacuo*. The obtained oil was suspended in Et₂O and stirred for 1.5 h. The resulting solid was filtered off and washed with Et₂O to afford the title compound (1.3 g, 3.60 mmol, 65% yield) as a white solid. [M+H]⁺ m/z = 362.2

[0280] Final compound [Reductive amination procedures]

[0281] Procedure A: A solution of the appropriate amine (0.970 mmol), Ti(OEt)₄ (88.36 mg, 0.390 mmol) and macrocyclic ketone intermediate (0.190 mmol) in THF (4.9 mL) was stirred at 70 °C for 2 h. The mixture was cooled to 0 °C and sodium borohydride (73.27 mg, 1.94 mmol) was added portionwise. The suspension was allowed to gradually reach room temperature and was stirred for 16 h. After cooling the mixture to 0 °C, saturated aqueous NaHCO₃ solution was added and stirring was continued for 15 minutes. The mixture was extracted with EtOAc and the organic layer was filtered through a hydrophobic frit (Phase Separator) and concentrated *in vacuo*.

[0282] Procedure B: A solution of the appropriate amine (0.500 mmol), macrocyclic ketone intermediate (0.170 mmol), and Ti(OEt)₄ (0.07 mL, 0.330 mmol) in THF (4.912 mL) was heated to 70 °C overnight. Then sodium cyanoborohydride (164.24 mg, 2.66 mmol) was added and the

mixture stirred for 5 h at room temperature. Water was added and the mixture was extracted three times with DCM. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*.

[0283] Procedure C: The appropriate macrocyclic ketone intermediate (0.170 mmol) and the appropriate amine (0.170 mmol) were suspended in DCM (2 mL). Sodium triacetoxyborohydride (148 mg, 0.700 mmol) and Na_2SO_4 (50 mg, 0.350 mmol) were added and the reaction mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc and the organic phase was washed with saturated aqueous NaHCO_3 solution. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*.

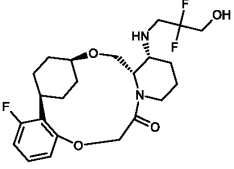
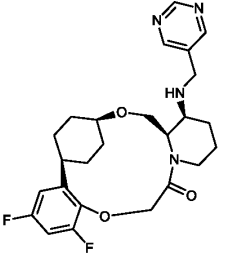
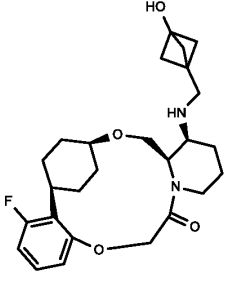
[0284] Procedure D: The appropriate macrocyclic ketone intermediate (0.140 mmol) and the appropriate amine (0.280 mmol) were suspended together in THF (1.4 mL) then sodium triacetoxyborohydride (176 mg, 0.830 mmol) was slowly added and the reaction mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc and washed with saturated aqueous NaHCO_3 solution, saturated aqueous NH_4Cl solution and brine. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*.

[0285] Procedure E: The appropriate macrocyclic ketone intermediate (0.190 mmol), the appropriate amine (0.390 mmol) and sodium triacetoxyborohydride (123 mg, 0.580 mmol) were dissolved in DCM (1.3 mL). The mixture was stirred for 3 h at room temperature. EtOAc was added and the suspension was filtered to remove inorganic salts. The filtrate was washed with saturated aqueous NH_4Cl solution, dried (Na_2SO_4) and evaporated *in vacuo*.

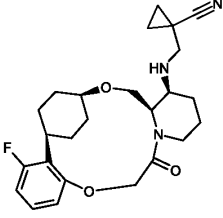
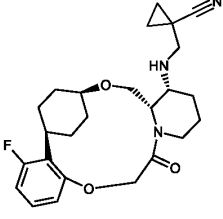
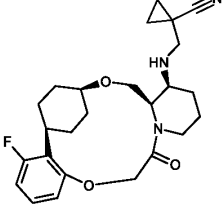
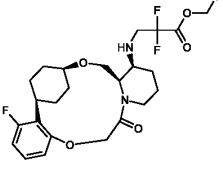
[0286] The products listed in the following table were obtained using the procedures above were purified using the most suitable method between direct or inverse phase column chromatography or using a SCX cartridge. Appropriate ketone intermediates were synthesized using a similar synthetic route to that described for Intermediate 23. Stereoisomers were separated by chiral HPLC purification using appropriate chiral columns and combinations of solvent mixtures; Chiralpak columns (AD-H, AS-H, IC, ID), Chiralcel columns (OD-H, OJ-H); solvent mixture of n-Hexane / EtOH, n-Hexane / (EtOH + 0.1% $i\text{PrNH}_2$), n-Hexane / (EtOH/MeOH 1:1 + 0.1% $i\text{PrNH}_2$), or by chiral SFC purification using appropriate chiral columns and combinations of solvent mixtures; Chiralpak columns (AD-H, ID), MeOH + 0.1% $i\text{PrNH}_2$ or EtOH + 0.1% $i\text{PrNH}_2$ as modifier.

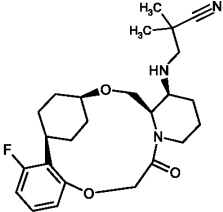
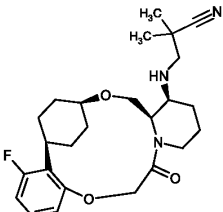
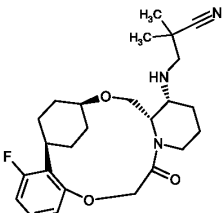
Table 4. Prepared Compounds and the Biological Activity Thereof

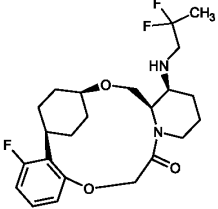
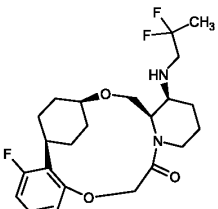
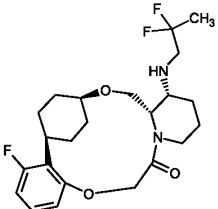
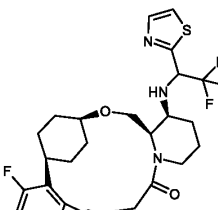
Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
29		(1s,15S,16R,19s)-3-fluoro-15-[[[(2R)-1,1,1-trifluoropropan-2-yl]amino]-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]tetricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 459.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.11 – 7.01 (m, 1H), 7.01 – 6.91 (m, 1H), 6.87 – 6.67 (m, 2H), 4.69 (dd, J = 11.2, 7.8 Hz, 1H), 4.40 – 4.20 (m, 2H), 3.96 – 3.61 (m, 3H), 3.54 – 3.37 (m, 2H), 3.26 – 3.03 (m, 2H), 2.84 – 2.70 (m, 1H), 2.66 – 2.14 (m, 7H), 1.93 – 1.62 (m, 3H), 1.55 – 1.14 (m, 5H).	A
30		(1s,15R,16S,19s)-3-fluoro-15-[[[(2R)-1,1,1-trifluoropropan-2-yl]amino]-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]tetricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 459.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.16 – 7.08 (m, 1H), 7.08 – 6.98 (m, 1H), 6.87 – 6.73 (m, 2H), 4.81 – 4.70 (m, 1H), 4.47 – 4.27 (m, 1H), 3.98 (dt, J = 7.9, 3.0 Hz, 1H), 3.89 – 3.67 (m, 2H), 3.66 – 3.46 (m, 3H), 3.30 – 3.10 (m, 2H), 2.93 – 2.73 (m, 1H), 2.72 – 2.53 (m, 1H), 2.55 – 2.36 (m, 4H), 2.34 – 2.21 (m, 1H), 1.99 – 1.48 (m, 6H), 1.44 – 1.21 (m, 3H).	C
31		Rel-(1s,15S,16R,19s)-15-[(2,2-difluoro-3-hydroxypropyl)amino]-3-fluoro-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]tetricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 457.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.09 (td, J=8.2, 6.5 Hz, 1 H), 6.70 (t, J=8.6 Hz, 1 H), 6.54 (d, J=8.2 Hz, 1 H), 5.21 – 5.32 (m, 1 H), 5.10 (d, J=10.3 Hz, 1 H), 4.30 (d, J=10.3 Hz, 1 H), 3.85 – 3.94 (m, 2 H), 3.79 – 3.87 (m, 1 H), 3.69 – 3.74 (m, 1 H), 3.61 – 3.69 (m, 1 H), 3.42 – 3.53 (m, 2 H), 3.18 – 3.34 (m, 2 H), 3.08 – 3.20 (m, 1 H), 2.93 – 3.01 (m, 1 H), 2.55 – 2.69 (m, 1 H), 2.18 – 2.30 (m, 1 H), 2.04 – 2.13 (m, 1 H), 1.81 – 1.96 (m, 3 H), 1.24 – 1.67 (m, 6 H).	B
32		(1s,15S,16R,19s)-15-[(2,2-difluoro-3-hydroxypropyl)amino]-3-fluoro-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]tetricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 457.2	¹ H NMR (400 MHz, MeOD) δ 7.13 (td, J = 8.2, 6.5 Hz, 1H), 6.72 – 6.63 (m, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.24 – 5.14 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.91 (dd, J = 11.0, 9.5 Hz, 1H), 3.77 (t, J = 13.1 Hz, 3H), 3.69 (br s, 1H), 3.54 – 3.42 (m, 2H), 3.13 (t, J = 14.3 Hz, 3H), 2.96 – 2.84 (m, 1H), 2.77 – 2.62 (m, 1H), 2.30 (qd, J = 13.0, 3.9 Hz, 1H), 2.22 – 2.12	A

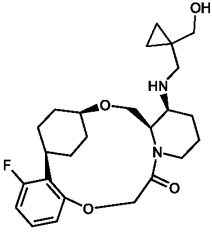
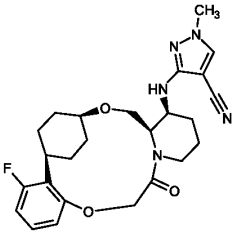
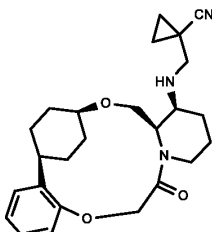
		ricosa-2(7),3,5-trien-10-one		(m, 1H), 1.94 – 1.78 (m, 3H), 1.69 – 1.16 (m, 7H).	
33		(1s,15R,16S,19s)-15-[(2,2-difluoro-3-hydroxypropyl)amino]-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 457.2	¹ H NMR (400 MHz, MeOD) δ 7.13 (td, J = 8.2, 6.5 Hz, 1H), 6.72 – 6.63 (m, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.24 – 5.14 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.91 (dd, J = 11.0, 9.5 Hz, 1H), 3.77 (t, J = 13.1 Hz, 3H), 3.69 (br s, 1H), 3.54 – 3.42 (m, 2H), 3.13 (t, J = 14.3 Hz, 3H), 2.96 – 2.84 (m, 1H), 2.77 – 2.62 (m, 1H), 2.30 (qd, J = 13.0, 3.9 Hz, 1H), 2.22 – 2.12 (m, 1H), 1.94 – 1.78 (m, 3H), 1.69 – 1.16 (m, 7H).	C
34		Rel-(1s,15S,16R,19s)-4,6-difluoro-15-[[[(pyrimidin-5-yl)methyl]amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 473.4	¹ H NMR (400 MHz, MeOD) δ 9.05 (s, 1H), 8.83 (s, 2H), 6.85 (ddd, J = 3.1, 8.4, 11.6 Hz, 1H), 6.77 – 6.71 (m, 1H), 5.46 (dd, J = 3.2, 12.4 Hz, 1H), 5.31 – 5.22 (m, 1H), 4.15 (dd, J = 1.7, 12.4 Hz, 1H), 4.02 – 3.86 (m, 4H), 3.76 – 3.69 (m, 1H), 3.60 – 3.44 (m, 2H), 2.94 – 2.84 (m, 1H), 2.78 – 2.65 (m, 1H), 2.65 – 2.55 (m, 1H), 2.26 – 2.15 (m, 1H), 2.15 – 2.04 (m, 1H), 1.97 – 1.80 (m, 3H), 1.72 – 1.57 (m, 1H), 1.55 – 1.29 (m, 5H).	D
35		Rel-(1s,15S,16R,19s)-3-fluoro-15-[[[3-hydroxybicyclo[1.1.1]pentan-1-yl)methyl]amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2,4,6-trien-10-one	[M+H] ⁺ 459.5	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.4, 8.2 Hz, 1H), 6.74 – 6.64 (m, 2H), 5.36 – 5.25 (m, 2H), 4.13 (d, J = 10.6 Hz, 1H), 4.03 – 3.91 (m, 1H), 3.81 (br d, J = 12.6 Hz, 1H), 3.73 (br d, J = 1.4 Hz, 1H), 3.51 (dt, J = 2.7, 13.0 Hz, 1H), 3.35 (dd, J = 3.8, 9.3 Hz, 1H), 3.20 – 3.09 (m, 3H), 2.74 – 2.63 (m, 1H), 2.28 (dq, J = 4.3, 13.0 Hz, 1H), 2.22 – 2.13 (m, 1H), 1.90 (s, 6H), 2.04 – 1.87 (m, 2H), 1.85 – 1.77 (m, 1H), 1.71 – 1.58 (m, 2H), 1.54 – 1.46 (m, 1H), 1.45 – 1.33 (m, 3H), 1.27 – 1.18 (m, 1H).	C

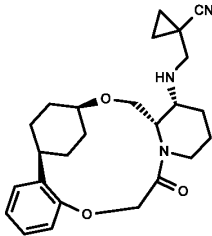
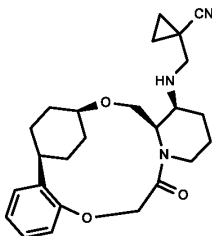
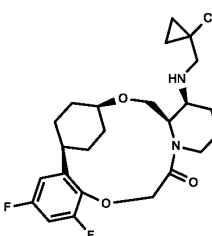
36		Rel- (1s,15S,16R,19s)-3-fluoro-15- [[[(1-fluorocyclopropyl)methyl]amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 435.6	¹ H NMR (500 MHz, MeOD) δ ppm 7.09 - 7.19 (m, 1 H), 6.66 - 6.73 (m, 2 H), 5.27 - 5.34 (m, 2 H), 4.13 (d, J=10.6 Hz, 1 H), 3.97 (dd, J=11.0, 9.4 Hz, 1 H), 3.77 - 3.85 (m, 1 H), 3.69 - 3.75 (m, 1 H), 3.47 - 3.56 (m, 1 H), 3.40 - 3.46 (m, 1 H), 3.22 - 3.29 (m, 2 H), 3.16 - 3.22 (m, 1 H), 3.10 - 3.17 (m, 1 H), 2.63 - 2.76 (m, 1 H), 2.29 (qd, J=13.0, 4.1 Hz, 1 H), 2.14 - 2.23 (m, 1 H), 1.96 - 2.05 (m, 1 H), 1.87 - 1.94 (m, 1 H), 1.77 - 1.86 (m, 1 H), 1.60 - 1.70 (m, 2 H), 1.45 - 1.56 (m, 1 H), 1.35 - 1.45 (m, 2 H), 1.19 - 1.28 (m, 1 H), 1.07 - 1.15 (m, 2 H), 0.73 - 0.90 (m, 2 H).	B
37		(1s,15R,16S,19s)-3-fluoro-15- [[[(1-fluorocyclopropyl)methyl]amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 435.6	¹ H NMR (400 MHz, MeOD) δ 7.13 (td, J = 8.2, 6.6 Hz, 1H), 6.73 - 6.64 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.27 - 5.19 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.94 (dd, J = 11.0, 9.6 Hz, 1H), 3.82 - 3.74 (m, 1H), 3.69 (br s, 1H), 3.54 - 3.47 (m, 1H), 3.46 (dd, J = 9.4, 4.0 Hz, 1H), 3.20 - 2.95 (m, 4H), 2.77 - 2.62 (m, 1H), 2.30 (qd, J = 13.0, 4.2 Hz, 1H), 2.23 - 2.12 (m, 1H), 1.96 - 1.76 (m, 3H), 1.70 - 1.52 (m, 2H), 1.54 - 1.44 (m, 1H), 1.43 - 1.32 (m, 2H), 1.28 - 1.17 (m, 1H), 1.10 - 0.94 (m, 2H), 0.81 - 0.64 (m, 2H).	D
38		(1s,15S,16R,19s)-3-fluoro-15- [[[(1-fluorocyclopropyl)methyl]amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 435.6	¹ H NMR (400 MHz, MeOD) δ 7.13 (td, J = 8.2, 6.6 Hz, 1H), 6.73 - 6.64 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.27 - 5.19 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.94 (dd, J = 11.0, 9.6 Hz, 1H), 3.82 - 3.74 (m, 1H), 3.69 (br s, 1H), 3.54 - 3.47 (m, 1H), 3.46 (dd, J = 9.4, 4.0 Hz, 1H), 3.20 - 2.95 (m, 4H), 2.77 - 2.62 (m, 1H), 2.30 (qd, J = 13.0, 4.2 Hz, 1H), 2.23 - 2.12 (m, 1H), 1.96 - 1.76 (m, 3H), 1.70 - 1.52 (m, 2H), 1.54 - 1.44 (m, 1H), 1.43 - 1.32 (m, 2H), 1.28 - 1.17 (m, 1H), 1.10 - 0.94 (m, 2H), 0.81 - 0.64 (m, 2H).	A

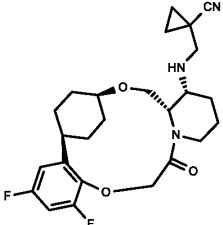
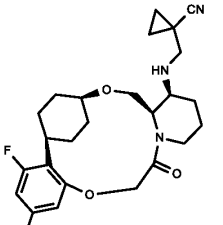
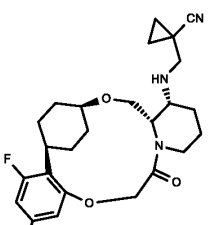
39		Rel-1- ((1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7,0^{11,16}}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 442.3	¹ H NMR (500 MHz, MeOD) δ 7.19 – 7.09 (m, 1H), 6.74 – 6.65 (m, 2H), 5.36 – 5.27 (m, 1H), 5.22 – 4.96 (m, 1H), 4.16 – 4.08 (m, J = 10.5 Hz, 1H), 4.04 – 3.89 (m, 1H), 3.87 – 3.74 (m, 1H), 3.70 (br s, 1H), 3.63 – 3.46 (m, 1H), 3.57 – 3.25 (m, 1H), 3.19 – 3.09 (m, 1H), 3.00 – 2.91 (m, 1H), 2.94 – 2.69 (m, 2H), 2.76 – 2.62 (m, 1H), 2.30 (qd, J = 13.0, 4.0 Hz, 1H), 2.24 – 2.13 (m, 1H), 1.98 – 1.75 (m, 3H), 1.69 – 1.53 (m, 2H), 1.53 – 1.44 (m, 1H), 1.43 – 1.32 (m, 2H), 1.28 – 1.18 (m, 3H), 1.08 – 0.96 (m, 2H).	A
40		1- ((1s,15R,16S, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7,0^{11,16}}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 442.2	¹ H NMR (400 MHz, MeOD) δ 7.16 – 7.09 (m, 1H), 6.72 – 6.65 (m, 2H), 5.30 (d, J = 10.4 Hz, 1H), 5.23 – 5.15 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 9.4, 11.1 Hz, 1H), 3.77 (br d, J = 13.8 Hz, 1H), 3.70 (br s, 1H), 3.54 (dd, J = 4.0, 9.4 Hz, 1H), 3.50 – 3.44 (m, 1H), 3.20 – 3.09 (m, 1H), 2.98 – 2.88 (m, 2H), 2.77 – 2.63 (m, 2H), 2.30 (dq, J = 4.2, 13.0 Hz, 1H), 2.19 (br d, J = 13.3 Hz, 1H), 1.92 – 1.77 (m, 3H), 1.70 – 1.32 (m, 5H), 1.27 – 1.18 (m, 3H), 1.09 – 0.96 (m, 2H).	C
41		1- ((1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7,0^{11,16}}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 442.3	¹ H NMR (400 MHz, MeOD) δ 7.16 – 7.09 (m, 1H), 6.72 – 6.65 (m, 2H), 5.30 (d, J = 10.4 Hz, 1H), 5.23 – 5.15 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 9.4, 11.1 Hz, 1H), 3.77 (br d, J = 13.8 Hz, 1H), 3.70 (br s, 1H), 3.54 (dd, J = 4.0, 9.4 Hz, 1H), 3.50 – 3.44 (m, 1H), 3.20 – 3.09 (m, 1H), 2.98 – 2.88 (m, 2H), 2.77 – 2.63 (m, 2H), 2.30 (dq, J = 4.2, 13.0 Hz, 1H), 2.19 (br d, J = 13.3 Hz, 1H), 1.92 – 1.77 (m, 3H), 1.70 – 1.32 (m, 5H), 1.27 – 1.18 (m, 3H), 1.09 – 0.96 (m, 2H).	A
42		Rel-ethyl 2,2- difluoro-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7,0^{11,16}}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carboxylate	[M+H] ⁺ 499.7	¹ H NMR (500 MHz, CDCl ₃) δ 7.05 – 7.13 (m, 1 H), 6.67 – 6.75 (m, 1 H), 6.53 (d, J=8.1 Hz, 1 H), 5.22 – 5.35 (m, 1 H), 5.09 (d, J=10.3 Hz, 1 H), 4.32 – 4.43 (m, 2 H), 4.29 (d, J=10.3 Hz, 1 H), 3.80 – 3.88 (m, 1 H), 3.71 (br s, 1 H), 3.62 –	C

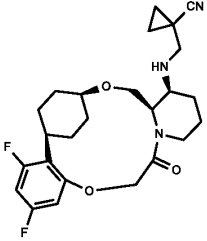
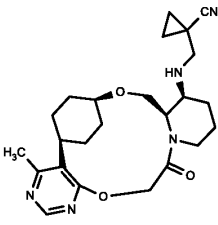
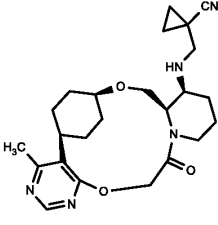
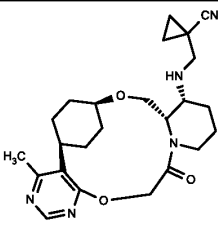
		7.2.2.0 ² , 7.0 ¹¹ , 1 ⁶ t ricosa-2(7),3,5- trien-15- yl]amino}propa noate		3.68 (m, 1 H), 3.36 - 3.59 (m, 4 H), 3.10 - 3.21 (m, 1 H), 3.01 - 3.10 (m, 1 H), 2.54 - 2.68 (m, 1 H), 2.17 - 2.29 (m, 1 H), 1.14 - 2.15 (m, 13 H).	
43		Rel-2,2- dimethyl-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² , 7.0 ¹¹ , 1 ⁶ t ricosa-2(7),3,5- trien-15- yl]amino}propa nenitrile	[M+H] ⁺ 444.3	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.16 (td, J=8.1, 6.9 Hz, 1 H), 6.75 (t, J=8.9 Hz, 1 H), 6.69 (d, J=8.1 Hz, 1 H), 5.31 (d, J=10.3 Hz, 1 H), 4.98 - 5.06 (m, 1 H), 3.98 (d, J=10.3 Hz, 1 H), 3.76 - 3.86 (m, 1 H), 3.65 (br d, J=12.3 Hz, 1 H), 3.60 (br s, 1 H), 3.41 (dd, J=9.3, 3.8 Hz, 1 H), 3.23 - 3.31 (m, 1 H), 2.97 - 3.07 (m, 1 H), 2.56 - 2.81 (m, 4 H), 2.24 (qd, J=12.9, 4.0 Hz, 1 H), 2.07 - 2.17 (m, 1 H), 1.94 - 2.05 (m, 1 H), 1.61 - 1.84 (m, 3 H), 1.36 - 1.51 (m, 3 H), 1.28 (d, J=4.0 Hz, 6 H), 1.24 - 1.35 (m, 2 H), 1.07 - 1.17 (m, 1 H).	A
44		2,2-dimethyl-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² , 7.0 ¹¹ , 1 ⁶ t ricosa-2(7),3,5- trien-15- yl]amino}propa nenitrile	[M+H] ⁺ 444.4	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.16 (td, J=8.1, 6.9 Hz, 1 H), 6.75 (t, J=8.9 Hz, 1 H), 6.69 (d, J=8.1 Hz, 1 H), 5.31 (d, J=10.3 Hz, 1 H), 4.98 - 5.06 (m, 1 H), 3.98 (d, J=10.3 Hz, 1 H), 3.76 - 3.86 (m, 1 H), 3.65 (br d, J=12.3 Hz, 1 H), 3.60 (br s, 1 H), 3.41 (dd, J=9.3, 3.8 Hz, 1 H), 3.23 - 3.31 (m, 1 H), 2.97 - 3.07 (m, 1 H), 2.56 - 2.81 (m, 4 H), 2.24 (qd, J=12.9, 4.0 Hz, 1 H), 2.07 - 2.17 (m, 1 H), 1.94 - 2.05 (m, 1 H), 1.61 - 1.84 (m, 3 H), 1.36 - 1.51 (m, 3 H), 1.28 (d, J=4.0 Hz, 6 H), 1.24 - 1.35 (m, 2 H), 1.07 - 1.17 (m, 1 H).	A
45		2,2-dimethyl-3- {[(1s,15R,16S, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² , 7.0 ¹¹ , 1 ⁶ t ricosa-2(7),3,5- trien-15- yl]amino}propa nenitrile	[M+H] ⁺ 444.4	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.16 (td, J=8.1, 6.9 Hz, 1 H), 6.75 (t, J=8.9 Hz, 1 H), 6.69 (d, J=8.1 Hz, 1 H), 5.31 (d, J=10.3 Hz, 1 H), 4.98 - 5.06 (m, 1 H), 3.98 (d, J=10.3 Hz, 1 H), 3.76 - 3.86 (m, 1 H), 3.65 (br d, J=12.3 Hz, 1 H), 3.60 (br s, 1 H), 3.41 (dd, J=9.3, 3.8 Hz, 1 H), 3.23 - 3.31 (m, 1 H), 2.97 - 3.07 (m, 1 H), 2.56 - 2.81 (m, 4 H), 2.24 (qd, J=12.9, 4.0 Hz, 1 H), 2.07 - 2.17 (m, 1 H), 1.94 - 2.05 (m, 1 H), 1.61 - 1.84 (m, 3 H), 1.36 - 1.51 (m, 3 H), 1.28 (d, J=4.0	C

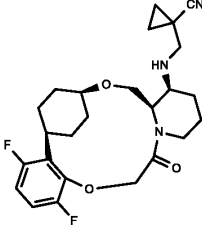
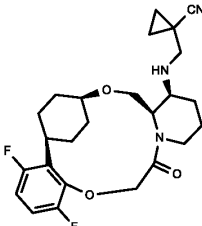
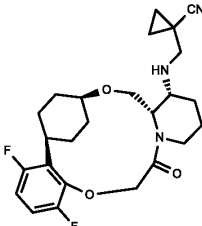
				Hz, 6 H), 1.24 - 1.35 (m, 2 H), 1.07 - 1.17 (m, 1 H).	
46		Rel-(1s,15S,16R,19s)-15-[(2,2-difluoropropyl)amino]-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 441.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (td, J=8.3, 6.5 Hz, 1 H), 6.67 - 6.73 (m, 2 H), 5.30 (d, J=10.4 Hz, 1 H), 5.14 - 5.24 (m, 1 H), 4.12 (d, J=10.4 Hz, 1 H), 3.89 - 3.95 (m, 1 H), 3.74 - 3.81 (m, 1 H), 3.69 (br s, 1 H), 3.43 - 3.53 (m, 2 H), 3.10 - 3.20 (m, 1 H), 3.03 (td, J=13.7, 3.4 Hz, 2 H), 2.87 - 2.93 (m, 1 H), 2.63 - 2.76 (m, 1 H), 2.30 (qd, J=13.0, 4.1 Hz, 1 H), 2.13 - 2.24 (m, 1 H), 1.77 - 1.94 (m, 3 H), 1.64 (t, J=18.8 Hz, 3 H), 1.44 - 1.64 (m, 3 H), 1.33 - 1.43 (m, 2 H), 1.18 - 1.27 (m, 1 H).	A
47		(1s,15S,16R,19s)-15-[(2,2-difluoropropyl)amino]-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 441.4	¹ H NMR (500 MHz, MeOD) δ 7.20 - 7.06 (m, 1H), 6.81 - 6.61 (m, 2H), 5.34 - 5.25 (m, 1H), 5.23 - 5.12 (m, 1H), 4.16 - 4.08 (m, 1H), 3.96 - 3.88 (m, 1H), 3.80 - 3.73 (m, 1H), 3.72 - 3.65 (m, 1H), 3.53 - 3.39 (m, 2H), 3.19 - 3.09 (m, 1H), 3.08 - 2.98 (m, 2H), 2.94 - 2.84 (m, 1H), 2.76 - 2.25 (m, 2H), 2.24 - 1.87 (m, 2H), 1.86 - 1.78 (m, 2H), 1.70 - 1.16 (m, 9H).	A
48		(1s,15R,16S,19s)-15-[(2,2-difluoropropyl)amino]-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 441.8	¹ H NMR (500 MHz, MeOD) δ 7.20 - 7.06 (m, 1H), 6.81 - 6.61 (m, 2H), 5.34 - 5.25 (m, 1H), 5.23 - 5.12 (m, 1H), 4.16 - 4.08 (m, 1H), 3.96 - 3.88 (m, 1H), 3.80 - 3.73 (m, 1H), 3.72 - 3.65 (m, 1H), 3.53 - 3.39 (m, 2H), 3.19 - 3.09 (m, 1H), 3.08 - 2.98 (m, 2H), 2.94 - 2.84 (m, 1H), 2.76 - 2.25 (m, 2H), 2.24 - 1.87 (m, 2H), 1.86 - 1.78 (m, 2H), 1.70 - 1.16 (m, 9H).	D
49		Rel-(1s,15S,16R,19s)-3-fluoro-15-[[2,2,2-trifluoro-1-(1,3-thiazol-2-yl)ethyl]amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 528.2	¹ H NMR (600 MHz, MeOD) δ 7.89 - 7.85 (m, 1H), 7.72 - 7.69 (m, 1H), 7.15 - 7.09 (m, 1H), 6.71 - 6.64 (m, 2H), 5.27 (d, J = 10.5 Hz, 1H), 5.25 - 5.05 (m, 1H), 5.07 - 4.97 (m, 1H), 4.12 - 4.07 (m, 1H), 4.02 - 3.91 (m, 1H), 3.79 - 3.71 (m, 1H), 3.73 - 3.63 (m, 1H), 3.68 - 3.46 (m, 1H), 3.51 - 3.44 (m, 1H), 3.18 - 3.08 (m, 1H), 2.98 - 2.83 (m, 1H), 2.74 - 2.61 (m, 1H), 2.36 - 2.23 (m, 1H), 2.22 - 2.12 (m, 1H), 1.79 (br dd, J = 13.0, 1.8 Hz, 1H), 2.02 -	A

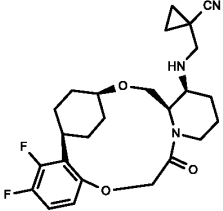
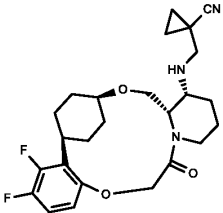
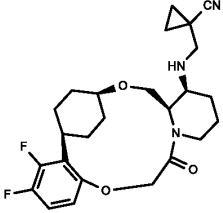
		ricosa-2(7),3,5-trien-10-one		1.49 (m, 4H), 1.51 – 1.41 (m, 1H), 1.41 – 1.33 (m, 2H), 1.27 – 1.17 (m, 1H).	
50		Rel-(1s,15S,16R,19s)-3-fluoro-15-({[1-(hydroxymethyl)cyclopropyl]methyl}amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]trien-10-one	[M+H] ⁺ 447.3	¹ H NMR (400 MHz, MeOD) δ 7.15 - 7.09 (m, 1H), 6.71 - 6.66 (m, 2H), 5.30 (d, J = 10.8 Hz, 1H), 5.22 (m, 1H), 4.11 (d, J = 10 Hz, 1H), 3.93 (t, J = 9.2 Hz, 1H), 3.76 (d, J = 13.6 Hz, 1H), 3.70 (m, 1H), 3.55 - 3.44 (m, 4H), 3.13 (m, 1H), 2.87 (m, 1H), 2.86 (d, J = 12 Hz, 1H), 2.70 (m, 1H), 2.65 (d, J = 12 Hz, 1H), 2.29 (m, 1H), 2.17 (m, 1H), 1.90 - 1.38 (m, 8H), 1.24 (m, 1H), 0.50 - 0.45 (m, 4H).	B
51		Rel-1-methyl-3-({[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]trien-15-yl]amino}-1H-pyrazole-4-carbonitrile	[M+H] ⁺ 468.5	ND	A
52		Rel-1-({[(1s,15S,16R,19s)-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]trien-15-yl]amino}methyl)cyclopropane-1-carbonitrile	[M+H] ⁺ 424.3	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.14 (dt, J = 1.7, 7.7 Hz, 1H), 7.07 (dd, J = 1.6, 7.3 Hz, 1H), 6.88 - 6.76 (m, 2H), 5.28 (d, J = 10.4 Hz, 1H), 5.05 - 4.93 (m, 1H), 3.94 (d, J = 10.4 Hz, 1H), 3.87 - 3.71 (m, 1H), 3.65 (br d, J = 12.9 Hz, 1H), 3.60 (br s, 1H), 3.39 (br dd, J = 3.8, 9.2 Hz, 1H), 3.32 - 3.22 (m, 1H), 2.81 - 2.71 (m, 2H), 2.69 - 2.58 (m, 2H), 2.56 - 2.51 (m, 1H), 2.25 (dq, J = 4.0, 12.8 Hz, 1H), 2.11 (br d, J = 13.6 Hz, 1H), 1.80 - 1.59 (m, 3H), 1.52 - 1.19 (m, 5H), 1.19 - 1.10 (m, 3H), 1.03 - 0.93 (m, 2H).	A

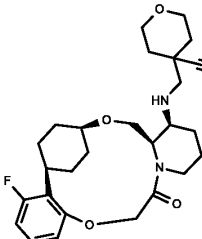
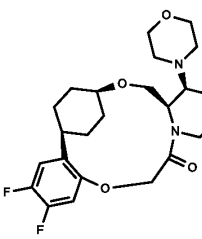
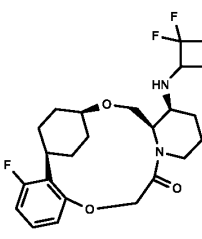
53		1- ((1s,15R,16S, 19s)-10-oxo- 8,18-dioxa-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 424.3	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.14 (dt, J = 1.6, 7.8 Hz, 1H), 7.07 (dd, J = 1.6, 7.4 Hz, 1H), 6.86 - 6.78 (m, 2H), 5.28 (d, J = 10.3 Hz, 1H), 5.03 - 4.95 (m, 1H), 3.94 (d, J = 10.4 Hz, 1H), 3.86 - 3.72 (m, 1H), 3.65 (br d, J = 12.9 Hz, 1H), 3.60 (br s, 1H), 3.39 (dd, J = 3.8, 9.2 Hz, 1H), 3.30 (br d, J = 2.3 Hz, 1H), 2.78 - 2.69 (m, 2H), 2.69 - 2.58 (m, 2H), 2.52 (br s, 1H), 2.31 - 2.19 (m, 1H), 2.17 - 2.07 (m, 2H), 1.80 - 1.60 (m, 3H), 1.52 - 1.20 (m, 5H), 1.18 - 1.10 (m, 3H), 1.02 - 0.92 (m, 2H).	C
54		1- ((1s,15S,16R, 19s)-10-oxo- 8,18-dioxa-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 424.4	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.14 (dt, J = 1.6, 7.8 Hz, 1H), 7.07 (dd, J = 1.6, 7.4 Hz, 1H), 6.86 - 6.78 (m, 2H), 5.28 (d, J = 10.3 Hz, 1H), 5.03 - 4.95 (m, 1H), 3.94 (d, J = 10.4 Hz, 1H), 3.86 - 3.72 (m, 1H), 3.65 (br d, J = 12.9 Hz, 1H), 3.60 (br s, 1H), 3.39 (dd, J = 3.8, 9.2 Hz, 1H), 3.30 (br d, J = 2.3 Hz, 1H), 2.78 - 2.69 (m, 2H), 2.69 - 2.58 (m, 2H), 2.52 (br s, 1H), 2.31 - 2.19 (m, 1H), 2.17 - 2.07 (m, 2H), 1.80 - 1.60 (m, 3H), 1.52 - 1.20 (m, 5H), 1.18 - 1.10 (m, 3H), 1.02 - 0.92 (m, 2H).	A
55		Rel-1- ((1s,15S,16R, 19s)-4,6- difluoro-10- oxo-8,18-dioxa- 11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 460.4	¹ H NMR (500 MHz, MeOD) δ 6.85 (ddd, J = 3.0, 8.3, 11.6 Hz, 1H), 6.77 - 6.69 (m, 1H), 5.45 (dd, J = 3.2, 12.4 Hz, 1H), 5.24 - 5.13 (m, 1H), 4.13 (dd, J = 1.7, 12.4 Hz, 1H), 3.94 - 3.82 (m, 2H), 3.70 (br s, 1H), 3.54 (dd, J = 3.6, 9.1 Hz, 1H), 3.49 (dt, J = 2.9, 13.4 Hz, 1H), 2.97 - 2.87 (m, 2H), 2.74 - 2.65 (m, 2H), 2.64 - 2.56 (m, 1H), 2.17 (br d, J = 14.3 Hz, 1H), 2.08 (dq, J = 4.0, 12.9 Hz, 1H), 1.91 - 1.78 (m, 3H), 1.69 - 1.56 (m, 1H), 1.56 - 1.42 (m, 3H), 1.41 - 1.30 (m, 2H), 1.30 - 1.17 (m, 2H), 1.07 - 0.97 (m, 2H).	A

56		1-((1S,15R,16S,19S)-4,6-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]tricyclo[2(7),3,5-trien-15-yl]amino)methylcyclopropane-1-carbonitrile	[M+H] ⁺ 460.7	¹ H NMR (500 MHz, MeOD) δ 6.85 (ddd, J = 3.0, 8.3, 11.6 Hz, 1H), 6.77 - 6.69 (m, 1H), 5.45 (dd, J = 3.2, 12.4 Hz, 1H), 5.24 - 5.13 (m, 1H), 4.13 (dd, J = 1.7, 12.4 Hz, 1H), 3.94 - 3.82 (m, 2H), 3.70 (br s, 1H), 3.54 (dd, J = 3.6, 9.1 Hz, 1H), 3.49 (dt, J = 2.9, 13.4 Hz, 1H), 2.97 - 2.87 (m, 2H), 2.74 - 2.65 (m, 2H), 2.64 - 2.56 (m, 1H), 2.17 (br d, J = 14.3 Hz, 1H), 2.08 (dq, J = 4.0, 12.9 Hz, 1H), 1.91 - 1.78 (m, 3H), 1.69 - 1.56 (m, 1H), 1.56 - 1.42 (m, 3H), 1.41 - 1.30 (m, 2H), 1.30 - 1.17 (m, 2H), 1.07 - 0.97 (m, 2H).	A
57		Rel-1-((1S,15S,16R,19S)-3,5-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]tricyclo[2(7),3,5-trien-15-yl]amino)methylcyclopropane-1-carbonitrile	[M+H] ⁺ 460.7	¹ H NMR (500 MHz, CDCl ₃) δ 6.45 (dt, J = 2.3, 9.4 Hz, 1H), 6.32 - 6.27 (m, 1H), 5.26 - 5.18 (m, 1H), 5.05 (d, J = 10.2 Hz, 1H), 4.26 (d, J = 10.2 Hz, 1H), 3.83 (dd, J = 9.5, 10.8 Hz, 1H), 3.70 (br s, 1H), 3.64 - 3.59 (m, 1H), 3.52 (dd, J = 4.1, 9.2 Hz, 1H), 3.49 - 3.41 (m, 1H), 3.13 - 3.06 (m, 1H), 3.06 - 2.99 (m, 1H), 2.92 (d, J = 12.9 Hz, 1H), 2.72 (d, J = 12.9 Hz, 1H), 2.60 - 2.49 (m, 1H), 2.20 (dq, J = 4.2, 13.0 Hz, 1H), 2.13 - 2.05 (m, 1H), 1.93 - 1.80 (m, 3H), 1.67 - 1.53 (m, 2H), 1.49 - 1.27 (m, 6H), 1.05 - 0.83 (m, 2H).	A
58		1-((1S,15R,16S,19S)-3,5-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]tricyclo[2(7),3,5-trien-15-yl]amino)methylcyclopropane-1-carbonitrile	[M+H] ⁺ 460.7	¹ H NMR (500 MHz, CDCl ₃) δ 6.45 (dt, J = 2.3, 9.4 Hz, 1H), 6.32 - 6.27 (m, 1H), 5.26 - 5.18 (m, 1H), 5.05 (d, J = 10.2 Hz, 1H), 4.26 (d, J = 10.2 Hz, 1H), 3.83 (dd, J = 9.5, 10.8 Hz, 1H), 3.70 (br s, 1H), 3.64 - 3.59 (m, 1H), 3.52 (dd, J = 4.1, 9.2 Hz, 1H), 3.49 - 3.41 (m, 1H), 3.13 - 3.06 (m, 1H), 3.06 - 2.99 (m, 1H), 2.92 (d, J = 12.9 Hz, 1H), 2.72 (d, J = 12.9 Hz, 1H), 2.60 - 2.49 (m, 1H), 2.20 (dq, J = 4.2, 13.0 Hz, 1H), 2.13 - 2.05 (m, 1H), 1.93 - 1.80 (m, 3H), 1.67 - 1.53 (m, 2H), 1.49 - 1.27 (m, 6H), 1.05 - 0.83 (m, 2H).	D

59		1- ({[(1s,15S,16R, 19s)-3,5- difluoro-10- oxo-8,18-dioxa- 11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 460.7	¹ H NMR (500 MHz, CDCl ₃) δ 6.45 (dt, J = 2.3, 9.4 Hz, 1H), 6.32 - 6.27 (m, 1H), 5.26 - 5.18 (m, 1H), 5.05 (d, J = 10.2 Hz, 1H), 4.26 (d, J = 10.2 Hz, 1H), 3.83 (dd, J = 9.5, 10.8 Hz, 1H), 3.70 (br s, 1H), 3.64 - 3.59 (m, 1H), 3.52 (dd, J = 4.1, 9.2 Hz, 1H), 3.49 - 3.41 (m, 1H), 3.13 - 3.06 (m, 1H), 3.06 - 2.99 (m, 1H), 2.92 (d, J = 12.9 Hz, 1H), 2.72 (d, J = 12.9 Hz, 1H), 2.60 - 2.49 (m, 1H), 2.20 (dq, J = 4.2, 13.0 Hz, 1H), 2.13 - 2.05 (m, 1H), 1.93 - 1.80 (m, 3H), 1.67 - 1.53 (m, 2H), 1.49 - 1.27 (m, 6H), 1.05 - 0.83 (m, 2H).	A
60		Rel-1- ({[(1s,15S,16R, 19s)-3-methyl- 10-oxo-8,18- dioxo-4,6,11- triazatetracyclo [17.2.2.0 ^{2,7} ,0 ^{11,1} 6]triosa- 2(7),3,5-trien- 15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 440.3	¹ H NMR (500 MHz, MeOD) δ 8.45 (s, 1H), 5.38 - 5.33 (m, 1H), 5.24 - 5.16 (m, 1H), 4.48 - 4.44 (m, 1H), 4.00 - 3.90 (m, 1H), 3.78 - 3.67 (m, 2H), 3.55 (dd, J = 4.1, 9.3 Hz, 1H), 3.49 - 3.41 (m, 1H), 3.13 - 2.84 (m, 3H), 2.78 - 2.65 (m, 1H), 2.59 - 2.51 (m, 1H), 2.51 - 2.45 (m, 3H), 2.38 - 2.27 (m, 1H), 2.25 - 2.17 (m, 1H), 1.97 - 1.77 (m, 3H), 1.69 - 1.36 (m, 5H), 1.36 - 1.13 (m, 3H), 1.10 - 0.88 (m, 2H).	B
61		1- ({[(1s,15S,16R, 19s)-3-methyl- 10-oxo-8,18- dioxo-4,6,11- triazatetracyclo [17.2.2.0 ^{2,7} ,0 ^{11,1} 6]triosa- 2(7),3,5-trien- 15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 440.3	¹ H NMR (500 MHz, MeOD) δ 8.44 - 8.41 (m, 1H), 5.37 - 5.33 (m, 1H), 5.23 - 5.16 (m, 1H), 4.48 - 4.44 (m, 1H), 4.00 - 3.90 (m, 1H), 3.78 - 3.68 (m, 2H), 3.58 - 3.52 (m, 1H), 3.49 - 3.41 (m, 1H), 3.13 - 2.84 (m, 3H), 2.78 - 2.65 (m, 1H), 2.59 - 2.51 (m, 1H), 2.51 - 2.46 (m, 3H), 2.38 - 2.27 (m, 1H), 2.25 - 2.17 (m, 1H), 1.91 - 1.79 (m, 3H), 1.69 - 1.37 (m, 5H), 1.36 - 1.13 (m, 3H), 1.08 - 0.89 (m, 2H).	A
62		1- ({[(1s,15R,16S, 19s)-3-methyl- 10-oxo-8,18- dioxo-4,6,11- triazatetracyclo [17.2.2.0 ^{2,7} ,0 ^{11,1} 6]triosa- 2(7),3,5-trien- 15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 440.3	¹ H NMR (500 MHz, MeOD) δ 8.44 - 8.41 (m, 1H), 5.37 - 5.33 (m, 1H), 5.23 - 5.16 (m, 1H), 4.48 - 4.44 (m, 1H), 4.00 - 3.90 (m, 1H), 3.78 - 3.68 (m, 2H), 3.58 - 3.52 (m, 1H), 3.49 - 3.41 (m, 1H), 3.13 - 2.84 (m, 3H), 2.78 - 2.65 (m, 1H), 2.59 - 2.51 (m, 1H), 2.51 - 2.46 (m, 3H), 2.38 - 2.27 (m, 1H), 2.25 - 2.17 (m, 1H), 1.91 - 1.79 (m, 3H), 1.69 - 1.37 (m, 5H), 1.36 - 1.13 (m, 3H), 1.08 - 0.89 (m, 2H).	D

		2(7),3,5-trien-15-yl]amino}methyl)cyclopropane-1-carbonitrile		1.79 (m, 3H), 1.69 - 1.37 (m, 5H), 1.36 - 1.13 (m, 3H), 1.08 - 0.89 (m, 2H).	
63		Rel-1-({[(1s,15S,16R,19s)-3,6-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]triosa-2(7),3,5-trien-15-yl]amino}methyl)cyclopropane-1-carbonitrile	[M+H] ⁺ 460.6	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.15 (ddd, J = 5.2, 9.2, 11.1 Hz, 1H), 6.90 (dt, J = 4.0, 9.2 Hz, 1H), 5.48 (dd, J = 3.6, 11.9 Hz, 1H), 5.05 - 4.95 (m, 1H), 4.06 (dd, J = 2.2, 11.9 Hz, 1H), 3.79 - 3.70 (m, 2H), 3.63 (br s, 1H), 3.42 (dd, J = 3.6, 9.1 Hz, 1H), 3.36 - 3.25 (m, 1H), 3.06 - 2.91 (m, 1H), 2.79 - 2.67 (m, 2H), 2.67 - 2.56 (m, 2H), 2.12 (br d, J = 13.7 Hz, 1H), 2.00 (dq, J = 3.8, 12.9 Hz, 1H), 1.82 - 1.71 (m, 2H), 1.70 - 1.63 (m, 1H), 1.55 - 1.34 (m, 3H), 1.34 - 1.24 (m, 2H), 1.24 - 1.17 (m, 1H), 1.16 - 1.10 (m, 2H), 0.98 (br s, 2H).	A
64		1-({[(1s,15S,16R,19s)-3,6-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]triosa-2(7),3,5-trien-15-yl]amino}methyl)cyclopropane-1-carbonitrile	[M+H] ⁺ 460.4	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.15 (ddd, J = 5.2, 9.2, 11.1 Hz, 1H), 6.90 (dt, J = 4.0, 9.2 Hz, 1H), 5.48 (dd, J = 3.6, 11.9 Hz, 1H), 5.05 - 4.95 (m, 1H), 4.06 (dd, J = 2.2, 11.9 Hz, 1H), 3.79 - 3.70 (m, 2H), 3.63 (br s, 1H), 3.42 (dd, J = 3.6, 9.1 Hz, 1H), 3.36 - 3.25 (m, 1H), 3.06 - 2.91 (m, 1H), 2.79 - 2.67 (m, 2H), 2.67 - 2.56 (m, 2H), 2.12 (br d, J = 13.7 Hz, 1H), 2.00 (dq, J = 3.8, 12.9 Hz, 1H), 1.82 - 1.71 (m, 2H), 1.70 - 1.63 (m, 1H), 1.55 - 1.34 (m, 3H), 1.34 - 1.24 (m, 2H), 1.24 - 1.17 (m, 1H), 1.16 - 1.10 (m, 2H), 0.98 (br s, 2H).	A
65		1-({[(1s,15R,16S,19s)-3,6-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]triosa-2(7),3,5-trien-15-yl]amino}methyl)cyclopropane-1-carbonitrile	[M+H] ⁺ 460.4	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.15 (ddd, J = 5.2, 9.2, 11.1 Hz, 1H), 6.90 (dt, J = 4.0, 9.2 Hz, 1H), 5.48 (dd, J = 3.6, 11.9 Hz, 1H), 5.05 - 4.95 (m, 1H), 4.06 (dd, J = 2.2, 11.9 Hz, 1H), 3.79 - 3.70 (m, 2H), 3.63 (br s, 1H), 3.42 (dd, J = 3.6, 9.1 Hz, 1H), 3.36 - 3.25 (m, 1H), 3.06 - 2.91 (m, 1H), 2.79 - 2.67 (m, 2H), 2.67 - 2.56 (m, 2H), 2.12 (br d, J = 13.7 Hz, 1H), 2.00 (dq, J = 3.8, 12.9 Hz, 1H), 1.82 - 1.71 (m, 2H), 1.70 - 1.63 (m, 1H), 1.55 - 1.34 (m, 3H), 1.34 - 1.24 (m, 2H),	C

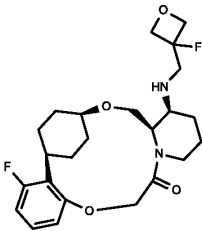
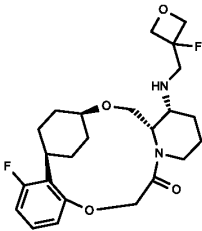
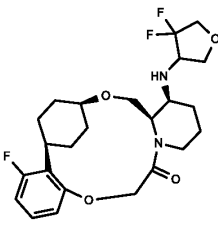
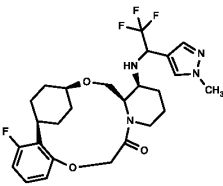
				1.24 - 1.17 (m, 1H), 1.16 - 1.10 (m, 2H), 0.98 (br s, 2H).	
66		Rel-1- ((1S,15S,16R, 19S)-3,4- difluoro-10- oxo-8,18-dioxa- 11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 460.7	¹ H NMR (400 MHz, MeOD) δ 7.08 - 6.96 (m, 1H), 6.64 (ddd, J = 2.0, 3.8, 9.1 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.25 - 5.15 (m, 1H), 4.10 (d, J = 10.6 Hz, 1H), 3.93 (dd, J = 9.5, 11.0 Hz, 1H), 3.78 (br d, J = 13.3 Hz, 1H), 3.71 (br s, 1H), 3.52 (dd, J = 3.9, 9.4 Hz, 1H), 3.52 - 3.42 (m, 1H), 3.21 - 3.10 (m, 1H), 3.02 - 2.94 (m, 1H), 2.95 (d, J = 12.9 Hz, 1H), 2.76 (d, J = 12.9 Hz, 1H), 2.74 - 2.62 (m, 1H), 2.35 - 2.22 (m, 1H), 2.20 (br d, J = 13.7 Hz, 1H), 1.94 - 1.76 (m, 3H), 1.70 - 1.53 (m, 2H), 1.55 - 1.45 (m, 1H), 1.45 - 1.34 (m, 2H), 1.29 - 1.19 (m, 3H), 1.10 - 0.98 (m, 2H).	A
67		1- ((1S,15R,16S, 19S)-3,4- difluoro-10- oxo-8,18-dioxa- 11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 460.4	¹ H NMR (400 MHz, MeOD) δ 7.08 - 6.96 (m, 1H), 6.64 (ddd, J = 2.0, 3.8, 9.1 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.25 - 5.15 (m, 1H), 4.10 (d, J = 10.6 Hz, 1H), 3.93 (dd, J = 9.5, 11.0 Hz, 1H), 3.78 (br d, J = 13.3 Hz, 1H), 3.71 (br s, 1H), 3.52 (dd, J = 3.9, 9.4 Hz, 1H), 3.52 - 3.42 (m, 1H), 3.21 - 3.10 (m, 1H), 3.02 - 2.94 (m, 1H), 2.95 (d, J = 12.9 Hz, 1H), 2.76 (d, J = 12.9 Hz, 1H), 2.74 - 2.62 (m, 1H), 2.35 - 2.22 (m, 1H), 2.20 (br d, J = 13.7 Hz, 1H), 1.94 - 1.76 (m, 3H), 1.70 - 1.53 (m, 2H), 1.55 - 1.45 (m, 1H), 1.45 - 1.34 (m, 2H), 1.29 - 1.19 (m, 3H), 1.10 - 0.98 (m, 2H).	D
68		1- ((1S,15S,16R, 19S)-3,4- difluoro-10- oxo-8,18-dioxa- 11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 460.4	¹ H NMR (400 MHz, MeOD) δ 7.08 - 6.96 (m, 1H), 6.64 (ddd, J = 2.0, 3.8, 9.1 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.25 - 5.15 (m, 1H), 4.10 (d, J = 10.6 Hz, 1H), 3.93 (dd, J = 9.5, 11.0 Hz, 1H), 3.78 (br d, J = 13.3 Hz, 1H), 3.71 (br s, 1H), 3.52 (dd, J = 3.9, 9.4 Hz, 1H), 3.52 - 3.42 (m, 1H), 3.21 - 3.10 (m, 1H), 3.02 - 2.94 (m, 1H), 2.95 (d, J = 12.9 Hz, 1H), 2.76 (d, J = 12.9 Hz, 1H), 2.74 - 2.62 (m, 1H), 2.35 - 2.22 (m, 1H), 2.20 (br d, J = 13.7 Hz, 1H), 1.94 - 1.76 (m, 3H), 1.70 - 1.53 (m, 2H), 1.55 - 1.45 (m, 1H), 1.45 - 1.34 (m, 2H), 1.29 - 1.19 (m, 3H), 1.10 - 0.98 (m, 2H).	A

