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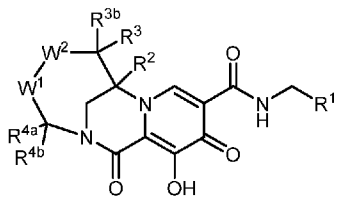
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(54) Title: BRIDGED TRICYCLIC CARBAMOYLPYRIDONE COMPOUNDS AND USES THEREOF



(57) Abstract: Compounds for use in treating or preventing human immunodeficiency virus (HIV) infection are disclosed. The compounds have the following Formula (I): (I) including stereoisomers and pharmaceutically acceptable salts thereof. Methods associated with the preparation and use of the disclosed compounds, as well as pharmaceutical compositions comprising such compounds are also disclosed.

BRIDGED TRICYCLIC CARBAMOYLPYRIDONE COMPOUNDS AND USES THEREOF

CROSS REFERENCE

[0001] This application claims priority to U.S. Provisional Application No. 63/085,704, filed September 30, 2020, which is incorporated herein in its entirety for all purposes.

FIELD

[0002] This disclosure relates generally to certain bridged tricyclic compounds, pharmaceutical compositions comprising said compounds, and methods of making and using said compounds and pharmaceutical compositions.

BACKGROUND

[0003] Human immunodeficiency virus infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains may limit their usefulness (Palella, *et al. N. Engl. J Med.* (1998) 338:853–860; Richman, D. D. *Nature* (2001) 410:995–1001). Accordingly, there is a need for new agents that inhibit the replication of HIV.

[0004] A goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient. Current treatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, *i.e.*, several drugs from at least two or more drug classes (Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in

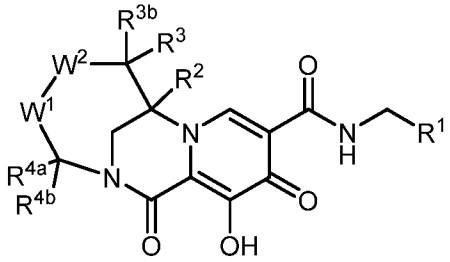
Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at https://files.aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed February 20, 2020). In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions. Because the standard of care requires the use of multiple different drugs to suppress HIV, as well as to treat other conditions the patient may be experiencing, the potential for drug interaction is a criterion for selection of a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for drug interactions.

[0005] In addition, the HIV virus is known to mutate in infected subjects (Tang, *et al. Drugs* (2012) 72 (9) e1-e25). Because of the proclivity of the HIV virus to mutate, there is a need for anti-HIV drugs to be effective against a range of known HIV variants (Hurt, *et al. HIV/AIDS CID* (2014) 58, 423-431).

[0006] For certain patients, for example, those with difficult or limited access to health care, adherence to daily oral treatment or prophylactic regimens can be challenging. Drugs that offer favorable pharmaceutical properties (for example, improved potency, long-acting pharmacokinetics, low solubility, low clearance, and/or other properties) are amenable to less frequent administration and provide for better patient compliance. Such improvements can, in turn, optimize drug exposure and limit the emergence of drug resistance.

SUMMARY

[0007] In some embodiments, the disclosure provides a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is C_{6-10}aryl or 5 to 10 membered heteroaryl, wherein the C_{6-10}aryl or 5 to 10 membered heteroaryl is optionally substituted with one to four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkyl–O–C_{1-4}alkyl;

R^2 is H, C_{1-6}alkyl, or C_{1-4}haloalkyl;

R^3 is halo or –OR^{3a}, wherein R^{3a} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl; or

R^{3a} and any one of R^2, R^{5a}, and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S;

R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl;

R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl;

R^{4b} is H, halo, –C_{1-6}alkyl, or –C_{1-4}haloalkyl;

W^1 is a bond or –$CR^{5a}R^{5b}$–;

R^{5a} and R^{5b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo; or

R^{5a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{5b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo;

W^2 is –$CR^{6a}R^{6b}$– or –CR^{7a}=CR^{7b}–;

R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkylene–O–C_{1-4}alkyl; or

R^{6a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkylene–O–C_{1-4}alkyl;

R^{7a} and R^{7b} are independently H, halo, C_{1-4}haloalkyl, or C_{1-6}alkyl; or

R^{7a} and R^{7b} together with the carbons to which they are attached form a C_{5-10}aryl optionally substituted with one to four R^{A2}, wherein each R^{A2} is independently halo, cyano, or C_{1-4}alkyl.

[0008] In some embodiments, the disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0009] In some embodiments, the disclosure provides a kit comprising a compound of Formal I, or a pharmaceutically acceptable salt thereof, and instructions for use.

[0010] In some embodiments, the disclosure provides a method of treating an HIV infection in a human having or at risk of having the infection, comprising administering to the human a therapeutically effective amount of a compound of Formula I, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0011] In some embodiments, the disclosure provides use of a compound of Formula I, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for treating an HIV infection in a human having or at risk of having the infection.

[0012] In some embodiments, the disclosure provides a compound of Formula I, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in medical therapy.

[0013] In some embodiments, the disclosure provides a compound of Formula I, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in treating an HIV infection.

[0014] In some embodiments, the disclosure provides use of a compound of Formula I, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an HIV infection in a human having or at risk of having the infection.

DETAILED DESCRIPTION

[0015] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments disclosed herein. However, one skilled in the art will understand that the embodiments disclosed herein may be practiced without these details. The description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

I. Definitions

[0016] Unless the context requires otherwise, throughout the present disclosure and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is as "including, but not limited to".

[0017] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment disclosed herein. Thus, the appearances of

the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0018] "Amino" refers to the $-NH_2$ radical.

[0019] "Hydroxy" or "hydroxyl" refers to the -OH radical.

[0020] "Oxo" refers to the =O substituent.

[0021] A prefix such as "C_{u-v}" or (C_u-C_v) indicates that the following group has from u to v carbon atoms. For example, "C_{1-6}alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0022] "Alkyl" refers to a straight or branched chain hydrocarbon radical consisting of carbon and hydrogen atoms, which is saturated, having from one to twelve carbon atoms (C_{1-12}alkyl), in certain embodiments one to eight carbon atoms (C_{1-8}alkyl), one to six carbon atoms (C_{1-6}alkyl), one to four carbon atoms (C_{1-4}alkyl), or one to three carbon atoms (C_{1-3}alkyl), and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, 1-methylpropyl (*sec*-butyl), 2-methylpropyl (iso-butyl), 1,1-dimethylethyl (t-butyl), *n*-pentyl, hexyl, 3-methylhexyl, 2-methylhexyl, and the like.

[0023] "Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene ($-CH_2-$), 1,1 ethyl ($-CH(CH_3)-$), 1,2-ethyl ($-CH_2CH_2-$), 1,1-propyl ($-CH(CH_2CH_3)-$), 1,2-propyl ($-CH_2CH(CH_3)-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

[0024] "Aryl" refers to an aromatic carbocyclic group having a single ring (e.g. monocyclic) or multiple rings (e.g. bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (*i.e.*, C_{6-20} aryl), 6 to 12 carbon ring atoms (*i.e.*, C_{6-12} aryl), or 6 to 10 carbon ring atoms (*i.e.*, C_{6-10} aryl). Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below.

[0025] "Cyano" refers to the carbonitrile group (-CN).

[0026] "Cycloalkyl" refers to a saturated or partially saturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e. the cyclic group having at least one double bond). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0027] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo.

[0028] "Haloalkyl" refers to an alkyl group, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0029] "Heteroaryl" refers to an aromatic group having a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 5 to 20 ring atoms (5 to 20 membered heteroaromatic ring), 5 to 12 ring atoms (5 to 12 membered heteroaromatic ring), 5 to 10 ring atoms (5 to 10 membered heteroaromatic ring) or 5 to 6 ring atoms (5 to 6 membered heteroaromatic ring); and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring

heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include pyrimidinyl, purinyl, pyridyl, pyridazinyl, benzothiazolyl, and pyrazolyl. Heteroaryl does not encompass or overlap with aryl as defined above.

[0030] "Heterocyclic ring" refers to a non-aromatic radical or ring having from three to fifteen atoms wherein from one to six atoms are heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and attached to the rest of the molecule by a single bond. In certain embodiments, "heterocyclyl" has from three to ten atoms, wherein from one to four atoms are heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, or from three to seven atoms, wherein from one to two atoms are heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen, carbon or sulfur atoms in the heterocyclyl may be optionally oxidized; the nitrogen atom may be optionally quaternized. As used herein, heterocyclic ring refers to rings that are saturated or partially saturated. Examples of such heterocyclic ring include, but are not limited to, dioxolanyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrofuranyl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. The term includes groups having a single ring or multiple rings including fused, bridged, and spiro ring systems.

[0031] The embodiments disclosed herein are also meant to encompass all pharmaceutically acceptable compounds of Formula I being isotopically-labeled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. In certain embodiments,

these radiolabeled compounds are useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of Formula I, Ia, Ib, Ic, Id, or II, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.*, ^{3}H, and carbon-14, *i.e.*, ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0032] In certain embodiments, substitution with heavier isotopes such as deuterium, *i.e.*, ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability. For example, *in vivo* half-life may increase or dosage requirements may be reduced. Thus, heavier isotopes may be preferred in some circumstances.

[0033] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O, and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Formula I, Ia, Ib, Ic, Id or II can be prepared by techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0034] The methods, compositions, kits and articles of manufacture provided herein use or include compounds (*e.g.*, a compound of Formula I, Ia, Ib, Ic, Id, or II) or pharmaceutically acceptable salts thereof, in which from 1 to n hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds increase resistance to metabolism, and thus are useful for increasing the half-life of compounds or pharmaceutically acceptable salts thereof, when administered to a mammal. See, *e.g.*, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", *Trends*

Pharmacol. Sci., 5(12):524-527 (1984). Such compounds can be synthesized by means known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

[0035] The embodiments disclosed herein are also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the embodiments disclosed herein include compounds produced by a process comprising administering a compound according to the embodiments disclosed herein to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabeled compound according to the embodiments disclosed herein in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

[0036] "Mammal" includes humans and both domestic animals such as laboratory animals and household pets (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

[0037] "Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means that the alkyl radical may or may not be substituted and that the description includes both substituted alkyl radicals and alkyl radicals having no substitution.

[0038] "Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer,

surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, emulsifier, or other pharmacologically inactive substance that is formulated in combination with a pharmacologically active ingredient of a pharmaceutical composition and is compatible with the other ingredients of the formulation and suitable for use in humans or domestic animals without undue toxicity, irritation, allergic response, and the like.

[0039] Examples of "pharmaceutically acceptable salts" of the compounds disclosed herein include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and NX_4^+ (wherein X is C_{1-4}alkyl). Pharmaceutically acceptable salts of a nitrogen atom or an amino group include, for example, salts of organic carboxylic acids such as acetic, trifluoroacetic, adipic, ascorbic, aspartic, butyric, camphoric, cinnamic, citric, digluconic, glutamic, glycolic, glycerophosphoric, formic, hexanoic, benzoic, lactic, fumaric, tartaric, maleic, hydroxymaleic, malonic, malic, mandelic, isethionic, lactobionic, nicotinic, oxalic, pamoic, pectinic, phenylacetic, 3-phenylpropionic, pivalic, propionic, pyruvic, salicylic, stearic, sulfanilic, tartaric, undecanoic, and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, camphorsulfonic, mesitylenesulfonic, benzenesulfonic, p-toluenesulfonic acids, naphthalenesulfonic, and 2-naphthalenesulfonic; and inorganic acids, such as hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, and sulfamic acids. Pharmaceutically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_{1-4}alkyl group).

[0040] For therapeutic use, salts of active ingredients of the compounds disclosed herein will typically be pharmaceutically acceptable, *i.e.*, they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a compound of Formula I or another compound of the embodiments disclosed herein. All salts, whether or not

derived from a physiologically acceptable acid or base, are within the scope of the embodiments disclosed herein.

[0041] Metal salts typically are prepared by reacting the metal hydroxide with a compound according to the embodiments disclosed herein. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

[0042] In addition, salts may be formed from acid addition of certain organic and inorganic acids, *e.g.*, HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines. Finally, it is to be understood that the compositions herein comprise compounds disclosed herein in their un-ionized, as well as zwitterionic form.

[0043] A "pharmaceutical composition" refers to a formulation of a compound of the embodiments disclosed herein and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable excipients.

[0044] "Effective amount" or "therapeutically effective amount" refers to an amount of a compound according to the embodiments disclosed herein, which when administered to a patient in need thereof, is sufficient to effect treatment of disease-states, conditions, or disorders disclosed herein. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the embodiments disclosed herein which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination, or

coincidentally, with the compounds of the embodiments disclosed herein, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

[0045] The terms "treating" and "treatment" as used herein are intended to mean the administration of a compound or composition according to the present embodiments disclosed herein to alleviate or eliminate one or more symptoms of HIV infection and/or to reduce viral load in a patient. In certain embodiments, the terms "treating" and "treatment" also encompass the administration of a compound or composition according to the present embodiments disclosed herein post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood, and the administration of a compound or composition according to the present embodiments disclosed herein to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life. The terms "treating" and "treatment" also encompass the administration of a compound or composition according to the present embodiments disclosed herein before the exposure of the individual to the virus (also called pre-exposure prophylaxis or PrEP), to prevent HIV infection from taking hold if the individual is exposed to the virus and/or to keep the virus from establishing a permanent infection and/or to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood. The terms "treating" and "treatment" also encompass the administration of a compound or composition according to the present embodiments disclosed herein both before and after the exposure of the individual to the virus.

[0046] As used herein, the terms "preventing" and "prevention" refer to the administration of a compound, composition, or pharmaceutically salt according to the present disclosure pre- or post-exposure of the human to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood. The terms also refer to prevention of the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood. The terms include both pre-exposure prophylaxis (PrEP), as well as post-exposure prophylaxis (PEP) and event driven or "on demand" prophylaxis. The terms also refer to prevention of perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life. The terms also refer to prevention of transmission of HIV through blood transfusion.

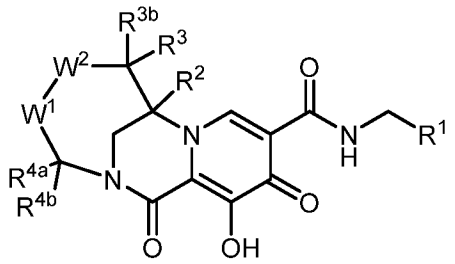
[0047] The compounds of the embodiments disclosed herein, or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic, scalemic, and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using methods such as 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). 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.

[0048] 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 non-superimposable mirror images of one another. In any of the embodiments disclosed herein, compounds disclosed herein may be in the form of a stereoisomer thereof.

[0049] "Partially saturated" refers to a cyclic group which contains at least one double bond but is not aromatic.

II. Compounds

[0050] In some embodiments, the present disclosure provides a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is C_{6-10}aryl or 5 to 10 membered heteroaryl, wherein the C_{6-10}aryl or 5 to 10 membered heteroaryl is optionally substituted with one to four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkyl–O–C_{1-4}alkyl;

R^2 is H, C_{1-6}alkyl, or C_{1-4}haloalkyl;

R^3 is halo or –OR^{3a}, wherein R^{3a} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl; or

R^{3a} and any one of R^2, R^{5a}, and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S;

R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl;

R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl;

R^{4b} is H, halo, –C_{1-6}alkyl, or –C_{1-4}haloalkyl;

W^1 is a bond or –$CR^{5a}R^{5b}$–;

R^{5a} and R^{5b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo; or

R^{5a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{5b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo;

W^2 is –$CR^{6a}R^{6b}$– or –CR^{7a}=CR^{7b}–;

R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkylene–O–C_{1-4}alkyl; or

R^{6a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkylene–O–C_{1-4}alkyl; and

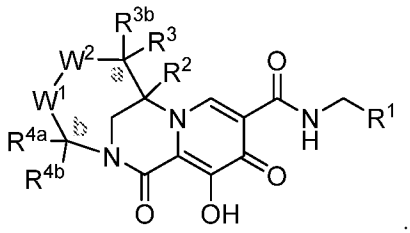
R^{7a} and R^{7b} are independently H, halo, C_{1-4}haloalkyl, or C_{1-6}alkyl; or

R^{7a} and R^{7b} together with the carbons to which they are attached form a C_{5-10}aryl optionally substituted with one to four R^{A2}, wherein each R^{A2} is independently halo, cyano, or C_{1-4}alkyl.

[0051] It is a desirable to discover compounds, or pharmaceutically acceptable salts thereof, that have good stability, *i.e.* physical, chemical stability, and/or metabolic stability. An increase in overall stability of a compound can provide an increase in circulation time in the body. With less degradation, a stable compound can be administered in lower doses and still maintain efficacy. Also, with less degradation there are less concerns about by-products from degradation of the compound. Higher stability of the drug means that more drug is available for target cells without being metabolized.

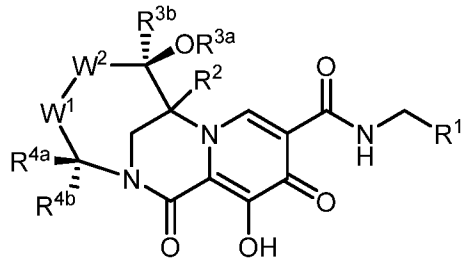
[0052] It is further desirable to discover compounds, or pharmaceutically acceptable salts thereof, that have improved pharmacokinetic and/or pharmacodynamic profiles and long half-life. It is advantageous for a drug to have a moderate or low clearance and a long half-life, as this can lead to a good bioavailability and high systemic exposure. Reducing the clearance and/or increasing half-life time of a compound could reduce the daily dose required for efficacy and therefore give a better efficacy and safety profile. Thus, improved pharmacokinetic and/or pharmacodynamic profiles and long half-life can provide for better patient compliance.

[0053] As shown below, the compounds of Formula I provided herein are characterized by (i) at least one oxygen linked or halogen substitution at the "a" position (R^3 is halo or $-OR^{3a}$) **and** (ii) at least one alkyl or haloalkyl substituent the "b" position (R^{4a} is $-C_{1-6}$alkyl or $-C_{1-4}$haloalkyl):



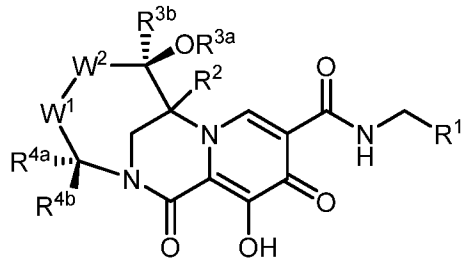
[0054] Advantageously, certain compounds of Formula I provided herein exhibit improved properties, for example improved stability as compared to structurally related compounds lacking (i) the at least one oxygen linked or halogen substitution at the "a" position **and** (ii) the at least one alkyl or haloalkyl substituent the "b" position. In some embodiments, the compounds of Formula I provided herein exhibit improved metabolic stability as compared to structurally related compounds lacking (i) the at least one oxygen linked or halogen substitution at the "a" position **and** (ii) the at least one alkyl or haloalkyl substituent the "b" position. In some embodiments, the improved metabolic stability of the compounds of Formula I provided herein results in their reduced intrinsic clearance, for example from their reduced intrinsic clearance in human liver microsomal assay (HLM).

[0055] In some embodiments, the compound of Formula I provided herein is a compound of Formula Ia:



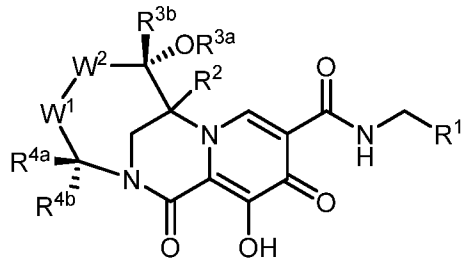
Formula Ia.

[0056] In some embodiments, the compound of Formula I provided herein is a compound of Formula Ib:



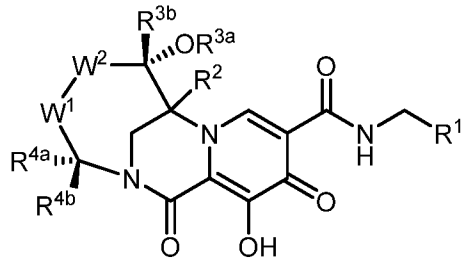
Formula Ib.

[0057] In some embodiments, the compound of Formula I provided herein is a compound of Formula Ic:



Formula Ic.

[0058] In some embodiments, the compound of Formula I provided herein is a compound of Formula Id:



Formula Id.

[0059] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, or Id, or the pharmaceutically acceptable salt thereof, R^1 is C_{6-10}aryl or 5 to 10 membered heteroaryl, wherein the C_{6-10}aryl or 5 to 10 membered heteroaryl is optionally substituted with one to four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkyl–O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine, wherein the phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkyl–O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine, optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-4}alkyl, C_{1-4}haloalkyl, or –O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine, optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-4}alkyl, or –O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine, optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo or C_{1-4}alkyl. In some embodiments, R^1 is phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine, optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo or –O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently a halogen. In some embodiments, R^1 is phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine substituted with two or three R^{A1}, wherein each R^{A1} is independently a halogen. In some embodiments, R^1 is phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine

substituted with two or three R^{A1}, wherein each R^{A1} is independently selected from chloro and fluoro.

[0060] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, or Id, or the pharmaceutically acceptable salt thereof, R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or –C_{1-4}alkyl–O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-4}alkyl, C_{1-4}haloalkyl, or –O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-4}alkyl, or –O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo or C_{1-4}alkyl. In some embodiments, R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo or –O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently a halogen. In some embodiments, R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with two or three R^{A1}, wherein each R^{A1} is independently a halogen. In some embodiments, R^1 is phenyl or pyridyl, wherein the phenyl of pyridyl is substituted with two or three R^{A1}, wherein each R^{A1} is independently selected from chloro and fluoro.

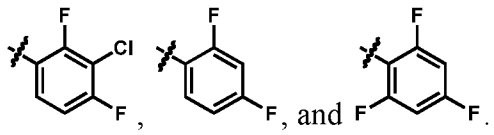
[0061] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, or Id, or the pharmaceutically acceptable salt thereof, R^1 is pyridyl, wherein the pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or –C_{1-4}alkyl–O–C_{1-4}alkyl. In some embodiments, R^1 is pyridyl, wherein the pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein

each R^{A1} is independently halo, C_{1-4}alkyl, C_{1-4}haloalkyl, or –O–C_{1-4}alkyl. In some embodiments, R^1 is pyridyl, wherein the pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-4}alkyl, or –O–C_{1-4}alkyl. In some embodiments, R^1 is pyridyl, wherein the pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo or C_{1-4}alkyl. In some embodiments, R^1 is pyridyl, wherein the pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo or –O–C_{1-4}alkyl. In some embodiments, R^1 is pyridyl, wherein the pyridyl is substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently a halogen. In some embodiments, R^1 is pyridyl, wherein the pyridyl is substituted with two or three R^{A1}, wherein each R^{A1} is independently a halogen. In some embodiments, R^1 is pyridyl, wherein the pyridyl is substituted with two or three R^{A1}, wherein each R^{A1} is independently selected from chloro and fluoro.

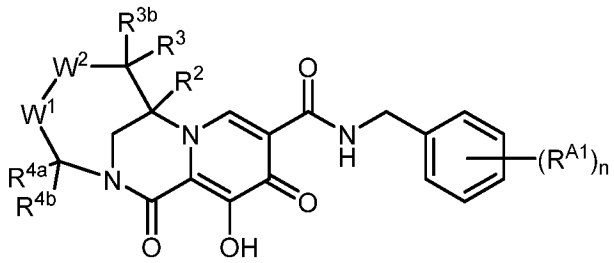
[0062] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, or Id, or the pharmaceutically acceptable salt thereof, R^1 is phenyl, wherein the phenyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or –C_{1-4}alkyl–O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl, wherein the phenyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-4}alkyl, C_{1-4}haloalkyl, or –O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl, wherein the phenyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-4}alkyl, or –O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl, wherein the phenyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo or C_{1-4}alkyl. In some embodiments, R^1 is phenyl, wherein the phenyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo or –O–C_{1-4}alkyl. In some embodiments, R^1 is phenyl, wherein the phenyl is substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently a halogen. In some embodiments, R^1 is phenyl, wherein the phenyl is substituted with two or three R^{A1},

wherein each R^{A1} is independently a halogen. In some embodiments, R^1 is phenyl, wherein the phenyl is substituted with two or three R^{A1}, wherein each R^{A1} is independently selected from chloro and fluoro.

[0063] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, or Id, or the pharmaceutically acceptable salt thereof, R^1 is selected from the group consisting of:



[0064] In some embodiments, the compound of Formula I, Ia, Ib, Ic, or Id is a compound of Formula II:



Formula II;

wherein n is 0, 1, 2, 3, or 4; and each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkyl–O–C_{1-4}alkyl.

[0065] In some embodiments of the compound of Formula II, n is 2, 3, or 4 and each R^{A1} is independently halo, C_{1-4}alkyl, C_{1-4}haloalkyl, cyano, or –O–C_{1-4}alkyl. In some embodiments, n is 2, 3, or 4 and each R^{A1} is independently halo, C_{1-4}alkyl, C_{1-4}haloalkyl, or –O–C_{1-4}alkyl. In some embodiments, n is 2, 3, or 4, and each R^{A1} is independently halo, C_{1-4}alkyl, or –O–C_{1-4}alkyl. In some embodiments, n is 2, 3, or 4, and each R^{A1} is independently halo or C_{1-4}alkyl. In some embodiments, n is 2, 3, or 4, and each R^{A1} is independently halo or –O–C_{1-4}alkyl. In some

embodiments, n is 2, 3, or 4, and each R^{A1} is independently a halogen. In some embodiments, n is 2, 3, or 4, and each R^{A1} is independently selected from chloro and fluoro.

[0066] In some embodiments of the compound of Formula II, n is 2 or 3 and each R^{A1} is independently halo, C_{1-4}alkyl, C_{1-4}haloalkyl, cyano, or –O–C_{1-4}alkyl. In some embodiments, n is 2 or 3 and each R^{A1} is independently halo, C_{1-4}alkyl, C_{1-4}haloalkyl, or –O–C_{1-4}alkyl. In some embodiments, n is 2 or 3, and each R^{A1} is independently halo, C_{1-4}alkyl, or –O–C_{1-4}alkyl. In some embodiments, n is 2 or 3, and each R^{A1} is independently halo or C_{1-4}alkyl. In some embodiments, n is 2 or 3, and each R^{A1} is independently halo or –O–C_{1-4}alkyl. In some embodiments, n is 2 or 3, and each R^{A1} is independently a halogen. In some embodiments, n is 2 or 3, and each R^{A1} is independently selected from chloro and fluoro.

[0067] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^2 is H, C_{1-6} alkyl, or C_{1-4}haloalkyl. In some embodiments, R^2 is H or C_{1-6}alkyl. In some embodiments, R^2 is H or C_{1-4}haloalkyl. In some embodiments, R^2 is C_{1-6}alkyl or C_{1-4}haloalkyl. In some embodiments, R2 is a C1-3alkyl. In some embodiments, R^2 is methyl. In some embodiments R^2 is H.

[0068] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^3 is halo. In some embodiments, R^3 is chloro.

[0069] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^3 is OR^{3a}, wherein R^{3a} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl and R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl; and R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl; and R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl; and R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-}

$_{4}$alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} is methyl or ethyl; and R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} is methyl; and R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl.

[0070] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^3 is OR^{3a}, wherein R^{3a} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl and R^{3b} is H, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl and R^{3b} is H, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl and R^{3b} is H, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl and R^{3b} is H, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{3a} is methyl or ethyl and R^{3b} is H, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{3a} is methyl and R^{3b} is H, –C_{1-6}alkyl, or –C_{1-4}haloalkyl.

[0071] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^3 is OR^{3a}, wherein R^{3a} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl and R^{3b} is H or –C_{1-6}alkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl and R^{3b} is H or –C_{1-6}alkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl and R^{3b} is H or –C_{1-6}alkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl; and R^{3b} is H or –C_{1-6}alkyl. In some embodiments, R^{3a} is methyl or ethyl and R^{3b} is H or –C_{1-6}alkyl. In some embodiments, R^{3a} is methyl and R^{3b} is H or –C_{1-6}alkyl.

[0072] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^3 is OR^{3a}, wherein R^{3a} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl and R^{3b} is H or –C_{1-3}alkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl and R^{3b} is H or –C_{1-3}alkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl and R^{3b} is H or –C_{1-3}alkyl. In some embodiments, R^{3a} is –C_{1-6}alkyl and R^{3b} is H or –C_{1-3}alkyl. In some embodiments, R^{3a} is methyl or ethyl and R^{3b} is H or –C_{1-6}alkyl. In some embodiments, R^{3a} is methyl and R^{3b} is H or –C_{1-3}alkyl.

[0073] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^3 is OR^{3a}, wherein R^{3a} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{3-6}$cycloalkyl and R^{3b} is H or methyl. In some embodiments, R^{3a} is $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{3-6}$cycloalkyl and R^{3b} is H or methyl. In some embodiments, R^{3a} is $–C_{1-6}$alkyl or $–C_{1-4}$haloalkyl and R^{3b} is H or methyl. In some embodiments, R^{3a} is $–C_{1-6}$alkyl and R^{3b} is H or methyl. In some embodiments, R^{3a} is methyl or ethyl and R^{3b} is H or methyl. In some embodiments, R^{3a} is methyl and R^{3b} is H or methyl.

[0074] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^3 is OR^{3a}, wherein R^{3a} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{3-6}$cycloalkyl and R^{3b} is H. In some embodiments, R^{3a} is $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{3-6}$cycloalkyl and R^{3b} is H. In some embodiments, R^{3a} is $–C_{1-6}$alkyl or $–C_{1-4}$haloalkyl and R^{3b} is H. In some embodiments, R^{3a} is $–C_{1-6}$alkyl and R^{3b} is H. In some embodiments, R^{3a} is methyl or ethyl and R^{3b} is H. In some embodiments, R^{3a} is methyl and R^{3b} is H.

[0075] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{1-4}$alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H, $–C_{1-6}$alkyl, or $–C_{1-4}$haloalkyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or $–C_{1-6}$alkyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they

are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or $–C_{1-3}$alkyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or methyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H.

[0076] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{1-4}$alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H, $–C_{1-6}$alkyl, or $–C_{1-4}$haloalkyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or $–C_{1-6}$alkyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or $–C_{1-3}$alkyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or methyl. In some embodiments, R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H.

[0077] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms

independently selected from N, O, and S; and R^{3b} is H, $-C_{1-6}$alkyl, $-C_{1-4}$haloalkyl, or $-C_{1-4}$alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H, $-C_{1-6}$alkyl, or $-C_{1-4}$haloalkyl. In some embodiments, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or $-C_{1-6}$alkyl. In some embodiments, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or $-C_{1-3}$alkyl. In some embodiments, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or methyl. In some embodiments, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H.

[0078] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H, $-C_{1-6}$alkyl, $-C_{1-4}$haloalkyl, or $-C_{1-4}$alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H, $-C_{1-6}$alkyl, or $-C_{1-4}$haloalkyl. In some embodiments, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or $-C_{1-6}$alkyl. In some embodiments, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or $-C_{1-3}$alkyl. In some embodiments, R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or methyl. In some embodiments,

R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H.

[0079] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{1-4}$alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H, $–C_{1-6}$alkyl, or $–C_{1-4}$haloalkyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or $–C_{1-6}$alkyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or $–C_{1-3}$alkyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H methyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H.

[0080] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{1-4}$alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H, $–C_{1-6}$alkyl, or $–C_{1-4}$haloalkyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered

heterocyclic ring containing one oxygen atom; and R^{3b} is H or $-C_{1-6}$alkyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or $-C_{1-3}$alkyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or methyl. In some embodiments, R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H.

[0081] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H, $-C_{1-6}$alkyl, $-C_{1-4}$haloalkyl, or $-C_{1-4}$alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H, $-C_{1-6}$alkyl, or $-C_{1-4}$haloalkyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or $-C_{1-6}$alkyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or $-C_{1-3}$alkyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H or methyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{3b} is H.

[0082] In some embodiments of the compound of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or –C_{1-6}alkyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or –C_{1-3}alkyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H or methyl. In some embodiments, R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom; and R^{3b} is H.

[0083] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-3}alkyl. In some embodiments, R^{4a} is methyl. In some embodiments, R^{4a} is –C_{1-4}haloalkyl.

[0084] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{4b} is H, halo, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{4b} is H, –C_{1-3}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{4b} is H or C_{1-3}alkyl. In some embodiments, R^{4b} is –C_{1-3}alkyl or –C_{1-4}haloalkyl. In some embodiments, R^{4b} is –C_{1-3}alkyl. In some embodiments, R^{4b} is –C_{1-4}haloalkyl. In some embodiments, R^{4b} is H.

[0085] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl and R^{4b} is H, halo, –

C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl and R^{4b} is H or C_{1-3}alkyl. In some embodiments, R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl and R^{4b} is –C_{1-3}alkyl or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl and R^{4b} is –C_{1-3}alkyl. In some embodiments, R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl and R^{4b} is –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl and R^{4b} is H.

[0086] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{4a} is –C_{1-3}alkyl and R^{4b} is H, halo, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-3}alkyl and R^{4b} is H, –C_{1-3}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-3}alkyl and R^{4b} is H or C_{1-3}alkyl. In some embodiments, R^{4a} is –C_{1-3}alkyl and R^{4b} is –C_{1-3}alkyl or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-3}alkyl and R^{4b} is –C_{1-3}alkyl. In some embodiments, R^{4a} is –C_{1-3}alkyl and R^{4b} is –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-3}alkyl and R^{4b} is H.

[0087] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{4a} is methyl and R^{4b} is H, halo, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is methyl and R^{4b} is H, –C_{1-3}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is methyl and R^{4b} is H or C_{1-3}alkyl. In some embodiments, R^{4a} is methyl and R^{4b} is –C_{1-3}alkyl or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is methyl and R^{4b} is –C_{1-3}alkyl. In some embodiments, R^{4a} is methyl and R^{4b} is –C_{1-4}haloalkyl. In some embodiments, R^{4a} is methyl and R^{4b} is H.

[0088] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, R^{4a} is –C_{1-4}haloalkyl and R^{4b} is H, halo, –C_{1-6}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-4}haloalkyl and R^{4b} is H, –C_{1-3}alkyl, or –C_{1-4}haloalkyl. In some embodiments, R^{4a} is –C_{1-4}haloalkyl and R^{4b} is H or C_{1-3}alkyl. In some embodiments, R^{4a} is –C_{1-4}haloalkyl and R^{4b} is –C_{1-3}alkyl or –C_{1-4}haloalkyl. In some

embodiments, R^{4a} is $-C_{1-4}$haloalkyl and R^{4b} is $-C_{1-3}$alkyl. In some embodiments, R^{4a} is $-C_{1-4}$haloalkyl and R^{4b} is $-C_{1-4}$haloalkyl. In some embodiments, R^{4a} is $-C_{1-4}$haloalkyl and R^{4b} is H.

[0089] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^1 is a bond.

[0090] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^1 is $-CR^{5a}R^{5b}-$, wherein R^{5a} and R^{5b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo. In some embodiments, R^{5a} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo and R^{5b} is H, C_{1-6}alkyl, or halo. In some embodiments, R^{5a} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo and R^{5b} is H or C_{1-6}alkyl. In some embodiments, R^{5a} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo and R^{5b} is C_{1-6}alkyl. In some embodiments, R^{5a} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo and R^{5b} is H.

[0091] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^1 is $-CR^{5a}R^{5b}-$, wherein R^{5a} is H, C_{1-6}alkyl, or C_{1-4}haloalkyl and R^{5b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo. In some embodiments, R^{5a} is H, C_{1-6}alkyl, or C_{1-4}haloalkyl and R^{5b} is H, C_{1-6}alkyl, or halo. In some embodiments, R^{5a} is H, C_{1-6}alkyl, or C_{1-4}haloalkyl and R^{5b} is H or C_{1-6}alkyl. In some embodiments, R^{5a} is H, C_{1-6}alkyl, or C_{1-4}haloalkyl and R^{5b} is C_{1-6}alkyl. In some embodiments, R^{5a} is H, C_{1-6}alkyl, or C_{1-4}haloalkyl and R^{5b} is H.