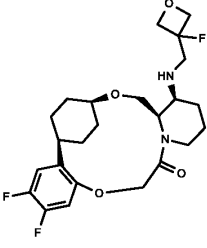
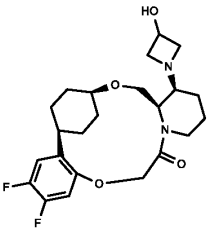
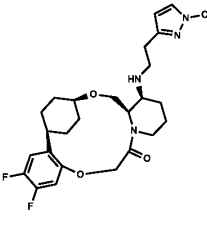
				2H), 1.29 - 1.19 (m, 3H), 1.10 - 0.98 (m, 2H).	
69		Rel-4- ({[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricyclo[2.2.1]hepta-2(7),3,5-trien-15-yl]amino}methyl)oxane-4-carbonitrile	[M+H] ⁺ 486.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.6, 8.2 Hz, 1H), 6.73 - 6.64 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.24 - 5.16 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 4.00 - 3.90 (m, 3H), 3.77 (br d, J = 12.1 Hz, 1H), 3.72 - 3.61 (m, 3H), 3.55 (dd, J = 4.0, 9.2 Hz, 1H), 3.49 (dt, J = 2.7, 13.2 Hz, 1H), 3.20 - 3.08 (m, 1H), 2.95 - 2.82 (m, 3H), 2.75 - 2.62 (m, 1H), 2.30 (dq, J = 4.0, 13.0 Hz, 1H), 2.23 - 2.13 (m, 1H), 1.96 - 1.78 (m, 5H), 1.72 - 1.63 (m, 2H), 1.63 - 1.44 (m, 3H), 1.43 - 1.33 (m, 2H), 1.27 - 1.17 (m, 1H).	A
70		Rel- (1s,15S,16R,19s)-4,5-difluoro-15-(morpholin-4-yl)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricyclo[2.2.1]hepta-2(7),3,5-trien-10-one	[M+H] ⁺ 451.2	¹ H NMR (400 MHz, MeOD) δ 7.06 - 6.95 (m, 1H), 6.84 (dd, J = 6.8, 11.7 Hz, 1H), 5.36 - 5.20 (m, 2H), 4.09 (d, J = 10.5 Hz, 1H), 3.91 (dd, J = 9.6, 11.1 Hz, 1H), 3.76 (br dd, J = 2.6, 13.6 Hz, 1H), 3.72 - 3.63 (m, 5H), 3.52 - 3.41 (m, 2H), 2.74 - 2.49 (m, 6H), 2.37 (td, J = 4.6, 12.1 Hz, 1H), 2.32 - 2.20 (m, 1H), 2.20 - 2.11 (m, 1H), 2.07 - 1.98 (m, 1H), 1.94 - 1.85 (m, 1H), 1.83 - 1.74 (m, 1H), 1.64 - 1.51 (m, 1H), 1.51 - 1.39 (m, 3H), 1.38 - 1.22 (m, 2H).	D
71		Rel- (1s,15S,16R,19s)-15-[(2,2-difluorocyclobutyl)amino]-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricyclo[2.2.1]hepta-2(7),3,5-trien-10-one	[M+H] ⁺ 453.8	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.21 - 7.13 (m, 1H), 6.75 (t, J = 8.9 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 5.30 (d, J = 10.3 Hz, 1H), 5.08 - 4.92 (m, 1H), 3.97 (d, J = 10.3 Hz, 1H), 3.83 - 3.71 (m, 1H), 3.73 - 3.54 (m, 3H), 3.45 - 3.36 (m, 1H), 3.30 - 3.22 (m, 1H), 3.07 - 2.96 (m, 1H), 2.80 (br s, 1H), 2.63 - 2.54 (m, 1H), 2.49 - 2.36 (m, 1H), 2.29 - 2.15 (m, 3H), 2.11 (br d, J = 12.3 Hz, 1H), 2.07 - 1.96 (m, 1H), 1.83 - 1.69 (m, 2H), 1.66 (br d, J = 13.3 Hz, 1H), 1.49 - 1.36 (m, 4H), 1.32 - 1.23 (m, 2H), 1.15 - 1.07 (m, 1H).	A

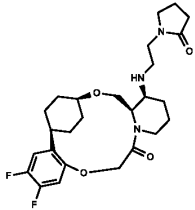
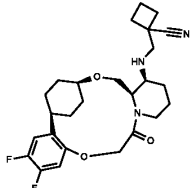
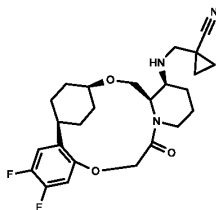
72		Rel-(1s,15S,16R,19s)-4,5-difluoro-15-(3-fluoroazetidin-1-yl)-8,18-dioxatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 439.7	¹ H NMR (400 MHz, MeOD) δ 7.00 (dd, J = 9.2, 11.2 Hz, 1H), 6.84 (dd, J = 6.8, 11.7 Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 5.07 - 4.99 (m, 1H), 5.23 - 4.93 (m, 1H), 4.08 (d, J = 10.5 Hz, 1H), 3.87 (dd, J = 9.5, 11.1 Hz, 1H), 3.80 - 3.73 (m, 1H), 3.73 - 3.61 (m, 3H), 3.42 (dt, J = 2.8, 13.3 Hz, 1H), 3.33 - 3.16 (m, 3H), 2.71 - 2.44 (m, 3H), 2.24 (dq, J = 4.2, 12.9 Hz, 1H), 2.14 (br d, J = 13.9 Hz, 1H), 1.88 - 1.70 (m, 3H), 1.57 (tq, J = 4.2, 13.2 Hz, 1H), 1.50 - 1.21 (m, 5H).	D
73		Rel-(1s,15S,16R,19s)-3-fluoro-15-[(3-hydroxy-2,2-dimethylpropyl)amino]-8,18-dioxatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 449.5	¹ H NMR (500 MHz, MeOD) δ 7.18 - 7.07 (m, 1H), 6.81 - 6.61 (m, 2H), 5.32 - 5.28 (m, 1H), 5.26 - 5.17 (m, 1H), 4.15 - 4.07 (m, 1H), 3.98 - 3.87 (m, 1H), 3.85 - 3.72 (m, 1H), 3.72 - 3.63 (m, 1H), 3.52 - 3.42 (m, 2H), 3.41 - 3.34 (m, 2H), 3.20 - 3.08 (m, 1H), 2.84 - 2.76 (m, 1H), 2.69 - 2.45 (m, 2H), 2.76 - 2.25 (m, 2H), 2.23 - 1.86 (m, 2H), 1.93 - 1.75 (m, 2H), 1.69 - 1.16 (m, 6H), 0.99 - 0.82 (m, 6H).	A
74		Rel-(1s,15S,16R,19s)-4,5-difluoro-15-[(1r,3r)-3-methoxycyclobutyl]amino-8,18-dioxatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 465.3	¹ H NMR (400 MHz, MeOD) δ 7.01 (dd, J = 9.1, 11.2 Hz, 1H), 6.84 (dd, J = 6.8, 11.7 Hz, 1H), 5.28 (d, J = 10.7 Hz, 1H), 5.22 - 5.13 (m, 1H), 4.10 (d, J = 10.6 Hz, 1H), 4.08 - 4.02 (m, 1H), 3.96 (t, J = 10.1 Hz, 1H), 3.90 - 3.82 (m, 1H), 3.80 (br d, J = 14.8 Hz, 1H), 3.71 (br s, 1H), 3.55 - 3.44 (m, 1H), 3.37 (dd, J = 3.8, 9.2 Hz, 1H), 3.26 (s, 3H), 3.16 - 3.06 (m, 1H), 2.72 - 2.58 (m, 1H), 2.60 - 2.50 (m, 1H), 2.43 - 2.31 (m, 2H), 2.31 - 2.20 (m, 3H), 2.20 - 2.10 (m, 1H), 2.00 - 1.86 (m, 2H), 1.84 - 1.75 (m, 1H), 1.71 - 1.53 (m, 2H), 1.53 - 1.41 (m, 2H), 1.42 - 1.31 (m, 1H), 1.33 - 1.25 (m, 1H).	D

75		Rel-(1s,15S,16R,19s)-4,5-difluoro-15-([(1s,3s)-3-methoxycyclobutyl]amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]tricyclo-2(7),3,5-trien-10-one	[M+H] ⁺ 465.3	¹ H NMR (400 MHz, MeOD) δ 7.01 (dd, J = 9.1, 11.2 Hz, 1H), 6.84 (dd, J = 6.9, 11.7 Hz, 1H), 5.28 (d, J = 10.6 Hz, 1H), 5.18 (td, J = 4.4, 11.3 Hz, 1H), 4.10 (d, J = 10.6 Hz, 1H), 3.95 (dd, J = 9.5, 10.7 Hz, 1H), 3.80 (br d, J = 13.6 Hz, 1H), 3.70 (br s, 1H), 3.76 - 3.68 (m, 1H), 3.49 (dt, J = 2.8, 13.2 Hz, 1H), 3.36 (dd, J = 3.8, 9.2 Hz, 1H), 3.29 (s, 1H), 3.26 (s, 3H), 3.13 (br td, J = 4.4, 11.7 Hz, 1H), 2.79 - 2.67 (m, 2H), 2.69 - 2.59 (m, 1H), 2.60 - 2.50 (m, 1H), 2.29 - 2.18 (m, 1H), 2.16 (br d, J = 13.0 Hz, 1H), 2.00 - 1.84 (m, 4H), 1.80 (br d, J = 13.2 Hz, 1H), 1.69 - 1.58 (m, 2H), 1.53 - 1.41 (m, 2H), 1.43 - 1.33 (m, 1H), 1.35 - 1.24 (m, 1H).	D
76		Rel-(1s,15S,16R,19s)-4,5-difluoro-15-([(2-(1H-1,2,3,4-tetrazol-1-yl)ethyl]amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]tricyclo-2(7),3,5-trien-10-one	[M+H] ⁺ 477.7	¹ H NMR (400 MHz, MeOD) δ 9.20 (s, 1H), 7.00 (dd, J = 9.1, 11.2 Hz, 1H), 6.83 (dd, J = 6.8, 11.8 Hz, 1H), 5.26 (d, J = 10.6 Hz, 1H), 5.10 (td, J = 4.6, 11.3 Hz, 1H), 4.63 - 4.56 (m, 2H), 4.07 (d, J = 10.5 Hz, 1H), 3.81 (dd, J = 9.5, 11.0 Hz, 1H), 3.78 - 3.70 (m, 1H), 3.62 (br s, 1H), 3.43 (dt, J = 2.6, 13.3 Hz, 1H), 3.22 - 3.16 (m, 3H), 2.85 (ddd, J = 4.4, 5.3, 12.3 Hz, 1H), 2.70 - 2.58 (m, 1H), 2.60 - 2.48 (m, 1H), 2.24 (dq, J = 4.1, 12.8 Hz, 1H), 2.11 (br d, J = 14.0 Hz, 1H), 1.87 - 1.73 (m, 3H), 1.59 (tq, J = 4.3, 13.4 Hz, 1H), 1.50 - 1.23 (m, 5H).	D
77		Rel-(1s,15S,16R,19s)-3-fluoro-15-[(2-hydroxy-2-methylpropyl]amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]tricyclo-2(7),3,5-trien-10-one	[M+H] ⁺ 435.3	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.75 - 8.63 (m, 1H), 8.30 - 8.21 (m, 2H), 6.97 - 6.84 (m, 2H), 5.70 (d, J = 10.5 Hz, 1H), 5.60 - 5.51 (m, 1H), 5.39 (br d, J = 13.2 Hz, 1H), 5.32 - 5.27 (m, 1H), 5.14 - 5.03 (m, 1H), 5.00 (dd, J = 3.8, 9.2 Hz, 1H), 4.82 - 4.65 (m, 2H), 4.57 - 4.45 (m, 2H), 4.32 - 4.18 (m, 1H), 3.96 - 3.70 (m, 2H), 3.65 - 3.55 (m, 1H), 3.49 (br d, J = 12.4 Hz, 1H), 3.43 - 3.33 (m, 1H), 3.33 - 2.88 (m, 5H), 2.85 (d, J = 3.4 Hz, 6H), 2.85 - 2.72 (m, 1H).	B

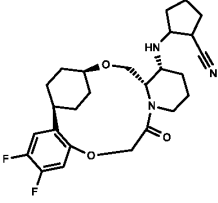
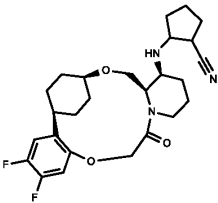
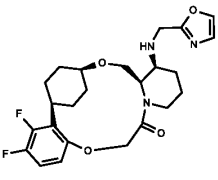
78		Rel-(1s,15S,16R,19s)-3-fluoro-15-[(1,1,1-trifluoro-4-hydroxybutan-2-yl)amino]-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 489.7	¹ H NMR (500 MHz, CDCl ₃) δ 7.12 – 7.04 (m, 1H), 6.69 (tt, J = 8.3, 0.9 Hz, 1H), 6.53 (dt, J = 8.3, 1.0 Hz, 1H), 5.25 (ddt, J = 35.4, 10.2, 4.6 Hz, 1H), 5.08 (dd, J = 10.3, 2.1 Hz, 1H), 4.28 (dd, J = 10.4, 1.4 Hz, 1H), 3.93 – 3.78 (m, 3H), 3.71 (s, 1H), 3.65 (d, J = 14.0 Hz, 1H), 3.54 (ddd, J = 9.1, 4.0, 2.5 Hz, 1H), 3.51 – 3.41 (m, 1H), 3.28 (d, J = 7.2 Hz, 1H), 3.13 (tt, J = 11.9, 5.3 Hz, 1H), 2.59 (qd, J = 13.0, 4.3 Hz, 1H), 2.20 (qd, J = 13.0, 4.3 Hz, 1H), 2.10 – 1.97 (m, 3H), 1.97 – 1.65 (m, 6H), 1.65 – 1.51 (m, 2H), 1.49 – 1.37 (m, 2H), 1.37 – 1.26 (m, 2H).	B
79		Rel-(1s,15S,16R,19s)-3-fluoro-15-[(oxetan-2-yl)methyl]amino-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 433.4	¹ H NMR (400 MHz, MeOD) δ 7.05 – 7.22 (m, 1 H), 6.61 – 6.75 (m, 2 H), 5.31 (d, J=10.4 Hz, 1 H), 5.21 – 5.29 (m, 1 H), 4.89 – 5.03 (m, 1 H), 4.66 – 4.75 (m, 1 H), 4.52 – 4.63 (m, 1 H), 4.13 (dd, J=10.5, 0.9 Hz, 1 H), 3.88 – 4.01 (m, 1 H), 3.79 (br d, J=12.2 Hz, 1 H), 3.70 (br s, 1 H), 3.41 – 3.58 (m, 2 H), 3.04 – 3.22 (m, 2 H), 2.87 – 3.01 (m, 2 H), 2.44 – 2.80 (m, 3 H), 2.24 – 2.39 (m, 1 H), 2.14 – 2.22 (m, 1 H), 1.33 – 1.96 (m, 9 H), 1.19 – 1.29 (m, 1 H).	C
80		Rel-(1s,15S,16R,19s)-15-{[3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl]amino}-3-fluoro-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 479.5	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.4, 8.2 Hz, 1H), 6.75 – 6.60 (m, 2H), 5.90 (t, J = 56.7 Hz, 1H), 5.30 (d, J = 10.6 Hz, 1H), 5.22 – 5.12 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.90 (dd, J = 9.3, 11.0 Hz, 1H), 3.76 (br dd, J = 2.7, 13.4 Hz, 1H), 3.69 (br s, 1H), 3.52 – 3.42 (m, 2H), 3.17 – 3.09 (m, 1H), 2.99 – 2.92 (m, 1H), 2.75 – 2.62 (m, 1H), 2.30 (dq, J = 4.0, 13.0 Hz, 1H), 2.22 – 2.13 (m, 1H), 2.01 – 1.91 (m, 6H), 1.88 – 1.76 (m, 3H), 1.63 (tq, J = 3.8, 13.2 Hz, 1H), 1.57 – 1.49 (m, 1H), 1.52 – 1.43 (m, 1H), 1.42 – 1.32 (m, 2H), 1.26 – 1.18 (m, 1H).	C

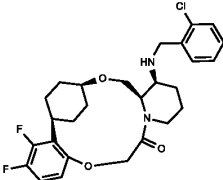
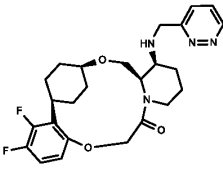
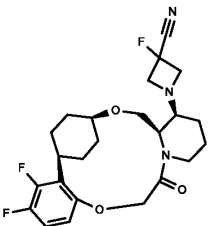
81		(1s,15S,16R,19s)-3-fluoro-15-{{[(3-fluorooxetan-3-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tetracosan-2(7),3,5-trien-10-one	[M+H] ⁺ 451.5	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.2 Hz, 1H), 6.74 - 6.62 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.26 - 5.17 (m, 1H), 4.78 - 4.60 (m, 4H), 4.12 (d, J = 10.5 Hz, 1H), 3.93 (dd, J = 9.5, 11.0 Hz, 1H), 3.78 (br d, J = 11.8 Hz, 1H), 3.70 (br s, 1H), 3.54 - 3.42 (m, 2H), 3.25 - 3.06 (m, 3H), 2.93 - 2.83 (m, 1H), 2.77 - 2.59 (m, 1H), 2.30 (dq, J = 4.2, 13.0 Hz, 1H), 2.23 - 2.11 (m, 1H), 1.94 - 1.72 (m, 3H), 1.70 - 1.30 (m, 5H), 1.28 - 1.15 (m, 1H).	A
82		(1s,15R,16S,19s)-3-fluoro-15-{{[(3-fluorooxetan-3-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tetracosan-2(7),3,5-trien-10-one	[M+H] ⁺ 451.2	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.2 Hz, 1H), 6.74 - 6.62 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.26 - 5.17 (m, 1H), 4.78 - 4.60 (m, 4H), 4.12 (d, J = 10.5 Hz, 1H), 3.93 (dd, J = 9.5, 11.0 Hz, 1H), 3.78 (br d, J = 11.8 Hz, 1H), 3.70 (br s, 1H), 3.54 - 3.42 (m, 2H), 3.25 - 3.06 (m, 3H), 2.93 - 2.83 (m, 1H), 2.77 - 2.59 (m, 1H), 2.30 (dq, J = 4.2, 13.0 Hz, 1H), 2.23 - 2.11 (m, 1H), 1.94 - 1.72 (m, 3H), 1.70 - 1.30 (m, 5H), 1.28 - 1.15 (m, 1H).	D
83		Rel-(1s,15S,16R,19s)-15-[(4,4-difluoro-3-yl)amino]-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tetracosan-2(7),3,5-trien-10-one	[M+H] ⁺ 469.4	¹ H NMR (400 MHz, MeOD) δ 7.19 - 7.01 (m, 1H), 6.81 - 6.61 (m, 2H), 5.33 - 5.27 (m, 1H), 5.27 - 5.12 (m, 1H), 4.28 - 4.18 (m, 1H), 4.15 - 4.09 (m, 1H), 4.09 - 3.98 (m, 1H), 3.97 - 3.85 (m, 2H), 3.84 - 3.73 (m, 1H), 3.72 - 3.61 (m, 2H), 3.60 - 3.41 (m, 3H), 3.20 - 2.99 (m, 2H), 2.77 - 2.24 (m, 2H), 2.22 - 1.89 (m, 2H), 1.88 - 1.78 (m, 2H), 1.70 - 1.37 (m, 4H), 1.37 - 1.17 (m, 2H).	B
84		Rel-(1s,15S,16R,19s)-3-fluoro-15-{{[2,2,2-trifluoro-1-(1-methyl-1H-pyrazol-4-yl)ethyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tetracosan-2(7),3,5-trien-10-one	[M+H] ⁺ 525.5	¹ H NMR (400 MHz, MeOD) δ 7.74 (d, J = 5.7 Hz, 1H), 7.58 (d, J = 6.7 Hz, 1H), 7.12 (tdd, J = 8.2, 6.5, 1.3 Hz, 1H), 6.72 - 6.64 (m, 2H), 5.27 (dd, J = 10.4, 1.4 Hz, 1H), 5.12 (ddt, J = 39.0, 10.1, 4.5 Hz, 1H), 4.53 - 4.42 (m, 1H), 4.10 (dd, J = 10.5, 4.8 Hz, 1H), 3.99 - 3.85 (m, 4H), 3.73 (d, J = 16.0 Hz, 2H), 3.67 - 3.56 (m, 1H), 3.51 - 3.36 (m, 1H), 3.14 (dq, J = 12.2, 6.1 Hz, 1H), 3.00 - 2.75 (m, 1H), 2.74 - 2.57 (m, 1H), 2.38 - 2.10	A

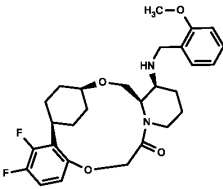
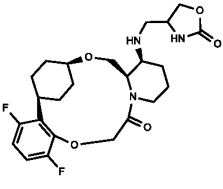
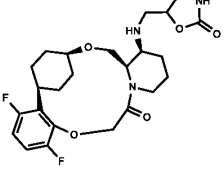
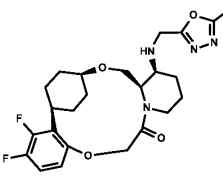
		ricosa-2(7),3,5-trien-10-one		(m, 2H), 1.79 (td, J = 38.2, 16.5 Hz, 4H), 1.64 – 1.14 (m, 6H).	
85		Rel- (1s,15S,16R,19s)-4,5-difluoro-15-{{(3-fluoro-4,5-difluoro-15-yl)methyl}amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 469.3	¹ H NMR (500 MHz, MeOD) δ 7.01 (dd, J = 9.1, 11.3 Hz, 1H), 6.84 (dd, J = 6.8, 11.7 Hz, 1H), 5.28 (d, J = 10.6 Hz, 1H), 5.25 - 5.18 (m, 1H), 4.79 - 4.61 (m, 4H), 4.09 (d, J = 10.6 Hz, 1H), 3.91 (dd, J = 9.5, 11.0 Hz, 1H), 3.77 (br dd, J = 3.1, 13.9 Hz, 1H), 3.68 (br s, 1H), 3.54 - 3.40 (m, 2H), 3.28 - 3.16 (m, 2H), 2.93 - 2.86 (m, 1H), 2.72 - 2.61 (m, 1H), 2.60 - 2.51 (m, 1H), 2.26 (dq, J = 4.3, 12.9 Hz, 1H), 2.16 (d, J = 14.0 Hz, 1H), 1.94 - 1.77 (m, 3H), 1.62 (tq, J = 3.9, 12.8 Hz, 1H), 1.54 (dt, J = 3.5, 12.4 Hz, 1H), 1.49 - 1.24 (m, 4H).	C
86		Rel- (1s,15S,16R,19s)-4,5-difluoro-15-(3-hydroxyazetidin-1-yl)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 437.7	¹ H NMR (400 MHz, MeOD) δ 7.00 (dd, J = 9.1, 11.2 Hz, 1H), 6.83 (dd, J = 6.8, 11.7 Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 5.09 - 5.00 (m, 1H), 4.34 (quin, J = 6.2 Hz, 1H), 4.08 (d, J = 10.5 Hz, 1H), 3.87 (dd, J = 9.5, 11.0 Hz, 1H), 3.76 (br d, J = 13.4 Hz, 1H), 3.72 - 3.63 (m, 3H), 3.42 (dt, J = 2.9, 13.4 Hz, 1H), 3.33 - 3.28 (m, 1H), 3.02 (t, J = 6.9 Hz, 1H), 2.88 (t, J = 6.9 Hz, 1H), 2.71 - 2.59 (m, 1H), 2.58 - 2.49 (m, 1H), 2.43 (td, J = 4.7, 12.2 Hz, 1H), 2.24 (dq, J = 4.1, 12.8 Hz, 1H), 2.14 (br d, J = 14.1 Hz, 1H), 1.88 - 1.72 (m, 3H), 1.56 (tq, J = 3.9, 13.2 Hz, 1H), 1.49 - 1.22 (m, 5H).	D
87		Rel- (1s,15S,16R,19s)-4,5-difluoro-15-{{2-(1-methyl-1H-pyrazol-3-yl)ethyl}amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 489.4	¹ H NMR (500 MHz, MeOD) δ 7.54 - 7.39 (m, 1H), 7.05 - 6.98 (m, 1H), 6.97 - 6.77 (m, 1H), 6.21 - 5.97 (m, 1H), 5.35 - 5.07 (m, 2H), 4.14 - 4.03 (m, 1H), 3.98 - 3.89 (m, 1H), 3.88 - 3.83 (m, 3H), 3.82 - 3.74 (m, 1H), 3.71 - 3.63 (m, 1H), 3.55 - 3.44 (m, 1H), 3.42 - 3.35 (m, 1H), 3.20 - 3.07 (m, 3H), 2.94 - 2.81 (m, 2H), 2.60 - 2.49 (m, 1H), 2.72 - 2.19 (m, 2H), 2.00 - 1.93 (m, 1H), 1.93 - 1.87 (m, 1H), 2.19 - 1.74 (m, 2H), 1.71 - 1.54 (m, 2H), 1.45 - 1.32 (m, 2H), 1.51 - 1.23 (m, 2H).	D

88		Rel- (1s,15S,16R,19s)-4,5-difluoro-15-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 492.6	¹ H NMR (500 MHz, CDCl ₃) δ 6.90 (dd, J = 9.1, 10.8 Hz, 1H), 6.57 (dd, J = 6.6, 11.3 Hz, 1H), 5.21 (td, J = 4.5, 11.1 Hz, 1H), 5.04 (d, J = 10.3 Hz, 1H), 4.23 (d, J = 10.3 Hz, 1H), 3.79 (dd, J = 9.3, 10.8 Hz, 1H), 3.68 (br s, 1H), 3.62 (br dd, J = 2.3, 13.4 Hz, 1H), 3.51 - 3.46 (m, 2H), 3.47 - 3.38 (m, 3H), 3.38 - 3.31 (m, 1H), 2.97 - 2.88 (m, 2H), 2.83 (td, J = 6.0, 11.8 Hz, 1H), 2.61 (dq, J = 4.5, 13.0 Hz, 1H), 2.52 - 2.44 (m, 1H), 2.43 - 2.38 (m, 2H), 2.20 (dq, J = 3.8, 12.7 Hz, 1H), 2.11 - 2.01 (m, 3H), 1.92 - 1.85 (m, 1H), 1.85 - 1.75 (m, 2H), 1.66 - 1.51 (m, 1H), 1.50 - 1.38 (m, 2H), 1.42 - 1.33 (m, 1H), 1.37 - 1.23 (m, 2H).	D
89		Rel-1- ({[(1s,15S,16R,19s)-4,5-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}methyl)cyclobutane-1-carbonitrile	[M+H] ⁺ 474.2	¹ H NMR (400 MHz, MeOD) δ 7.00 (dd, J = 9.1, 11.2 Hz, 1H), 6.84 (dd, J = 6.9, 11.8 Hz, 1H), 5.28 (d, J = 10.6 Hz, 1H), 5.20 (td, J = 4.5, 11.3 Hz, 1H), 4.08 (d, J = 10.6 Hz, 1H), 3.91 (dd, J = 9.5, 10.9 Hz, 1H), 3.77 (br d, J = 12.4 Hz, 1H), 3.68 (br s, 1H), 3.53 (dd, J = 3.9, 9.3 Hz, 1H), 3.47 (dt, J = 2.8, 13.1 Hz, 1H), 3.02 (s, 2H), 2.90 (td, J = 4.5, 12.3 Hz, 1H), 2.67 (dq, J = 4.3, 12.7 Hz, 1H), 2.55 (tt, J = 5.7, 12.4 Hz, 1H), 2.50 - 2.39 (m, 2H), 2.33 - 2.04 (m, 6H), 1.94 - 1.76 (m, 3H), 1.69 - 1.56 (m, 1H), 1.59 - 1.50 (m, 1H), 1.50 - 1.23 (m, 4H).	B
90		Rel-1- ({[(1s,15S,16R,19s)-4,5-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}methyl)cyclopropane-1-carbonitrile	[M+H] ⁺ 460.7	¹ H NMR (400 MHz, CDCl ₃) δ 6.90 (dd, J = 9.0, 10.8 Hz, 1H), 6.57 (dd, J = 6.7, 11.2 Hz, 1H), 5.28 - 5.18 (m, 1H), 5.04 (d, J = 10.4 Hz, 1H), 4.23 (d, J = 10.3 Hz, 1H), 3.87 - 3.79 (m, 1H), 3.70 (br s, 1H), 3.64 (br d, J = 13.4 Hz, 1H), 3.53 (dd, J = 4.1, 9.2 Hz, 1H), 3.49 - 3.40 (m, 1H), 3.09 - 3.00 (m, 1H), 2.94 (d, J = 12.8 Hz, 1H), 2.73 (d, J = 12.9 Hz, 1H), 2.68 - 2.55 (m, 1H), 2.54 - 2.43 (m, 1H), 2.27 - 2.13 (m, 1H), 2.12 - 2.04 (m, 1H), 1.95 - 1.79 (m, 3H), 1.70 - 1.20 (m, 8H), 1.11 - 0.82 (m, 2H).	B

91		Rel-(1s,15S,16R,19s)-4,6-difluoro-15-([(oxetan-3-yl)methyl]amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]trien-10-one	[M+H] ⁺ 451.4	¹ H NMR (400 MHz, MeOD) δ 6.85 (ddd, J = 3.1, 8.4, 11.6 Hz, 1H), 6.77 - 6.69 (m, 1H), 5.52 - 5.41 (m, 1H), 5.27 - 5.17 (m, 1H), 4.82 (dd, J = 6.2, 7.7 Hz, 2H), 4.48 - 4.41 (m, 2H), 4.19 - 4.09 (m, 1H), 3.91 (br dd, J = 3.0, 13.9 Hz, 1H), 3.85 (dd, J = 9.3, 11.0 Hz, 1H), 3.70 (br s, 1H), 3.54 - 3.45 (m, 1H), 3.44 (dd, J = 3.6, 9.2 Hz, 1H), 3.20 - 3.08 (m, 1H), 3.08 - 2.95 (m, 2H), 2.83 (ddd, J = 3.8, 5.0, 12.1 Hz, 1H), 2.76 - 2.64 (m, 1H), 2.65 - 2.55 (m, 1H), 2.22 - 2.14 (m, 1H), 2.15 - 2.03 (m, 1H), 1.92 - 1.79 (m, 3H), 1.63 (tq, J = 4.4, 13.4 Hz, 1H), 1.54 - 1.27 (m, 5H).	B
92		Rel-1-[(1s,15S,16R,19s)-3,4-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]trien-15-yl]azetidine-3-carbonitrile	[M+H] ⁺ 446.4	¹ H NMR (400 MHz, MeOD) δ 7.08 - 6.97 (m, 1H), 6.70 - 6.59 (m, 1H), 5.30 (d, J = 10.6 Hz, 1H), 5.08 - 4.96 (m, 1H), 4.09 (d, J = 10.5 Hz, 1H), 3.89 (dd, J = 9.7, 11.0 Hz, 1H), 3.76 (br dd, J = 1.9, 14.1 Hz, 1H), 3.72 - 3.65 (m, 1H), 3.65 - 3.55 (m, 2H), 3.51 - 3.34 (m, 5H), 3.23 - 3.09 (m, 1H), 2.75 - 2.58 (m, 1H), 2.49 (td, J = 4.7, 12.1 Hz, 1H), 2.36 - 2.13 (m, 2H), 1.91 - 1.78 (m, 2H), 1.77 - 1.67 (m, 1H), 1.64 - 1.45 (m, 2H), 1.44 - 1.20 (m, 4H).	C
93		Rel-(1s,15S,16R,19s)-4,5-difluoro-15-([(3-fluorooxolan-3-yl)methyl]amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0^{11,16}}]trien-10-one	[M+H] ⁺ 483.2	¹ H NMR (500 MHz, MeOD) δ 7.01 (dd, J = 9.1, 11.1 Hz, 1H), 6.84 (dd, J = 6.8, 11.7 Hz, 1H), 5.28 (d, J = 10.6 Hz, 1H), 5.23 - 5.15 (m, 1H), 4.08 (d, J = 10.6 Hz, 1H), 3.94 - 3.90 (m, 1H), 4.01 - 3.75 (m, 4H), 3.79 - 3.74 (m, 1H), 3.70 - 3.65 (m, 1H), 3.51 - 3.42 (m, 2H), 3.19 - 2.98 (m, 2H), 2.91 - 2.84 (m, 1H), 2.67 (dq, J = 4.3, 13.0 Hz, 1H), 2.60 - 2.50 (m, 1H), 2.31 - 2.21 (m, 1H), 2.19 - 2.14 (m, 1H), 2.23 - 2.03 (m, 2H), 1.92 - 1.82 (m, 2H), 1.82 - 1.75 (m, 1H), 1.68 - 1.57 (m, 1H), 1.58 - 1.48 (m, 1H), 1.49 - 1.39 (m, 2H), 1.38 - 1.31 (m, 1H), 1.30 - 1.25 (m, 1H).	D

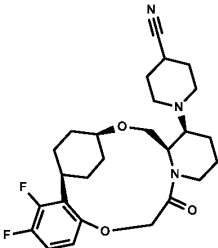
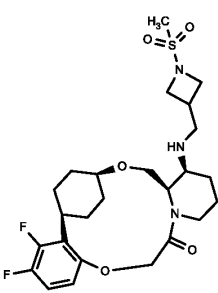
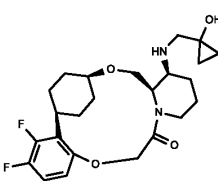
94		Rel-2- {[(1s,15R,16S, 19s)-4,5- difluoro-10- oxo-8,18-dioxa- 11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}cyclo pentane-1- carbonitrile	[M+H] ⁺ 474.4	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.23 - 7.14 (m, 1H), 7.03 - 6.94 (m, 1H), 5.27 (d, J = 10.4 Hz, 1H), 5.03 - 4.93 (m, 1H), 4.01 - 3.93 (m, 1H), 3.86 - 3.71 (m, 1H), 3.67 - 3.54 (m, 2H), 3.46 - 3.32 (m, 2H), 3.30 - 3.15 (m, 1H), 2.89 - 2.79 (m, 1H), 2.71 - 2.59 (m, 1H), 2.58 - 2.52 (m, 2H), 2.24 - 2.14 (m, 1H), 2.13 - 1.10 (m, 16H).	C
95		Rel-2- {[(1s,15S,16R, 19s)-4,5- difluoro-10- oxo-8,18-dioxa- 11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}cyclo pentane-1- carbonitrile	[M+H] ⁺ 474.4	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.28 - 7.14 (m, 1H), 6.98 (dd, J = 6.9, 12.0 Hz, 1H), 5.27 (d, J = 10.6 Hz, 1H), 5.06 - 4.94 (m, 1H), 4.00 - 3.93 (m, 1H), 3.84 - 3.71 (m, 1H), 3.67 - 3.56 (m, 2H), 3.47 - 3.33 (m, 2H), 3.30 - 3.12 (m, 2H), 2.87 - 2.75 (m, 1H), 2.62 - 2.52 (m, 2H), 2.25 - 2.14 (m, 1H), 2.10 (br d, J = 14.0 Hz, 1H), 2.04 - 1.12 (m, 15H).	B
96		Rel- (1s,15S,16R,19 s)-3,4-difluoro- 15- oxazol-2- yl)methyl]amin o}-8,18-dioxa- 11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-10-one	[M+H] ⁺ 462.4	¹ H NMR (500 MHz, MeOD) δ 7.89 (d, J = 0.8 Hz, 1H), 7.14 (d, J = 0.7 Hz, 1H), 7.07 - 6.96 (m, 1H), 6.64 (ddd, J = 2.0, 3.8, 9.0 Hz, 1H), 5.29 (d, J = 10.6 Hz, 1H), 5.20 (td, J = 4.5, 11.3 Hz, 1H), 4.09 (d, J = 10.6 Hz, 1H), 4.00 (s, 2H), 3.92 (dd, J = 9.2, 11.1 Hz, 1H), 3.80 - 3.73 (m, 1H), 3.70 (br s, 1H), 3.50 (dd, J = 4.0, 9.2 Hz, 1H), 3.50 - 3.41 (m, 1H), 3.20 - 3.08 (m, 1H), 2.89 (td, J = 5.2, 11.4 Hz, 1H), 2.75 - 2.64 (m, 1H), 2.28 (dq, J = 4.2, 13.0 Hz, 1H), 2.22 - 2.13 (m, 1H), 1.91 - 1.76 (m, 3H), 1.64 - 1.46 (m, 3H), 1.44 - 1.34 (m, 2H), 1.28 - 1.20 (m, 1H).	B

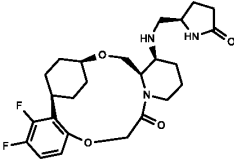
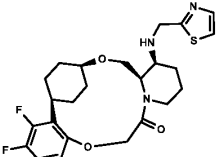
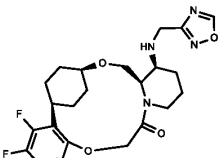
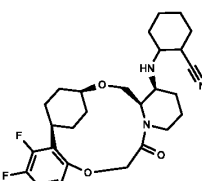
97		Rel-(1s,15S,16R,19s)-15-[(2-chlorophenyl)methyl]amino}-3,4-difluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0} ^{11,16}]triosa-2(7),3,5-trien-10-one	[M+H] ⁺ 505.4	¹ H NMR (400 MHz, MeOD) δ 7.53 (dd, J = 1.8, 7.3 Hz, 1H), 7.40 (dd, J = 1.4, 7.6 Hz, 1H), 7.34 - 7.23 (m, 2H), 7.02 (q, J = 9.1 Hz, 1H), 6.64 (ddd, J = 1.9, 3.7, 9.0 Hz, 1H), 5.29 (br d, J = 10.5 Hz, 2H), 4.10 (d, J = 10.5 Hz, 1H), 4.05 - 3.86 (m, 3H), 3.77 (br d, J = 13.6 Hz, 1H), 3.71 (br s, 1H), 3.57 (dd, J = 3.9, 9.2 Hz, 1H), 3.53 - 3.42 (m, 1H), 3.22 - 3.10 (m, 1H), 2.94 - 2.81 (m, 1H), 2.78 - 2.60 (m, 1H), 2.29 (dq, J = 4.2, 13.0 Hz, 1H), 2.23 - 2.11 (m, 1H), 1.94 - 1.75 (m, 3H), 1.65 - 1.19 (m, 6H).	C
98		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-[[[(pyridazin-3-yl)methyl]amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0} ^{11,16}]triosa-2(7),3,5-trien-10-one	[M+H] ⁺ 473.4	¹ H NMR (500 MHz, MeOD) δ 9.09 (dd, J = 1.6, 4.9 Hz, 1H), 7.87 (dd, J = 1.6, 8.4 Hz, 1H), 7.72 (dd, J = 4.9, 8.5 Hz, 1H), 7.06 - 6.96 (m, 1H), 6.64 (ddd, J = 1.9, 3.7, 9.1 Hz, 1H), 5.29 (d, J = 10.6 Hz, 1H), 5.24 (td, J = 4.5, 11.3 Hz, 1H), 4.24 - 4.15 (m, 2H), 4.09 (d, J = 10.6 Hz, 1H), 3.97 (dd, J = 9.5, 10.9 Hz, 1H), 3.77 (br d, J = 14.4 Hz, 1H), 3.71 (br s, 1H), 3.56 (dd, J = 3.8, 9.2 Hz, 1H), 3.48 (dt, J = 2.4, 12.9 Hz, 1H), 3.21 - 3.11 (m, 1H), 2.92 (td, J = 5.1, 11.5 Hz, 1H), 2.76 - 2.65 (m, 1H), 2.29 (dq, J = 4.1, 13.0 Hz, 1H), 2.23 - 2.16 (m, 1H), 2.00 - 1.91 (m, 1H), 1.88 - 1.77 (m, 2H), 1.65 - 1.53 (m, 2H), 1.54 - 1.45 (m, 1H), 1.45 - 1.34 (m, 2H), 1.29 - 1.20 (m, 1H).	D
99		Rel-3-fluoro-1-[(1s,15S,16R,19s)-3,4-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0} ^{11,16}]triosa-2(7),3,5-trien-15-yl]azetidine-3-carbonitrile	[M+H] ⁺ 464.4	¹ H NMR (500 MHz, CDCl ₃) δ 6.97 - 6.87 (m, 1H), 6.48 - 6.38 (m, 1H), 5.12 - 5.04 (m, 2H), 4.26 (d, J = 10.4 Hz, 1H), 3.98 (br dd, J = 10.1, 13.4 Hz, 2H), 3.87 - 3.77 (m, 1H), 3.72 (br s, 1H), 3.71 - 3.63 (m, 1H), 3.70 - 3.51 (m, 2H), 3.48 - 3.34 (m, 2H), 3.21 - 3.09 (m, 1H), 2.68 - 2.53 (m, 2H), 2.22 - 2.12 (m, 1H), 2.14 - 2.06 (m, 1H), 1.96 - 1.82 (m, 2H), 1.72 (br dd, J = 3.2, 12.6 Hz, 1H), 1.59 - 1.26 (m, 6H).	C

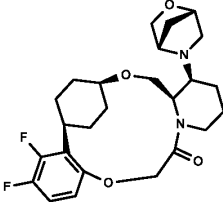
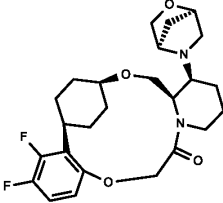
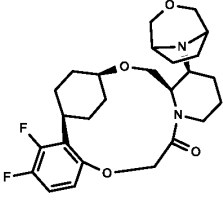
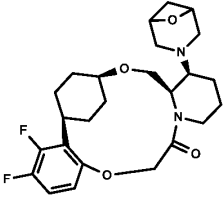
100		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-{[(2-methoxyphenyl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 501.4	¹ H NMR (400 MHz, MeOD) δ 7.34 - 7.23 (m, 2H), 7.07 - 6.96 (m, 2H), 6.92 (dt, J = 0.8, 7.4 Hz, 1H), 6.64 (ddd, J = 1.9, 3.7, 9.0 Hz, 1H), 5.35 - 5.29 (m, 1H), 5.29 (d, J = 10.5 Hz, 1H), 4.09 (d, J = 10.5 Hz, 1H), 4.00 - 3.90 (m, 2H), 3.88 (s, 3H), 3.86 - 3.69 (m, 3H), 3.53 (dd, J = 3.9, 9.2 Hz, 1H), 3.50 - 3.41 (m, 1H), 3.22 - 3.13 (m, 1H), 2.91 - 2.82 (m, 1H), 2.77 - 2.63 (m, 1H), 2.39 - 2.23 (m, 1H), 2.26 - 2.13 (m, 1H), 1.95 - 1.20 (m, 9H).	D
101		Rel- (1s,15S,16R,19s)-3,6-difluoro-15-{[(2-oxo-1,3-oxazolidin-4-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 480.4	¹ H NMR (500 MHz, MeOD) δ 7.00 (ddd, J = 5.1, 9.2, 11.1 Hz, 1H), 6.78 (dt, J = 4.0, 9.2 Hz, 1H), 5.52 (dd, J = 3.4, 12.2 Hz, 1H), 5.23 - 5.13 (m, 1H), 4.50 (dt, J = 2.9, 8.7 Hz, 1H), 4.26 - 4.16 (m, 2H), 3.97 (dtd, J = 3.2, 5.7, 8.8 Hz, 1H), 3.92 - 3.83 (m, 2H), 3.77 - 3.69 (m, 1H), 3.56 - 3.45 (m, 2H), 3.19 - 3.07 (m, 1H), 2.89 - 2.85 (m, 1H), 2.85 - 2.80 (m, 2H), 2.79 - 2.68 (m, 1H), 2.19 (br d, J = 13.7 Hz, 1H), 2.08 (dq, J = 3.9, 13.0 Hz, 1H), 1.94 - 1.76 (m, 3H), 1.71 - 1.58 (m, 1H), 1.55 - 1.26 (m, 5H).	B
102		Rel- (1s,15S,16R,19s)-3,6-difluoro-15-{[(2-oxo-1,3-oxazolidin-5-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 480.4	¹ H NMR (400 MHz, MeOD) δ 7.00 (ddd, J = 5.0, 9.3, 11.0 Hz, 1H), 6.78 (dt, J = 4.1, 9.2 Hz, 1H), 5.52 (dd, J = 3.5, 12.2 Hz, 1H), 5.29 - 5.11 (m, 1H), 4.82 - 4.70 (m, 1H), 4.19 (dd, J = 1.8, 12.3 Hz, 1H), 3.97 - 3.81 (m, 2H), 3.78 - 3.62 (m, 2H), 3.56 - 3.43 (m, 2H), 3.38 (ddd, J = 6.9, 8.9, 12.4 Hz, 1H), 3.19 - 3.06 (m, 1H), 3.03 - 2.96 (m, 2H), 2.95 - 2.85 (m, 1H), 2.78 - 2.58 (m, 2H), 2.20 (br d, J = 14.3 Hz, 1H), 2.08 (dq, J = 3.7, 13.0 Hz, 1H), 1.95 - 1.77 (m, 3H), 1.72 - 1.58 (m, 1H), 1.57 - 1.44 (m, 2H), 1.44 - 1.27 (m, 3H).	B
103		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-{[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 477.4	¹ H NMR (400 MHz, MeOD) δ 7.09 - 6.94 (m, 1H), 6.64 (ddd, J = 1.9, 3.7, 9.1 Hz, 1H), 5.29 (d, J = 10.6 Hz, 1H), 5.23 - 5.13 (m, 1H), 4.14 - 4.02 (m, 3H), 3.98 - 3.87 (m, 1H), 3.77 (br d, J = 12.8 Hz, 1H), 3.73 - 3.66 (m, 1H), 3.57 - 3.42 (m, 2H), 3.23 - 3.13 (m, 1H), 2.97 - 2.88 (m,	D

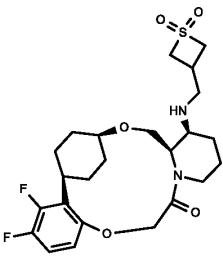
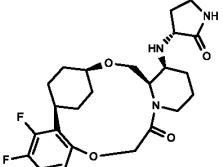
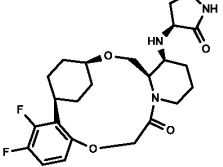
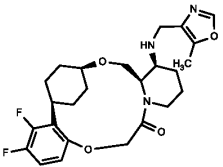
		11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]triosa-2(7),3,5-trien-10-one		¹ H, 2.77 - 2.63 (m, 1H), 2.54 (s, 3H), 2.36 - 2.13 (m, 2H), 1.95 - 1.77 (m, 3H), 1.71 - 1.18 (m, 6H).	
104		Rel-1-({[(1s,15S,16R,19s)-3,4-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]triosa-2(7),3,5-trien-15-yl]amino}methyl)cyclopentane-1-carbonitrile	[M+H] ⁺ 488.4	¹ H NMR (500 MHz, MeOD) δ 7.09 - 6.95 (m, 1H), 6.64 (ddd, J = 1.8, 3.7, 9.0 Hz, 1H), 5.30 (d, J = 10.6 Hz, 1H), 5.25 - 5.15 (m, 1H), 4.10 (d, J = 10.6 Hz, 1H), 3.99 - 3.89 (m, 1H), 3.77 (br d, J = 12.5 Hz, 1H), 3.73 - 3.68 (m, 1H), 3.55 (dd, J = 3.9, 9.3 Hz, 1H), 3.47 (dt, J = 2.3, 13.1 Hz, 1H), 3.20 - 3.09 (m, 1H), 2.94 - 2.83 (m, 3H), 2.76 - 2.64 (m, 1H), 2.28 (dq, J = 4.1, 13.0 Hz, 1H), 2.23 - 2.16 (m, 1H), 2.15 - 2.05 (m, 2H), 1.94 - 1.75 (m, 9H), 1.69 - 1.46 (m, 3H), 1.45 - 1.20 (m, 3H).	B
105		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-({[(pyrazin-2-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]triosa-2(7),3,5-trien-10-one	[M+H] ⁺ 473.4	¹ H NMR (400 MHz, MeOD) δ 8.71 (d, J = 1.2 Hz, 1H), 8.59 (dd, J = 1.5, 2.5 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H), 7.09 - 6.95 (m, 1H), 6.63 (dd, J = 3.7, 9.1 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.27 - 5.21 (m, 1H), 4.09 (d, J = 10.5 Hz, 1H), 4.06 (d, J = 3.5 Hz, 2H), 3.96 (dd, J = 9.4, 11.0 Hz, 1H), 3.77 (br d, J = 12.7 Hz, 1H), 3.73 - 3.68 (m, 1H), 3.54 (dd, J = 3.9, 9.3 Hz, 1H), 3.51 - 3.42 (m, 1H), 3.23 - 3.12 (m, 1H), 2.99 - 2.86 (m, 1H), 2.77 - 2.62 (m, 1H), 2.39 - 2.25 (m, 1H), 2.25 - 2.12 (m, 1H), 1.98 - 1.77 (m, 3H), 1.70 - 1.20 (m, 6H).	D
106		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-({[(2S)-5-oxopyrrolidin-2-yl]methyl}amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]triosa-2(7),3,5-trien-10-one	[M+H] ⁺ 478.3	¹ H NMR (400 MHz, MeOD) δ 7.02 (q, J = 9.1 Hz, 1H), 6.65 (ddd, J = 1.9, 3.6, 9.0 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.25 - 5.16 (m, 1H), 4.10 (d, J = 10.5 Hz, 1H), 3.98 - 3.87 (m, 1H), 3.86 - 3.74 (m, 2H), 3.71 (br s, 1H), 3.53 - 3.42 (m, 2H), 3.22 - 3.11 (m, 1H), 3.00 - 2.61 (m, 4H), 2.46 - 2.14 (m, 5H), 1.97 - 1.77 (m, 4H), 1.71 - 1.20 (m, 6H).	D

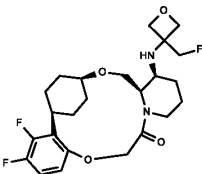
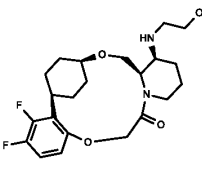
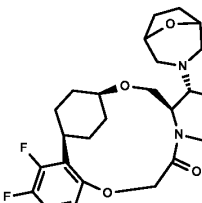
107		Rel-4-[(1s,15S,16R,19s)-3,4-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricycose-2(7),3,5-trien-15-yl)morpholine-2-carbonitrile	[M+H] ⁺ 476.3	¹ H NMR (400 MHz, MeOD) δ 7.01 (q, J = 9.1 Hz, 1H), 6.69 - 6.54 (m, 1H), 5.38 - 5.18 (m, 2H), 4.83 - 4.80 (m, 1H), 4.15 - 4.03 (m, 1H), 4.03 - 3.86 (m, 2H), 3.86 - 3.74 (m, 2H), 3.74 - 3.66 (m, 1H), 3.66 - 3.56 (m, 1H), 3.53 - 3.41 (m, 1H), 3.22 - 3.07 (m, 1H), 3.02 - 2.78 (m, 2H), 2.65 - 2.55 (m, 1H), 2.55 - 2.32 (m, 2H), 2.76 - 2.24 (m, 2H), 2.06 - 1.87 (m, 2H), 2.23 - 1.75 (m, 2H), 1.67 - 1.18 (m, 6H).	B
108		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-(morpholin-4-yl)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricycose-2(7),3,5-trien-10-one	[M+H] ⁺ 451.5	¹ H NMR (400 MHz, MeOD) δ 7.10 - 6.95 (m, 1H), 6.64 (ddd, J = 1.9, 3.7, 9.0 Hz, 1H), 5.38 - 5.25 (m, 2H), 4.10 (d, J = 10.6 Hz, 1H), 3.96 - 3.87 (m, 1H), 3.77 (br dd, J = 2.3, 13.3 Hz, 1H), 3.73 - 3.67 (m, 5H), 3.51 - 3.41 (m, 2H), 3.21 - 3.10 (m, 1H), 2.77 - 2.63 (m, 1H), 2.65 - 2.53 (m, 4H), 2.37 (td, J = 4.6, 11.9 Hz, 1H), 2.33 - 2.22 (m, 1H), 2.22 - 2.15 (m, 1H), 2.07 - 1.98 (m, 1H), 1.94 - 1.86 (m, 1H), 1.85 - 1.76 (m, 1H), 1.64 - 1.52 (m, 1H), 1.53 - 1.44 (m, 2H), 1.44 - 1.34 (m, 2H), 1.28 - 1.20 (m, 1H).	D
109		Rel-(1s,15S,16R,19s)-4,5-difluoro-15-([(1r,3r)-3-hydroxycyclobutyl]amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricycose-2(7),3,5-trien-10-one	[M+H] ⁺ 451.3	¹ H NMR (400 MHz, MeOD) δ 7.07 - 6.96 (m, 1H), 6.89 - 6.79 (m, 1H), 5.28 (br d, J = 10.6 Hz, 1H), 5.22 - 5.13 (m, 1H), 4.49 - 4.38 (m, 1H), 4.09 (br d, J = 10.7 Hz, 1H), 3.95 (br t, J = 9.6 Hz, 1H), 3.91 - 3.83 (m, 1H), 3.79 (br d, J = 13.8 Hz, 1H), 3.70 (br s, 1H), 3.49 (br t, J = 12.4 Hz, 1H), 3.38 (br d, J = 8.4 Hz, 1H), 3.12 - 3.01 (m, 1H), 2.72 - 2.50 (m, 2H), 2.37 - 2.11 (m, 6H), 2.00 - 1.85 (m, 2H), 1.80 (br d, J = 13.0 Hz, 1H), 1.71 - 1.52 (m, 2H), 1.52 - 1.24 (m, 4H).	D
110		Rel-(1s,15S,16R,19s)-4,5-difluoro-15-([(1s,3s)-3-hydroxycyclobutyl]amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricycose-2(7),3,5-trien-10-one	[M+H] ⁺ 451.3	¹ H NMR (500 MHz, MeOD) δ 7.01 (dd, J = 9.1, 11.1 Hz, 1H), 6.84 (dd, J = 6.8, 11.7 Hz, 1H), 5.27 (d, J = 10.6 Hz, 1H), 5.20 - 5.11 (m, 1H), 4.09 (d, J = 10.6 Hz, 1H), 4.04 - 3.97 (m, 1H), 3.93 (dd, J = 9.3, 11.0 Hz, 1H), 3.78 (br d, J = 12.6 Hz, 1H), 3.69 (br s, 1H), 3.52 - 3.44 (m, 1H), 3.38 (dd, J = 3.8, 9.2 Hz, 1H), 3.16 - 3.09 (m, 1H), 3.06 - 3.00 (m, 1H), 2.75	D

		ricosa-2(7),3,5-trien-10-one		- 2.51 (m, 4H), 2.24 (dq, J = 4.2, 12.9 Hz, 1H), 2.19 - 2.12 (m, 1H), 1.95 - 1.70 (m, 5H), 1.70 - 1.51 (m, 2H), 1.51 - 1.25 (m, 4H).	
111		Rel-1-[(1s,15S,16R,19s)-3,4-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trien-15-yl]piperidine-4-carbonitrile	[M+H] ⁺ 471.3	¹ H NMR (400 MHz, MeOD) δ 7.09 - 6.96 (m, 1H), 6.64 (ddd, J = 1.9, 3.8, 9.0 Hz, 1H), 5.35 - 5.23 (m, 2H), 4.10 (d, J = 10.6 Hz, 1H), 3.96 - 3.86 (m, 1H), 3.76 (br d, J = 13.0 Hz, 1H), 3.69 (br s, 1H), 3.51 - 3.40 (m, 2H), 3.21 - 3.10 (m, 1H), 2.96 - 2.76 (m, 3H), 2.75 - 2.62 (m, 1H), 2.56 - 2.38 (m, 3H), 2.27 (dq, J = 3.9, 13.0 Hz, 1H), 2.21 - 2.13 (m, 1H), 2.06 - 1.87 (m, 4H), 1.87 - 1.74 (m, 3H), 1.64 - 1.44 (m, 3H), 1.44 - 1.33 (m, 2H), 1.30 - 1.19 (m, 1H).	C
112		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-[(1-methanesulfonylazetidino-3-yl)methyl]amino-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trien-10-one	[M+H] ⁺ 528.4	¹ H NMR (400 MHz, MeOD) δ 7.02 (q, J = 9.2 Hz, 1H), 6.64 (td, J = 1.9, 9.1 Hz, 1H), 5.30 (d, J = 10.6 Hz, 1H), 5.25 - 5.16 (m, 1H), 4.10 (d, J = 10.5 Hz, 1H), 4.00 (t, J = 8.2 Hz, 2H), 3.95 - 3.88 (m, 1H), 3.81 - 3.73 (m, 1H), 3.73 - 3.66 (m, 3H), 3.50 - 3.41 (m, 2H), 3.21 - 3.10 (m, 1H), 2.97 - 2.91 (m, 5H), 2.90 - 2.82 (m, 1H), 2.81 - 2.72 (m, 1H), 2.73 - 2.62 (m, 1H), 2.34 - 2.22 (m, 1H), 2.22 - 2.14 (m, 1H), 1.92 - 1.78 (m, 3H), 1.69 - 1.55 (m, 1H), 1.55 - 1.45 (m, 2H), 1.44 - 1.33 (m, 2H), 1.29 - 1.20 (m, 1H).	C
113		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-[(1-hydroxycyclopropyl)methyl]amino-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]trien-10-one	[M+H] ⁺ 451.5	¹ H NMR (400 MHz, MeOD) δ 7.09 - 6.98 (m, 1H), 6.71 - 6.62 (m, 1H), 5.39 - 5.27 (m, 2H), 4.12 (d, J = 10.6 Hz, 1H), 4.04 - 3.94 (m, 1H), 3.83 (br d, J = 13.4 Hz, 1H), 3.74 (br s, 1H), 3.56 - 3.46 (m, 1H), 3.41 (dd, J = 3.8, 9.2 Hz, 1H), 3.39 - 3.34 (m, 1H), 3.14 (d, J = 12.8 Hz, 1H), 3.23 - 3.11 (m, 1H), 3.08 (d, J = 12.8 Hz, 1H), 2.75 - 2.61 (m, 1H), 2.32 - 2.15 (m, 2H), 2.06 (br d, J = 9.8 Hz, 1H), 1.94 (br d, J = 11.6 Hz, 1H), 1.88 - 1.78 (m, 1H), 1.78 - 1.60 (m, 2H), 1.58 - 1.48 (m, 1H), 1.48 - 1.36 (m, 2H), 1.31 - 1.22 (m, 1H), 0.89 - 0.80 (m, 2H), 0.77 - 0.65 (m, 2H).	B

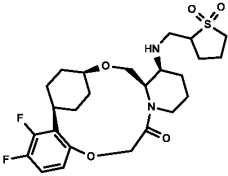
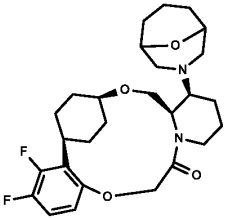
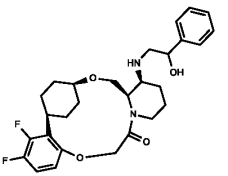
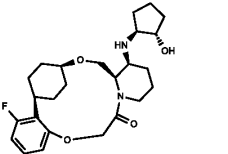
114		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-({[(2R)-5-oxopyrrolidin-2-yl]methyl}amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 478.3	¹ H NMR (400 MHz, MeOD) δ 7.02 (q, J = 9.1 Hz, 1H), 6.65 (ddd, J = 1.9, 3.7, 9.0 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.26 - 5.17 (m, 1H), 4.10 (d, J = 10.6 Hz, 1H), 3.93 (br t, J = 10.2 Hz, 1H), 3.87 - 3.74 (m, 2H), 3.71 (br s, 1H), 3.54 - 3.40 (m, 2H), 3.22 - 3.09 (m, 1H), 2.98 - 2.59 (m, 4H), 2.44 - 2.15 (m, 5H), 1.98 - 1.76 (m, 4H), 1.72 - 1.19 (m, 6H).	D
115		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-({[(1,3-thiazol-2-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 478.4	¹ H NMR (400 MHz, MeOD) δ 7.72 (d, J = 3.4 Hz, 1H), 7.51 (d, J = 3.4 Hz, 1H), 7.09 - 6.95 (m, 1H), 6.64 (ddd, J = 2.0, 3.8, 9.0 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.26 - 5.16 (m, 1H), 4.26 - 4.14 (m, 2H), 4.09 (d, J = 10.5 Hz, 1H), 3.96 (dd, J = 9.5, 10.9 Hz, 1H), 3.76 (br d, J = 14.0 Hz, 1H), 3.71 (br s, 1H), 3.56 (dd, J = 3.9, 9.2 Hz, 1H), 3.52 - 3.39 (m, 1H), 3.22 - 3.10 (m, 1H), 2.99 - 2.85 (m, 1H), 2.78 - 2.61 (m, 1H), 2.36 - 2.23 (m, 1H), 2.25 - 2.15 (m, 1H), 1.99 - 1.74 (m, 3H), 1.65 - 1.18 (m, 6H).	D
116		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-({[(1,2,4-oxadiazol-3-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 463.4	¹ H NMR (400 MHz, MeOD) δ 9.20 (s, 1H), 7.10 - 6.93 (m, 1H), 6.64 (ddd, J = 1.9, 3.7, 9.0 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.25 - 5.18 (m, 1H), 4.09 (d, J = 10.5 Hz, 1H), 4.05 (s, 2H), 3.94 (dd, J = 9.6, 11.2 Hz, 1H), 3.76 (br d, J = 12.8 Hz, 1H), 3.70 (br s, 1H), 3.53 (dd, J = 3.9, 9.3 Hz, 1H), 3.51 - 3.39 (m, 1H), 3.21 - 3.10 (m, 1H), 2.97 - 2.88 (m, 1H), 2.77 - 2.61 (m, 1H), 2.36 - 2.22 (m, 1H), 2.26 - 2.11 (m, 1H), 1.96 - 1.75 (m, 3H), 1.59 - 1.14 (m, 6H).	D
117		Rel-2- {[(1s,15S,16R,19s)-3,4-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-	[M+H] ⁺ 488.4	¹ H NMR (500 MHz, MeOD) δ 7.02 (q, J = 9.2 Hz, 1H), 6.70 - 6.58 (m, 1H), 5.36 - 5.25 (m, 1H), 5.20 - 5.05 (m, 1H), 4.10 (dd, J = 1.9, 10.6 Hz, 1H), 4.00 - 3.86 (m, 1H), 3.85 - 3.73 (m, 1H), 3.73 - 3.67 (m, 1H), 3.63 - 3.47 (m, 1H), 3.48 - 3.41 (m, 1H), 3.25 - 3.11 (m, 1H), 3.11 - 2.93	A

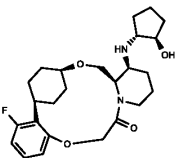
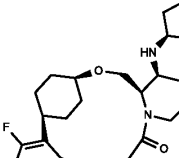
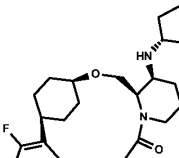
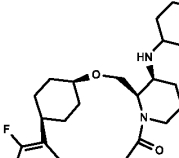
		trien-15-yl]amino}cyclohexane-1-carbonitrile		(m, 1H), 2.92 - 2.73 (m, 1H), 3.46 - 2.39 (m, 1H), 2.76 - 0.96 (m, 20H).	
118		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]trien-10-one	[M+H] ⁺ 463.3	¹ H NMR (500 MHz, MeOD) δ 7.11 - 6.95 (m, 1H), 6.82 - 6.56 (m, 1H), 5.36 - 5.28 (m, 1H), 5.20 - 5.04 (m, 1H), 4.59 - 4.38 (m, 1H), 4.13 - 4.08 (m, 1H), 3.93 - 3.83 (m, 1H), 3.75 - 3.66 (m, 1H), 4.25 - 3.38 (m, 6H), 3.22 - 3.06 (m, 2H), 2.92 - 2.78 (m, 1H), 2.75 - 2.55 (m, 2H), 2.43 - 1.14 (m, 13H).	C
119		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]trien-10-one	[M+H] ⁺ 463.6	¹ H NMR (400 MHz, MeOD) δ 7.12 - 6.92 (m, 1H), 6.75 - 6.54 (m, 1H), 5.37 - 5.26 (m, 1H), 5.24 - 5.02 (m, 1H), 4.46 (br s, 1H), 4.23 - 3.95 (m, 3H), 3.94 - 3.84 (m, 1H), 3.83 - 3.39 (m, 5H), 3.22 - 3.09 (m, 2H), 2.97 - 2.79 (m, 1H), 2.78 - 2.58 (m, 2H), 2.38 - 1.18 (m, 13H).	D
120		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-{3-oxa-8-azabicyclo[3.2.1]octan-8-yl}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]trien-10-one	[M+H] ⁺ 477.3	¹ H NMR (500 MHz, MeOD) δ 7.11 - 6.90 (m, 1H), 6.79 - 6.52 (m, 1H), 5.38 - 5.26 (m, 1H), 5.26 - 5.12 (m, 1H), 4.17 - 4.09 (m, 1H), 4.08 - 3.40 (m, 11H), 3.23 - 3.09 (m, 1H), 2.77 - 2.69 (m, 1H), 2.68 (br s, 2H), 2.23 - 1.73 (m, 8H), 1.68 - 1.40 (m, 4H), 1.40 - 1.20 (m, 2H).	C
121		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-{6-oxa-3-azabicyclo[3.1.1]heptan-3-yl}-8,18-dioxo-11-azatetracyclo[1	[M+H] ⁺ 463.3	¹ H NMR (500 MHz, MeOD) δ 7.21 (q, J = 9.3 Hz, 1H), 6.76 - 6.64 (m, 1H), 5.32 (d, J = 10.4 Hz, 1H), 5.21 - 5.09 (m, 1H), 4.53 - 4.39 (m, 2H), 3.99 (d, J = 10.3 Hz, 1H), 3.86 (br t, J = 10.3 Hz, 1H), 3.68 (br d, J = 11.9 Hz, 1H), 3.64 - 3.60 (m, 1H), 3.41 - 3.31 (m, 2H), 3.23 - 3.13 (m, 1H), 3.09 - 2.99 (m, 2H), 2.88 - 2.79 (m, 1H),	D

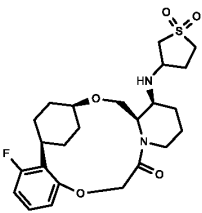
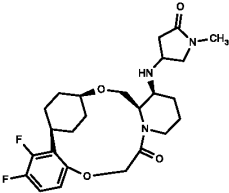
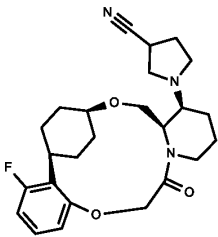
		7.2.2.0 ^{2,7,011,16} t ricosa-2(7),3,5- trien-10-one		2.72 - 2.60 (m, 3H), 2.60 - 2.51 (m, 1H), 2.31 - 2.13 (m, 2H), 2.13 - 2.07 (m, 1H), 2.03 - 1.07 (m, 9H).	
122		Rel-3- ({(1s,15S,16R, 19s)-3,4- difluoro-10- oxo-8,18-dioxa- 11- azatetracyclo[1 7.2.2.0 ^{2,7,011,16} t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)-1λ ⁶ - thietane-1,1- dione	[M+H] ⁺ 499.3	¹ H NMR (500 MHz, MeOD) δ 7.03 (q, J = 9.1 Hz, 1H), 6.73 - 6.59 (m, 1H), 5.32 (d, J = 10.6 Hz, 2H), 4.41 - 4.27 (m, 2H), 4.13 (d, J = 10.7 Hz, 1H), 4.08 - 3.95 (m, 3H), 3.84 (br d, J = 13.3 Hz, 1H), 3.79 - 3.71 (m, 1H), 3.59 - 3.48 (m, 1H), 3.46 - 3.33 (m, 4H), 3.23 - 3.12 (m, 1H), 2.98 - 2.83 (m, 1H), 2.75 - 2.59 (m, 1H), 2.34 - 2.18 (m, 2H), 2.15 - 1.21 (m, 9H).	C
123		Rel- (1s,15S,16R,19 s)-3,4-difluoro- 15-{{(3R)-2- oxopyrrolidin- 3-yl]amino}- 8,18-dioxa-11- azatetracyclo[1 7.2.2.0 ^{2,7,011,16} t ricosa-2(7),3,5- trien-10-one	[M+H] ⁺ 464.4	¹ H NMR (500 MHz, MeOD) δ 7.09 - 6.94 (m, 1H), 6.80 - 6.55 (m, 1H), 5.33 - 5.05 (m, 2H), 4.14 - 4.07 (m, 1H), 4.01 - 3.91 (m, 1H), 3.89 - 3.43 (m, 5H), 3.40 - 3.32 (m, 2H), 3.21 - 3.10 (m, 1H), 3.07 - 2.97 (m, 1H), 2.60 - 2.49 (m, 1H), 2.76 - 2.23 (m, 2H), 2.00 - 1.76 (m, 3H), 2.22 - 1.75 (m, 2H), 1.70 - 1.53 (m, 2H), 1.53 - 1.40 (m, 2H), 1.39 - 1.21 (m, 2H).	D
124		Rel- (1s,15S,16R,19 s)-3,4-difluoro- 15-{{(3S)-2- oxopyrrolidin- 3-yl]amino}- 8,18-dioxa-11- azatetracyclo[1 7.2.2.0 ^{2,7,011,16} t ricosa-2(7),3,5- trien-10-one	[M+H] ⁺ 464.4	¹ H NMR (400 MHz, MeOD) δ 7.13 - 6.90 (m, 1H), 6.81 - 6.56 (m, 1H), 5.30 (d, J = 10.6 Hz, 1H), 5.29 - 5.07 (m, 1H), 4.10 (d, J = 10.6 Hz, 1H), 4.02 - 3.90 (m, 1H), 3.78 (br d, J = 13.7 Hz, 1H), 3.74 - 3.68 (m, 1H), 3.68 - 3.54 (m, 1H), 3.55 - 3.40 (m, 2H), 3.40 - 3.33 (m, 2H), 3.24 - 3.10 (m, 1H), 3.08 - 2.96 (m, 1H), 2.78 - 2.63 (m, 1H), 2.61 - 2.48 (m, 1H), 2.37 - 2.14 (m, 2H), 2.01 - 1.77 (m, 4H), 1.73 - 1.19 (m, 6H).	D
125		Rel- (1s,15S,16R,19 s)-3,4-difluoro- 15-{{[(5-methyl- 1,3-oxazol-4- yl)methyl]amin o}-8,18-dioxa- 11-	[M+H] ⁺ 476.4	¹ H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.06 - 6.93 (m, 1H), 6.78 - 6.49 (m, 1H), 5.31 - 5.26 (m, 1H), 5.26 - 5.17 (m, 1H), 4.13 - 4.04 (m, 1H), 3.97 - 3.87 (m, 1H), 3.80 - 3.68 (m, 4H), 3.55 - 3.41 (m, 2H), 3.22 - 3.06 (m, 1H), 2.96 - 2.79 (m, 1H), 2.41 - 2.36 (m, 3H), 2.76 - 2.24 (m,	D

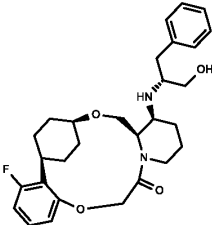
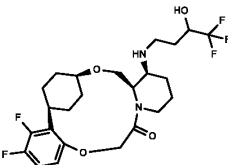
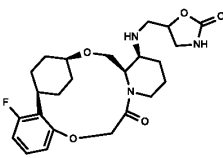
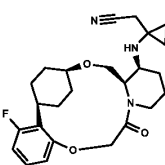
		azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-10-one		2H), 2.24 - 1.85 (m, 2H), 1.85 - 1.74 (m, 2H), 1.69 - 1.53 (m, 2H), 1.52 - 1.20 (m, 4H).	
126		Rel- (1s,15S,16R,19 s)-3,4-difluoro- 15-{[3- (fluoromethyl)oxetan-3- yl]amino}- 8,18-dioxa-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-10-one	[M+H] ⁺ 469.4	¹ H NMR (400 MHz, MeOD) δ 7.06 - 6.97 (m, 1H), 6.64 (ddd, J = 2.0, 3.6, 9.0 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 4.99 - 4.91 (m, 1H), 4.67 - 4.56 (m, 2H), 4.79 - 4.55 (m, 2H), 4.50 (d, J = 6.5 Hz, 2H), 4.10 (d, J = 10.5 Hz, 1H), 3.99 - 3.90 (m, 1H), 3.79 - 3.68 (m, 2H), 3.63 (dd, J = 3.9, 9.0 Hz, 1H), 3.51 - 3.41 (m, 1H), 3.22 - 3.09 (m, 1H), 3.06 - 2.98 (m, 1H), 2.76 - 2.63 (m, 1H), 2.35 - 2.24 (m, 1H), 2.23 - 2.11 (m, 1H), 1.88 - 1.68 (m, 3H), 1.68 - 1.33 (m, 5H), 1.31 - 1.21 (m, 1H).	B
127		Rel- (1s,15S,16R,19 s)-3,4-difluoro- 15-[(2- hydroxyethyl)amino]-8,18- dioxa-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-10-one	[M+H] ⁺ 425.4	¹ H NMR (400 MHz, MeOD) δ 7.10 - 6.97 (m, 1H), 6.65 (ddd, J = 1.9, 3.8, 8.9 Hz, 1H), 5.38 - 5.26 (m, 2H), 4.12 (d, J = 10.5 Hz, 1H), 4.02 - 3.93 (m, 1H), 3.82 (br d, J = 11.6 Hz, 1H), 3.80 - 3.75 (m, 2H), 3.74 (br s, 1H), 3.56 - 3.46 (m, 1H), 3.40 (dd, J = 3.8, 9.2 Hz, 1H), 3.26 - 3.19 (m, 1H), 3.21 - 3.11 (m, 1H), 3.07 (t, J = 5.3 Hz, 2H), 2.75 - 2.61 (m, 1H), 2.33 - 2.15 (m, 2H), 2.03 (br d, J = 8.8 Hz, 1H), 1.93 (br d, J = 6.9 Hz, 1H), 1.83 (br d, J = 13.4 Hz, 1H), 1.73 - 1.60 (m, 2H), 1.57 - 1.48 (m, 1H), 1.47 - 1.35 (m, 2H), 1.32 - 1.22 (m, 1H).	C
128		Rel- (1s,15R,16R,19 s)-3,4-difluoro- 15-{8-oxa-3- azabicyclo[3.2. 1]octan-3-yl}- 8,18-dioxa-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-10-one	[M+H] ⁺ 477.3	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.21 (q, J = 9.3 Hz, 1H), 6.72 - 6.62 (m, 1H), 5.34 (d, J = 10.3 Hz, 1H), 4.92 (br d, J = 9.9 Hz, 1H), 4.28 - 4.17 (m, 2H), 3.95 (d, J = 10.3 Hz, 1H), 3.89 (t, J = 9.6 Hz, 1H), 3.69 (br d, J = 10.9 Hz, 1H), 3.65 - 3.60 (m, 1H), 3.48 - 3.39 (m, 1H), 3.14 (br dd, J = 3.6, 8.9 Hz, 1H), 3.09 - 2.95 (m, 2H), 2.71 - 2.56 (m, 2H), 2.29 - 2.09 (m, 4H), 1.85 - 1.09 (m, 14H).	D

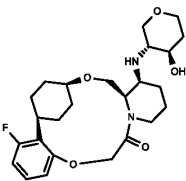
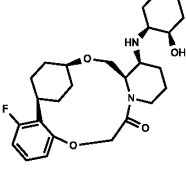
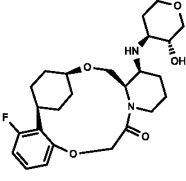
129		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-{8-oxa-3-azabicyclo[3.2.1]octan-3-yl}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-10-one	[M+H] ⁺ 477.6	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.30 - 7.13 (m, 1H), 6.67 (td, J = 2.0, 7.3 Hz, 1H), 5.30 (d, J = 10.4 Hz, 1H), 5.15 - 5.01 (m, 1H), 4.32 - 4.17 (m, 2H), 3.97 (d, J = 10.4 Hz, 1H), 3.81 (t, J = 10.4 Hz, 1H), 3.69 - 3.58 (m, 2H), 3.39 - 3.30 (m, 1H), 3.29 - 3.20 (m, 1H), 3.10 - 2.97 (m, 1H), 2.84 - 2.72 (m, 1H), 2.70 - 2.56 (m, 2H), 2.28 - 2.09 (m, 4H), 1.87 - 1.09 (m, 14H).	C
130		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-[(1-methanesulfonylcyclobutyl)methylamino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-10-one	[M+H] ⁺ 527.4	¹ H NMR (400 MHz, MeOD) δ 7.10 - 6.94 (m, 1H), 6.65 (ddd, J = 1.9, 3.6, 9.0 Hz, 1H), 5.31 (d, J = 10.5 Hz, 1H), 5.26 - 5.17 (m, 1H), 4.11 (d, J = 10.5 Hz, 1H), 3.98 - 3.89 (m, 1H), 3.78 (br d, J = 11.8 Hz, 1H), 3.70 (br s, 1H), 3.54 - 3.41 (m, 2H), 3.29 - 3.23 (m, 2H), 3.20 - 3.09 (m, 1H), 2.96 (s, 3H), 2.93 - 2.82 (m, 1H), 2.77 - 2.56 (m, 3H), 2.37 - 2.23 (m, 1H), 2.22 - 1.96 (m, 5H), 1.95 - 1.76 (m, 3H), 1.70 - 1.56 (m, 1H), 1.56 - 1.45 (m, 2H), 1.45 - 1.33 (m, 2H), 1.30 - 1.20 (m, 1H).	B
131		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-[(2-methanesulfonylpropyl)amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-10-one	[M+H] ⁺ 501.6	¹ H NMR (500 MHz, MeOD) δ 7.09 - 6.96 (m, 1H), 6.70 - 6.59 (m, 1H), 5.30 (d, J = 10.6 Hz, 1H), 5.23 - 5.12 (m, 1H), 4.10 (d, J = 10.4 Hz, 1H), 3.97 - 3.86 (m, 1H), 3.77 (br d, J = 11.8 Hz, 1H), 3.70 (br s, 1H), 3.52 - 3.42 (m, 2H), 3.28 - 3.11 (m, 3H), 3.04 - 2.99 (m, 3H), 2.98 - 2.91 (m, 1H), 2.90 - 2.82 (m, 1H), 2.76 - 2.63 (m, 1H), 2.28 (dq, J = 3.8, 12.9 Hz, 1H), 2.19 (br d, J = 13.2 Hz, 1H), 1.91 - 1.77 (m, 3H), 1.69 - 1.57 (m, 1H), 1.56 - 1.46 (m, 2H), 1.44 - 1.34 (m, 5H), 1.29 - 1.20 (m, 1H).	C
132		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-[(1-methanesulfonylcyclopropyl)methylamino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-10-one	[M+H] ⁺ 513.4	¹ H NMR (400 MHz, MeOD) δ 7.02 (q, J = 9.2 Hz, 1H), 6.64 (ddd, J = 1.9, 3.7, 9.1 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.24 - 5.12 (m, 1H), 4.10 (d, J = 10.5 Hz, 1H), 3.99 - 3.87 (m, 1H), 3.77 (br d, J = 12.8 Hz, 1H), 3.73 - 3.66 (m, 1H), 3.53 - 3.41 (m, 2H), 3.22 - 3.15 (m, 1H), 3.13 (s, 3H), 3.14 - 3.08 (m, 1H), 3.08 - 3.01 (m, 1H), 2.86 (td, J = 4.7, 11.5 Hz, 1H), 2.79 - 2.63 (m, 1H), 2.38 - 2.22 (m, 1H), 2.22	B

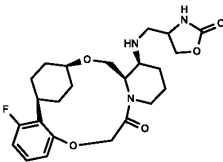
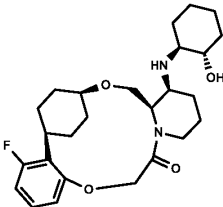
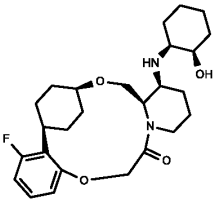
		ricosa-2(7),3,5-trien-10-one		- 2.13 (m, 1H), 1.96 - 1.77 (m, 3H), 1.70 - 0.98 (m, 10H).	
133		Rel-2- ({(1s,15S,16R,19s)-3,4-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5-trien-15-yl]amino}methyl)-1λ ⁶ -thiolane-1,1-dione	[M+H] ⁺ 513.6	¹ H NMR (400 MHz, MeOD) δ 7.03 (q, J = 9.1 Hz, 1H), 6.75 - 6.60 (m, 1H), 5.49 - 5.38 (m, 1H), 5.32 (d, J = 10.6 Hz, 1H), 4.14 (d, J = 10.6 Hz, 1H), 4.03 (dt, J = 4.7, 10.1 Hz, 1H), 3.92 - 3.82 (m, 1H), 3.81 - 3.76 (m, 1H), 3.75 - 3.65 (m, 1H), 3.63 - 3.51 (m, 2H), 3.50 - 3.34 (m, 3H), 3.27 - 2.98 (m, 3H), 2.77 - 1.21 (m, 16H).	D
134		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-{9-oxa-3-azabicyclo[3.3.1]nonan-3-yl}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 491.6	¹ H NMR (400 MHz, MeOD) δ 7.02 (q, J = 9.1 Hz, 1H), 6.65 (ddd, J = 1.9, 3.8, 9.0 Hz, 1H), 5.31 (d, J = 10.5 Hz, 1H), 5.28 - 5.20 (m, 1H), 4.11 (d, J = 10.5 Hz, 1H), 3.94 - 3.87 (m, 1H), 4.01 - 3.85 (m, 4H), 3.84 - 3.73 (m, 1H), 3.68 (br s, 1H), 3.53 - 3.42 (m, 2H), 3.39 - 3.33 (m, 1H), 3.21 - 3.07 (m, 1H), 3.06 - 2.87 (m, 2H), 2.80 - 1.19 (m, 18H).	C
135		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-[(2-hydroxy-2-phenylethyl)amino]-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5-trien-10-one	[M+H] ⁺ 501.4	¹ H NMR (400 MHz, MeOD) δ 7.52 - 7.27 (m, 5H), 7.09 - 6.97 (m, 1H), 6.65 (ddd, J = 2.0, 3.5, 9.2 Hz, 1H), 5.42 - 5.25 (m, 2H), 4.92 (dd, J = 3.3, 9.7 Hz, 1H), 4.16 - 4.09 (m, 1H), 4.04 - 3.96 (m, 1H), 3.89 - 3.80 (m, 1H), 3.78 - 3.72 (m, 1H), 3.58 - 3.45 (m, 1H), 3.43 - 3.33 (m, 2H), 3.25 - 3.09 (m, 3H), 2.76 - 2.60 (m, 1H), 2.38 - 1.21 (m, 11H).	D
136		Rel- (1s,15S,16R,19s)-3-fluoro-15-[(1S,2S)-2-hydroxycyclopentyl]amino-8,18-dioxo-11-azatetracyclo[1	[M+H] ⁺ 447.5	¹ H NMR (400 MHz, MeOD) δ 7.21 - 7.07 (m, 1H), 6.78 - 6.63 (m, 2H), 5.45 - 5.26 (m, 2H), 4.20 - 4.12 (m, 1H), 4.11 - 4.05 (m, 1H), 4.04 - 3.96 (m, 1H), 3.84 (br d, J = 13.7 Hz, 1H), 3.75 (br s, 1H), 3.60 - 3.34 (m, 4H), 3.22 - 3.10 (m, 1H), 2.76 - 2.61 (m, 1H), 2.35 - 2.14 (m, 3H), 2.13 - 1.99 (m, 2H), 1.94 (br d, J = 9.1	C

		7.2.2.0 ² , 7.0 ¹¹ , ¹⁶ t ricosa-2,4,6- trien-10-one		Hz, 1H), 1.88 - 1.73 (m, 3H), 1.73 - 1.60 (m, 3H), 1.60 - 1.49 (m, 2H), 1.47 - 1.35 (m, 2H), 1.28 - 1.20 (m, 1H).	
137		Rel- (1s,15S,16R,19 s)-3-fluoro-15- {[(1R,2R)-2- hydroxycyclope ntyl]amino}- 8,18-dioxa-11- azatetracyclo[1 7.2.2.0 ² , 7.0 ¹¹ , ¹⁶ t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 447.5	¹ H NMR (400 MHz, MeOD) δ 7.19 - 7.08 (m, 1H), 6.76 - 6.61 (m, 2H), 5.33 (d, J = 10.6 Hz, 1H), 5.49 - 5.28 (m, 1H), 4.21 - 4.10 (m, 2H), 4.07 - 3.96 (m, 1H), 3.86 (br d, J = 13.6 Hz, 1H), 3.76 (br s, 1H), 3.69 - 3.50 (m, 2H), 3.50 - 3.41 (m, 1H), 3.40 - 3.34 (m, 1H), 3.23 - 3.09 (m, 1H), 2.76 - 2.60 (m, 1H), 2.34 - 2.18 (m, 3H), 2.18 - 2.12 (m, 1H), 2.11 - 2.01 (m, 1H), 1.97 (br d, J = 14.0 Hz, 1H), 1.88 - 1.76 (m, 3H), 1.77 - 1.56 (m, 4H), 1.57 - 1.46 (m, 1H), 1.48 - 1.36 (m, 2H), 1.28 - 1.19 (m, 1H).	C
138		Rel- (1s,15S,16R,19 s)-3-fluoro-15- {[(1S,2R)-2- hydroxycyclope ntyl]amino}- 8,18-dioxa-11- azatetracyclo[1 7.2.2.0 ² , 7.0 ¹¹ , ¹⁶ t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 447.5	¹ H NMR (500 MHz, CDCl ₃) δ 7.09 (q, J = 7.7 Hz, 1H), 6.71 (t, J = 8.9 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 5.41 - 5.30 (m, 1H), 5.09 (d, J = 10.3 Hz, 1H), 4.36 - 4.28 (m, 1H), 4.28 - 4.13 (m, 1H), 3.99 - 3.87 (m, 1H), 3.79 - 3.72 (m, 1H), 3.67 (br d, J = 10.2 Hz, 1H), 3.55 - 3.44 (m, 2H), 3.39 - 3.23 (m, 1H), 3.22 - 3.09 (m, 2H), 2.65 - 2.53 (m, 1H), 2.26 - 2.15 (m, 1H), 2.17 - 1.36 (m, 15H), 1.33 (br d, J = 15.9 Hz, 1H).	C
139		Rel- (1s,15S,16R,19 s)-3-fluoro-15- {[(1R,2S)-2- hydroxycyclope ntyl]amino}- 8,18-dioxa-11- azatetracyclo[1 7.2.2.0 ² , 7.0 ¹¹ , ¹⁶ t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 447.5	¹ H NMR (500 MHz, CDCl ₃) δ 7.13 - 7.06 (m, 1H), 6.74 - 6.67 (m, 1H), 6.54 (d, J = 8.1 Hz, 1H), 5.40 - 5.30 (m, 1H), 5.09 (d, J = 10.4 Hz, 1H), 4.31 (dd, J = 4.4, 10.4 Hz, 1H), 4.29 - 4.14 (m, 1H), 3.99 - 3.87 (m, 1H), 3.75 (br d, J = 16.1 Hz, 1H), 3.72 - 3.64 (m, 1H), 3.55 - 3.45 (m, 2H), 3.38 - 3.24 (m, 1H), 3.22 - 3.10 (m, 2H), 2.66 - 2.55 (m, 1H), 2.26 - 2.15 (m, 1H), 2.17 - 1.37 (m, 15H), 1.36 - 1.29 (m, 1H).	B
140		Rel-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxa-11- azatetracyclo[1 7.2.2.0 ² , 7.0 ¹¹ , ¹⁶ t	[M+H] ⁺ 495.4	¹ H NMR (400 MHz, MeOD) δ 7.20 - 7.07 (m, 1H), 6.75 - 6.61 (m, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.18 - 5.05 (m, 1H), 4.12 (d, J = 10.5 Hz, 1H), 3.92 (br t, J = 10.1 Hz, 1H), 3.83 - 3.74 (m, 1H), 3.70 (br s, 1H), 3.55 - 3.41 (m, 2H), 3.36 - 3.19 (m, 2H), 3.20 - 3.08 (m, 1H), 3.06 -	D

		ricosa-2,4,6-trien-15-yl]amino}-1 λ^6 -thiane-1,1-dione		2.96 (m, 3H), 2.93 - 2.81 (m, 1H), 2.77 - 2.61 (m, 1H), 2.30 (dq, J = 4.0, 13.0 Hz, 1H), 2.22 - 2.09 (m, 1H), 2.22 - 1.90 (m, 3H), 1.88 - 1.73 (m, 3H), 1.72 - 1.58 (m, 1H), 1.58 - 1.43 (m, 2H), 1.43 - 1.31 (m, 3H), 1.27 - 1.17 (m, 1H).	
141		Rel-3- {[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tetracyclic-ricosa-2,4,6-trien-15-yl]amino}-1 λ^6 -thiolane-1,1-dione	[M+H] ⁺ 481.4	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.6, 8.2 Hz, 1H), 6.75 - 6.61 (m, 2H), 5.31 (d, J = 10.5 Hz, 1H), 5.20 - 5.08 (m, 1H), 4.13 (d, J = 10.5 Hz, 1H), 3.92 (t, J = 10.2 Hz, 1H), 3.83 - 3.73 (m, 2H), 3.70 (br s, 1H), 3.55 - 3.42 (m, 3H), 3.34 - 3.24 (m, 1H), 3.20 - 3.05 (m, 2H), 2.99 - 2.85 (m, 2H), 2.76 - 2.62 (m, 1H), 2.55 - 2.39 (m, 1H), 2.30 (dq, J = 3.9, 13.0 Hz, 1H), 2.18 (br d, J = 13.2 Hz, 1H), 2.12 - 1.97 (m, 1H), 1.94 - 1.76 (m, 3H), 1.71 - 1.56 (m, 1H), 1.58 - 1.44 (m, 2H), 1.44 - 1.32 (m, 2H), 1.28 - 1.18 (m, 1H).	B
142		Rel- (1s,15S,16R,19s)-3,4-difluoro-15-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tetracyclic-ricosa-2,4,6-trien-10-one	[M+H] ⁺ 478.4	¹ H NMR (400 MHz, MeOD) δ 7.09 - 6.96 (m, 1H), 6.70 - 6.60 (m, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.22 - 5.09 (m, 1H), 4.10 (d, J = 10.6 Hz, 1H), 3.92 (t, J = 10.2 Hz, 1H), 3.82 - 3.65 (m, 4H), 3.53 - 3.40 (m, 2H), 3.29 - 3.21 (m, 1H), 3.21 - 3.10 (m, 1H), 3.00 - 2.88 (m, 1H), 2.85 (s, 3H), 2.76 - 2.63 (m, 2H), 2.35 - 2.22 (m, 2H), 2.19 (br d, J = 13.3 Hz, 1H), 1.94 - 1.77 (m, 3H), 1.70 - 1.57 (m, 1H), 1.58 - 1.45 (m, 2H), 1.45 - 1.33 (m, 2H), 1.30 - 1.20 (m, 1H).	D
143		Rel-1- [(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tetracyclic-ricosa-2,4,6-trien-15-yl]pyrrolidine-3-carbonitrile	[M+H] ⁺ 442.4	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.2 Hz, 1H), 6.75 - 6.64 (m, 2H), 5.31 (d, J = 10.5 Hz, 1H), 5.24 - 5.15 (m, 1H), 4.13 (d, J = 10.5 Hz, 1H), 3.97 (t, J = 10.4 Hz, 1H), 3.82 - 3.74 (m, 1H), 3.73 - 3.66 (m, 1H), 3.56 - 3.44 (m, 2H), 3.25 - 3.08 (m, 2H), 2.99 - 2.84 (m, 3H), 2.77 - 2.58 (m, 2H), 2.42 (td, J = 4.7, 11.4 Hz, 1H), 2.36 - 2.24 (m, 2H), 2.23 - 2.13 (m, 1H), 2.12 - 2.00 (m, 1H), 2.00 - 1.92 (m, 1H), 1.91 - 1.84 (m, 1H), 1.84 - 1.77 (m, 1H), 1.69 - 1.54 (m, 2H), 1.54 - 1.44 (m, 1H), 1.44 - 1.32 (m, 2H), 1.27 - 1.19 (m, 1H).	C

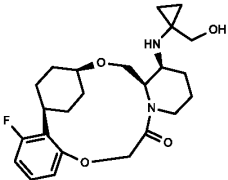
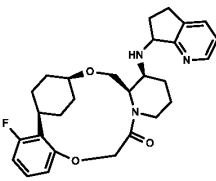
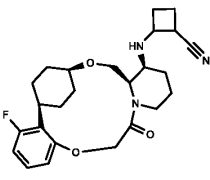
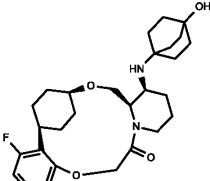
144		Rel-(1s,15S,16R,19s)-3-fluoro-15-([(2R)-1-hydroxy-3-phenylpropan-2-yl]amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 515.4	¹ H NMR (400 MHz, MeOD) δ 7.35 - 7.24 (m, 4H), 7.24 - 7.15 (m, 1H), 7.07 - 6.95 (m, 1H), 6.68 - 6.56 (m, 1H), 5.32 - 5.23 (m, 1H), 5.29 - 5.00 (m, 1H), 4.13 - 4.04 (m, 1H), 3.93 - 3.34 (m, 6H), 3.20 - 3.10 (m, 1H), 3.10 - 3.01 (m, 1H), 2.97 (td, J = 4.8, 12.1 Hz, 1H), 3.55 - 2.74 (m, 1H), 2.90 - 2.53 (m, 3H), 2.36 - 2.17 (m, 1H), 2.20 - 1.98 (m, 1H), 1.87 - 1.67 (m, 3H), 1.64 - 1.16 (m, 6H).	C
145		Rel-(1s,15S,16R,19s)-3,4-difluoro-15-[(4,4,4-trifluoro-3-hydroxybutyl)amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 507.4	¹ H NMR (400 MHz, MeOD) δ 7.13 - 6.94 (m, 1H), 6.72 - 6.59 (m, 1H), 5.31 (d, J = 10.5 Hz, 1H), 5.29 - 5.19 (m, 1H), 4.19 - 4.05 (m, 2H), 4.00 - 3.88 (m, 1H), 3.80 (br d, J = 13.3 Hz, 1H), 3.72 (br s, 1H), 3.55 - 3.45 (m, 1H), 3.44 - 3.38 (m, 1H), 3.24 - 3.10 (m, 1H), 3.09 - 2.95 (m, 3H), 2.77 - 2.60 (m, 1H), 2.35 - 2.12 (m, 2H), 2.01 - 1.77 (m, 5H), 1.74 - 1.33 (m, 5H), 1.32 - 1.19 (m, 1H).	D
146		Rel-(1s,15S,16R,19s)-3-fluoro-15-([(2-oxo-1,3-oxazolidin-5-yl)methyl]amino)-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 462.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.74 - 6.64 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.26 - 5.16 (m, 1H), 4.83 - 4.72 (m, 1H), 4.12 (d, J = 10.6 Hz, 1H), 3.98 - 3.89 (m, 1H), 3.78 (br d, J = 13.9 Hz, 1H), 3.73 - 3.65 (m, 2H), 3.54 - 3.42 (m, 2H), 3.38 (ddd, J = 6.8, 8.9, 15.5 Hz, 1H), 3.19 - 3.10 (m, 1H), 3.05 - 2.98 (m, 2H), 2.98 - 2.90 (m, 1H), 2.75 - 2.64 (m, 1H), 2.30 (dq, J = 4.0, 13.0 Hz, 1H), 2.19 (br d, J = 13.3 Hz, 1H), 1.94 - 1.83 (m, 2H), 1.81 (br dd, J = 1.8, 13.0 Hz, 1H), 1.69 - 1.58 (m, 1H), 1.61 - 1.53 (m, 1H), 1.52 - 1.44 (m, 1H), 1.44 - 1.32 (m, 2H), 1.27 - 1.18 (m, 1H).	B
147		Rel-2-(1-([(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 442.4	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.6, 8.2 Hz, 1H), 6.74 - 6.61 (m, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.12 - 5.01 (m, 1H), 4.12 (d, J = 10.5 Hz, 1H), 3.93 - 3.84 (m, 1H), 3.80 - 3.72 (m, 1H), 3.67 (br s, 1H), 3.53 (dd, J = 3.8, 9.4 Hz, 1H), 3.52 - 3.42 (m, 1H), 3.19 - 3.07 (m, 2H),	A

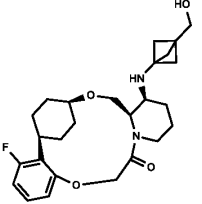
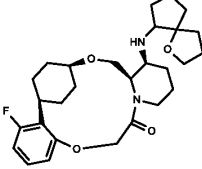
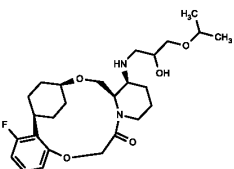
		ricosa-2,4,6-trien-15-yl]amino}cyclopropyl)acetonitrile		2.84 (d, J = 17.3 Hz, 1H), 2.78 - 2.65 (m, 1H), 2.65 (d, J = 17.3 Hz, 1H), 2.30 (dq, J = 3.9, 13.0 Hz, 1H), 2.21 - 2.11 (m, 1H), 1.89 - 1.76 (m, 3H), 1.73 - 1.59 (m, 1H), 1.58 - 1.31 (m, 4H), 1.27 - 1.17 (m, 1H), 0.89 - 0.65 (m, 4H).	
148		Rel-(1s,15S,16R,19s)-3-fluoro-15-yl]amino}cyclopropyl)acetonitrile	[M+H] ⁺ 463.5	¹ H NMR (500 MHz, CDCl ₃) δ 7.15 - 7.07 (m, 1H), 6.72 (t, J = 8.6 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 5.57 - 5.43 (m, 1H), 5.09 (d, J = 10.6 Hz, 1H), 4.36 - 4.29 (m, 1H), 4.25 (br dd, J = 4.7, 11.3 Hz, 1H), 4.21 - 4.09 (m, 1H), 4.06 - 3.96 (m, 2H), 3.88 - 3.73 (m, 2H), 3.77 - 3.50 (m, 3H), 3.50 - 3.40 (m, 2H), 3.23 (br s, 1H), 3.21 - 3.10 (m, 1H), 2.61 - 2.49 (m, 1H), 2.48 - 2.32 (m, 1H), 2.23 - 2.02 (m, 4H), 2.00 - 1.75 (m, 3H), 1.71 - 1.64 (m, 1H), 1.50 - 1.29 (m, 4H).	C
149		Rel-(1s,15S,16R,19s)-3-fluoro-15-yl]amino}cyclopropyl)acetonitrile	[M+H] ⁺ 463.5	¹ H NMR (500 MHz, MeOD) δ 7.20 - 7.08 (m, 1H), 6.75 - 6.64 (m, 2H), 5.37 - 5.29 (m, 1H), 5.30 - 5.21 (m, 1H), 4.14 (d, J = 10.4 Hz, 1H), 4.25 - 4.11 (m, 1H), 4.03 - 3.96 (m, 1H), 3.74 (br d, J = 2.3 Hz, 1H), 3.87 - 3.57 (m, 5H), 3.57 - 3.49 (m, 1H), 3.51 - 3.42 (m, 1H), 3.35 (s, 1H), 3.27 (br s, 1H), 3.19 - 3.09 (m, 1H), 2.74 - 2.63 (m, 1H), 2.34 - 2.23 (m, 1H), 2.20 (br d, J = 12.9 Hz, 1H), 2.08 - 1.89 (m, 2H), 1.93 - 1.77 (m, 3H), 1.76 - 1.64 (m, 2H), 1.55 - 1.46 (m, 1H), 1.46 - 1.35 (m, 2H), 1.28 - 1.20 (m, 1H).	C
150		Rel-(1s,15S,16R,19s)-3-fluoro-15-yl]amino}cyclopropyl)acetonitrile	[M+H] ⁺ 463.5	¹ H NMR (500 MHz, CDCl ₃) δ 7.14 - 7.06 (m, 1H), 6.70 (t, J = 8.9 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 5.34 - 5.13 (m, 1H), 5.13 - 5.06 (m, 1H), 4.34 - 4.26 (m, 1H), 4.06 (dd, J = 4.8, 11.0 Hz, 1H), 4.00 - 3.94 (m, 1H), 3.91 - 3.83 (m, 1H), 3.71 (br s, 1H), 3.70 - 3.62 (m, 1H), 3.59 - 3.52 (m, 1H), 3.52 - 3.33 (m, 3H), 3.25 - 3.09 (m, 3H), 2.67 - 2.56 (m, 1H), 2.91 - 2.56 (m, 1H), 2.29 - 2.03 (m, 3H), 2.02 - 1.52 (m, 5H), 1.50 - 1.28 (m, 5H).	C

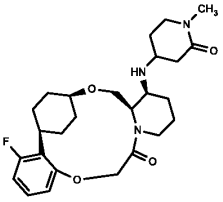
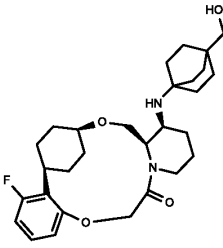
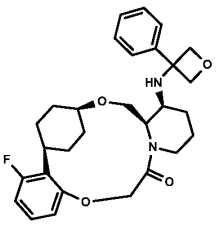
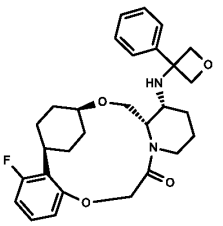
151		Rel-(1s,15S,16R,19s)-3-fluoro-15-{{[(2-oxo-1,3-oxazolidin-4-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 462.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.75 - 6.64 (m, 2H), 5.31 (d, J = 10.6 Hz, 1H), 5.22 - 5.13 (m, 1H), 4.54 - 4.46 (m, 1H), 4.24 - 4.18 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 4.02 - 3.95 (m, 1H), 3.95 - 3.89 (m, 1H), 3.78 (br dd, J = 2.3, 12.9 Hz, 1H), 3.70 (br s, 1H), 3.53 - 3.43 (m, 2H), 3.19 - 3.10 (m, 1H), 2.91 - 2.84 (m, 2H), 2.85 - 2.80 (m, 1H), 2.74 - 2.66 (m, 1H), 2.30 (dq, J = 4.1, 13.0 Hz, 1H), 2.23 - 2.13 (m, 1H), 1.92 - 1.83 (m, 2H), 1.84 - 1.77 (m, 1H), 1.62 (tq, J = 4.0, 13.0 Hz, 1H), 1.56 - 1.45 (m, 2H), 1.44 - 1.33 (m, 2H), 1.27 - 1.18 (m, 1H).	B
152		Rel-(1s,15S,16R,19s)-3-fluoro-15-{{[Rel-(1S,2S)-2-hydroxycyclohexyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 461.5	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.2 Hz, 1H), 6.75 - 6.61 (m, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.16 (dt, J = 4.9, 11.5 Hz, 1H), 4.12 (d, J = 10.5 Hz, 1H), 3.99 - 3.91 (m, 1H), 4.07 - 3.88 (m, 1H), 3.78 (br d, J = 13.6 Hz, 1H), 3.70 (br s, 1H), 3.48 (dt, J = 4.0, 9.0 Hz, 2H), 3.22 - 3.00 (m, 2H), 2.88 - 2.77 (m, 1H), 2.76 - 2.59 (m, 1H), 2.30 (dq, J = 3.8, 13.1 Hz, 1H), 2.19 (br d, J = 13.4 Hz, 1H), 1.96 - 1.78 (m, 3H), 1.86 - 1.12 (m, 14H).	C
153		Rel-(1s,15S,16R,19s)-3-fluoro-15-{{[(1S,2R)-2-hydroxycyclohexyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 461.5	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.2 Hz, 1H), 6.75 - 6.61 (m, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.16 (dt, J = 4.9, 11.5 Hz, 1H), 4.12 (d, J = 10.5 Hz, 1H), 3.99 - 3.91 (m, 1H), 4.07 - 3.88 (m, 1H), 3.78 (br d, J = 13.6 Hz, 1H), 3.70 (br s, 1H), 3.48 (dt, J = 4.0, 9.0 Hz, 2H), 3.22 - 3.00 (m, 2H), 2.88 - 2.77 (m, 1H), 2.76 - 2.59 (m, 1H), 2.30 (dq, J = 3.8, 13.1 Hz, 1H), 2.19 (br d, J = 13.4 Hz, 1H), 1.96 - 1.78 (m, 3H), 1.86 - 1.12 (m, 14H).	B

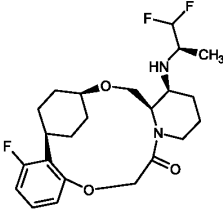
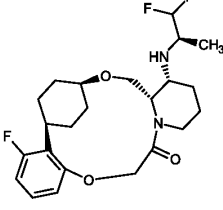
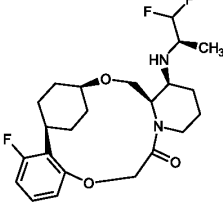
154		Rel-2- ({(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2,4,6- trien-15- yl]amino}meth yl)-1λ ⁶ - thietane-1,1- dione	[M+H] ⁺ 481.6	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.2 Hz, 1H), 6.80 - 6.63 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.26 - 5.14 (m, 1H), 4.58 - 4.48 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 4.10 - 3.93 (m, 2H), 3.95 - 3.86 (m, 1H), 3.82 - 3.73 (m, 1H), 3.70 (br s, 1H), 3.62 - 3.43 (m, 2H), 3.36 - 3.22 (m, 1H), 3.20 - 3.01 (m, 2H), 2.93 - 2.82 (m, 1H), 2.77 - 2.61 (m, 1H), 2.37 - 2.24 (m, 2H), 2.18 (br d, J = 14.1 Hz, 1H), 1.92 - 1.76 (m, 4H), 1.69 - 1.56 (m, 1H), 1.56 - 1.43 (m, 2H), 1.43 - 1.32 (m, 2H), 1.27 - 1.20 (m, 1H).	B
155		Rel-4-(2- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2,4,6- trien-15- yl]amino}ethyl) -1λ ⁶ - thiomorpholine -1,1-dione	[M+H] ⁺ 524.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.4, 8.2 Hz, 1H), 6.76 - 6.63 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.27 - 5.18 (m, 1H), 4.13 (d, J = 10.4 Hz, 1H), 3.94 (dd, J = 9.4, 11.0 Hz, 1H), 3.83 - 3.74 (m, 1H), 3.70 (br s, 1H), 3.55 - 3.46 (m, 1H), 3.45 (dd, J = 3.8, 9.3 Hz, 1H), 3.20 - 3.09 (m, 5H), 3.04 (br dd, J = 4.0, 6.2 Hz, 4H), 2.91 - 2.85 (m, 1H), 2.85 - 2.80 (m, 2H), 2.76 - 2.63 (m, 3H), 2.30 (dq, J = 4.1, 13.0 Hz, 1H), 2.24 - 2.14 (m, 1H), 1.92 - 1.77 (m, 3H), 1.68 - 1.58 (m, 1H), 1.58 - 1.45 (m, 2H), 1.45 - 1.33 (m, 2H), 1.27 - 1.18 (m, 1H).	D
156		Rel- (1s,15S,16R,19 s)-3-fluoro-15- {[3- (fluoromethyl)o xetan-3- yl]amino}- 8,18-dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 451.5	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.73 - 6.63 (m, 2H), 5.30 (d, J = 10.4 Hz, 1H), 5.00 - 4.93 (m, 1H), 4.77 - 4.61 (m, 3H), 4.62 - 4.57 (m, 1H), 4.51 (d, J = 6.6 Hz, 2H), 4.12 (d, J = 10.4 Hz, 1H), 3.95 (dd, J = 9.2, 11.0 Hz, 1H), 3.75 (br d, J = 13.7 Hz, 1H), 3.70 (br s, 1H), 3.63 (dd, J = 3.8, 9.1 Hz, 1H), 3.52 - 3.43 (m, 1H), 3.19 - 3.09 (m, 1H), 3.05 - 2.98 (m, 1H), 2.75 - 2.62 (m, 1H), 2.30 (dq, J = 4.2, 13.0 Hz, 1H), 2.23 - 2.13 (m, 1H), 1.87 - 1.79 (m, 2H), 1.77 - 1.71 (m, 1H), 1.69 - 1.56 (m, 2H), 1.48 (ddt, J = 1.4, 4.4, 13.4 Hz, 1H), 1.43 - 1.33 (m, 2H), 1.27 - 1.18 (m, 1H).	A

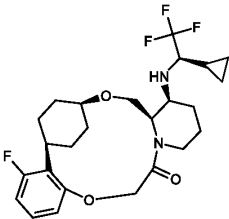
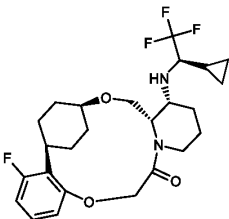
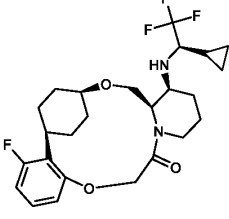
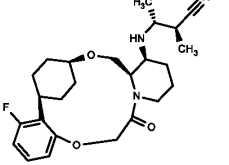
157		Rel-(1s,15S,16R,19s)-3-fluoro-15-{{[(1-hydroxycyclopropyl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 433.5	¹ H NMR (400 MHz, MeOD) δ 7.20 - 7.03 (m, 1H), 6.75 - 6.59 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.26 - 5.12 (m, 1H), 4.12 (d, J = 10.5 Hz, 1H), 4.00 - 3.89 (m, 1H), 3.78 (br d, J = 14.4 Hz, 1H), 3.69 (br s, 1H), 3.55 - 3.41 (m, 2H), 3.21 - 3.08 (m, 1H), 2.99 (td, J = 4.5, 11.7 Hz, 1H), 2.85 (d, J = 12.6 Hz, 1H), 2.77 (d, J = 12.6 Hz, 1H), 2.75 - 2.62 (m, 1H), 2.30 (dq, J = 4.2, 13.0 Hz, 1H), 2.23 - 2.13 (m, 1H), 1.94 - 1.74 (m, 3H), 1.70 - 1.52 (m, 2H), 1.53 - 1.43 (m, 1H), 1.44 - 1.31 (m, 2H), 1.27 - 1.16 (m, 1H), 0.79 - 0.45 (m, 4H).	C
158		Rel-(1s,15S,16R,19s)-3-fluoro-15-{{[(3-fluorooxolan-3-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 465.5	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.4, 8.2 Hz, 1H), 6.74 - 6.61 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.27 - 5.18 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 4.02 - 3.89 (m, 4H), 3.87 - 3.75 (m, 2H), 3.70 (br s, 1H), 3.54 - 3.42 (m, 2H), 3.21 - 3.03 (m, 3H), 2.97 - 2.86 (m, 1H), 2.75 - 2.64 (m, 1H), 2.37 - 2.25 (m, 1H), 2.25 - 2.04 (m, 3H), 1.93 - 1.84 (m, 2H), 1.83 - 1.76 (m, 1H), 1.69 - 1.59 (m, 1H), 1.62 - 1.53 (m, 1H), 1.53 - 1.45 (m, 1H), 1.44 - 1.33 (m, 2H), 1.27 - 1.18 (m, 1H).	B
159		Rel-3-{{[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2,4,6-trien-15-yl]amino}-1λ ⁶ -thietane-1,1-dione	[M+H] ⁺ 467.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.74 - 6.61 (m, 2H), 5.30 (d, J = 10.4 Hz, 1H), 5.16 - 5.05 (m, 1H), 4.40 - 4.32 (m, 2H), 4.12 (d, J = 10.4 Hz, 1H), 3.99 - 3.89 (m, 3H), 3.88 - 3.81 (m, 1H), 3.78 (br dd, J = 3.0, 13.9 Hz, 1H), 3.69 (br s, 1H), 3.55 - 3.45 (m, 2H), 3.19 - 3.10 (m, 1H), 2.86 - 2.79 (m, 1H), 2.74 - 2.63 (m, 1H), 2.29 (dq, J = 4.1, 13.0 Hz, 1H), 2.22 - 2.13 (m, 1H), 1.88 - 1.83 (m, 2H), 1.83 - 1.77 (m, 1H), 1.69 - 1.57 (m, 1H), 1.57 - 1.44 (m, 2H), 1.43 - 1.32 (m, 2H), 1.27 - 1.19 (m, 1H).	B