[0092] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^1 is $-CR^{5a}R^{5b}-$, wherein R^{5a} is H or C_{1-6}alkyl and R^{5b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo. In some embodiments, R^{5a} is H or C_{1-6}alkyl and R^{5b} is H, C_{1-6}alkyl, or halo. In some embodiments, R^{5a} is H or C_{1-6}alkyl and R^{5b} is H or C_{1-6}alkyl. In some embodiments, R^{5a} is H or C_{1-6}alkyl and R^{5b} is C_{1-6}alkyl. In some embodiments, R^{5a} is H or C_{1-6}alkyl and R^{5b} is H.

[0093] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^1 is $–CR^{5a}R^{5b}–$, wherein R^{5a} is C_{1-6}alkyl and R^{5b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo. In some embodiments, R^{5a} is C_{1-6}alkyl and R^{5b} is H, C_{1-6}alkyl, or halo. In some embodiments, R^{5a} is C_{1-6}alkyl and R^{5b} is H or C_{1-6}alkyl. In some embodiments, R^{5a} is C_{1-6}alkyl and R^{5b} is C_{1-6}alkyl. In some embodiments, R^{5a} is C_{1-6}alkyl and R^{5b} is H.

[0094] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^1 is $–CR^{5a}R^{5b}–$, wherein R^{5a} is H and R^{5b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo. In some embodiments, R^{5a} is H and R^{5b} is H, C_{1-6}alkyl, or halo. In some embodiments, R^{5a} is H and R^{5b} is H or C_{1-6}alkyl. In some embodiments, R^{5a} is H and R^{5b} is C_{1-6}alkyl. In some embodiments, R^{5a} is H and R^{5b} is H.

[0095] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^2 is $–CR^{6a}R^{6b}–$, wherein R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, $–O–C_{1-4}$alkyl, or C_{1-4}alkylene–$O–C_{1-4}$alkyl. In some embodiments, R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, or $–O–C_{1-4}$alkyl. In some embodiments, R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl or cyano. In some embodiments, R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, or hydroxyl. In some embodiments, R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo. In some embodiments, R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, or C_{1-4}haloalkyl. In some embodiments, R^{6a} and R^{6b} are independently H or C_{1-6}alkyl. In some embodiments, R^{6a} and R^{6b} are both H.

[0096] In some embodiments of the compound of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^2 is $–CR^{6a}R^{6b}–$, wherein R^{6a} is H and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, $–O–C_{1-4}$alkyl, or C_{1-4}alkylene–$O–C_{1-4}$alkyl. In some embodiments, R^{6a} is H and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, or $–O–C_{1-4}$alkyl. In some embodiments, R^{6a} is H and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl or

cyano. In some embodiments, R^{6a} is H and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, or hydroxyl. In some embodiments, R^{6a} is H and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo. In some embodiments, R^{6a} is H and R^{6b} is H, C_{1-6}alkyl, or C_{1-4}haloalkyl. In some embodiments, R^{6a} is H and R^{6b} is H or C_{1-6}alkyl. In some embodiments, R^{6a} is H and R^{6b} is H.

[0097] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof W^2 is $–CR^{6a}R^{6b}–$, R^{6a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, $–O–C_{1-4}$alkyl, or C_{1-4}alkylene$–O–C_{1-4}$alkyl. In some embodiments, R^{6a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo. In some embodiments, R^{6a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{6b} is H.

[0098] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof W^2 is $–CR^{6a}R^{6b}–$, R^{6a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one heteroatom selected from N, O, and S; and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, $–O–C_{1-4}$alkyl, or C_{1-4}alkylene$–O–C_{1-4}$alkyl. In some embodiments, R^{6a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one heteroatom selected from N, O, and S; and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo. In some embodiments, R^{6a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one heteroatom selected from N, O, and S; and R^{6b} is H.

[0099] In some embodiments of the compound of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^2 is $–CR^{7a}=CR^{7b}–$, wherein R^{7a} and R^{7b} are

independently H, halo, C_{1-4}haloalkyl, or C_{1-6}alkyl or R^{7a} and R^{7b} together with the carbons to which they are attached form a C_{5-10}aryl optionally substituted with one to four R^{A2}, wherein each R^{A2} is independently halo, cyano, or C_{1-4}alkyl. In some embodiments, W^2 is $–CR^{7a}=CR^{7b}–$, wherein R^{7a} and R^{7b} are independently H, halo, C_{1-4}haloalkyl, or C_{1-6}alkyl. In some embodiments, W^2 is $–CR^{7a}=CR^{7b}–$, wherein R^{7a} and R^{7b} are independently H, halo, or C_{1-6}alkyl. In some embodiments, W^2 is $–CR^{7a}=CR^{7b}–$, wherein R^{7a} and R^{7b} are independently H or C_{1-6}alkyl. In some embodiments, W^2 is $–CR^{7a}=CR^{7b}–$, wherein R^{7a} and R^{7b} are both H.

[0100] In some embodiments of the compound of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof, W^2 is $–CR^{7a}=CR^{7b}–$, wherein R^{7a} and R^{7b} together with the carbon atoms to which they are attached form a C_{5-10}aryl optionally substituted with one to four R^{A2}, wherein each R^{A2} is independently halo, cyano, or C_{1-4}alkyl. In some embodiments, R^{7a} and R^{7b} together with the carbon atoms to which they are attached form a fused phenyl optionally substituted with one to four R^{A2}, wherein each R^{A4} is independently halo, cyano, or C_{1-4}alkyl. In some embodiments, R^{7a} and R^{7b} together with the carbon atoms to which they are attached form an unsubstituted fused phenyl.

[0101] In some embodiments, the compound of Formula I, Ia, Ib, Ic, or Id, or the pharmaceutically acceptable salt thereof,

R^1 is C_{6-10}aryl, wherein the C_{6-10}aryl is optionally substituted with one to four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, $–O–C_{1-4}$alkyl, or C_{1-4}alkyl$–O–C_{1-4}$alkyl;

R^2 is H, C_{1-6}alkyl, or C_{1-4}haloalkyl;

R^3 is halo or $–OR^{3a}$, wherein R^{3a} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{3-6}$cycloalkyl;

R^{3b} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{1-4}$alkylene$–O–C_{1-4}$alkyl;

R^{4a} is $–C_{1-6}$alkyl or $–C_{1-4}$haloalkyl;

R^{4b} is H, halo, $–C_{1-6}$alkyl, or $–C_{1-4}$haloalkyl;

W^1 is a bond or $–CR^{5a}R^{5b}–$;

R^{5a} and R^{5b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo;

W^2 is $–CR^{6a}R^{6b}–$ or $–CR^{7a}=CR^{7b}–$;

R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, $–O–C_{1-4}$alkyl, or C_{1-4}alkylene$–O–C_{1-4}$alkyl; and

R^{7a} and R^{7b} are independently H, halo, C_{1-4}haloalkyl, or C_{1-6}alkyl.

[0102] In some embodiments, the compound of Formula I, Ia, Ib, Ic, or Id, or the pharmaceutically acceptable salt thereof,

R^1 is C_{6-10}aryl, wherein the C_{6-10}aryl is optionally substituted with one to four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, $–O–C_{1-4}$alkyl, or C_{1-4}alkyl$–O–C_{1-4}$alkyl;

R^2 is H, C_{1-6}alkyl, or C_{1-4}haloalkyl;

R^3 is $–OR^{3a}$, wherein R^{3a} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{3-6}$cycloalkyl;

R^{3b} is H, $–C_{1-6}$alkyl, $–C_{1-4}$haloalkyl, or $–C_{1-4}$alkylene$–O–C_{1-4}$alkyl;

R^{4a} is $–C_{1-6}$alkyl or $–C_{1-4}$haloalkyl;

R^{4b} is H, halo, $–C_{1-6}$alkyl, or $–C_{1-4}$haloalkyl;

W^1 is a bond or $–CR^{5a}R^{5b}–$;

R^{5a} and R^{5b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo;

W^2 is $–CR^{6a}R^{6b}–$ or $–CR^{7a}=CR^{7b}–$;

R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, $–O–C_{1-4}$alkyl, or C_{1-4}alkylene$–O–C_{1-4}$alkyl; and

R^{7a} and R^{7b} are independently H, halo, C_{1-4}haloalkyl, or C_{1-6}alkyl.

[0103] In some embodiments, the compound of Formula I, Ia, Ib, Ic, Id, or II, or the pharmaceutically acceptable salt thereof,

R^1 is phenyl substituted with two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkyl–O–C_{1-4}alkyl;

R^2 is H, C_{1-6}alkyl, or C_{1-4}haloalkyl;

R^3 is –OR^{3a}, wherein R^{3a} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl;

R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl;

R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl;

R^{4b} is H, halo, –C_{1-6}alkyl, or –C_{1-4}haloalkyl;

W^1 is a bond or –$CR^{5a}R^{5b}$–;

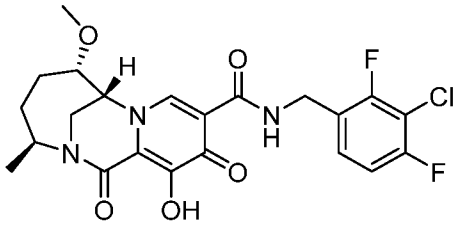
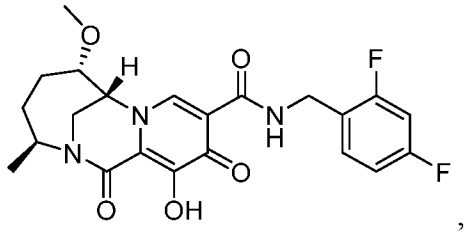
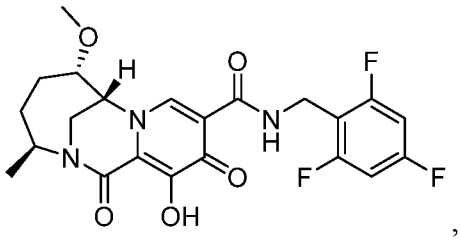
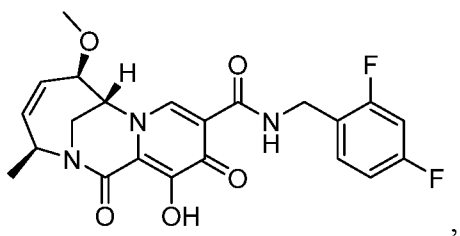
R^{5a} and R^{5b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo;

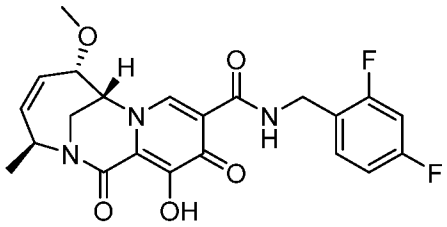
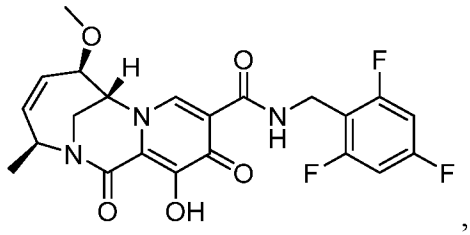
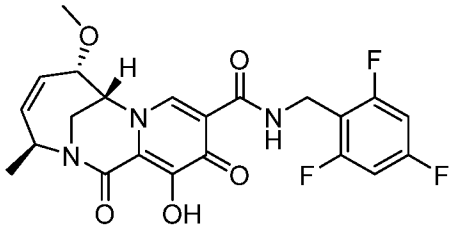
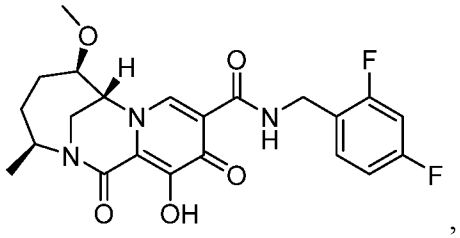
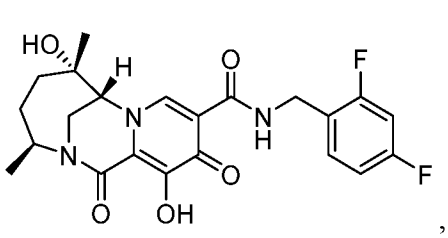
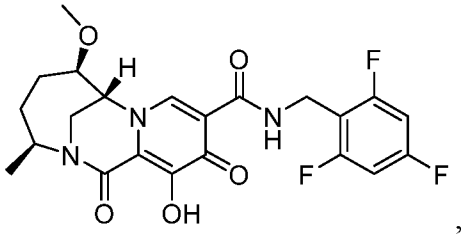
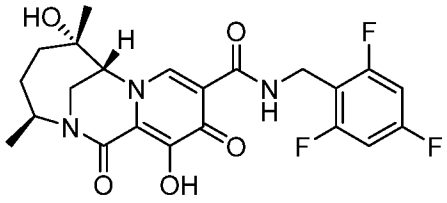
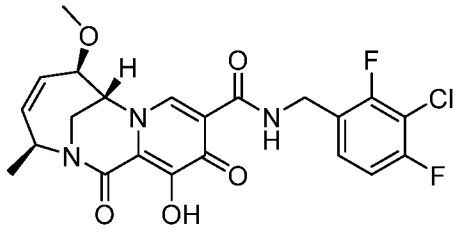
W^2 is –$CR^{6a}R^{6b}$– or –CR^{7a}=CR^{7b}–;

R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkylene–O–C_{1-4}alkyl; and

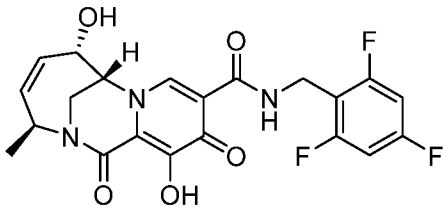
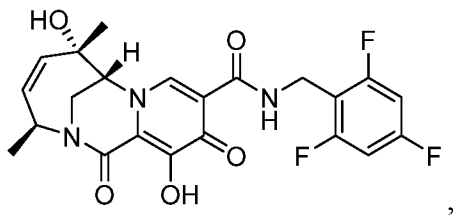
R^{7a} and R^{7b} are independently H, halo, C_{1-4}haloalkyl, or C_{1-6}alkyl.

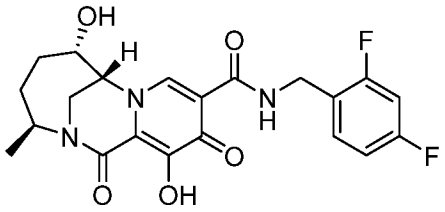
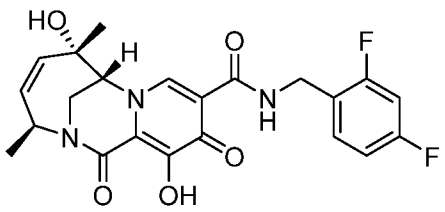
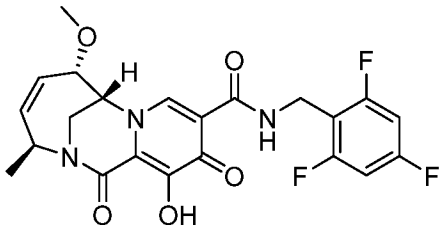
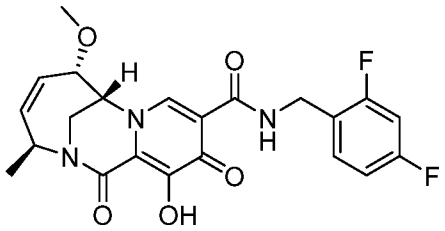
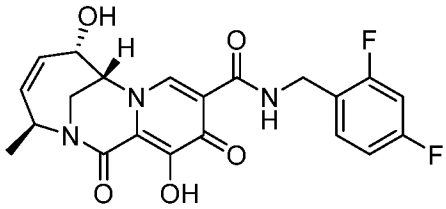
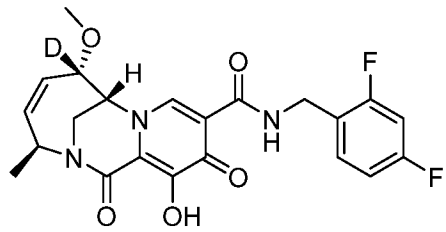
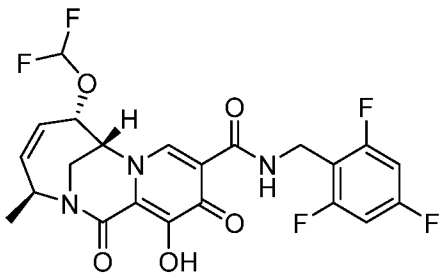
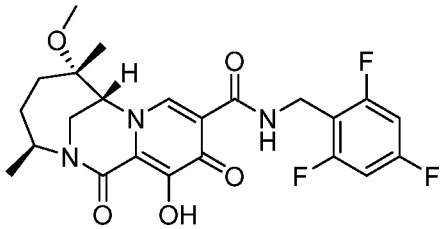
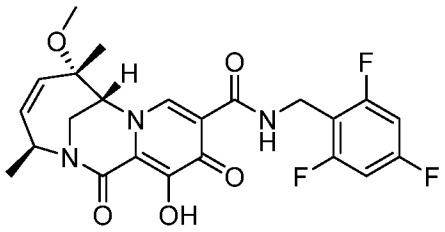
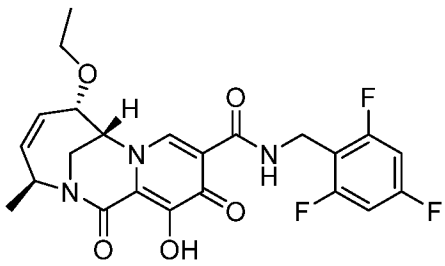
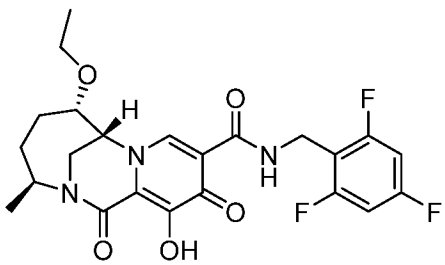
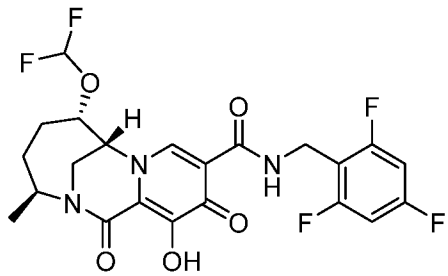
[0104] In some embodiments, the compound of Formula I, Ia, Ib, Ic, Id or II, is selected form the group consisting of:

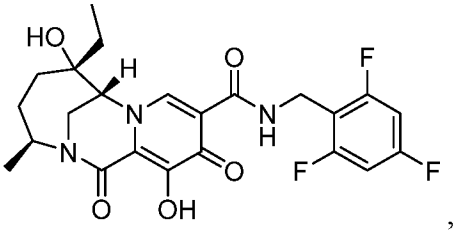
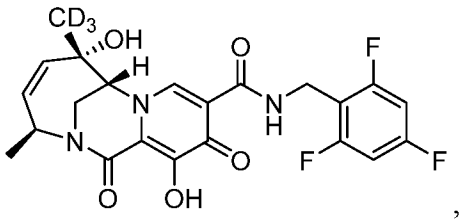
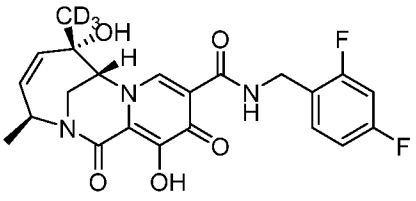
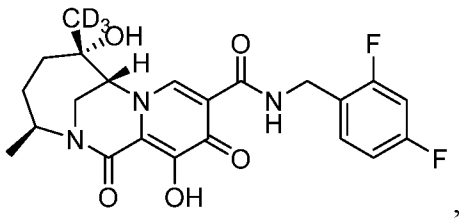
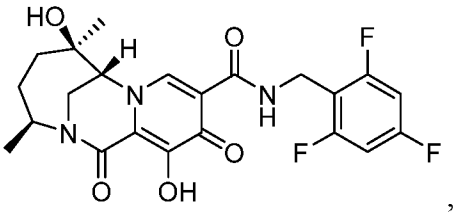
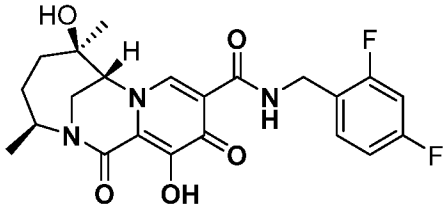
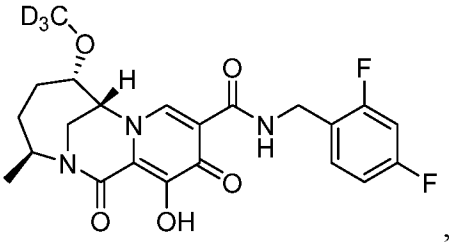
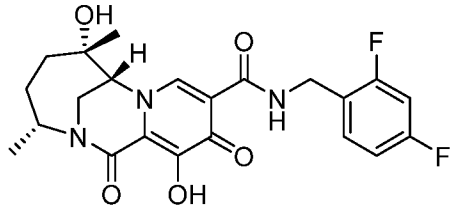
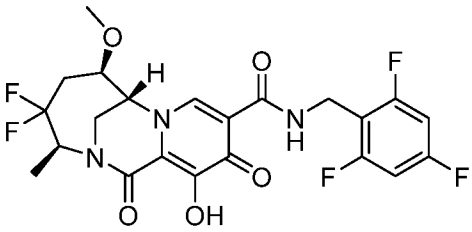
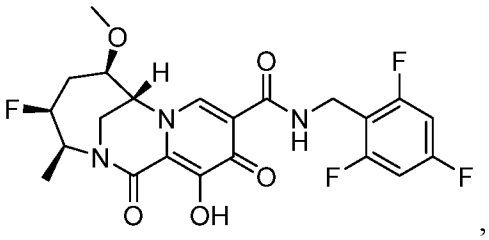
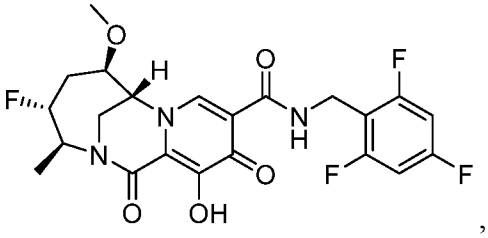
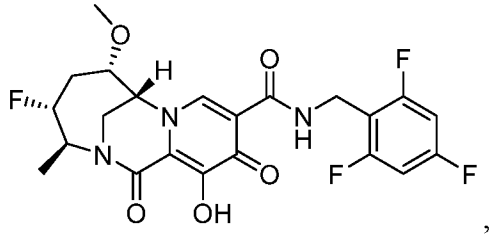
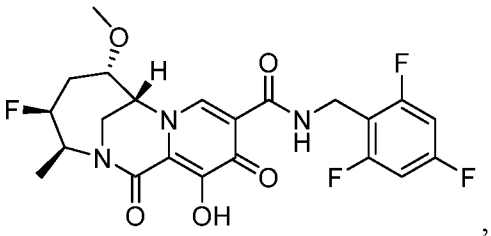
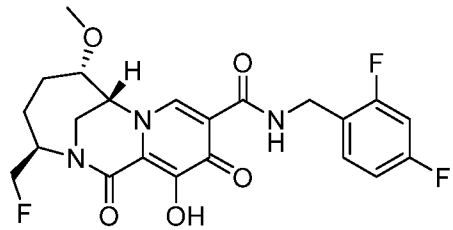

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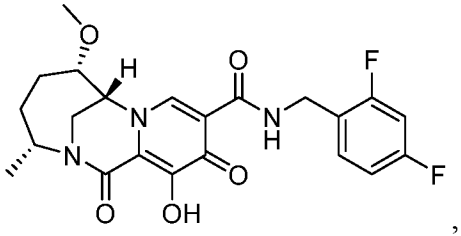
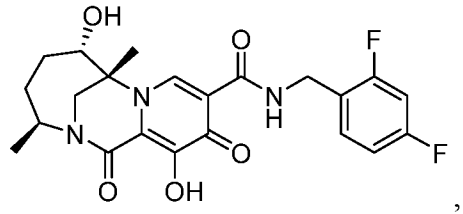
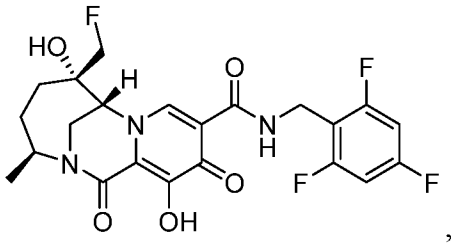
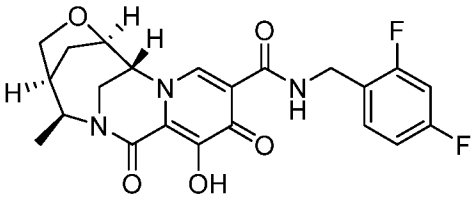
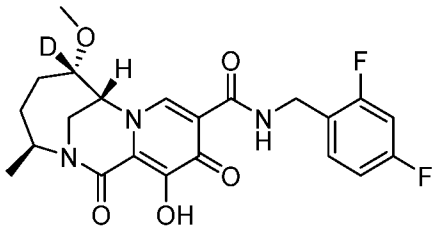

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[0105] In some embodiments, the compound of Formula I, Ia, Ib, Ic, Id or II, is selected form the group consisting of:

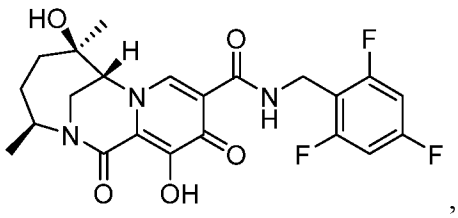
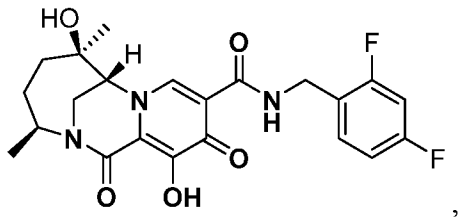
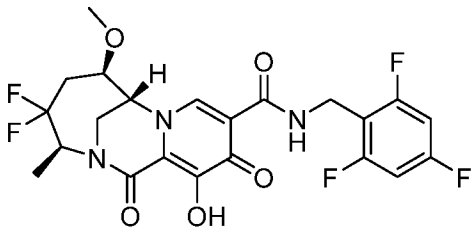
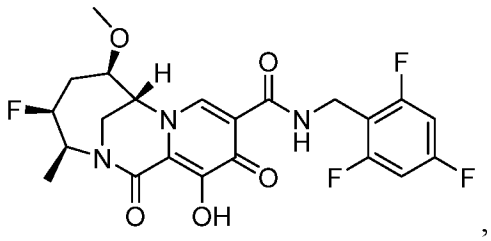
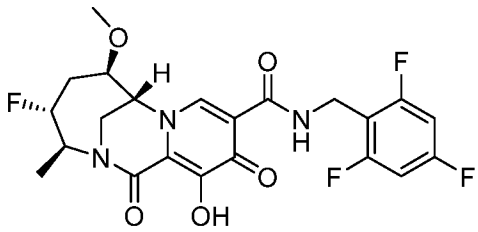
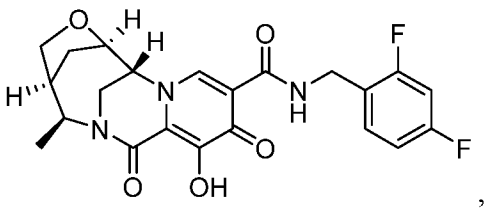

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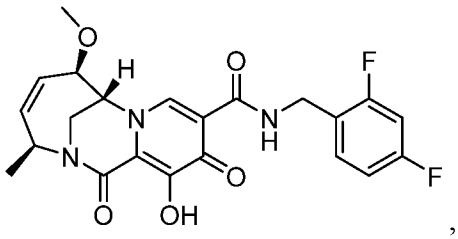
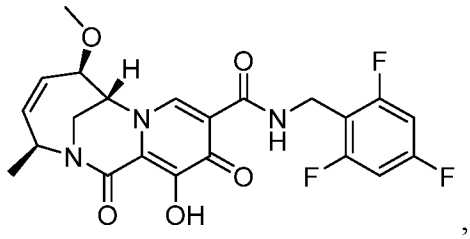
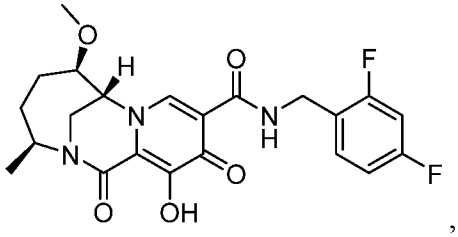
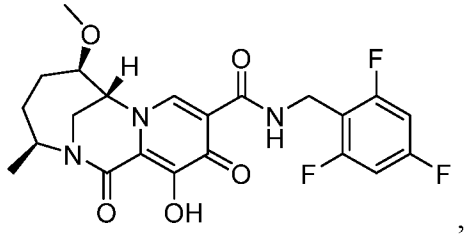
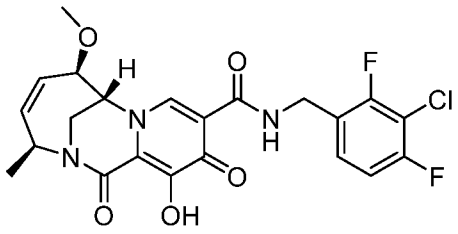
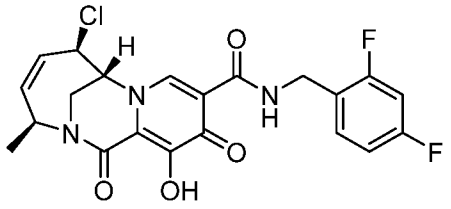

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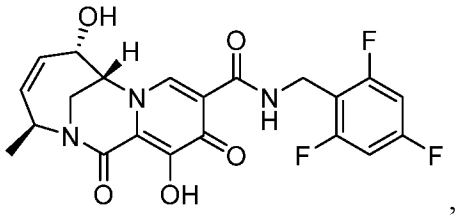
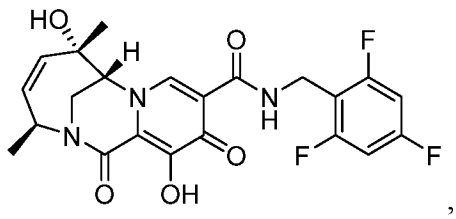
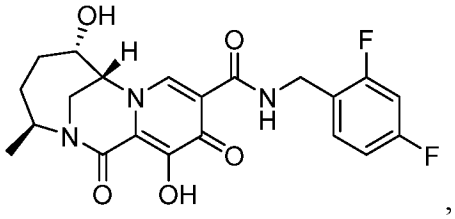
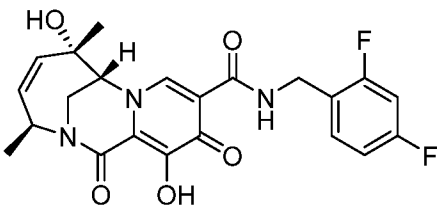
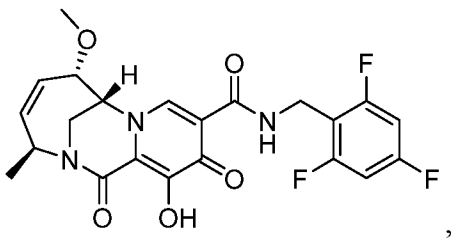
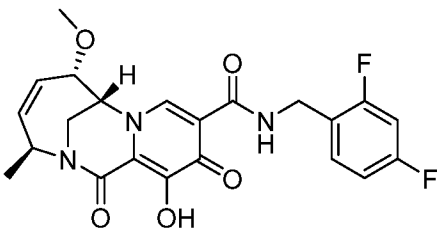

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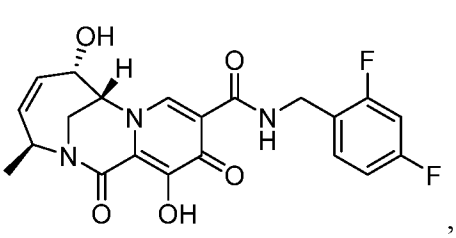
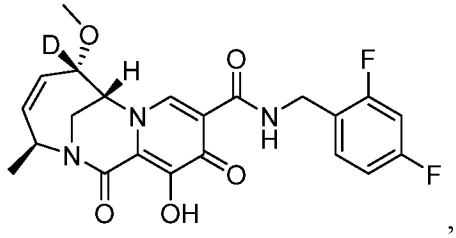
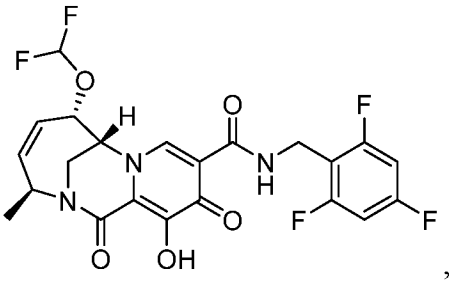
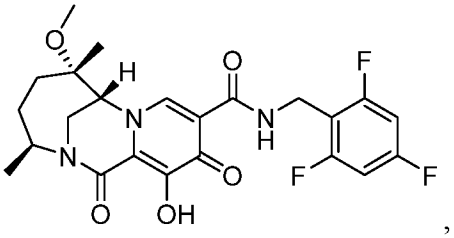
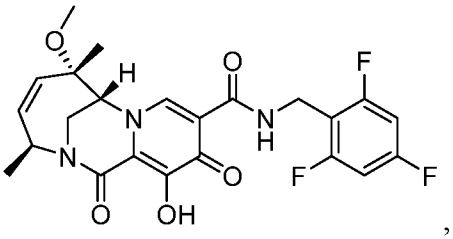
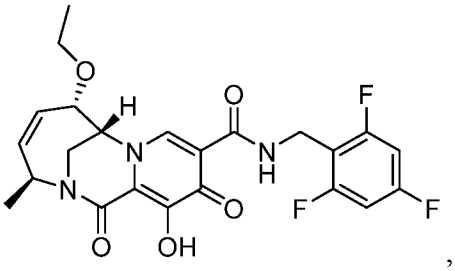
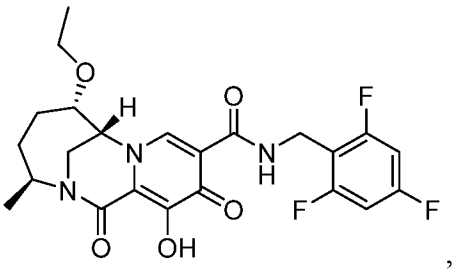
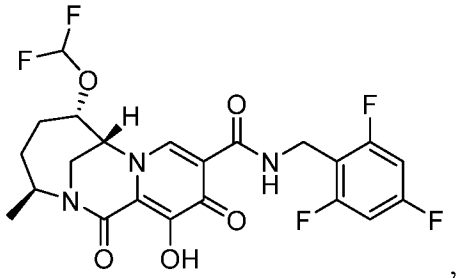
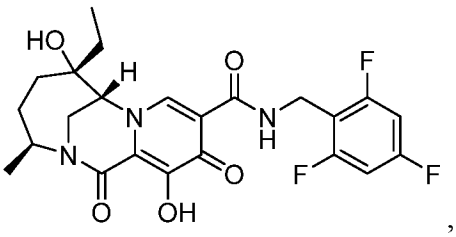
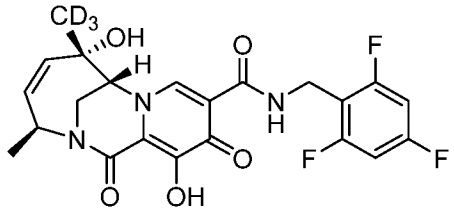
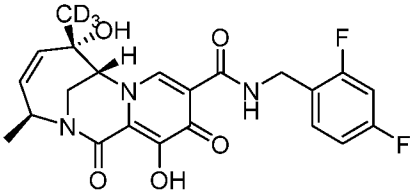
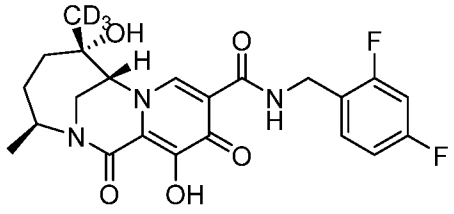
[0106] In some embodiments, the compound of Formula I, Ia, or II is selected from the group consisting of:

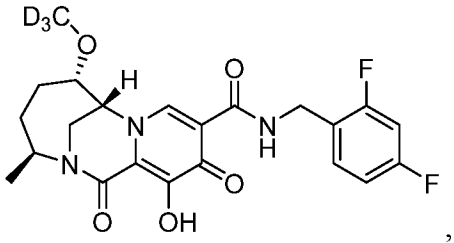
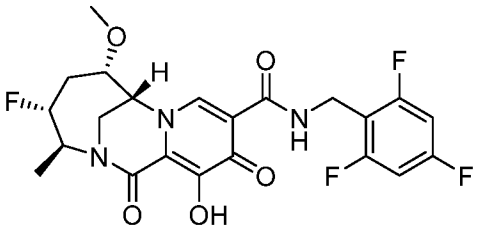
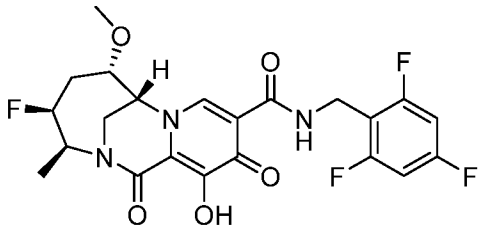
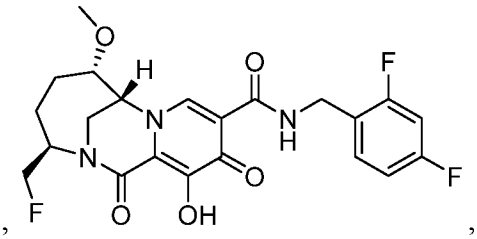
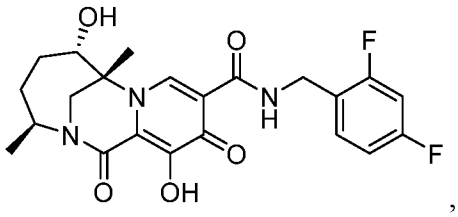
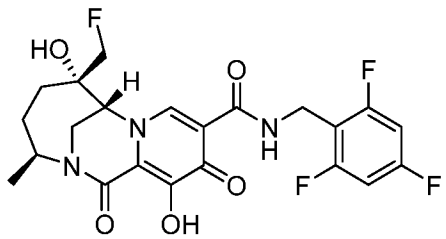
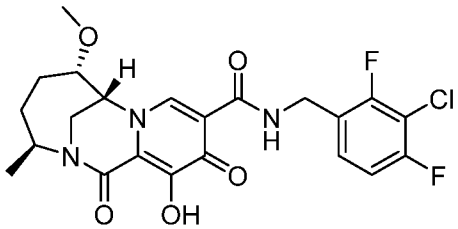
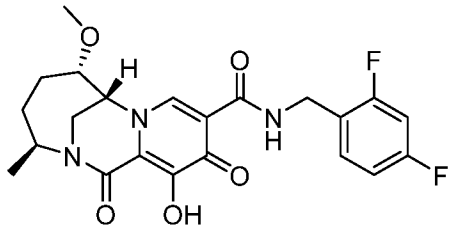
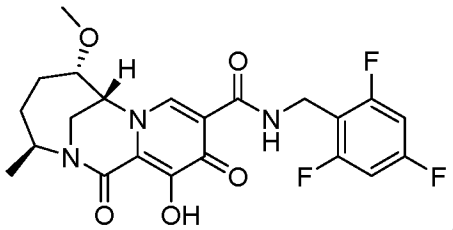
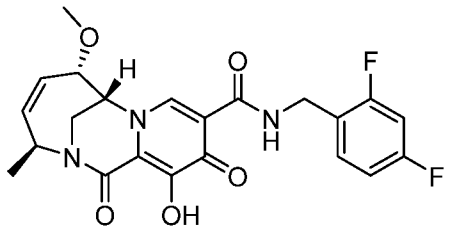
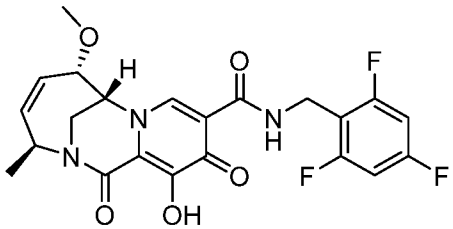
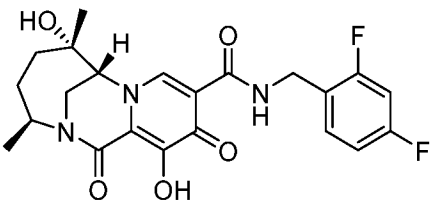
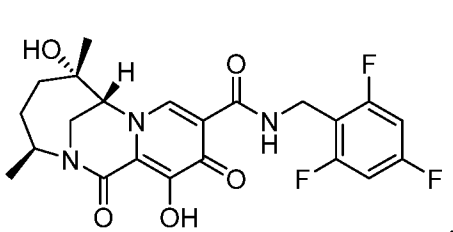
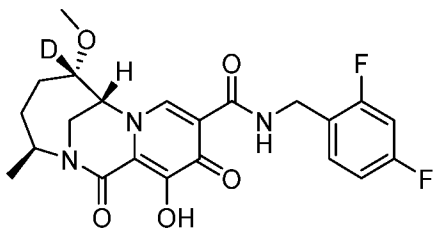

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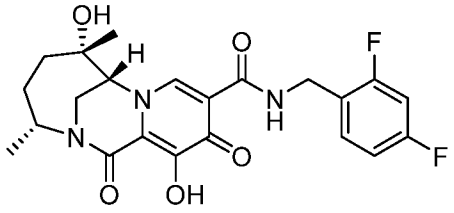
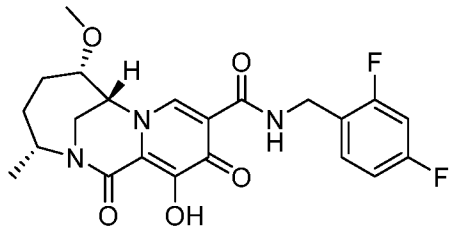
[0107] In some embodiments, the compound of Formula I, Ic, or II is selected from the group consisting of:


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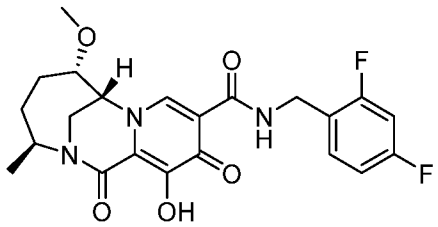

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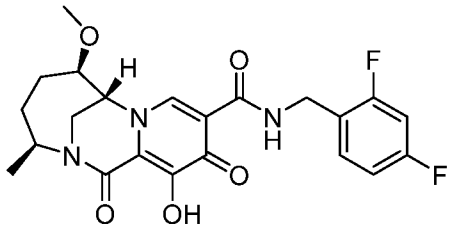
[0108] In some embodiments, the compound of Formula I, Id, or II is selected from the group consisting of:


and


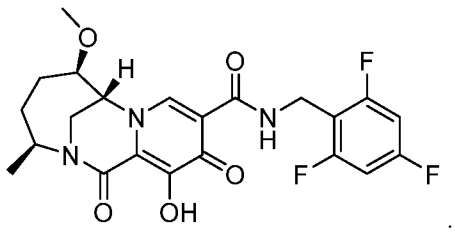
[0109] In some embodiments, the compound of Formula I is



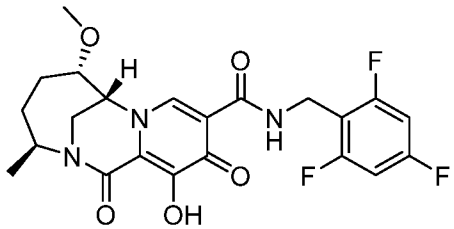
[0110] In some embodiments, the compound of Formula I is



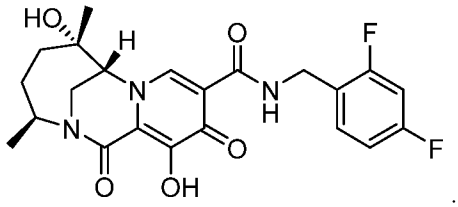
[0111] In some embodiments, the compound of Formula I is



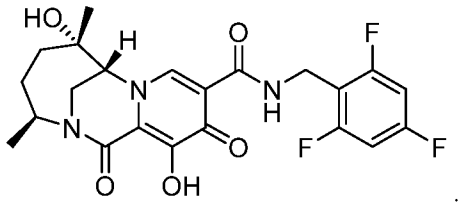
[0112] In some embodiments, the compound of Formula I is



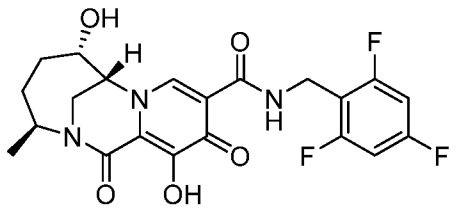
[0113] In some embodiments, the compound of Formula I is



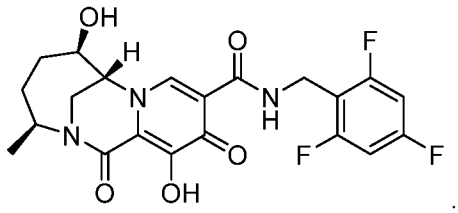
[0114] In some embodiments, the compound of Formula I is



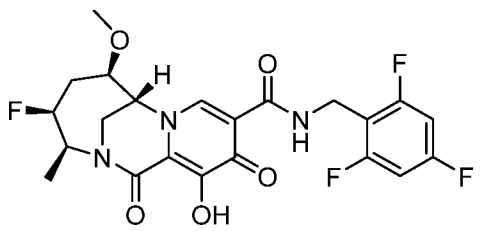
[0115] In some embodiments, the compound of Formula I is



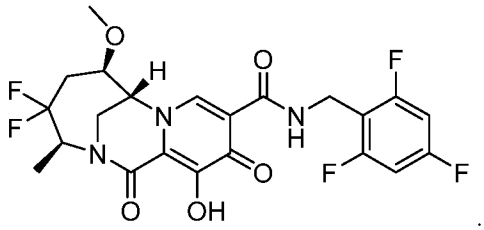
[0116] In some embodiments, the compound of Formula I is



[0117] In some embodiments, the compound of Formula I is



[0118] In some embodiments, the compound of Formula I is



III. Compositions and Kits

[0119] Compounds provided herein are usually administered in the form of pharmaceutical compositions. Thus, provided herein are also pharmaceutical compositions that comprise one or more of the compounds provided herein or pharmaceutically acceptable salts, isomer, or a mixture thereof and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants and excipients. The compounds provided herein may be the sole active ingredient or one of the active ingredients of the pharmaceutical compositions. Suitable pharmaceutically acceptable vehicles may include, for example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. *See, e.g.*, Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0120] In one aspect, provided herein are pharmaceutical compositions comprising a compound provided herein (*e.g.*, a compound of Formula I, Ia, Ib, Ic, Id, or II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier. In some embodiments, the pharmaceutical compositions comprise a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

[0121] In some embodiments, the pharmaceutical compositions provided herein further comprise one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical compositions further comprise a therapeutically effective amount of the one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents, or a pharmaceutically acceptable salt thereof.

[0122] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical compositions may be administered by various methods including, for example, rectal, buccal, intranasal and transdermal routes. In some embodiments, the pharmaceutical compositions may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[0123] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0124] Oral administration may be another route for administration of the compounds provided herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound provided herein or pharmaceutically acceptable salts, isomer, or a mixture thereof, the active ingredient (such as a compound provided herein) is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the pharmaceutical compositions can

be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0125] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose or any combinations thereof. The pharmaceutical compositions can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents; or any combinations thereof.

[0126] The pharmaceutical compositions that include at least one compound described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof can be formulated so as to provide quick, sustained or delayed release of the active ingredient (such as a compound provided herein) after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the methods of the present disclosure employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds provided herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0127] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0128] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with materials such as shellac, cetyl alcohol, and cellulose acetate.

[0129] Pharmaceutical compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution,

suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[0130] In one aspect, provided herein are kits that comprise a compound provided herein (*e.g.*, a compound of Formula I, Ia, Ib, Ic, Id, or II), or a pharmaceutically acceptable salt, stereoisomer, prodrug, or solvate thereof, and suitable packaging. In some embodiments, the kit further comprises instructions for use. In some embodiments, the kit comprises a compound provided herein (*e.g.*, a compound of Formula I, Ia, Ib, Ic, Id, or II), or a pharmaceutically acceptable salt, stereoisomer, prodrug, or solvate thereof, and a label and/or instructions for use of the compounds in the treatment of the indications, including the diseases or conditions, described herein.

[0131] In some embodiments, the kits further comprise one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents, or a pharmaceutically acceptable salt thereof.

[0132] In one aspect, provided herein are articles of manufacture that comprise a compound described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof in a suitable container. In some embodiments, the container may be a vial, jar, ampoule, preloaded syringe, or intravenous bag.

IV. Methods

[0133] In one embodiment, methods of treating an HIV (*e.g.*, HIV-1 and/or HIV-2) infection in a human having or at risk of having the infection comprising administering to the human a therapeutically effective amount of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, are provided.

[0134] In some embodiments, the methods further comprise administering to the human a therapeutically effective amount of one, two, three, or four additional therapeutic agents. In certain embodiments, the additional therapeutic agent or agents are anti-HIV agents. In particular embodiments, the additional therapeutic agent or agents are HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV capsid inhibitors, gp41 inhibitors, CXCR4 inhibitors, gpl20 inhibitors, CCR5 inhibitors, latency reversing agents, capsid polymerization inhibitors, HIV bNAbs (broadly neutralizing HIV antibodies), TLR7 agonists, pharmacokinetic enhancers, other drugs for treating HIV, or combinations thereof. In one embodiment, the additional therapeutic agent or agents are abacavir, tenofovir alafenamide, tenofovir disoproxil, N-((*S*)-l-(3-(4-chloro-3-(methylsulfonamido)-l-(2,2,2-trifluoroethyl)-l*H*-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-l-yn-l-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-l*H*-cyclopropa[3,4]cyclopenta[l,2-*c*]pyrazol-l-yl)acetamide, or a pharmaceutically acceptable salt thereof.

[0135] In another embodiment, a use of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, for treating an HIV (*e.g.,* HIV-1 and/or HIV-2) infection in a human having or at risk of having the infection is provided.

[0136] In another embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, for use in medical therapy is provided.

[0137] In another embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Formula I, Ia, Ib,

Ic, Id, or II, or pharmaceutically acceptable salt thereof, for use in treating an HIV infection is provided.

[0138] In another embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof for use in a method of treating an HIV infection in a human having or at risk of having the infection, is provided.

[0139] In another embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof for use in a method of treating an HIV infection in a human having or at risk of having the infection, is provided wherein said method further comprises administering to the human one, two, three, or four additional therapeutic agents.

[0140] In another embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof for use in a method of treating an HIV infection in a human having or at risk of having the infection, is provided wherein said method further comprises administering to the human one, two, three, or four additional therapeutic agents selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV capsid inhibitors, gp41 inhibitors, CXCR4 inhibitors, gpl20 inhibitors, CCR5 inhibitors, latency reversing agents, capsid polymerization inhibitors, HIV bNAbs, TLR7 agonists, pharmacokinetic enhancers, other drugs for treating HIV, or combinations thereof. In one embodiment, the one, two, three, or four additional therapeutic agents are selected from HIV protease inhibitors, HIV non-nucleoside inhibitors of

reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, latency reversing agents, HIV capsid inhibitors, HIV bNAbs, TLR7 agonists, and combinations thereof.

[0141] In another embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof for use in a method of treating an HIV infection in a human having or at risk of having the infection, is provided wherein said method further comprises administering to the human a therapeutically effective amount of tenofovir disoproxil and emtricitabine.

[0142] In another embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof for use in a method of treating an HIV infection in a human having or at risk of having the infection, is provided wherein said method further comprises administering to the human a therapeutically effective amount of tenofovir alafenamide and emtricitabine.

[0143] In another embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof for use in a method of treating an HIV infection in a human having or at risk of having the infection, is provided wherein said method further comprises administering to the human a therapeutically effective amount of tenofovir disoproxil.

[0144] In another embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof for use in a method of treating an HIV infection in a human having or at risk of having the infection, is provided

wherein said method further comprises administering to the human a therapeutically effective amount of tenofovir alafenamide.

[0145] In another embodiment, a method of using a compound of Formula I, Ia, Ib, Ic, Id, or II in therapy is provided. In particular, a method of treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms in a mammal (*e.g.*, a human) is provided, comprising administering to the mammal a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0146] In another embodiment, a composition comprising a compound of Formula I, Ia, Ib, Ic, Id, or II, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, for use in a method of treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms in a mammal (*e.g.*, a human) is provided.

[0147] In one embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, is provided for use in preventing HIV infection.

[0148] For example, in one embodiment, a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, is provided for use in pre-exposure prophylaxis (PrEP), i.e., before the exposure of the individual to the HIV virus to prevent HIV infection from taking hold if the individual is exposed to the virus and/or to keep the virus from establishing a permanent infection and/or to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood.

[0149] In another embodiment, the use of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating an HIV infection in a human being having or at risk of having the infection is disclosed.

[0150] In another embodiment, the use of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof, as a research tool is disclosed.

[0151] In another embodiment, an article of manufacture comprising a composition effective to treat an HIV infection; and packaging material comprising a label which indicates that the composition can be used to treat infection by HIV is disclosed. Exemplary compositions comprise a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt thereof.

[0152] In still another embodiment, a method of inhibiting the replication of HIV is disclosed. The method comprises exposing the virus to an effective amount of the compound of Formula I, Ia, Ib, Ic, Id, or II, or a salt thereof, under conditions where replication of HIV is inhibited.

[0153] In another embodiment, the use of a compound of Formula I, Ia, Ib, Ic, Id, or II, to inhibit the activity of the HIV integrase enzyme is disclosed.

[0154] In another embodiment, the use of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a salt thereof, to inhibit the replication of HIV is disclosed.

V. Administration

[0155] The compounds of the present disclosure (also referred to herein as the active ingredients), can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal,

intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with, for example, the condition of the recipient. An advantage of certain compounds disclosed herein is that they are orally bioavailable and can be dosed orally.

[0156] A compound of the present disclosure may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer. In some embodiments, the compound is administered on a daily or intermittent schedule for the duration of the individual's life.

[0157] The specific dose level of a compound of the present disclosure for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a dosage may be expressed as a number of milligrams of a compound described herein per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.1 and 150 mg/kg may be appropriate. In some embodiments, about 0.1 and 100 mg/kg may be appropriate. In other embodiments a dosage of between 0.5 and 60 mg/kg may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

[0158] The daily dosage may also be described as a total amount of a compound described herein administered per dose or per day. Daily dosage of a compound of Formula I, Ia, Ib, Ic, Id, or II, or a pharmaceutically acceptable salt or pharmaceutically acceptable tautomer thereof, may be between about 1 mg and 4,000 mg, between about 2,000 to 4,000 mg/day, between about 1 to 2,000 mg/day, between about 1 to 1,000 mg/day, between about 10 to 500 mg/day,

between about 20 to 500 mg/day, between about 50 to 300 mg/day, between about 75 to 200 mg/day, or between about 15 to 150 mg/day.

[0159] The dosage or dosing frequency of a compound of the present disclosure may be adjusted over the course of the treatment, based on the judgment of the administering physician.

[0160] The compounds of the present disclosure may be administered to an individual (*e.g.*, a human) in a therapeutically effective amount. In some embodiments, the compound is administered once daily.

[0161] The compounds provided herein can be administered by any useful route and means, such as by oral or parenteral (e.g., intravenous) administration. Therapeutically effective amounts of the compound may include from about 0.00001 mg/kg body weight per day to about 10 mg/kg body weight per day, such as from about 0.0001 mg/kg body weight per day to about 10 mg/kg body weight per day, or such as from about 0.001 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.01 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.05 mg/kg body weight per day to about 0.5 mg/kg body weight per day. In some embodiments, a therapeutically effective amount of the compounds provided herein include from about 0.3 mg to about 30 mg per day, or from about 30 mg to about 300 mg per day, or from about 0.3 μg to about 30 mg per day, or from about 30 μg to about 300 μg per day.

[0162] A compound of the present disclosure may be combined with one or more additional therapeutic agents in any dosage amount of the compound of the present disclosure (e.g., from 1 mg to 1000 mg of compound). Therapeutically effective amounts may include from about 0.1 mg per dose to about 1000 mg per dose, such as from about 50 mg per dose to about 500 mg per dose, or such as from about 100 mg per dose to about 400 mg per dose, or such as from about 150 mg per dose to about 350 mg per dose, or such as from about 200 mg per dose to about 300

mg per dose, or such as from about 0.01 mg per dose to about 1000 mg per dose, or such as from about 0.01 mg per dose to about 100 mg per dose, or such as from about 0.1 mg per dose to about 100 mg per dose, or such as from about 1 mg per dose to about 100 mg per dose, or such as from about 1 mg per dose to about 10 mg per dose, or such as from about 1 mg per dose to about 1000 mg per dose. Other therapeutically effective amounts of the compound of Formula I, Ia, Ib, Ic, Id, or II are about 1 mg per dose, or about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or about 100 mg per dose. Other therapeutically effective amounts of the compound of the present disclosure are about 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, or about 1000 mg per dose.

[0163] In some embodiments, the methods described herein comprise administering to the subject an initial daily dose of about 1 to 500 mg of a compound p herein and increasing the dose by increments until clinical efficacy is achieved. Increments of about 5, 10, 25, 50, or 100 mg can be used to increase the dose. The dosage can be increased daily, every other day, twice per week, once per week, once every two weeks, once every three weeks, or once a month.

[0164] When administered orally, the total daily dosage for a human subject may be between about 1 mg and 1,000 mg, between about 10-500 mg/day, between about 50-300 mg/day, between about 75-200 mg/day, or between about 100-150 mg/day. In some embodiments, the total daily dosage for a human subject may be about 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 200, 300, 400, 500, 600, 700, or 800 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 300, 400, 500, or 600 mg/day administered in a single dose.

[0165] In some embodiments, the total daily dosage for a human subject may be about 100 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human

subject may be about 150 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 200 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 250 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 300 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 350 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 400 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 450 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 500 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 550 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 600 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 650 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 700 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 750 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 800 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 850 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 900 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 950 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 1000 mg/day administered in a single dose.

[0166] A single dose can be administered hourly, daily, weekly, or monthly. For example, a single dose can be administered once every 1 hour, 2, 3, 4, 6, 8, 12, 16 or once every 24 hours. A single dose can also be administered once every 1 day, 2, 3, 4, 5, 6, or once every 7 days. A

single dose can also be administered once every 1 week, 2, 3, or once every 4 weeks. In certain embodiments, a single dose can be administered once every week. A single dose can also be administered once every month. In some embodiments, a compound disclosed herein is administered once daily in a method disclosed herein. In some embodiments, a compound disclosed herein is administered twice daily in a method disclosed herein.

[0167] The frequency of dosage of the compound of the present disclosure will be determined by the needs of the individual patient and can be, for example, once per day or twice, or more times, per day. Administration of the compound continues for as long as necessary to treat the HBV infection, HIV infection, cancer, hyper-proliferative disease, or any other indication described herein. For example, a compound can be administered to a human being infected with HBV for a period of from 20 days to 180 days or, for example, for a period of from 20 days to 90 days or, for example, for a period of from 30 days to 60 days.

[0168] Administration can be intermittent, with a period of several or more days during which a patient receives a daily dose of the compound of the present disclosure followed by a period of several or more days during which a patient does not receive a daily dose of the compound. For example, a patient can receive a dose of the compound every other day, or three times per week. Again by way of example, a patient can receive a dose of the compound each day for a period of from 1 to 14 days, followed by a period of 7 to 21 days during which the patient does not receive a dose of the compound, followed by a subsequent period (e.g., from 1 to 14 days) during which the patient again receives a daily dose of the compound. Alternating periods of administration of the compound, followed by non-administration of the compound, can be repeated as clinically required to treat the patient.

[0169] The compounds of the present disclosure or the pharmaceutical compositions thereof may be administered once, twice, three, or four times daily, using any suitable mode described above. Also, administration or treatment with the compounds may be continued for a number of

days; for example, commonly treatment would continue for at least 7 days, 14 days, or 28 days, for one cycle of treatment. Treatment cycles are well known in cancer chemotherapy, and are frequently alternated with resting periods of about 1 to 28 days, commonly about 7 days or about 14 days, between cycles. The treatment cycles, in other embodiments, may also be continuous.

VI. Combination Therapy

[0170] In certain embodiments, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents.

[0171] In one embodiment, pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent, or excipient are provided.

[0172] In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0173] In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four, or more additional therapeutic agents. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The one, two, three, four, or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

Administration of HIV Combination Therapy

[0174] In certain embodiments, a compound disclosed herein is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein and the one or more additional therapeutic agents are both present in the body of the patient. When administered sequentially, the combination may be administered in two or more administrations.

[0175] Co-administration includes administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents. For example, the compound disclosed herein may be administered within seconds, minutes, or hours of the administration of the one or more additional therapeutic agents. In some embodiments, a unit dose of a compound disclosed herein is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional

therapeutic agents. Alternatively, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein within seconds or minutes. In other embodiments, a unit dose of a compound disclosed herein is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In yet other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein.

[0176] In certain embodiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration.

[0177] In certain embodiments, a compound of Formula I, Ia, Ib, Ic, Id, or II is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can contain another active ingredient for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[0178] In certain embodiments, such tablets are suitable for once daily dosing.

HIV Combination Therapy

[0179] In the above embodiments, the additional therapeutic agent may be an anti-HIV agent. HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, immunomodulators, immunotherapeutic agents, antibody-drug conjugates,

gene modifiers, gene editors (such as CRISPR/Cas9, zinc finger nucleases, homing nucleases, synthetic nucleases, TALENs), cell therapies (such as chimeric antigen receptor T-cell, CAR-T, and engineered T cell receptors, TCR-T, autologous T cell therapies), latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, CD4 modulators, CD4 antagonists, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, CCR5 chemokine antagonists, CCR5 gene modulators, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, hyaluronidase inhibitors, Nef antagonists, Nef inhibitors, Protease-activated receptor-1 antagonists, TNF alpha ligand inhibitors, PDE4 inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, HIV vaccines, and combinations thereof.

[0180] In some embodiments, the additional therapeutic agent is selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry (fusion) inhibitors, HIV maturation inhibitors, latency

reversing agents, capsid inhibitors, immune-based therapies, PI3K inhibitors, HIV antibodies, and bispecific antibodies, and "antibody-like" therapeutic proteins, and combinations thereof.

HIV Combination Drugs

[0181] Examples of combination drugs include ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF+FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); SYMTUZA® (darunavir, tenofovir alafenamide hemifumarate, emtricitabine, and cobicistat); SYMFITM (efavirenz, lamivudine, and tenofovir disoproxil fumarate); CIMDUTM (lamivudine and tenofovir disoproxil fumarate); tenofovir and lamivudine; tenofovir alafenamide and emtricitabine; tenofovir alafenamide hemifumarate and emtricitabine; tenofovir alafenamide hemifumarate, emtricitabine, and rilpivirine; tenofovir alafenamide hemifumarate, emtricitabine, cobicistat, and elvitegravir; COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); KALETRA® (ALUVIA®; lopinavir and ritonavir); TRIUMEQ® (dolutegravir, abacavir, and lamivudine); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); atazanavir and cobicistat; atazanavir sulfate and cobicistat; atazanavir sulfate and ritonavir; darunavir and cobicistat; dolutegravir and rilpivirine; dolutegravir and rilpivirine hydrochloride; dolutegravir, abacavir sulfate, and lamivudine; lamivudine, nevirapine, and zidovudine; raltegravir and lamivudine; doravirine, lamivudine, and tenofovir disoproxil fumarate; doravirine, lamivudine, and tenofovir disoproxil; dapivirine + levonorgestrel, dolutegravir + lamivudine, dolutegravir + emtricitabine + tenofovir alafenamide, elsulfavirine + emtricitabine +

tenofovir disoproxil, lamivudine + abacavir + zidovudine, lamivudine + abacavir, lamivudine + tenofovir disoproxil fumarate, lamivudine + zidovudine + nevirapine, lopinavir + ritonavir, lopinavir + ritonavir + abacavir + lamivudine, lopinavir + ritonavir + zidovudine + lamivudine, tenofovir + lamivudine, and tenofovir disoproxil fumarate + emtricitabine + rilpivirine hydrochloride, lopinavir, ritonavir, zidovudine and lamivudine.

Other HIV Drugs

[0182] Examples of other drugs for treating HIV include acemannan, alisporivir, astodrimer, BanLec, CC-11050, deferiprone, Gamimune, griffithsin, metenkefalin, naltrexone, Prolastin, REP 9, RPI-MN, Vorapaxar, VSSP, H1viral, SB-728-T, 1,5-dicaffeoylquinic acid, rHIV7-shl-TAR-CCR5RZ, MazF gene therapy, MK-8527, BlockAide, PSC-RANTES, ABX-464, AG-1105, APH-0812, BIT-225, CYT-107, HGTV-43, HPH-116, HS-10234, IMO-3100, IND-02, MK-1376, MK-2048, MK-4250, MK-8507, MK-8591, NOV-205, PA-1050040 (PA-040), PGN-007, SCY-635, SB-9200, SCB-719, TR-452, TEV-90110, TEV-90112, TEV-90111, TEV-90113, RN-18, Immuglo, and VIR-576.

HIV Protease Inhibitors

[0183] Examples of HIV protease inhibitors include amprenavir, atazanavir, brecanavir, darunavir, fosamprenavir, fosamprenavir calcium, indinavir, indinavir sulfate, lopinavir, nelfinavir, nelfinavir mesylate, ritonavir, saquinavir, saquinavir mesylate, tipranavir, DG-17, TMB-657 (PPL-100), T-169, BL-008, MK-8122, TMB-607, and TMC-310911.

HIV Reverse Transcriptase Inhibitors

[0184] Examples of HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase include dapivirine, delavirdine, delavirdine mesylate, doravirine, efavirenz, etravirine, lentinan, MK-8583, nevirapine, rilpivirine, TMC-278LA, ACC-007, AIC-292, KM-023, PC-1005, and elsulfavirine (VM-1500).

[0185] Examples of HIV nucleoside or nucleotide inhibitors of reverse transcriptase include adefovir, adefovir dipivoxil, azvudine, emtricitabine, tenofovir, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, VIDEX® and VIDEX EC® (didanosine, ddl), abacavir, abacavir sulfate, alovudine, apricitabine, censavudine, didanosine, elvucitabine, festinavir, fosalvudine tidoxil, CMX-157, dapivirine, doravirine, etravirine, OCR-5753, tenofovir disoproxil orotate, fozivudine tidoxil, islatravir, lamivudine, phosphazid, stavudine, zalcitabine, zidovudine, rovafovir etalafenamide (GS-9131), GS-9148, MK-8504, MK-8591, MK-858, VM-2500 and KP-1461.

HIV Integrase Inhibitors

[0186] Examples of HIV integrase inhibitors include elvitegravir, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, raltegravir, dolutegravir, JTK-351, bictegravir, AVX-15567, BMS-986197, cabotegravir (long-acting injectable), diketo quinolin-4-1 derivatives, integrase-LEDGF inhibitor, ledgins, M-522, M-532, NSC-310217, NSC-371056, NSC-48240, NSC-642710, NSC-699171, NSC-699172, NSC-699173, NSC-699174, stilbenedisulfonic acid, T-169, VM-3500 and cabotegravir.

[0187] Examples of HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) include CX-05045, CX-05168, and CX-14442.

HIV Entry Inhibitors

[0188] Examples of HIV entry (fusion) inhibitors include cenicriviroc, CCR5 inhibitors, gp41 inhibitors, CD4 attachment inhibitors, DS-003 (BMS-599793), gp120 inhibitors, and CXCR4 inhibitors.

[0189] Examples of CCR5 inhibitors include aplaviroc, vicriviroc, maraviroc, cenicriviroc, leronlimab (PRO-140), adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

[0190] Examples of gp41 inhibitors include albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer and sifuvirtide.

[0191] Examples of CD4 attachment inhibitors include ibalizumab and CADA analogs.

[0192] Examples of gp120 inhibitors include Radha-108 (receptol) 3B3-PE38, BanLec, bentonite-based nanomedicine, fostemsavir tromethamine, IQP-0831, and BMS-663068.

[0193] Examples of CXCR4 inhibitors include plerixafor, ALT-1188, N15 peptide, and vMIP (Haimipu).

HIV Maturation Inhibitors

[0194] Examples of HIV maturation inhibitors include BMS-955176, BMS-986197, GSK-3640254 and GSK-2838232.

Latency Reversing Agents

[0195] Examples of latency reversing agents include histone deacetylase (HDAC) inhibitors, proteasome inhibitors such as velcade, and ixazomib citrate, protein kinase C (PKC) activators, Smyd2 inhibitors, BET-bromodomain 4 (BRD4) inhibitors, ionomycin, PMA, SAHA

(suberanilohydroxamic acid, or suberoyl, anilide, and hydroxamic acid), IL-15 modulating antibodies, JQ1, disulfiram, amphotericin B, and ubiquitin inhibitors such as largazole analogs, APH-0812, and GSK-343.

[0196] Examples of HDAC inhibitors include romidepsin, vorinostat, and panobinostat.

[0197] Examples of PKC activators include indolactam, prostratin, ingenol B, and DAG-lactones.

Capsid Inhibitors

[0198] Examples of capsid inhibitors include capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors such as azodicarbonamide, HIV p24 capsid protein inhibitors, GS-6207 (lenacapvir), AVI-621, AVI-101, AVI-201, AVI-301, and AVI-CAN1-15 series. In some embodiments, the compounds disclosed herein are used in combination with lenacapvir.

Immune-based Therapies

[0199] Examples of immune-based therapies include toll-like receptors modulators such as tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12, and tlr13; programmed cell death protein 1 (Pd-1) modulators; programmed death-ligand 1 (Pd-L1) modulators; IL-15 modulators; DermaVir; interleukin-7; plaquenil (hydroxychloroquine); proleukin (aldesleukin, IL-2); interferon alfa; interferon alfa-2b; interferon alfa-n3; pegylated interferon alfa; interferon gamma; hydroxyurea; mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF); ribavirin;polymer polyethyleneimine (PEI); gepon; IL-12; WF-10; VGV-1; MOR-22; BMS-936559; CYT-107, interleukin-15/Fc fusion protein, AM-0015, ALT-803, NIZ-985, NKTR-255, NKTR-262, NKTR-214, normferon, peginterferon alfa-2a, peginterferon alfa-2b, recombinant interleukin-15, Xmab-24306, RPI-MN, , STING modulators, RIG-I modulators, NOD2 modulators, SB-9200, and IR-103.

[0200] Examples of TLR agonists: vesatolimod (GS-9620), GS-986, IR-103, lefitolimod, tilsotolimod, rintatolimod, DSP-0509, AL-034, G-100, cobitolimod, AST-008, motolimod, GSK-1795091, GSK-2245035, VTX-1463, GS-9688, LHC-165, BDB-001, RG-7854, telratolimod.RO-7020531.

Phosphatidylinositol 3-kinase (PI3K) Inhibitors

[0201] Examples of PI3K inhibitors include idelalisib, alpelisib, buparlisib, CAI orotate, copanlisib, duvelisib, gedatolisib, neratinib, panulisib, perifosine, pictilisib, pilaralisib, puquitinib mesylate, rigosertib, rigosertib sodium, sonolisib, taselisib, AMG-319, AZD-8186, BAY-1082439, CLR-1401, CLR-457, CUDC-907, DS-7423, EN-3342, GSK-2126458, GSK-2269577, GSK-2636771, INCB-040093, LY-3023414, MLN-1117, PQR-309, RG-7666, RP-6530, RV-1729, SAR-245409, SAR-260301, SF-1126, TGR-1202, UCB-5857, VS-5584, XL-765, and ZSTK-474.