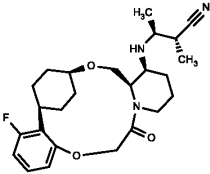
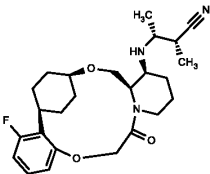
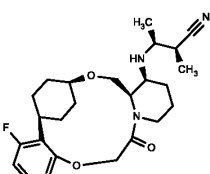
160		Rel- (1s,15S,16R,19s)-3-fluoro-15- {[1-(hydroxymethyl)cyclopropyl]amino}-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 433.5	¹ H NMR (500 MHz, MeOD) δ 7.18 - 7.06 (m, 1H), 6.75 - 6.62 (m, 2H), 5.39 - 5.27 (m, 1H), 5.18 - 5.05 (m, 1H), 4.17 - 4.07 (m, 1H), 4.01 - 3.85 (m, 1H), 3.85 - 3.35 (m, 6H), 3.29 - 3.09 (m, 2H), 2.77 - 2.62 (m, 1H), 2.37 - 2.24 (m, 1H), 2.23 - 2.12 (m, 1H), 1.94 - 0.47 (m, 13H).	B
161		Rel- (1s,15S,16R,19s)-15- ({5H,6H,7H-cyclopentyl}pyridin-7-yl)amino)-3-fluoro-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 480.4	¹ H NMR (500 MHz, MeOD) δ 8.39 - 8.32 (m, 1H), 7.75 - 7.68 (m, 1H), 7.24 (td, J = 4.8, 7.7 Hz, 1H), 7.17 - 7.09 (m, 1H), 6.74 - 6.65 (m, 2H), 5.33 (d, J = 10.4 Hz, 1H), 5.46 - 5.17 (m, 1H), 4.53 - 4.34 (m, 1H), 4.14 (dd, J = 1.4, 10.4 Hz, 1H), 4.08 - 3.96 (m, 1H), 3.80 (br d, J = 14.0 Hz, 1H), 3.76 - 3.68 (m, 1H), 3.66 - 3.56 (m, 1H), 3.56 - 3.48 (m, 1H), 3.23 - 3.10 (m, 2H), 3.11 - 2.84 (m, 2H), 2.80 - 2.67 (m, 1H), 2.65 - 2.54 (m, 1H), 2.31 (dq, J = 4.2, 13.0 Hz, 1H), 2.26 - 1.15 (m, 11H).	D
162		Rel-2- {[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} ,0 ^{11,16}]tricoso-2,4,6-trien-15-yl]amino}cyclobutane-1-carbonitrile	[M+H] ⁺ 442.5	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.21 - 7.11 (m, 1H), 6.75 (t, J = 8.9 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 5.31 (d, J = 10.3 Hz, 1H), 5.03 - 4.95 (m, 1H), 3.97 (d, J = 10.3 Hz, 1H), 3.79 (t, J = 10.3 Hz, 1H), 3.71 - 3.62 (m, 2H), 3.61 (br s, 1H), 3.50 - 3.43 (m, 1H), 3.42 - 3.37 (m, 1H), 3.30 - 3.23 (m, 1H), 3.07 - 2.95 (m, 1H), 2.79 - 2.68 (m, 1H), 2.65 - 2.55 (m, 1H), 2.36 (br dd, J = 2.7, 10.6 Hz, 1H), 2.30 - 2.16 (m, 2H), 2.14 - 1.96 (m, 3H), 1.90 - 1.79 (m, 1H), 1.76 - 1.59 (m, 3H), 1.54 - 1.05 (m, 6H).	A
163		Rel- (1s,15S,16R,19s)-3-fluoro-15- ({4-hydroxybicyclo[2.2.2]octan-1-yl}amino)-8,18-dioxa-11-	[M+H] ⁺ 487.4	¹ H NMR (400 MHz, MeOD) δ 7.18 - 6.99 (m, 1H), 6.85 - 6.49 (m, 2H), 5.34 - 5.21 (m, 1H), 4.99 - 4.88 (m, 1H), 4.15 - 4.08 (m, 1H), 3.92 - 3.82 (m, 1H), 3.76 - 3.64 (m, 2H), 3.63 - 3.54 (m, 1H), 3.51 - 3.37 (m, 1H), 3.20 - 3.07 (m, 1H), 2.97 -	C

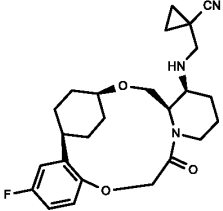
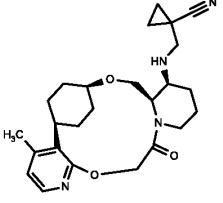
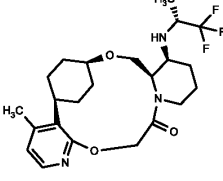
		azatetracyclo[1 7.2.2.0 ^{2,7} , ^{11,16}]t ricosa-2,4,6- trien-10-one		2.88 (m, 1H), 2.75 - 2.21 (m, 2H), 2.20 - 1.15 (m, 22H).	
164		Rel- (1s,15S,16R,19 s)-3-fluoro-15- {[3- (hydroxymethyl)bicyclo[1.1.1]p entan-1- yl]amino}- 8,18-dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} , ^{11,16}]t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 459.5	¹ H NMR (400 MHz, MeOD) δ 7.20 - 7.04 (m, 1H), 6.74 - 6.60 (m, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.27 - 5.18 (m, 1H), 4.12 (d, J = 10.5 Hz, 1H), 3.91 (t, J = 10.1 Hz, 1H), 3.82 - 3.73 (m, 1H), 3.69 (br s, 1H), 3.62 (s, 2H), 3.54 - 3.42 (m, 2H), 3.19 - 3.08 (m, 1H), 3.07 - 2.97 (m, 1H), 2.80 - 2.60 (m, 1H), 2.30 (dq, J = 3.9, 13.0 Hz, 1H), 2.18 (br d, J = 13.5 Hz, 1H), 1.83 (s, 6H), 1.92 - 1.17 (m, 9H).	C
165		Rel- (1s,15S,16R,19 s)-3-fluoro-15- ({1- oxaspiro[4.4]no nan-6- yl]amino)- 8,18-dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} , ^{11,16}]t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 487.4	¹ H NMR (400 MHz, MeOD) δ 7.22 - 7.02 (m, 1H), 6.77 - 6.58 (m, 2H), 5.34 - 5.26 (m, 1H), 5.24 - 5.08 (m, 1H), 4.17 - 4.08 (m, 1H), 3.98 - 3.89 (m, 1H), 3.86 - 3.82 (m, 2H), 3.81 - 3.72 (m, 1H), 3.71 - 3.64 (m, 1H), 3.55 - 3.42 (m, 2H), 3.20 - 3.09 (m, 1H), 3.16 - 2.97 (m, 1H), 3.01 - 2.93 (m, 1H), 2.77 - 2.62 (m, 1H), 2.37 - 2.24 (m, 1H), 2.23 - 1.19 (m, 20H).	B
166		Rel- (1s,15S,16R,19 s)-3-fluoro-15- {[2-hydroxy-3- (propan-2- yloxy)propyl]a mino}-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} , ^{11,16}]t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 479.5	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.2 Hz, 1H), 6.75 - 6.63 (m, 2H), 5.31 (d, J = 10.6 Hz, 1H), 5.25 (td, J = 5.0, 15.6 Hz, 1H), 4.13 (d, J = 10.6 Hz, 1H), 3.95 (t, J = 10.2 Hz, 1H), 3.91 - 3.83 (m, 1H), 3.80 (br d, J = 13.3 Hz, 1H), 3.74 - 3.69 (m, 1H), 3.68 - 3.60 (m, 1H), 3.57 - 3.40 (m, 4H), 3.21 - 3.09 (m, 1H), 3.09 - 3.00 (m, 1H), 3.02 - 2.67 (m, 3H), 2.29 (dq, J = 4.0, 13.0 Hz, 1H), 2.23 - 2.15 (m, 1H), 1.99 - 1.79 (m, 3H), 1.73 - 1.21 (m, 6H), 1.17 (d, J = 6.2 Hz, 6H).	D

167		Rel- (1s,15S,16R,19 s)-3-fluoro-15- [(1-methyl-2- oxopiperidin-4- yl)amino]-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 474.5	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.6, 8.2 Hz, 1H), 6.73 - 6.65 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.23 - 5.12 (m, 1H), 4.19 - 4.08 (m, 1H), 3.95 (d, J = 10.1 Hz, 1H), 3.79 (br d, J = 13.3 Hz, 1H), 3.71 (br s, 1H), 3.56 - 3.37 (m, 4H), 3.35 - 3.25 (m, 1H), 3.21 - 3.01 (m, 2H), 2.94 (s, 3H), 2.78 - 2.60 (m, 2H), 2.38 - 2.07 (m, 4H), 1.94 - 1.78 (m, 3H), 1.77 - 1.33 (m, 6H), 1.27 - 1.17 (m, 1H).	D
168		Rel- (1s,15S,16R,19 s)-3-fluoro-15- {[4- (hydroxymethyl) bicyclo[2.2.2]o ctan-1- yl]amino}- 8,18-dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 501.4	¹ H NMR (500 MHz, MeOD) δ 7.19 - 7.08 (m, 1H), 6.75 - 6.60 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.15 - 5.04 (m, 1H), 4.14 (d, J = 10.6 Hz, 1H), 4.00 (t, J = 10.0 Hz, 1H), 3.79 (br d, J = 12.9 Hz, 1H), 3.72 (br s, 1H), 3.61 - 3.49 (m, 1H), 3.48 - 3.35 (m, 2H), 3.24 - 3.10 (m, 3H), 2.74 - 2.57 (m, 1H), 2.35 - 2.08 (m, 2H), 2.01 - 1.31 (m, 20H), 1.30 - 1.16 (m, 1H).	D
169		(1s,15S,16R,19 s)-3-fluoro-15- [(3- phenyloxetan- 3-yl)amino]- 8,18-dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 495.4	¹ H NMR (400 MHz, MeOD) δ 7.48 - 7.33 (m, 2H), 7.43 - 7.13 (m, 2H), 7.22 - 7.06 (m, 1H), 7.33 - 6.77 (m, 1H), 6.75 - 6.57 (m, 2H), 5.37 - 4.60 (m, 4H), 5.24 - 4.25 (m, 1H), 4.07 - 3.83 (m, 1H), 3.76 - 3.69 (m, 1H), 4.00 - 3.65 (m, 2H), 4.32 - 3.56 (m, 1H), 4.84 - 3.46 (m, 1H), 3.22 - 3.06 (m, 1H), 3.44 - 2.72 (m, 1H), 2.71 - 2.48 (m, 1H), 2.69 - 1.04 (m, 12H).	B
170		(1s,15R,16S,19 s)-3-fluoro-15- [(3- phenyloxetan- 3-yl)amino]- 8,18-dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2,4,6- trien-10-one	[M+H] ⁺ 495.4	¹ H NMR (400 MHz, MeOD) δ 7.48 - 7.33 (m, 2H), 7.43 - 7.13 (m, 2H), 7.22 - 7.06 (m, 1H), 7.33 - 6.77 (m, 1H), 6.75 - 6.57 (m, 2H), 5.37 - 4.60 (m, 4H), 5.24 - 4.25 (m, 1H), 4.07 - 3.83 (m, 1H), 3.76 - 3.69 (m, 1H), 4.00 - 3.65 (m, 2H), 4.32 - 3.56 (m, 1H), 4.84 - 3.46 (m, 1H), 3.22 - 3.06 (m, 1H), 3.44 - 2.72 (m, 1H), 2.71 - 2.48 (m, 1H), 2.69 - 1.04 (m, 12H).	D

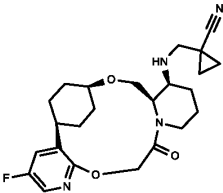
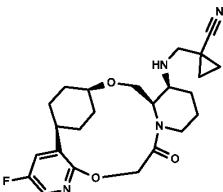
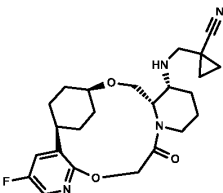
171		Rel-(1s,15S,16R,19s)-15-[(2R)-1,1-difluoropropan-2-yl]amino}-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]trien-10-one	[M+H] ⁺ 441.1	¹ H NMR (500 MHz, MeOD) δ 7.13 (td, J = 8.2, 6.7 Hz, 1H), 6.73 – 6.65 (m, 2H), 5.87 – 5.56 (m, J = 56.6, 56.6, 3.6 Hz, 1H), 5.30 (d, J = 10.4 Hz, 1H), 5.21 – 5.08 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.76 (br d, J = 11.7 Hz, 1H), 3.69 (br s, 1H), 3.56 – 3.48 (m, 1H), 3.51 – 3.43 (m, 1H), 3.19 – 3.09 (m, 2H), 3.10 – 2.97 (m, 1H), 2.76 – 2.62 (m, 1H), 2.30 (qd, J = 13.0, 3.8 Hz, 1H), 2.23 – 2.13 (m, 1H), 1.91 – 1.77 (m, 3H), 1.69 – 1.44 (m, 3H), 1.43 – 1.31 (m, 2H), 1.26 – 1.20 (m, 1H), 1.20 – 1.12 (m, J = 6.7 Hz, 3H).	B
172		(1s,15R,16S,19s)-15-[(2R)-1,1-difluoropropan-2-yl]amino}-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]trien-10-one	[M+H] ⁺ 441.7	¹ H NMR (500 MHz, MeOD) δ 7.07 - 7.20 (m, 1 H), 6.64 - 6.74 (m, 2 H), 5.73 (td, J=56.6, 3.6 Hz, 1 H), 5.30 (d, J=10.4 Hz, 1 H), 5.14 - 5.22 (m, 1 H), 4.12 (d, J=10.6 Hz, 1 H), 3.93 (dd, J=11.0, 9.4 Hz, 1 H), 3.76 (br dd, J=13.7, 3.2 Hz, 1 H), 3.69 (br s, 1 H), 3.43 - 3.53 (m, 2 H), 3.03 - 3.20 (m, 3 H), 2.62 - 2.77 (m, 1 H), 2.30 (qd, J=13.0, 4.1 Hz, 1 H), 2.19 (br dd, J=11.9, 4.3 Hz, 1 H), 1.76 - 1.90 (m, 3 H), 1.43 - 1.71 (m, 3 H), 1.33 - 1.43 (m, 2 H), 1.19 - 1.29 (m, 1 H), 1.15 (d, J=6.7 Hz, 3 H).	D
173		(1s,15S,16R,19s)-15-[(2R)-1,1-difluoropropan-2-yl]amino}-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]trien-10-one	[M+H] ⁺ 441.8	¹ H NMR (500 MHz, MeOD) δ 7.07 - 7.20 (m, 1 H), 6.61 - 6.75 (m, 2 H), 5.55 - 5.84 (m, 1 H), 5.30 (d, J=10.4 Hz, 1 H), 5.08 - 5.17 (m, 1 H), 4.12 (d, J=10.4 Hz, 1 H), 3.87 - 3.95 (m, 1 H), 3.73 - 3.81 (m, 1 H), 3.69 (br s, 1 H), 3.51 - 3.57 (m, 1 H), 3.47 (td, J=13.1, 2.7 Hz, 1 H), 3.05 - 3.19 (m, 2 H), 2.96 - 3.04 (m, 1 H), 2.61 - 2.77 (m, 1 H), 2.24 - 2.36 (m, 1 H), 2.14 - 2.23 (m, 1 H), 1.77 - 1.91 (m, 3 H), 1.45 - 1.70 (m, 3 H), 1.32 - 1.43 (m, 2 H), 1.20 - 1.28 (m, 1 H), 1.12 - 1.19 (m, 3 H).	A

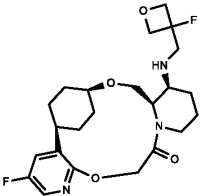
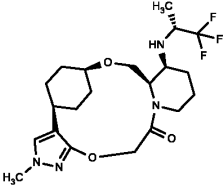
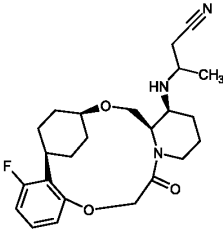
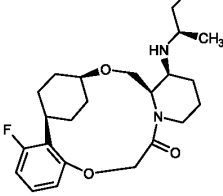
174		Rel-(1s,15S,16R,19s)-15-{[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]amino}-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0} ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 485.2	¹ H NMR (400 MHz, MeOD) δ 7.13 (q, J=7.7 Hz, 1 H), 6.57 (d, J=7.9 Hz, 2 H), 5.23 - 5.38 (m, 1 H), 5.16 (br dd, J=10.4, 4.7 Hz, 1 H), 4.12 (d, J=10.4 Hz, 1 H), 3.88 - 4.02 (m, 1 H), 3.74 - 3.87 (m, 1 H), 3.70 (br s, 1 H), 3.42 - 3.59 (m, 2 H), 3.31 (s, 1 H), 3.07 - 3.22 (m, 1 H), 2.80 - 3.00 (m, 1 H), 2.61 - 2.79 (m, 1 H), 2.23 - 2.39 (m, 1 H), 2.19 (br d, J=14.3 Hz, 1 H), 1.77 - 1.97 (m, 3 H), 1.17 - 1.72 (m, 6 H), 0.92 - 1.06 (m, 1 H), 0.41 - 0.81 (m, 4 H).	A
175		(1s,15R,16S,19s)-15-{[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]amino}-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0} ^{11,16}]tricoso-2(7),3,5-trien-10-one	ND	¹ H NMR (500 MHz, MeOD) δ 7.18 - 7.07 (m, 1H), 6.72 - 6.63 (m, 2H), 5.32 - 5.26 (m, 1H), 5.15 - 5.05 (m, 1H), 4.15 - 4.08 (m, 1H), 3.90 (dd, J = 9.4, 11.0 Hz, 1H), 3.79 - 3.72 (m, 1H), 3.71 - 3.65 (m, 1H), 3.57 - 3.52 (m, 1H), 3.51 - 3.43 (m, 1H), 3.18 - 3.05 (m, 2H), 2.66 - 2.58 (m, 1H), 2.77 - 2.24 (m, 2H), 2.23 - 1.78 (m, 2H), 1.83 - 1.55 (m, 4H), 1.54 - 1.40 (m, 2H), 1.42 - 1.20 (m, 2H), 1.00 - 0.86 (m, 1H), 0.68 - 0.45 (m, 4H).	D
176		(1s,15S,16R,19s)-15-{[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]amino}-3-fluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0} ^{11,16}]tricoso-2(7),3,5-trien-10-one	ND	¹ H NMR (500 MHz, MeOD) δ 7.18 - 7.07 (m, 1H), 6.72 - 6.63 (m, 2H), 5.32 - 5.26 (m, 1H), 5.15 - 5.05 (m, 1H), 4.15 - 4.08 (m, 1H), 3.90 (dd, J = 9.4, 11.0 Hz, 1H), 3.79 - 3.72 (m, 1H), 3.71 - 3.65 (m, 1H), 3.57 - 3.52 (m, 1H), 3.51 - 3.43 (m, 1H), 3.18 - 3.05 (m, 2H), 2.66 - 2.58 (m, 1H), 2.77 - 2.24 (m, 2H), 2.23 - 1.78 (m, 2H), 1.83 - 1.55 (m, 4H), 1.54 - 1.40 (m, 2H), 1.42 - 1.20 (m, 2H), 1.00 - 0.86 (m, 1H), 0.68 - 0.45 (m, 4H).	A
177		Rel-(2S,3R)-2-methyl-3-{[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0} ^{11,16}]tricoso-2,4,6-trien-15-yl]amino}-2-methylpropanenitrile	[M+H] ⁺ 444.5	¹ H NMR (600 MHz, MeOD) δ 7.13 (dt, J = 6.4, 8.2 Hz, 1H), 6.72 - 6.64 (m, 2H), 5.30 (d, J = 10.4 Hz, 1H), 5.16 - 5.08 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 9.5, 11.0 Hz, 1H), 3.77 (br dd, J = 2.8, 13.3 Hz, 1H), 3.69 (br s, 1H), 3.53 - 3.44 (m, 2H), 3.18 - 3.11 (m, 1H), 3.11 - 3.06 (m, 1H), 3.04 - 2.96 (m, 2H), 2.74 - 2.64 (m, 1H), 2.30 (dq, J = 4.0, 13.0 Hz, 1H), 2.19 (br dd, J = 4.0, 12.1 Hz, 1H), 1.89 - 1.77 (m, 3H), 1.68 - 1.58 (m, 1H),	A

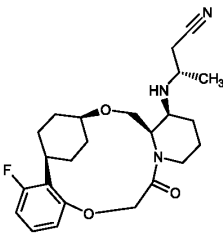
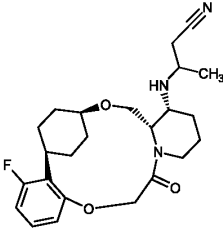
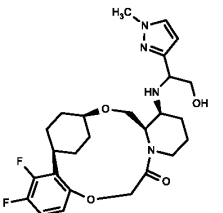
		yl]amino}butan enitrile		1.57 - 1.45 (m, 2H), 1.42 - 1.34 (m, 2H), 1.30 (d, J = 7.1 Hz, 3H), 1.26 - 1.20 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H).	
178		Rel-(2R,3S)-2- methyl-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2,4,6- trien-15- yl]amino}butan enitrile	[M+H] ⁺ 444.5	¹ H NMR (600 MHz, MeOD) δ 7.13 (dt, J = 6.4, 8.2 Hz, 1H), 6.72 - 6.65 (m, 2H), 5.30 (d, J = 10.4 Hz, 1H), 5.14 - 5.04 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.92 (dd, J = 9.4, 10.9 Hz, 1H), 3.76 (br d, J = 11.0 Hz, 1H), 3.69 (br s, 1H), 3.58 (dd, J = 3.9, 9.1 Hz, 1H), 3.48 (dt, J = 2.7, 13.3 Hz, 1H), 3.18 - 3.10 (m, 1H), 3.00 - 2.88 (m, 3H), 2.75 - 2.64 (m, 1H), 2.30 (dq, J = 4.2, 13.0 Hz, 1H), 2.18 (br d, J = 12.7 Hz, 1H), 1.89 - 1.78 (m, 3H), 1.69 - 1.59 (m, 1H), 1.59 - 1.44 (m, 2H), 1.42 - 1.34 (m, 2H), 1.30 (d, J = 7.1 Hz, 3H), 1.23 (d, J = 6.4 Hz, 3H), 1.23 - 1.18 (m, 1H).	A
179		Rel-(2R,3R)-2- methyl-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2,4,6- trien-15- yl]amino}butan enitrile	[M+H] ⁺ 444.5	¹ H NMR (600 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.73 - 6.64 (m, 2H), 5.30 (d, J = 10.4 Hz, 1H), 5.17 - 5.06 (m, 1H), 4.13 (d, J = 10.4 Hz, 1H), 3.94 (dd, J = 9.5, 11.0 Hz, 1H), 3.76 (br dd, J = 3.0, 13.8 Hz, 1H), 3.70 (br s, 1H), 3.52 (dd, J = 4.0, 9.4 Hz, 1H), 3.51 - 3.44 (m, 1H), 3.18 - 3.11 (m, 1H), 3.10 - 3.04 (m, 1H), 3.00 - 2.93 (m, 1H), 2.89 (dq, J = 5.0, 7.1 Hz, 1H), 2.75 - 2.64 (m, 1H), 2.30 (dq, J = 4.1, 13.0 Hz, 1H), 2.18 (br d, J = 12.8 Hz, 1H), 1.89 - 1.78 (m, 3H), 1.66 - 1.56 (m, 1H), 1.54 - 1.44 (m, 2H), 1.42 - 1.34 (m, 2H), 1.27 (d, J = 7.2 Hz, 3H), 1.25 - 1.21 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H).	A
180		Rel-(2S,3S)-2- methyl-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2,4,6- trien-15- yl]amino}butan enitrile	[M+H] ⁺ 444.5	¹ H NMR (600 MHz, MeOD) δ 7.13 (dt, J = 6.4, 8.2 Hz, 1H), 6.72 - 6.65 (m, 2H), 5.30 (d, J = 10.4 Hz, 1H), 5.14 - 5.05 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.99 - 3.90 (m, 1H), 3.81 - 3.74 (m, 1H), 3.69 (br s, 1H), 3.64 (dd, J = 4.0, 9.2 Hz, 1H), 3.49 (dt, J = 2.9, 13.2 Hz, 1H), 3.17 - 3.11 (m, 1H), 3.03 - 2.92 (m, 2H), 2.80 - 2.74 (m, 1H), 2.74 - 2.65 (m, 1H), 2.30 (dq, J = 4.1, 13.0 Hz, 1H), 2.22 - 2.15 (m, 1H), 1.89 - 1.76 (m, 3H), 1.71 - 1.54 (m, 2H), 1.48 (ddt, J = 1.2, 4.2, 13.4 Hz,	A

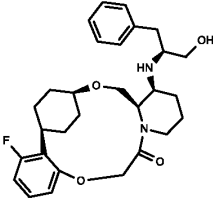
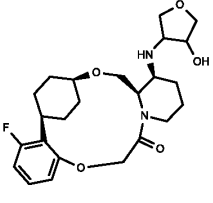
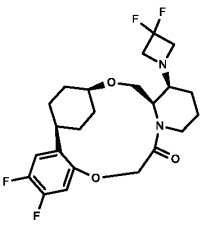
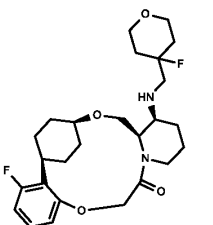
				¹ H, 1.42 - 1.35 (m, 2H), 1.34 (d, J = 7.1 Hz, 3H), 1.22 (d, J = 6.4 Hz, 3H), 1.26 - 1.20 (m, 1H).	
181		Rel-1- ({[(1s,15S,16R, 19s)-4-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 442.7	¹ H NMR (400 MHz, CDCl ₃) δ 6.87 - 6.78 (m, 2H), 6.67 (dd, J = 4.6, 8.3 Hz, 1H), 5.26 - 5.18 (m, 1H), 5.09 (d, J = 10.4 Hz, 1H), 4.25 (d, J = 10.4 Hz, 1H), 3.87 - 3.78 (m, 1H), 3.74 - 3.62 (m, 2H), 3.52 (dd, J = 4.1, 9.3 Hz, 1H), 3.49 - 3.40 (m, 1H), 3.07 - 2.98 (m, 1H), 2.92 (d, J = 12.8 Hz, 1H), 2.72 (d, J = 12.8 Hz, 1H), 2.72 - 2.60 (m, 1H), 2.57 - 2.44 (m, 1H), 2.29 - 2.15 (m, 1H), 2.14 - 2.04 (m, 1H), 1.95 - 1.77 (m, 3H), 1.30 - 1.26 (m, 2H), 1.71 - 1.18 (m, 6H), 1.05 - 0.81 (m, 2H).	A
182		Rel-1- ({[(1s,15S,16R, 19s)-3-methyl- 10-oxo-8,18- dioxo-6,11- diazatetracyclo[17.2.2.0 ^{2,7} ,0 ^{11,16}]tricoso-2,4,6- trien-15- yl]amino}meth yl)cyclopropan e-1-carbonitrile	[M+H] ⁺ 439.3	¹ H NMR (500 MHz, MeOD) δ 7.82 - 7.76 (m, 1H), 6.83 - 6.76 (m, 1H), 5.26 (d, J = 11.1 Hz, 1H), 5.24 - 5.17 (m, 1H), 4.36 (d, J = 11.1 Hz, 1H), 4.00 - 3.92 (m, 1H), 3.74 (br d, J = 12.9 Hz, 1H), 3.70 (br s, 1H), 3.54 (dd, J = 4.0, 9.3 Hz, 1H), 3.52 - 3.42 (m, 1H), 3.06 - 2.98 (m, 1H), 2.97 - 2.89 (m, 2H), 2.70 (d, J = 12.8 Hz, 1H), 2.71 - 2.59 (m, 1H), 2.42 - 2.29 (m, 1H), 2.32 (s, 3H), 2.20 (br d, J = 12.5 Hz, 1H), 1.93 - 1.79 (m, 3H), 1.73 - 1.51 (m, 2H), 1.53 - 1.46 (m, 1H), 1.45 - 1.27 (m, 2H), 1.22 - 1.12 (m, 1H), 1.26 - 0.97 (m, 4H).	A
183		Rel- (1s,15S,16R,19 s)-3-methyl-15- yl]amino}- 8,18-dioxo- 6,11- diazatetracyclo[17.2.2.0 ^{2,7} ,0 ^{11,16}]tricoso-2,4,6- trien-10-one	[M+H] ⁺ 456.3	¹ H NMR (400 MHz, MeOD) δ 7.83 - 7.75 (m, 1H), 6.85 - 6.76 (m, 1H), 5.34 - 5.23 (m, 1H), 5.22 - 5.15 (m, 1H), 4.36 (d, J = 11.1 Hz, 1H), 3.99 - 3.90 (m, 1H), 3.78 - 3.64 (m, 2H), 3.52 - 3.41 (m, 3H), 3.09 (br dd, J = 5.3, 11.9 Hz, 1H), 3.04 - 2.97 (m, 1H), 2.73 - 2.58 (m, 1H), 2.42 - 2.32 (m, 1H), 2.32 (s, 3H), 2.26 - 2.10 (m, 1H), 1.92 - 1.77 (m, 3H), 1.73 - 1.13 (m, 9H).	A

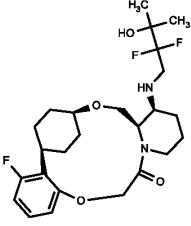
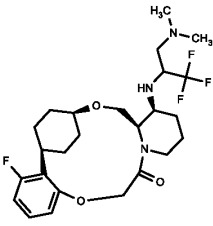
184		(2S)-2-methyl-3- {[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-15-yl]amino}propenenitrile	[M+H] ⁺ 430.5	¹ H NMR (500 MHz, MeOD) δ 7.16 - 7.10 (m, 1H), 6.72 - 6.65 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.22 - 5.13 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.96 - 3.89 (m, 1H), 3.77 (dd, J = 2.6, 13.7 Hz, 1H), 3.70 (br s, 1H), 3.55 - 3.45 (m, 2H), 3.19 - 3.10 (m, 1H), 2.95 - 2.83 (m, 4H), 2.75 - 2.62 (m, 1H), 2.30 (dq, J = 4.1, 13.0 Hz, 1H), 2.22 - 2.15 (m, 1H), 1.92 - 1.78 (m, 3H), 1.68 - 1.44 (m, 3H), 1.33 - 1.31 (m, 3H), 1.43 - 1.29 (m, 2H), 1.28 - 1.19 (m, 1H).	A
185		(2S)-2-methyl-3- {[(1s,15R,16S,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-15-yl]amino}propenenitrile	[M+H] ⁺ 430.2	¹ H NMR (600 MHz, MeOD) δ 7.13 (td, J = 8.2, 6.6 Hz, 1H), 6.72 - 6.64 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.22 - 5.15 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.97 - 3.89 (m, 1H), 3.80 - 3.73 (m, 1H), 3.70 (br s, 1H), 3.55 (dd, J = 9.3, 3.9 Hz, 1H), 3.49 (td, J = 13.2, 2.3 Hz, 1H), 3.18 - 3.10 (m, 1H), 2.94 - 2.84 (m, 4H), 2.75 - 2.64 (m, 1H), 2.30 (qd, J = 13.0, 4.0 Hz, 1H), 2.23 - 2.13 (m, 1H), 1.88 - 1.78 (m, 3H), 1.68 - 1.59 (m, 1H), 1.59 - 1.52 (m, 1H), 1.49 (td, J = 13.9, 3.7 Hz, 1H), 1.44 - 1.34 (m, 2H), 1.33 (br d, J = 6.4 Hz, 3H), 1.27 - 1.19 (m, 1H).	C
186		(2R)-2-methyl-3- {[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-15-yl]amino}propenenitrile	[M+H] ⁺ 430.5	¹ H NMR (500 MHz, CDCl ₃) δ 7.13 - 7.03 (m, 1H), 6.71 (t, J = 8.6 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 5.36 - 5.24 (m, 1H), 5.10 (d, J = 10.3 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 3.87 (br t, J = 10.0 Hz, 1H), 3.74 (br s, 1H), 3.67 (br d, J = 13.3 Hz, 1H), 3.56 (br dd, J = 3.8, 9.2 Hz, 1H), 3.52 - 3.43 (m, 1H), 3.20 - 3.10 (m, 1H), 2.99 (br s, 5H), 2.61 (dq, J = 4.3, 12.8 Hz, 1H), 2.23 (dq, J = 4.0, 13.0 Hz, 1H), 2.15 - 2.07 (m, 1H), 1.94 - 1.80 (m, 3H), 1.58 (br s, 2H), 1.49 - 1.28 (m, 7H).	A
187		(2R)-2-methyl-3- {[(1s,15R,16S,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-15-yl]amino}propenenitrile	[M+H] ⁺ 430.5	¹ H NMR (500 MHz, CDCl ₃) δ 7.13 - 7.05 (m, 1H), 6.71 (t, J = 8.8 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 5.38 - 5.26 (m, 1H), 5.09 (d, J = 10.3 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 3.97 - 3.84 (m, 1H), 3.74 (br s, 1H), 3.67 (br d, J = 13.6 Hz, 1H), 3.55 (br dd, J = 3.2, 8.9 Hz, 1H), 3.49 (br	C

		tricoso-2,4,6-trien-15-yl]amino}propenenitrile		t, J = 13.1 Hz, 1H), 3.19 - 3.11 (m, 1H), 4.00 - 2.81 (m, 5H), 2.60 (dq, J = 3.8, 12.9 Hz, 1H), 2.26 - 2.15 (m, 1H), 2.13 (br d, J = 13.2 Hz, 1H), 1.87 (br d, J = 11.1 Hz, 1H), 2.04 - 1.80 (m, 2H), 1.58 (br s, 2H), 1.50 - 1.29 (m, 7H).	
188		Rel-1-({[(1s,15S,16R,19s)-4-fluoro-10-oxo-8,18-dioxa-6,11-diazatetracyclo[17.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2,4,6-trien-15-yl]amino}methylcyclopropane-1-carbonitrile	[M+H] ⁺ 443.4	¹ H NMR (500 MHz, CDCl ₃) δ 7.84 - 7.80 (m, 1H), 7.17 (dd, J = 3.0, 8.1 Hz, 1H), 5.36 - 5.23 (m, 1H), 5.44 - 5.12 (m, 1H), 4.53 (d, J = 11.1 Hz, 1H), 3.89 (br t, J = 10.2 Hz, 1H), 3.85 - 3.70 (m, 1H), 4.59 - 3.63 (m, 1H), 3.56 (dd, J = 4.0, 9.4 Hz, 1H), 3.15 (br s, 1H), 3.04 (br d, J = 13.0 Hz, 1H), 2.84 - 2.76 (m, 1H), 3.49 - 2.75 (m, 1H), 2.68 - 2.50 (m, 2H), 2.30 (dq, J = 4.3, 12.8 Hz, 1H), 2.14 - 2.07 (m, 1H), 1.99 - 1.79 (m, 3H), 1.73 - 1.57 (m, 2H), 1.53 - 1.23 (m, 6H), 1.21 - 1.07 (m, 1H), 1.04 - 0.86 (m, 1H).	A
189		1-({[(1s,15S,16R,19s)-4-fluoro-10-oxo-8,18-dioxa-6,11-diazatetracyclo[17.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2,4,6-trien-15-yl]amino}methylcyclopropane-1-carbonitrile	[M+H] ⁺ 443.4	¹ H NMR (500 MHz, CDCl ₃) δ 7.88 - 7.76 (m, 1H), 7.21 - 7.11 (m, 1H), 5.28 - 5.20 (m, 1H), 5.19 - 5.12 (m, 1H), 4.56 - 4.51 (m, 1H), 3.90 - 3.80 (m, 1H), 3.73 - 3.62 (m, 2H), 3.56 - 3.49 (m, 1H), 3.47 - 3.38 (m, 1H), 3.08 - 2.99 (m, 1H), 2.97 - 2.90 (m, 1H), 2.72 - 2.67 (m, 1H), 2.66 - 2.50 (m, 2H), 2.36 - 2.26 (m, 1H), 2.16 - 2.06 (m, 1H), 1.94 - 1.86 (m, 1H), 1.78 (br d, J = 4.1 Hz, 2H), 1.72 - 1.50 (m, 2H), 1.49 - 1.19 (m, 6H), 1.05 - 0.79 (m, 2H).	A
190		1-({[(1s,15R,16S,19s)-4-fluoro-10-oxo-8,18-dioxa-6,11-diazatetracyclo[17.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2,4,6-trien-15-yl]amino}methylcyclopropane-1-carbonitrile	[M+H] ⁺ 443.4	¹ H NMR (500 MHz, CDCl ₃) δ 7.93 - 7.73 (m, 1H), 7.22 - 7.11 (m, 1H), 5.27 - 5.20 (m, 1H), 5.19 - 5.13 (m, 1H), 4.57 - 4.51 (m, 1H), 3.90 - 3.81 (m, 1H), 3.75 - 3.62 (m, 2H), 3.57 - 3.49 (m, 1H), 3.47 - 3.38 (m, 1H), 3.07 - 2.98 (m, 1H), 2.97 - 2.91 (m, 1H), 2.74 - 2.67 (m, 1H), 2.66 - 2.50 (m, 2H), 2.37 - 2.26 (m, 1H), 2.16 - 2.06 (m, 1H), 1.94 - 1.86 (m, 1H), 1.86 - 1.76 (m, 2H), 1.70 - 1.54 (m, 2H), 1.52 - 1.20 (m, 6H), 1.04 - 0.77 (m, 2H).	C

191		Rel-(1s,15S,16R,19s)-4-fluoro-15-[[[(3-fluorooxetan-3-yl)methyl]amino]-8,18-dioxo-6,11-diazatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 452.3	¹ H NMR (500 MHz, MeOD) δ 7.87 - 7.79 (m, 1H), 7.40 - 7.31 (m, 1H), 5.29 (d, J = 11.1 Hz, 1H), 5.26 - 5.20 (m, 1H), 4.79 - 4.61 (m, 4H), 4.39 (d, J = 11.1 Hz, 1H), 3.98 - 3.92 (m, 1H), 3.76 (br d, J = 13.2 Hz, 1H), 3.69 (br s, 1H), 3.53 - 3.43 (m, 2H), 3.27 - 3.18 (m, 2H), 2.96 - 2.86 (m, 1H), 2.74 - 2.58 (m, 2H), 2.41 - 2.28 (m, 1H), 2.18 (br d, J = 13.7 Hz, 1H), 1.95 - 1.78 (m, 3H), 1.69 - 1.33 (m, 5H), 1.31 - 1.23 (m, 1H).	A
192		Rel-(1s,14S,15R,18s)-4-methyl-14-[[[(2R)-1,1,1-trifluoropropan-2-yl]amino]-7,17-dioxo-4,5,10-triazatetracyclo[16.2.2.0 ^{2,6} .0 ^{10,15}]docosa-2,5-dien-9-one	[M+H] ⁺ 445.2	¹ H NMR (500 MHz, MeOD) δ 7.16 - 7.12 (m, 1H), 5.25 - 5.19 (m, 1H), 5.16 - 5.01 (m, 1H), 4.32 - 4.24 (m, 1H), 3.94 - 3.88 (m, 1H), 3.89 - 3.80 (m, 1H), 3.70 - 3.64 (m, 4H), 3.63 - 3.50 (m, 1H), 3.50 - 3.43 (m, 1H), 3.43 - 3.33 (m, 1H), 3.04 - 2.86 (m, 1H), 2.56 - 2.40 (m, 2H), 2.20 - 2.10 (m, 1H), 1.92 - 1.69 (m, 4H), 1.67 - 1.29 (m, 6H), 1.26 (dd, J = 11.7, 6.7 Hz, 3H).	D
193		Rel-3-[[[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile	[M+H] ⁺ 430.3	¹ H NMR (400 MHz, MeOD) δ 7.07 - 7.23 (m, 1H), 6.63 - 6.75 (m, 1H), 5.31 (d, J=10.4 Hz, 1H), 5.15 (br dd, J=10.4, 4.9 Hz, 1H), 4.13 (d, J=10.5 Hz, 1H), 3.90 - 4.00 (m, 1H), 3.79 (br d, J=13.3 Hz, 1H), 3.67 - 3.74 (m, 1H), 3.43 - 3.61 (m, 2H), 3.23 - 3.31 (m, 1H), 3.09 - 3.22 (m, 2H), 3.06 (br d, J=4.5 Hz, 1H), 2.52 - 2.81 (m, 3H), 2.30 (qd, J=13.0, 4.0 Hz, 1H), 2.14 - 2.23 (m, 1H), 1.77 - 1.93 (m, 3H), 1.15 - 1.74 (m, 9H).	A
194		(3R)-3-[[[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile	ND	¹ H NMR (500 MHz, MeOD) δ 7.08 (td, J = 8.3, 6.4 Hz, 1H), 6.69 (ddd, J = 9.4, 8.3, 1.1 Hz, 1H), 6.53 (dt, J = 8.2, 1.0 Hz, 1H), 5.19 (dd, J = 8.5, 3.0 Hz, 1H), 5.09 (d, J = 10.3 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 3.84 (t, J = 10.4 Hz, 1H), 3.71 (s, 1H), 3.65 (d, J = 13.7 Hz, 1H), 3.56 (dd, J = 9.2, 4.0 Hz, 1H), 3.52 - 3.41 (m, 1H), 3.29 (s, 1H), 3.14 (tt, J = 12.0, 5.5 Hz, 1H), 3.04 (s, 1H), 2.70 - 2.38 (m, 3H), 2.22 (qd, J = 13.0, 4.3 Hz,	A

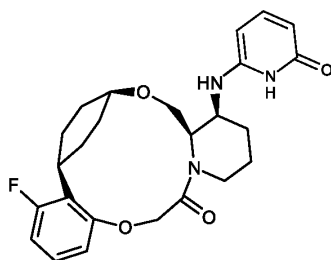
				¹ H, 2.12 – 2.06 (m, 1H), 1.93 – 1.73 (m, 3H), 1.70 – 1.15 (m, 10H).	
195		(3S)-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]t ricosa-2(7),3,5- trien-15- yl]amino}butan enitrile	ND	¹ H NMR (500 MHz, MeOD) δ 7.13 – 7.04 (m, 1H), 6.70 (ddd, J = 9.3, 8.3, 1.1 Hz, 1H), 6.53 (dt, J = 8.2, 1.0 Hz, 1H), 5.21 (s, 1H), 5.11 – 5.05 (m, 1H), 4.34 – 4.26 (m, 1H), 3.87 (d, J = 8.2 Hz, 1H), 3.72 (s, 1H), 3.66 (d, J = 12.9 Hz, 1H), 3.54 – 3.43 (m, 2H), 3.37 (s, 1H), 3.14 (tt, J = 12.1, 5.5 Hz, 1H), 3.06 (s, 1H), 2.75 (td, J = 16.8, 7.8 Hz, 1H), 2.66 – 2.52 (m, 1H), 2.26 – 2.14 (m, 1H), 2.11 (d, J = 14.4 Hz, 1H), 1.86 (d, J = 12.7 Hz, 3H), 1.75 – 1.14 (m, 10H).	A
196		Rel-3- {[(1s,15R,16S, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]t ricosa-2(7),3,5- trien-15- yl]amino}butan enitrile	ND	¹ H NMR (500 MHz, MeOD) δ 7.12 – 7.03 (m, 1H), 6.69 (ddd, J = 9.4, 8.3, 1.1 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 5.19 (dd, J = 11.0, 5.3 Hz, 1H), 5.09 (dd, J = 10.3, 1.3 Hz, 1H), 4.28 (dd, J = 10.3, 1.7 Hz, 1H), 3.84 (t, J = 10.2 Hz, 1H), 3.73 – 3.68 (m, 1H), 3.65 (d, J = 13.7 Hz, 1H), 3.52 – 3.40 (m, 1H), 3.30 (s, 1H), 3.14 (tt, J = 12.0, 5.5 Hz, 1H), 3.59 – 2.68 (m, 1H), 2.98 (d, J = 26.9 Hz, 1H), 2.66 – 2.35 (m, 2H), 2.22 (qd, J = 13.1, 4.2 Hz, 1H), 2.09 (d, J = 14.1 Hz, 1H), 1.84 (q, J = 18.3 Hz, 3H), 1.69 – 1.16 (m, 10H).	C
197		Rel- (1s,15S,16R,19 s)-3,4-difluoro- 15-{[2- hydroxy-1-(1- methyl-1H- pyrazol-3- yl)ethyl]amino} -8,18-dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,1 ⁶]t ricosa-2(7),3,5- trien-10-one	[M+H] ⁺ 505.4	ND	C

198		Rel-(1s,15S,16R,19s)-3-fluoro-15-[(2S)-1-hydroxy-3-phenylpropan-2-yl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 515.4	¹ H NMR (400 MHz, MeOD) δ 7.33 – 7.23 (m, 4H), 7.24 – 7.16 (m, 1H), 7.12 – 6.96 (m, 1H), 6.68 – 6.58 (m, 1H), 5.32 – 5.00 (m, 2H), 4.09 (dd, J = 15.8, 10.5 Hz, 1H), 3.93 – 3.33 (m, 7H), 3.21 – 2.93 (m, 3H), 2.91 – 2.52 (m, 3H), 2.36 – 1.96 (m, 2H), 1.76 (dd, J = 31.1, 13.3 Hz, 4H), 1.65 – 1.13 (m, 7H).	D
199		Rel-(1s,15S,16R,19s)-3-fluoro-15-[(4-hydroxyoxolan-3-yl)amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 449.5	¹ H NMR (500 MHz, MeOD) δ 7.13 (td, J = 8.3, 6.4 Hz, 1H), 6.69 (dd, J = 9.7, 7.9 Hz, 2H), 5.37 – 5.27 (m, 1H), 5.27 – 4.97 (m, 1H), 4.23 – 4.04 (m, 3H), 4.03 – 3.96 (m, 1H), 3.93 (ddd, J = 11.7, 9.3, 2.7 Hz, 1H), 3.87 – 3.73 (m, 1H), 3.70 (s, 1H), 3.65 (dt, J = 9.5, 2.0 Hz, 1H), 3.62 – 3.43 (m, 3H), 3.35 (dddd, J = 10.5, 8.5, 4.2, 2.5 Hz, 1H), 3.20 – 3.09 (m, 1H), 3.03 – 2.90 (m, 1H), 2.69 (qd, J = 13.6, 5.4 Hz, 1H), 2.30 (qd, J = 13.0, 4.2 Hz, 1H), 2.18 (d, J = 14.3 Hz, 1H), 1.96 – 1.77 (m, 3H), 1.70 – 1.16 (m, 7H).	B
200		Rel-(1s,15S,16R,19s)-15-(3,3-difluoroazetidin-1-yl)-4,5-difluoro-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 457.2	¹ H NMR (400 MHz, CDCl ₃) δ 6.90 (dd, J = 9.0, 10.8 Hz, 1H), 6.57 (dd, J = 6.6, 11.2 Hz, 1H), 5.14 – 5.06 (m, 1H), 5.04 (d, J = 10.3 Hz, 1H), 4.24 (d, J = 10.3 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.75 – 3.53 (m, 6H), 3.48 – 3.35 (m, 2H), 2.69 – 2.41 (m, 3H), 2.27 – 2.11 (m, 1H), 2.07 (br d, J = 14.0 Hz, 1H), 1.95 – 1.81 (m, 2H), 1.73 (br dd, J = 3.2, 12.6 Hz, 1H), 1.54 – 1.17 (m, 6H).	D
201		Rel-(1s,15S,16R,19s)-3-fluoro-15-[(4-fluorooxan-4-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ^{2,7,0¹¹,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 479.2	¹ H NMR (500 MHz, MeOD) δ 8.18 (s, 1H), 7.17 – 7.10 (m, 1H), 6.74 – 6.65 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.28 – 5.22 (m, 1H), 4.13 (d, J = 10.5 Hz, 1H), 3.94 (dd, J = 11.2, 9.3 Hz, 1H), 3.81 (tq, J = 11.6, 3.4 Hz, 3H), 3.76 – 3.67 (m, 3H), 3.51 (dd, J = 13.1, 3.0 Hz, 1H), 3.45 (dd, J = 9.3, 3.9 Hz, 1H), 3.20 – 3.08 (m, 1H), 2.99 (dd, J = 20.4, 2.6 Hz, 2H), 2.76 – 2.63 (m, 1H), 2.30 (qd, J = 13.0, 4.1 Hz, 1H), 2.19 (dt, J = 12.9, 3.8 Hz, 1H),	C

		ricosa-2,4,6-trien-10-one		1.96 – 1.74 (m, 7H), 1.69 – 1.55 (m, 2H), 1.49 (tdd, J = 13.4, 4.4, 1.8 Hz, 1H), 1.44 – 1.34 (m, 2H), 1.23 (dq, J = 12.3, 2.9 Hz, 1H).	
202		Rel-(1s,15S,16R,19s)-15-[(2,2-difluoro-3-hydroxy-3-methylbutyl)amino]-3-fluoro-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 485.7	¹ H NMR (400 MHz, MeOD) δ 7.18 – 7.08 (m, 1H), 6.69 (t, J = 8.8 Hz, 2H), 5.31 (d, J = 10.5 Hz, 1H), 5.22 (dt, J = 10.2, 4.6 Hz, 1H), 4.12 (d, J = 10.5 Hz, 1H), 3.93 (dd, J = 11.2, 9.3 Hz, 1H), 3.78 (d, J = 13.6 Hz, 1H), 3.69 (s, 1H), 3.54 – 3.41 (m, 2H), 3.28 – 3.06 (m, 2H), 2.94 (dt, J = 9.6, 4.5 Hz, 1H), 2.78 – 2.63 (m, 1H), 2.30 (qd, J = 13.0, 4.1 Hz, 1H), 2.19 (d, J = 13.8 Hz, 1H), 1.94 – 1.77 (m, 3H), 1.69 – 1.43 (m, 3H), 1.43 – 1.18 (m, 9H).	C
203		Rel-(1s,15S,16R,19s)-15-{[3-(dimethylamino)-1,1,1-trifluoropropan-2-yl]amino}-3-fluoro-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2,4,6-trien-10-one	[M+H] ⁺ 502.2	ND	D

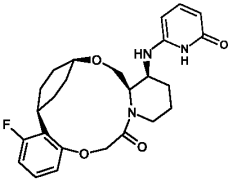
[0287] Example 204

[0288] Rel-(1s,15S,16R,19s)-3-fluoro-15-[(6-oxo-1,6-dihydropyridin-2-yl)amino]-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-10-one



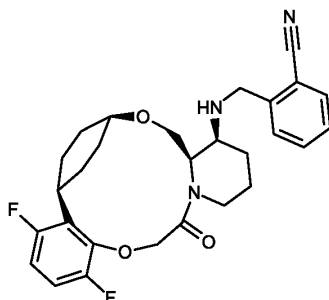
[0289] A solution of Intermediate 23 (100 mg, 0.280 mmol), 6-amino-1H-pyridin-2-one (61 mg, 0.550 mmol) and Ti(EtO)₄ (0.12 mL, 0.550 mmol) in THF (6 mL) was heated to 70 °C overnight. Then sodium cyanoborohydride (171 mg, 2.77 mmol) was added and the mixture was stirred for 5 h at room temperature. Reduction of the imine intermediate was not observed, so the mixture was diluted with EtOAc and washed with saturated aqueous NaHCO₃ solution, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resulting solid (125 mg, 0.280 mmol) was dissolved in methanol (6 mL), ammonium formate (348 mg, 5.51 mmol) and 10% wt. Pd/C (32 mg, 0.300 mmol) were added and the mixture was stirred at 60 °C overnight. The suspension was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with water, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The product was purified by column chromatography using a C18 cartridge (0-40% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) followed by preparative HPLC to afford the title compound (2.5 mg, 0.005 mmol, 2% yield) as white solid.

Table 5. Prepared Compound and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
204		Rel-(1s,15S,16R,19s)-3-fluoro-15-[(6-oxo-1,6-dihydropyridin-2-yl)amino]-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 456.4	¹ H NMR (500 MHz, MeOD) δ 7.44 (t, J = 8.3 Hz, 1H), 7.13 (dt, J = 6.4, 8.2 Hz, 1H), 6.75 - 6.64 (m, 2H), 5.81 - 5.74 (m, 2H), 5.41 - 5.33 (m, 1H), 5.33 (d, J = 10.4 Hz, 1H), 4.15 (d, J = 10.6 Hz, 1H), 4.00 (dd, J = 9.2, 10.7 Hz, 1H), 3.83 (br d, J = 12.6 Hz, 1H), 3.78 - 3.71 (m, 1H), 3.69 (br s, 1H), 3.54 (dt, J = 2.4, 12.9 Hz, 1H), 3.37 (dd, J = 3.8, 8.9 Hz, 1H), 3.20 - 3.08 (m, 1H), 2.75 - 2.62 (m, 1H), 2.33 - 2.22 (m, 1H), 2.22 - 2.14 (m, 1H), 2.03 - 1.87 (m, 2H), 1.84 - 1.77 (m, 1H), 1.78 - 1.67 (m, 2H), 1.51 - 1.43 (m, 1H), 1.44 - 1.35 (m, 2H), 1.25 - 1.18 (m, 1H).	B

[0290] Example 205

[0291] Rel-2-({[(1s,15S,16R,19s)-3,6-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}methyl)benzonitrile



[0292] To a solution of the (1s,19s)-3,6-difluoro-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-triene-10,15-dione (synthesized via a similar route to that described for Intermediate 23) (150 mg, 0.400 mmol) and 2-cyanobenzylamine (105 mg, 0.790 mmol) in THF (7 mL), Ti(EtO)₄ (180 mg, 0.790 mmol) was added and the resulting mixture was heated to 70 °C overnight. Saturated aqueous NaHCO₃ solution was added and the mixture was extracted with EtOAc. The organic layer was dried (Na₂SO₄), filtered and evaporated *in vacuo*. The intermediate was purified by column chromatography using a C18 cartridge (0-30% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH). The intermediate obtained (63.0 mg, 0.130 mmol) was dissolved in methanol (6 mL). Ammonium formate (161 mg, 2.55 mmol) and 10% wt. Pd/C (15 mg, 0.140 mmol) were added and the mixture was stirred at 70 °C overnight. The suspension was filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in EtOAc and washed with water, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The product was purified by preparative HPLC to afford the title compound (5.3 mg, 0.011 mmol, 8% yield) as a white solid.