Alpha-4/beta-7 antagonists

[0202] Examples of Integrin alpha-4/beta-7 antagonists include PTG-100, TRK-170, abrilumab, etrolizumab, carotegrast methyl, and vedolizumab.

HIV Antibodies, Bispecific Antibodies, and "Antibody-like" Therapeutic Proteins

[0203] Examples of HIV antibodies, bispecific antibodies, and "antibody-like" therapeutic proteins include DARTs®, DUOBODIES®, BITES®, XmAbs®, TandAbs®, Fab derivatives, bispecific antibodies, trispecific antibodies, multivalent antibodies, bnABs (broadly neutralizing HIV-1 antibodies), BMS-936559, TMB-360, and those targeting HIV gp120 or gp41, antibody-recruiting Molecules targeting HIV, anti-CD63 monoclonal antibodies, CD3 bispecific antibodies, CD16 bispecific antibodies, anti-GB virus C antibodies, anti-GP120/CD4, CCR5 bispecific antibodies, anti-Nef single domain antibodies, anti-Rev antibody, camelid derived anti-CD18 antibodies, camelid-derived anti-ICAM-1 antibodies, DCVax-001, gp140 targeted

antibodies, gp41-based HIV therapeutic antibodies, human recombinant mAbs (PGT-121), ibalizumab, Immuglo, MB-66.

[0204] Examples of those targeting HIV in such a manner include bavituximab, UB-421, C2F5, 2G12, C4E10, C2F5+C2G12+C4E10, 8ANC195, 3BNC117, 3BNC117-LS, 3BNC60, D1D2, 10-1074, 10-1074-LS, GS-9722, DH411-2, BG18, PGT145, PGT121, PGT122, PGT-151, PGT-133, PGT-135, PGT-128, MDX010 (ipilimumab), DH511, DH511-2, N6, N6LS, N49P6, N49P7, N49P7.1, N49P9, N49P11, N60P1.1, N60P25.1, N60P2.1, N60P31.1, N60P22, NIH 45-46, PG9, PG16, 8ANC195, 2Dm2m, 4Dm2m, 6Dm2m, VRC-01, VRC-01-LS, PGDM1400, A32, 7B2, 10E8, 10E8VLS, 3810109, 10E8v4, 10E8.4/iMab, VRC-01/PGDM-1400/10E8v4, IMC-HIV, iMabm36, 10E8v4/PGT121-VRC01, eCD4-Ig, IOMA, CAP256-VRC26.25, DRVIA7, SAR-441236, VRC-07-523, VRC07-523LS, VRC-HIVMAB080-00-AB, VRC-HIVMAB060-00-AB, P2G12, and VRC07. Examples of HIV bispecific antibodies include MGD014, TMB-bispecific.

[0205] Example of in vivo delivered bnABs such as AAV8-VRC07; mRNA encoding anti-HIV antibody VRC01.

Pharmacokinetic Enhancers

[0206] Examples of pharmacokinetic enhancers include cobicistat and ritonavir.

Additional Therapeutic Agents

[0207] Examples of additional therapeutic agents include the compounds disclosed in WO 2004/096286 (Gilead Sciences), WO 2006/015261 (Gilead Sciences), WO 2006/110157 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2013/006738 (Gilead Sciences), WO 2013/159064 (Gilead Sciences), WO 2014/100323 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), US 2014/0221378 (Japan Tobacco), US 2014/0221380 (Japan Tobacco), WO 2009/062285

(Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/006792 (Pharma Resources), US 20140221356 (Gilead Sciences), US 20100143301 (Gilead Sciences) and WO 2013/091096 (Boehringer Ingelheim).

HIV Vaccines

[0208] Examples of HIV vaccines include peptide vaccines, recombinant subunit protein vaccines, live vector vaccines using viral vectors such as arenavirus, lymphocytic choriomeningitis virus (LCMV), pichinde virus, modified vaccinia Ankara virus (MVA), adenovirus, adeno-associated virus (AAV), vesicular stomatitis virus (VSV) and Chimpanzee adenovirus (ChAd), DNA vaccines, CD4-derived peptide vaccines, vaccine combinations, BG505 SOSIP.664 gp140, rgp120 (AIDSVAX), ALVAC HIV, (vCP1521)/AIDSVAX B/E (gp120) (RV144), monomeric gp120 HIV-1 subtype C vaccine, Remune, ITV-1, Contre Vir, Ad4-Env145NFL, Ad5-ENVA-48, HB-500, DCVax-001 (CDX-2401), Vacc-4x, Vacc-C5, Vacc-CRX, VVX-004, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAd5), rAd5 gag-pol env A/B/C vaccine, Pennvax-G, Pennvax-GP/MVA-CMDR, HIV-TriMix-mRNA vaccine, HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, TatImmune, GTU-multiHIV (FIT-06), gp140[delta]V2.TV1+MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, ad35-Grin/ENV, TBC-M4, HIVAX, HIVAX-2, NYVAC-HIV-PT1, NYVAC-HIV-PT4, DNA-HIV-PT123, rAAV1-PG9DP, GOVX-B11, GOVX-B21, TVI-HIV-1, Ad-4 (Ad4-env Clade C+Ad4-mGag), Paxvax, EN41-UGR7C, EN41-FPA2, PreVaxTat, AE-H, MYM-V101, CombiHIVvac, ADVAX, MYM-V201, MVA-CMDR, DNA-Ad5 gag/pol/nef/nev (HVTN505), MVATG-17401, ETV-01, CDX-1401, rcAD26.MOS1.HIV-Env, Ad26.Mod.HIV vaccine, Ad26.Mod.HIV + MVA mosaic vaccine + gp140, AGS-004, AVX-101, AVX-201, PEP-6409, SAV-001, ThV-01, TL-01, TUTI-16, VGX-3300, IHV-001, and virus-like particle vaccines such as pseudovirion vaccine, CombiVICHvac, LFn-p24 B/C fusion vaccine, GTU-based DNA vaccine, HIV gag/pol/nef/env DNA vaccine,

anti-TAT HIV vaccine, conjugate polypeptides vaccine, dendritic-cell vaccines, gag-based DNA vaccine, GI-2010, gp41 HIV-1 vaccine, HIV vaccine (PIKA adjuvant), I i-key/MHC class II epitope hybrid peptide vaccines, ITV-2, ITV-3, ITV-4, LIPO-5, multiclade Env vaccine, MVA vaccine, Pennvax-GP, pp71-deficient HCMV vector HIV gag vaccine, recombinant peptide vaccine (HIV infection), NCI, rgp160 HIV vaccine, RNActive HIV vaccine, SCB-703, Tat Oyi vaccine, TBC-M4, therapeutic HIV vaccine, UBI HIV gp120, Vacc-4x + romidepsin, variant gp120 polypeptide vaccine, rAd5 gag-pol env A/B/C vaccine, DNA.HTI, DNA.HTI and MVA.HTI, VRC-HIVDNA016-00-VP + VRC-HIVADV014-00-VP, INO-6145, JNJ-9220, gp145 C.6980; eOD-GT8 60mer based vaccine, PD-201401, env (A, B, C, A/E)/gag (C) DNA Vaccine, gp120 (A,B,C,A/E) protein vaccine, PDPHV-201401, Ad4-EnvCN54, EnvSeq-1 Envs HIV-1 vaccine (GLA-SE adjuvanted), HIV p24gag prime-boost plasmid DNA vaccine, arenavirus vector-based immunotherapies (Vaxwave, TheraT), MVA-BN HIV-1 vaccine regimen, MVA.tHIVconsv4, MVA.tHIVconsv3, UBI HIV gp120, mRNA based prophylactic vaccines, TBL-1203HI, VRC-HIVRGP096-00-VP, VAX-3S, HIV MAG DNA vaccine,

HIV Combination Therapy

[0209] In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four or more additional therapeutic agents selected from ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF +FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); adefovir; adefovir dipivoxil; cobicistat; emtricitabine; tenofovir; tenofovir disoproxil; tenofovir disoproxil fumarate; tenofovir alafenamide; tenofovir alafenamide

hemifumarate; TRIUMEQ® (dolutegravir, abacavir, and lamivudine); dolutegravir, abacavir sulfate, and lamivudine; raltegravir; raltegravir and lamivudine; maraviroc; enfuvirtide; ALUVIA® (KALETRA®; lopinavir and ritonavir); COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); rilpivirine; rilpivirine hydrochloride; atazanavir sulfate and cobicistat; atazanavir and cobicistat; darunavir and cobicistat; atazanavir; atazanavir sulfate; dolutegravir; elvitegravir; ritonavir; atazanavir sulfate and ritonavir; darunavir; lamivudine; prolastin; fosamprenavir; fosamprenavir calcium efavirenz; etravirine; nelfinavir; nelfinavir mesylate; interferon; didanosine; stavudine; indinavir; indinavir sulfate; tenofovir and lamivudine; zidovudine; nevirapine; saquinavir; saquinavir mesylate; aldesleukin; zalcitabine; tipranavir; amprenavir; delavirdine; delavirdine mesylate; Radha-108 (receptol); lamivudine and tenofovir disoproxil fumarate; efavirenz, lamivudine, and tenofovir disoproxil fumarate; phosphazid; lamivudine, nevirapine, and zidovudine; abacavir; and abacavir sulfate.

[0210] It will be appreciated by one of skill in the art that the additional therapeutic agents listed above may be included in more than one of the classes listed above. The particular classes are not intended to limit the functionality of those compounds listed in those classes.

[0211] In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a

pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[0212] In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

[0213] In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

[0214] In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

[0215] In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

[0216] A compound as disclosed herein (e.g., any compound of Formula I, Ia, Ib, Ic, Id, or II) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formula I, Ia, Ib, Ic, Id, or II (e.g., from 1 mg to 500 mg of compound).

[0217] In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 5-10, 5-15, 5-20, 5-25, 25-30, 20-30, 15-30, or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula I) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0218] In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 200-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 200-250, 200-300, 200-350, 250-350, 250-400, 350-400, 300-400, or 250-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a

pharmaceutically acceptable salt thereof, is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula I) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0219] In one embodiment, kits comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

Birth control (contraceptive) combination therapy

[0220] Therapeutic agents used for birth control (contraceptive) include cyproterone acetate, desogestrel, dienogest, drospirenone, estradiol valerate, ethinyl Estradiol, ethynodiol, etonogestrel, levomefolate, levonorgestrel, lynestrenol, medroxyprogesterone acetate, mestranol, mifepristone , misoprostol, nomegestrol acetate, norelgestromin, norethindrone, noretynodrel, norgestimate, ormeloxifene, segestersone acetate, ulipristal acetate, and any combinations thereof.

Gene Therapy and Cell Therapy

[0221] Gene Therapy and Cell Therapy including the genetic modification to silence a gene; genetic approaches to directly kill the infected cells; the infusion of immune cells designed to replace most of the patient's own immune system to enhance the immune response to infected cells, or activate the patient's own immune system to kill infected cells, or find and kill the infected cells; genetic approaches to modify cellular activity to further alter endogenous immune responsiveness against the infection.

[0222] Examples of dendritic cell therapy include AGS-004.

[0223] Example of CCR5 gene editing drugs such as SB-728T.

[0224] Example of CCR5 gene inhibitors such as Cal-1.

[0225] C34-CCR5/C34-CXCR4 expressing CD4-positive T cells.

[0226] AGT-103-transduced autologous T cell therapy.

[0227] AAV-eCD4-Ig gene therapy.

Gene Editors

[0228] The genome editing system is selected from the group consisting of: a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system, a homing endonucleases system, and a meganuclease system.

[0229] Examples of HIV targeting CRISPR/Cas9 systems include EBT-101.

CAR-T cell therapy

[0230] A population of immune effector cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an HIV antigen-binding domain. The HIV antigen include an HIV envelope protein or a portion thereof, gp120 or a portion thereof, a CD4 binding site on gp120, the CD4-induced binding site on gp120, N glycan on gp120, the V2 of gp120, the membrane proximal region on gp41. The immune effector cell is a T cell or an NK cell. In some embodiments, the T cell is a CD4+ T cell, a CD8+ T cell, or a combination thereof. Cells can be autologous or allogeneic.

[0231] Examples of HIV CAR-T include VC-CAR-T, anti-CD4 CART cell therapy, autologous hematopoietic stem cells genetically engineered to express a CD4 CAR and the C46 peptide.

TCR-T cell therapy

[0232] TCR-T cells are engineered to target HIV derived peptides present on the surface of virus-infected cells.

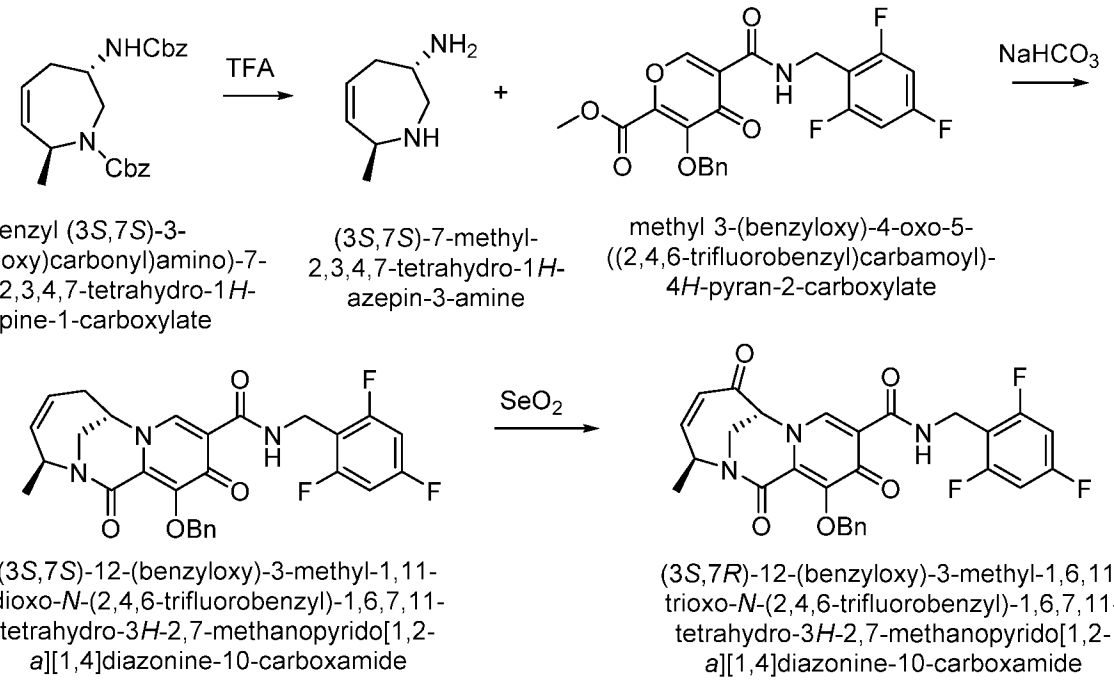
VII. Examples

[0233] Exemplary chemical entities of the present disclosure are provided in the specific examples that follow. Those skilled in the art will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Furthermore, one of skill in the art will recognize that the transformations shown in the schemes below may be performed in any order that is compatible with the functionality of the particular pendant groups.

[0234] The Examples provided herein describe the synthesis of compounds disclosed herein as well as intermediates used to prepare the compounds. It is to be understood that individual steps described herein may be combined. It is also to be understood that separate batches of a compound may be combined and then carried forth in the next synthetic step.

[0235] In the following description of the Examples, specific embodiments are described. These embodiments are described in sufficient detail to enable those skilled in the art to practice certain embodiments of the present disclosure. Other embodiments may be utilized and logical and other changes may be made without departing from the scope of the disclosure. The following description is, therefore, not intended to limit the scope of the present disclosure.

Intermediate A: (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



benzyl (3*S*,7*S*)-3-(((benzyloxy)carbonyl)amino)-7-methyl-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate

(3*S*,7*S*)-7-methyl-2,3,4,7-tetrahydro-1*H*-azepin-3-amine

methyl 3-(benzyloxy)-4-oxo-5-((2,4,6-trifluorobenzyl)carbamoyl)-4*H*-pyran-2-carboxylate

(3*S*,7*S*)-12-(benzyloxy)-3-methyl-1,11-dioxo-*N*-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3*H*-2,7-methanopyrido[1,2-*a*][1,4]diazonine-10-carboxamide

(3*S*,7*R*)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-*N*-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3*H*-2,7-methanopyrido[1,2-*a*][1,4]diazonine-10-carboxamide

Synthesis of (3S,7S)-7-methyl-2,3,4,7-tetrahydro-1H-azepin-3-amine:

[0236] Trifluoacetic acid (20 mL) was added to benzyl (3S,7S)-3-(((benzyloxy)carbonyl)amino)-7-methyl-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate (6.2 g, 15.7 mmol) and the reaction was heated to 100 °C for 4 hours. The reaction mixture was concentrated down and the crude was used directly in next step.

Synthesis of (3S,7S)-12-(benzyloxy)-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

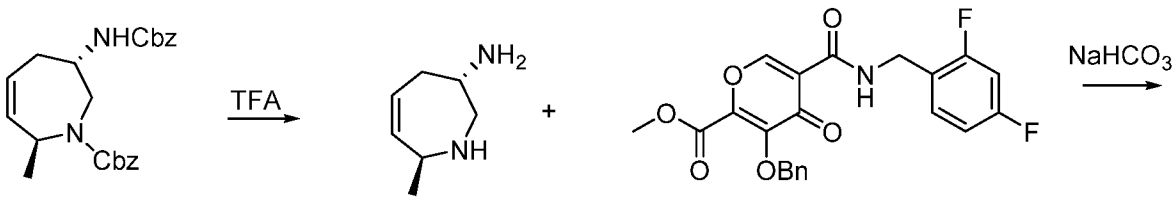
[0237] Methanol (300 mL) and water (30 mL) were added to methyl 3-(benzyloxy)-4-oxo-5-((2,4,6-trifluorobenzyl)carbamoyl)-4H-pyran-2-carboxylate (6.75 g, 15.7 mmol) and (3S,7S)-7-methyl-2,3,4,7-tetrahydro-1H-azepin-3-amine (the reaction crude from the previous step). At room temperature, $NaHCO_3$ (13.2 g, 157 mmol) was added to the reaction mixture. The reaction

was stirred at. room temperature overnight, then heat to 60 °C for 5 hours. The reaction mixture was concentrated down, then added ethyl acetate, washed with saturated ammonium chloride solution. The organic layer was concentrated an d purified via silica chromatograph (eluting with 0-10% MeOH/DCM) to give (3S,7S)-12-(benzyloxy)-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 524.11 $[M+H]^+$.

Synthesis of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0238] Selenium dioxide (17.4 g, 157 mmol.) was added to (3S,7S)-12-(benzyloxy)-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (product of previous step, 15.7 mmol) in dioxane (160 mL). Then the reaction was heated to 105 °C overnight. The reaction mixture was cooled down and the solid was filtered off the solid. The filtrate was extracted using ethyl acetate and saturated ammonium chloride solution. The organic layer was concentrated and purified via silica chromatograph (eluting with 40-100% Ethyl acetate/hexane) to give (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 538.095 $[M+H]^+$.

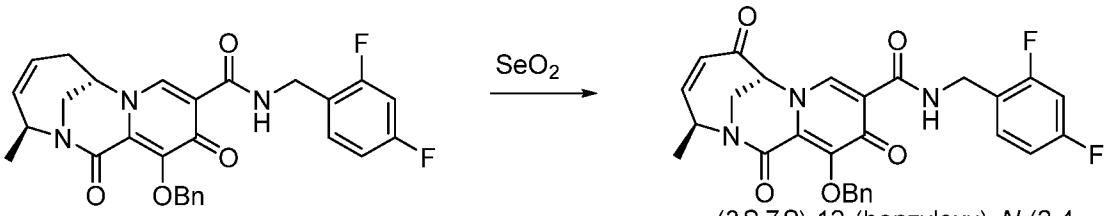
Intermediate B: (3S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



benzyl (3*S*,7*S*)-3-(((benzyloxy)carbonyl)amino)-7-methyl-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate

(3*S*,7*S*)-7-methyl-2,3,4,7-tetrahydro-1*H*-azepin-3-amine

methyl 3-(benzyloxy)-5-((2,4-difluorobenzyl)carbamoyl)-4-oxo-4*H*-pyran-2-carboxylate

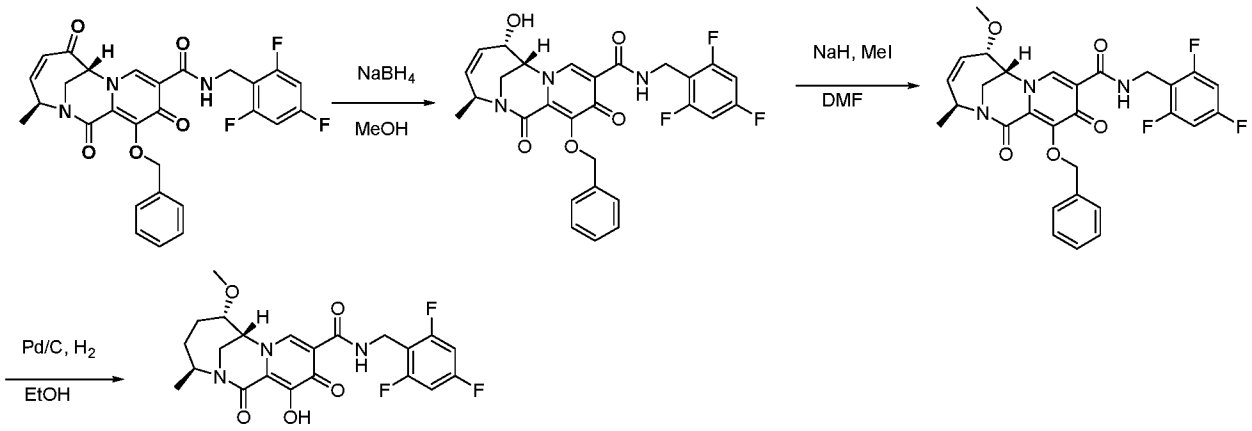


(3*S*,7*S*)-12-(benzyloxy)-*N*-(2,4-difluorobenzyl)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3*H*-2,7-methanopyrido[1,2-*a*][1,4]diazonine-10-carboxamide

(3*S*,7*S*)-12-(benzyloxy)-*N*-(2,4-difluorobenzyl)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3*H*-2,7-methanopyrido[1,2-*a*][1,4]diazonine-10-carboxamide

[0239] This intermediate was prepared by following the procedure of making (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (intermediate A), except that methyl 3-(benzyloxy)-5-((2,4-difluorobenzyl)carbamoyl)-4-oxo-4H-pyran-2-carboxylate was used in the 2nd step. MS (*m/z*) 520.200 $[M+H]^+$.

Example 1: (3S,6S,7R)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Preparation of (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide :

[0240] To a solution of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (intermediate A) (122 mg, 0.227 mmol) in methanol (5 mL) was added cerium (III) chloride heptahydrate (85 mg, 0.227 mmol). Then to the mixture was added sodium borohydride (2.1 mg, 0.057 mmol) slowly at 0°C. After 5 min, the reaction was quenched by adding sat. $NaHCO_3$ solution and extracted with DCM. The organic phase was separated and concentrated down. The residue was then dissolved in DCM, washed with brine. The organic phase was dried over $MgSO_4$, filtered, concentrated down and further used without purification.

Preparation of (3S,6S,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0241] To a solution of (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (16 mg, 0.030 mmol) in DMF (1 mL) was added sodium hydride (1.8 mg, 0.045 mmol, 60%) and iodomethane (2.8 uL, 0.045 mmol). The reaction mixture was stirred at room temperature for half an hour. The reaction was quenched by adding sat. $NaHCO_3$, extracted with EtOAc, the organic phase was separated, dried over $MgSO_4$, filtered, concentrated down and to the resulting product was used in next step without further purification.

Preparation of (3S,6S,7R)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

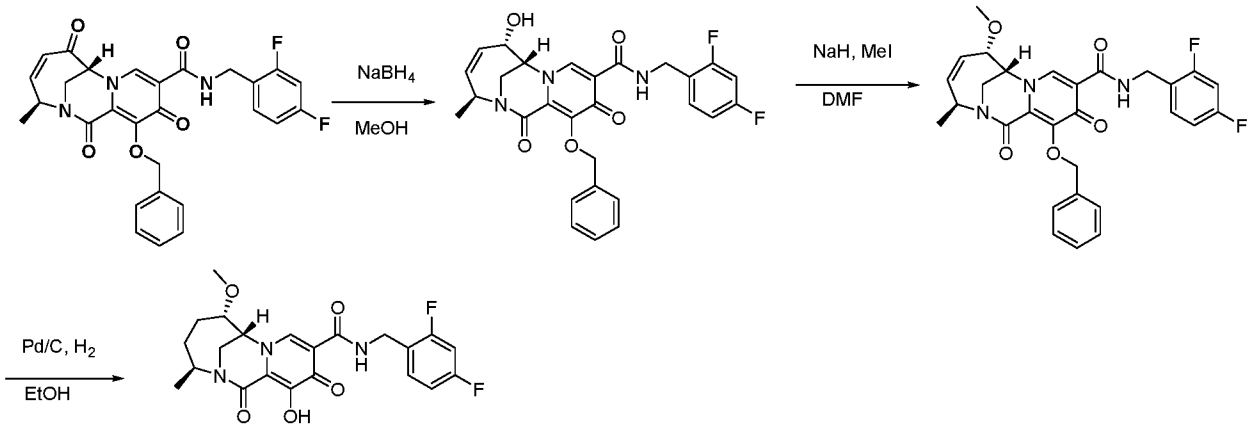
[0242] To a solution of (3S,6S,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (15 mg, 0.018 mmol) in ethanol (1 mL), was added palladium on carbon (10 mg). The reaction was stirred under H_2 balloon for half an hour. The reaction mixture was filtered through celite. The filtrated was concentrated down and the residue was purified by reverse phase HPLC chromatography (eluting with 5-100% acetonitrile in water, containing 0.1% TFA) to give the title product. MS (*m/z*) 466.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.34 (s, 1H), 6.98 – 6.85 (m, 2H), 4.74 (s, 1H), 4.68 (s, 2H), 4.66 – 4.58 (m, 1H), 3.80 – 3.69 (m, 2H), 3.55 (d, J = 11.8 Hz, 1H), 3.46 (s, 3H), 2.18 – 1.99 (m, 3H), 1.61 – 1.49 (m, 1H), 1.28 (d, J = 6.7 Hz, 3H), 1.00 (dt, J = 14.9, 11.6 Hz, 1H).

Example 2: (3S,6S,7R)-6,12-dihydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide

[0243] To a solution of (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-

carboxamide (10 mg, 0.018 mmol) in ethanol (1 mL), was added palladium on carbon (10 mg). The reaction was stirred under H_2 balloon for half an hour. The reaction mixture was filtered through celite. The filtrated was concentrated down and the residue was purified by reverse phase HPLC chromatography (eluting with 5-100% acetonitrile in water, containing 0.1% TFA) to give the title product. MS (*m/z*) 452.3 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.40 (s, 1H), 6.98 – 6.86 (m, 2H), 4.68 (s, 2H), 4.67 – 4.60 (m, 1H), 4.56 (s, 1H), 4.02 – 3.90 (m, 1H), 3.75 (s, 2H), 2.07 (dt, J = 14.5, 7.1 Hz, 1H), 1.81 (ddd, J = 14.8, 7.6, 3.8 Hz, 1H), 1.59 (dt, J = 15.0, 11.3 Hz, 1H), 1.28 (d, J = 6.7 Hz, 3H), 1.19 (dt, J = 14.8, 11.7 Hz, 1H).

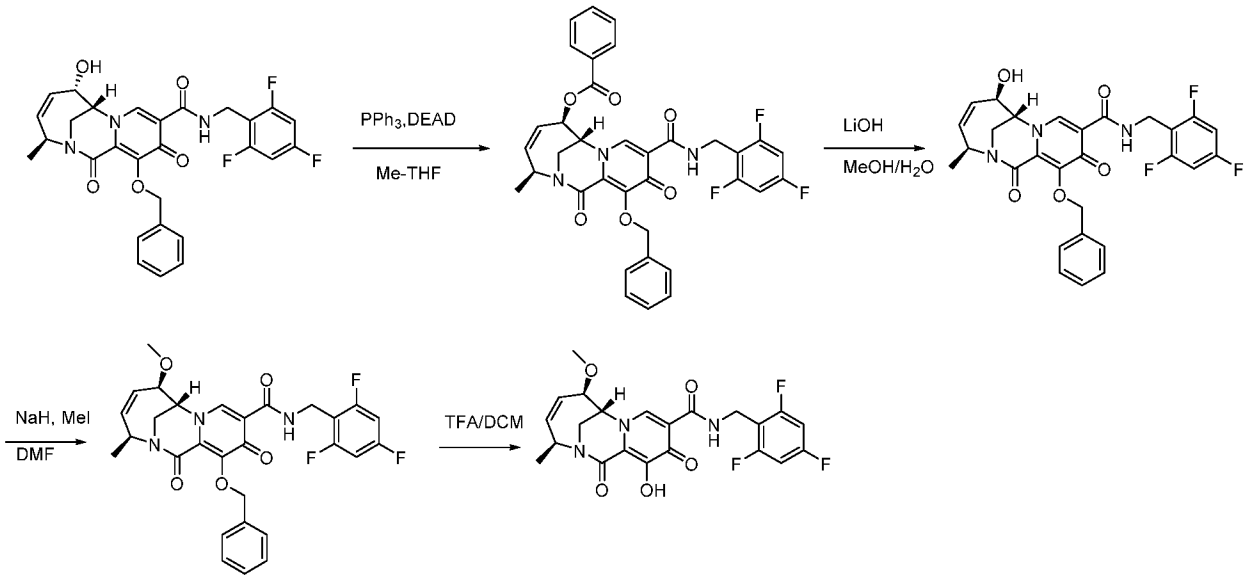
Example 3: (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0244] (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was made similar to Example 1, except that (3S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (intermediate B) was used instead of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (intermediate A). MS (*m/z*) 448.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.37 (s, 1H), 7.45 (q, J = 7.8 Hz, 1H), 7.09 – 6.88 (m, 2H), 4.65 (s, 4H), 3.75 (s, 2H), 3.56 (d, J =

11.1 Hz, 1H), 3.46 (s, 3H), 2.18 – 1.98 (m, 2H), 1.54 (dd, J = 25.7, 11.4 Hz, 1H), 1.29 (d, J = 6.6 Hz, 3H), 1.01 (q, J = 12.1 Hz, 1H).

Example 4: (3S,6R,7R)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Preparation of (3S,6R,7R)-12-(benzyloxy)-3-methyl-1,11-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonin-6-yl benzoate:

[0245] To a solution of (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (29 mg, 0.054 mmol) in Me-THF (3 mL), was added benzoic acid (16 mg, 0.134 mmol), triphenylphosphine (35 mg, 0.134 mmol) and diisopropyl axodicarboxylate (27.2 mg, 0.134 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, the organic phase was separated, dried over $MgSO_4$, filtered, concentrated down and purified by silica gel column chromatography (0-100% EtOAc/hexane) to give the title product (30 mg).

Preparation of (3S,6R,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0246] The reaction mixture of (3S,6R,7R)-12-(benzyloxy)-3-methyl-1,11-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonin-6-yl benzoate (30 mg, 0.047 mmol), $LiOH.H_2O$ (5.6 mg, 0.233 mmol) in MeOH (2 mL) and H_2O (0.5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated down. The residue was washed with brine, extracted with EtOAc, the organic phase was separated, dried over $MgSO_4$, filtered, concentrated down and used in next step without purification.

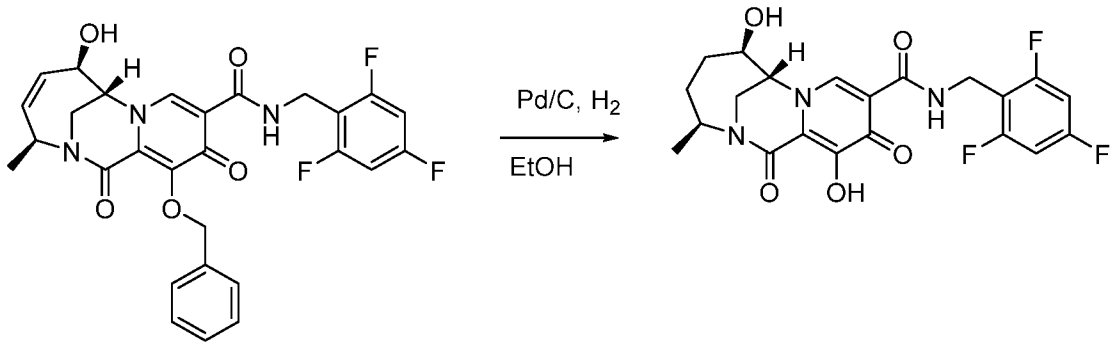
Preparation of (3S,6R,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0247] To a solution of (3S,6R,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (20 mg, 0.037 mmol) in DMF (1 mL) was added sodium hydride (1.8 mg, 0.045 mmol, 60%) and iodomethane (3.5 uL, 0.056 mmol). The reaction mixture was stirred at room temperature for half an hour. The reaction was quenched by adding sat. $NaHCO_3$, extracted with EtOAc, the organic phase was separated, dried over $MgSO_4$, filtered, concentrated down and go to next step without purification.

Preparation of (3S,6R,7R)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0248] The reaction mixture of (3S,6R,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide in DCM (1 mL) and TFA (1 mL) was stirred at rt for 3 h. The reaction mixture was concentrated down. The residue was purified by reverse phase HPLC chromatography (eluting with 5-100% acetonitrile in water, containing 0.1% TFA) to give the title compound. MS (*m/z*) 464.1 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.45 (s, 1H), 6.98 – 6.85 (m, 2H), 5.77 (dt, J = 11.8, 2.8 Hz, 1H), 5.56 (ddd, J = 11.9, 2.7, 1.7 Hz, 1H), 5.33 (dq, J = 7.6, 2.8 Hz, 1H), 4.69 (s, 2H), 4.59 (s, 1H), 4.27 (dq, J = 5.7, 3.0 Hz, 1H), 4.11 (d, J = 13.7 Hz, 1H), 3.65 (d, J = 14.4 Hz, 1H), 3.32 (s, 3H), 1.39 (d, J = 7.2 Hz, 3H).

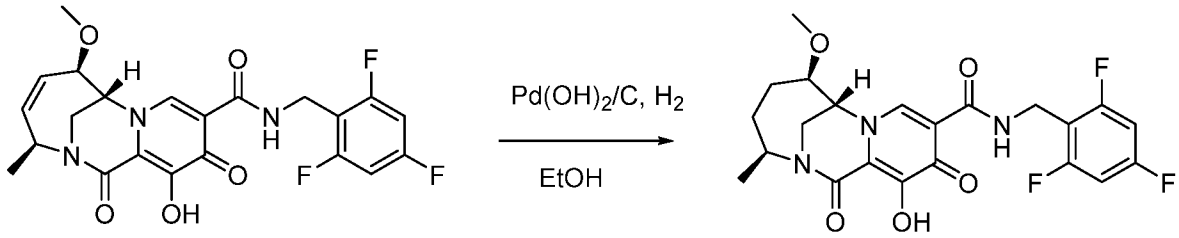
Example 5: (3S,6R,7R)-6,12-dihydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0249] To a solution of (3S,6R,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (10 mg, 0.018 mmol) in ethanol (1 mL), was added palladium on carbon (10 mg). The reaction was stirred under H_2 balloon for half an hour. The reaction mixture was filtered through celite. The filtrated was concentrated down and the residue was purified by reverse phase HPLC chromatography (eluting with 5-100% acetonitrile in water, containing 0.1% TFA) to give the title product. MS (*m/z*) 452.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.46 (s, 1H), 6.99 – 6.85 (m, 2H), 4.68 (s, 2H), 4.58 (dt, J = 10.7, 6.5 Hz, 1H), 4.40 (s, 1H), 4.04 (d, J =

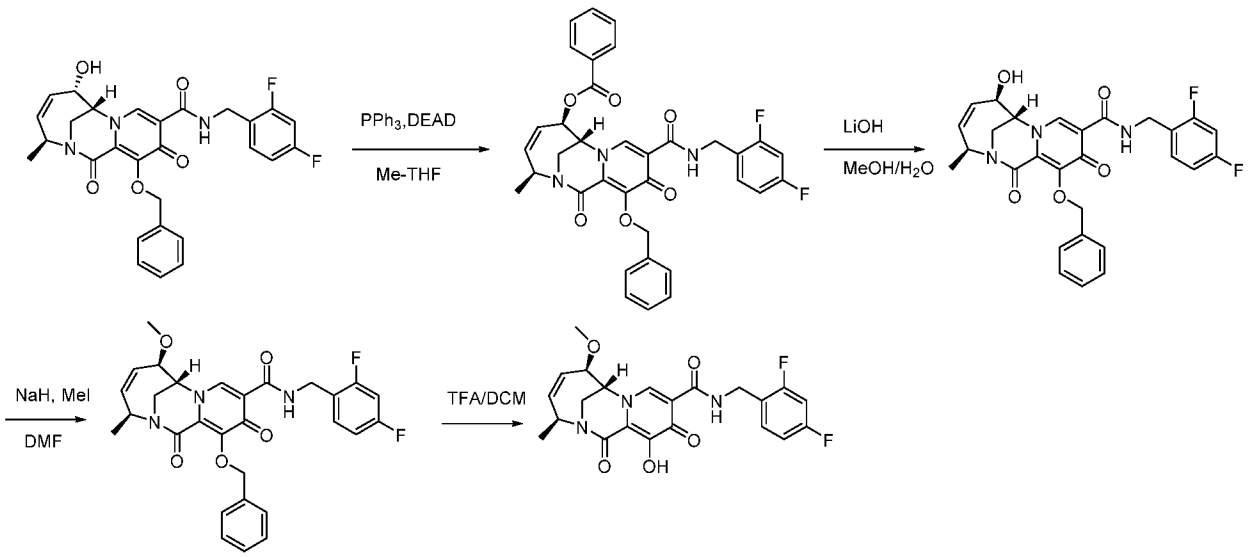
3.9 Hz, 1H), 3.81 (d, J = 14.8 Hz, 1H), 3.69 (d, J = 14.7 Hz, 1H), 2.01 (dd, J = 14.5, 11.3 Hz, 1H), 1.95 – 1.79 (m, 2H), 1.38 – 1.30 (m, 1H), 1.29 (d, J = 6.6 Hz, 3H).

Example 6: (3S,6R,7R)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



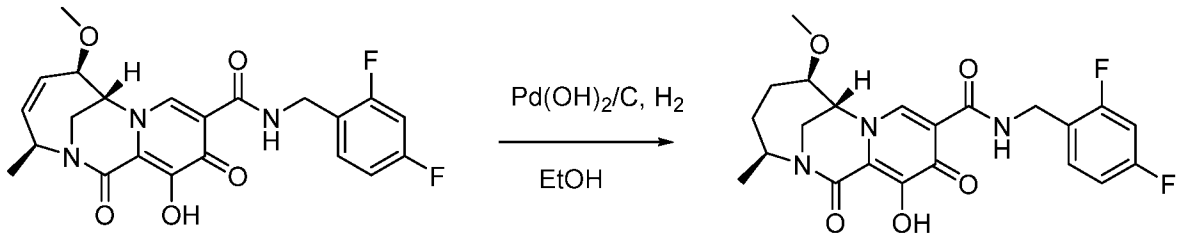
[0250] To a solution of (3S,6R,7R)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (Example 4) (18 mg, 0.039 mmol) in EtOH (2 mL) was added $Pd(OH)_2/C$ (10 mg). The reaction mixture was stirred at rt for half an hour with attachment of H_2 balloon. The reaction mixture was filtered through celite, the filtrate was concentrated down and the residue was purified by reverse phase chromatography (eluting with 5-100% acetonitrile in water, containing 0.1% TFA) to give the title product. MS (*m/z*) 466.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.37 (s, 1H), 7.45 (q, J = 7.8 Hz, 1H), 7.09 – 6.88 (m, 2H), 4.65 (s, 4H), 3.75 (s, 2H), 3.56 (d, J = 11.1 Hz, 1H), 3.46 (s, 3H), 2.18 – 1.98 (m, 2H), 1.54 (dd, J = 25.7, 11.4 Hz, 1H), 1.29 (d, J = 6.6 Hz, 3H), 1.01 (q, J = 12.1 Hz, 1H). 1H NMR (400 MHz, Methanol-d4) δ 8.51 (s, 1H), 6.98 – 6.85 (m, 2H), 4.68 (s, 2H), 4.66 – 4.50 (m, 2H), 3.75 (d, J = 14.9 Hz, 1H), 3.72 – 3.60 (m, 2H), 3.48 (s, 3H), 2.09 (dt, J = 15.0, 4.6 Hz, 1H), 1.86 (td, J = 9.6, 2.7 Hz, 2H), 1.28 (d, J = 6.7 Hz, 3H), 1.24 – 1.15 (m, 1H).

Example 7: (3S,6R,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



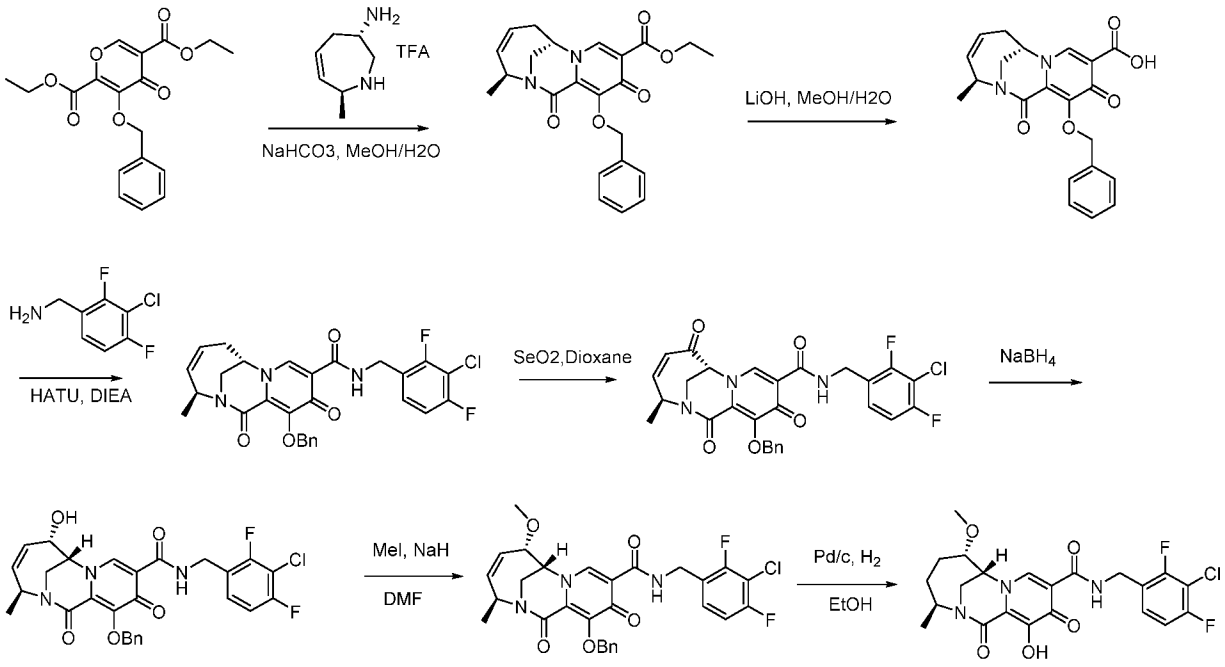
[0251] (3S,6R,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was prepared in similar method to prepare (3S,6R,7R)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (Example 4) except that (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (see Example 3) was used instead of (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 446.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.47 (s, 1H), 7.45 (td, J = 8.4, 6.3 Hz, 1H), 7.03 – 6.90 (m, 2H), 5.77 (dt, J = 11.8, 2.8 Hz, 1H), 5.56 (ddd, J = 11.8, 2.7, 1.7 Hz, 1H), 5.34 (dq, J = 7.4, 2.8 Hz, 1H), 4.67 – 4.56 (m, 3H), 4.29 (dq, J = 5.6, 2.9 Hz, 1H), 4.11 (dd, J = 14.4, 3.0 Hz, 1H), 3.65 (d, J = 14.2 Hz, 1H), 3.34 (s, 3H), 1.39 (d, J = 7.3 Hz, 3H).

Example 8: (3S,6R,7R)-6,12-dihydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0252] To a solution of (3S,6R,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (Example 7) (20 mg, 0.045 mmol) in EtOH (2 mL) was added $Pd(OH)_2/C$ (7 mg). The reaction mixture was stirred at room temperature for half an hour with attachment of H_2 balloon. The reaction mixture was filtered through celite, the filtrated was concentrated down and the residue was purified by reverse phase chromatography (eluting with 5-100% acetonitrile in water, containing 0.1% TFA) to give the title product. MS (*m/z*) 448.3 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.53 (s, 1H), 7.50 – 7.40 (m, 1H), 6.97 (dddd, J = 12.6, 11.1, 8.9, 2.6 Hz, 2H), 4.65 (s, 2H), 4.62 – 4.52 (m, 2H), 3.80 – 3.59 (m, 3H), 3.48 (s, 3H), 2.10 (dt, J = 15.1, 4.6 Hz, 1H), 1.85 (tt, J = 9.4, 5.2 Hz, 2H), 1.36 – 1.16 (m, 4H).

Example 9: (3S,6S,7R)-N-(3-chloro-2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Preparation of ethyl (3S,7S)-12-(benzyloxy)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxylate:

[0253] A reaction mixture of (3S,7S)-7-methyl-2,3,4,7-tetrahydro-1H-azepin-3-amine (0.39 g, 3.1 mmol), (diethyl 3-(benzyloxy)-4-oxo-4H-pyran-2,5-dicarboxylate (1.07 g, 3.09 mmol) and sodium bicarbonate (2.6 g, 30.9 mmol) in MeOH (10 mL) and water (2 mL) was stirred at rt overnight. Then the reaction mixture was stirred at 60 °C for 8 h. The reaction mixture was cooled and concentrated down. The residue was washed with water, extracted with EtOAc. The organic phase was separated, dried over $MgSO_4$, filtered, concentrated down and purified by silica gel chromatography, eluting by 0-100% hexane/EtOAc to give title compound.

Preparation of (3S,7S)-12-(benzyloxy)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxylic acid:

[0254] A reaction mixture of ethyl (3S,7S)-12-(benzyloxy)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxylate (1.02g, 2.5 mmol) and sodium hydroxide (2N, 3.75 mL) in MeOH (5 mL) was stirred at 60 °C for 1 h. The reaction mixture is cooled and concentrated down. The residue was dissolved in water, using HCl to adjust the pH to 4, extracted with EtOAc. The organic phase was separated, dried over $MgSO_4$, filtered, concentrated down and used in next reaction without further purification

Preparation of (3S,7S)-12-(benzyloxy)-N-(3-chloro-2,4-difluorobenzyl)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0255] To a solution of (3S,7S)-12-(benzyloxy)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxylic acid (0.88g, 2.31 mmol) in DCM (10 mL) was added diisopropylethylamine (1.61 mL, 9.25 mmol) and 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (0.88g, 2.31 mmol) at 0 °C. The reaction mixture was stirred at 0°C for 2h. The reaction mixture was washed with sat. $NaHCO_3$, extracted with EtOAc, the organic phase was separated, dried over $MgSO_4$, filtered, concentrated down and purified by silica gel chromatography, eluting by 0-100% hexane/EtOAc to give titled compound.

Preparation of (3S,7R)-12-(benzyloxy)-N-(3-chloro-2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

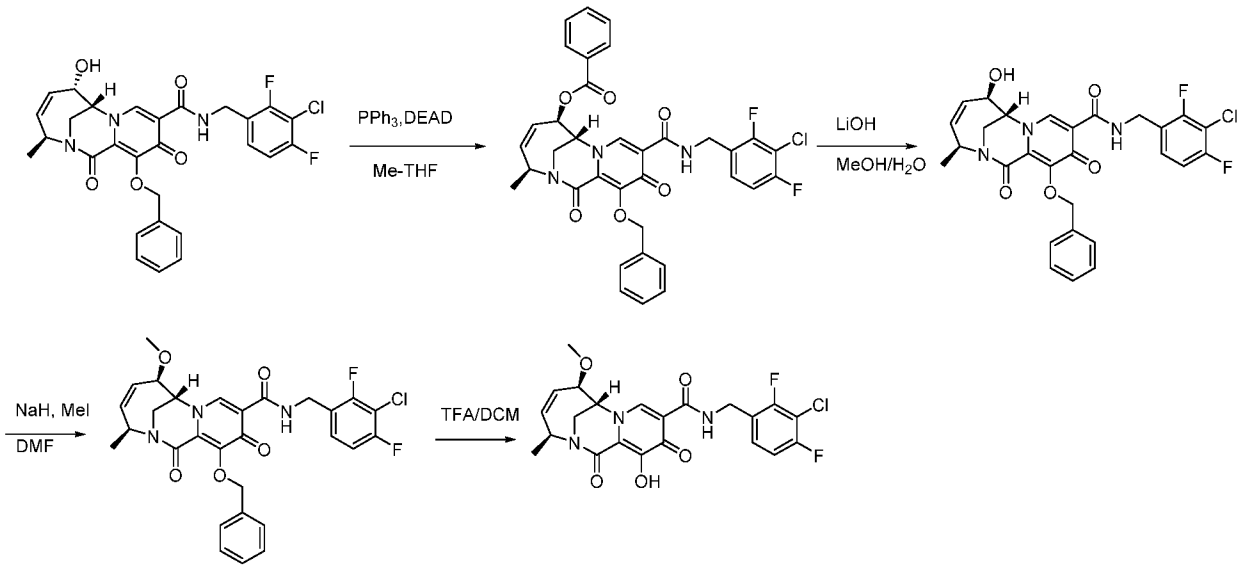
[0256] The reaction mixture of (3S,7S)-12-(benzyloxy)-N-(3-chloro-2,4-difluorobenzyl)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (0.48 g, 0.89 mmol) and selenium dioxide (0.986 g, 8.9 mmol) in dioxane was stirred at 100 °C overnight. The reaction mixture was cooled down and filtered to remove solid. The filtrate was diluted with EtOAc, washed with sat. NaHCO3. The organic phase was dried

over $MgSO_4$, filtered, concentrated down and purified by silica gel chromatography, eluting with 0-100% hexane/EtOAc to give titled compound .

Preparation of (3S,6S,7R)-N-(3-chloro-2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

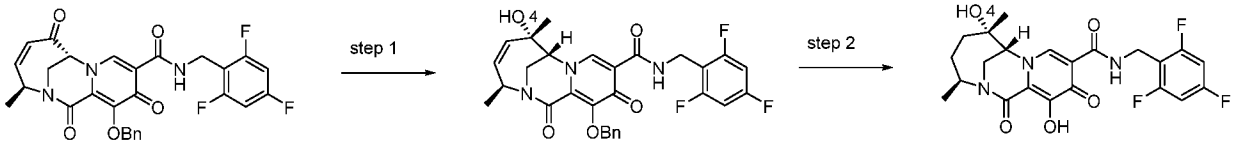
[0257] (3S,6S,7R)-N-(3-chloro-2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was prepared in similar method to make Example 1, except that (3S,7R)-12-(benzyloxy)-N-(3-chloro-2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was used instead of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (intermediate A). MS (*m/z*) 482.4 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.35 (s, 1H), 7.40 (td, J = 8.4, 6.0 Hz, 1H), 7.11 (td, J = 8.7, 1.9 Hz, 1H), 4.74 (s, 1H), 4.71 – 4.57 (m, 3H), 3.83 – 3.67 (m, 2H), 3.61 – 3.50 (m, 1H), 3.46 (s, 3H), 2.18 – 1.98 (m, 3H), 1.54 (dt, J = 14.4, 11.2 Hz, 1H), 1.28 (d, J = 6.7 Hz, 3H), 1.01 (dt, J = 14.9, 11.7 Hz, 1H).

Example 10: (3S,6R,7R)-N-(3-chloro-2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0258] (3S,6R,7R)-N-(3-chloro-2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was prepared in similar method to make Example 4, except that (3S,6S,7R)-12-(benzyloxy)-N-(3-chloro-2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was used instead of (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 480.2 $[M+H]^+$. ^1H NMR (400 MHz, Acetonitrile-d3) δ 10.38 (s, 1H), 8.35 (s, 1H), 7.39 (q, J = 8.1 Hz, 1H), 7.18 – 7.04 (m, 1H), 5.72 (dq, J = 8.7, 2.8 Hz, 1H), 5.63 – 5.48 (m, 1H), 5.30 (s, 1H), 4.73 – 4.60 (m, 3H), 4.46 (s, 1H), 4.27 (s, 1H), 4.01 (dd, J = 14.4, 2.9 Hz, 1H), 3.58 (d, J = 14.4 Hz, 1H), 3.29 (d, J = 4.3 Hz, 3H), 1.34 (d, J = 7.3 Hz, 3H).

Example 11. (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Synthesis of (3S,6S,7R)-6,12-dihydroxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide :

[0259] (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (132mg, 0.246 mmol) was dissolved in anhydrous THF (3.0 mL) and the resulting mixture was cooled to -20 °C. To this stirred cold mixture was added 3.0 M ether solution of methyl magnesium bromide (0.41 mL, 1.23 mmol). After stirring for 20 minutes, the reaction was quenched with saturated NH_4Cl. The mixture was extracted with EtOAc, the organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The resulting product was purified by normal phase chromatography (4 g silica gel, 0-100% EtOAc/Hexanes). LCMS-ESI+ (m/z): calcd H+ for $C_{29}H_{26}F_3N_3O_5$, Theoretical: 553.18, Found: 553.95.

Synthesis of (1R,10S,13S)-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide:

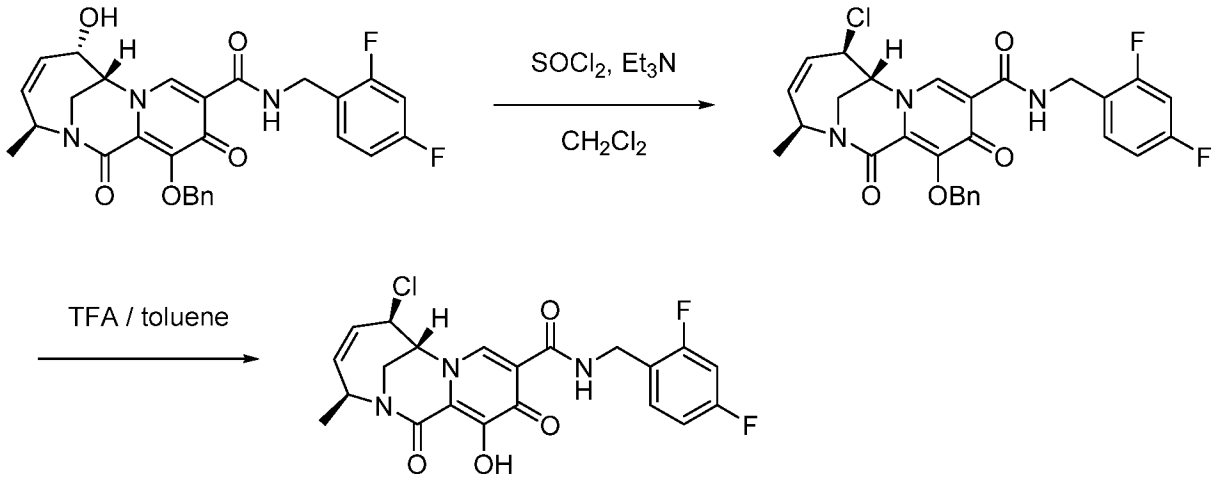
[0260] (3S,6S,7R)-6,12-dihydroxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (20.0mg, 0.0361 mmol) was dissolved in MeOH (15.0 mL) at room temperature and treated with 7 mg of 20% $Pd(OH)_2/C$ (50 wt% water). The mixture was degassed and flushed with hydrogen 3 times before it was hydrogenated under hydrogen balloon for overnight. The reaction was then

degassed and flushed with nitrogen, filtered through a pad of Celite, concentrated, the resulting residue was redissolved in DMF, filtered and purified by reverse phase HPLC. LCMS-ESI+ (m/z): calcd H+ for $C_{22}H_{22}F_3N_3O_5$, Theoretical: 465.15, Found: 466.24. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 10.46 (t, J = 5.8 Hz, 1H), 8.31 (s, 1H), 7.21 (t, J = 8.6 Hz, 2H), 4.93 (s, 1H), 4.62 – 4.41 (m, 3H), 4.26 (s, 1H), 3.66 (d, J = 2.5 Hz, 2H), 1.91 – 1.81 (m, 1H), 1.41 (dd, J = 14.6, 7.7 Hz, 2H), 1.34 (s, 3H), 1.17 (d, J = 6.6 Hz, 4H).

Example 12: [(3S,6S,7R)-N-(2,4-difluorobenzyl)-6,12-dihydroxy-3,6-dimethyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide]

[0261] This compound was prepared by following the same sequence as for the synthesis of Example 11 except in step 1, (3S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was used instead of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. Stereochemistry not confirmed . LCMS-ESI+ (m/z): calcd H+ for C22H23F2N3O5, Theoretical: 447.16, Found: 448.22. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 10.46 (t, J = 6.0 Hz, 1H), 8.34 (s, 1H), 7.40 (td, J = 8.7, 6.7 Hz, 1H), 7.25 (ddd, J = 10.6, 9.3, 2.6 Hz, 1H), 7.12 – 7.03 (m, 1H), 5.03 – 4.83 (m, 1H), 4.56 (d, J = 5.9 Hz, 2H), 4.47 (dt, J = 12.2, 6.5 Hz, 1H), 4.28 (s, 1H), 3.67 (d, J = 3.2 Hz, 2H), 1.87 (dt, J = 14.3, 7.1 Hz, 1H), 1.42 (dd, J = 14.4, 7.7 Hz, 2H), 1.35 (s, 3H), 1.25 – 1.12 (m, 4H).

Example 13: Preparation of (3S,6R,7R)-6-chloro-N-(2,4-difluorobenzyl)-12-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



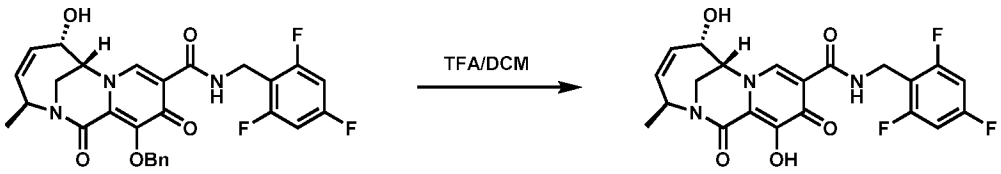
Preparation of (3S,6R,7R)-12-(benzyloxy)-6-chloro-N-(2,4-difluorobenzyl)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0262] To a solution (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (110 mg, 0.211 mmol) in DCM (27 mL) under N_2 was added triethylamine (1.18 mL, 8.44 mmol) and thionyl chloride (0.615 mL, 8.44 mmol). After 5 min, the reaction was quenched by adding sat. $NaHCO_3$ solution and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated down and purified by flash column chromatography on silica gel using DCM/MeOH as a solvent system (1:0 -> 95:5 -> 8:2 gradient) to afford (3S,6R,7R)-12-(benzyloxy)-6-chloro-N-(2,4-difluorobenzyl)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide as a red/brown solid (111 mg, 98%).

Preparation (3S,6R,7R)-6-chloro-N-(2,4-difluorobenzyl)-12-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0263] A solution (3S,6R,7R)-12-(benzyloxy)-6-chloro-N-(2,4-difluorobenzyl)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (63 mg, 0.116 mmol) in toluene/TFA (1:1) (10 mL) was stirred at room temperature for 2.75h. The reaction was quenched with saturated aqueous sodium bicarbonate until the pH was greater than 7. EtOAc was added and the layers were separated. The aqueous layer was washed with EtOAc. Then combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated down and purified by reverse phase HPLC chromatography (eluting with 5-100% acetonitrile in water, containing 0.1% TFA) to give the title product (34 mg, 65%). MS (*m/z*) 450.100 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 8.50 (s, 1H), 7.46-7.40 (m, 1H), 6.99-6.91 (m, 2H), 5.76 (dt, J = 11.9, 3.1 Hz, 1H), 5.55 (dt, J = 11.9, 2.3 Hz, 1H), 5.35-5.33 (m, 1H), 5.13 (s, 1H), 4.98 (s, 1H), 4.63 (s, 2H), 4.20 (d, J = 14.5 Hz, 1H), 3.73 (d, J = 14.5 Hz, 1H), 1.39 (d, J = 7.3 Hz, 3H).

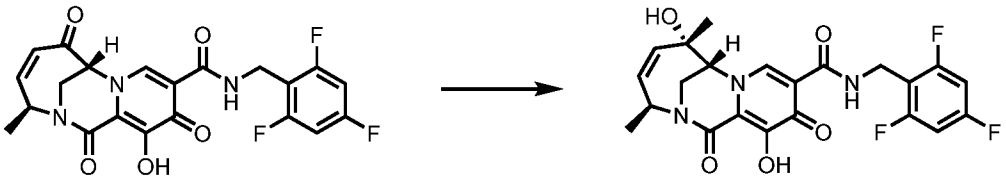
Example 14: (3S,6S,7R)-6,12-dihydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0264] (3S,6S,7R)-6,12-dihydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was prepared in a similar manner as Example 4 except using (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (prepared according to Example 1) instead of (3S,6R,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 449.1 $[M+H]^+$. 1H NMR

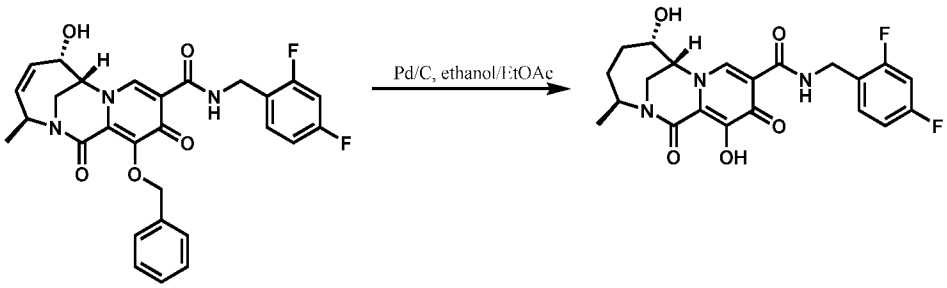
(400 MHz, MeOD) δ 8.45 (s, 1H), 6.91 (t, J = 8.4 Hz, 2H), 5.85 (ddd, J = 11.9, 6.1, 2.3 Hz, 1H), 5.63 (dd, J = 11.9, 2.7 Hz, 1H), 5.33 (d, J = 7.4 Hz, 1H), 4.70 (d, J = 7.8 Hz, 2H), 4.4 (m, 1H), 4.05 – 3.87 (m, 1H), 3.73 (d, J = 14.6 Hz, 1H), 3.03 (m, 2H), 1.39 (d, J = 7.3 Hz, 3H).

Example 15: Preparation of (1R,10S,13S)-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide



[0265] (1R,10S)-6-hydroxy-10-methyl-5,8,13-trioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide (15 mg, 0.0335 mmol) was dissolved in THF (0.5 mL) and cooled to -78 °C. To this stirred cold mixture was added 3.0 M MeMgBr in diethylether (0.056 mL, 0.168 mmol) dropwise. The resulting mixture was stirred at -78 °C for 5 minute and then was warmed up to 0 °C for 5 minutes. The reaction was quenched with acetic acid, filtered and purified by reverse phase prep HPLC. LCMS-ESI+ (m/z): calcd H+ for C22H20F3N3O5, Theoretical: 463.14, Found: 464.02. 1H NMR (400 MHz, DMSO-d6) δ 10.46 (t, J = 5.8 Hz, 1H), 8.36 (s, 1H), 7.25 – 7.23 (m, 1H), 7.22 – 7.19 (m, 2H), 5.54 (dd, J = 11.9, 2.3 Hz, 1H), 5.39 (dd, J = 11.8, 2.6 Hz, 1H), 5.18 – 5.08 (m, 1H), 4.68 (s, 1H), 4.59 – 4.55 (m, 3H), 3.86 (dd, J = 14.7, 2.6 Hz, 1H), 3.63 (d, J = 14.2 Hz, 1H), 1.38 (s, 3H), 1.27 (d, J = 7.3 Hz, 3H).

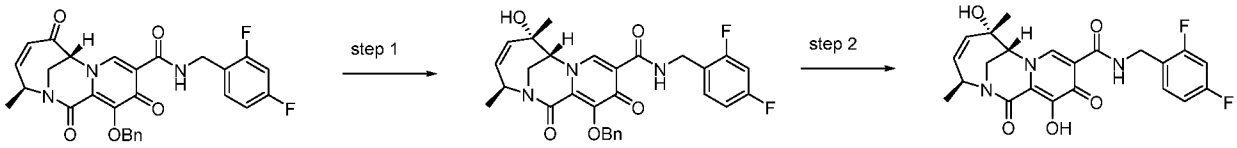
Example 16: (3S,6S,7R)-N-(2,4-difluorobenzyl)-6,12-dihydroxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Synthesis of (3S,6S,7R)-N-(2,4-difluorobenzyl)-6,12-dihydroxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0266] (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (10 mg, 0.019 mmol), was dissolved in 3 mL of ethanol and 3 ml of ethyl acetate and was sparged under an argon atmosphere. Palladium on carbon (10 wt%, wet) E101 NE/W (4.08 mg, 0.0038 mmol) was added. The mixture was sparged under a hydrogen atmosphere (1 atm, balloon) and stirred vigorously for two hours, then sparged under an argon atmosphere. It was filtered through a pad of Celite®. The Celite® was washed with absolute ethanol and the filtrate was concentrated to dryness. The residue was purified by RP-HPLC to afford the title compound. MS (m/z): 434.113 [M+H]+. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.43 (s, 1H), 7.56 – 7.31 (m, 1H), 7.03 – 6.91 (m, 2H), 4.70 – 4.55 (m, 4H), 3.95 (dt, J = 11.8, 4.4 Hz, 1H), 3.76 (d, J = 1.8 Hz, 2H), 2.14 – 2.01 (m, 1H), 1.82 (ddd, J = 14.7, 7.6, 3.8 Hz, 1H), 1.59 (dt, J = 15.0, 11.3 Hz, 1H), 1.28 (d, J = 6.7 Hz, 3H), 1.27 – 1.13 (m, 1H).

Example 17: Preparation of (1R,10S,13S)-N-[(2,4-difluorophenyl)methyl]-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide



Step 1: Synthesis of (1R,10S,13S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-13-hydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide:

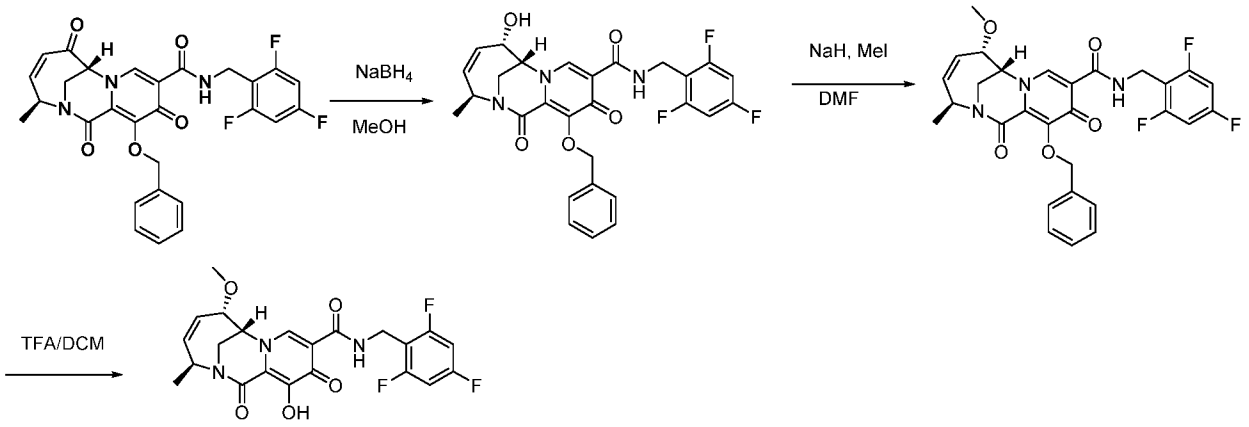
[0267] The compound was prepared by following step 1 for the synthesis of Example 11, except in step 1 , (3S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was used instead of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. LCMS-ESI+ (m/z): calcd H+ for C29H27F2N3O5, Theoretical: 535.19, Found: 535.94.

Step 2: Synthesis of (1R,10S,13S)-N-[(2,4-difluorophenyl)methyl]-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide:

[0268] (1R,10S,13S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-13-hydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide from step 1 (13.0 mg, 0.0243 mmol) was treated with a mixture of DCM (0.2 mL) and TFA (0.2 mL) at room temperature for 4 hrs. The reaction was concentrated, redissolved in DMF, filtered and purified by reverse phase prep HPLC. LCMS-ESI+ (m/z): calcd H+ for C22H21F2N3O5, Theoretical: 445.14, Found: 446.04. 1H NMR (400 MHz, Acetone-d6) δ 10.51 (s, 1H), 8.38 (s, 1H), 7.49 (q, J = 8.3 Hz, 1H), 7.08 – 6.95 (m, 2H), 6.25 (s, 1H), 5.74 (dd, J = 11.9, 2.5 Hz, 1H), 5.53 (dd, J = 11.8, 2.5 Hz, 1H), 5.35 – 5.23 (m, 1H), 4.79 – 4.69 (m, 2H), 4.63 (d, J = 6.0 Hz,

2H), 4.12 (dd, J = 14.7, 2.7 Hz, 1H), 3.85 (dd, J = 14.6, 1.8 Hz, 1H), 1.60 (s, 3H), 1.39 (d, J = 7.3 Hz, 3H).

Example 18: (3S,6S,7R)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Preparation of (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide :

[0269] To a solution of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (intermediate A) (122 mg, 0.227 mmol) in methanol (5 mL) was added cerium (III) chloride heptahydrate (85 mg, 0.227 mmol). Then to the mixture was added sodium borohydride (2.1 mg, 0.057 mmol) slowly at 0 °C. After 5 min, the reaction was quenched by adding saturated $NaHCO_3$ solution and extracted with DCM. The organic phase was separated and concentrated down. The residue was then dissolved in DCM, washed with brine. The organic phase was dried over $MgSO_4$, filtered, concentrated down and further used without purification.

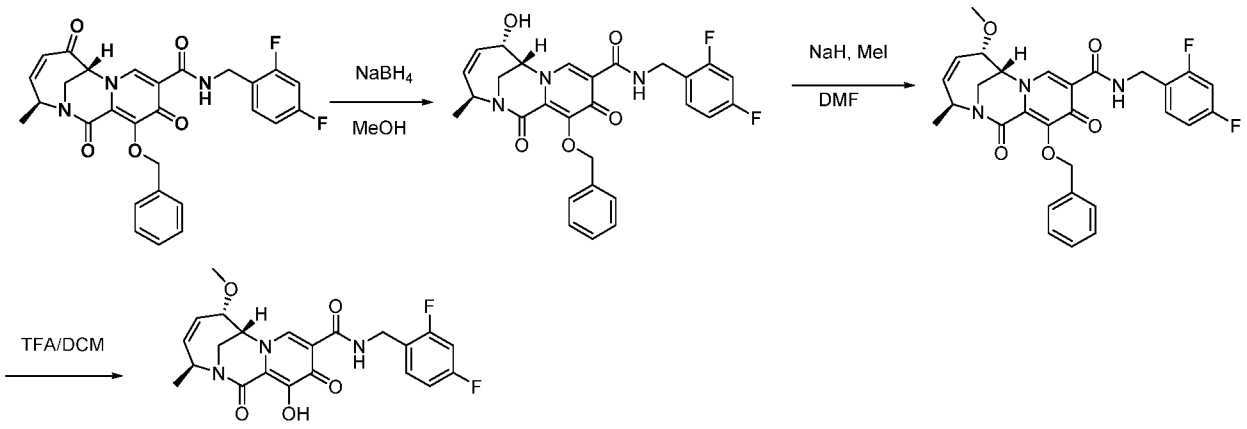
Preparation of (3S,6S,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0270] To a solution of (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (16 mg, 0.030 mmol) in DMF (1 mL) was added sodium hydride (1.8 mg, 0.045 mmol, 60%) and iodomethane (2.8 uL, 0.045 mmol). The reaction mixture was stirred at room temperature for half an hour. The reaction was quenched by adding saturated $NaHCO_3$, extracted with EtOAc, the organic phase was separated, dried over $MgSO_4$, filtered, concentrated down and the resulting product was used in next step without further purification.