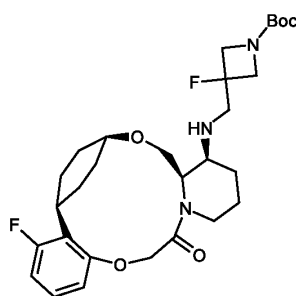
Table 6. Prepared Compound and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
205		Rel-2-((1s,15S,16R,19s)-3,6-difluoro-10-oxo-8,18-dioxa-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-	[M+H] ⁺ 496.4	¹ H NMR (500 MHz, MeOD) δ 8.21 (d, J = 8.0 Hz, 1H), 7.88 - 7.76 (m, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.03 (ddd, J = 5.1, 9.3, 11.0 Hz, 1H), 6.81 (dt, J = 4.0, 9.1 Hz, 1H), 5.61 (dd, J = 3.5, 12.4 Hz, 1H), 5.39 - 5.29 (m, 1H), 5.03 - 4.90 (m, 2H), 4.26 (dd, J = 1.8, 12.3 Hz, 1H), 4.16 - 4.09 (m, 1H), 4.09 - 3.99 (m, 2H), 3.71 (br s, 1H), 3.64 (dt, J = 2.5, 13.5 Hz, 1H), 3.40 (dd, J = 3.4, 8.8 Hz, 1H), 3.20 - 3.09 (m, 1H), 2.77 - 2.66 (m, 1H), 2.22 (br d,	D

		yl]amino}methylbenzonitrile		J = 14.1 Hz, 1H), 2.14 - 1.98 (m, 4H), 1.85 - 1.73 (m, 2H), 1.54 - 1.38 (m, 3H), 1.37 - 1.30 (m, 1H).	
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[0293] SYNTHESIS OF INTERMEDIATE 24

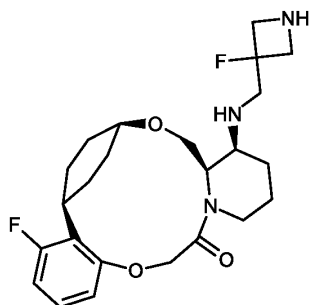
[0294] Rel-tert-butyl 3-fluoro-3-({[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}methyl)azetidine-1-carboxylate



[0295] A solution of tert-butyl 3-(aminomethyl)-3-fluoro-azetidine-1-carboxylate (424 mg, 2.08 mmol), Intermediate 23 (150 mg, 0.415 mmol) and Ti(OEt)₄ (189 mg, 0.830 mmol) in THF (8 mL) was stirred at 70 °C overnight. The mixture was cooled to room temperature and sodium cyanoborohydride (411 mg, 6.64 mmol) was added. The mixture was then stirred for 5 h. Saturated aqueous NaHCO₃ solution was added and the mixture was extracted with EtOAc. The organic layer was dried (Na₂SO₄) and evaporated *in vacuo*. The product was purified by column chromatography using a silica cartridge (30-80% EtOAc in cHex) to afford the title compound (242 mg, quant. yield) as a white solid. [M+H]⁺ m/z = 550.4

[0296] Example 206

[0297] Rel-(1s,15S,16R,19s)-3-fluoro-15-{{[(3-fluoroazetidin-3-yl)methyl]amino}-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-10-one



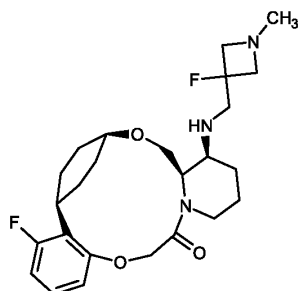
[0298] To a solution of Intermediate 24 (242 mg, 0.440 mmol) in 1,4-dioxane (2 mL), a 4 M solution of HCl in 1,4-dioxane (2.2 mL, 8.81 mmol) was added. The mixture was stirred at room temperature for 3 h. The mixture was evaporated *in vacuo*, then the residue was dissolved in MeOH and loaded onto a SCX cartridge (2g), which was then washed with MeOH and eluted with a 7 M NH₃ solution in MeOH. The basic fractions were evaporated *in vacuo* to afford the title compound (158 mg, 0.351 mmol, 80% yield) as a white solid.

Table 7. Prepared Compound and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
206		(1s,15S,16R,19s)-3-fluoro-15-{{[(3-fluoroazetidin-3-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 450.3	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.20 - 7.11 (m, 1H), 6.79 - 6.71 (m, 1H), 6.69 (d, J = 8.2 Hz, 1H), 5.31 (d, J = 10.3 Hz, 1H), 5.11 - 4.96 (m, 1H), 3.98 (d, J = 10.3 Hz, 1H), 3.85 - 3.75 (m, 1H), 3.70 - 3.59 (m, 2H), 3.58 - 3.20 (m, 6H), 3.11 - 2.91 (m, 3H), 2.77 - 2.68 (m, 1H), 2.66 - 2.54 (m, 1H), 2.32 - 2.18 (m, 1H), 2.16 - 2.07 (m, 1H), 1.83 - 1.62 (m, 3H), 1.52 - 1.35 (m, 3H), 1.34 - 1.22 (m, 2H), 1.18 - 1.07 (m, 1H).	D

[0299] Example 207

[0300] Rel-(1s,15S,16R,19s)-3-fluoro-15-{{[(3-fluoro-1-methylazetidin-3-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-10-one

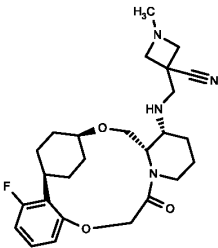
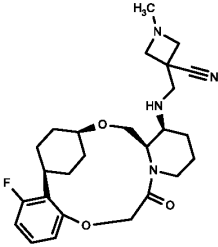
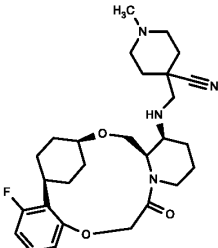


[0301] To a solution of Example 202 (50 mg, 0.110 mmol) in DCM (3 mL), formaldehyde (0.41 mL, 0.110 mmol) and triethylamine (0.05 mL, 0.330 mmol) were added, followed by sodium triacetoxyborohydride (47 mg, 0.220 mmol). The mixture was stirred at room temperature overnight. Saturated aqueous NaHCO₃ solution was added and the mixture was extracted with DCM. The combined organic layer was dried (Na₂SO₄), filtered and evaporated *in vacuo*. The product was purified by preparative HPLC to afford the title compound (1.7 mg, 0.004 mmol, 3% yield) as a white solid.

[0302] The examples reported in the table below were synthesized using a similar procedure to that described for Example 207 starting from the appropriate amine intermediate. Stereoisomers were separated by chiral SFC purification using appropriate chiral columns and eluent modifiers; Chiralcel columns (OD-H); methanol + 0.1 % isopropylamine.

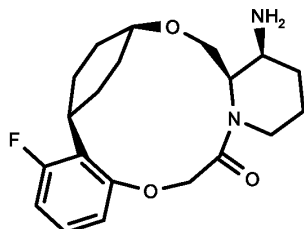
Table 8. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
207		(1s,15S,16R,19s)-3-fluoro-15-[[[(3-fluoro-1-methylazetidin-3-yl)methyl]amino]-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tetracosan-2(7),3,5-trien-10-one	[M+H] ⁺ 464.3	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.22 - 7.06 (m, 1H), 6.90 - 6.72 (m, 1H), 6.71 - 6.58 (m, 1H), 5.35 - 5.25 (m, 1H), 5.07 - 4.96 (m, 1H), 4.03 - 3.93 (m, 1H), 3.86 - 3.72 (m, 1H), 3.71 - 3.62 (m, 1H), 3.62 - 3.56 (m, 1H), 3.45 - 3.38 (m, 2H), 3.37 - 3.34 (m, 1H), 3.30 - 3.24 (m, 1H), 3.09 - 2.87 (m, 5H), 2.76 - 2.67 (m, 1H), 2.33 - 2.18 (m, 3H), 2.66 - 2.17 (m, 2H), 1.89 - 1.79 (m, 1H), 2.17 - 1.27 (m, 8H), 1.27 - 1.06 (m, 2H).	D

208		1-methyl-3-((1S,15R,16S,19S)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-15-yl)amino}methyl)azetidine-3-carbonitrile	[M+H] ⁺ 471.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.75 - 6.63 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.25 - 5.16 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 9.5, 11.0 Hz, 1H), 3.81 - 3.74 (m, 1H), 3.70 (br s, 1H), 3.57 - 3.48 (m, 4H), 3.40 (t, J = 8.5 Hz, 2H), 3.15 (s, 2H), 3.19 - 3.09 (m, 1H), 2.90 (td, J = 4.7, 12.0 Hz, 1H), 2.77 - 2.63 (m, 1H), 2.36 (s, 3H), 2.35 - 2.25 (m, 1H), 2.22 - 2.12 (m, 1H), 1.95 - 1.77 (m, 3H), 1.70 - 1.44 (m, 3H), 1.44 - 1.33 (m, 2H), 1.29 - 1.21 (m, 1H).	A
209		1-methyl-3-((1S,15S,16R,19S)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-15-yl)amino}methyl)azetidine-3-carbonitrile	[M+H] ⁺ 471.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.75 - 6.63 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.25 - 5.16 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 9.5, 11.0 Hz, 1H), 3.81 - 3.74 (m, 1H), 3.70 (br s, 1H), 3.57 - 3.48 (m, 4H), 3.40 (t, J = 8.5 Hz, 2H), 3.15 (s, 2H), 3.19 - 3.09 (m, 1H), 2.90 (td, J = 4.7, 12.0 Hz, 1H), 2.77 - 2.63 (m, 1H), 2.36 (s, 3H), 2.35 - 2.25 (m, 1H), 2.22 - 2.12 (m, 1H), 1.95 - 1.77 (m, 3H), 1.70 - 1.44 (m, 3H), 1.44 - 1.33 (m, 2H), 1.29 - 1.21 (m, 1H).	A
210		Rel-1-methyl-4-((1S,15S,16R,19S)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]trien-15-yl)amino}methyl)piperidine-4-carbonitrile	[M+H] ⁺ 499.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.6, 8.2 Hz, 1H), 6.74 - 6.64 (m, 2H), 5.31 (d, J = 10.6 Hz, 1H), 5.23 - 5.15 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 9.5, 10.9 Hz, 1H), 3.77 (br d, J = 12.5 Hz, 1H), 3.69 (br s, 1H), 3.54 (dd, J = 3.8, 9.2 Hz, 1H), 3.48 (dt, J = 2.7, 13.2 Hz, 1H), 3.19 - 3.09 (m, 1H), 2.95 (br d, J = 12.1 Hz, 2H), 2.89 (d, J = 1.4 Hz, 2H), 2.88 - 2.84 (m, 1H), 2.76 - 2.64 (m, 1H), 2.37 (s, 3H), 2.43 - 2.24 (m, 3H), 2.22 - 2.13 (m, 1H), 2.08 - 1.97 (m, 2H), 1.93 - 1.77 (m, 3H), 1.71 - 1.62 (m, 2H), 1.64 - 1.51 (m, 2H), 1.51 - 1.44 (m, 1H), 1.43 - 1.33 (m, 2H), 1.27 - 1.17 (m, 1H).	C

[0303] SYNTHESIS OF INTERMEDIATE 25

[0304] Rel-(1s,15S,16R,19s)-15-amino-3-fluoro-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2-(7),3,5-trien-10-one

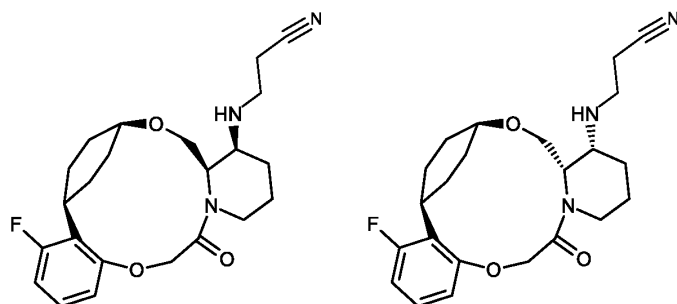


[0305] Intermediate 23 (1200 mg, 3.09 mmol) was dissolved in DCM (10 mL) and Na₂SO₄ (890 mg, 6.18 mmol) was added followed by (4-methoxyphenyl)methanamine (0.86 mL, 6.18 mmol). The reaction mixture was stirred while sodium triacetoxymethylborohydride (1309 mg, 6.18 mmol) was added portionwise over 1 h and then stirred at room temperature for 1 h. The mixture was diluted with DCM and washed with saturated aqueous NaHCO₃ solution and brine. The organic layer was dried (Na₂SO₄), filtered and then concentrated *in vacuo*. The residue was dissolved in EtOH (37.2 mL) and then ammonium formate (5842 mg, 92.64 mmol) followed by palladium on Carbon 10% wet (3286 mg, 1.54 mmol) were added to the reaction mixture. The round-bottomed flask was subjected to three cycles of vacuum/N_{2(g)} and then it was heated at 80°C for 2 h. The mixture was filtered over a Celite pad and the filtrate evaporated *in vacuo*. The product was purified through precipitation in MeCN to afford the title compound (1000 mg, 2.76 mmol, 89% yield) as a white solid. [M+H]⁺ m/z = 363.4

[0306] Examples 211, 212

[0307] Example 211: 3-{[(1s,15R,16R,19s)-3-fluoro-10-oxo-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}propanenitrile

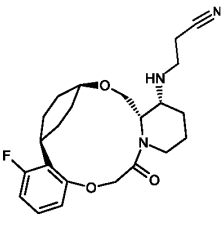
[0308] Example 212: 3-{[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}propanenitrile



[0309] To a solution of Intermediate 25 (250 mg, 0.690 mmol) in MeOH (3 mL), 2-propenenitrile (0.07 mL, 1.03 mmol) was added and the mixture was stirred at 70 °C overnight. The solvent was evaporated *in vacuo*. The product was purified by column chromatography using a silica cartridge (0-5% MeOH in DCM) followed by another column chromatography using a C18 cartridge (0-30% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) to afford a mixture of stereoisomers. The latter was submitted to chiral preparative SFC separation using a Chiralpak ID column (25 x 2.0 cm), 5 μ modifier (methanol + 0.1% isopropylamine) 20%, flow rate (ml/min) 45, pressure (bar) 120, temperature (°C) 40, to afford the title compounds (Example 210, 12.8 mg, 100% ee; Example 211, 20.1 mg, 99.2% ee).

Table 9. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
211		3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}propa nenitrile	[M+H] ⁺ 416.2	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.11 - 7.22 (m, 1 H), 6.75 (t, J=8.9 Hz, 1 H), 6.69 (d, J=8.2 Hz, 1 H), 5.31 (d, J=10.3 Hz, 1 H), 4.93 - 5.02 (m, 1 H), 3.98 (d, J=10.3 Hz, 1 H), 3.75 - 3.83 (m, 1 H), 3.66 (br d, J=13.4 Hz, 1 H), 3.57 - 3.62 (m, 1 H), 3.38 (dd, J=9.2, 3.8 Hz, 1 H), 3.23 - 3.31 (m, 1 H), 2.97 - 3.09 (m, 1 H), 2.80 (q, J=6.8 Hz, 2 H), 2.66 - 2.76 (m, 1 H), 2.53 - 2.64 (m, 3 H), 2.24 (qd, J=12.9, 3.8 Hz, 1 H), 2.12 (br d, J=13.0 Hz, 1 H), 2.01 - 2.09 (m, 1 H), 1.62 - 1.78 (m, 3 H), 1.21 - 1.56 (m, 5 H), 1.05 - 1.19 (m, 1 H).	A

212		3- {[(1s,15R,16S, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7,0^{11,16}} t ricosa-2(7),3,5- trien-15- yl]amino}propa nenitrile	[M+H] ⁺ 416.2	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.16 (td, J=8.2, 6.8 Hz, 1 H), 6.68 - 6.79 (m, 2 H), 5.32 (d, J=10.3 Hz, 1 H), 4.81 (br d, J=8.8 Hz, 1 H), 3.97 (d, J=10.3 Hz, 1 H), 3.81 - 3.91 (m, 1 H), 3.66 (br d, J=12.5 Hz, 1 H), 3.58 - 3.63 (m, 1 H), 3.33 - 3.43 (m, 1 H), 3.17 (dd, J=8.9, 3.6 Hz, 1 H), 2.97 - 3.09 (m, 1 H), 2.78 - 2.92 (m, 2 H), 2.70 - 2.77 (m, 1 H), 2.54 - 2.67 (m, 3 H), 2.18 - 2.30 (m, 1 H), 2.07 - 2.18 (m, 1 H), 1.98 (q, J=7.2 Hz, 1 H), 1.53 - 1.85 (m, 4 H), 1.21 - 1.50 (m, 4 H), 1.08 - 1.16 (m, 1 H).	B
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[0310] Examples 213, 214, 215, 216, 217, 218

[0311] Example 213: Rel-4,4,4-trifluoro-3-{[(1s,15R,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7,0^{11,16}}]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile

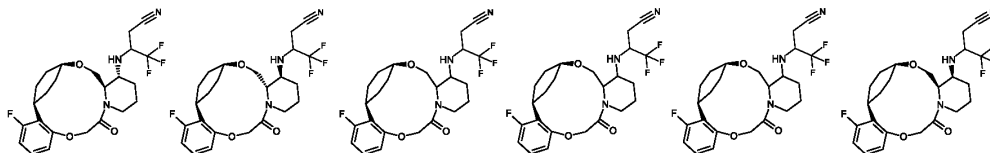
[0312] Example 214: Rel-4,4,4-trifluoro-3-{[(1s,15S,16S,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7,0^{11,16}}]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile

[0313] Example 215: 4,4,4-trifluoro-3-{[(1s,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7,0^{11,16}}]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile

[0314] Example 216: 4,4,4-trifluoro-3-{[(1s,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7,0^{11,16}}]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile

[0315] Example 217: 4,4,4-trifluoro-3-{[(1s,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7,0^{11,16}}]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile

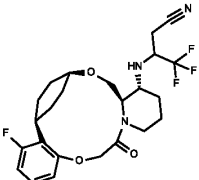
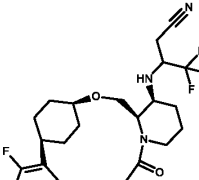
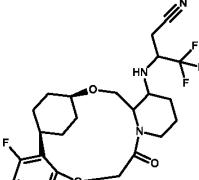
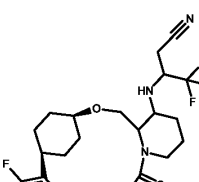
[0316] Example 218: Rel-4,4,4-trifluoro-3-{[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7,0^{11,16}}]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile

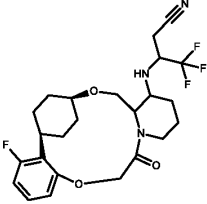
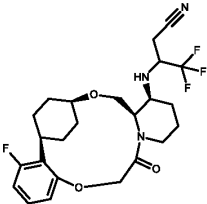


[0317] To a mixture of (1s,19s)-3-fluoro-15-nitro-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricos-2(7),3,5-trien-10-one (1.2 g, 3.06 mmol) in AcOH (5 mL) and EtOH (40 mL) at 0 °C, was added Zn powder (2.0 g, 30.58 mmol) portionwise and the mixture was stirred for 16 h, allowing the mixture to warm to room temperature. The reaction mixture was filtered through a pad of Celite, rinsing with MeOH. The filtrate was concentrated, then saturated aqueous NaHCO₃ solution and DCM were added and an emulsion was formed. This emulsion was filtered over a pad of Celite, then the two phases of the filtrate were separated and the aqueous phase was extracted with DCM. The combined organic phases were dried over Na₂SO₄, filtered and concentrated. A portion of the residue (250 mg, 0.690 mmol) was dissolved in MeCN (5 mL), 4,4,4-trifluorobut-2-enenitrile (0.1 mL, 1.03 mmol) was added followed by DBU (0.1 mL, 0.690 mmol). The mixture was shaken at room temperature for 5 h. Additional 4,4,4-trifluorobut-2-enenitrile (0.1 mL, 1.03 mmol) was added and the reaction was shaken at room temperature overnight. The mixture was evaporated *in vacuo* and the residue was dissolved in EtOAc and washed with saturated aqueous NH₄Cl solution. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product was purified by column chromatography using a C18 cartridge (5-80% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) to afford a mixture of diastereoisomers. The latter was submitted to chiral preparative separation using a Whelk O1 column (25 x 2.0 cm), Eluent: hexane/(ethanol + 0.1% isopropylamine) 80%/20%, flow rate (ml/min) 17. Using this chiral HPLC method the mixture of stereoisomeric products was separated into six peaks. Fractions corresponding to the six peaks were collected separately to give Examples 209-214 (Example 209, 6 mg, 100% a/a% peak 1 rt=9.8min; Example 210, 13.1 mg, 100% a/a% peak 2 rt=11.1min; Example 211, 6.8 mg, 99.1% a/a% peak 3 rt=14.6min; Example 212, 7.7 mg, 83.9% a/a% peak 4 rt=15.8min; Example 213, 17 mg, 93.4% a/a% peak 5 rt=17.4min; Example 214, 11.3 mg, 99.6% a/a% peak 6 rt=20.5min). NMR spectra of these six examples indicate that some were single stereoisomers whereas others were mixtures of stereoisomers (NMR peak list is provided in the table below for single stereoisomers but not for mixtures).

Table 10. Prepared Compounds and the Biological Activity Thereof

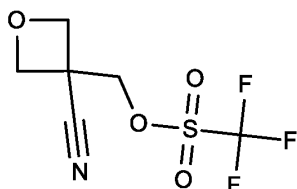
Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
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213		Rel-4,4,4-trifluoro-3-([(1s,15R,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile	[M+H] ⁺ 484.2	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.2 Hz, 1H), 6.73 - 6.63 (m, 2H), 5.31 (d, J = 10.5 Hz, 1H), 5.01 (br d, J = 10.7 Hz, 1H), 4.13 (d, J = 10.5 Hz, 1H), 4.00 (dd, J = 9.2, 10.6 Hz, 1H), 3.94 - 3.87 (m, 1H), 3.80 (br dd, J = 3.3, 13.4 Hz, 1H), 3.71 (br s, 1H), 3.59 (dt, J = 3.2, 13.4 Hz, 1H), 3.29 - 3.25 (m, 1H), 3.19 (br s, 1H), 3.16 - 3.09 (m, 1H), 2.98 - 2.81 (m, 2H), 2.78 - 2.63 (m, 1H), 2.31 (dq, J = 3.9, 13.0 Hz, 1H), 2.24 - 1.14 (m, 10H).	B
214		Rel-4,4,4-trifluoro-3-([(1s,15S,16S,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile	[M+H] ⁺ 484.2	¹ H NMR (400 MHz, MeOD) δ 7.13 (dt, J = 6.5, 8.2 Hz, 1H), 6.73 - 6.63 (m, 2H), 5.31 (d, J = 10.5 Hz, 1H), 5.01 (br d, J = 10.7 Hz, 1H), 4.13 (d, J = 10.5 Hz, 1H), 4.00 (dd, J = 9.2, 10.6 Hz, 1H), 3.94 - 3.87 (m, 1H), 3.80 (br dd, J = 3.3, 13.4 Hz, 1H), 3.71 (br s, 1H), 3.59 (dt, J = 3.2, 13.4 Hz, 1H), 3.29 - 3.25 (m, 1H), 3.19 (br s, 1H), 3.16 - 3.09 (m, 1H), 2.98 - 2.81 (m, 2H), 2.78 - 2.63 (m, 1H), 2.31 (dq, J = 3.9, 13.0 Hz, 1H), 2.24 - 1.14 (m, 10H).	A
215		4,4,4-trifluoro-3-([(1s,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile	[M+H] ⁺ 484.2	Peaks not assigned as compound isolated as mixture of stereoisomers	A
216		4,4,4-trifluoro-3-([(1s,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile	[M+H] ⁺ 484.2	Peaks not assigned as compound isolated as mixture of stereoisomers	A

217		4,4,4-trifluoro-3- $\{[(1S,19S)$ -3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ³ ,7.0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile	$[M+H]^+$ 484.3	Peaks not assigned as compound isolated as mixture of stereoisomers	A
218		Rel-4,4,4-trifluoro-3- $\{[(1S,15S,16R,19S)$ -3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ³ ,7.0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}butanenitrile	$[M+H]^+$ 484.2	¹ H NMR (400 MHz, METHANOL-d ₄) δ = 7.24 - 7.04 (m, 1H), 6.81 - 6.61 (m, 2H), 5.40 - 5.26 (m, 1H), 5.24 - 5.14 (m, 1H), 4.24 - 4.07 (m, 1H), 4.07 - 3.85 (m, 2H), 3.83 - 3.65 (m, 3H), 3.58 - 3.44 (m, 1H), 3.25 - 3.06 (m, 2H), 2.98 - 2.70 (m, 2H), 2.72 - 2.59 (m, 1H), 2.42 - 2.24 (m, 1H), 2.23 - 2.12 (m, 1H), 1.96 - 1.77 (m, 3H), 1.69 - 1.55 (m, 1H), 1.54 - 1.17 (m, 5H)	A

[0318] SYNTHESIS OF INTERMEDIATE 26

[0319] (3-cyanooxetan-3-yl)methyl trifluoromethanesulfonate

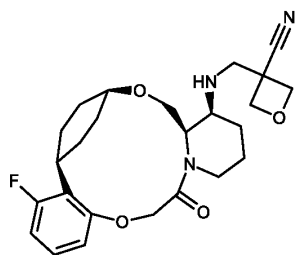


[0320] 3-(hydroxymethyl)oxetane-3-carbonitrile (120 mg, 1.06 mmol) was dissolved in DCM (9.0 mL) and then triethylamine (0.19 mL, 1.38 mmol) was added at 0 °C followed by trifluoromethanesulfonic anhydride (0.2 mL, 1.17 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with DCM and then washed with saturated aqueous NaHCO₃ solution and brine. The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the title compound (250 mg, 1.02 mmol, 96% yield) as a

colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.07 (d, $J = 7.0$ Hz, 2H), 4.91 (s, 2H), 4.59 (d, $J = 7.0$ Hz, 2H).

[0321] Example 219

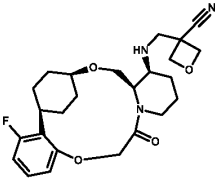
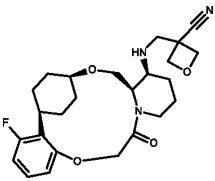
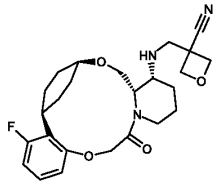
[0322] Rel-3-3-({[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}methyl)oxetane-3-carbonitrile

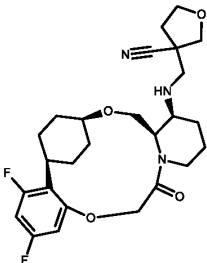
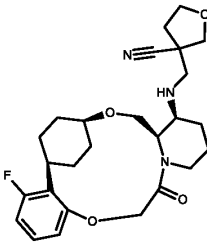
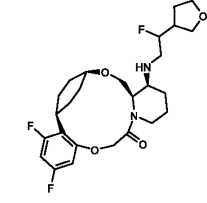
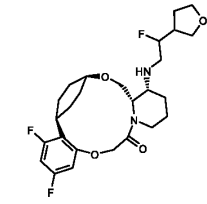


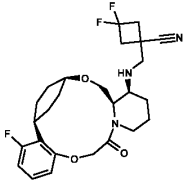
[0323] Intermediate 25 (120 mg, 0.330 mmol) was dissolved in MeCN (1.6 mL) and then potassium carbonate (92 mg, 0.660 mmol) was added followed by Intermediate 26 (162 mg, 0.660 mmol). The reaction mixture was heated to 60°C for 30 minutes and then concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO_3 solution, saturated aqueous NH_4Cl solution and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The product was purified by column chromatography using a silica cartridge (0-100% EtOAc in cHex), then by a second column chromatography using a C18 cartridge (0-45% MeCN + 0.1% HCOOH in H_2O + 0.1% HCOOH) to afford the title compound (12.6 mg, 0.028 mmol, 8% yield) as a white powder.

[0324] The examples reported in the table below were synthesized using a similar procedure to that described for Example 219 starting from the appropriate amine alkyl trifluoromethanesulfonate. Stereoisomers were separated by chiral SFC purification using appropriate chiral columns and eluent modifiers; Chiralcel columns (OD-H); methanol + 0.1 % isopropylamine.

Table 11. Prepared Compounds and the Biological Activity Thereof

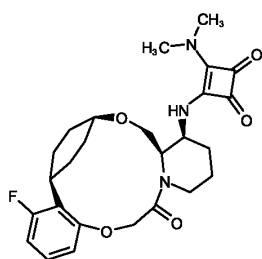
Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
219		Rel-3- ({[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)oxetane-3- carbonitrile	[M+H] ⁺ 458.7	¹ H NMR (400 MHz, MeOD) δ 7.20 - 7.04 (m, 1H), 6.80 - 6.63 (m, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.25 - 5.17 (m, 1H), 4.60 (dd, J = 6.5, 7.8 Hz, 2H), 4.12 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 9.4, 11.1 Hz, 1H), 3.82 - 3.72 (m, 1H), 3.69 (br s, 1H), 3.52 (dd, J = 4.0, 9.3 Hz, 1H), 3.51 - 3.44 (m, 1H), 3.32 - 3.28 (m, 2H), 3.19 - 3.09 (m, 1H), 2.98 - 2.88 (m, 1H), 2.77 - 2.63 (m, 1H), 2.30 (dq, J = 3.8, 12.9 Hz, 1H), 2.22 - 2.13 (m, 1H), 1.98 - 1.76 (m, 3H), 1.70 - 1.58 (m, 1H), 1.60 - 1.51 (m, 1H), 1.51 - 1.41 (m, 1H), 1.46 - 1.27 (m, 2H), 1.26 - 1.18 (m, 1H).	A
220		3- ({[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)oxetane-3- carbonitrile	[M+H] ⁺ 458.7	¹ H NMR (400 MHz, MeOD) δ 7.20 - 7.04 (m, 1H), 6.80 - 6.63 (m, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.25 - 5.17 (m, 1H), 4.60 (dd, J = 6.5, 7.8 Hz, 2H), 4.12 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 9.4, 11.1 Hz, 1H), 3.82 - 3.72 (m, 1H), 3.69 (br s, 1H), 3.52 (dd, J = 4.0, 9.3 Hz, 1H), 3.51 - 3.44 (m, 1H), 3.32 - 3.28 (m, 2H), 3.19 - 3.09 (m, 1H), 2.98 - 2.88 (m, 1H), 2.77 - 2.63 (m, 1H), 2.30 (dq, J = 3.8, 12.9 Hz, 1H), 2.22 - 2.13 (m, 1H), 1.98 - 1.76 (m, 3H), 1.70 - 1.58 (m, 1H), 1.60 - 1.51 (m, 1H), 1.51 - 1.41 (m, 1H), 1.46 - 1.27 (m, 2H), 1.26 - 1.18 (m, 1H).	A
221		3- ({[(1s,15R,16S, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} ,0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}meth yl)oxetane-3- carbonitrile	[M+H] ⁺ 458.7	¹ H NMR (400 MHz, MeOD) δ 7.20 - 7.04 (m, 1H), 6.80 - 6.63 (m, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.25 - 5.17 (m, 1H), 4.60 (dd, J = 6.5, 7.8 Hz, 2H), 4.12 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 9.4, 11.1 Hz, 1H), 3.82 - 3.72 (m, 1H), 3.69 (br s, 1H), 3.52 (dd, J = 4.0, 9.3 Hz, 1H), 3.51 - 3.44 (m, 1H), 3.32 - 3.28 (m, 2H), 3.19 - 3.09 (m, 1H), 2.98 - 2.88 (m, 1H), 2.77 - 2.63 (m, 1H), 2.30 (dq, J = 3.8, 12.9 Hz, 1H), 2.22 - 2.13 (m, 1H), 1.98 - 1.76 (m, 3H), 1.70 - 1.58 (m, 1H), 1.60 - 1.51 (m, 1H), 1.51 - 1.41 (m, 1H), 1.46 - 1.27 (m, 2H), 1.26 - 1.18 (m, 1H).	B

222		Rel-3-((1s,15S,16R,19s)-3,5-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7,0^{11,16}}]tricyclic-2(7),3,5-trien-15-yl)amino}methyl)oxolane-3-carbonitrile	[M+H] ⁺ 490.4	¹ H NMR (400 MHz, MeOD) δ 6.59 - 6.46 (m, 2H), 5.30 (d, J = 10.3 Hz, 1H), 5.24 - 5.12 (m, 1H), 4.12 (d, J = 10.3 Hz, 1H), 4.01 (dd, J = 4.6, 9.0 Hz, 1H), 3.98 - 3.89 (m, 3H), 3.84 - 3.80 (m, 1H), 3.75 (br d, J = 11.9 Hz, 1H), 3.69 (br s, 1H), 3.58 - 3.42 (m, 2H), 3.15 - 3.04 (m, 1H), 3.03 - 2.85 (m, 3H), 2.70 - 2.55 (m, 1H), 2.41 - 2.22 (m, 2H), 2.22 - 2.08 (m, 2H), 1.94 - 1.76 (m, 3H), 1.74 - 1.17 (m, 6H).	A
223		Rel-3-((1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7,0^{11,16}}]tricyclic-2(7),3,5-trien-15-yl)amino}methyl)oxolane-3-carbonitrile	[M+H] ⁺ 472.3	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.6, 8.2 Hz, 1H), 6.74 - 6.63 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 5.24 - 5.16 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 4.03 - 3.98 (m, 1H), 3.98 - 3.90 (m, 3H), 3.85 - 3.80 (m, 1H), 3.77 (br d, J = 14.4 Hz, 1H), 3.70 (br s, 1H), 3.59 - 3.45 (m, 2H), 3.20 - 3.10 (m, 1H), 3.09 - 2.85 (m, 3H), 2.77 - 2.64 (m, 1H), 2.43 - 2.25 (m, 2H), 2.24 - 2.09 (m, 2H), 1.96 - 1.76 (m, 3H), 1.72 - 1.18 (m, 6H).	A
224		Rel-(1s,15S,16R,19s)-3,5-difluoro-15-{[2-fluoro-2-(oxolan-3-yl)ethyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7,0^{11,16}}]tricyclic-2(7),3,5-trien-10-one	[M+H] ⁺ 497.4	ND	D
225		Rel-(1s,15R,16S,19s)-3,5-difluoro-15-{[2-fluoro-2-(oxolan-3-yl)ethyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7,0^{11,16}}]tricyclic-2(7),3,5-trien-10-one	[M+H] ⁺ 497.5	ND	D

226		Rel-3,3-difluoro-1-((1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-yl)amino}methyl)cyclobutane-1-carbonitrile	[M+H] ⁺ 492.4	¹ H NMR (500 MHz, MeOD) δ 7.13 (dt, J = 6.4, 8.2 Hz, 1H), 6.75 - 6.62 (m, 2H), 5.31 (d, J = 10.6 Hz, 1H), 5.24 - 5.13 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.94 (dd, J = 9.5, 10.9 Hz, 1H), 3.77 (br d, J = 12.1 Hz, 1H), 3.70 (br s, 1H), 3.53 (dd, J = 3.9, 9.3 Hz, 1H), 3.52 - 3.45 (m, 1H), 3.19 - 3.09 (m, 1H), 3.08 (s, 2H), 2.94 - 2.88 (m, 1H), 3.06 - 2.86 (m, 4H), 2.75 - 2.64 (m, 1H), 2.30 (dq, J = 4.1, 13.0 Hz, 1H), 2.22 - 2.14 (m, 1H), 1.95 - 1.78 (m, 3H), 1.68 - 1.58 (m, 1H), 1.58 - 1.52 (m, 1H), 1.52 - 1.44 (m, 1H), 1.44 - 1.33 (m, 2H), 1.27 - 1.19 (m, 1H).	B
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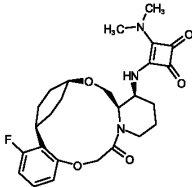
[0325] Example 227

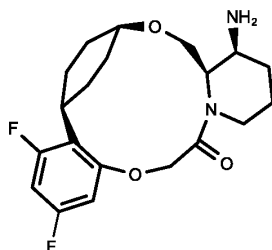
[0326] Rel-3-(dimethylamino)-4-{{[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}cyclobut-3-ene-1,2-dione



[0327] To a solution of Intermediate 25 (15 mg, 0.040 mmol) and DIPEA (0.01 mL, 0.060 mmol) in ethanol (0.8 mL) at 0 °C was added 3,4-diethoxycyclobut-3-ene-1,2-dione (0.01 mL, 0.060 mmol). The reaction mixture was stirred at this temperature for 1 h. After complete consumption of the starting material, the reaction mixture was warmed to room temperature and further DIPEA (0.11 mL, 0.620 mmol) was added. *N,N*-dimethylamine hydrochloride (51 mg, 0.620 mmol) was added to the reaction mixture and it was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc and then washed with saturated aqueous NH₄Cl solution, saturated aqueous NaHCO₃ solution and brine. The organic phase was dried over (Na₂SO₄), filtered and then concentrated to dryness *in vacuo*. The product was purified by column chromatography using a silica cartridge (0-75% EtOAc in cHex) to afford the title compound (19 mg, 0.039 mmol, 95% yield) as a white solid.

Table 12. Prepared Compound and the Biological Activity Thereof

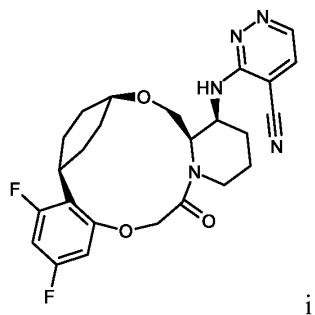
Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
227		Rel-3-(dimethylamino)-4-([(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}cyclobut-3-ene-1,2-dione	[M+H] ⁺ 486.4	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.58 - 7.30 (m, 1H), 7.22 - 7.09 (m, 1H), 6.97 - 6.61 (m, 2H), 5.40 - 5.28 (m, 1H), 5.06 - 4.93 (m, 1H), 4.51 - 4.38 (m, 1H), 4.01 - 3.92 (m, 1H), 3.90 - 3.80 (m, 1H), 3.74 - 3.62 (m, 2H), 3.42 - 3.35 (m, 1H), 3.31 - 3.29 (m, 1H), 3.25 - 3.17 (m, 6H), 3.09 - 2.95 (m, 1H), 2.62 - 2.15 (m, 2H), 2.15 - 1.60 (m, 5H), 1.58 - 1.08 (m, 5H).	D

[0328] SYNTHESIS OF INTERMEDIATE 27**[0329]** Rel-(1s,15S,16R,19s)-15-amino-3,5-difluoro-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-10-one

[0330] Intermediate 27 was synthesized using a similar procedure to that described for Intermediate 25 using the appropriate ketone starting material to afford the title compound (0.6 g) as a white solid. [M+H]⁺ m/z = 381.3

[0331] Example 228

Rel-3-{[(1s,15S,16R,19s)-3,5-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo
[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}pyridazine-4-carbonitrile

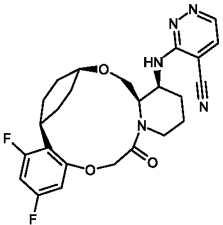
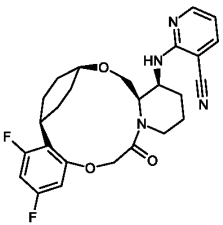
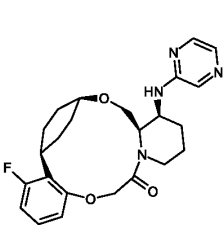


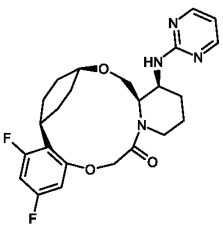
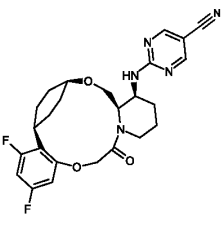
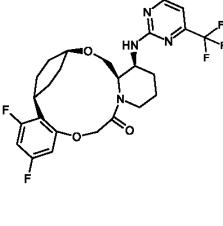
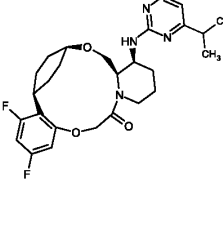
[0332] 3-Chloropyridazine-4-carbonitrile (16.5 mg, 0.120 mmol), CsF (12 mg, 0.080 mmol), and Intermediate 27 (30.0 mg, 0.080 mmol) were dissolved in DMSO (1.5 mL). The mixture was stirred at room temperature for 30 minutes, then it was diluted with saturated aqueous NaHCO₃ solution and extracted with EtOAc. The combined organic layers were evaporated *in vacuo* and purified by column chromatography using a C18 cartridge (5-60% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) followed by column chromatography using a silica cartridge (0-60% EtOAc in DCM). The residue was triturated to afford the title compound (4 mg, 0.008 mmol, 10% yield) as a white solid.

[0333] The examples reported in the table below were synthesized using a similar procedure to that described for Example 228 starting from the appropriate amine intermediate and the appropriate heteroarylhalide. A different reaction temperature was used for the synthesis of Example 229 (40 °C), Examples 235 and 236 (80 °C), Examples 232 and 233, 237 (60 °C), Examples 231 and 234 (100 °C), Example 230 (120 °C). For Examples 235 and 236, in addition to the standard procedure triethylamine (2 eq.) was also added to the reaction mixture. For Example 235 MeCN was used as reaction solvent. Stereoisomers were separated by chiral purification using appropriate chiral columns and combinations of solvent mixtures.

Table 13. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
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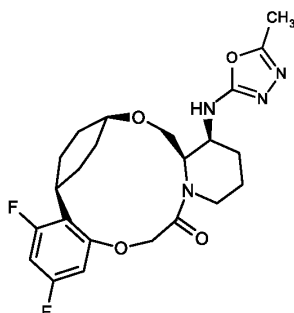
228		Rel-3-([(1s,15S,16R,19s)-3,5-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}pyridazine-4-carbonitrile	[M+H] ⁺ 484.4	¹ H NMR (400 MHz, CDCl ₃) δ 8.78 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 4.8 Hz, 1H), 6.46 (dt, J = 2.5, 9.5 Hz, 1H), 6.36 - 6.28 (m, 1H), 5.50 - 5.42 (m, 1H), 5.23 (br d, J = 7.1 Hz, 1H), 5.11 (d, J = 10.1 Hz, 1H), 4.85 - 4.77 (m, 1H), 4.30 (d, J = 10.1 Hz, 1H), 3.86 (t, J = 8.7 Hz, 1H), 3.74 (br s, 2H), 3.69 - 3.60 (m, 1H), 3.60 (dd, J = 4.2, 8.9 Hz, 1H), 3.14 - 3.04 (m, 1H), 2.63 - 2.49 (m, 1H), 2.23 - 2.03 (m, 2H), 1.99 - 1.76 (m, 5H), 1.50 - 1.23 (m, 4H).	B
229		Rel-2-([(1s,15S,16R,19s)-3,5-difluoro-10-oxo-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}pyridine-3-carbonitrile	[M+H] ⁺ 483.4	¹ H NMR (500 MHz, MeOD) δ 8.34 (dd, J = 1.9, 4.9 Hz, 1H), 7.82 (dd, J = 1.9, 7.7 Hz, 1H), 6.72 (dd, J = 4.9, 7.6 Hz, 1H), 6.57 (td, J = 1.9, 10.0 Hz, 1H), 6.52 (dt, J = 2.5, 9.5 Hz, 1H), 5.53 (ddd, J = 4.9, 5.8, 10.3 Hz, 1H), 5.34 (d, J = 10.3 Hz, 1H), 4.41 (td, J = 5.2, 11.8 Hz, 1H), 4.13 (d, J = 10.3 Hz, 1H), 4.03 (dd, J = 9.3, 11.0 Hz, 1H), 3.82 (br dd, J = 3.4, 13.8 Hz, 1H), 3.66 (br s, 1H), 3.53 (dt, J = 2.5, 13.4 Hz, 1H), 3.37 - 3.33 (m, 1H), 3.13 - 3.02 (m, 1H), 2.72 - 2.57 (m, 1H), 2.31 - 2.17 (m, 2H), 2.00 - 1.87 (m, 3H), 1.84 - 1.66 (m, 2H), 1.50 - 1.40 (m, 1H), 1.42 - 1.33 (m, 2H), 1.24 - 1.15 (m, 1H).	B
230		Rel-[(1s,15S,16R,19s)-3,5-difluoro-15-[(pyrazin-2-yl)amino]-8,18-dioxo-11-azatetracyclo[1.7.2.2.0 ² ,7,0 ¹¹ ,16]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 459.4	¹ H NMR (500 MHz, CDCl ₃) δ 8.05 (dd, J = 1.4, 2.7 Hz, 1H), 7.95 (d, J = 1.5 Hz, 1H), 7.87 (d, J = 2.7 Hz, 1H), 6.45 (ddd, J = 2.5, 9.0, 9.8 Hz, 1H), 6.32 (td, J = 2.0, 9.7 Hz, 1H), 5.54 (td, J = 4.9, 10.1 Hz, 1H), 5.09 (d, J = 10.0 Hz, 1H), 4.42 (br d, J = 7.1 Hz, 1H), 4.30 (d, J = 10.2 Hz, 1H), 4.23 - 4.15 (m, 1H), 3.89 - 3.83 (m, 1H), 3.73 - 3.64 (m, 2H), 3.61 - 3.52 (m, 1H), 3.51 - 3.45 (m, 1H), 3.15 - 3.02 (m, 1H), 2.68 - 2.48 (m, 1H), 2.18 (dq, J = 4.1, 13.0 Hz, 1H), 2.11 - 1.99 (m, 2H), 1.98 - 1.84 (m, 2H), 1.82 - 1.68 (m, 3H), 1.46 - 1.34 (m, 3H), 1.32 - 1.22 (m, 1H).	D

231		Rel- (1s,15S,16R,19s)-3,5-difluoro-15-[(pyrimidin-2-yl)amino]-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 459.4	¹ H NMR (500 MHz, CDCl ₃) δ 8.43 - 8.10 (m, 2H), 6.66 (t, J = 4.8 Hz, 1H), 6.52 - 6.38 (m, 1H), 6.31 (td, J = 1.9, 9.6 Hz, 1H), 5.96 - 5.61 (m, 1H), 5.60 - 5.49 (m, 1H), 5.08 (d, J = 10.0 Hz, 1H), 4.37 - 4.25 (m, 2H), 3.88 (dd, J = 9.1, 10.2 Hz, 1H), 3.73 - 3.64 (m, 2H), 3.59 - 3.50 (m, 2H), 3.14 - 3.02 (m, 1H), 2.61 - 2.47 (m, 1H), 2.26 - 2.13 (m, 1H), 2.12 - 1.74 (m, 6H), 1.46 - 1.06 (m, 4H).	D
232		Rel-2- {[(1s,15S,16R,19s)-3,5-difluoro-10-oxo-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}pyrimidine-5-carbonitrile	[M+H] ⁺ 484.4	¹ H NMR (500 MHz, CDCl ₃) δ 8.73 - 8.31 (m, 2H), 6.46 (dt, J = 2.1, 9.3 Hz, 1H), 6.32 (br d, J = 9.6 Hz, 1H), 5.56 (br d, J = 7.4 Hz, 1H), 5.50 (td, J = 4.8, 9.8 Hz, 1H), 5.09 (d, J = 10.2 Hz, 1H), 4.40 - 4.26 (m, 2H), 3.89 - 3.82 (m, 1H), 3.76 - 3.66 (m, 2H), 3.61 - 3.52 (m, 1H), 3.46 (dd, J = 4.0, 8.6 Hz, 1H), 3.14 - 3.03 (m, 1H), 2.60 - 2.48 (m, 1H), 2.21 - 2.10 (m, 1H), 2.09 - 0.81 (m, 10H).	C
233		Rel- (1s,15S,16R,19s)-3,5-difluoro-15-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 527.4	¹ H NMR (500 MHz, CDCl ₃) δ 8.69 - 8.36 (m, 1H), 6.91 (d, J = 4.9 Hz, 1H), 6.45 (dt, J = 2.5, 9.4 Hz, 1H), 6.32 (td, J = 1.8, 9.7 Hz, 1H), 5.67 - 5.15 (m, 2H), 5.09 (d, J = 10.2 Hz, 1H), 4.40 - 4.31 (m, 1H), 4.30 (d, J = 10.2 Hz, 1H), 3.87 (t, J = 9.5 Hz, 1H), 3.74 - 3.64 (m, 2H), 3.65 - 3.48 (m, 2H), 3.14 - 3.03 (m, 1H), 2.63 - 2.49 (m, 1H), 2.18 (dq, J = 4.1, 13.0 Hz, 1H), 2.11 - 1.66 (m, 6H), 1.51 - 1.08 (m, 4H).	D
234		Rel- (1s,15S,16R,19s)-3,5-difluoro-15-{[4-(propan-2-yl)pyrimidin-2-yl]amino}-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 501.5	¹ H NMR (400 MHz, CDCl ₃) δ 8.31 - 8.16 (m, 1H), 6.54 (d, J = 5.2 Hz, 1H), 6.50 - 6.38 (m, 1H), 6.31 (br d, J = 9.8 Hz, 1H), 6.04 - 5.66 (m, 1H), 5.64 - 5.51 (m, 1H), 5.08 (d, J = 10.1 Hz, 1H), 4.39 - 4.22 (m, 2H), 3.93 - 3.83 (m, 1H), 3.72 - 3.61 (m, 2H), 3.58 - 3.47 (m, 2H), 3.18 - 3.01 (m, 1H), 2.94 - 2.81 (m, 1H), 2.66 - 2.46 (m, 1H), 2.19 (dq, J = 4.2, 13.0 Hz, 1H), 2.13 - 2.05 (m, 1H), 1.35 - 1.26 (m, 6H), 2.04 - 1.21 (m, 9H).	D

235		Rel-4- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2(7),3,5- trien-15- yl]amino}pyrim idine-5- carbonitrile	[M+H] ⁺ 466.4	¹ H NMR (500 MHz, MeOD) δ 8.68 (s, 1H), 8.54 (s, 1H), 7.14 (dt, J = 6.4, 8.2 Hz, 1H), 6.75 - 6.65 (m, 2H), 5.52 - 5.43 (m, 1H), 5.35 (d, J = 10.4 Hz, 1H), 4.53 (td, J = 5.1, 13.0 Hz, 1H), 4.14 (d, J = 10.3 Hz, 1H), 4.03 (dd, J = 9.3, 11.0 Hz, 1H), 3.85 (br d, J = 13.6 Hz, 1H), 3.68 (br s, 1H), 3.54 (dt, J = 2.9, 13.4 Hz, 1H), 3.34 - 3.32 (m, 1H), 3.16 - 3.09 (m, 1H), 2.75 - 2.64 (m, 1H), 2.31 - 2.21 (m, 1H), 2.23 - 2.16 (m, 1H), 2.12 - 1.86 (m, 3H), 1.82 - 1.76 (m, 1H), 1.78 - 1.67 (m, 1H), 1.47 - 1.26 (m, 3H), 1.25 - 1.18 (m, 1H).	A
236		Rel-2-methyl- 4- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2(7),3,5- trien-15- yl]amino}pyrim idine-5- carbonitrile	[M+H] ⁺ 480.4	¹ H NMR (500 MHz, MeOD) δ 8.45 (s, 1H), 7.14 (dt, J = 6.6, 8.2 Hz, 1H), 6.74 - 6.65 (m, 2H), 5.55 - 5.47 (m, 1H), 5.35 (d, J = 10.4 Hz, 1H), 4.53 (td, J = 5.0, 13.0 Hz, 1H), 4.14 (d, J = 10.4 Hz, 1H), 4.02 (dd, J = 9.4, 10.9 Hz, 1H), 3.85 (br d, J = 13.4 Hz, 1H), 3.68 (br s, 1H), 3.59 - 3.49 (m, 1H), 3.32 - 3.29 (m, 1H), 3.22 - 3.10 (m, 1H), 2.80 - 2.63 (m, 1H), 2.55 (s, 3H), 2.34 - 2.15 (m, 2H), 2.07 - 1.62 (m, 5H), 1.55 - 1.12 (m, 4H).	A
237		Rel-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2(7),3,5- trien-15- yl]amino}pyridi ne-4- carbonitrile	[M+H] ⁺ 465.4	¹ H NMR (500 MHz, MeOD) δ 8.45 (s, 1H), 7.95 (d, J = 4.9 Hz, 1H), 7.44 (d, J = 5.1 Hz, 1H), 7.14 (dt, J = 6.5, 8.3 Hz, 1H), 6.76 - 6.62 (m, 2H), 5.42 - 5.37 (m, 1H), 5.35 (d, J = 10.6 Hz, 1H), 4.16 (d, J = 10.4 Hz, 1H), 4.10 - 4.01 (m, 2H), 3.85 (br dd, J = 3.8, 13.7 Hz, 1H), 3.68 (br s, 1H), 3.56 (dt, J = 2.5, 13.4 Hz, 1H), 3.37 (dd, J = 3.8, 9.2 Hz, 1H), 3.20 - 3.09 (m, 1H), 2.77 - 2.64 (m, 1H), 2.35 - 2.17 (m, 2H), 2.04 - 1.91 (m, 3H), 1.87 - 1.71 (m, 2H), 1.54 - 1.35 (m, 3H), 1.26 - 1.14 (m, 1H).	A

[0334] Example 238

[0335] Rel-(1s,15S,16R,19s)-3,5-difluoro-15-[(5-methyl-1,3,4-oxadiazol-2-yl)amino]-8,18-dioxo-11-azatetracyclo[17.2.2.0²,7,0¹¹,16]tricoso-2(7),3,5-trien-10-one



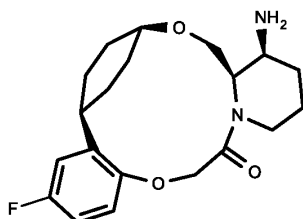
[0336] Intermediate 27 (30 mg, 0.080 mmol) was dissolved in MeCN (0.5 mL) and then triethylamine (0.02 mL, 0.160 mmol) was added followed by 2-bromo-5-methyl-1,3,4-oxadiazole (13 mg, 0.080 mmol). The reaction mixture was heated at 80 °C overnight. After 18 h the reaction mixture was cooled, diluted with saturated aqueous NaHCO₃ solution and extracted three times with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product was purified by column chromatography using a C18 cartridge (0-45% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) to afford the title compound (30 mg, 0.065 mmol, 82% yield) as a white solid.

Table 14. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
238		Rel-(1s,15S,16R,19s)-3,5-difluoro-15-[(5-methyl-1,3,4-oxadiazol-2-yl)amino]-8,18-dioxatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricosan-2(7),3,5-trien-10-one	[M+H] ⁺ 463.4	¹ H NMR (500 MHz, CDCl ₃) δ 8.11 (br s, 1H), 6.46 (dt, J = 2.4, 9.4 Hz, 1H), 6.31 (td, J = 1.8, 9.6 Hz, 1H), 5.36 (td, J = 4.5, 9.9 Hz, 1H), 5.08 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.2 Hz, 1H), 3.98 - 3.89 (m, 2H), 3.72 (br s, 1H), 3.67 (br dd, J = 3.4, 13.9 Hz, 1H), 3.57 (dd, J = 3.9, 9.1 Hz, 1H), 3.52 (dt, J = 2.6, 13.4 Hz, 1H), 3.13 - 3.04 (m, 1H), 2.57 - 2.47 (m, 1H), 2.47 (s, 3H), 2.20 - 2.11 (m, 1H), 2.14 - 2.07 (m, 2H), 2.00 - 1.91 (m, 2H), 1.88 (br d, J = 13.8 Hz, 1H), 1.67 (tq, J = 4.3, 13.2 Hz, 1H), 1.47 - 1.33 (m, 3H), 1.32 - 1.25 (m, 1H).	D

[0337] SYNTHESIS OF INTERMEDIATE 28

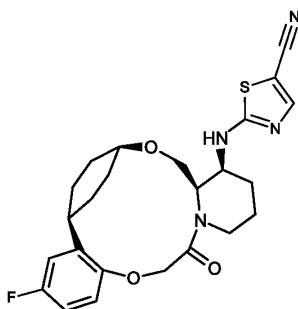
[0338] Rel-(1s,15S,16R,19s)-15-amino-4-fluoro-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-10-one



[0339] Intermediate 28 was synthesized using a similar procedure to that described for Intermediate 25 using the appropriate ketone starting material to afford the title compound (0.7 g) as a white solid. $[M+H]^+$ $m/z = 363.4$

[0340] Example 239

[0341] Rel-2-{[(1s,15S,16R,19s)-4-fluoro-10-oxo-8,18-dioxa-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}-1,3-thiazole-5-carbonitrile

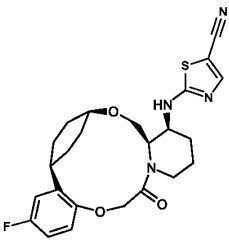
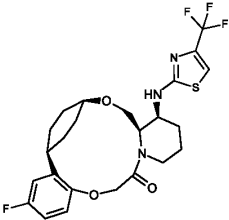


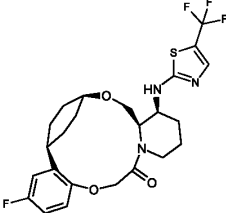
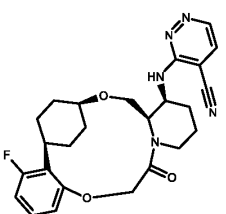
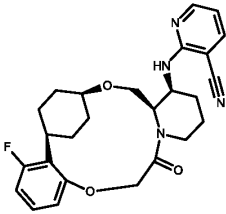
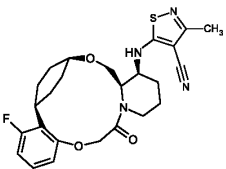
[0342] Intermediate 28 (30 mg, 0.080 mmol) and 2-bromo-5-cyanothiazole (15.6 mg, 0.080 mmol) were dissolved in DMSO (2 mL). The mixture was heated at 180 °C for 10 minutes, then it was cooled to room temperature, diluted with saturated aqueous NaHCO₃ solution and extracted twice with EtOAc. The combined organic layers were evaporated *in vacuo* and the product was

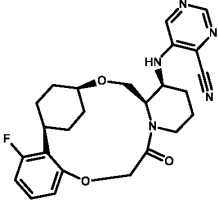
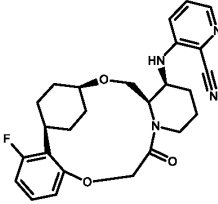
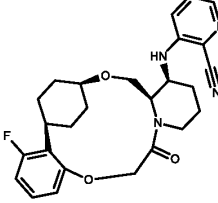
purified by column chromatography using a C18 cartridge (5-70% MeCN + HCOOH in H₂O + 0.1% HCOOH) to afford the title compound (3 mg, 0.006 mmol, 8% yield) as a white solid.