Preparation of (3S,6S,7R)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

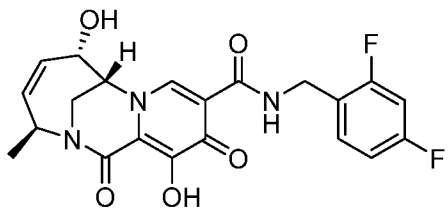
[0271] The reaction mixture of (3S,6S,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (16 mg, 0.029 mmol) in TFA (1 mL) and DCM (1 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated down and the residue was purified by reverse phase HPLC chromatography (eluting with 5-100% acetonitrile in water, containing 0.1% TFA) to give the title product. MS (*m/z*) 464.16 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.47 (s, 1H), 6.98 – 6.85 (m, 2H), 6.00 (ddd, J = 11.6, 6.6, 2.6 Hz, 1H), 5.75 (dd, J = 11.6, 2.0 Hz, 1H), 5.27 (qt, J = 7.4, 2.4 Hz, 1H), 5.00 (d, J = 7.3 Hz, 1H), 4.69 (s, 2H), 4.29 (t, J = 7.0 Hz, 1H), 3.96 (dd, J = 14.6, 2.5 Hz, 1H), 3.66 (d, J = 14.5 Hz, 1H), 3.12 (s, 3H), 1.39 (d, J = 7.4 Hz, 3H).

Example 19: (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



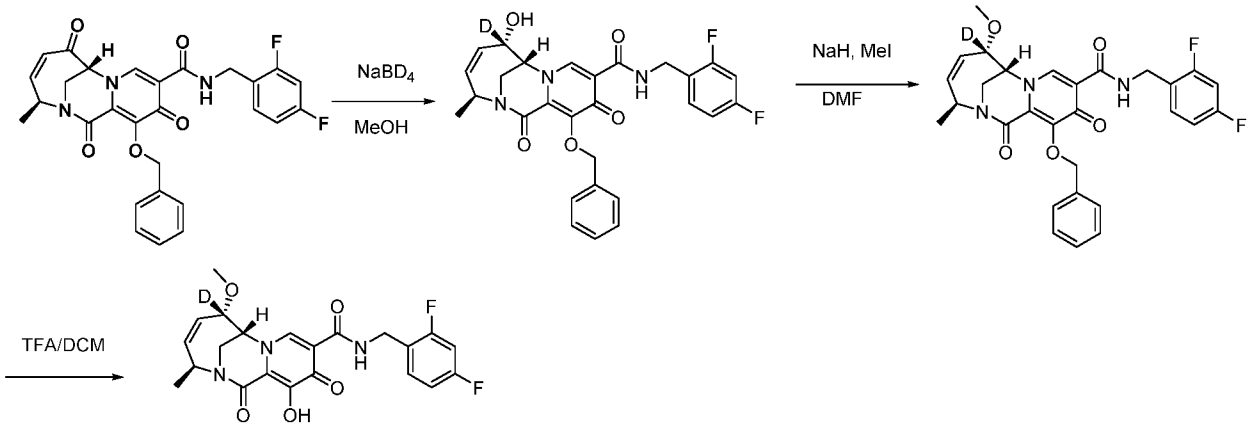
[0272] (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was made similar to Example 18, except that (3S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was used instead of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 446.22 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.50 (s, 1H), 7.45 (td, J = 8.4, 6.3 Hz, 1H), 7.04 – 6.90 (m, 2H), 6.00 (ddd, J = 11.6, 6.6, 2.6 Hz, 1H), 5.76 (dd, J = 11.7, 2.0 Hz, 1H), 5.28 (tdt, J = 7.4, 4.7, 2.4 Hz, 1H), 5.00 (d, J = 6.9 Hz, 1H), 4.65 (s, 2H), 4.29 (t, J = 7.0 Hz, 1H), 3.97 (dd, J = 14.6, 2.4 Hz, 1H), 3.66 (d, J = 14.5 Hz, 1H), 3.13 (s, 3H), 1.39 (d, J = 7.3 Hz, 3H).

Example 20: (3S,6S,7R)-N-(2,4-difluorobenzyl)-6,12-dihydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0273] (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (10 mg, 0.19 mmol), prepared according to Example 3, was dissolved in 1 mL of toluene and 1 mL of TFA. It was stirred at room temperature for 1 hour and concentrated to dryness. The residue was purified by RP-HPLC to afford the title compound. MS (*m/z*): 432.124 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.49 – 10.39 (m, 2H), 8.42 (s, 1H), 7.41 (td, J = 8.7, 6.6 Hz, 1H), 7.25 (ddd, J = 10.5, 9.3, 2.6 Hz, 1H), 7.07 (td, J = 8.5, 2.6 Hz, 1H), 5.67 (ddd, J = 11.9, 5.6, 2.1 Hz, 1H), 5.57 – 5.48 (m, 2H), 5.20 – 5.12 (m, 1H), 4.93 (d, J = 7.3 Hz, 1H), 4.58 (dd, J = 13.2, 6.2 Hz, 3H), 3.83 (dd, J = 14.8, 2.4 Hz, 1H), 3.68 (dd, J = 14.7, 2.0 Hz, 1H), 1.28 (d, J = 7.3 Hz, 3H).

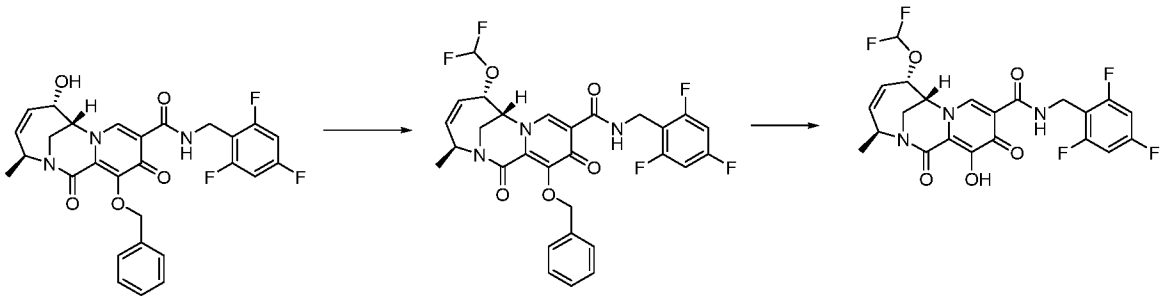
Example 21: (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-6-d-10-carboxamide



[0274] (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-6-d-10-carboxamide was made similar to Example 18, except that sodium borodeuteride was used instead of sodium borohydride and that (3S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was used instead of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 447.2 $[M+H]^+$. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.50 (s, 1H), 7.45 (td, J = 8.4, 6.4 Hz, 1H), 7.04 –

6.90 (m, 2H), 6.00 (dd, J = 11.6, 2.7 Hz, 1H), 5.76 (dd, J = 11.6, 2.0 Hz, 1H), 5.28 (dddd, J = 9.9, 7.6, 4.9, 2.5 Hz, 1H), 5.00 (s, 1H), 4.65 (s, 2H), 3.96 (dd, J = 14.6, 2.7 Hz, 1H), 3.66 (d, J = 14.4 Hz, 1H), 3.12 (s, 3H), 1.39 (d, J = 7.3 Hz, 3H).

Example 22: (3S,6S,7R)-6-(difluoromethoxy)-12-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



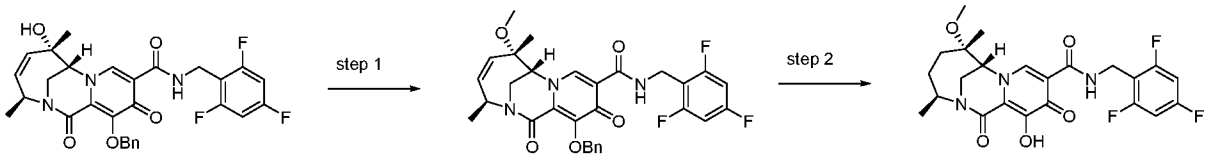
Step 1: Synthesis of (3S,6S,7R)-12-(benzyloxy)-6-(difluoromethoxy)-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0275] (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (60 mg, 0.11 mmol) was dissolved in 1 mL of acetonitrile, and copper iodide (4.24 mg, 0.022 mmol) was added. The mixture was heated to 50 °C, and a solution of 2-fluorosulfonyl-2,2-difluoroacetic acid (0.017 mL, 0.17 mmol) in 1 mL of acetonitrile was added dropwise. The reaction mixture was heated for 10 minutes at 50 °C. Then cooled to 0 °C, ethyl acetate was added, washed with saturated sodium bicarbonate aqueous solution and brine. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated to dryness. the residue was purified by RP-HPLC to afford the title product. MS (m/z): 590.200 [M+H]+.

Step 2: Synthesis of (3S,6S,7R)-6-(difluoromethoxy)-12-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0276] (3S,6S,7R)-12-(benzyloxy)-6-(difluoromethoxy)-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (10 mg) was dissolved in 0.5 ml of toluene and 0.5 ml of TFA, stirred at room temperature for 1.5 hour, then removed the solvent and purified by RP-HPLC to afford the title product. MS (m/z): 500.100 [M+H]+. 1H NMR (400 MHz, Methanol-d4) δ 10.54 (s, 1H), 8.46 (s, 1H), 6.92 (t, J = 8.4 Hz, 2H), 6.25 (t, J = 73.1 Hz, 1H), 5.95 – 5.86 (m, 1H), 5.79 (dd, J = 11.8, 2.3 Hz, 1H), 5.35 (d, J = 7.5 Hz, 1H), 5.27 (t, J = 7.0 Hz, 1H), 5.10 (d, J = 7.5 Hz, 1H), 4.68 (s, 3H), 3.98 (d, J = 14.5 Hz, 1H), 3.74 (d, J = 14.6 Hz, 1H), 1.41 (d, J = 7.3 Hz, 3H).

Example 23: (3S,6S,7R)-12-hydroxy-6-methoxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Synthesis of (3S,6S,7R)-12-(benzyloxy)-6-methoxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0277] (3S,6S,7R)-6,12-dihydroxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (product from Step 1 of Example 11, 25 mg, 0.045 mmol) was dissolved in anhydrous DMF (0.90 mL) and the resulting mixture was cooled to 0 °C. To this stirred cold mixture was added 60%

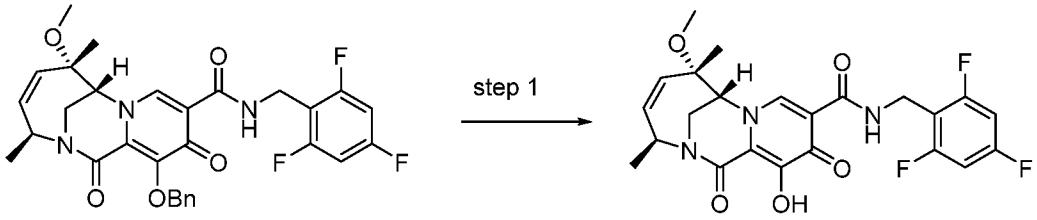
sodium hydride in mineral oil (2.6 mg, 0.068 mmol), then iodomethane (10 mg, 0.068 mmol). After stirring for 5 minutes, the reaction was quenched with 10% aqueous citric acid. The mixture was extracted with EtOAc, the organic layer was washed with water, then saturated aqueous sodium bicarbonate then brine, dried over magnesium sulfate, filtered and concentrated. Flash column chromatography (silica gel, EtOAc/Hexane) yielded the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Chloroform-d) δ 10.47 (s, 1H), 8.35 (s, 1H), 7.59 – 7.53 (m, 2H), 7.37 – 7.27 (m, 3H), 6.66 (dd, J = 8.8, 7.5 Hz, 2H), 5.63 (dd, J = 11.6, 1.8 Hz, 1H), 5.52 – 5.41 (m, 2H), 5.39 – 5.29 (m, 1H), 5.21 (d, J = 10.3 Hz, 1H), 4.66 (d, J = 5.4 Hz, 2H), 4.11 (s, 1H), 3.78 (dd, J = 14.5, 2.9 Hz, 1H), 3.27 (dd, J = 14.5, 1.3 Hz, 1H), 3.00 (s, 3H), 1.45 (s, 3H), 1.29 (d, J = 7.4 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{30}H_{28}F_3N_3O_5$, Theoretical: 568.21, Found: 568.19.

Synthesis of (3S,6S,7R)-12-hydroxy-6-methoxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0278] (3S,6S,7R)-12-(benzyloxy)-6-methoxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (20.0 mg, 0.035 mmol) was dissolved in EtOH (1.0 mL) at room temperature and treated with 1.2 mg of 20% $Pd(OH)_2/C$ (50 wt% water). The mixture was degassed and flushed with hydrogen 3 times, then stirred under hydrogen atmosphere for 45 min. The reaction was then degassed and flushed with nitrogen, filtered through a pad of Celite, concentrated, the resulting residue was purified by flash column chromatography (silica gel, dichloromethane/methanol) to yield the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Chloroform-d) δ 10.48 (s, 1H), 6.65 (dd, J = 8.8, 7.5 Hz, 2H), 4.75 – 4.58 (m, 3H), 3.67 (dd, J = 15.3, 3.0 Hz, 1H), 3.44 (d, J = 15.2 Hz, 1H), 3.12 (s, 3H), 2.13 – 2.01 (m, 1H), 1.91 (dd, J = 14.8, 7.7 Hz, 1H), 1.41 (s, 3H), 1.36 – 1.28 (m, 1H), 1.26 (d, J = 6.7 Hz, 3H), 1.24

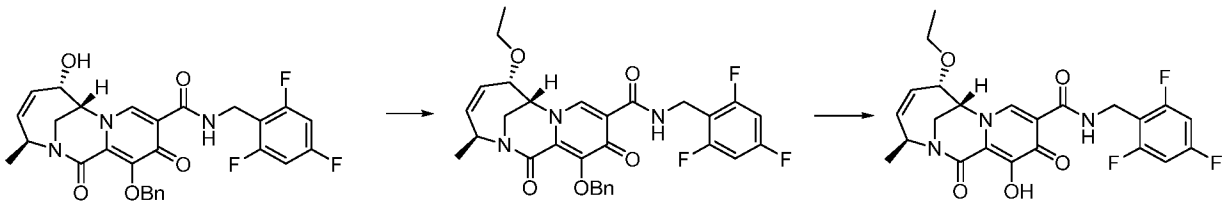
– 1.06 (m, 2H). LCMS-ESI+ (m/z): calcd H+ for $C_{23}H_{24}F_3N_3O_5$, Theoretical: 480.18, Found: 480.30.

Example 24: Synthesis of (3S,6S,7R)-12-hydroxy-6-methoxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0279] (3S,6S,7R)-12-(benzyloxy)-6-methoxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (from Step 1 of Example 23, 16 mg, 0.028 mmol) was dissolved in 1:1 toluene:trifluoroacetic acid (1.16 mL). The resulting solution was stirred at 20 °C for 8 hr, then allowed to stand at 0 °C for 12 hr. The solution was diluted with acetonitrile and concentrated in vacuo, and the resulting crude was purified by flash column chromatography (silica gel, dichloromethane/methanol) to yield the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Chloroform-d) δ 10.36 (s, 1H), 8.32 (s, 1H), 6.65 (dd, J = 8.7, 7.5 Hz, 2H), 5.64 (dd, J = 11.6, 1.8 Hz, 1H), 5.53 (dd, J = 11.6, 2.7 Hz, 1H), 5.29 – 5.20 (m, 1H), 4.77 – 4.55 (m, 2H), 4.23 (s, 1H), 3.93 (dd, J = 14.3, 3.0 Hz, 1H), 3.54 (dd, J = 14.3, 1.3 Hz, 1H), 2.97 (s, 3H), 1.45 (s, 3H), 1.36 (d, J = 7.4 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{23}H_{22}F_3N_3O_5$, Theoretical: 478.16, Found: 478.25.

Example 25: Preparation of (3S,6S,7R)-6-ethoxy-12-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Synthesis of (3S,6S,7R)-12-(benzyloxy)-6-ethoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

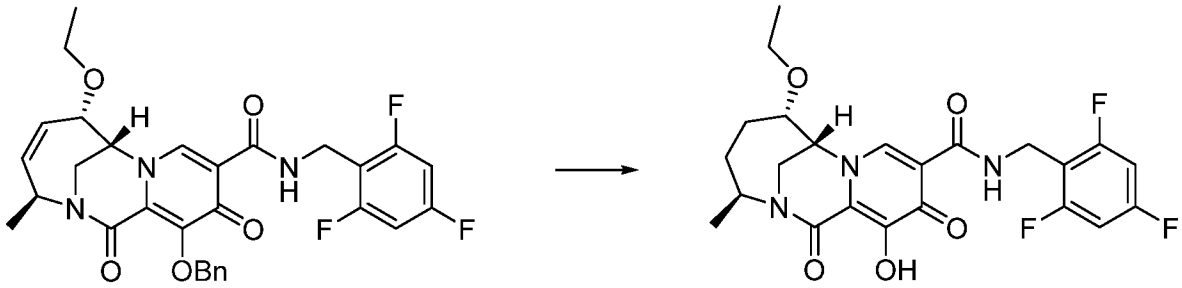
[0280] Dissolve (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (24 mg, 0.04 mmol) in 2 mL anhydrous DMF, cool to 0 °C, NaH (1.5 eq.) was added, followed by EtI (1.2 eq.). After 10 minutes, the reaction was complete. A drop of water was added to quench the reaction. The crude reaction was purified via preparative HPLC, eluting 10-60% acetonitrile (0.1% TFA) in water (0.1% TFA) to give (3S,6S,7R)-12-(benzyloxy)-6-ethoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 568.24 $[M+H]^+$.

Synthesis of (3S,6S,7R)-6-ethoxy-12-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0281] At room temperature (3S,6S,7R)-12-(benzyloxy)-6-ethoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (5 mg) was dissolved in toluene (0.5 mL), TFA (0.5 mL) was added. The reaction was stirred at room temperature for one hour. The reaction mixture was concentrated down, purified via preparative HPLC, eluting 10-60% acetonitrile (0.1% TFA) in water (0.1% TFA).

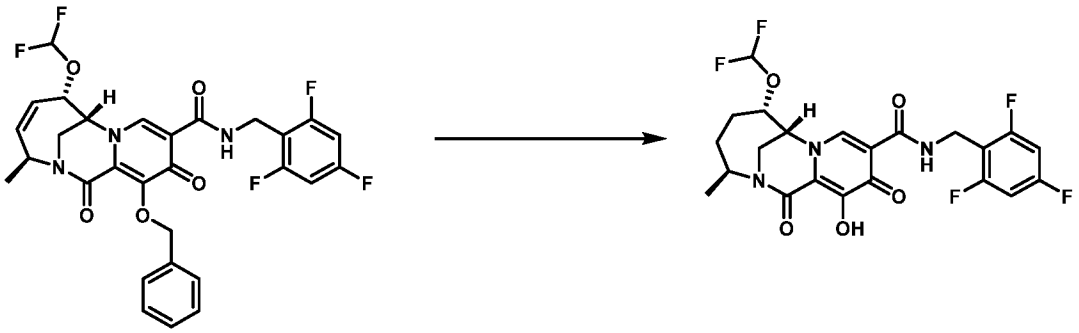
Combined fractions were freeze-dried to afford the title compound. MS (*m/z*) 478.32 $[M+H]^+$. 1H NMR (400 MHz, Acetonitrile-d3) δ 8.44 (d, J = 22.1 Hz, 1H), 7.00 – 6.81 (m, 1H), 6.73 (t, J = 8.5 Hz, 1H), 6.02 – 5.84 (m, 1H), 5.79 – 5.60 (m, 1H), 5.24 (d, J = 7.9 Hz, 1H), 5.03 (dd, J = 42.6, 7.4 Hz, 1H), 4.82 (dd, J = 15.0, 6.8 Hz, 1H), 4.70 – 4.58 (m, 1H), 4.52 (d, J = 12.9 Hz, 1H), 4.44 – 4.29 (m, 1H), 3.81 (t, J = 12.5 Hz, 1H), 3.70 – 3.54 (m, 1H), 3.41 (p, J = 6.9 Hz, 1H), 1.43 – 1.24 (m, 3H), 0.92 – 0.68 (m, 3H).

Example 26: Preparation of (3S,6S,7R)-6-ethoxy-12-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



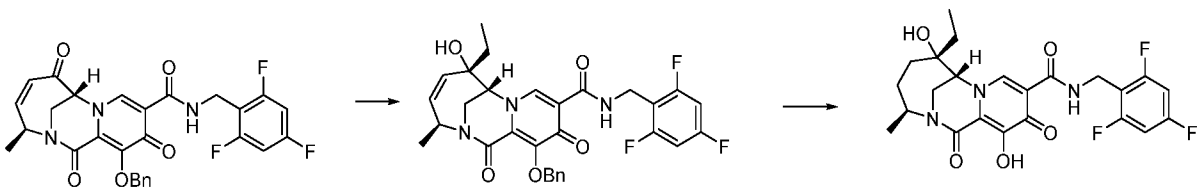
[0282] Dissolved (3S,6S,7R)-12-(benzyloxy)-6-ethoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (7 mg) in 2 mL ethanol and 2 mL ethyl acetate. 2 mg 10% Pd/C was added and hydrogen balloon was applied. After 2 hours, the catalyst was filtered off through celite. The filtrate was concentrated down. The crude reaction was purified via preparative HPLC, eluting 10-60% acetonitrile (0.1% TFA) in water (0.1% TFA) to give (3S,6S,7R)-6-ethoxy-12-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 480.27 $[M+H]^+$. 1H NMR (400 MHz, Acetonitrile-d3) δ 8.46 – 8.26 (m, 1H), 6.87 (t, J = 8.5 Hz, 1H), 6.69 (t, J = 8.5 Hz, 1H), 4.97 – 4.38 (m, 4H), 3.86 – 3.49 (m, 5H), 1.87 (m, 2H), 1.44 (d, J = 17.7 Hz, 2H), 1.25 – 1.08 (m, 3H), 1.08 – 0.82 (m, 3H).

Example 27: (3S,6S,7R)-6-(difluoromethoxy)-12-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0283] Prepared in a manner similar to (3S,6S,7R)-N-(2,4-difluorobenzyl)-6,12-dihydroxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (Example 16) except using (3S,6S,7R)-12-(benzyloxy)-6-(difluoromethoxy)-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (prepared according to Example 22) instead of (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (m/z): 502.137 [M+H]+. 1H NMR (400 MHz, Methanol-d4) δ 10.56 (s, 1H), 8.35 (s, 1H), 6.92 (t, J = 8.4 Hz, 2H), 6.58 (t, J = 73.8 Hz, 1H), 4.79 – 4.44 (m, 5H), 3.81 (s, 2H), 2.14 (dt, J = 14.7, 7.2 Hz, 1H), 2.02 – 1.81 (m, 1H), 1.74 – 1.60 (m, 1H), 1.45 – 1.30 (m, 1H), 1.29 (d, J = 6.7 Hz, 3H).

Example 28: Preparation of (3S,6S,7R)-6-ethyl-6,12-dihydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



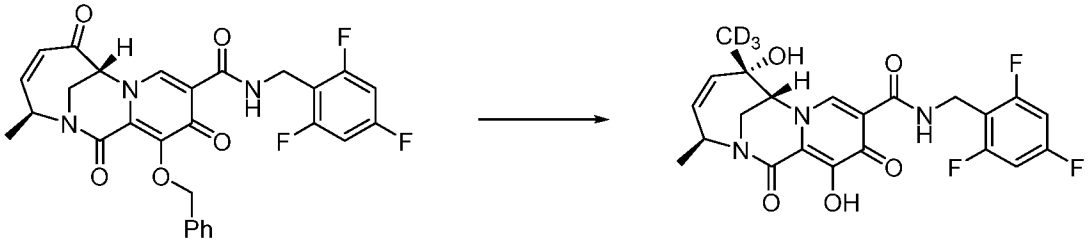
Synthesis of (3S,6S,7R)-12-(benzyloxy)-6-ethyl-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0284] Dissolved (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (43 mg, 0.08 mmol) is 2 mL anhydrous THF. The mixture was cooled to 0 °C and EtMgBr (3.4 M, 3eq., 0.07 mL) was added. The reaction was kept at 0 °C for one hour. A drop of water was added to quench the reaction. The reaction crude was filtered and purified via preparative HPLC, eluting 10-60% acetonitrile (0.1% TFA) in water (0.1% TFA) to give (3S,6S,7R)-12-(benzyloxy)-6-ethyl-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 568.21 $[M+H]^+$.

Synthesis of (3S,6S,7R)-6-ethyl-6,12-dihydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

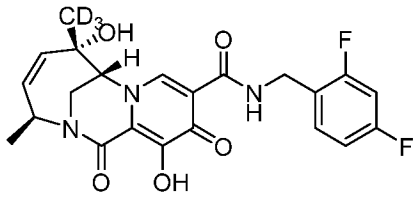
[0285] At room temperature (3S,6S,7R)-12-(benzyloxy)-6-ethyl-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (3 mg) was dissolved in in 2 mL ethanol and 2 mL ethyl acetate. Then 2 mg 10% Pd/C was added and hydrogen balloon was applied. After 2 hours, filtered off the catalyst through celite. The filtrate was concentrated down. The reaction crude was purified via preparative HPLC, eluting 10-60% acetonitrile (0.1% TFA) in water (0.1% TFA) to give the title compound. MS (*m/z*) 480.20 $[M+H]^+$. 1H NMR (400 MHz, Acetonitrile-d3) δ 10.44 (s, 1H), 8.27 (s, 1H), 6.87 (t, J = 8.6 Hz, 2H), 6.69 (d, J = 7.5 Hz, 1H), 4.79 – 4.51 (m, 2H), 4.06 (m, 1H), 3.76 – 3.48 (m, 3H), 1.90 – 1.74 (m, 2H), 1.65 (td, J = 14.8, 7.5 Hz, 2H), 1.49 – 1.32 (m, 1H), 1.32 – 1.09 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H).

Example 29: Synthesis of (1R,10S,13S)-6,13-dihydroxy-10-methyl-5,8-dioxo-13-(trideuteriomethyl)-N-[(2,4,6-trifluorophenyl)methyl]-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide



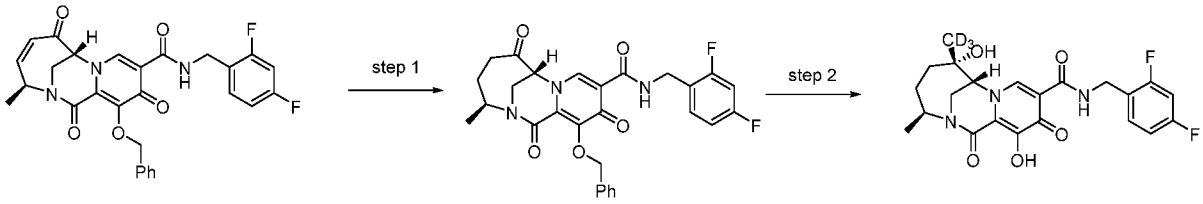
[0286] To a cold solution of (1R,10S)-6-benzyloxy-10-methyl-5,8,13-trioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide (50 mg, 0.093 mmol) in THF (1.0 mL) at 0 °C was added 1.0 M CD3MgI in diethylether (0.279 mmol, 0.279 mL). The reaction was stirred at 0 °C for 30 minutes before it was quenched with ice and methanol. The reaction was then concentrated, redissolved in DMF, filtered and purified by reverse phase prep HPLC. (LCMS-ESI+ (m/z): calcd H+ for C22H17D3F3N3O5, Theoretical: 466.15, Found: 467.35. 1H NMR (400 MHz, DMSO-d6) δ 10.46 (t, J = 5.8 Hz, 1H), 8.36 (s, 1H), 7.21 (t, J = 8.6 Hz, 2H), 5.54 (dd, J = 11.8, 2.3 Hz, 1H), 5.39 (dd, J = 11.8, 2.6 Hz, 1H), 5.32 (s, 1H), 5.13 (dt, J = 7.3, 2.6 Hz, 1H), 4.67 (d, J = 2.3 Hz, 1H), 4.59 (dt, J = 11.3, 6.0 Hz, 2H), 3.86 (dd, J = 14.8, 2.6 Hz, 1H), 3.63 (dd, J = 14.8, 1.9 Hz, 1H), 1.27 (d, J = 7.3 Hz, 3H).

Example 30: Synthesis of (1R,10S,13S)-N-[(2,4-difluorophenyl)methyl]-6,13-dihydroxy-10-methyl-5,8-dioxo-13-(trideuteriomethyl)-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide



[0287] The title compound was prepared following the same method for the synthesis of Example 29 except (1R,10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8,13-trioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide was used instead of (1R,10S)-6-benzyloxy-10-methyl-5,8,13-trioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide. LCMS-ESI+ (m/z): calcd H+ for C22H18D3F2N3O5, Theoretical: 448.16, Found: 449.23. 1H NMR (400 MHz, DMSO-d6) δ 10.44 (t, J = 5.9 Hz, 1H), 8.38 (s, 1H), 7.42 (td, J = 8.7, 6.6 Hz, 1H), 7.25 (ddd, J = 11.9, 9.3, 2.6 Hz, 1H), 7.08 (td, J = 8.5, 2.7 Hz, 1H), 5.54 (dd, J = 11.9, 2.3 Hz, 1H), 5.40 (dd, J = 11.9, 2.6 Hz, 2H), 5.13 (dt, J = 7.1, 2.3 Hz, 1H), 4.70 (d, J = 2.2 Hz, 1H), 4.56 (d, J = 5.9 Hz, 2H), 3.87 (dd, J = 14.7, 2.7 Hz, 1H), 3.65 (dd, J = 14.7, 1.9 Hz, 1H), 1.28 (d, J = 7.3 Hz, 3H).

Example 31: Synthesis of (1R,10S,13S)-N-[(2,4-difluorophenyl)methyl]-6,13-dihydroxy-10-methyl-5,8-dioxo-13-(trideuteriomethyl)-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide



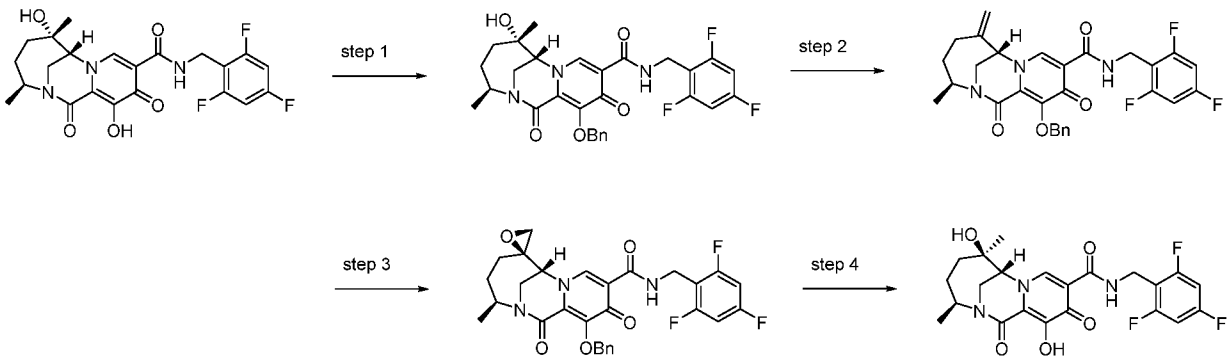
Step 1: Synthesis of (1R,10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8,13-trioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide:

[0288] To a solution of (1R,10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8,13-trioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide (215 mg, 0.41 mmol) in EtOH (50 mL) at room temperature was added 20% Pd(OH)2/C (50 mg, 50 wt% water). The resulting suspension was degassed, flushed with nitrogen three times, then it was degassed and flushed with hydrogen three times before it was hydrogenated under hydrogen balloon for 3 hours. The reaction was then degassed and flushed with nitrogen and filtered through a pad of Celite. The filtrate was concentrated, and dried over the vacuum line. The residue was then dissolved in DMF (4.0 mL) and treated with potassium carbonate (171 mg, 1.24 mmol) and benzyl bromide (212 mg, 1.24 mmol) at room temperature for overnight. The reaction was then diluted with EtOAc, washed with water, then brine, dried over sodium sulfate, filtered and concentrated, purified by normal phase chromatography.

Step 2: Synthesis of (1R,10S,13S)-N-[(2,4-difluorophenyl)methyl]-6,13-dihydroxy-10-methyl-5,8-dioxo-13-(trideuteriomethyl)-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide:

[0289] The compound was prepared by following the synthesis of Example 29 except (1R,10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8,13-trioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide was used instead of (1R,10S)-6-benzyloxy-10-methyl-5,8,13-trioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide. LCMS-ESI+ (m/z): calcd H+ for C22H20D3F2N3O5, Theoretical: 450.18, Found: 451.28. 1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 10.46 (t, J = 6.0 Hz, 1H), 8.34 (s, 1H), 7.40 (td, J = 8.7, 6.6 Hz, 1H), 7.25 (ddd, J = 10.5, 9.3, 2.6 Hz, 1H), 7.07 (td, J = 8.5, 2.6 Hz, 1H), 4.93 (s, 1H), 4.56 (d, J = 5.9 Hz, 2H), 4.47 (dt, J = 10.4, 6.5 Hz, 1H), 4.28 (s, 1H), 3.67 (t, J = 2.5 Hz, 2H), 1.87 (dt, J = 14.4, 7.0 Hz, 1H), 1.52 – 1.34 (m, 2H), 1.17 (t, J = 7.6 Hz, 4H).

Example 32: Synthesis of (3S,6R,7R)-6,12-dihydroxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Synthesis of (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0290] To ((1R,10S,13S)-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide (Example 11, 165 mg, 0.355 mmol) was added DMF (7.0 mL), then potassium carbonate, then

benzyl bromide. The mixture was stirred at 20 °C for 4 hr. The reaction was extracted with EtOAc, the organic layer was washed with water, then brine, dried over magnesium sulfate, filtered and concentrated. Flash column chromatography (silica gel, EtOAc/Hexane) yielded the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Chloroform-d) δ 10.40 (t, J = 5.6 Hz, 1H), 8.46 (s, 1H), 7.59 – 7.49 (m, 2H), 7.39 – 7.27 (m, 3H), 6.62 (dd, J = 8.8, 7.4 Hz, 2H), 5.28 (d, J = 10.3 Hz, 1H), 5.15 (d, J = 10.3 Hz, 1H), 4.78 (dt, J = 10.5, 6.7 Hz, 1H), 4.57 (dd, J = 14.5, 5.7 Hz, 1H), 4.49 (dd, J = 14.5, 5.4 Hz, 1H), 4.38 (s, 1H), 4.03 (s, 1H), 3.26 (dd, J = 15.3, 3.0 Hz, 1H), 3.06 (dd, J = 15.0, 1.5 Hz, 1H), 1.98 (dt, J = 13.4, 6.8 Hz, 1H), 1.62 – 1.47 (m, 2H), 1.39 (s, 3H), 1.15 (d, J = 6.7 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{23}H_{22}F_3N_3O_5$, Theoretical: 556.21, Found: 556.20.