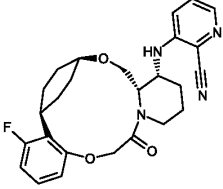
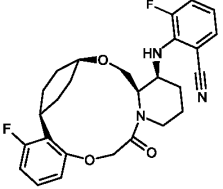
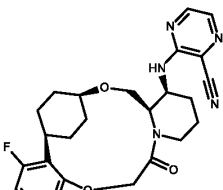
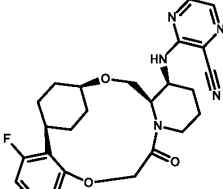
[0343] The examples reported in the table below were synthesized using a similar procedure to that described for Example 239 starting from the appropriate amine intermediate and the appropriate heteroarylhalide. A different reaction temperature was used for the synthesis of Example 242 (60 °C), Examples 244, 245, 250 and 254 (120 °C), Examples 246 and 253 (80 °C), Example 249 (150 °C). Stereoisomers were separated by chiral SFC purification using appropriate chiral columns and eluent modifiers; Chiralpak columns (AD-H); methanol + 0.1 % isopropylamine.

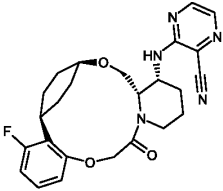
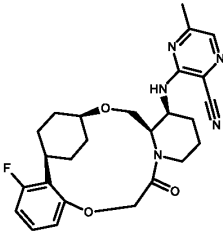
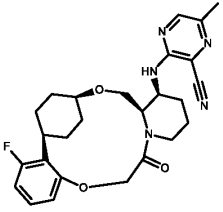
Table 15. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
239		Rel-2- {[(1s,15S,16R,19s)-4-fluoro-10-oxo-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-15-yl]amino}-1,3-thiazole-5-carbonitrile	[M+H] ⁺ 471.3	¹ H NMR (500 MHz, CDCl ₃) δ 7.68 (s, 1H), 6.89 - 6.79 (m, 2H), 6.69 (dd, J = 4.5, 8.8 Hz, 1H), 6.51 - 6.09 (m, 1H), 5.48 (td, J = 4.8, 9.7 Hz, 1H), 5.12 (d, J = 10.7 Hz, 1H), 4.28 (d, J = 10.7 Hz, 1H), 3.73 - 3.68 (m, 1H), 3.93 - 3.45 (m, 5H), 2.62 (dt, J = 4.2, 13.1 Hz, 1H), 2.58 - 2.47 (m, 1H), 2.47 - 1.29 (m, 11H).	D
240		Rel-(1s,15S,16R,19s)-4-fluoro-15-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 514.3	¹ H NMR (400 MHz, MeOD) δ 7.13 (d, J = 1.0 Hz, 1H), 6.92 - 6.78 (m, 3H), 5.52 - 5.42 (m, 1H), 5.32 (d, J = 10.6 Hz, 1H), 4.13 - 4.02 (m, 2H), 4.01 - 3.93 (m, 1H), 3.84 (br d, J = 13.4 Hz, 1H), 3.68 (br s, 1H), 3.59 - 3.49 (m, 1H), 3.39 (dd, J = 3.9, 9.0 Hz, 1H), 2.73 (dq, J = 4.7, 13.0 Hz, 1H), 2.63 - 2.48 (m, 1H), 2.32 - 2.10 (m, 2H), 2.01 - 1.61 (m, 5H), 1.52 - 1.23 (m, 4H).	C

241		Rel-(1s,15S,16R,19s)-4-fluoro-15-{{[5-(trifluoromethyl)-1,3-thiazol-2-yl]amino}-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 514.3	¹ H NMR (400 MHz, MeOD) δ 7.50 - 7.36 (m, 1H), 6.93 - 6.79 (m, 3H), 5.61 - 5.44 (m, 1H), 5.32 (d, J = 10.6 Hz, 1H), 4.13 - 4.07 (m, 1H), 4.08 - 4.01 (m, 1H), 3.97 (dd, J = 9.2, 10.6 Hz, 1H), 3.84 (br d, J = 13.5 Hz, 1H), 3.67 (br s, 1H), 3.59 - 3.49 (m, 1H), 3.39 - 3.33 (m, 1H), 2.80 - 2.64 (m, 1H), 2.62 - 2.48 (m, 1H), 2.30 - 2.19 (m, 1H), 2.20 - 2.11 (m, 1H), 2.04 - 1.55 (m, 6H), 1.50 - 1.21 (m, 3H).	C
242		Rel-3-{{[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}pyridazine-4-carbonitrile	[M+H] ⁺ 466.4	¹ H NMR (500 MHz, CDCl ₃) δ 8.78 (d, J = 4.8 Hz, 1H), 7.40 (d, J = 4.9 Hz, 1H), 7.10 (dt, J = 6.6, 8.2 Hz, 1H), 6.71 (t, J = 8.5 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 5.49 - 5.41 (m, 1H), 5.24 (br d, J = 7.3 Hz, 1H), 5.15 (d, J = 10.4 Hz, 1H), 4.86 - 4.77 (m, 1H), 4.32 (d, J = 10.3 Hz, 1H), 3.87 (t, J = 8.8 Hz, 1H), 3.83 - 3.72 (m, 2H), 3.71 - 3.63 (m, 1H), 3.60 (dd, J = 4.1, 8.8 Hz, 1H), 3.22 - 3.10 (m, 1H), 2.70 - 2.56 (m, 1H), 2.24 - 2.14 (m, 1H), 2.12 (br d, J = 14.5 Hz, 1H), 2.09 - 2.04 (m, 1H), 1.97 - 1.90 (m, 2H), 1.89 - 1.78 (m, 2H), 1.51 - 1.38 (m, 3H), 1.35 - 1.28 (m, 1H).	A
243		Rel-2-{{[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}pyridine-3-carbonitrile	[M+H] ⁺ 465.4	¹ H NMR (500 MHz, CDCl ₃) δ 8.35 (dd, J = 1.9, 4.9 Hz, 1H), 7.67 (dd, J = 1.9, 7.6 Hz, 1H), 7.15 - 7.00 (m, 1H), 6.73 - 6.62 (m, 2H), 6.54 (d, J = 8.1 Hz, 1H), 5.60 - 5.50 (m, 1H), 5.12 (d, J = 10.3 Hz, 1H), 4.96 (br d, J = 6.6 Hz, 1H), 4.53 - 4.41 (m, 1H), 4.31 (d, J = 10.3 Hz, 1H), 3.89 - 3.83 (m, 1H), 3.72 (br d, J = 11.8 Hz, 1H), 3.70 - 3.66 (m, 1H), 3.62 - 3.51 (m, 1H), 3.45 (dd, J = 4.0, 8.7 Hz, 1H), 3.19 - 3.08 (m, 1H), 2.69 - 2.54 (m, 1H), 2.24 - 2.14 (m, 1H), 2.13 - 2.06 (m, 1H), 2.01 - 1.84 (m, 3H), 1.78 - 1.68 (m, 2H), 1.50 - 1.34 (m, 3H), 1.33 - 1.25 (m, 1H).	A
244		Rel-3-methyl-5-{{[(1s,15S,16R,19s)-3-fluoro-10-oxo-8,18-dioxa-11-azatetracyclo[1.7.2.2.0 ² ,7.0 ¹¹ ,16]tricoso-2(7),3,5-trien-15-yl]amino}pyridine-3-carbonitrile	[M+H] ⁺ 485.4	¹ H NMR (400 MHz, CDCl ₃) δ = 7.17 - 7.05 (m, 1H), 6.72 (t, J = 8.8 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 5.69 (br d, J = 7.2 Hz, 1H), 5.47 - 5.34 (m, 1H), 5.12 (d, J = 10.5 Hz, 1H), 4.32 (d, J = 10.4 Hz, 1H), 3.86 - 3.71 (m, 3H), 3.67 - 3.45 (m, 3H), 3.26 - 3.09 (m, 1H), 2.65 - 2.50 (m,	B

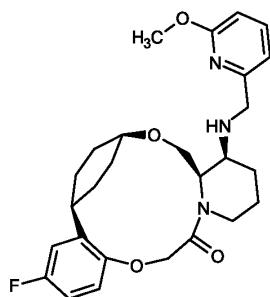
		7.2.2.0 ^{2,7,011,16} t ricosa-2(7),3,5- trien-15- yl]amino}-1,2- thiazole-4- carbonitrile		¹ H, 2.43 (s, 3H), 2.23 - 2.00 (m, 3H), 1.99 - 1.66 (m, 4H), 1.53 - 1.21 (m, 4H).	
245		Rel-5- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7,011,16} t ricosa-2(7),3,5- trien-15- yl]amino}pyrim idine-4- carbonitrile	[M+H] ⁺ 466.4	¹ H NMR (500 MHz, MeOD) δ 8.74 (s, 1H), 8.54 (s, 1H), 7.14 (dt, J = 6.5, 8.3 Hz, 1H), 6.77 - 6.63 (m, 2H), 5.40 - 5.29 (m, 2H), 4.16 (d, J = 10.4 Hz, 1H), 4.10 - 4.00 (m, 2H), 3.86 (br dd, J = 3.2, 13.9 Hz, 1H), 3.70 (br s, 1H), 3.56 (dt, J = 2.4, 13.4 Hz, 1H), 3.38 (dd, J = 3.8, 9.2 Hz, 1H), 3.19 - 3.10 (m, 1H), 2.77 - 2.63 (m, 1H), 2.32 - 2.17 (m, 2H), 2.04 - 1.92 (m, 3H), 1.83 - 1.73 (m, 2H), 1.52 - 1.43 (m, 1H), 1.42 - 1.35 (m, 2H), 1.26 - 1.17 (m, 1H).	A
246		Rel-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7,011,16} t ricosa-2(7),3,5- trien-15- yl]amino}pyridi ne-2- carbonitrile	[M+H] ⁺ 465.4	¹ H NMR (500 MHz, MeOD) δ 7.97 (dd, J = 1.2, 4.3 Hz, 1H), 7.58 - 7.52 (m, 1H), 7.51 - 7.47 (m, 1H), 7.14 (dt, J = 6.5, 8.3 Hz, 1H), 6.74 - 6.66 (m, 2H), 5.35 (d, J = 10.4 Hz, 1H), 5.33 - 5.28 (m, 1H), 4.16 (d, J = 10.6 Hz, 1H), 4.06 (dd, J = 9.4, 10.8 Hz, 1H), 3.93 - 3.82 (m, 2H), 3.68 (br s, 1H), 3.56 (dt, J = 2.5, 13.4 Hz, 1H), 3.38 - 3.33 (m, 1H), 3.19 - 3.08 (m, 1H), 2.76 - 2.63 (m, 1H), 2.33 - 2.16 (m, 2H), 2.03 - 1.90 (m, 3H), 1.83 - 1.70 (m, 2H), 1.52 - 1.42 (m, 1H), 1.42 - 1.34 (m, 2H), 1.26 - 1.16 (m, 1H).	A
247		3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7,011,16} t ricosa-2(7),3,5- trien-15- yl]amino}pyridi ne-2- carbonitrile	[M+H] ⁺ 465.4	¹ H NMR (500 MHz, MeOD) δ 7.97 (dd, J = 1.2, 4.3 Hz, 1H), 7.58 - 7.52 (m, 1H), 7.51 - 7.47 (m, 1H), 7.14 (dt, J = 6.5, 8.3 Hz, 1H), 6.74 - 6.66 (m, 2H), 5.35 (d, J = 10.4 Hz, 1H), 5.33 - 5.28 (m, 1H), 4.16 (d, J = 10.6 Hz, 1H), 4.06 (dd, J = 9.4, 10.8 Hz, 1H), 3.93 - 3.82 (m, 2H), 3.68 (br s, 1H), 3.56 (dt, J = 2.5, 13.4 Hz, 1H), 3.38 - 3.33 (m, 1H), 3.19 - 3.08 (m, 1H), 2.76 - 2.63 (m, 1H), 2.33 - 2.16 (m, 2H), 2.03 - 1.90 (m, 3H), 1.83 - 1.70 (m, 2H), 1.52 - 1.42 (m, 1H), 1.42 - 1.34 (m, 2H), 1.26 - 1.16 (m, 1H).	A

248		3- {[(1s,15R,16S, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2(7),3,5- trien-15- yl]amino}pyridi ne-2- carbonitrile	[M+H] ⁺ 465.4	¹ H NMR (500 MHz, MeOD) δ 7.97 (dd, J = 1.2, 4.3 Hz, 1H), 7.58 - 7.52 (m, 1H), 7.51 - 7.47 (m, 1H), 7.14 (dt, J = 6.5, 8.3 Hz, 1H), 6.74 - 6.66 (m, 2H), 5.35 (d, J = 10.4 Hz, 1H), 5.33 - 5.28 (m, 1H), 4.16 (d, J = 10.6 Hz, 1H), 4.06 (dd, J = 9.4, 10.8 Hz, 1H), 3.93 - 3.82 (m, 2H), 3.68 (br s, 1H), 3.56 (dt, J = 2.5, 13.4 Hz, 1H), 3.38 - 3.33 (m, 1H), 3.19 - 3.08 (m, 1H), 2.76 - 2.63 (m, 1H), 2.33 - 2.16 (m, 2H), 2.03 - 1.90 (m, 3H), 1.83 - 1.70 (m, 2H), 1.52 - 1.42 (m, 1H), 1.42 - 1.34 (m, 2H), 1.26 - 1.16 (m, 1H).	C
249		Rel-3-fluoro-2- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2(7),3,5- trien-15- yl]amino}benzo nitrile	[M+H] ⁺ 482.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.26 - 7.16 (m, 2H), 7.14 - 7.03 (m, 1H), 6.82 - 6.74 (m, 1H), 6.73 - 6.66 (m, 1H), 6.55 (d, J = 8.1 Hz, 1H), 5.39 - 5.31 (m, 1H), 5.11 (d, J = 10.3 Hz, 1H), 4.30 (d, J = 10.2 Hz, 1H), 4.30 - 4.21 (m, 1H), 4.12 - 4.03 (m, 1H), 3.94 - 3.85 (m, 1H), 3.78 - 3.67 (m, 2H), 3.61 - 3.43 (m, 2H), 3.21 - 3.06 (m, 1H), 2.70 - 2.52 (m, 1H), 2.28 - 2.04 (m, 3H), 1.98 - 1.63 (m, 4H), 1.51 - 1.19 (m, 4H).	A
250		Rel-3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2(7),3,5- trien-15- yl]amino}pyraz ine-2- carbonitrile	[M+H] ⁺ 466.4	¹ H NMR (500 MHz, MeOD) δ 8.35 (d, J = 2.3 Hz, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.75 - 6.65 (m, 2H), 5.53 - 5.44 (m, 1H), 5.35 (d, J = 10.4 Hz, 1H), 4.38 (td, J = 5.0, 12.7 Hz, 1H), 4.13 (d, J = 10.4 Hz, 1H), 4.08 - 4.01 (m, 1H), 3.90 - 3.81 (m, 1H), 3.68 (br s, 1H), 3.55 (dt, J = 2.7, 13.4 Hz, 1H), 3.38 - 3.34 (m, 1H), 3.17 - 3.09 (m, 1H), 2.77 - 2.65 (m, 1H), 2.32 - 2.22 (m, 1H), 2.20 (br s, 1H), 2.09 - 1.90 (m, 3H), 1.83 - 1.75 (m, 1H), 1.77 - 1.67 (m, 1H), 1.51 - 1.42 (m, 1H), 1.42 - 1.35 (m, 2H), 1.24 - 1.17 (m, 1H).	A
251		3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ² ,7,0 ¹¹ ,16]t ricosa-2(7),3,5- trien-15- yl]amino}pyraz	[M+H] ⁺ 466.4	¹ H NMR (500 MHz, MeOD) δ 8.35 (d, J = 2.3 Hz, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.75 - 6.65 (m, 2H), 5.53 - 5.44 (m, 1H), 5.35 (d, J = 10.4 Hz, 1H), 4.38 (td, J = 5.0, 12.7 Hz, 1H), 4.13 (d, J = 10.4 Hz, 1H), 4.08 - 4.01 (m, 1H), 3.90 - 3.81 (m, 1H), 3.68 (br s, 1H), 3.55 (dt, J = 2.7, 13.4 Hz, 1H), 3.38 - 3.34 (m, 1H), 3.17 - 3.09 (m, 1H), 2.77 - 2.65 (m, 1H), 2.32 - 2.22 (m, 1H),	A

		ine-2-carbonitrile		2.20 (br s, 1H), 2.09 - 1.90 (m, 3H), 1.83 - 1.75 (m, 1H), 1.77 - 1.67 (m, 1H), 1.51 - 1.42 (m, 1H), 1.42 - 1.35 (m, 2H), 1.24 - 1.17 (m, 1H).	
252		3- {[(1s,15R,16S, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}pyraz ine-2- carbonitrile	[M+H] ⁺ 466.4	¹ H NMR (500 MHz, MeOD) δ 8.35 (d, J = 2.3 Hz, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.13 (dt, J = 6.5, 8.3 Hz, 1H), 6.75 - 6.65 (m, 2H), 5.53 - 5.44 (m, 1H), 5.35 (d, J = 10.4 Hz, 1H), 4.38 (td, J = 5.0, 12.7 Hz, 1H), 4.13 (d, J = 10.4 Hz, 1H), 4.08 - 4.01 (m, 1H), 3.90 - 3.81 (m, 1H), 3.68 (br s, 1H), 3.55 (dt, J = 2.7, 13.4 Hz, 1H), 3.38 - 3.34 (m, 1H), 3.17 - 3.09 (m, 1H), 2.77 - 2.65 (m, 1H), 2.32 - 2.22 (m, 1H), 2.20 (br s, 1H), 2.09 - 1.90 (m, 3H), 1.83 - 1.75 (m, 1H), 1.77 - 1.67 (m, 1H), 1.51 - 1.42 (m, 1H), 1.42 - 1.35 (m, 2H), 1.24 - 1.17 (m, 1H).	C
253		Rel-5-methyl- 3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}pyraz ine-2- carbonitrile	[M+H] ⁺ 480.5	¹ H NMR (500 MHz, CDCl ₃) δ 7.85 (s, 1H), 7.14 - 7.06 (m, 1H), 6.75 - 6.65 (m, 1H), 6.56 (d, J = 8.1 Hz, 1H), 5.51 (td, J = 4.8, 10.1 Hz, 1H), 5.14 (d, J = 10.3 Hz, 1H), 5.03 (d, J = 7.3 Hz, 1H), 4.50 - 4.40 (m, 1H), 4.31 (d, J = 10.3 Hz, 1H), 3.86 (t, J = 9.3 Hz, 1H), 3.78 - 3.69 (m, 2H), 3.65 - 3.55 (m, 1H), 3.46 (dd, J = 4.0, 8.7 Hz, 1H), 3.21 - 3.10 (m, 1H), 2.67 - 2.57 (m, 1H), 2.51 (s, 3H), 2.25 - 2.14 (m, 1H), 2.13 - 2.06 (m, 1H), 2.02 - 1.68 (m, 6H), 1.50 - 1.37 (m, 2H), 1.36 - 1.24 (m, 1H).	A
254		Rel-6-methyl- 3- {[(1s,15S,16R, 19s)-3-fluoro- 10-oxo-8,18- dioxo-11- azatetracyclo[1 7.2.2.0 ^{2,7} .0 ^{11,16}]t ricosa-2(7),3,5- trien-15- yl]amino}pyraz ine-2- carbonitrile	[M+H] ⁺ 480.5	¹ H NMR (500 MHz, MeOD) δ 7.84 (s, 1H), 7.14 (dt, J = 6.4, 8.2 Hz, 1H), 6.72 - 6.66 (m, 2H), 5.56 - 5.48 (m, 1H), 5.35 (d, J = 10.4 Hz, 1H), 4.40 (td, J = 5.0, 12.6 Hz, 1H), 4.14 (d, J = 10.4 Hz, 1H), 4.03 (dd, J = 9.4, 11.0 Hz, 1H), 3.89 - 3.82 (m, 1H), 3.67 (br s, 1H), 3.55 (dt, J = 2.6, 13.4 Hz, 1H), 3.36 - 3.32 (m, 1H), 3.16 - 3.10 (m, 1H), 2.76 - 2.66 (m, 1H), 2.49 (s, 3H), 2.32 - 2.18 (m, 2H), 2.01 - 1.88 (m, 3H), 1.83 - 1.66 (m, 2H), 1.49 - 1.35 (m, 3H), 1.25 - 1.17 (m, 1H).	A

[0344] Example 255

[0345] Rel-(1s,15S,16R,19s)-4-fluoro-15-{[(6-methoxypyridin-2-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-10-one

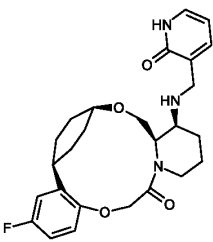
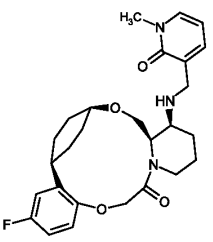
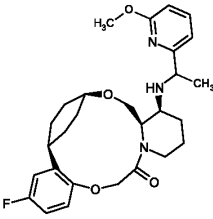


[0346] A mixture of Intermediate 28 (22 mg, 0.060 mmol), 6-methoxy-2-pyridinecarboxaldehyde (0.01 mL, 0.060 mmol) and Ti(OEt)₄ (0.03 mL, 0.120 mmol) in THF (0.6 mL) was shaken at 70 °C overnight. The mixture was cooled to room temperature, then sodium cyanoborohydride (23 mg, 0.360 mmol) was added and the mixture was shaken at room temperature for 4 h. The mixture was evaporated *in vacuo* and the product was purified by column chromatography using a C18 cartridge (3-30% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) to afford the title compound (13.1 mg, 0.027 mmol, 45% yield) as a white solid.

[0347] The examples reported in the table below were synthesized using a similar procedure to that described for Example 252 starting from the appropriate amine intermediate and the appropriate aldehyde or ketone.

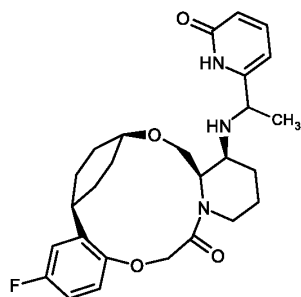
Table 16. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
255		Rel-(1s,15S,16R,19s)-4-fluoro-15-{[(6-methoxypyridin-2-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 484.4	¹ H NMR (400 MHz, MeOD) δ 7.67 - 7.58 (m, 1H), 6.97 (d, J = 7.2 Hz, 1H), 6.92 - 6.77 (m, 3H), 6.66 (d, J = 8.2 Hz, 1H), 5.35 - 5.20 (m, 2H), 4.08 (d, J = 10.6 Hz, 1H), 4.00 - 3.91 (m, 4H), 3.89 (d, J = 2.7 Hz, 2H), 3.83 - 3.74 (m, 1H), 3.69 (br s, 1H), 3.58 - 3.43 (m, 2H), 2.91 (td, J = 4.8, 11.5 Hz, 1H), 2.73 (dq, J = 4.4, 12.9 Hz, 1H), 2.62 - 2.49 (m, 1H), 2.28 (dq, J = 4.1,	D

				12.9 Hz, 1H), 2.22 - 2.13 (m, 1H), 1.95 - 1.76 (m, 3H), 1.63 - 1.53 (m, 2H), 1.52 - 1.23 (m, 4H).	
256		Rel-(1s,15S,16R,19s)-4-fluoro-15-[(2-oxo-1,2-dihydropyridin-3-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricos-2(7),3,5-trien-10-one	[M+H] ⁺ 470.4	¹ H NMR (400 MHz, MeOD) δ 7.65 (dd, J = 1.6, 6.8 Hz, 1H), 7.37 (dd, J = 1.9, 6.5 Hz, 1H), 6.90 - 6.78 (m, 3H), 6.39 (t, J = 6.6 Hz, 1H), 5.35 - 5.20 (m, 2H), 4.08 (d, J = 10.6 Hz, 1H), 3.99 - 3.88 (m, 1H), 3.86 - 3.74 (m, 2H), 3.74 - 3.64 (m, 2H), 3.54 (dd, J = 3.9, 9.3 Hz, 1H), 3.52 - 3.42 (m, 1H), 2.90 - 2.81 (m, 1H), 2.80 - 2.66 (m, 1H), 2.61 - 2.49 (m, 1H), 2.28 (dq, J = 4.0, 12.9 Hz, 1H), 2.17 (br d, J = 14.1 Hz, 1H), 1.91 - 1.77 (m, 3H), 1.67 - 1.51 (m, 2H), 1.52 - 1.40 (m, 2H), 1.40 - 1.23 (m, 2H).	D
257		Rel-(1s,15S,16R,19s)-4-fluoro-15-[(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricos-2(7),3,5-trien-10-one	[M+H] ⁺ 484.5	¹ H NMR (400 MHz, MeOD) δ 7.65 - 7.54 (m, 2H), 6.89 - 6.78 (m, 3H), 6.36 (t, J = 6.8 Hz, 1H), 5.32 - 5.18 (m, 2H), 4.08 (d, J = 10.6 Hz, 1H), 3.94 (t, J = 10.2 Hz, 1H), 3.86 - 3.75 (m, 2H), 3.74 - 3.65 (m, 2H), 3.58 (s, 3H), 3.54 (dd, J = 3.9, 9.3 Hz, 1H), 3.52 - 3.43 (m, 1H), 2.90 - 2.80 (m, 1H), 2.73 (dq, J = 4.5, 12.9 Hz, 1H), 2.61 - 2.47 (m, 1H), 2.28 (dq, J = 4.2, 12.9 Hz, 1H), 2.17 (br d, J = 13.9 Hz, 1H), 1.94 - 1.74 (m, 3H), 1.71 - 1.17 (m, 6H).	D
258		Rel-(1s,15S,16R,19s)-4-fluoro-15-[(1-(6-methoxypyridin-2-yl)ethyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricos-2(7),3,5-trien-10-one	[M+H] ⁺ 498.5	¹ H NMR (500 MHz, MeOD) δ 7.65 - 7.56 (m, 1H), 7.02 - 6.95 (m, 1H), 6.88 - 6.82 (m, 2H), 6.82 - 6.77 (m, 1H), 6.68 - 6.59 (m, 1H), 5.26 - 5.17 (m, 1H), 5.33 - 5.03 (m, 1H), 4.07 - 4.01 (m, 1H), 4.01 - 3.91 (m, 5H), 3.76 - 3.66 (m, 2H), 3.60 - 3.50 (m, 1H), 3.47 - 3.39 (m, 1H), 2.79 - 2.65 (m, 1H), 2.80 - 2.50 (m, 1H), 2.63 - 2.49 (m, 1H), 2.33 - 2.22 (m, 1H), 2.22 - 2.12 (m, 1H), 1.99 - 1.34 (m, 8H), 1.41 - 1.33 (m, 3H), 1.33 - 1.23 (m, 1H).	C

[0348] Example 259

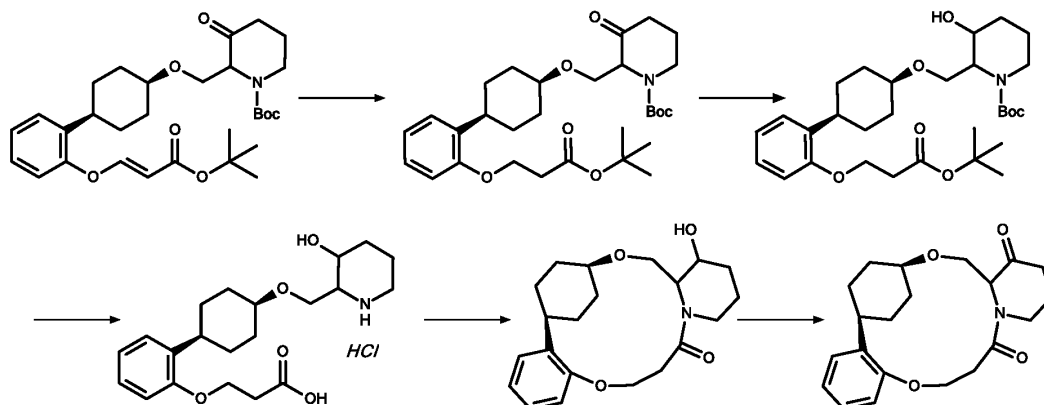
[0349] Rel-(1s,15S,16R,19s)-4-fluoro-15-{{[1-(6-oxo-1,6-dihydropyridin-2-yl)ethyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0^{2,7}.0^{11,16}]tricoso-2(7),3,5-trien-10-one



[0350] A mixture of Example 258 (20 mg, 0.040 mmol), sodium iodide (12 mg, 0.080 mmol) and chloro(trimethyl)silane (5 uL, 0.040 mmol) in MeCN (1 mL) was shaken at 85 °C for 1.5 h. The mixture was cooled to room temperature, the pH was adjusted to pH~10 by addition of a 20% wt. aqueous NH₄OH solution and the mixture was extracted twice with DCM. The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product was purified by column chromatography using a C18 cartridge (3-33% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) to afford the title compound (10.8 mg, 0.022 mmol, 56% yield) as a white solid.

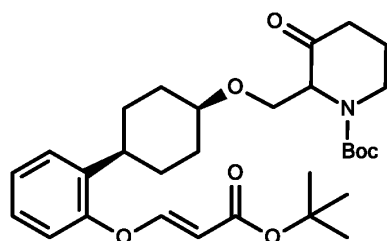
Table 17. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
259		Rel-(1s,15S,16R,19s)-4-fluoro-15-{{[1-(6-oxo-1,6-dihydropyridin-2-yl)ethyl]amino}-8,18-dioxo-11-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{11,16}]tricoso-2(7),3,5-trien-10-one	[M+H] ⁺ 484.4	¹ H NMR (500 MHz, MeOD) δ 7.60 - 7.51 (m, 1H), 6.89 - 6.78 (m, 3H), 6.45 (d, J = 7.0 Hz, 1H), 6.41 (d, J = 9.1 Hz, 1H), 5.25 (d, J = 10.7 Hz, 1H), 5.24 - 4.96 (m, 1H), 4.08 - 4.01 (m, 1H), 4.00 - 3.88 (m, 2H), 3.77 - 3.65 (m, 2H), 3.56 - 3.47 (m, 1H), 3.49 - 3.40 (m, 1H), 2.77 - 2.65 (m, 2H), 2.60 - 2.49 (m, 1H), 2.34 - 2.20 (m, 1H), 2.21 - 2.10 (m, 1H), 1.41 - 1.36 (m, J = 6.8 Hz, 3H), 1.62 (dd, J = 10.2, 18.9 Hz, 8H), 1.32 - 1.23 (m, 1H).	C



[0351] SYNTHESIS OF INTERMEDIATE 29

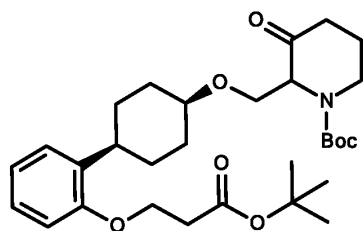
[0352] tert-butyl-3-oxo-2-({[(1s,4s)-4-(2-({[(1E)-3-(tert-butoxy)-3-oxoprop-1-en-1-yl]oxy}phenyl)cyclohexyl]oxy} methyl)piperidine-1-carboxylate



[0353] To a solution of tert-butyl prop-2-ynoate (0.78 mL, 5.68 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.21 mL, 1.89 mmol) in anhydrous THF (20 mL) at 0 °C under nitrogen was added Intermediate 3 (2.10 g, 4.74 mmol) in anhydrous THF (20 mL) and the solution was stirred at room temperature for 2 h. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to afford the crude material. The crude material was purified by column chromatography (0-100% EtOAc in heptane) to afford the title compound (2.40 g) as a colorless oil. $[M+Na]^+$ m/z = 552.3

[0354] SYNTHESIS OF INTERMEDIATE 30

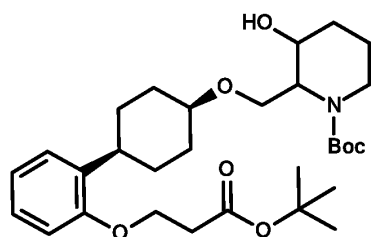
[0355] tert-butyl 3-oxo-2-({[(1s,4s)-4-{2-[3-(tert-butoxy)-3-oxopropoxy]phenyl}cyclohexyl]-oxy}methyl)piperidine-1-carboxylate



[0356] Intermediate 29 (2.40 g, 4.30 mmol) was dissolved in ethanol (75 mL) and the atmosphere above the reaction mixture was evacuated and backfilled with nitrogen 3 times. Palladium on C (10%, 687 mg, 0.646 mmol) was added and the atmosphere above the reaction mixture was evacuated and backfilled with nitrogen then repeated with hydrogen 3 times. The reaction was stirred for 2 h and then filtered through a pad of Celite, washing with EtOAc. The filtrate was concentrated *in vacuo* to afford the title compound (2.40 g) as a grey oil. $[M+Na]^+$ $m/z = 554.3$

[0357] SYNTHESIS OF INTERMEDIATE 31

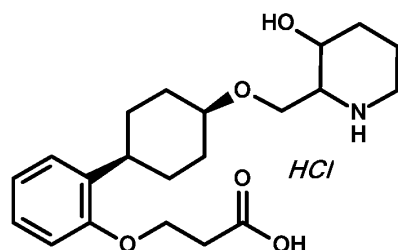
[0358] tert-butyl-3-hydroxy-2-({[(1s,4s)-4-{2-[3-(tert-butoxy)-3-oxopropoxy]phenyl}cyclohexyl]oxy}methyl) piperidine-1-carboxylate



[0359] Sodium borohydride (0.17 g, 4.51 mmol) was added portionwise to a stirred solution of Intermediate 30 (2.40 g, 4.51 mmol) in anhydrous DCM (20 mL) and methanol (20 mL) at 0 °C and the mixture was stirred for 1 h. The reaction mixture was concentrated *in vacuo*. The residue was resuspended in water (30 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound (2.50 g) as a colourless oil. $[M+Na]^+$ $m/z = 556.3$

[0360] SYNTHESIS OF INTERMEDIATE 32

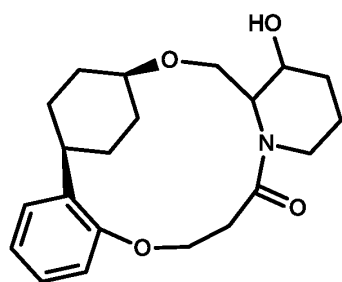
[0361] 3-{2-[(1s,4s)-4-[(3-hydroxypiperidin-2-yl)methoxy]cyclohexyl]phenoxy}propanoic acid hydrochloride



[0362] A 4 M solution of HCl in 1,4-dioxane (12 mL, 46.8 mmol) was added to Intermediate 31 (2.50 g, 4.68 mmol) at room temperature and the reaction mixture was stirred for 3 h. The reaction mixture was concentrated *in vacuo* to afford the title compound (2.00 g) as a white foam. $[M+H]^+$ $m/z = 378.3$

[0363] SYNTHESIS OF INTERMEDIATE 33

[0364] (1s,20s)-16-hydroxy-8,19-dioxa-12-azatetracyclo[18.2.2.0^{2,7}.0^{12,17}]tetracos-2(7),3,5-trien-11-one

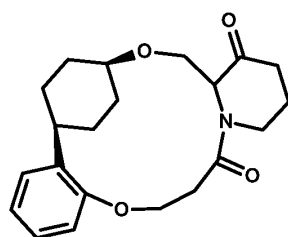


[0365] To a stirred solution of HATU (2.48 g, 6.52 mmol) and DIPEA (3797 μ L, 21.7 mmol) in acetonitrile (135 mL) was added Intermediate 32 (2.00 g, 4.35 mmol) in anhydrous DMF (9 mL) over 2h using a syringe pump. The resulting solution was stirred for 1 hour. The reaction mixture was concentrated *in vacuo* to afford the crude material. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the crude product. The crude

material was purified by column chromatography (0-100% 3:1 EtOAc/EtOH in heptane) to afford the title compound (1.10 g) as a white solid. $[M+H]^+$ $m/z = 360.3$

[0366] SYNTHESIS OF INTERMEDIATE 34

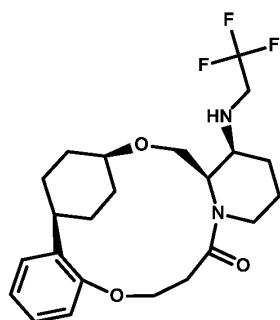
[0367] (1s,20s)-8,19-dioxa-12-azatetracyclo[18.2.2.0^{2,7}.0^{12,17}]tetracos-2(7),3,5-triene-11,16-dione



[0368] To a solution of Intermediate 33 (1.10 g, 3.06 mmol) in anhydrous DCM (22 mL) at 0 °C was added Dess-Martin periodinane (1.69 g, 3.98 mmol). The mixture was stirred at room temperature for 2 h. The mixture was diluted with DCM (30 mL), then washed with saturated aqueous NaHCO₃ solution (30 mL), 1 M aqueous Na₂S₂O₃ solution (30 mL), and 1M aqueous Na₂CO₃ solution (30 mL). The organic layer was dried by passing through a hydrophobic frit (Phase Separator) and concentrated to dryness to give the crude product. The crude product was purified by column chromatography (0-40% 3:1 EtOAc/EtOH in heptane) to afford the title compound (807 mg) as a white solid. $[M+H]^+$ $m/z = 358.2$

[0369] Example 260

[0370] Rel-(1s,16S,17R,20s)-16-[(2,2,2-trifluoroethyl)amino]-8,19-dioxa-12-azatetracyclo[18.2.2.0^{2,7}.0^{12,17}]tetracos-2(7),3,5-trien-11-one

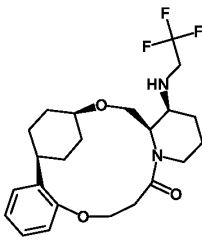


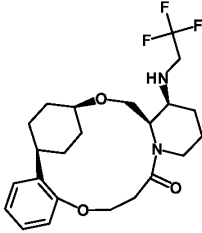
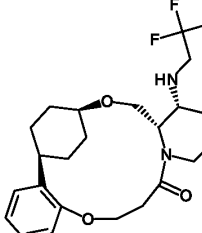
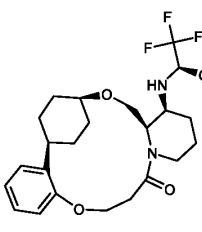
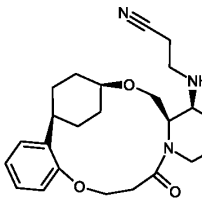
[0371] A solution of 2,2,2-trifluoroethanamine (125 mg, 1.26 mmol), $\text{Ti}(\text{OEt})_4$ (191 mg, 0.839 mmol) and Intermediate 34 (150 mg, 0.420 mmol) in anhydrous THF (5 mL) was heated to 70 °C for 16 h. The reaction mixture was cooled to room temperature, then sodium borohydride (254 mg, 6.71 mmol) was added and the mixture was stirred for 3h. The reaction was quenched with water (15 mL) and diluted with EtOAc (15 mL). The mixture was filtered through a pad of Celite and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo* to afford the crude material. The crude material was purified by basic reverse phase column chromatography (10-100% acetonitrile in water (0.1% ammonia) to afford the title compound (108 mg) as a white solid.

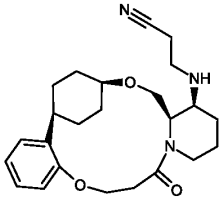
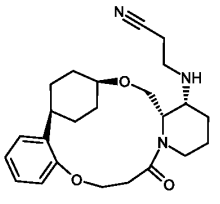
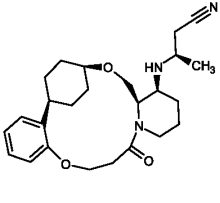
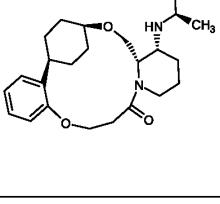
[0372] The examples reported in the table below were synthesized using similar procedures to those described for Example 1 and Example 260 using the appropriate reagents.

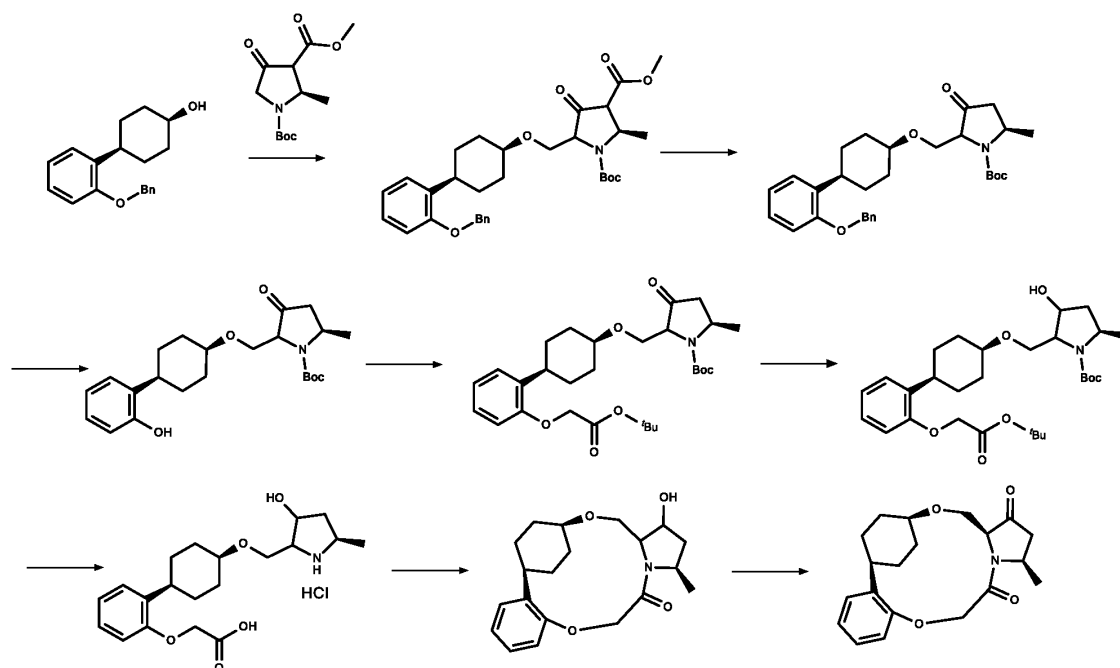
[0373] Enantiomers were separated by chiral purification using appropriate chiral columns and combinations of solvent mixtures; Chiralpak columns (AD-H, IC, OJ-H, AS-H); solvent mixture of n-Hexane / EtOH, n-Hexane / (EtOH + 0.1% $i\text{PrNH}_2$), n-Hexane / (EtOH/MeOH 1:1 + 0.1% $i\text{PrNH}_2$).

Table 18. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	^1H NMR	EC50 hOX2
260		Rel-(1s,16S,17R,20s)-16-[(2,2,2-trifluoroethyl)amino]-8,19-dioxo-12-azatetracyclo[18.2.2.0 ^{2,7} .0 ^{12,17}]tetracosan-2(7),3,5-trien-11-one	$[\text{M}+\text{H}]^+$ 441.2	^1H NMR (500 MHz, CDCl_3) δ 7.13 (qd, J = 7.9, 1.8 Hz, 1H), 7.03 (ddd, J = 20.6, 7.4, 1.8 Hz, 1H), 6.86 – 6.74 (m, 2H), 4.76 (ddt, J = 12.3, 5.9, 2.9 Hz, 2H), 4.43 (ddt, J = 8.9, 6.6, 3.0 Hz, 1H), 3.99 (dt, J = 8.0, 3.0 Hz, 1H), 3.90 – 3.69 (m, 2H), 3.62 – 3.46 (m, 2H), 3.39 – 3.11 (m, 3H), 2.89 (ddt, J = 27.0, 12.2, 4.7 Hz, 1H), 2.71 – 2.55 (m, 1H), 2.48 – 2.43 (m, 2H), 2.37 – 2.22 (m, 1H), 1.94 – 1.72 (m, 4H), 1.59 – 1.21 (m, 6H). NH missing	B

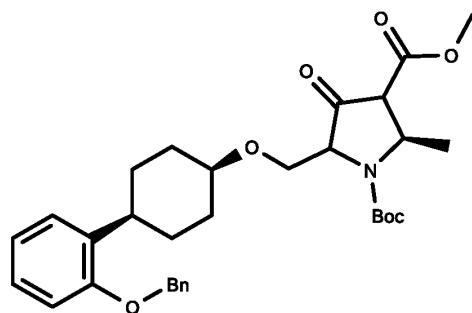
261		(1s,16S,17R,20s)-16-[(2,2,2-trifluoroethyl)amino]-8,19-dioxo-12-azatetracyclo[18.2.2.0 ^{2,7} .0 ^{12,17}]tetracosan-2(7),3,5-trien-11-one	[M+H] ⁺ 441.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.10 - 7.19 (m, 1H), 6.99 - 7.09 (m, 1H), 6.74 - 6.95 (m, 2H), 4.65 - 4.87 (m, 1H), 4.40 - 5.49 (m, 1H), 4.27 - 4.84 (m, 1H), 4.00 (dt, J = 7.8, 2.9 Hz, 1H), 3.57 - 3.93 (m, 2H), 3.57 - 3.65 (m, 1H), 3.48 - 3.58 (m, 1H), 3.25 - 3.39 (m, 2H), 2.82 - 3.04 (m, 1H), 2.62 - 2.76 (m, 1H), 2.37 - 2.53 (m, 1H), 2.20 - 2.35 (m, 1H), 1.14 - 2.60 (m, 12H).	B
262		(1s,16R,17S,20s)-16-[(2,2,2-trifluoroethyl)amino]-8,19-dioxo-12-azatetracyclo[18.2.2.0 ^{2,7} .0 ^{12,17}]tetracosan-2(7),3,5-trien-11-one	[M+H] ⁺ 441.3	¹ H NMR (400 MHz, CDCl ₃) δ 7.10 - 7.19 (m, 1H), 6.99 - 7.09 (m, 1H), 6.74 - 6.95 (m, 2H), 4.65 - 4.87 (m, 1H), 4.40 - 5.49 (m, 1H), 4.27 - 4.84 (m, 1H), 4.00 (dt, J = 7.8, 2.9 Hz, 1H), 3.57 - 3.93 (m, 2H), 3.57 - 3.65 (m, 1H), 3.48 - 3.58 (m, 1H), 3.25 - 3.39 (m, 2H), 2.82 - 3.04 (m, 1H), 2.62 - 2.76 (m, 1H), 2.37 - 2.53 (m, 1H), 2.20 - 2.35 (m, 1H), 1.14 - 2.60 (m, 12H).	D
263		Rel-(1s,16S,17R,20s)-16-[(2R)-1,1,1-trifluoropropan-2-yl]amino-8,19-dioxo-12-azatetracyclo[18.2.2.0 ^{2,7} .0 ^{12,17}]tetracosan-2,4,6-trien-11-one	[M+H] ⁺ 455.4	¹ H NMR (500 MHz, CDCl ₃) δ 7.17 - 7.09 (m, 1H), 7.07 - 6.99 (m, 1H), 6.92 - 6.75 (m, 2H), 4.80 - 4.71 (m, 1H), 4.47 - 4.29 (m, 1H), 4.02 - 3.96 (m, 1H), 3.82 (dd, J = 29.1, 11.9 Hz, 1H), 3.76 - 3.67 (m, 1H), 3.63 - 3.47 (m, 2H), 3.38 - 3.35 (m, 1H), 3.30 - 3.11 (m, 1H), 3.01 (s, 1H), 2.71 - 2.56 (m, 1H), 2.52 - 2.37 (m, 2H), 2.34 - 2.22 (m, 1H), 1.99 - 1.71 (m, 5H), 1.46 - 1.24 (m, 9H).	B
264		Rel-3-[(1s,16S,17R,20s)-11-oxo-8,19-dioxo-12-azatetracyclo[18.2.2.0 ^{2,7} .0 ^{12,17}]tetracosan-2,4,6-trien-16-yl]amino}propanenitrile	[M+H] ⁺ 412.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.16 - 7.08 (m, 1H), 7.03 (ddd, J = 16.2, 7.4, 1.8 Hz, 1H), 6.94 - 6.73 (m, 2H), 4.81 - 4.70 (m, 1H), 4.47 - 4.29 (m, 1H), 4.02 - 3.68 (m, 3H), 3.62 - 3.50 (m, 2H), 3.29 - 2.95 (m, 3H), 2.91 - 2.74 (m, 1H), 2.74 - 2.21 (m, 7H), 1.99 - 1.72 (m, 4H), 1.53 - 1.22 (m, 6H).	A

265		3- {[(1s,16S,17R,20s) -11-oxo-8,19- dioxo-12- azatetracyclo[18.2. 2.0 ² ,7.0 ¹² ,17]tetracos a-2,4,6-trien-16- yl]amino}propanenit rile	[M+H] ⁺ 412.3	¹ H NMR (400 MHz, CD ₃ OD) δ 7.06 - 7.14 (m, 1H), 6.98 - 7.05 (m, 1H), 6.81 - 6.86 (m, 1H), 6.69 - 6.81 (m, 1H), 4.53 - 4.60 (m, 1H), 4.50 - 4.69 (m, 2H), 3.95 - 4.03 (m, 1H), 3.78 - 3.84 (m, 2H), 3.60 - 3.64 (m, 1H), 3.53 - 3.64 (m, 1H), 2.91 - 3.05 (m, 2H), 2.74 - 2.87 (m, 2H), 2.57 - 2.65 (m, 2H), 2.44 - 2.50 (m, 1H), 2.30 - 2.38 (m, 1H), 1.10 - 2.10 (m, 12H).	A
266		3- {[(1s,16R,17S,20s) -11-oxo-8,19- dioxo-12- azatetracyclo[18.2. 2.0 ² ,7.0 ¹² ,17]tetracos a-2,4,6-trien-16- yl]amino}propanenit rile	[M+H] ⁺ 412.3	¹ H NMR (400 MHz, CD ₃ OD) δ 7.06 - 7.14 (m, 1H), 6.98 - 7.05 (m, 1H), 6.81 - 6.86 (m, 1H), 6.69 - 6.81 (m, 1H), 4.53 - 4.60 (m, 1H), 4.50 - 4.69 (m, 2H), 3.95 - 4.03 (m, 1H), 3.78 - 3.84 (m, 2H), 3.60 - 3.64 (m, 1H), 3.53 - 3.64 (m, 1H), 2.91 - 3.05 (m, 2H), 2.74 - 2.87 (m, 2H), 2.57 - 2.65 (m, 2H), 2.44 - 2.50 (m, 1H), 2.30 - 2.38 (m, 1H), 1.10 - 2.10 (m, 12H).	C
267		(3R)-3- {[(1s,16S,17R,20s) -11-oxo-8,19- dioxo-12- azatetracyclo[18.2. 2.0 ² ,7.0 ¹² ,17]tetracos a-2,4,6-trien-16- yl]amino}butanenit rile	[M+H] ⁺ 426.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.17 - 7.09 (m, 1H), 7.09 - 6.98 (m, 1H), 6.93 - 6.74 (m, 2H), 4.84 - 4.67 (m, 2H), 4.48 - 4.26 (m, 1H), 4.02 - 3.43 (m, 6H), 3.36 - 3.05 (m, 2H), 2.91 - 2.17 (m, 8H), 2.03 - 1.23 (m, 12H).	A
268		(3R)-3- {[(1s,16R,17S,20s) -11-oxo-8,19- dioxo-12- azatetracyclo[18.2. 2.0 ² ,7.0 ¹² ,17]tetracos a-2,4,6-trien-16- yl]amino}butanenit rile	[M+H] ⁺ 426.4	¹ H NMR (400 MHz, CDCl ₃) δ 7.16 - 7.07 (m, 1H), 7.07 - 6.98 (m, 1H), 6.95 - 6.73 (m, 2H), 4.81 - 4.69 (m, 1H), 4.48 - 4.26 (m, 1H), 4.05 - 3.63 (m, 3H), 3.62 - 3.44 (m, 2H), 3.34 - 3.10 (m, 2H), 2.91 - 2.19 (m, 8H), 2.06 - 1.26 (m, 14H).	D



[0374] SYNTHESIS OF INTERMEDIATE 35

[0375] 1-tert-butyl 3-methyl (2R)-2-methyl-4-oxo-5-({[(1s,4s)-4-[2-(benzyloxy)phenyl]-cyclohexyl]oxy} methyl) pyrrolidine-1,3-dicarboxylate

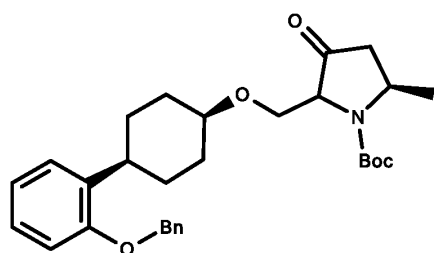


[0376] In a flask, a 2.5 M solution of *n*BuLi in heptane (55.9 mL, 0.140 mol) was added to a stirred solution of N-(propan-2-yl)propan-2-amine (19.7 mL, 0.140 mol) in anhydrous THF (50 mL) at -5 °C. The reaction was held at this temperature for 30 minutes. This freshly prepared LDA solution was transferred to an addition funnel, and added over 0.5 h, to a stirred solution of 1-tert-butyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (16.3 g, 63.5 mmol) and DMPU (30.6 g, 0.254 mol) in

anhydrous THF (115 mL) at -78 °C, ensuring the reaction temperature did not rise above -65 °C. The solution was held at this temperature for 1h. A solution of 1-benzyloxy-2-[4-(chloromethoxy)cyclohexyl]benzene (22.9 g, 69.2 mmol, prepared as described in WO2022233872A1) in anhydrous THF (41 mL) was added to the reaction mixture over 30 minutes. The reaction mixture was stirred at -78 °C for 1 h, warmed to room temperature, and stirred for 2 h. The reaction was quenched with saturated aqueous NH₄Cl solution, diluted with water (100 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The product was purified by column chromatography (0 - 25% EtOAc in heptane) to afford the title compound (17.50 g) as a yellow oil. (M+Na)⁺ m/z = 574.3

[0377] SYNTHESIS OF INTERMEDIATE 36

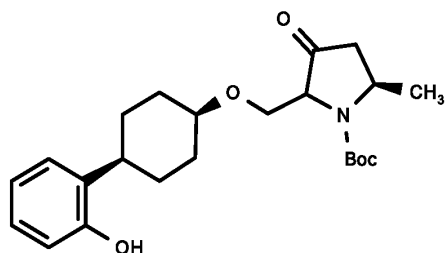
[0378] tert-butyl-(5R)-5-methyl-3-oxo-2-({[(CIS)-4-[2-(benzyloxy)phenyl]-cyclohexyl]oxy}methyl)pyrrolidine-1-carboxylate



[0379] A Vapourtec flow setup was equipped with a 10mL high temperature high-pressure stainless-steel reactor and a set of backpressure regulators equal to a total of 250 psi (20 bar). A solution of Intermediate 35 (31.2 g, 56.56 mmol) in a mixture of acetone (206 mL) and water (36 mL) (final substrate concentration 0.25 M) was pumped through the reactor at 155 °C with a residence time of 5 minutes (flow = 2 mL/min, pressure of ca. 20 bar). The collected fraction was concentrated *in vacuo*. The crude mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by acidic reverse phase column chromatography (5-85% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) to afford the title compound (13.3 g) as a colorless oil. [M+H]⁺ m/z = 494.4

[0380] SYNTHESIS OF INTERMEDIATE 37

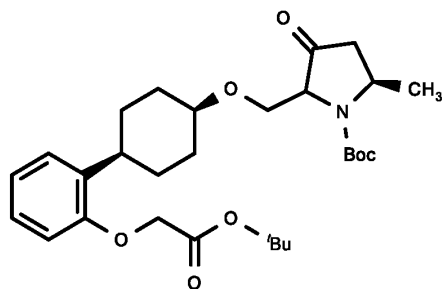
[0381] tert-butyl-(5R)-5-methyl-3-oxo-2-({[(1s,4s)-4-(2-hydroxyphenyl)cyclohexyl]oxy}methyl)pyrrolidine-1-carboxylate



[0382] To a solution of Intermediate 36 (13.0 g, 26.34 mmol) in ethanol (180 mL), palladium on carbon 10% (4.2 g, 3.95 mmol) was added. The mixture was placed under a hydrogen atmosphere (1 atm) and stirred for 6 h at room temperature. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to afford the title compound (10.6 g) as a colourless oil. $[M+H]^+$ $m/z = 404.3$

[0383] SYNTHESIS OF INTERMEDIATE 38

[0384] tert-butyl-(5R)-5-methyl-3-oxo-2-({[(1s,4s)-4-{2-[2-(tert-butoxy)-2-oxoethoxy]phenyl}cyclohexyl]oxy}methyl)pyrrolidine-1-carboxylate

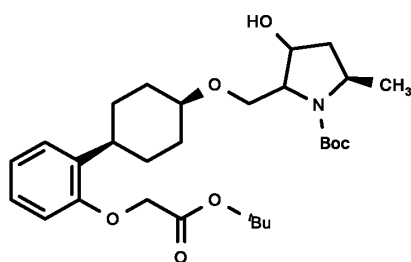


[0385] To a solution of Intermediate 37 (10.35 g, 25.65 mmol) and potassium carbonate (8.86 g, 64.12 mmol) in MeCN (320 mL) was added 2-bromoacetic acid tert-butyl ester (3.96 mL, 27.45 mmol) and the solution was heated to 55 °C for 3 h. The suspension was filtered and the filtrate was concentrated *in vacuo*. The residue was suspended in water and extracted with DCM. The

combined organic layers were concentrated *in vacuo* to afford the title compound (13.5 g) as a colorless oil. $[M+H]^+$ m/z = 518.4

[0386] SYNTHESIS OF INTERMEDIATE 39

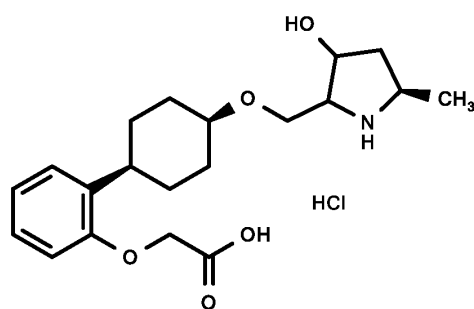
[0387] tert-butyl(5R)-3-hydroxy-5-methyl-2-({[(1s,4s)-4-{2-[2-(tert-butoxy)-2-oxoethoxy]phenyl}cyclohexyl]oxy} methyl)pyrrolidine-1-carboxylate



[0388] Sodium borohydride (0.99 g, 26.08 mmol) was added portionwise to a stirred solution of Intermediate 38 (13.5 g, 26.08 mmol) in DCM (125 mL) and MeOH (125 mL) at 0 °C and the mixture was stirred for 5 h. The reaction mixture was concentrated *in vacuo*. The residue was suspended in water and extracted with DCM. The organic phase was washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and brine. The organic phase was dried over MgSO_4 , filtered and concentrated *in vacuo* to afford the title compound (12.9 g) as a colorless oil. $[M+H]^+$ m/z = 520.4

[0389] SYNTHESIS OF INTERMEDIATE 40

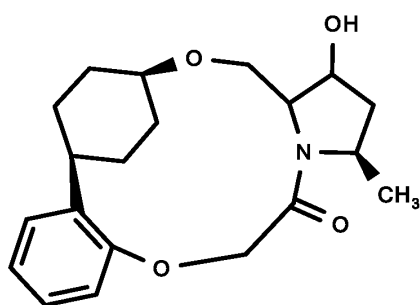
[0390] 2-{2-[(1s,4s)-4-{[(5R)-3-hydroxy-5-methylpyrrolidin-2-yl]methoxy}cyclohexyl]-phenoxy}acetic acid hydrochloride



[0391] To a stirred solution of Intermediate 39 (12.9 g, 24.82 mmol) in 1,4-dioxane (100 mL), a 4N solution of hydrogen chloride in 1,4-dioxane (51.53 mL, 206.14 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated *in vacuo* to afford the title compound (14 g) as a white solid. $[M+H]^+$ m/z = 364.3

[0392] SYNTHESIS OF INTERMEDIATE 41

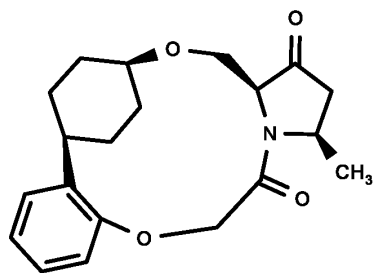
[0393] (1s,12R,18s)-14-hydroxy-12-methyl-8,17-dioxo-11-azatetracyclo[16.2.2.0^{2,7}.0^{11,15}]docosa-2(7),3,5-trien-10-one



[0394] Three 4L round-bottomed flasks were each charged with HATU (5.7 g, 15 mmol), DIPEA (7.0 mL, 40 mmol) and MeCN (3.5 L). A solution of Intermediate 40 (4 g, 10 mmol) in DMA (100 mL) was added dropwise at room temperature using a syringe pump over a period of 6 h to each flask. After addition was complete the reaction mixtures were stirred for 60 minutes and then concentrated *in vacuo*. The crude mixtures were merged and then taken up with diethyl ether, washed with water (200 mL) and brine, filtered through a hydrophobic frit (Phase Separator), and concentrated *in vacuo* to afford the title compound (8 g) as an orange solid. $[M+H]^+$ m/z = 346.3

[0395] SYNTHESIS OF INTERMEDIATE 42

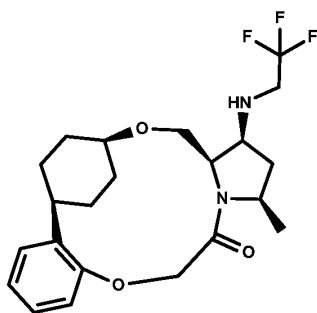
[0396] (1s,12R,15S,18s)-12-methyl-8,17-dioxo-11-azatetracyclo[16.2.2.0^{2,7}.0^{11,15}]docosa-2(7),3,5-triene-10,14-dione



[0397] To a solution of Intermediate 41 (7.9 g, 20.81 mmol) in DCM (198 mL) at 0 °C was added Dess-Martin Periodinane (11.48 g, 27.06 mmol). The mixture was stirred at room temperature for 4 h. The mixture was diluted with DCM and 0.2 mL of H₂O and it was filtered. The filtrate was washed with saturated aqueous NaHCO₃ solution, 1M aqueous Na₂S₂O₃ solution, and 1M aqueous Na₂CO₃ solution. The organic layer was dried by passing through a hydrophobic frit (Phase Separator) and concentrated *in vacuo*. The product was purified by acidic reverse phase column chromatography (9-95% MeCN +0.1% HCOOH in H₂O +0.1% HCOOH) to afford the title compound (1.95 g) as a pale-brown solid. [M+H]⁺ m/z = 344.3

[0398] Example 269

[0399] (1s,12R,14S,15R,18s)-12-methyl-14-[(2,2,2-trifluoroethyl)amino]-8,17-dioxa-11-azatetracyclo[16.2.2.0^{2,7}.0^{11,15}] docosa-2(7),3,5-trien-10-one



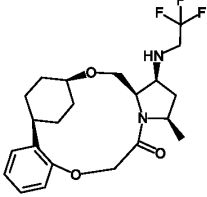
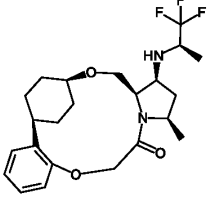
[0400] A solution of 2,2,2-trifluoroethanamine (70 µL, 0.87 mmol), Ti(OEt)₄ (0.12 mL, 0.58 mmol) and Intermediate 42 (100 mg, 0.29 mmol) in anhydrous THF (7 mL) was heated to 70 °C for 16 h. The reaction mixture was cooled to room temperature, then sodium cyanoborohydride (288 mg, 4.66 mmol) was added and the reaction mixture was stirred for 12 h. Water was added and the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated in

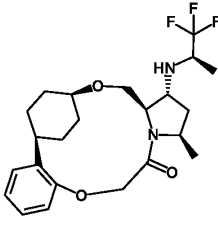
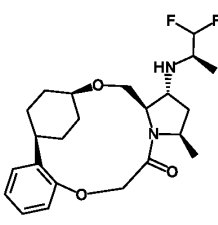
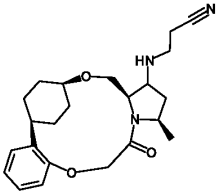
vacuo and the residue obtained was loaded onto a SCX cartridge, which was washed with MeOH and then eluted with a 2M solution of NH₃ in MeOH. The basic fractions were concentrated *in vacuo*. The product was purified by column chromatography (0-10% EtOAc in cHex) to afford the title compound (23 mg, 0.054 mmol, 18% yield) as a pale orange solid.

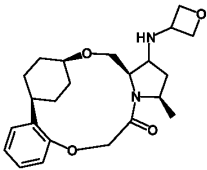
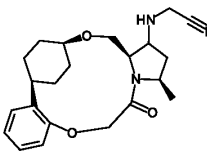
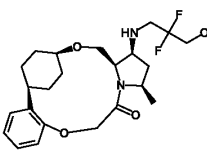
[0401] The examples reported in the table below were synthesized using similar procedures to those described for Examples 1, 260 and 269 using the appropriate reagents.

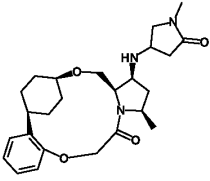
[0402] Enantiomers were separated by chiral purification using appropriate chiral columns and combination of solvent mixtures; Chiralpak columns (AD-H, IC, OJ-H, AS-H); solvent mixture of n-Hexane / EtOH, n-Hexane / (EtOH + 0.1% iPrNH₂), n-Hexane / (EtOH/MeOH 1:1 + 0.1% iPrNH₂).

Table 19. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
269		(1s,12R,14S,15R,18s)-12-methyl-14-[(2,2,2-trifluoroethyl)amino]-8,17-dioxo-11-azatetracyclo[16.2.2.0 ^{2,7} .0 ^{11,15}]docosa-2(7),3,5-trien-10-one	[M+H] ⁺ 427.3	¹ H NMR (400 MHz, MeOD) δ 7.21 – 7.12 (m, 1H), 7.08 (br d, J = 7.8 Hz, 2H), 6.86 (br t, J = 7.1 Hz, 1H), 4.85 (s, 1H), 4.56 (br d, J = 11.0 Hz, 2H), 4.33 – 4.15 (m, 1H), 3.86 – 3.67 (m, 2H), 3.55 (br t, J = 10.6 Hz, 1H), 3.43 – 3.18 (m, 3H), 2.81 – 2.68 (m, 1H), 2.68 – 2.56 (m, 1H), 2.50 (dt, J = 12.7, 8.0 Hz, 1H), 2.39 – 2.23 (m, 1H), 2.06 (br d, J = 13.3 Hz, 1H), 1.96 – 1.83 (m, 1H), 1.38 (br d, J = 6.2 Hz, 3H), 1.62 – 1.34 (m, 5H).	C
270		(1s,12R,14S,15R,18s)-12-methyl-14-[(2R)-1,1,1-trifluoropropan-2-yl]amino-8,17-dioxo-11-azatetracyclo[16.2.2.0 ^{2,7} .0 ^{11,15}]docosa-2(7),3,5-trien-10-one	[M+H] ⁺ 441.3	¹ H NMR (400 MHz, MeOD) δ 7.20 – 7.11 (m, 1H), 7.08 (br d, J = 7.7 Hz, 2H), 6.86 (br t, J = 7.3 Hz, 1H), 4.89 – 4.85 (m, 1H), 5.10 – 4.52 (m, 1H), 4.69 – 4.43 (m, 1H), 4.30 – 4.15 (m, 1H), 4.03 – 3.81 (m, 1H), 3.75 (br s, 1H), 3.59 – 3.44 (m, 1H), 3.67 – 3.34 (m, 1H), 3.29 – 3.20 (m, 1H), 2.99 – 2.69 (m, 1H), 2.62 (tt, J = 11.8, 5.9 Hz, 1H), 2.47 (dt, J = 12.4, 8.1 Hz, 1H), 2.40 – 2.20 (m, 1H), 2.14 – 1.95 (m, 1H), 1.94 – 1.75 (m, 1H), 1.62 – 1.52 (m, 1H), 1.39 (br d, J = 6.6 Hz, 3H), 1.53 –	B

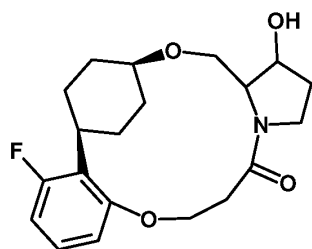
				1.31 (m, 4H), 1.25 (d, J = 6.8 Hz, 3H).	
271		(1s,12R,14R,15R,18s)-12-methyl-14-([(2R)-1,1,1-trifluoropropan-2-yl]amino)-8,17-dioxo-11-azatetracyclo[16.2.2.0.2,7,0 ^{11,15}]docosa-2(7),3,5-trien-10-one	[M+H] ⁺ 441.3	¹ H NMR (400 MHz, MeOD) δ 7.14 (td, J = 7.7, 1.4 Hz, 1H), 7.05 (br d, J = 7.1 Hz, 1H), 6.89 – 6.80 (m, 2H), 5.10 (d, J = 9.8 Hz, 1H), 4.36 (quin, J = 6.9 Hz, 1H), 4.26 (dd, J = 8.8, 2.8 Hz, 1H), 4.18 (d, J = 9.6 Hz, 1H), 3.83 – 3.71 (m, 3H), 3.38 (dt, J = 14.1, 7.1 Hz, 1H), 3.25 (d, J = 8.8 Hz, 1H), 2.86 (qd, J = 13.0, 4.3 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.26 (qd, J = 13.2, 3.9 Hz, 1H), 2.15 (br d, J = 14.0 Hz, 1H), 2.02 (br dd, J = 11.7, 5.3 Hz, 1H), 1.94 – 1.80 (m, 2H), 1.48 (d, J = 6.7 Hz, 3H), 1.56 – 1.43 (m, 1H), 1.29 (d, J = 6.8 Hz, 3H), 1.41 – 1.17 (m, 3H).	C
272		(1s,12R,14R,15R,18s)-14-([(2R)-1,1-difluoropropan-2-yl]amino)-12-methyl-8,17-dioxo-11-azatetracyclo[16.2.2.0.2,7,0 ^{11,15}]docosa-2(7),3,5-trien-10-one	[M+H] ⁺ 423.3	¹ H NMR (500 MHz, MeOD) δ 7.15 (td, J=7.8, 1.8 Hz, 1 H), 7.06 (dd, J=7.8, 1.7 Hz, 1 H), 6.84 - 6.89 (m, 2 H), 5.72 (td, J=56.6, 4.1 Hz, 1 H), 5.23 (d, J=10.6 Hz, 1 H), 4.54 - 4.61 (m, 1 H), 4.33 (dd, J=7.8, 2.5 Hz, 1 H), 4.23 (dd, J=9.5, 2.9 Hz, 1 H), 4.10 (d, J=10.6 Hz, 1 H), 3.82 (dt, J=12.2, 7.3 Hz, 1 H), 3.75 (br s, 1 H), 3.28 - 3.32 (m, 1 H), 3.01 - 3.13 (m, 1 H), 2.54 (tt, J=12.2, 4.9 Hz, 1 H), 2.37 (td, J=11.7, 8.5 Hz, 1 H), 2.13 - 2.70 (m, 2 H), 1.85 - 1.92 (m, 1 H), 1.77 - 2.13 (m, 2 H), 1.36 - 1.39 (m, 3 H), 1.30 - 1.55 (m, 2 H), 1.23 - 1.45 (m, 2 H), 1.18 (d, J=6.6 Hz, 3 H)	D
273		3-([(1s,12R,15R,18s)-12-methyl-10-oxo-8,17-dioxo-11-azatetracyclo[16.2.2.0.2,7,0 ^{11,15}]docosa-2(7),3,5-trien-14-	[M+H] ⁺ 398.3	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.10 - 7.17 (m, 2 H), 7.08 (d, J=7.5 Hz, 1 H), 6.80 - 6.85 (m, 1 H), 4.49 - 4.95 (m, 1 H), 4.42 - 4.67 (m, 1 H), 4.02 - 4.87 (m, 1 H), 4.01 - 4.19 (m, 1 H), 3.61 - 3.77 (m, 2 H), 3.34 - 3.44 (m, 1 H), 3.07 - 3.36 (m, 1 H), 2.70 - 2.82 (m, 2 H), 2.52 - 2.67 (m,	C

		yl]amino}propaneni trile		3 H), 2.25 - 2.41 (m, 1 H), 2.22 - 2.68 (m, 2 H), 1.73 - 2.03 (m, 2 H), 1.30 - 1.41 (m, 1 H), 1.18 - 1.28 (m, 3 H), 1.16 - 1.42 (m, 4 H).	
274		(1s,12R,15R,18s)- 12-methyl-14- [(oxetan-3- yl)amino]-8,17- dioxo-11- azatetracyclo[16.2.2 .0 ² ,7.0 ¹¹ ,15]docosa- 2(7),3,5-trien-10- one	[M+H] ⁺ 401.3	¹ H NMR (500 MHz, MeOD) δ 7.20 - 7.12 (m, 1H), 7.08 (br d, J = 7.7 Hz, 2H), 6.86 (br t, J = 7.3 Hz, 1H), 4.91 - 4.86 (m, 1H), 4.79 (q, J = 7.0 Hz, 2H), 4.55 (d, J = 11.3 Hz, 1H), 4.52 - 4.44 (m, 3H), 4.26 - 4.16 (m, 1H), 4.06 - 3.97 (m, 1H), 3.77 (br s, 1H), 3.72 (br dd, J = 10.5, 4.2 Hz, 1H), 3.55 (t, J = 10.6 Hz, 1H), 3.19 (dt, J = 11.5, 6.7 Hz, 1H), 2.79 - 2.68 (m, 1H), 2.63 (tt, J = 12.0, 6.2 Hz, 1H), 2.42 (dt, J = 12.4, 7.9 Hz, 1H), 2.31 (qd, J = 12.8, 4.6 Hz, 1H), 2.07 (br d, J = 13.7 Hz, 1H), 1.95 - 1.85 (m, 1H), 1.38 (br d, J = 6.3 Hz, 3H), 1.58 - 1.34 (m, 5H).	D
275		2- {[(1s,12R,15R,18s)- 12-methyl-10-oxo- 8,17-dioxo-11- azatetracyclo[16.2.2 .0 ² ,7.0 ¹¹ ,15]docosa- 2(7),3,5-trien-14- yl]amino}acetonitril e	[M+H] ⁺ 383.3	¹ H NMR (500 MHz, MeOD) δ 7.11 - 7.22 (m, 1 H), 7.04 - 7.11 (m, 2 H), 6.76 - 6.91 (m, 1 H), 4.58 - 4.83 (m, 1 H), 4.51 - 5.10 (m, 1 H), 4.17 - 4.95 (m, 1 H), 4.16 - 4.35 (m, 1 H), 3.69 - 3.80 (m, 2 H), 3.61 - 3.71 (m, 2 H), 3.53 (t, J=10.7 Hz, 1 H), 3.33 - 3.53 (m, 1 H), 2.69 - 3.03 (m, 1 H), 2.58 - 2.74 (m, 1 H), 2.53 (dt, J=12.4, 8.0 Hz, 1 H), 2.20 - 2.60 (m, 1 H), 1.82 - 2.19 (m, 2 H), 1.55 (br s, 1 H), 1.33 - 1.42 (m, 3 H), 1.28 - 1.59 (m, 4 H).	D
276		(1s,12R,14S,15R,18 s)-14-[(2,2- difluoro-3- hydroxypropyl)ami no]-12-methyl- 8,17-dioxo-11- azatetracyclo[16.2.2 .0 ² ,7.0 ¹¹ ,15]docosa- 2(7),3,5-trien-10- one	[M+H] ⁺ 439.2	¹ H NMR (500 MHz, MeOD) δ 7.12 - 7.20 (m, 1 H), 7.02 - 7.11 (m, 2 H), 6.86 (br t, J=7.3 Hz, 1 H), 4.86 - 4.90 (m, 1 H), 4.52 - 4.60 (m, 2 H), 4.17 - 4.30 (m, 1 H), 3.69 - 3.85 (m, 4 H), 3.56 (br t, J=10.7 Hz, 1 H), 3.26 - 3.36 (m, 1 H), 2.90 - 3.24 (m, 2 H), 2.74 (qd, J=12.6, 4.7 Hz, 1 H), 2.62 (tt, J=12.0, 6.2 Hz, 1 H), 2.49 (dt, J=12.5, 8.0 Hz, 1 H), 2.24 - 2.36 (m, 1 H), 2.10 (br d, J=13.3 Hz, 1	B

				H), 1.86 - 1.93 (m, 1 H), 1.40 - 1.60 (m, 5 H), 1.39 (br d, J=6.3 Hz, 3 H).	
277		(1s,12R,14S,15R,18s)-12-methyl-14-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-8,17-dioxo-11-azatetracyclo[16.2.2.0 ^{2,7,0^{11,15}}]docosa-2(7),3,5-trien-10-one	[M+H] ⁺ 442.1	Peaks not assigned as compound isolated as mixture of diastereoisomers	D

[0403] SYNTHESIS OF INTERMEDIATE 43

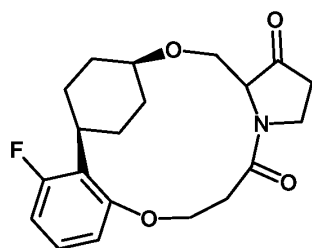
[0404] (1s,19s)-3-fluoro-15-hydroxy-8,18-dioxo-12-azatetracyclo[17.2.2.0^{2,7,0^{12,16}}]tricoso-2(7),3,5-trien-11-one



[0405] Intermediate 43 was synthesized using a similar synthetic route to that described for Intermediate 33 using the appropriate starting materials to afford the title compound (3.5 g) as a pale-brown solid. [M+H]⁺ m/z = 364.6

[0406] SYNTHESIS OF INTERMEDIATE 44

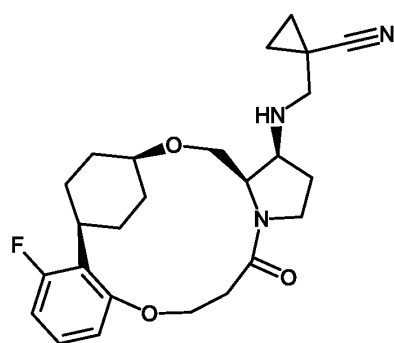
[0407] (1s,19s)-3-fluoro-8,18-dioxo-12-azatetracyclo[17.2.2.0^{2,7,0^{12,16}}]tricoso-2(7),3,5-triene-11,15-dione



[0408] To a solution of Intermediate 43 (3.4 g, 9.36 mmol) in MeCN (94 mL), was added tetrakis(acetonitrile)copper(I) trifluoromethanesulfonate (176 mg, 0.470 mmol), ABNO (13 mg, 0.090 mmol), 4-4'-dimethoxy-2,2'-bipyridine (101 mg, 0.470 mmol) and then *N*-methylimidazole (0.07 mL, 0.940 mmol). The reaction mixture was stirred at room temperature for 30 minutes with air bubbling through the solution. The precipitate was filtered off and washed with cold MeCN and cHex. The solid was kept aside while the filtrate was concentrated *in vacuo* and then suspended in cold MeCN. The filtration was repeated once again keeping the obtained solid. The filtrate was concentrated again and the process was repeated reducing the amount of MeCN used. The collected solids were combined to afford the title compound (3.2 g, 8.854 mmol, 95% yield) as a white solid. $[M+H]^+$ $m/z = 362.5$

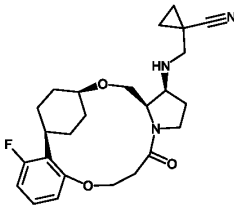
[0409] Example 278

[0410] Rel-1-({[(1*s*,15*S*,16*R*,19*s*)-3-fluoro-11-oxo-8,18-dioxa-12-azatetracyclo[17.2.2.0^{2,7}.0^{12,16}]triosa-2(7),3,5-trien-15-yl]amino}methyl)cyclopropane-1-carbonitrile



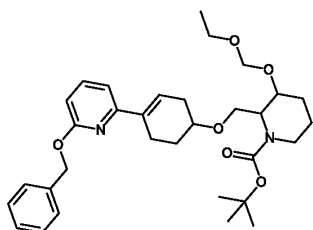
[0411] Intermediate 44 (50 mg, 0.140 mmol) and 1-(aminomethyl)cyclopropanecarbonitrile hydrochloride (37 mg, 0.280 mmol) were suspended in THF (1.4 mL). Sodium triacetoxyborohydride (176 mg, 0.830 mmol) was slowly added and the reaction mixture was stirred at room temperature for 3 h. Further 1-(aminomethyl)cyclopropanecarbonitrile hydrochloride (18 mg, 0.140 mmol) and sodium triacetoxyborohydride (59 mg, 0.280 mmol) were added. The reaction mixture was stirred at room temperature for 1 h and then it was diluted with EtOAc. The suspension was washed with saturated aqueous NaHCO₃ solution, saturated aqueous NH₄Cl solution and brine. The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product was purified by column chromatography using a C18 cartridge (0-40% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) to afford the title compound (51 mg, 0.116 mmol, 83% yield) as a white solid.

Table 20. Prepared Compound and the Biological Activity Thereof

Cmpd	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
278		Rel-1-((1s,15S,16R,19s)-3-fluoro-11-oxo-8,18-dioxo-12-azatetracyclo[17.2.2.0 ^{2,7} .0 ^{12,16}]trienosa-2(7),3,5-trien-15-yl)amino)methyl)cyclopropane-1-carbonitrile	[M+H] ⁺ 442.7	¹ H NMR (500 MHz, CDCl ₃) δ 7.11 - 7.01 (m, 1H), 6.80 - 6.55 (m, 2H), 4.88 - 4.36 (m, 1H), 4.37 - 4.29 (m, 1H), 4.31 - 3.86 (m, 1H), 3.94 - 3.81 (m, 1H), 4.26 - 3.74 (m, 1H), 3.80 - 3.61 (m, 1H), 3.59 - 3.45 (m, 1H), 3.48 - 3.35 (m, 1H), 3.44 - 3.28 (m, 1H), 3.56 - 3.08 (m, 1H), 3.11 - 3.00 (m, 1H), 2.89 - 2.79 (m, 1H), 2.78 - 2.67 (m, 1H), 2.45 - 2.29 (m, 1H), 2.28 - 2.07 (m, 2H), 2.58 - 1.17 (m, 10H), 1.03 - 0.81 (m, 2H).	A

[0412] SYNTHESIS OF INTERMEDIATE 45

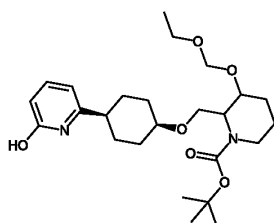
[0413] tert-butyl 2-[(4-[6-(benzyloxy)pyridin-2-yl]cyclohex-3-en-1-yl)oxy)methyl]-3-(ethoxymethoxy)piperidine-1-carboxylate



[0414] A mixture of Intermediate 17 (500 mg, 1.01 mmol), 2-benzyloxy-6-bromo-pyridine (293 mg, 1.11 mmol) and potassium carbonate (697 mg, 5.05 mmol) in 1,2-dimethoxyethane (9.6 mL) and water (9.6 mL) was degassed by bubbling $N_{2(g)}$ through the mixture for 10 minutes, then $Pd(PPh_3)_4$ (117 mg, 0.100 mmol) was added. The mixture was degassed again by bubbling $N_{2(g)}$ through the mixture for 10 minutes and stirred at 80 °C for 1 h. After cooling the mixture to room temperature, the suspension was diluted with EtOAc and washed with water and brine. The organic phase was filtered through a hydrophobic frit (Phase Separator) and concentrated *in vacuo*. The residue was purified by column chromatography using a silica cartridge (0-15% EtOAc in cHex) to afford the title compound (519 mg, 0.939 mmol, 93% yield) as a colorless oil. $[M+H]^+$ m/z = 553.3

[0415] SYNTHESIS OF INTERMEDIATE 46

[0416] tert-butyl 3-(ethoxymethoxy)-2-({[(1s,4s)-4-(6-hydroxypyridin-2-yl)cyclohexyl]oxy} methyl)piperidine-1-carboxylate

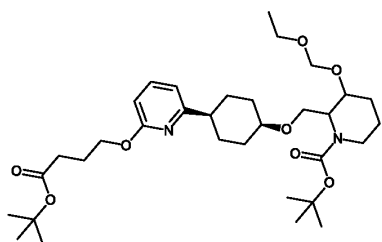


[0417] To a solution of Intermediate 45 (519 mg, 0.940 mmol) in EtOH (30 mL), were added ammonium formate (1.18 g, 18.78 mmol) and 10% wt. Pd/C (100 mg, 0.090 mmol) and the mixture was stirred at 80 °C overnight. The mixture was then cooled to room temperature and filtered over a Celite cartridge, and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with water and saturated aqueous $NaHCO_3$ solution. The organic phase was filtered

through a hydrophobic frit (Phase Separator) and concentrated *in vacuo* to afford the title compound (406 mg, 0.874 mmol, 93% yield) as a white solid. $[M+H]^+$ m/z = 465.3

[0418] SYNTHESIS OF INTERMEDIATE 47

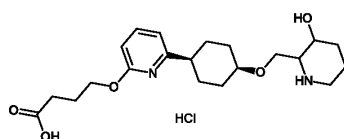
[0419] tert-butyl 3-(ethoxymethoxy)-2-({[(1s,4s)-4-{6-[4-(tert-butoxy)-4-oxobutoxy]pyridin-2-yl}cyclohexyl]oxy}methyl)piperidine-1-carboxylate



[0420] Intermediate 46 (406 mg, 0.870 mmol), silver carbonate (482 mg, 1.75 mmol) and tertbutyl-4-bromobutyrate (585 mg, 2.62 mmol) in toluene (1.7 mL) was degassed by bubbling $N_{2(g)}$ through the mixture, then stirred at 120 °C for 16 h. The suspension was cooled to room temperature, diluted with DCM and filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography using a C18 cartridge (3-90% MeCN + 0.1% HCOOH in H_2O + 0.1% HCOOH) to afford the title compound (363 mg, 0.598 mmol, 68% yield) as a colorless solid. $[M+H]^+$ m/z = 608.0

[0421] SYNTHESIS OF INTERMEDIATE 48

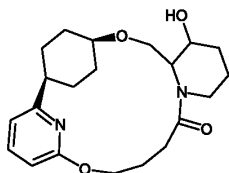
[0422] 4-({6-[(1s,4s)-4-[(3-hydroxypiperidin-2-yl)methoxy]cyclohexyl]pyridin-2-yl}oxy)butanoic acid hydrochloride



[0423] Intermediate 48 was synthesized using a similar procedure to that described for Intermediate 6 to afford the title compound (0.301 g) as a white solid. $[M+H]^+$ m/z = 393.6

[0424] SYNTHESIS OF INTERMEDIATE 49

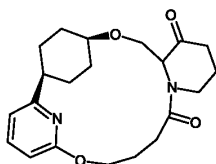
[0425] (1s,20s)-16-hydroxy-7,19-dioxo-12,25-diazatetracyclo[18.2.2.1²,6.0^{12,17}]pentacosa-2(25),3,5-trien-11-one



[0426] Intermediate 49 was synthesized using a similar procedure to that described for Intermediate 7 to afford the title compound (0.114 g) as a white solid. $[M+H]^+$ $m/z = 375.3$

[0427] SYNTHESIS OF INTERMEDIATE 50

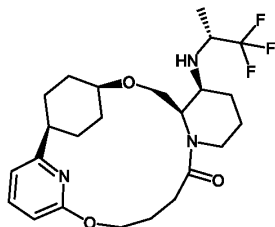
[0428] (1s,20s)-7,19-dioxo-12,25-diazatetracyclo[18.2.2.1²,6.0^{12,17}]pentacosa-2(25),3,5-triene-11,16-dione



[0429] Intermediate 50 was synthesized using a similar procedure to that described for Intermediate 8 to afford the title compound (0.093 g) as a white solid. $[M+H]^+$ $m/z = 373.6$

[0430] Example 279

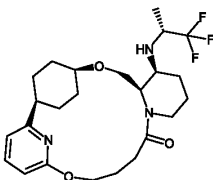
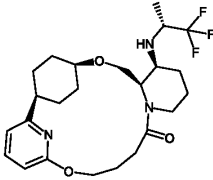
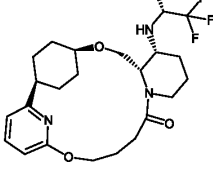
[0431] Rel-(1s,16S,17R,20s)-16-{[(2R)-1,1,1-trifluoropropan-2-yl]amino}-7,19-dioxo-12,25-diazatetracyclo[18.2.2.1²,6.0^{12,17}]pentacosa-2(25),3,5-trien-11-one



[0432] Example 279 was synthesized using a similar procedure to that described for Example 269 to afford the title compound (40 mg, 0.085 mmol, 35% yield) as a white solid.

[0433] Enantiomers were separated by chiral SFC purification using Chiralcel OD-H column and 10% (ethanol + 0.1% isopropylamine) as modifier.

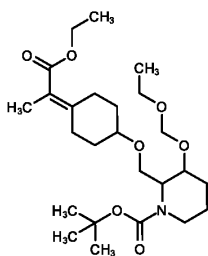
Table 21. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
279		Rel-(1s,16S,17R,20s)-16-{[(2R)-1,1,1-trifluoropropan-2-yl]amino}-7,19-dioxadiazatetracyclo[18.2.2.1 ^{2,6} .0 ^{12,17}]pentacosan-2(25),3,5-trien-11-one	[M+H] ⁺ 470.3	ND	A
280		(1s,16S,17R,20s)-16-{[(2R)-1,1,1-trifluoropropan-2-yl]amino}-7,19-dioxadiazatetracyclo[18.2.2.1 ^{2,6} .0 ^{12,17}]pentacosan-2(25),3,5-trien-11-one	[M+H] ⁺ 470.2	¹ H NMR (600 MHz, MeOD) δ 7.44 (ddd, J = 14.4, 8.2, 7.1 Hz, 1H), 6.65 (ddd, J = 15.2, 7.2, 0.8 Hz, 1H), 6.46 (ddd, J = 26.2, 8.2, 0.8 Hz, 1H), 5.26 – 5.12 (m, 1H), 4.47 – 4.34 (m, 1H), 4.22 (dt, J = 11.2, 7.7 Hz, 1H), 4.00 – 3.67 (m, 3H), 3.61 (d, J = 16.2 Hz, 1H), 3.51 – 3.32 (m, 1H), 3.27 – 3.14 (m, 1H), 2.98 – 2.73 (m, 2H), 2.71 – 2.53 (m, 1H), 2.53 – 2.24 (m, 2H), 2.16 (d, J = 14.2 Hz, 1H), 2.05 (d, J = 15.0 Hz, 3H), 1.94 – 1.71 (m, 4H), 1.59 – 1.30 (m, 6H), 1.27 (t, J = 6.1 Hz, 3H).	A
281		(1s,16R,17S,20s)-16-{[(2R)-1,1,1-trifluoropropan-2-yl]amino}-7,19-dioxadiazatetracyclo[18.2.2.1 ^{2,6} .0 ^{12,17}]pentacosan-	[M+H] ⁺ 470.2	¹ H NMR (600 MHz, MeOD) δ 7.45 (ddd, J = 15.3, 8.3, 7.1 Hz, 1H), 6.69 – 6.62 (m, 1H), 6.50 – 6.42 (m, 1H), 5.22 (dt, J = 11.1, 7.5 Hz, 1H), 4.45 (dq, J = 9.4, 5.1 Hz, 1H), 4.24 – 3.81 (m, 2H), 3.78 – 3.68 (m, 1H), 3.66 – 3.36 (m, 3H), 3.21 – 2.95 (m, 3H), 2.89 – 2.75 (m, 1H), 2.69 – 2.54 (m, 1H), 2.53 – 2.23 (m, 2H), 2.16 (d, J = 14.1 Hz, 1H), 2.10 – 1.98 (m, 2H), 1.94 – 1.82 (m, 2H), 1.76 (t, J =	D

		2(25),3,5-trien-11-one		13.4 Hz, 2H), 1.58 – 1.28 (m, 6H), 1.26 (t, J = 6.9 Hz, 3H).	
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[0434] SYNTHESIS OF INTERMEDIATE 51

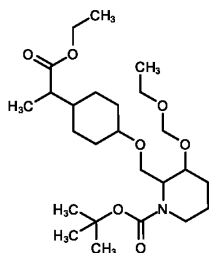
[0435] tert-butyl 2-({[4-(1-ethoxy-1-oxopropan-2-ylidene)cyclohexyl]oxy}methyl)-3-(ethoxymethoxy)piperidine-1-carboxylate



[0436] A suspension of sodium hydride (60% in mineral oil, 451 mg, 11.28 mmol) in THF (65 mL) was cooled to 0 °C. A solution of 2-diethoxyphosphorylpropanoic acid ethyl ester (2.42 mL, 11.28 mmol) was slowly added and the mixture was stirred for 30 minutes at room temperature. A solution of Intermediate 15 (2.9 g, 7.52 mmol) in THF (10 mL) was added and the reaction mixture was stirred at room temperature overnight. The mixture was quenched by addition of saturated aqueous NaHCO₃ solution. EtOAc was added and the mixture was washed with water. The organic phase was dried (Na₂SO₄) and evaporated *in vacuo*. The product was purified by column chromatography using a silica cartridge (0-30 EtOAc in cHex) to afford the title compound (3.06 g, 6.52 mmol, 87% yield) as a colorless oil. [M+Na]⁺ m/z = 492.5

[0437] SYNTHESIS OF INTERMEDIATE 52

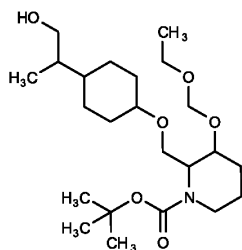
[0438] tert-butyl 2-({[4-(1-ethoxy-1-oxopropan-2-yl)cyclohexyl]oxy}methyl)-3-(ethoxymethoxy)piperidine-1-carboxylate



[0439] To a mixture of Intermediate 51 (2.9 g, 6.18 mmol) in ethanol (62 mL), was added 10% wt. Pd/C (1.31 g, 1.24 mmol) and ammonium formate (0.31 mL, 6.18 mmol). The suspension was stirred at room temperature for 12 h. The mixture was filtered over a pad of Celite and concentrated *in vacuo* to afford the title compound (2.9 g, 6.149 mmol, 99% yield) as a colorless oil. $[M+Na]^+$ $m/z = 494.5$

[0440] SYNTHESIS OF INTERMEDIATE 53

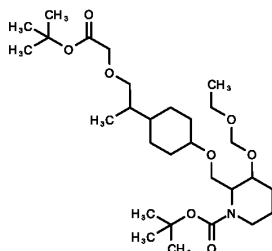
[0441] tert-butyl 3-(ethoxymethoxy)-2-({[4-(1-hydroxypropan-2-yl)cyclohexyl]oxy}methyl)piperidine-1-carboxylate



[0442] To a solution of Intermediate 52 (1.84g, 3.90 mmol) in anhydrous THF (19.5 mL) under a $N_{2(g)}$ atmosphere was added sodium borohydride (738 mg, 19.52 mmol) portionwise. The reaction mixture was stirred under reflux overnight. Further sodium borohydride (290 mg, 7.80 mmol) was added and the reaction mixture was stirred overnight under reflux. The mixture was cooled to room temperature and saturated aqueous NH_4Cl solution was added. The mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by column chromatography using a C18 cartridge (0-100% MeCN + 0.1% $HCOOH$ in H_2O + 0.1% $HCOOH$) to afford the title compound (0.955 mg, 2.23 mmol, 57% yield) as a white solid. $[M+Na]^+$ $m/z = 452.6$

[0443] SYNTHESIS OF INTERMEDIATE 54

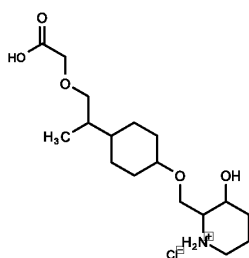
[0444] tert-butyl 2-{{[4-{1-[2-(tert-butoxy)-2-oxoethoxy]propan-2-yl}cyclohexyl]oxy)methyl}-3-(ethoxymethoxy)piperidine-1-carboxylate



[0445] Intermediate 54 was synthesized using a similar procedure to that described for Intermediate 20 to afford the title compound (1.33 g) as a white solid. $[M+Na]^+$ $m/z = 566.2$

[0446] SYNTHESIS OF INTERMEDIATE 55

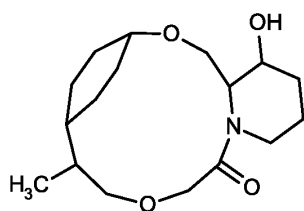
[0447] 2-[(4-[1-(carboxymethoxy)propan-2-yl]cyclohexyl)oxy)methyl]-3-hydroxypiperidin-1-ium chloride



[0448] Intermediate 55 was synthesized using a similar procedure to that described for Intermediate 21 to afford the title compound (1.47 g) as a white solid. $[M+H]^+$ $m/z = 330.3$

[0449] SYNTHESIS OF INTERMEDIATE 56

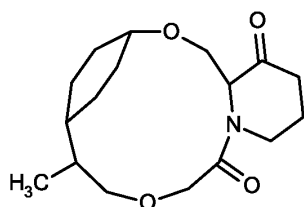
[0450] 5-hydroxy-14-methyl-2,12-dioxo-9-azatricyclo[13.2.2.0^{4,9}]nonadecan-10-one



[0451] Intermediate 56 was synthesized using a similar procedure to that described for Intermediate 22 to afford the title compound (0.153 g) as a white solid. $[M+H]^+$ $m/z = 312.2$

[0452] SYNTHESIS OF INTERMEDIATE 57

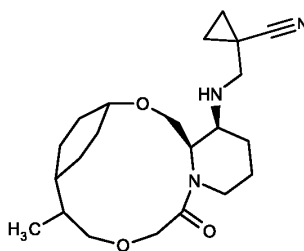
[0453] 14-methyl-2,12-dioxa-9-azatricyclo[13.2.2.0^{4,9}]nonadecane-5,10-dione



[0454] Intermediate 57 was synthesized using a similar procedure to that described for Intermediate 23 to afford the title compound (0.174 g) as a white solid. $[M+H]^+$ $m/z = 310.2$

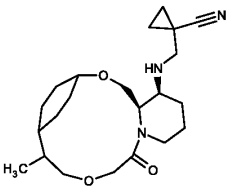
[0455] **Example 282**

[0456] Rel-1-({[(4R,5S)-14-methyl-10-oxo-2,12-dioxa-9-azatricyclo[13.2.2.0^{4,9}]nonadecan-5-yl]amino}methyl)cyclopropane-1-carbonitrile



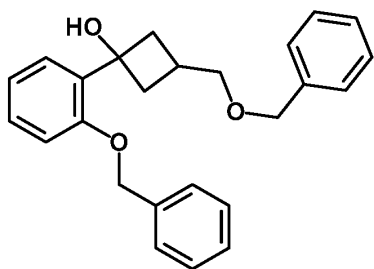
[0457] A mixture of Intermediate 57 (50 mg, 0.160 mmol), (1-cyanocyclopropyl)methylammonium chloride (43 mg, 0.320 mmol) and DIPEA (56 μ L, 0.320 mmol) in THF (1.8 mL) was shaken at room temperature for 15 minutes, then AcOH (0.5 μ L, 0.010 mmol) was added and the mixture was shaken at room temperature for 8 h. In a separate vessel further (1-cyanocyclopropyl)methylammonium chloride (28 mg, 0.210 mmol) and DIPEA (56 μ L, 0.320 mmol) were shaken at room temperature for 15 minutes and then this mixture was added to the main reaction mixture followed by AcOH (0.5 μ L, 0.010 mmol). The reaction mixture was shaken at 50 °C overnight, then cooled to room temperature. Sodium cyanoborohydride (60 mg, 0.970 mmol) was added and the reaction mixture was shaken at room temperature for 7 h. The mixture was diluted with EtOAc (100 mL) and washed 3 times with saturated aqueous NaHCO₃ solution. The organic phase was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product was purified column chromatography using a C18 cartridge (5-100% MeCN + 0.1% HCOOH in H₂O + 0.1% HCOOH) to afford the title compound (29.5 mg, 0.076 mmol, 47% yield) as a white solid.

Table 22. Prepared Compound and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
282		Rel-1-((4R,5S)-14-methyl-10-oxo-2,12-dioxo-9-azatricyclo[13.2.2.0 ^{4,9}]nonadecan-5-yl)amino}methylcyclopropane-1-carbonitrile	[M+H] ⁺ 390.3	¹ H NMR (500 MHz, MeOD) δ 5.23 - 5.14 (m, 1H), 4.67 - 4.52 (m, 1H), 3.88 - 3.76 (m, 2H), 3.68 - 3.62 (m, 1H), 3.62 - 3.49 (m, 4H), 3.31 - 3.25 (m, 1H), 3.03 - 2.96 (m, 1H), 2.95 - 2.88 (m, 1H), 2.84 - 2.76 (m, 1H), 2.20 - 0.98 (m, 18H), 0.84 - 0.78 (m, 3H).	B

[0458] SYNTHESIS OF INTERMEDIATE 58

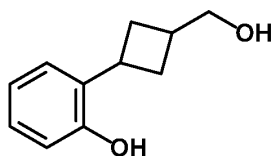
[0459] 3-[(benzyloxy)methyl]-1-[2-(benzyloxy)phenyl]cyclobutan-1-ol



[0460] To a solution of 1-bromo-2-phenylmethoxybenzene (14.47 mL, 76.01 mmol) in THF (200 mL) cooled to -78°C , a 2.5 M solution of *n*BuLi in hexane (33.44 mL, 83.61 mmol) was slowly added and the mixture was stirred for 2 h. A solution of 3-(benzyloxymethyl)cyclobutanone (15.77 mL, 91.21 mmol) in THF (20 mL) was slowly added. The mixture was allowed to slowly reach room temperature and stirred overnight. Saturated aqueous NH_4Cl solution (4 mL) was added and the mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine and the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound (34.3 g, quant. yield) as an orange oil. $[\text{M}+\text{Na}]^+$ $m/z = 397.2$

[0461] SYNTHESIS OF INTERMEDIATE 59

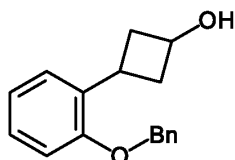
[0462] 2-[3-(hydroxymethyl)cyclobutyl]phenol



[0463] Intermediate 59 was synthesized using a similar procedure to that described for Intermediate 3 to afford the title compound (37.5 g) as a white solid. $[\text{M}-\text{H}]^-$ $m/z = 177.1$

[0464] SYNTHESIS OF INTERMEDIATE 60

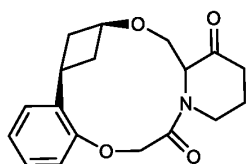
[0465] 3-[2-(benzyloxy)phenyl]cyclobutan-1-ol



[0466] To a mixture of Intermediate 59 (27.09 g, 152.02 mmol) in MeCN (280 mL) and DMF (35 mL), was added potassium carbonate (63 g, 456.06 mmol) portionwise followed by the slow addition of bromomethylbenzene (20.43 mL, 167.22 mmol). The mixture was stirred at 50 °C overnight. Additional bromomethylbenzene (4.64 mL, 38.01 mmol) was added and the mixture was stirred at 50 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with DCM and filtered. The filtrate was concentrated *in vacuo* and the product was purified by flash chromatography using a silica cartridge (0-25% EtOAc/EtOH 3:1 in cHex) to afford the title compound (27.68 g, 103.15 mmol, 68% yield) as a yellow oil. $[M+H]^+$ m/z = 269.1

[0467] SYNTHESIS OF INTERMEDIATE 61

[0468] (1s,19s)-8,18-dioxa-11-azatetracyclo[17.1.1.0^{2,7}.0^{11,16}]henicosa-2(7),3,5-triene-10,15-dione



[0469] Intermediate 61 was synthesized using a similar route to that described for Intermediate 8 starting from Intermediate 60 to afford the title compound (0.235 g) as a white solid. $[M+H]^+$ m/z = 330.2

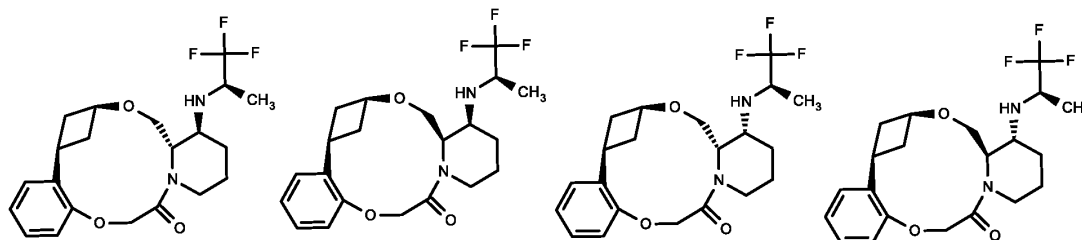
[0470] Examples 283, 284, 285, 286

[0471] Example 283: (1s,15S,16S,19s)-15-{[(2R)-1,1,1-trifluoropropan-2-yl]amino}-8,18-dioxa-11-azatetracyclo[17.1.1.0^{2,7}.0^{11,16}]henicosa-2(7),3,5-trien-10-one

[0472] Example 284: (1s,15S,16R,19s)-15-{[(2R)-1,1,1-trifluoropropan-2-yl]amino}-8,18-dioxa-11-azatetracyclo[17.1.1.0^{2,7}.0^{11,16}]henicosa-2(7),3,5-trien-10-one

[0473] Example 285: (1s,15R,16S,19s)-15-{[(2R)-1,1,1-trifluoropropan-2-yl]amino}-8,18-dioxa-11-azatetracyclo[17.1.1.0^{2,7}.0^{11,16}]henicosa-2(7),3,5-trien-10-one

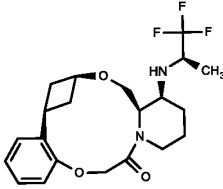
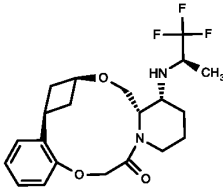
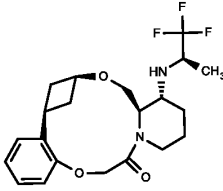
[0474] Example 286: (1s,15R,16R,19s)-15-{[(2R)-1,1,1-trifluoropropan-2-yl]amino}-8,18-dioxa-11-azatetracyclo[17.1.1.0^{2,7}.0^{11,16}]henicosa-2(7),3,5-trien-10-one



[0475] To a solution of Intermediate 61 (60 mg, 0.180 mmol) and (R)-1,1,1-trifluoro-2-propylamine (0.07 mL, 0.730 mmol) in THF (2 mL), was added $\text{Ti}(\text{OEt})_4$ (0.08 mL, 0.360 mmol) and the mixture was stirred at 60 °C for 20 h. The mixture was cooled to room temperature and sodium cyanoborohydride (180 mg, 2.91 mmol) was added. The reaction mixture was stirred for 1 h at room temperature. The mixture was partitioned between EtOAc and saturated aqueous NaHCO_3 solution and the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by column chromatography using a silica cartridge (0-40% EtOAc in cHex) to afford a mixture of different diastereoisomers that was submitted to chiral preparative SFC separation using a Chiralpak AD-H column (25 x 2.0 cm), 5 μ modifier (ethanol + 0.1% isopropylamine) 10%, flow rate (ml/min) 45, pressure (bar) 120, temperature (°C) 40, to afford the title compounds (Example 280, 6 mg, 86.1% ee; Example 281, 12 mg, 98.5% ee; Example 282, 16 mg, 100% ee, Example 283, 4 mg, 71.8% ee).