Synthesis of (3S,7S)-12-(benzyloxy)-3-methyl-6-methylene-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0291] (3S,6S,7R)-12-(benzyloxy)-6-hydroxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (82 mg, 0.148 mmol) was dissolved in toluene (4.1 mL), then Martin sulfurane (506 mg, 0.75 mmol) was added. The mixture was stirred at 20 °C for 1 hr. The reaction mixture was purified directly by flash column chromatography (silica gel, EtOAc/Hexane) to yield the product. 1H NMR (400 MHz, Chloroform-d) δ 10.43 (t, J = 5.8 Hz, 1H), 8.47 (s, 1H), 7.64 – 7.53 (m, 2H), 7.42 – 7.30 (m, 3H), 6.68 (dd, J = 8.7, 7.5 Hz, 2H), 5.56 (d, J = 10.2 Hz, 1H), 5.31 (s, 1H), 5.21 – 5.11 (m, 2H), 4.86 (dp, J = 10.2, 6.7 Hz, 1H), 4.68 (d, J = 5.7 Hz, 2H), 4.60 (s, 1H), 3.52 (dd, J = 14.9, 2.6 Hz, 1H), 3.44 (dd, J = 14.9, 1.9 Hz, 1H), 2.36 (dd, J = 14.9, 7.3 Hz, 1H), 2.22 (dt, J = 14.2, 7.0 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.35 (dt, J = 14.5, 10.8 Hz, 1H), 1.22 (d, J = 6.8 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{29}H_{26}F_3N_3O_4$, Theoretical: 538.20, Found: 538.16.

Synthesis of (2R,3'S,7'R)-12'-(benzyloxy)-3'-methyl-1',11'-dioxo-N-(2,4,6-trifluorobenzyl)-1',4',5',11'-tetrahydro-3'H,7'H-spiro[oxirane-2,6'-[2,7]methanopyrido[1,2-a][1,4]diazonine]-10'-carboxamide:

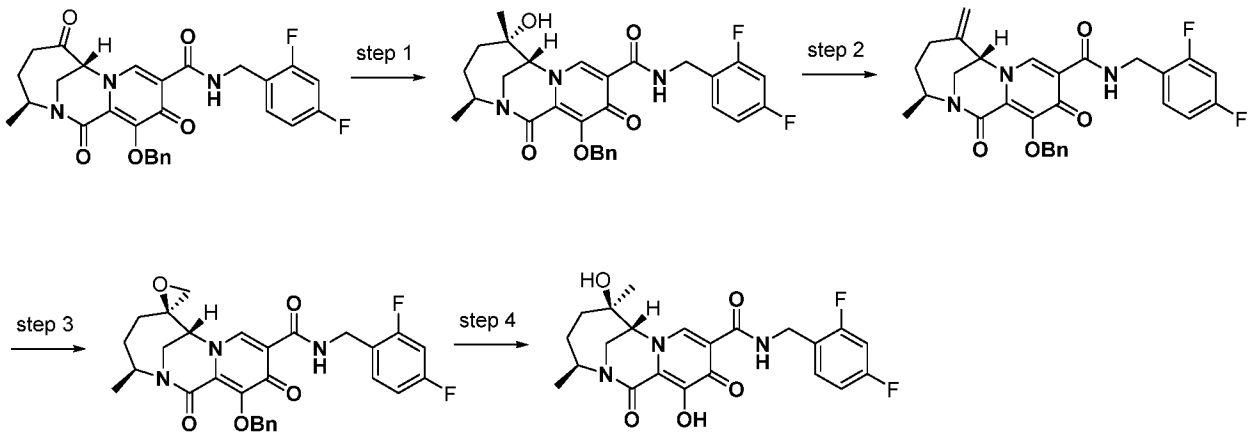
[0292] (3S,7S)-12-(benzyloxy)-3-methyl-6-methylene-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (30 mg, 0.0558 mmol) was dissolved in dichloromethane (3.0 mL), then 3-chloroperoxybenzoic acid (88 mg, 0.391 mmol) was added. The mixture was stirred in a metal heating block at 45 °C for 48 hr. The reaction mixture was diluted with more dichloromethane, then the organic phase was washed with 2 N aqueous sodium hydroxide, then brine. The combined aqueous phases were extracted with additional dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. Flash column chromatography (silica gel, EtOAc/Hexane) yielded the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Chloroform-d) δ 10.33 (s, 1H), 8.33 (s, 1H), 7.61 – 7.51 (m, 2H), 7.32 (dd, J = 12.1, 7.2 Hz, 3H), 6.67 (t, J = 8.1 Hz, 2H), 5.54 (d, J = 10.2 Hz, 1H), 5.17 (d, J = 10.2 Hz, 1H), 4.90 (dt, J = 10.7, 6.6 Hz, 1H), 4.66 (dd, J = 5.6, 3.1 Hz, 2H), 3.64 (dd, J = 14.9, 1.8 Hz, 1H), 3.52 (s, 1H), 3.44 (dd, J = 15.1, 2.5 Hz, 1H), 3.21 (d, J = 3.7 Hz, 1H), 2.79 (d, J = 3.7 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.79 (ddd, J = 39.5, 15.0, 11.6 Hz, 2H), 1.24 (d, J = 6.8 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{29}H_{26}F_3N_3O_5$, Theoretical: 554.19, Found: 554.21.

Synthesis of (3S,6R,7R)-6,12-dihydroxy-3,6-dimethyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0293] ((2R,3'S,7'R)-12'-(benzyloxy)-3'-methyl-1',11'-dioxo-N-(2,4,6-trifluorobenzyl)-1',4',5',11'-tetrahydro-3'H,7'H-spiro[oxirane-2,6'-[2,7]methanopyrido[1,2-a][1,4]diazonine]-10'-carboxamide (4 mg, 0.007 mmol) was dissolved in ethanol (0.5 mL), then ammonium formate (23 mg, 0.36 mmol) was added, followed by 10% palladium on carbon (1.54 mg, 0.0015 mmol). The mixture was stirred in a metal heating block at 70 °C for 12 hr. The reaction mixture was

diluted with 1:1 DMF:water, filtered, and purified by reverse-phase HPLC (acetonitrile/water, 0.1% trifluoroacetic acid) to yield the product (stereochemistry assignment tentative). 1H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 10.45 – 10.33 (m, 1H), 8.35 (s, 1H), 7.21 (t, J = 8.8 Hz, 2H), 5.16 (s, 1H), 4.56 (d, J = 5.5 Hz, 2H), 4.48 (s, 1H), 4.27 (s, 1H), 3.70 (d, J = 14.9 Hz, 1H), 3.60 (d, J = 14.7 Hz, 1H), 1.87 – 1.75 (m, 2H), 1.75 – 1.65 (m, 1H), 1.52 (dd, J = 16.0, 6.6 Hz, 1H), 1.16 (d, J = 7.0 Hz, 3H), 1.02 (s, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{22}H_{22}F_3N_3O_5$, Theoretical: 466.16, Found: 466.27.

Example 33: Synthesis of (1R,10S,13R)-N-[(2,4-difluorophenyl)methyl]-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide



Step 1: Synthesis of (1R, 10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-13-hydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide:

[0294] (1R,10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8,13-trioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide (200 mg, 0.384 mmol) was dissolved in THF (4.0 mL) and cooled to 0 °C. To this cold mixture was added 3.0 M MeMgBr in Et_2O (0.38 mL, 1.15 mmol) dropwise. The reaction was stirred at 0 °C for 20 minutes before it was quenched with ice water. The mixture was then diluted with EtOAc, washed with saturated ammonium chloride, brine, dried over sodium sulfate, filtered and concentrated,

purified by normal phase chromatography. LCMS-ESI+ (m/z): calcd H+ for C29H29F2N3O5, Theoretical: 537.21, Found:538.17.

Step 2: Synthesis of (1S,10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-13-methylene-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide:

[0295] (1R, 10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-13-hydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide (81 mg, 0.151 mmol) was dissolved in Toluene (3.0 mL) at room temperature and treated with martin sulfurane dehydration reagent (507 mg, 0.753 mmol) for 20 min. the reaction was concentrated and purified by normal phase chromatography. LCMS-ESI+ (m/z): calcd H+ for C29H27F2N3O4, Theoretical: 519.20, Found: 520.22.

Step 3: Synthesis of (1R,10S,13R)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8-dioxo-spiro[2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-13,2'-oxirane]-4-carboxamide:

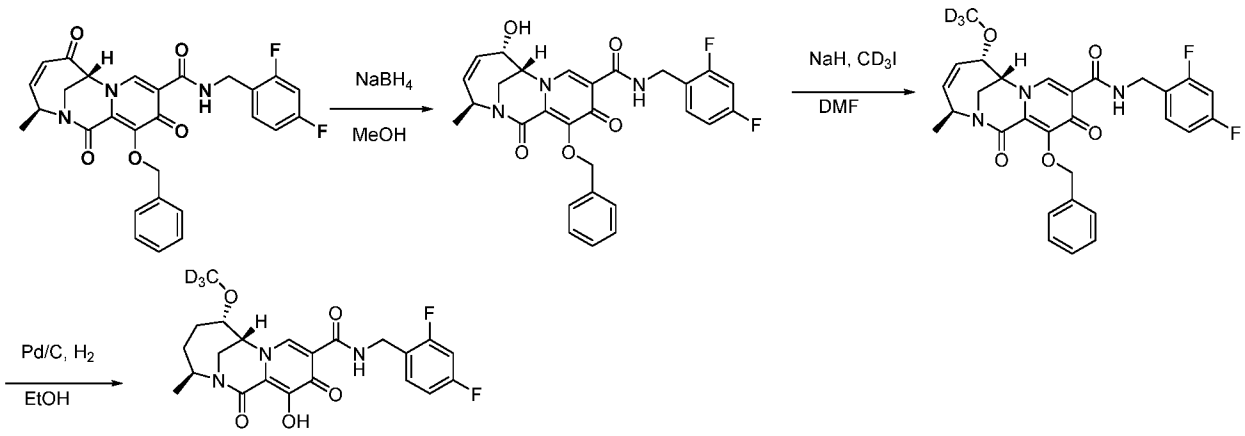
[0296] (1S,10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-13-methylene-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide (57 mg, 0.11 mmol) was dissolved in DCE (2.0 mL) and treated with MCPBA (56.8 mg, 0.329 mmol) at 60 °C for 3 hours. The reaction was cooled to room temperature, diluted with DCM, mixed with 1:1 mixture of 1 N sodium thiosulfate and saturated sodium bicarbonate, stirred vigorously for 10 minutes. Layers were separated. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated, purified by normal phase chromatography. LCMS-ESI+ (m/z): calcd H+ for C29H27F2N3O5, Theoretical: 535.19, Found: 536.17.

Step 4: Synthesis of (1R,10S,13R)-N-[(2,4-difluorophenyl)methyl]-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide:

[0297] (1R,10S,13R)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8-dioxo-spiro[2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-13,2'-oxirane]-4-carboxamide (10 mg,

0.0187 mmol) was dissolved in EtOH (0.5 mL), treated with ammonium formate (59 mg, 0.934 mmol) and 10% Pd/C (3.97 mg). The resulting mixture was degassed and flushed with nitrogen three times and then heated at 70 °C for 3 hours under nitrogen. The reaction was then cooled to room temperature, filtered and concentrated, redissolved in DMF, filtered and purified by reverse phase prep HPLC. LCMS-ESI+ (m/z): calcd H+ for C22H23F2N3O5, Theoretical: 447.16, Found: 448.256. 1H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 10.37 (t, J = 6.0 Hz, 1H), 8.38 (s, 1H), 7.41 (td, J = 8.6, 6.5 Hz, 1H), 7.34 – 7.18 (m, 1H), 7.08 (td, J = 8.6, 2.7 Hz, 1H), 5.16 (s, 1H), 4.52 (dt, J = 22.6, 6.3 Hz, 3H), 4.30 (s, 1H), 3.75 – 3.61 (m, 2H), 1.92 – 1.64 (m, 2H), 1.53 (dd, J = 15.3, 6.7 Hz, 1H), 1.17 (d, J = 6.7 Hz, 4H), 1.03 (s, 3H).

Example 34: (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-(methoxy-d3)-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Preparation of (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-(methoxy-d3)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

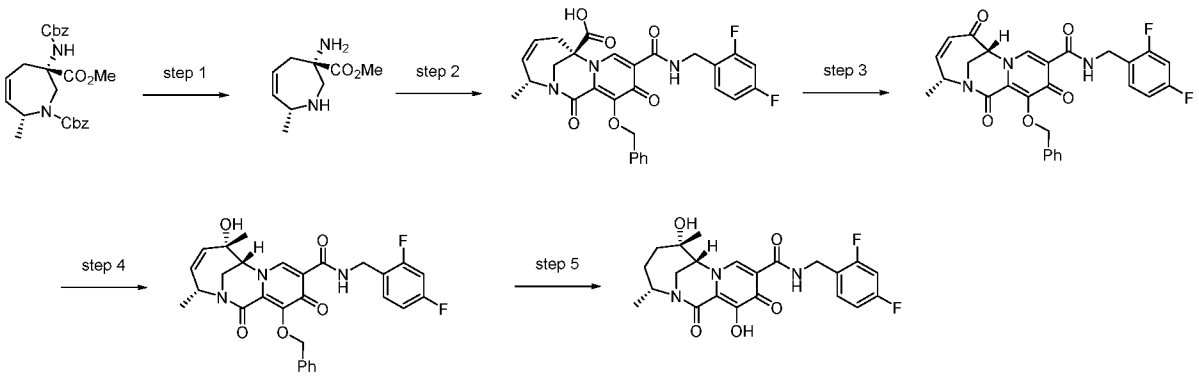
[0298] (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-(methoxy-d3)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was made similar to (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide in Example 18, except that iodomethane-d3 was used instead of iodomethane and that (3S,7R)-12-

(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was used instead of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide.

Preparation of (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-(methoxy-d3)-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0299] To a solution of (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-(methoxy-d3)-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3 H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (35 mg, 0.065 mmol) in EtOH (3 mL) was added Pd/C (10 mg). The reaction mixture was stirred at room temperature under H2 balloon. After the reaction was finished, the reaction mixture was filtered through celite, the filtrate was concentrated down and the residue was purified by reverse phase chromatography (eluting with 5-100% acetonitrile in water, containing 0.1% TFA) to give the title compound. MS (*m/z*) 451.2 $[M+H]^+$. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.36 (s, 1H), 7.45 (q, J = 8.3 Hz, 1H), 7.04 – 6.85 (m, 2H), 4.80 – 4.53 (m, 4H), 3.94 – 3.64 (m, 2H), 3.55 (d, J = 11.7 Hz, 1H), 2.19 – 1.96 (m, 2H), 1.54 (dt, J = 14.5, 11.2 Hz, 1H), 1.28 (d, J = 6.7 Hz, 3H), 1.01 (dt, J = 14.8, 11.6 Hz, 1H).

Example 35: Synthesis of (1R,10R,13S)-N-[(2,4-difluorophenyl)methyl]-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide



Step 1: Synthesis of methyl (3S,7R)-3-amino-7-methyl-1,2,4,7-tetrahydroazepine-3-carboxylate;2,2,2-trifluoroacetic acid:

[0300] O1-benzyl O3-methyl (3S,7R)-3-(benzyloxycarbonylamino)-7-methyl-4,7-dihydro-2H-azepine-1,3-dicarboxylate (1.2 g, 2.65 mmol) was mixed with TFA (10.0 mL). The resulting mixture was sealed and heated at 100 °C for 4 hours. The reaction was cooled to room temperature and concentrated, the residue was coevaporated with EtOAc for 4 times to give desired product, which was used directly in next step. LCMS-ESI+ (m/z): calcd H+ for C9H16N2O2, Theoretical: 184.12, Found: 185.01.

Step 2: Synthesis of (1S,10R)-6-benzyloxy-4-[(2,4-difluorophenyl)methylcarbamoyl]-10-methyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-1-carboxylic acid:

[0301] The residue from previous step (2.36 g, 5.72 mmol) and methyl 3-benzyloxy-4-oxo-5-[(2,4,6-trifluorophenyl)methylcarbamoyl]pyran-2-carboxylate (1.08 g, 2.52 mmol) was suspended in a mixture of THF (6.0 mL), ethanol (1.0 mL) and triethylamine (5.36 g, 53 mmol). The resulting mixture was heated at 40 °C for overnight. The reaction was cooled to room temperature. The residue was partitioned between EtOAc and water, organic layer was washed with 10% citric acid, water, brine, dried over sodium sulfate, filtered, concentrated and purified

by normal phase chromatography. LCMS-ESI+ (m/z): calcd H+ for C29H25F2N3O6, Theoretical: 549.17, Found: 550.10.

Step 3: Synthesis of (1R,10R)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8,13-trioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide:

[0302] (1S,10R)-6-benzyloxy-4-[(2,4-difluorophenyl)methylcarbamoyl]-10-methyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-1-carboxylic acid (470 mg, 0.855 mmol) was dissolved in 1,4-dioxane (8.0 mL) and treated with Selenium dioxide (753 mg, 6.84 mmol) at 100 °C for 8 hours. The reaction was cooled to room temperature, filtered and concentrated, purified by normal phase chromatography. LCMS-ESI+ (m/z): calcd H+ for C29H23F2N3O6, Theoretical: 519.16, Found: 520.04.

Step 4: synthesis of (1R,10R,13S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-13-hydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide:

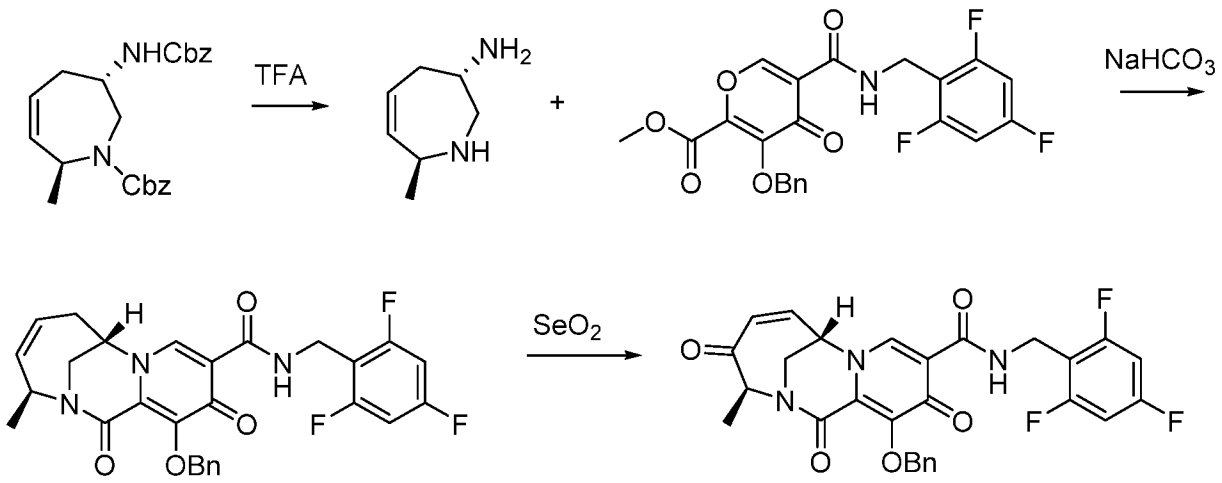
[0303] The compound was prepared following Step 1 of the preparation of Example 17 except (1R,10R)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8,13-trioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide was used instead of (1R,10S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-10-methyl-5,8,13-trioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide. LCMS-ESI+ (m/z): calcd H+ for C29H27F2N3O5, Theoretical: 535.19, Found: 536.13. Stereochemistry at C13 not confirmed.

Step 5: Synthesis of (1R,10R,13S)-N-[(2,4-difluorophenyl)methyl]-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide:

[0304] (1R,10R,13S)-6-benzyloxy-N-[(2,4-difluorophenyl)methyl]-13-hydroxy-10,13-dimethyl-5,8-dioxo-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6,11-triene-4-carboxamide (40 mg, 0.0747 mmol) was dissolved in EtOH (10 mL) at room temperature. To this mixture was added

10% Pd/C (30 mg) and ammonium formate (235 mg, 3.73 mmol). The resulting mixture was degassed and flushed with nitrogen then it was heated at 70 °C for 1 hr. The reaction was cooled to room temperature, filtered, concentrated and purified by reverse phase prep HPLC. Stereochemistry at C13 not confirmed. LCMS-ESI+ (m/z): calcd H+ for C22H23F2N3O5, Theoretical: 447.16, Found: 448.23. 1H NMR (400 MHz, Acetone-d6) δ 11.11 (s, 1H), 10.55 (s, 1H), 8.32 (s, 1H), 7.53 – 7.44 (m, 1H), 7.08 – 6.96 (m, 2H), 4.62 (t, J = 4.5 Hz, 2H), 4.53 – 4.46 (m, 1H), 4.08 (dd, J = 15.2, 2.1 Hz, 1H), 3.83 (dd, J = 15.1, 2.5 Hz, 1H), 3.73 (dt, J = 14.5, 7.0 Hz, 1H), 2.18 (q, J = 5.6, 5.0 Hz, 1H), 2.05 – 1.89 (m, 3H), 1.87 – 1.77 (m, 1H), 1.74 (d, J = 7.1 Hz, 3H), 1.55 (s, 3H).

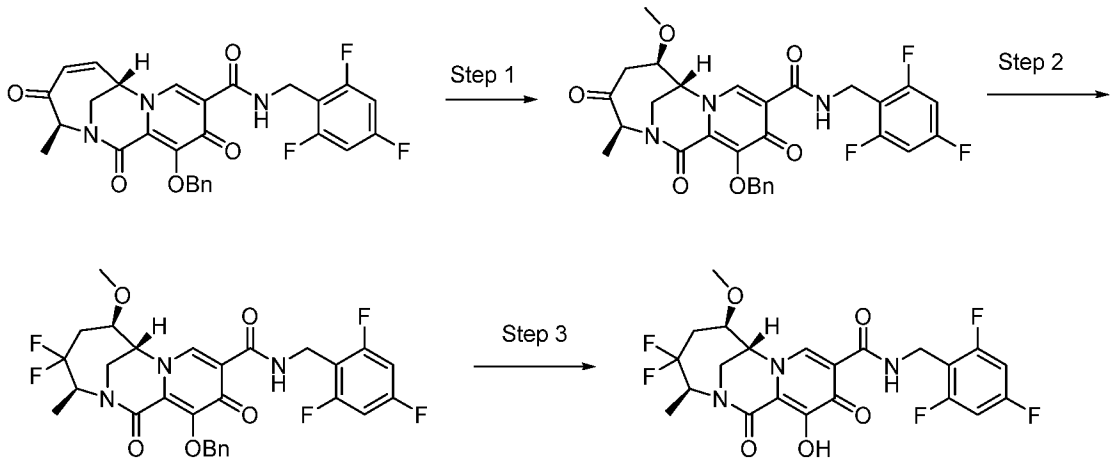
Intermediate C: (3S,7S)-12-(benzyloxy)-3-methyl-1,4,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,4,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0305] (3S,7S)-12-(benzyloxy)-3-methyl-1,4,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,4,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (Intermediate C) was synthesized in the same manner as for Intermediate A, and was isolated as an additional product from the identical reaction conditions. 1H NMR (400 MHz, Chloroform-d) δ 10.41 (t, J = 5.8 Hz, 1H), 8.66 (s, 1H), 7.58 – 7.46 (m, 2H), 7.41 – 7.27 (m, 3H), 6.76 – 6.56 (m, 2H), 6.31 (d, J = 12.4 Hz, 1H), 6.11 (d, J = 12.2 Hz, 1H), 5.50 (d, J = 10.2 Hz, 1H), 5.28 (q, J = 7.0 Hz, 1H), 5.15 (d, J = 10.2 Hz, 1H), 4.98 (s, 1H), 4.66 (d, J = 5.7 Hz, 2H), 3.75 (d, J = 15.0 Hz, 1H), 3.50 (d, J

= 14.9 Hz, 1H), 1.46 (d, J = 7.0 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{28}H_{22}F_3N_3O_5$, Theoretical: 538.16, Found: 538.10.

Example 36: Synthesis of (3S,6R,7R)-4,4-difluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Step 1: Synthesis of (3S,6R,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,4,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0306] To (3S,7S)-12-(benzyloxy)-3-methyl-1,4,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,4,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (Intermediate C, 50 mg, 0.093 mmol) was added triethylamine hydrochloride (12.8 mg, 0.093 mmol), then methanol (2.0 mL), then water (0.5 mL), then triethylamine (30 µL, 0.214 mmol), then potassium cyanide (6.0 mg, 0.093 mmol). The reaction was stirred in metal heating block at 60 °C for 1 hr. The reaction was partitioned between EtOAc, 10% aqueous sodium carbonate. The organic phase was washed with saturated aqueous ammonium chloride, then brine. The aqueous Na_2CO_3 phase was extracted with more ethyl acetate. The combined organic phases were dried

over $MgSO_4$, filtered, concentrated in vacuo. Flash column chromatography (silica gel, EtOAc/Hexane) yielded the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Chloroform-d) δ 10.27 (t, J = 6.0 Hz, 1H), 8.52 (s, 1H), 7.61 – 7.48 (m, 2H), 7.46 – 7.29 (m, 3H), 6.67 (dd, J = 8.7, 7.5 Hz, 2H), 5.57 (d, J = 10.3 Hz, 1H), 5.16 (d, J = 10.3 Hz, 1H), 5.10 (d, J = 7.0 Hz, 1H), 4.67 (dd, J = 5.7, 3.6 Hz, 2H), 4.24 (s, 1H), 3.80 (t, J = 4.1 Hz, 1H), 3.55 (dt, J = 15.3, 1.8 Hz, 1H), 3.48 (s, 3H), 3.45 (dd, J = 15.2, 1.8 Hz, 1H), 2.91 (dd, J = 13.6, 5.7 Hz, 1H), 2.70 (dd, J = 13.5, 1.6 Hz, 1H), 1.36 (d, J = 7.0 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{29}H_{26}F_3N_3O_6$, Theoretical: 570.18, Found: 570.13.

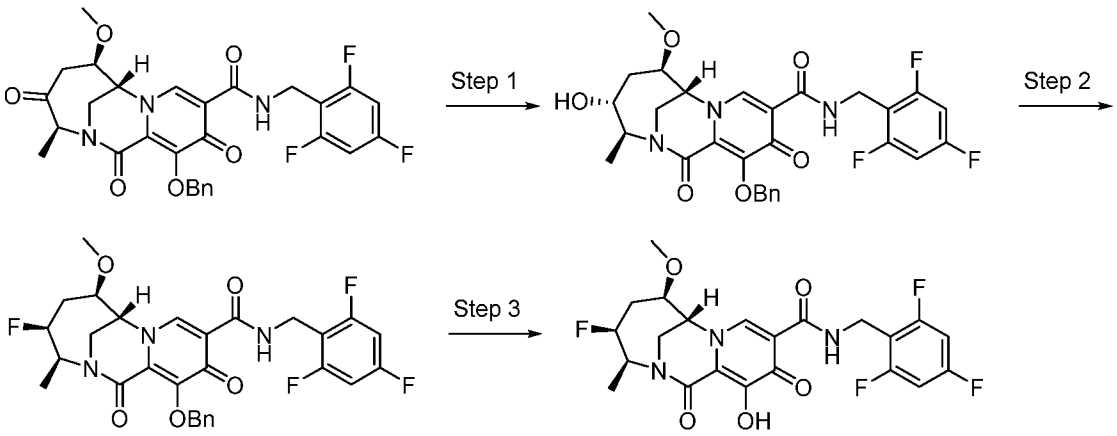
Step 2: Synthesis of (3S,6R,7R)-12-(benzyloxy)-4,4-difluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0307] To ((1R,10S,13S)-6,13-dihydroxy-10,13-dimethyl-5,8-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,9-diazatricyclo[7.4.1.02,7]tetradeca-3,6-diene-4-carboxamide (50 mg, 0.355 mmol) was added DCM (0.88 mL), then 2.7 M solution in toluene of Deoxo-Fluor (3.25 mL, 8.8 mmol). The mixture was stirred at 20 °C for 60 hr. The reaction was quenched by slow addition into ice-cold 10% aqueous potassium carbonate, then extracted with EtOAc. The organic layer was washed with saturated aqueous ammonium chloride, then brine, dried over magnesium sulfate, filtered and concentrated. Flash column chromatography (silica gel, EtOAc/Hexane) yielded the product (stereochemistry assignment tentative). LCMS-ESI+ (m/z): calcd H+ for $C_{29}H_{26}F_5N_3O_5$, Theoretical: 592.19, Found: 592.11.

Step 3: Synthesis of (3S,6R,7R)-4,4-difluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0308] (3S,6R,7R)-12-(benzyloxy)-4,4-difluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (30 mg) was dissolved in 1:1 toluene:trifluoroacetic acid (2.2 mL). The resulting solution was stirred at 60 °C for 30 min. The solution was diluted with acetonitrile and concentrated in vacuo, and the resulting crude was purified by reverse-phase preparative HPLC (acetonitrile/water, 0.1% trifluoroacetic acid). Crude residue was further washed with a minimal amount of dichloromethane to yield the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Acetonitrile-d3) δ 10.29 (s, 1H), 8.39 (s, 1H), 6.88 (dd, J = 9.2, 8.1 Hz, 2H), 4.95 (dt, J = 13.8, 7.0 Hz, 1H), 4.63 (d, J = 5.9 Hz, 2H), 4.49 (d, J = 2.9 Hz, 1H), 3.91 (dd, J = 15.4, 2.6 Hz, 1H), 3.75 – 3.61 (m, 2H), 3.38 (s, 3H), 2.58 (ddd, J = 27.6, 15.6, 8.5 Hz, 1H), 2.36 – 2.21 (m, 1H), 1.39 (dd, J = 7.2, 2.8 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{22}H_{20}F_5N_3O_5$, Theoretical: 502.14, Found: 502.24.

Example 37: (3S,4S,6R,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Step 1: Synthesis of (3S,4R,6R,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-

dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0309] A mixture of (3S,6R,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,4,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (770.8 mg, 1.35 mmol), prepared according to Example 36, in methanol (30 mL) was stirred at 0 °C and NaBH4 (57.7 mg, 1.53 mmol) was added. After 3 min, THF (~10 mL) was to dissolve the insoluble material. The reaction mixture was concentrated, and the residue was dissolved in ethyl acetate (~50 mL) and saturated NaHCO3 (~25 mL) and water (~25 mL). After separation of two layers, the aqueous fraction was extracted with ethyl acetate (~50 mL). The two organic fractions were washed with brine, combined, dried (MgSO4), and concentrated. The residue was purified by column chromatography on silica gel (80 g column) eluting 0-10% methanol in CH2Cl2 to get (3S,4R,6R,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. ES/MS m/z: calculated for C29H29F3N3O6 (M+H): 572.20, found: 572.20.

Step 2: Synthesis of (3S,4S,6R,7R)-12-(benzyloxy)-4-fluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0310] A solution of (3S,4R,6R,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (811.2 mg, 1.42 mmol) in CH2Cl2 (14 mL) was stirred at 0 °C as 2.7 M Deoxo-Fluor (bis(2-methoxyethyl)aminosulfur trifluoride) solution in toluene (1.39 mL, 3.75 mmol) was added. After 30 min, the reaction mixture was stirred at room temperature overnight. The reaction mixture was cooled and stirred at 0 °C as saturated NaHCO3 (~40 mL) was added. After water was added (~40 mL). the product was extracted with ethyl acetate (~70

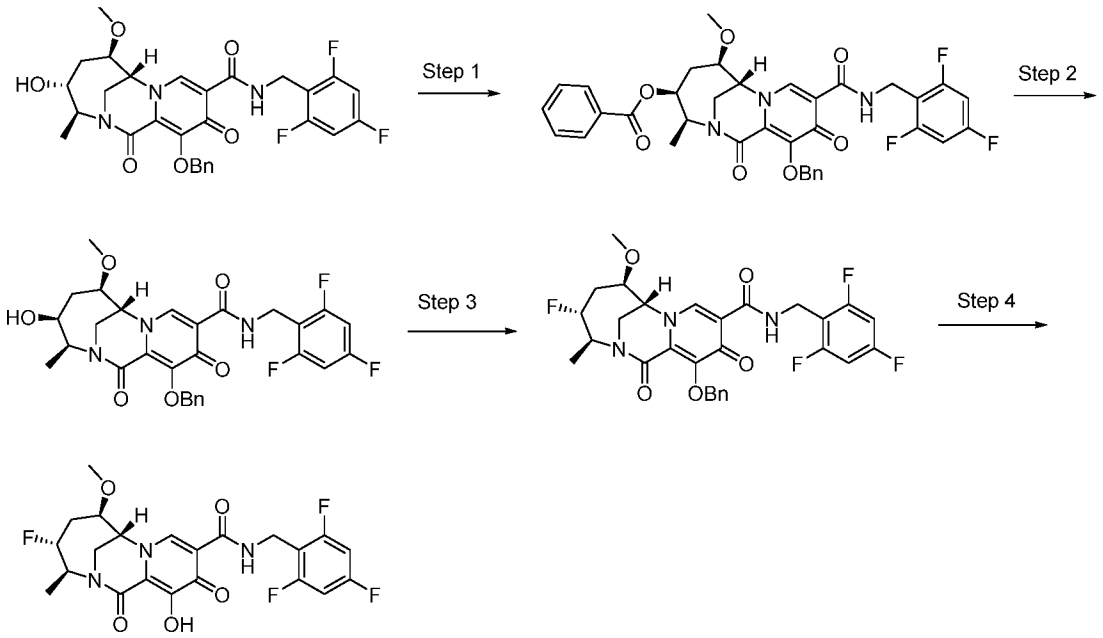
mL x 2). After the extracts were washed with brine (~70 mL x 1), the combined organic fractions were dried (MgSO4). The residue was purified by column chromatography on silica gel (80 g column) eluting 50-100% ethyl acetate in hexane to get (3S,4S,6R,7R)-12-(benzyloxy)-4-fluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide: ES/MS m/z: calculated for C29H28F4N3O5 (M+H): 574.20, found: 574.30.

[0311] Step 3: Synthesis of (3S,4S,6R,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0312] (3S,4S,6R,7R)-12-(benzyloxy)-4-fluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (556.5 mg, 0.970 mmol) was dissolved in toluene (0.25 mL) and trifluoroacetic acid (10 mL). The resulting mixture was stirred at room temperature for 1 h and at 60 °C for 1 h. The reaction mixture was concentrated, and the residue was dissolved in ethyl acetate (~25 mL) before washed with saturated NaHCO3 (~25 mL). After separating two layers, the aqueous fraction was extracted with ethyl acetate (~25 mL). The organic fractions were washed with brine, combined, dried (MgSO4), and concentrated. The residue was purified by column chromatography on silica gel (50 g column) eluting 0-10% methanol in CH2Cl2 to get the product. The impure product was purified again using column chromatography on silica gel (40 g column) eluting 0-10% methanol in ethyl acetate to get (3S,4S,6R,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide: 1H NMR (400 MHz, Acetonitrile-d3) δ 10.62 (s, 1H), 10.31 (t, J = 6.0 Hz, 1H), 8.37 (s, 1H), 6.84 (t, J = 8.5 Hz, 2H), 5.01 – 4.70 (m, 2H), 4.60 (d, J = 5.9 Hz, 2H), 4.48 (q, J = 2.4 Hz, 1H), 3.91 (dd, J = 15.1, 2.3 Hz, 1H), 3.73 – 3.57 (m, 2H), 3.37 (s, 3H), 2.53 (ddd, J = 15.3, 8.4, 6.5 Hz, 1H), 1.85 – 1.65 (m, 1H), 1.33 (dd, J

= 7.1, 2.7 Hz, 3H); 19F NMR (376 MHz, Acetonitrile-d3) δ -111.21 (ddd, J = 15.3, 9.1, 6.1 Hz), -113.91 (t, J = 7.0 Hz), -193.86 (ddd, J = 46.9, 31.9, 16.7 Hz); ES/MS m/z: calculated for C22H22F4N3O5 (M+H): 484.15, found: 484.20.