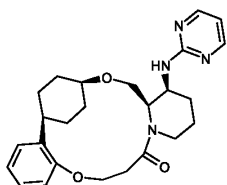
Table 23. Prepared Compounds and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	^1H NMR	EC50 hOX2
283		(1s,15S,16S,19s)-15-[[[(2R)-1,1,1-trifluoropropan-2-yl]amino]-8,18-dioxa-11-azatetracyclo[17.1.1.0 ^{2,7} .0 ^{11,16}]henicosa-2(7),3,5-trien-10-one	$[\text{M}+\text{H}]^+$ 427.2	^1H NMR (400 MHz, MeOD) δ 7.12 - 7.19 (m, 1 H), 7.03 (dd, J=7.3, 1.6 Hz, 1 H), 6.77 - 6.88 (m, 2 H), 5.28 (d, J=9.9 Hz, 1 H), 5.02 - 5.09 (m, 1 H), 4.13 (d, J=9.9 Hz, 1 H), 3.79 - 3.88 (m, 1 H), 3.54 - 3.73 (m, 3 H), 3.24 - 3.52 (m, 2 H), 3.09 - 3.22 (m, 2 H), 2.85 - 3.23 (m, 3 H), 2.29 - 2.43 (m, 1 H), 1.80 - 2.05 (m, 4 H), 1.68 - 1.79 (m, 1 H), 1.49 - 1.59 (m, 1 H), 1.26 (d, J=6.8 Hz, 3 H).	D

284		(1s,15S,16R,19s)-15-[(2R)-1,1,1-trifluoropropan-2-yl]amino}-8,18-dioxa-11-azatetracyclo[17.1.1.0 ^{2,7} .0 ^{11,16}]henicosa-2(7),3,5-trien-10-one	[M+H] ⁺ 427.2	¹ H NMR (400 MHz, MeOD) δ 7.15 (td, J=7.8, 1.6 Hz, 1 H), 7.02 (dd, J=7.3, 1.5 Hz, 1 H), 6.78 - 6.86 (m, 2 H), 5.25 (d, J=9.9 Hz, 1 H), 5.17 (dt, J=11.0, 5.6 Hz, 1 H), 4.13 (d, J=9.9 Hz, 1 H), 3.80 (br d, J=12.2 Hz, 1 H), 3.64 - 3.78 (m, 2 H), 3.60 (dd, J=10.2, 2.5 Hz, 1 H), 3.27 - 3.40 (m, 2 H), 3.13 - 3.24 (m, 1 H), 3.12 (d, J=9.4 Hz, 1 H), 2.92 - 3.06 (m, 3 H), 2.30 - 2.46 (m, 1 H), 1.79 - 1.91 (m, 2 H), 1.78 - 2.06 (m, 2 H), 1.56 - 1.72 (m, 2 H), 1.27 (d, J=6.7 Hz, 3 H).	C
285		(1s,15R,16S,19s)-15-[(2R)-1,1,1-trifluoropropan-2-yl]amino}-8,18-dioxa-11-azatetracyclo[17.1.1.0 ^{2,7} .0 ^{11,16}]henicosa-2(7),3,5-trien-10-one	[M+H] ⁺ 427.2	¹ H NMR (400 MHz, MeOD) δ 7.15 (td, J=7.8, 1.6 Hz, 1 H), 7.02 (dd, J=7.4, 1.6 Hz, 1 H), 6.78 - 6.87 (m, 2 H), 5.21 - 5.30 (m, 2 H), 4.13 (d, J=9.9 Hz, 1 H), 3.81 (br d, J=13.8 Hz, 1 H), 3.58 - 3.74 (m, 3 H), 3.38 - 3.46 (m, 1 H), 3.28 - 3.36 (m, 1 H), 3.14 - 3.24 (m, 1 H), 3.11 - 3.15 (m, 1 H), 2.91 - 3.12 (m, 3 H), 2.31 - 2.46 (m, 1 H), 1.79 - 1.91 (m, 2 H), 1.78 - 2.05 (m, 2 H), 1.52 - 1.71 (m, 2 H), 1.24 (d, J=6.8 Hz, 3 H).	D
286		(1s,15R,16R,19s)-15-[(2R)-1,1,1-trifluoropropan-2-yl]amino}-8,18-dioxa-11-azatetracyclo[17.1.1.0 ^{2,7} .0 ^{11,16}]henicosa-2(7),3,5-trien-10-one	[M+H] ⁺ 427.2	¹ H NMR (400 MHz, MeOD) δ 7.15 (t, J=7.7 Hz, 1 H), 7.02 (dd, J=7.4, 1.5 Hz, 1 H), 6.78 - 6.87 (m, 2 H), 5.28 (d, J=9.8 Hz, 1 H), 4.95 - 5.03 (m, 1 H), 4.09 - 4.14 (m, 1 H), 3.76 - 3.89 (m, 1 H), 3.56 - 3.72 (m, 3 H), 3.25 - 3.52 (m, 2 H), 3.07 - 3.22 (m, 2 H), 2.88 - 3.21 (m, 3 H), 2.29 - 2.45 (m, 1 H), 1.50 - 2.06 (m, 6 H), 1.25 (d, J=6.7 Hz, 3 H).	D

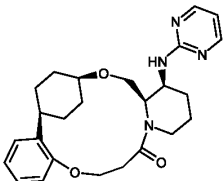
[0476] Example 287

[0477] Rel-(1s,16S,17R,20s)-16-[(pyrimidin-2-yl)amino]-8,19-dioxa-12-azatetracyclo[18.2.2.0^{2,7}.0^{12,17}]tetracosa-2(7),3,5-trien-11-one



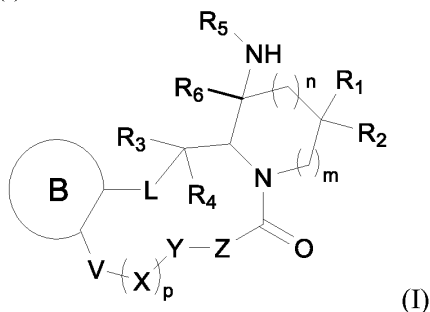
[0478] 2-Chloropyrimidine (42 mg, 0.368 mmol) was added to a stirred solution of the appropriate macrocyclic amine intermediate (synthesized starting from Intermediate 34 using a similar procedure to the one described to synthesize Intermediate 25) (120 mg, 0.335 mmol) and triethylamine (0.093 mL, 0.670 mmol) in anhydrous DMF (1.5 mL) at room temperature and the mixture was heated to 150 °C under microwave irradiation for 1 h. The reaction was then subjected to 2 further rounds of heating to 150 °C for 1 h each time. The reaction was quenched with water (10 mL) and diluted with EtOAc (10 mL). The organic phase was separated and the aqueous phase was extracted with further EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The crude material was subjected to achiral preparative purification using X-Bridge, 100 x 19mm, 5µm column eluting with 5-95% MeCN in H₂O (0.2% ammonia) to afford the title compound (17 mg, 0.0372 mmol, 11% yield) as a colorless solid.

Table 24. Prepared Compound and the Biological Activity Thereof

Comp	Structure	Name	Obs. Mass	¹ H NMR	EC50 hOX2
287		Rel- (1s,16S,17R,20s)-16-[(pyrimidin-2-yl)amino]-8,19-dioxa-12-azatetracyclo[18.2.2.0 ^{2,7} .0 ^{12,17}]tetracosan-2(7),3,5-trien-11-one	[M+H] ⁺ 437.3	¹ H NMR (400 MHz, CDCl ₃) δ 8.32 (d, J = 4.8 Hz, 2H), 7.11 (td, J = 7.7, 1.7 Hz, 1H), 7.08 – 6.97 (m, 1H), 6.87 – 6.72 (m, 2H), 6.65 – 6.55 (m, 1H), 5.12 (d, J = 7.1 Hz, 1H), 4.94 – 4.85 (m, 1H), 4.84 – 4.71 (m, 2H), 4.07 (ddt, J = 12.0, 6.9, 4.8 Hz, 1H), 4.03 – 3.97 (m, 1H), 3.83 (t, J = 9.8 Hz, 1H), 3.69 (dd, J = 9.5, 2.4 Hz, 1H), 3.60 – 3.50 (m, 2H), 2.73 (td, J = 13.5, 3.3 Hz, 1H), 2.65 – 2.31 (m, 4H), 2.00 – 1.20 (m, 10H).	C

CLAIMS

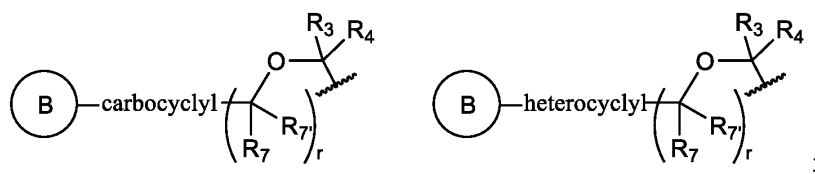
1. A compound of Formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

L is a linker selected from heteroaryl, $-\text{carbocyclyl}-(\text{CR}_7\text{CR}_{7'})_r\text{O}-$, and $-\text{heterocyclyl}-(\text{CR}_7\text{CR}_{7'})_r\text{O}-$, wherein $-\text{carbocyclyl}-(\text{CR}_7\text{CR}_{7'})_r\text{O}-$ and $-\text{heterocyclyl}-(\text{CR}_7\text{CR}_{7'})_r\text{O}-$ have the following orientation:



(B) is phenyl, 5- or 6-membered heteroaryl, cycloalkyl, or heterocyclyl;

V and Z are each independently $-\text{O}-$, $-\text{CR}_8\text{R}_9-$, or $-\text{NR}_{10}-$;

X is $-O-$, $-CR_{11}R_{12}-$, or $-NR_{13}-$;

Y is a bond, $-O-$, $-CR_8R_9-$, or $-NR_{10}-$;

R₁ and R₂ are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl, or R₁ and R₂ together with the atom to which they are attached form a carbocycle or heterocycle;

R₃ and R₄ are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl, or R₃ and R₄ together with the atom to which they are attached form a carbocycle or heterocycle;

R₅ is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, aryl, heteroaryl, alkylene-heteroaryl, or alkylene-SO₂-alkyl;

R₆ is H, alkyl, cycloalkyl, heterocyclyl, alkylene-cycloalkyl, alkylene-heterocyclyl, or -CN;

R₇ and R_{7'} are each independently H, halogen, or alkyl;

R₈ and R₉ are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl, or R₈ and R₉ together with the atom to which they are attached form a carbocycle or heterocycle;

R₁₁ and R₁₂ are each independently H, halogen, alkyl, cycloalkyl, or heterocyclyl; or R₁₁ and R₁₂ together with the atom to which they are attached form a carbocycle or heterocycle;

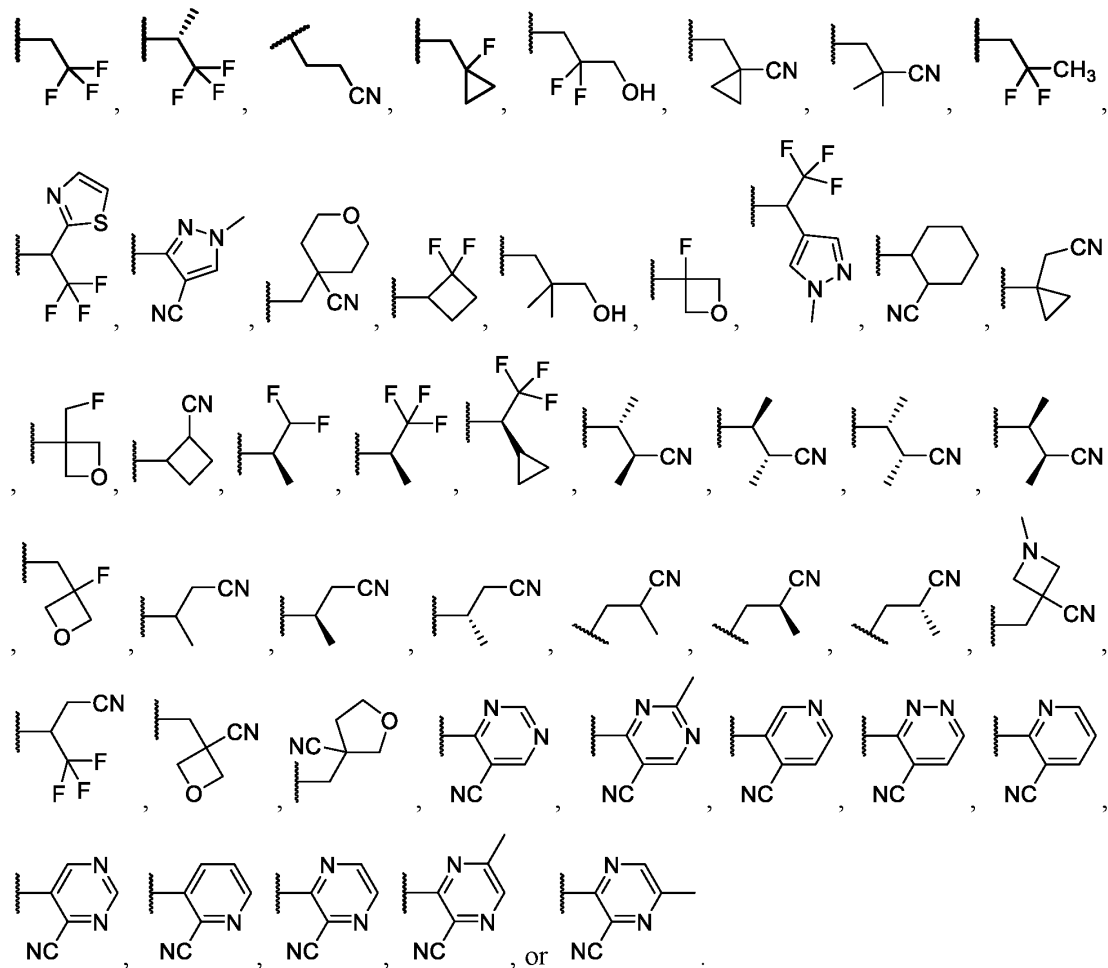
R₁₀ and R₁₃ are each independently H, alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, -(C=O)alkyl, -(C=O)cycloalkyl, -(C=O)heterocyclyl, -(C=O)-O-alkyl, -(C=O)-O-cycloalkyl, -(C=O)-O-heterocyclyl, -(C=O)-O-heteroaryl, -S(O)₂-alkyl, -S(O)₂-cycloalkyl, or -S(O)₂-heterocyclyl;

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

r is 0 or 1.

2. The compound of claim 1, wherein R₅ is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, alkylene-heterocyclyl, heteroaryl, or alkylene-heteroaryl.
3. The compound of claim 1 or 2, wherein R₅ is alkyl, cycloalkyl, alkylene-cycloalkyl, heterocyclyl, or alkylene-heterocyclyl.
4. The compound of claim 1 or 2, wherein R₅ is heteroaryl or alkylene-heteroaryl.
5. The compound of any one of claims 1-3, wherein R₅ is alkyl.
6. The compound of any one of claims 1-5, wherein R₅ is C₁₋₅ alkyl, C₁₋₅ haloalkyl, C₃₋₆ cycloalkyl, C₃₋₆ halocycloalkyl, 4- to 6-membered heterocyclyl, 5- or 6-membered heteroaryl, C₁₋₃ alkylene-C₃₋₆ cycloalkyl, C₁₋₃ alkylene-(4- to 6-membered heterocyclyl), or C₁₋₃ alkylene-(5- or 6-membered heteroaryl).
7. The compound of any one of claims 1-6, wherein R₅ is cyclopropyl or cyclobutyl.

8. The compound of any one of claims 1-6, wherein R₅ is a 5-membered heteroaryl having 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S.
9. The compound of any one of claims 1-8, wherein R₅ is optionally substituted with one or more F, CH₃, CH₂CH₃, CH(CH₃)₂, -CN, CF₃, and/or CHF₂.
10. The compound of claim 1 or 2, wherein R₅ is:



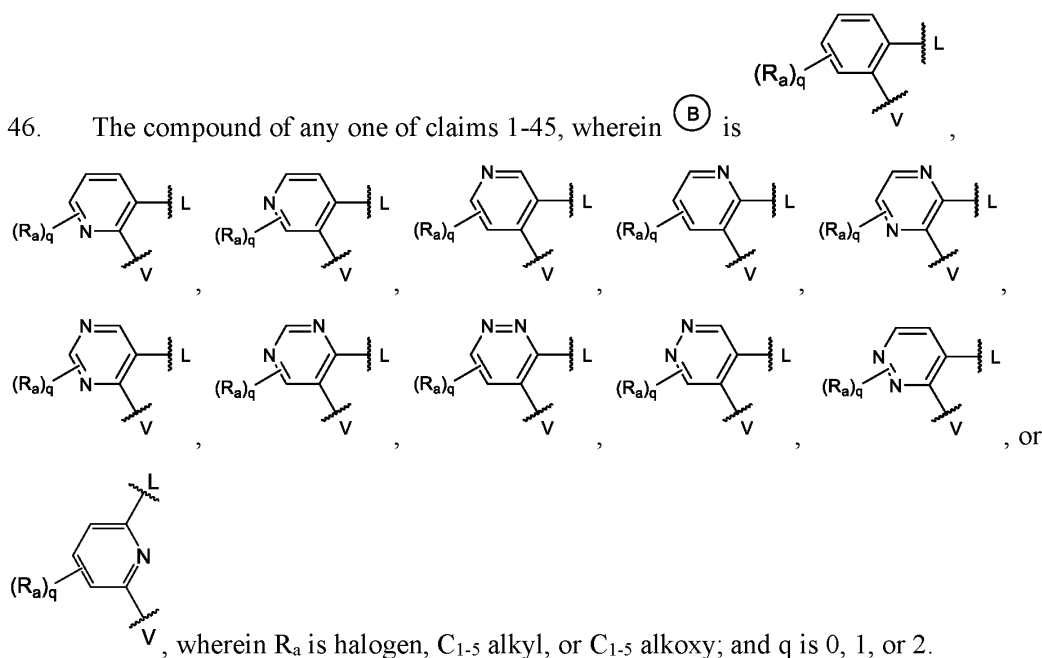
11. The compound of claim 1 or 2, wherein R₅ is , , or .
12. The compound of any one of claims 1-11, wherein R₆ is H or -CN.

13. The compound of any one of claims 1-11, wherein R_6 is H.
14. The compound of any one of claims 1-12, wherein R_1 and R_2 are each independently H, halogen, or alkyl.
15. The compound of any one of claims 1-12, wherein R_1 and R_2 are each independently H or halogen.
16. The compound of any one of claims 1-12, wherein R_1 and R_2 are H.
17. The compound of any one of claims 1-12, wherein R_1 and R_2 together with the carbon atom to which they are attached form a carbocycle or heterocycle.
18. The compound of any one of claims 1-12, wherein R_1 and R_2 together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl.
19. The compound of any one of claims 1-12, wherein R_1 and R_2 together with the carbon atom to which they are attached form a 3- or 6-membered heterocycle.
20. The compound of any one of claims 1-12, wherein R_1 and R_2 together with the carbon atom to which they are attached form a heterocycle, comprising 1 or 2 heteroatoms selected from the group consisting of N, O, and S.
21. The compound of any one of claims 1-20, wherein R_3 and R_4 are each independently H, halogen, or alkyl.
22. The compound of any one of claims 1-21, wherein R_3 and R_4 are each independently H or C_{1-5} alkyl.
23. The compound of any one of claims 1-22, wherein R_3 and R_4 are each independently methyl or ethyl.
24. The compound of any one of claims 1-22, wherein R_3 and R_4 are H.
25. The compound of any one of claims 1-21, wherein R_3 and R_4 are halogen.
26. The compound of any one of claims 1-21, wherein R_3 and R_4 are fluorine.
27. The compound of any one of claims 1-21, wherein R_3 and R_4 together with the carbon atom to which they are attached form a carbocycle or heterocycle.

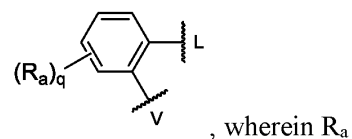
28. The compound of any one of claims 1-21, wherein R_3 and R_4 together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl.
29. The compound of any one of claims 1-21, wherein R_3 and R_4 together with the carbon atom to which they are attached form a 3- or 6-membered heterocycle.
30. The compound of any one of claims 1-21, wherein R_3 and R_4 together with the carbon atom to which they are attached form a heterocycle, comprising 1 or 2 heteroatoms selected from the group consisting of N, O, and S.
31. The compound of any one of claims 1-30, wherein V is $-O-$ or $-CR_8R_9-$.
32. The compound of any one of claims 1-30, wherein V is $-O-$ or $-NR_{10}-$.
33. The compound of any one of claims 1-30, wherein V is $-O-$.
34. The compound of any one of claims 1-33, wherein Y is a bond or $-CR_8R_9-$.
35. The compound of any one of claims 1-34, wherein Y is a bond.
36. The compound of any one of claims 1-35, wherein Z is a $-NR_{10}-$ or $-CR_8R_9-$.
37. The compound of any one of claims 1-35, wherein Z is $-CR_8R_9-$.
38. The compound of any one of claims 1-37, wherein R_8 and R_9 are each independently H or C_{1-5} alkyl.
39. The compound of any one of claims 1-37, wherein R_8 and R_9 together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl.
40. The compound of any one of claims 1-39, wherein R_{10} is H or C_{1-5} alkyl.
41. The compound of any one of claims 1-39, wherein R_{10} is methyl, ethyl, or isopropyl.
42. The compound of any one of claims 1-41, wherein X is $-CR_{11}R_{12}-$.
43. The compound of any one of claims 1-42, wherein R_{11} and R_{12} are each independently H or C_{1-5} alkyl.
44. The compound of any one of claims 1-42, wherein R_{11} and R_{12} are each independently methyl or ethyl.

45. The compound of any one of claims 1-42, wherein R₁₁ and R₁₂ together with the carbon atom to which they are attached form a C₃₋₆ cycloalkyl.

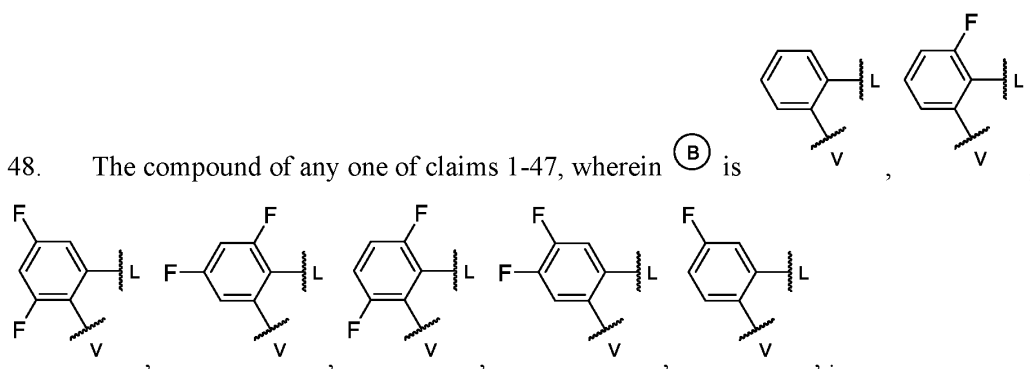
46. The compound of any one of claims 1-45, wherein (B) is

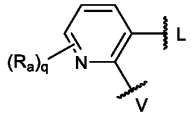
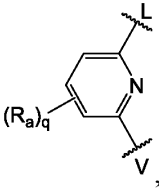
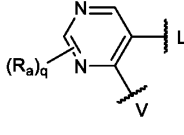


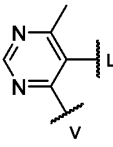
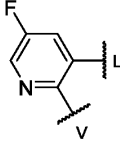
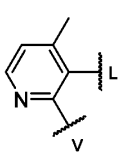
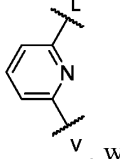
47. The compound of any one of claims 1-46, wherein (B) is:
is halogen, C₁₋₅ alkyl, or C₁₋₅ alkoxy; and q is 0, 1, or 2.

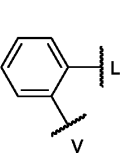
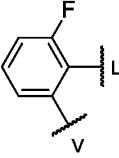
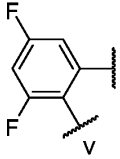
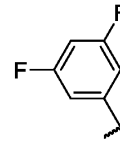
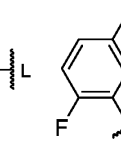
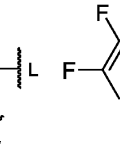
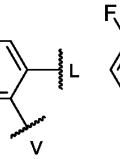
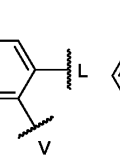
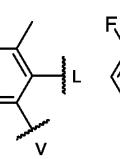
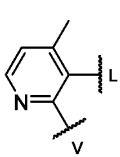
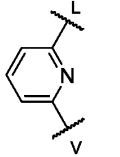


48. The compound of any one of claims 1-47, wherein (B) is

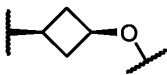
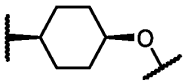
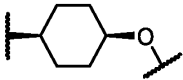
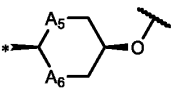


49. The compound of any one of claims 1-46, wherein (B) is: , , or , wherein R_a is halogen, C₁₋₅ alkyl, or C₁₋₅ alkoxy; and q is 0, 1, or 2.

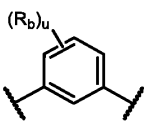
50. The compound of any one of claims 1-46 and 49, wherein (B) is , , , or , wherein R_a is halogen, C₁₋₅ alkyl, or C₁₋₅ alkoxy; and q is 0, 1, or 2.

51. The compound of any one of claims 1-46, wherein (B) is , , , , , , , , , , or .

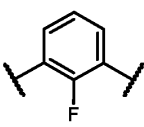
52. The compound of any one of claims 46, 47, and 49, wherein q is 0 or 1.

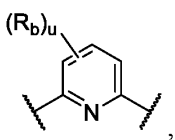
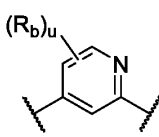
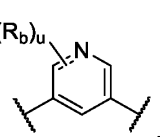
53. The compound of any one of claims 46, 47, 49, and 52, wherein q is 0.
54. The compound of any one of claims 1-53, wherein m is 0 or 1.
55. The compound of any one of claims 1-54, wherein m is 1.
56. The compound of any one of claims 1-55, wherein n is 0 or 1.
57. The compound of any one of claims 1-56, wherein n is 1.
58. The compound of any one of claims 1-57, wherein p is 0 or 1.
59. The compound of any one of claims 1-58, wherein p is 0.
60. The compound of any one of claims 1-58, wherein p is 1.
61. The compound of any one of claims 1-60, wherein L is –carbocyclyl-(CH₂)_r-O– or –heterocyclyl-(CH₂)_r-O–.
62. The compound of any one of claims 1-60, wherein L is –carbocyclyl-(CH₂)_r-O–.
63. The compound of any one of claims 1-62, wherein L is  or .
64. The compound of any one of claims 1-62, wherein L is .
65. The compound of any one of claims 1-64, wherein r is 0.
66. The compound of any one of claims 1-64, wherein r is 1.
67. The compound of any one of claims 1-61, wherein when r is 0, L is a –carbocyclyl-O– or –heterocyclyl-O– linker having the structure , wherein A₅ and A₆ are each independently –O– or –CH₂–, and * represents the point of attachment to .
68. The compound of claim 67, wherein A₅ is –O–.

69. The compound of claim 67, wherein A_5 is $-\text{CH}_2-$.
70. The compound of any one of claims 67-69, wherein A_6 is $-\text{O}-$.
71. The compound of any one of claims 67-69, wherein A_6 is $-\text{CH}_2-$.

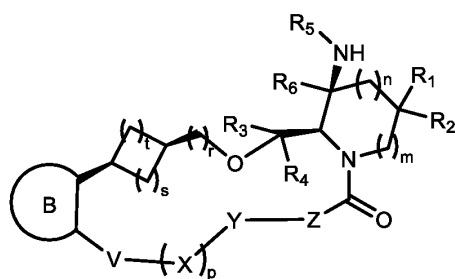
72. The compound of any one of claims 1-61, wherein L is , wherein R_b is halogen, alkyl, or alkoxy; and u is 0, 1, or 2.

73. The compound of claim 72, wherein R_b is halogen.
74. The compound of claim 73, wherein R_b is fluoride.
75. The compound of any one of claims 72-74, wherein u is 1.
76. The compound of any one of claims 72-74, wherein u is 0.

77. The compound of any one of claims 1-75, wherein L is .
78. The compound of any one of claims 1-61, wherein L is a 5- or 6-membered heteroaryl linker having 1-2 nitrogen atoms.

79. The compound of any one of claims 1-61 and 78, wherein L is , , or , wherein R_b is halogen, alkyl, or alkoxy; and u is 0 or 1.

80. The compound of any one of claims 1-71, having the structure:



(IC-1), or a pharmaceutically acceptable salt thereof,

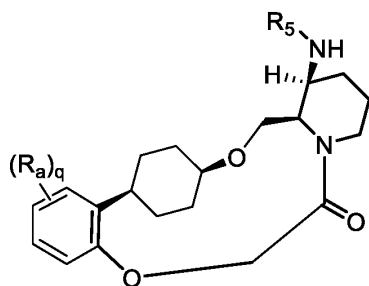
wherein:

r is 0 or 1;

s is 1 or 2; and

t is 1 or 2.

81. The compound of claim 80, wherein r is 0.
82. The compound of claim 80 or 81, wherein s is 2.
83. The compound of any one of claims 80-82, wherein t is 2.
84. The compound of any one of claims 1-11, having the structure:



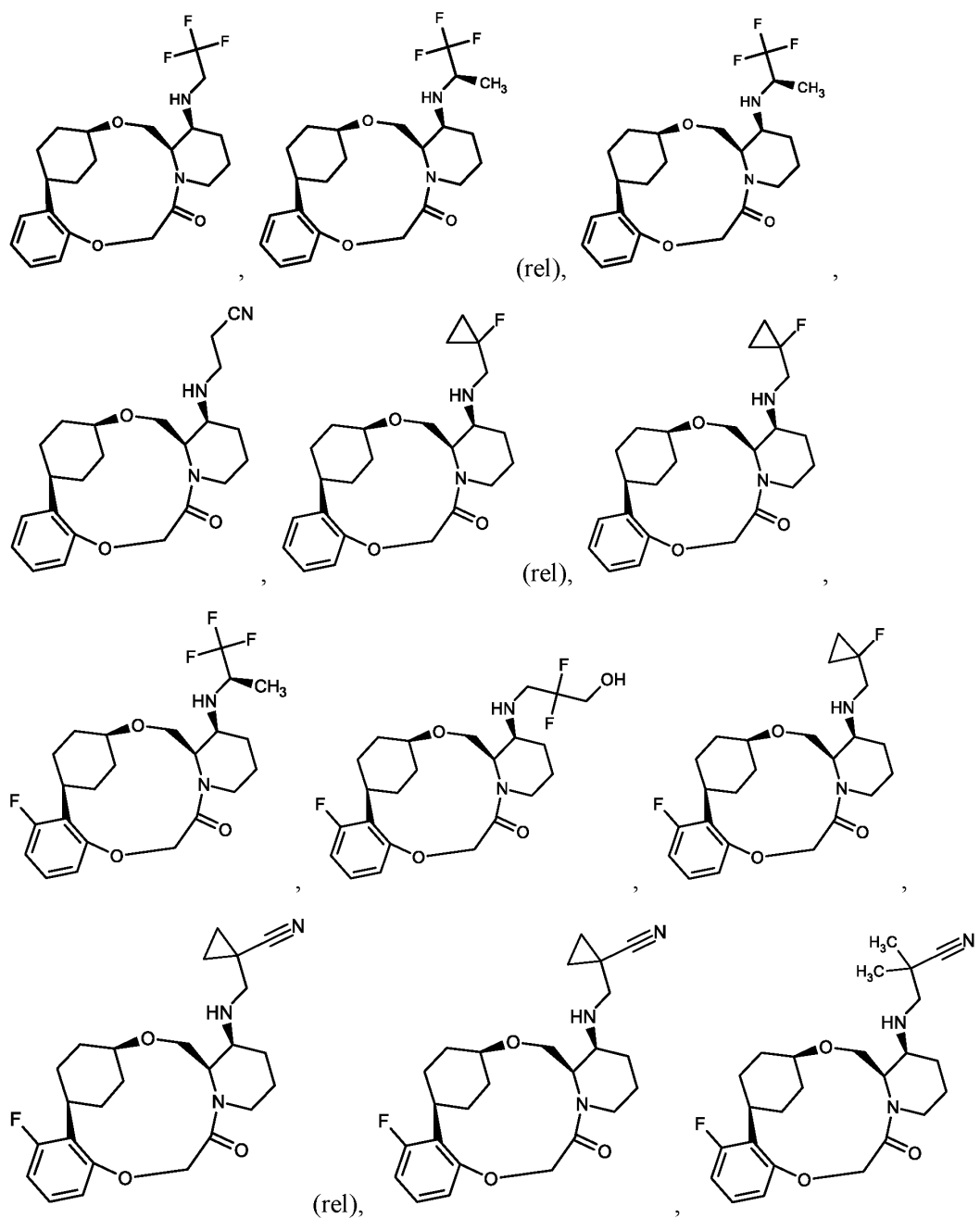
(IC-2e), or a pharmaceutically acceptable salt thereof,

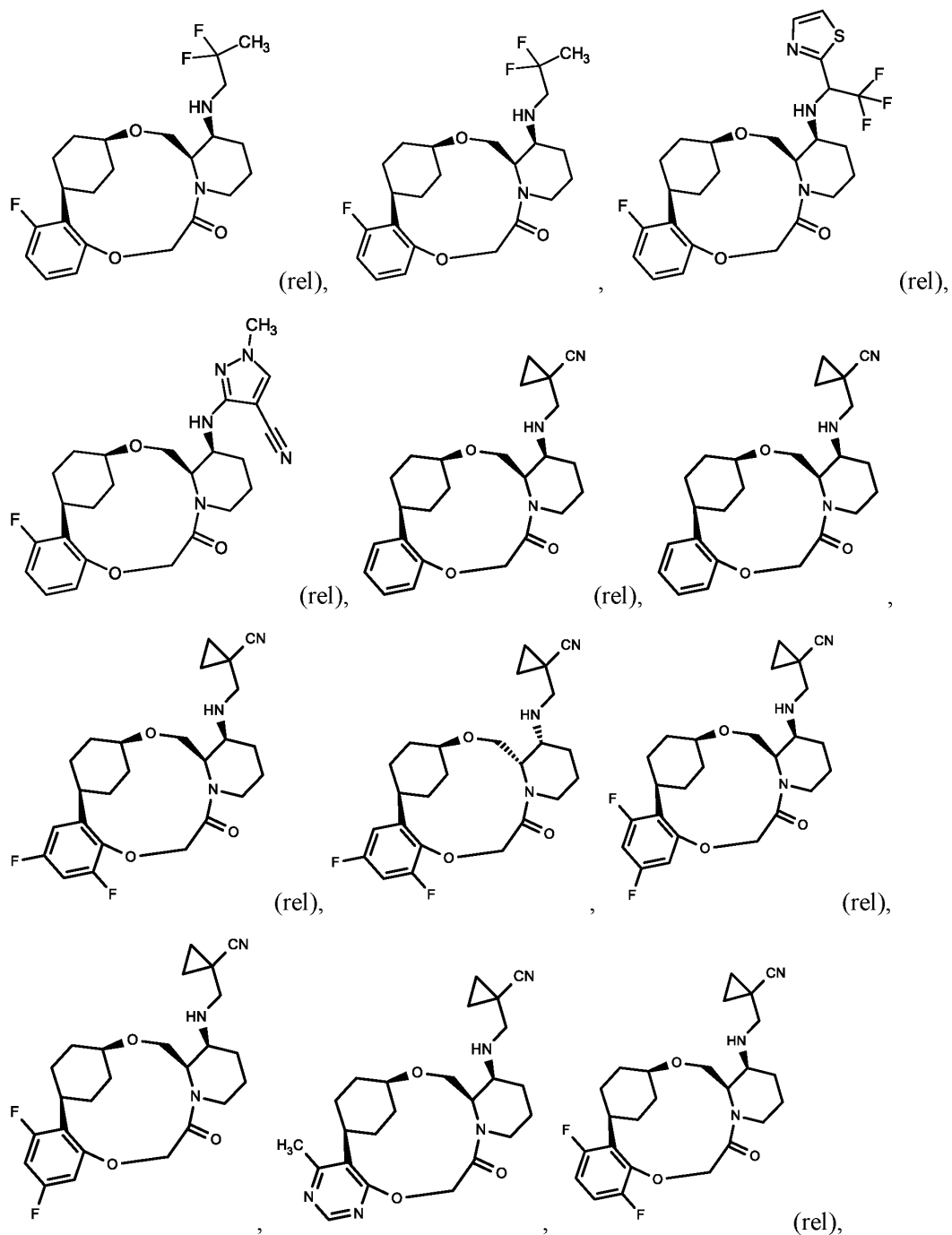
wherein R_a is halogen, C_{1-5} alkyl, or C_{1-5} alkoxy; and q is 0, 1, or 2.

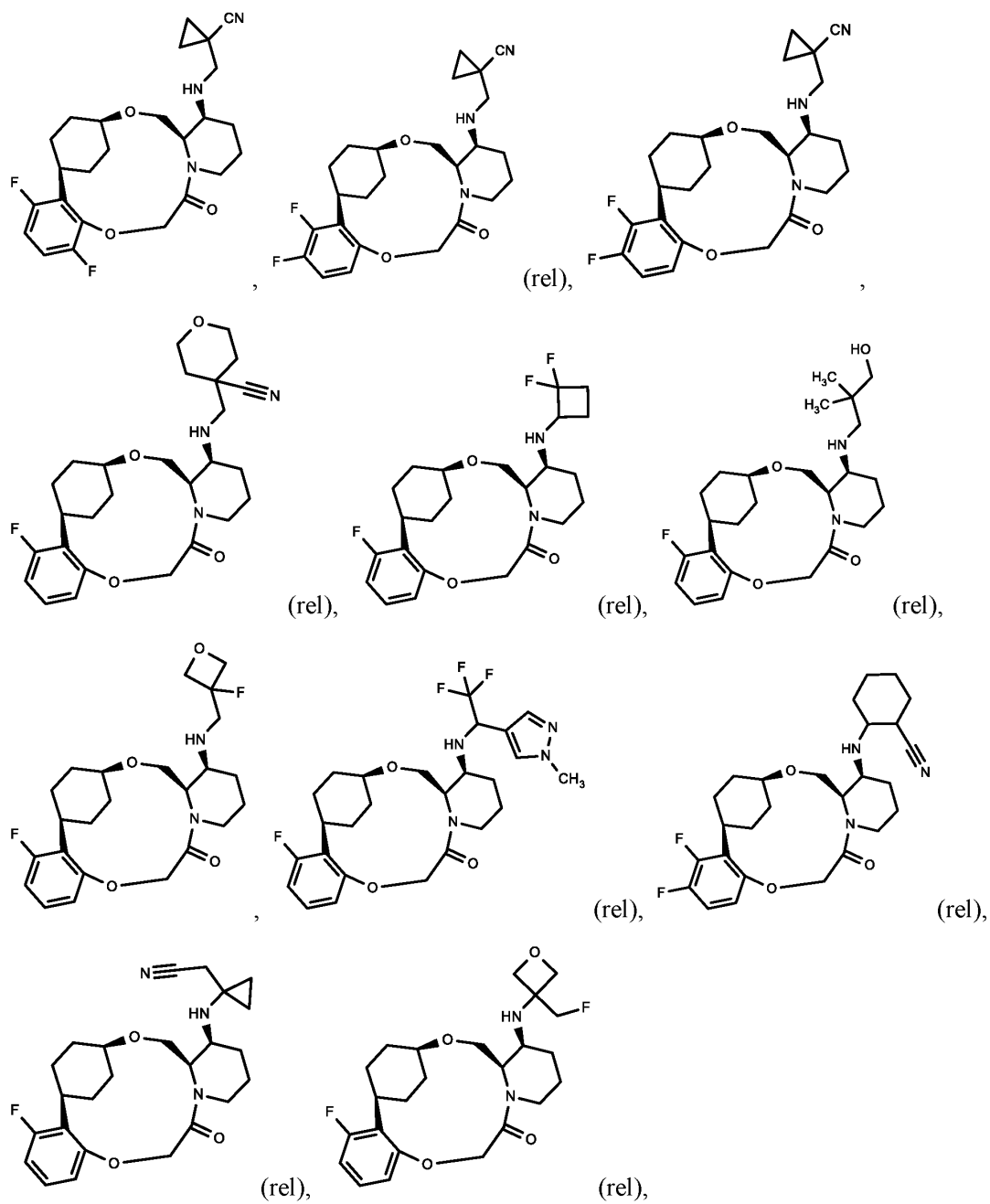
85. The compound of any one of claims 46, 47, 49, and 84, wherein each R_a is independently F or Me.
86. The compound of any one of claims 46, 47, 49, 84, and 85, wherein each R_a is F.

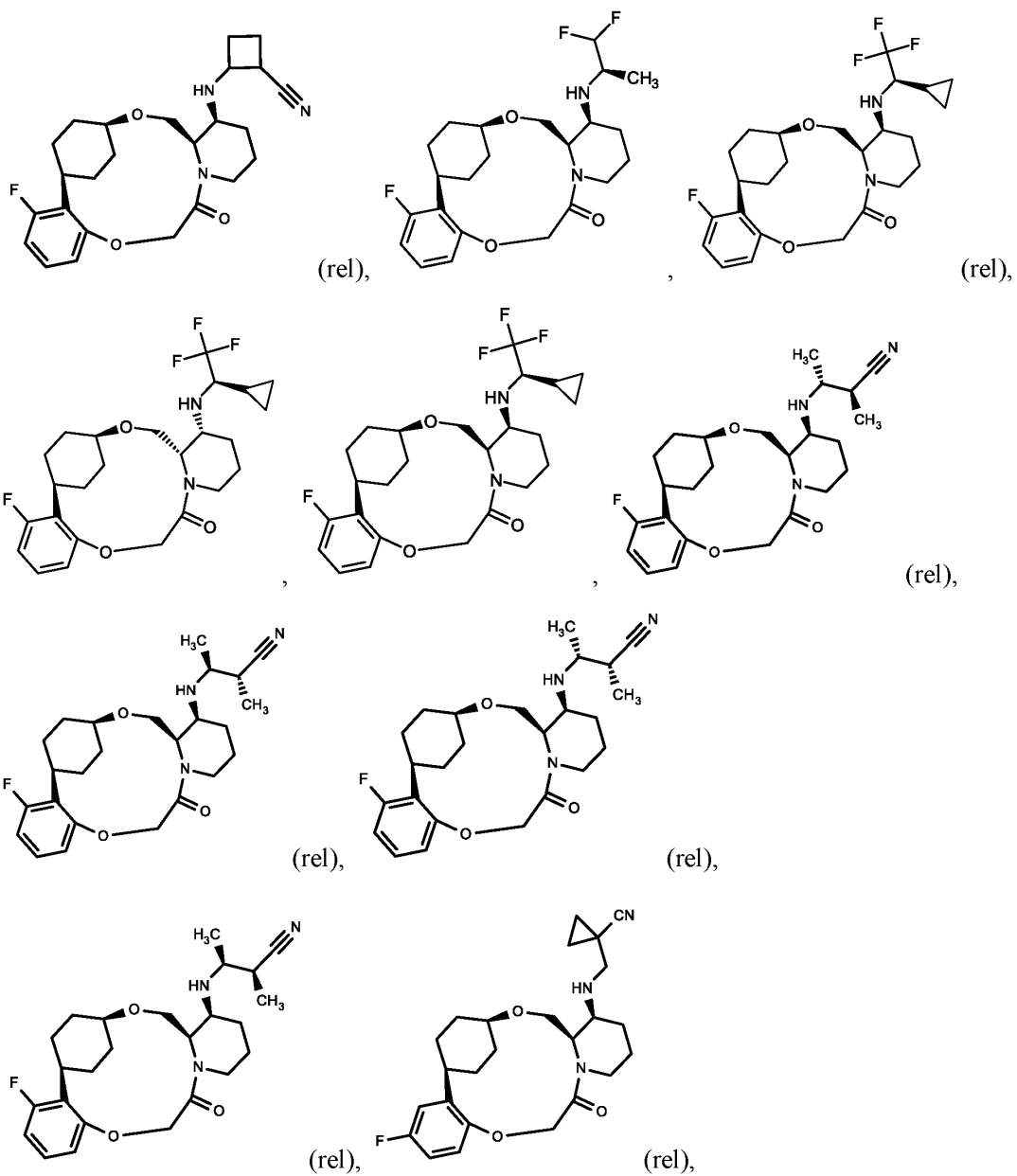
87. The compound of any one of claims 46, 47, 49, and 84-86, wherein q is 1 or 2.

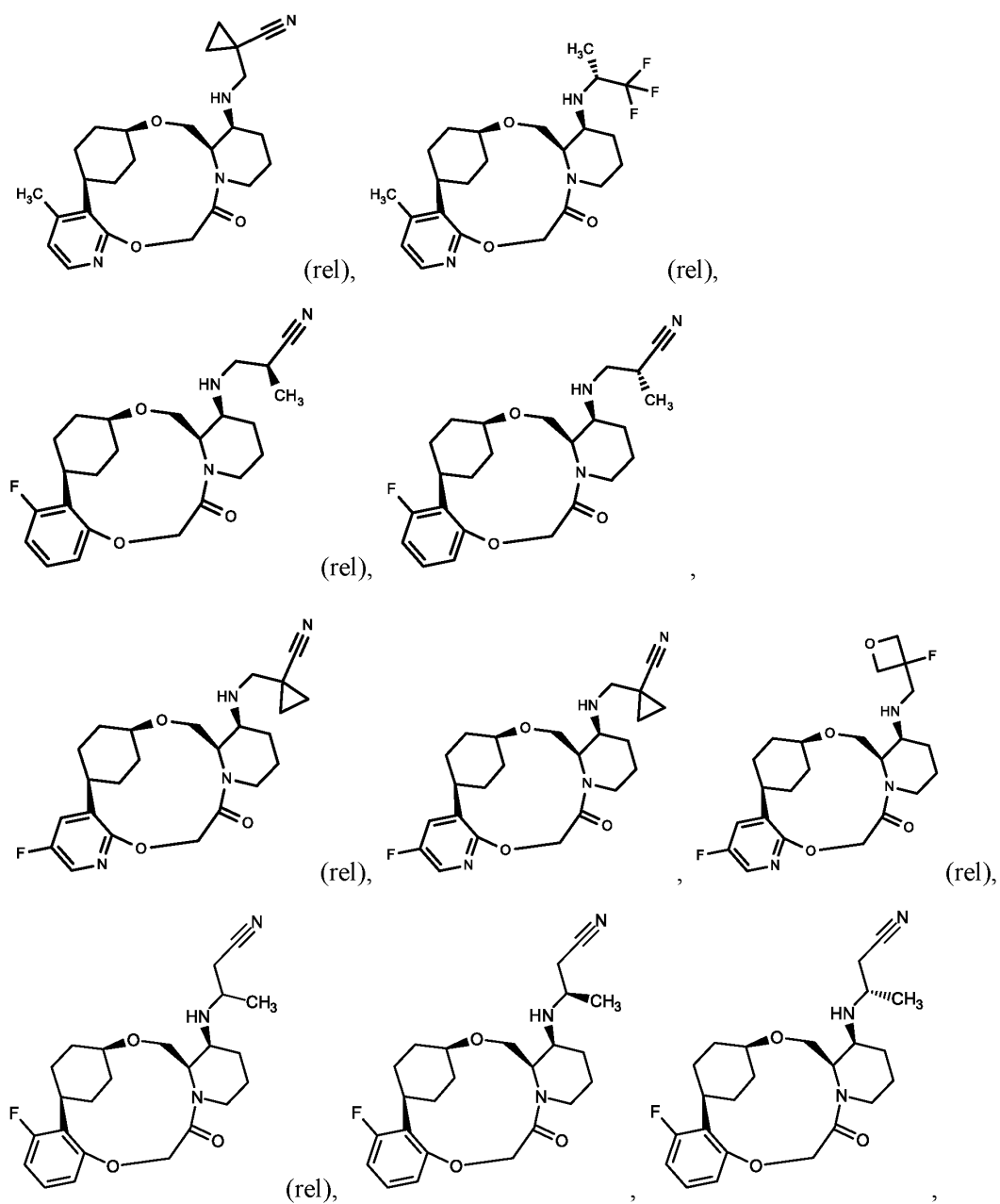
88. The compound of claim 1, wherein the compound is:

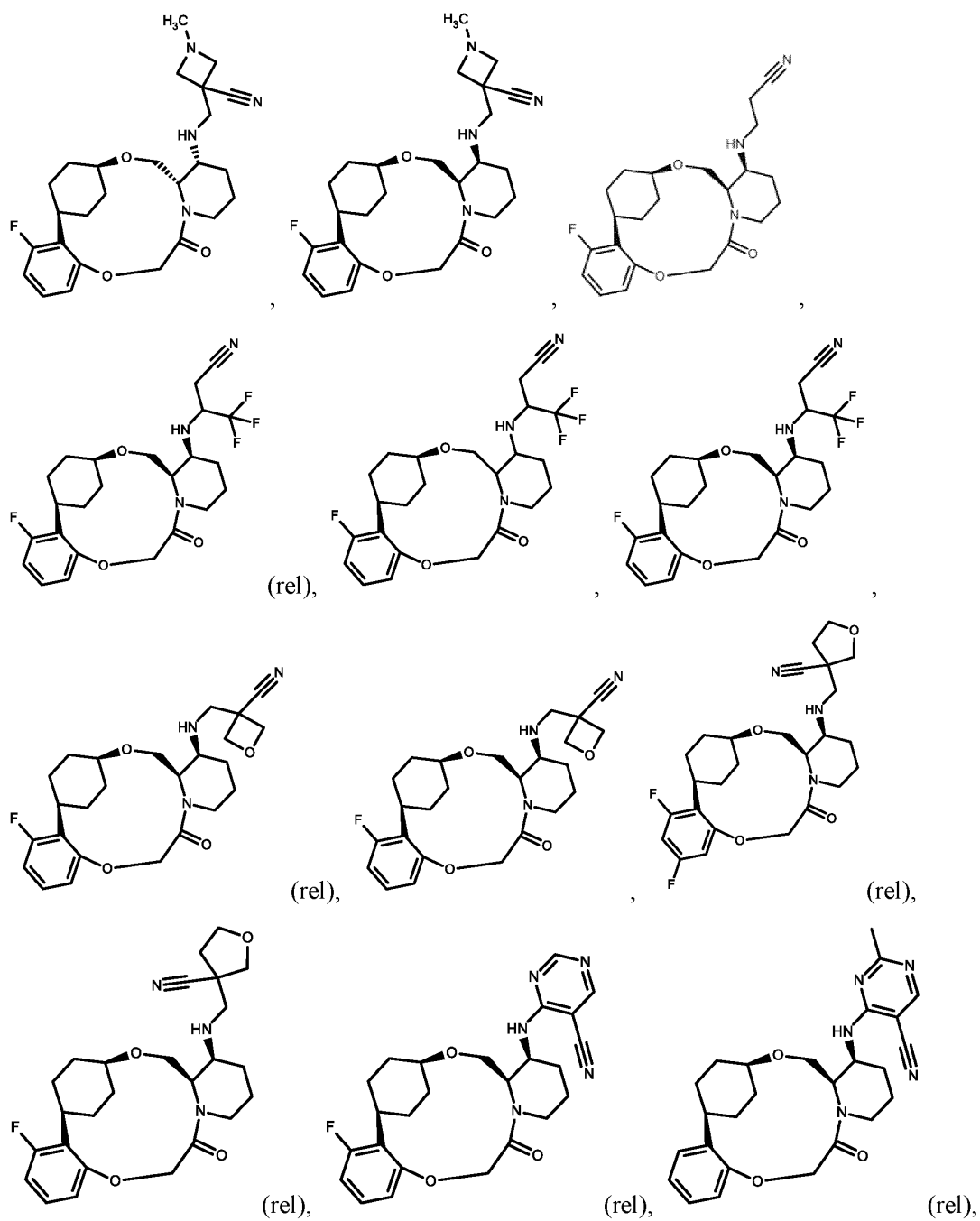


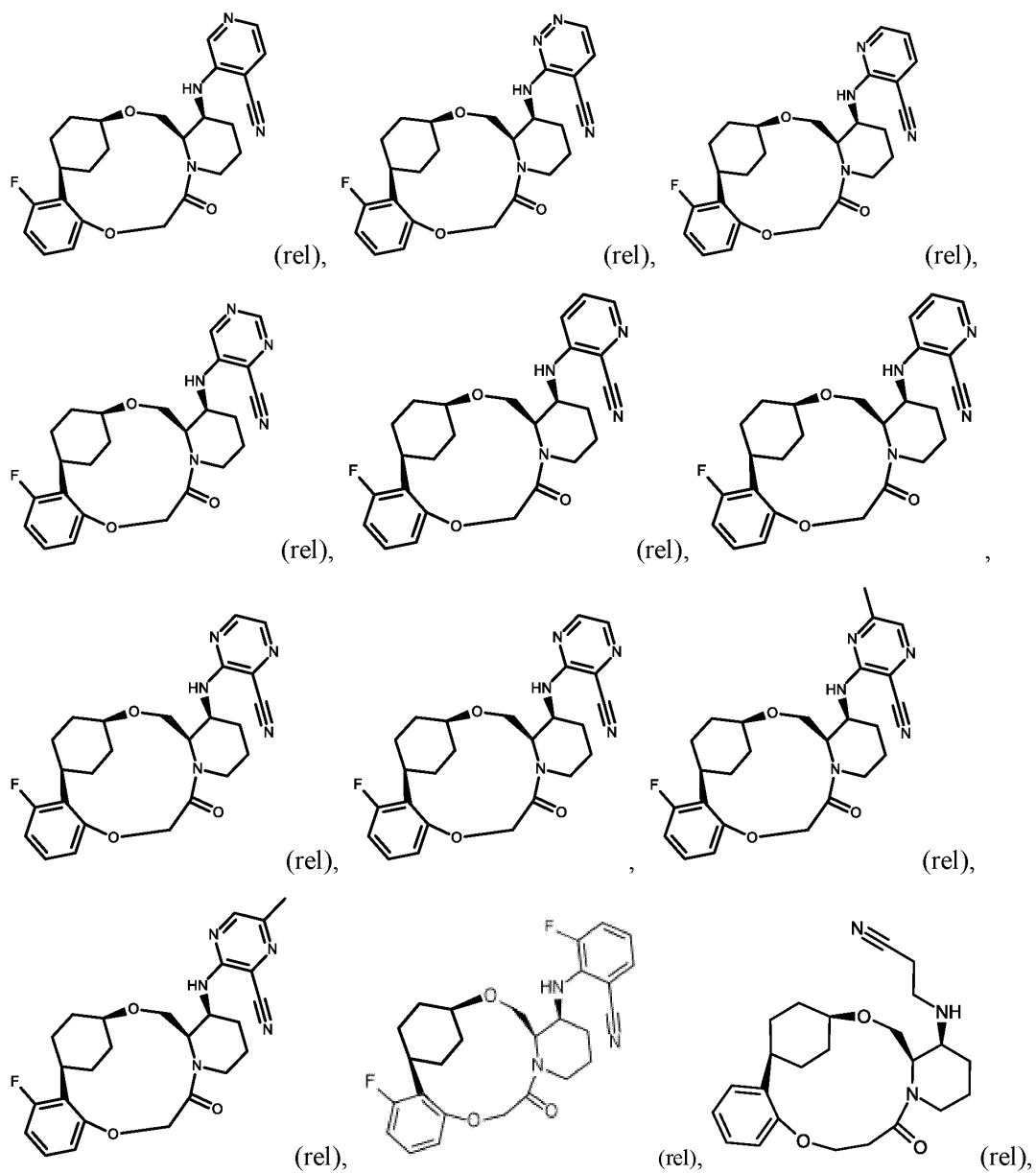


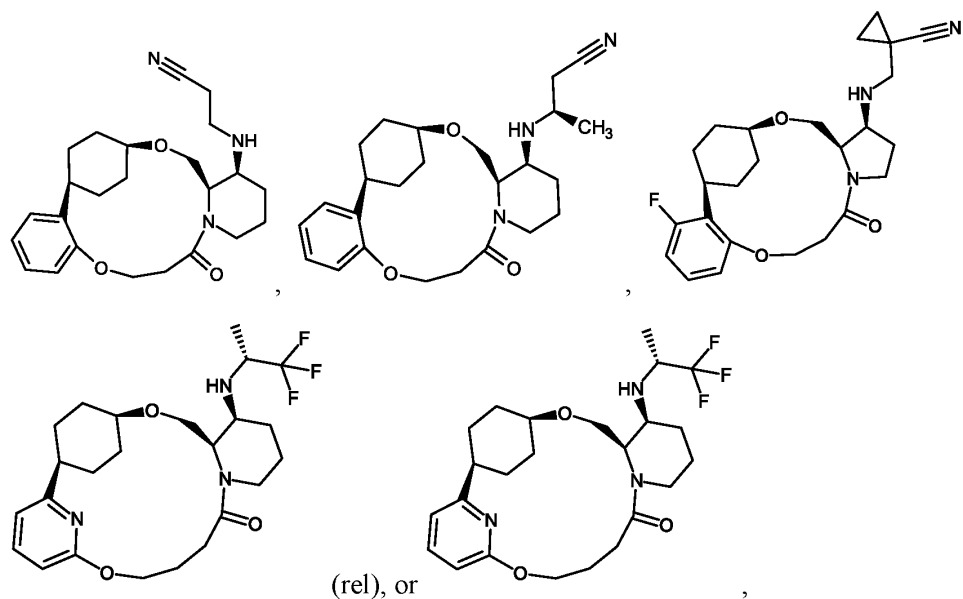












or a pharmaceutically acceptable salt thereof.

89. A pharmaceutical composition comprising a compound of any one of claims 1-88 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

90. A method of treating a disease or disorder that is treatable by administration of an orexin agonist, the method comprising administering to a subject in need thereof a therapeutically effective amount of the compound of any one of claims 1-88 or the pharmaceutical composition of claim 89.

91. A method of treating a disease or disorder by modulating one or more orexin receptors, the method comprising administering to a subject in need thereof a therapeutically effective amount of the compound of any one of claims 1-88 or the pharmaceutical composition of claim 89.

92. A method of treating, preventing, ameliorating, controlling, or reducing the risk of a disease or disorder associated with one or more orexin receptors, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-88 or the pharmaceutical composition of claim 89.