Example 38: (3S,4R,6R,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Step 1: Synthesis of (3S,4S,6R,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonin-4-yl benzoate:

[0313] To (3S,4R,6R,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (prepared according to Example 37, 45 mg, 0.079 mmol) was added 2-methyltetrahydrofuran (1.6 mL), then triphenylphosphine (54 mg, 0.205 mmol), then benzoic acid (25 mg, 0.205 mmol), then diisopropylazodicarboxylate (41 mg, 0.205 mmol). The

reaction was stirred at 20 °C for 1.5 hr. Then the reaction was diluted with dichloromethane and concentrated in vacuo. Flash column chromatography (silica gel, EtOAc/hexane) yielded the product (stereochemistry assignment tentative). LCMS-ESI+ (m/z): calcd H+ for $C_{36}H_{32}F_3N_3O_7$, Theoretical: 676.23, Found: 676.13.

Step 2: Synthesis of (3S,4S,6R,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0314] To (3S,4S,6R,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonin-4-yl benzoate (65 mg, 0.0962 mmol) was added methanol (2 mL), then THF (2 mL), then water (0.5 mL), then lithium hydroxide monohydrate (40 mg, 0.962 mmol). The reaction was stirred at 20 °C for 1.5 hr. Then the reaction was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was washed with brine, dried over MgSO4, filtered, concentrated in vacuo. Flash column chromatography (silica gel, EtOAc/hexane) yielded the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Chloroform-d) δ 10.35 (t, J = 5.8 Hz, 1H), 8.46 (s, 1H), 7.57 – 7.48 (m, 2H), 7.34 (d, J = 6.6 Hz, 3H), 6.72 – 6.61 (m, 2H), 5.50 (d, J = 10.3 Hz, 1H), 5.13 (d, J = 10.3 Hz, 1H), 4.74 – 4.59 (m, 2H), 4.53 – 4.43 (m, 1H), 4.12 (d, J = 7.0 Hz, 1H), 3.86 (t, J = 9.3 Hz, 1H), 3.64 – 3.57 (m, 1H), 3.45 (s, 3H), 3.45 – 3.38 (m, 1H), 3.36 – 3.27 (m, 1H), 2.18 – 2.10 (m, 1H), 1.76 (ddd, J = 15.4, 10.6, 1.5 Hz, 1H), 1.34 (d, J = 6.8 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{29}H_{28}F_3N_3O_6$, Theoretical: 572.20, Found 572.16.

Step 3: Synthesis of (3S,4R,6R,7R)-12-(benzyloxy)-4-fluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

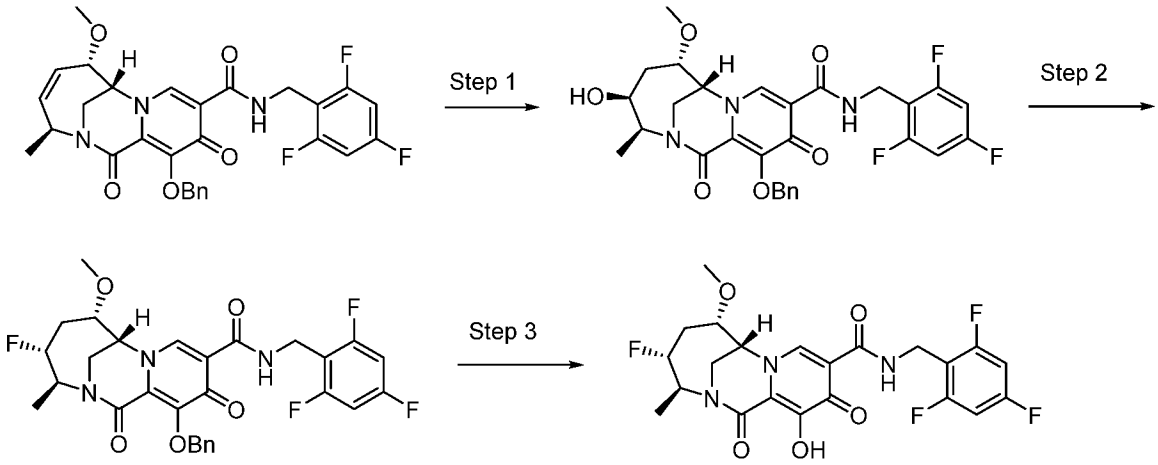
[0315] To (3S,4S,6R,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (13 mg, 0.0227 mmol) was added DCM (1.3 mL), then 2.7 M solution in toluene of Deoxo-Fluor (0.020 mL, 0.0546 mmol). The mixture was stirred at 20 °C for 1.5 hr. The reaction was quenched by slow addition into ice-cold 10% aqueous potassium carbonate, then extracted with EtOAc. The organic layer was washed with saturated aqueous ammonium chloride, then brine, dried over magnesium sulfate, filtered and concentrated. Preparative thin-layer chromatography (silica gel, EtOAc) yielded the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Chloroform-d) δ 10.35 (t, J = 5.7 Hz, 1H), 8.50 (s, 1H), 7.61 – 7.46 (m, 2H), 7.44 – 7.27 (m, 3H), 6.67 (dd, J = 8.7, 7.5 Hz, 2H), 5.54 (d, J = 10.3 Hz, 1H), 5.13 (d, J = 10.3 Hz, 1H), 4.93 – 4.85 (m, 1H), 4.67 (d, J = 5.6 Hz, 2H), 4.28 (d, J = 2.2 Hz, 1H), 3.87 (dd, J = 15.0, 2.1 Hz, 1H), 3.70 (s, 1H), 3.45 (s, 3H), 3.42 – 3.36 (m, 1H), 2.63 (dt, J = 15.9, 6.3 Hz, 1H), 1.78 – 1.68 (m, 1H), 1.63 (dd, J = 15.8, 2.8 Hz, 1H), 1.34 (dd, J = 6.8, 2.6 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{29}H_{27}F_4N_3O_5$, Theoretical: 574.20, Found: 574.14.

Step 4: Synthesis of (3S,4R,6R,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0316] (3S,4R,6R,7R)-12-(benzyloxy)-4-fluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (7 mg) was dissolved in 1:1 toluene:trifluoroacetic acid (0.48 mL). The resulting solution was stirred at 60 °C for 30 min. The solution was diluted with acetonitrile and concentrated in vacuo, and the resulting crude was purified by reverse-phase preparative HPLC (acetonitrile/water, 0.1% trifluoroacetic acid) to yield the product (stereochemistry assignment tentative). 1H NMR (400 MHz, Acetonitrile-d3) δ 10.31 (s, 1H), 8.37 (s, 1H), 6.85 (dd, J = 9.1, 8.0 Hz, 2H), 5.00 – 4.73 (m, 2H), 4.60 (d, J = 5.7 Hz, 2H), 4.48 (d, J = 2.5 Hz, 1H), 3.91 (dd, J =

15.1, 2.3 Hz, 1H), 3.65 (d, J = 8.1 Hz, 1H), 3.63 (s, 1H), 3.37 (s, 3H), 2.53 (ddd, J = 15.3, 8.2, 6.4 Hz, 1H), 1.86 – 1.66 (m, 1H), 1.33 (dd, J = 7.1, 2.7 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{22}H_{21}F_4N_3O_5$, Theoretical: 484.15, Found: 484.23.

Example 39: (3S,4R,6S,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Step 1: Synthesis of ((3S,4S,6S,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

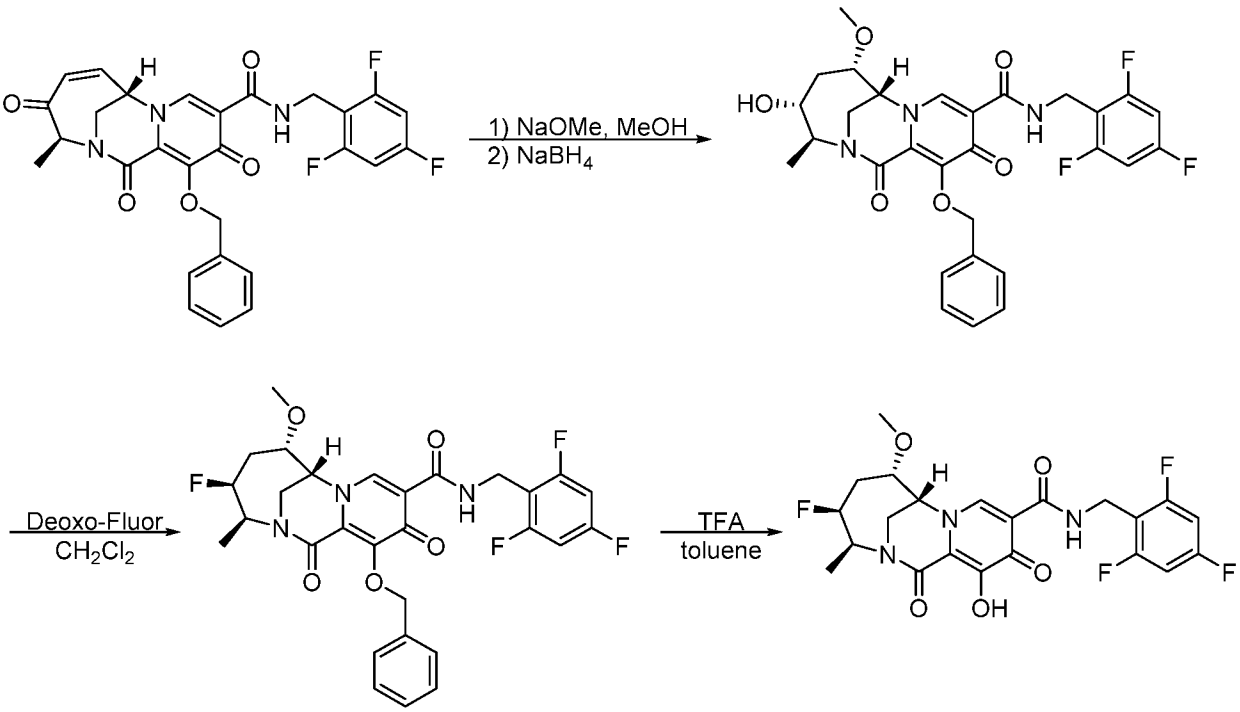
[0317] To (3S,6S,7R)-12-(benzyloxy)-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (from Step 2 for Example 1, 50 mg, 0.0903 mmol) was added isopropanol (2.5 mL), then phenylsilane (20 mg, 0.181 mmol), then benzoic acid (25 mg, 0.205 mmol), then tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III) (1.6 mg, 0.0027 mmol). The reaction was cycled between vacuum and oxygen three times, then stirred vigorously under oxygen at 20 °C for 45 min, then more tris(2,2,6,6-tetramethyl-3,5-

heptanedionato)manganese(III) (0.5 mg, 0.0009 mmol) was added. The reaction was stirred vigorously under oxygen at 20 °C for 45 min. Then 1 N aqueous sodium thiosulfate was added, and the phases mixed for 60 min. Then the reaction was extracted with ethyl acetate. The organic phase was washed with brine, dried over MgSO4, filtered, concentrated in vacuo. Flash column chromatography (silica gel, EtOAc/hexane) yielded the product as the major diastereomer (stereochemistry assignment tentative). 1H NMR (400 MHz, Chloroform-d) δ 10.43 (s, 1H), 8.48 (s, 1H), 7.66 – 7.50 (m, 2H), 7.46 – 7.27 (m, 3H), 6.66 (t, J = 8.1 Hz, 2H), 5.42 (d, J = 10.3 Hz, 1H), 5.14 (d, J = 10.3 Hz, 1H), 4.72 – 4.59 (m, 2H), 4.54 (q, J = 7.2 Hz, 1H), 4.40 (s, 1H), 3.52 – 3.28 (m, 3H), 3.41 (s, 3H), 3.12 (d, J = 15.3 Hz, 1H), 2.06 (d, J = 13.2 Hz, 1H), 1.72 – 1.57 (m, 1H), 1.33 (d, J = 6.7 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{29}H_{28}F_3N_3O_6$, Theoretical: 572.20, Found: 572.02.

Steps 2-3: Synthesis of (3S,4R,6S,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0318] (3S,4R,6S,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was synthesized in a manner similar to Example 38, starting with (3S,4S,6S,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. 1H NMR (400 MHz, Acetonitrile-d3) δ 10.33 (s, 1H), 8.27 (s, 1H), 6.84 (t, J = 8.5 Hz, 2H), 5.03 (ddd, J = 48.0, 7.1, 4.9 Hz, 1H), 4.79 – 4.63 (m, 2H), 4.60 (d, J = 5.8 Hz, 2H), 3.90 (ddd, J = 11.8, 5.1, 3.7 Hz, 1H), 3.74 (dt, J = 15.1, 2.6 Hz, 1H), 3.61 (d, J = 15.2 Hz, 1H), 3.42 (s, 3H), 2.51 (ddd, J = 15.3, 7.3, 3.6 Hz, 1H), 1.45 – 1.35 (m, 1H), 1.33 (dd, J = 7.1, 2.3 Hz, 3H). LCMS-ESI+ (m/z): calcd H+ for $C_{22}H_{21}F_4N_3O_5$, Theoretical: 484.15, Found: 484.11.

Example 40: (3S,4S,6S,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Step 1: Synthesis of (3S,4R,6S,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0319] To a mixture of Intermediate C (706.9 mg, 1.32 mmol) in methanol (10 mL) was added 0.5 M sodium methoxide (3 mL, 1. 5 mmol) at rt. The reaction mixture was stirred in at 50 °C. After 2 h, the reaction mixture was stirred at 0 °C and added 4 N HCl in dioxane (0.375 mL, 1.5 mmol): ES/MS m/z: calculated for C29H27F3N3O6 (M+H): 570.19, found: 570.30.

[0320] The above solution was stirred at 0 °C as NaBH4 (157 mg, 4.15 mmol) was added. After 30 min at 0 °C, the reaction mixture was concentrated, and the residue was dissolved in saturated NaHCO3 before the product was extracted with ethyl acetate (x 2). After the organic extracts were washed with brine (x 1), the organic fractions were combined, dried (MgSO4), and

concentrated. The residue was purified by repeated column chromatography on silica gel (80 g column) eluting 0-5% methanol in CH2Cl2, and preparative HPLC (column, Gemini 5 um C18 110A, LC column 100 x 30 mm) eluting 23-90% acetonitrile (0.1% TFA) in water (0.1% TFA) over 20 min. After the combined fractions were neutralized by adding saturated NaHCO3 (~1 mL), the solution was concentrated to remove most of acetonitrile. The resulting aqueous mixture was extracted with EA (~25 mL x 2), and the extracts were washed with brine (x 1) combined, dried (MgSO4), and concentrated to get (3S,4R,6S,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. ES/MS m/z: calculated for C29H29F3N3O6 (M+H): 572.20, found: 572.27.

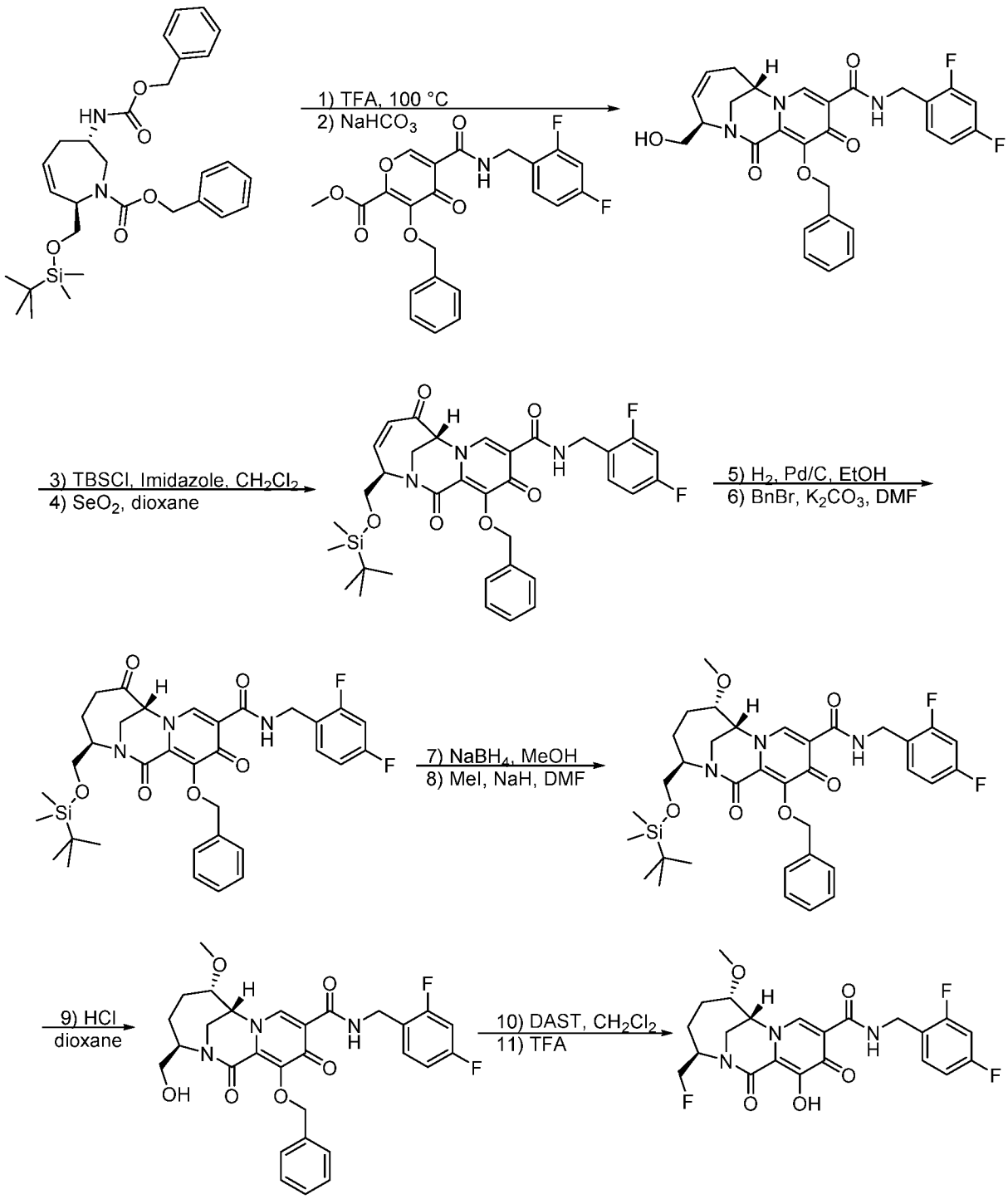
Step 2: Synthesis of (3S,4S,6S,7R)-12-(benzyloxy)-4-fluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0321] A solution of (3S,4R,6S,7R)-12-(benzyloxy)-4-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (81.8 mg, 0.143 mmol) in CH2Cl2 (2 mL) was stirred at 0 °C as 2.7 M bis(2-methoxyethyl)aminosulfur trifluoride solution in toluene (0.14 mL, 0.378 mmol) was added. After 30 min, the reaction mixture was stirred at room temperature for 2.5 h and cooled to 0 °C as saturated NaHCO3 (10 mL) was added. After water was added (20 mL). The product was extracted with ethyl acetate (25 mL x 2). After the extracts were combined, it was dried (MgSO4) and concentrated. The residue was purified by column chromatography on silica gel (12 g column used) eluting 20-100%EA in hexane to get (3S,4S,6S,7R)-12-(benzyloxy)-4-fluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide: ES/MS m/z: calculated for C29H28F4N3O5 (M+H): 574.20, found: 574.30.

Step 3: Synthesis of (3S,4S,6S,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0322] (3S,4S,6S,7R)-12-(benzyloxy)-4-fluoro-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (50.3 mg, 0.0877 mmol) was dissolved in toluene (0.02 mL) and trifluoroacetic acid (2 mL). After stirring at room temperature for 1 h, the reaction mixture was concentrated completely, and the residue was purified by preparative HPLC (2 injections; column, Gemini 5um C18 110A, LC column 100 x 30 mm) eluting 20-65% acetonitrile (0.1% TFA) in water (0.1% TFA) over 20 min. The combined fractions were neutralized by addition of saturated NaHCO3 (~1 mL) before concentration to remove most of acetonitrile. The concentrated solution was extracted with ethyl acetate (~20 mL x 2). The extracted fractions were washed with brine (x 1), combined, dried (MgSO4), concentrated, and dried in vacuum to obtain (3S,4S,6S,7R)-4-fluoro-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. 1H NMR (400 MHz, Chloroform-d) δ 10.39 (s, 1H), 10.19 (s, 1H), 8.44 (s, 1H), 6.74 – 6.59 (m, 2H), 4.97 (dt, J = 46.8, 6.4 Hz, 1H), 4.82 (dp, J = 19.9, 6.8 Hz, 1H), 4.74 – 4.59 (m, 2H), 4.39 (d, J = 2.4 Hz, 1H), 4.02 (dd, J = 14.7, 2.1 Hz, 1H), 3.73 – 3.58 (m, 2H), 3.45 (s, 3H), 2.68 (ddd, J = 16.0, 7.5, 5.1 Hz, 1H), 1.73 – 1.55 (m, 1H), 1.41 (dd, J = 7.1, 2.6 Hz, 3H); 19F NMR (376 MHz, Acetonitrile-d3) δ -111.29 (q, J = 7.8, 7.3 Hz), -113.92 (t, J = 7.1 Hz), -200.03 – -200.69 (m); ES/MS m/z: calculated for C22H22F4N3O5 (M+H): 484.15, found: 484.20.

Example 41: (3R,6S,7R)-N-(2,4-difluorobenzyl)-3-(fluoromethyl)-12-hydroxy-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Steps 1-2: Synthesis of (3R,7S)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-(hydroxymethyl)-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0323] (3R,7S)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-(hydroxymethyl)-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was prepared by following the procedure of making Intermediate B, except that Benzyl (3S,7R)-3-

(((benzyloxy)carbonyl)amino)-7-(((tert-butyldimethylsilyl)oxy)methyl)-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate was used in the 1st step. ES/MS m/z: calculated for C28H26F2N3O5 (M+H): 522.18, found: 522.20.

Steps 3-4: Synthesis of (3R,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0324] To a solution of (3R,7S)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-(hydroxymethyl)-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (2971.9 mg, 5.70 mmol) and imidazole (601.0 mg, 8.83 mmol) in CH2Cl2 (45 mL) was added tert-butyldimethylsilyl chloride (1039.7 mg, 6.90 mmol) at room temperature and the resulting solution was stirred at rt. After 16 h, the reaction mixture was diluted with CH2Cl2, washed with water (x 1), and the two layers were separated. After the aqueous fraction was extracted with ethyl acetate (x 1), the organic fractions were combined, dried (MgSO4), and concentrated. The residue was purified by column chromatography on silica gel (120 g column) eluting 0-100% ethyl acetate in hexane to get (3R,7S)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. ES/MS m/z: calculated for C34H40F2N3O5Si (M+H): 636.27, found: 636.30.

[0325] (3R,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was prepared by following the procedure of making Intermediate B, except that (3R,7S)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was used. ES/MS m/z: calculated for C34H38F2N3O6Si (M+H): 650.25, found: 650.30.

Steps 5-6: Synthesis of (3R,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-1,6,11-trioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0326] A mixture of (3R,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (1420.6 mg, 2.19 mmol) and 10% palladium on carbon (151.3 mg) in ethanol (30 mL) was stirred under H2 atmosphere at rt. After 2 h, the reaction mixture was filtered, and the filtrate was concentrated and dried in vacuum for 30 min. ES/MS m/z: calculated for C29H40F2N3O7Si (M +EtOH+H): 608.26, found: 608.30.

[0327] The above residue and potassium carbonate (614.5 mg, 4.45 mmol) in DMF (13 mL) was stirred at room temperature when benzyl bromide (0.35 mL, 2.94 mmol) was added. After stirring at room temperature overnight, the reaction mixture was diluted with water (~30 mL) and the product was extracted with ethyl acetate (x 2). After the extracts were washed with water (x 1), combined, dried (MgSO4), and concentrated. The residue was purified by column chromatography on silica gel (40 g column) eluting 0-10% methanol in CH2Cl2 to get (3R,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-1,6,11-trioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide: ES/MS m/z: calculated for C34H42F2N3O7Si (M+H2O+H): 670.28, found: 670.30; calculated for C35H44F2N3O7Si (M+MeOH+H): 684.29, found: 684.40.

Steps 7-8: Synthesis of (3R,6S,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0328] A solution of (3R,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-1,6,11-trioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-

a][1,4]diazonine-10-carboxamide (1234.0 mg, 1.89 mmol) in methanol (18 mL) was stirred at 0 °C as NaBH4 (156.2 mg, 4.13 mmol) was added. After 1 h at 0 °C, the reaction mixture was concentrated, and the residue was dissolved in water before extraction with EtOAc (x 2). The combined extracts were dried (MgSO4), and concentrated. The residue was purified by column chromatography on silica gel (80 g column) eluting 0-10% methanol in CH2Cl2 to get (3R,6S,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-6-hydroxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. ES/MS m/z: calculated for C34H42F2N3O6Si (M+H): 654.28, found: 654.30.

[0329] A solution of the above product (221.3 mg, 0.338 mmol) in DMF (2.25 mL) was stirred at 0 °C as 60% sodium hydride dispersion (19.1 mg, 0.498 mmol) was added. After 20 min at 0 °C, a solution of iodomethane (0.021 mL, 0.337 mmol) was added. After 1 h at 0 °C, additional iodomethane (0.021 mL, 0.337 mmol) to the reaction mixture. After ~1 h at 0 °C, the reaction mixture was diluted with saturated NH4Cl and the product was extracted with ethyl acetate (x 2). After the extracts were washed with water (x 1), the organic fractions were combined, dried (MgSO4), and concentrated. The residue was purified by column chromatography on silica gel (120 g column) eluting 0-10% methanol in CH2Cl2. The fractions containing product were combined and concentrated and the residue was purified again by column chromatography on silica gel (24 g column) eluting 20-100% ethyl acetate in hexane to get a mixture the reactant and (3R,6S,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. ES/MS m/z: calculated for C35H44F2N3O6Si (M+H): 668.30, found: 668.30.

Step 9: Synthesis of (3R,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-(hydroxymethyl)-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0330] (3R,6S,7R)-12-(benzyloxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (333 mg, 0.494 mmol) from above was dissolved in 4 N HCl in dioxane (3 mL) in 0 °C bath and stirred at 0 °C for 30 min. The reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel (24 g column) eluting 0-15% methanol in CH2Cl2 to get (3R,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-(hydroxymethyl)-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. ES/MS m/z: calculated for C28H28F2N3O6 (M+H): 554.21, found: 554.30.

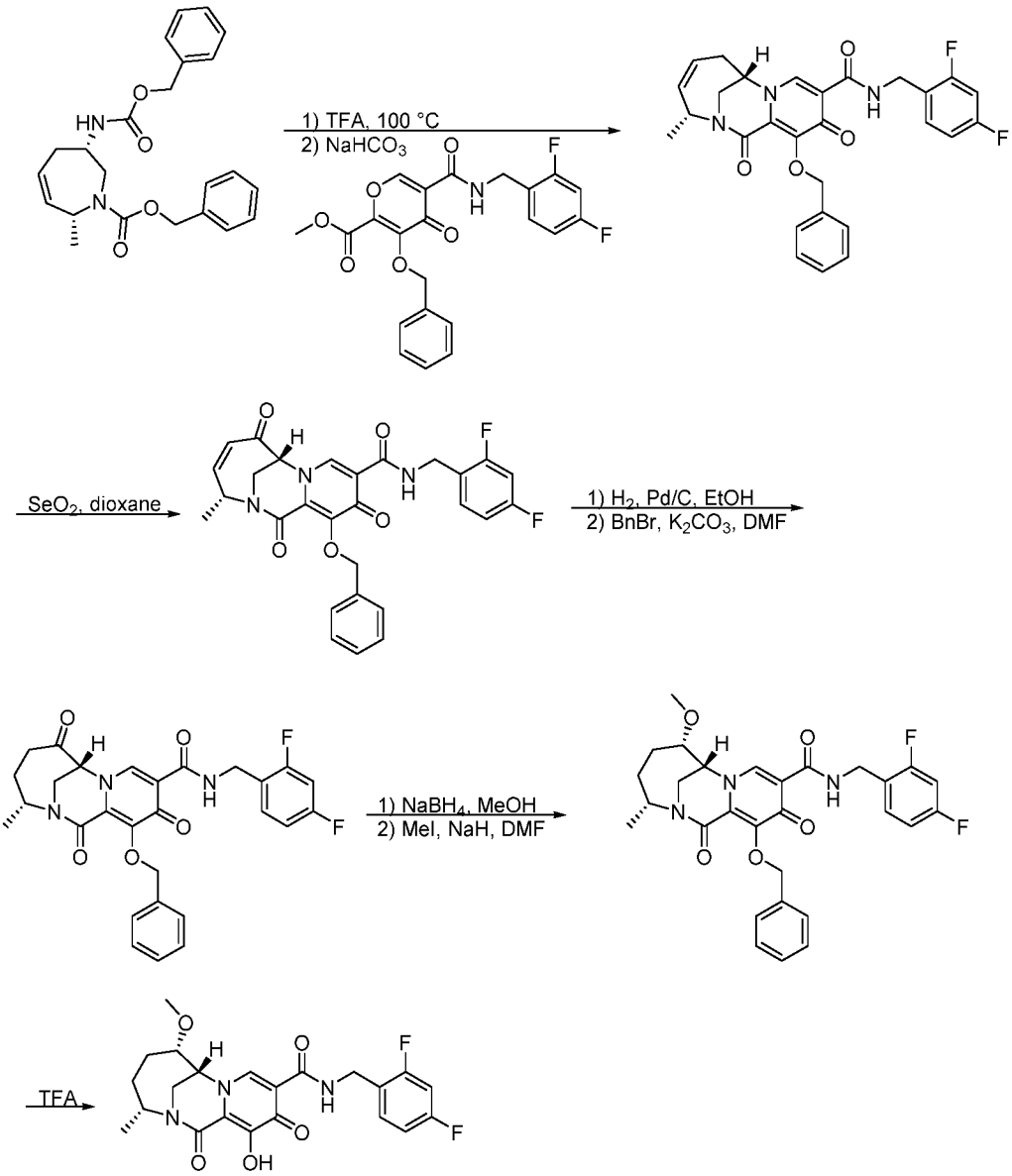
Steps 10-11: Synthesis of (3R,6S,7R)-N-(2,4-difluorobenzyl)-3-(fluoromethyl)-12-hydroxy-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0331] A solution of (3R,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-(hydroxymethyl)-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (50.3 mg, 0.0909 mmol) in CH2Cl2 (2.5 mL) was stirred at 0 °C as (diethylamino)sulfur trifluoride (0.05 mL, 0.378 mmol) was added. After 30 min, the reaction mixture was stirred at room temperature overnight. The reaction mixture was stirred at 0 °C and added saturated NaHCO3 (5 mL). After the mixture was diluted with water (20 mL), the product was extracted with CH2Cl2 (2 x 20 mL). The combined extracts were dried (MgSO4), and concentrated to get the crude product, (3R,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-(fluoromethyl)-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. ES/MS m/z: calculated for C29H29F3N3O5 (M+H): 556.21, found: 556.30.

[0332] The crude fluorinated product was dissolved in trifluoroacetic acid (3 mL) and stirred at room temperature for 1.5 h. The reaction mixture was concentrated and the residue was

purified by preparative HPLC (column, Gemini 5um C18 110A, LC column 100 x 30 mm) eluting 15-70% acetonitrile (0.1% TFA) in water (0.1% TFA) over 20 min to get (3R,6S,7R)-N-(2,4-difluorobenzyl)-3-(fluoromethyl)-12-hydroxy-6-methoxy-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. 1H NMR (400 MHz, Chloroform-d) δ 10.49 (t, J = 5.9 Hz, 1H), 9.63 (s, 2H), 8.44 (s, 1H), 7.36 (td, J = 8.6, 6.6 Hz, 1H), 6.87 – 6.74 (m, 2H), 4.84 – 4.67 (m, 1H), 4.67 – 4.62 (m, 3H), 4.62 – 4.50 (m, 1H), 4.48 (dd, J = 5.7, 2.8 Hz, 1H), 3.86 (dd, J = 15.5, 3.1 Hz, 1H), 3.74 (dt, J = 15.5, 1.3 Hz, 1H), 3.50 – 3.42 (m, 1H), 3.41 (s, 3H), 2.20 – 2.01 (m, 2H), 1.98 – 1.79 (m, 1H), 1.14 (dt, J = 13.9, 11.6 Hz, 1H); 19F NMR (376 MHz, Chloroform-d) δ -76.43, -111.94 (p, J = 7.8 Hz), -114.64 – -114.87 (m); ES/MS m/z: calculated for C22H23F3N3O5 (M+H): 466.16, found: 466.20.

Example 42: (3R,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Steps 1-2: Synthesis of (3R,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0333] (3R,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was prepared by following the procedure of making Intermediate B, except that benzyl (3S,7R)-3-(((benzyloxy)carbonyl)amino)-7-methyl-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate was used in the 1st step. ES/MS m/z: calculated for C28H24F2N3O5 (M+H): 520.17, found: 520.20.

[0334] Step 3: Synthesis of (3R,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0335] A mixture of (3R,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (0.637 mmol) and 10% palladium on carbon (70 mg) in ethanol (10 mL) was stirred under H2 atmosphere at room temperature for 4 h. The reaction mixture was filtered, and the filtrate was concentrated and dried in vacuum for 30 min.

[0336] The residue and potassium carbonate (179.0 mg, 1.3 mmol) in DMF (3.8 mL) was stirred at room temperature when benzyl bromide (0.1 mg, 0.841 mmol) was added. After overnight, the reaction mixture was diluted with water (30 mL) and the product was extracted with ethyl acetate (x 2). After the extracts were washed with water (x 1), combined, dried (MgSO4), and concentrated. The residue was purified by column chromatography on silica gel (40 g column) eluting 20-100% ethyl acetate in hexane to get (3R,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. ES/MS m/z: calculated for C28H26F2N3O5 (M+H): 522.18, found: 522.20.

Step 4: Synthesis of (3R,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-methoxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0337] A solution of (3R,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (125.1 mg, 0.24 mmol) in methanol (3 mL) was stirred at 0 °C as NaBH4 (28.9 mg, 0.764 mmol) was added. After 1 h at 0 °C, the reaction mixture was concentrated, and the residue was

dissolved in water (~30 mL) before extraction with ethyl acetate (20 mL x 2). The combined extracts were dried (MgSO4), and concentrated. The residue was purified by column chromatography on silica gel (24 g column) eluting 0-20% methanol in CH2Cl2 to get (3R,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide: ES/MS m/z: calculated for C28H28F2N3O5 (M+H): 524.20, found: 524.30.

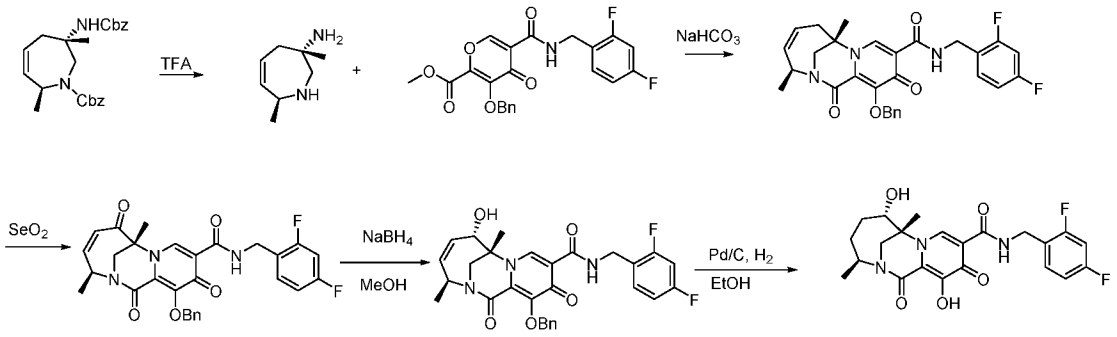
[0338] A solution of the above alcohol (73.2 mg, 0.140 mmol) in DMF (1.5 mL) was stirred at 0 °C as 60% sodium hydride dispersion (10.5 mg, 0.274 mmol) was added After 20 min at 0 °C, a solution of iodomethane (0.0104 mL 0.168 mmol), 0.21 mL, 0.337 mmol) was added. After 1 h at 0 °C, After the reaction mixture was diluted with saturated NaHCO3 solution, the product was extracted with ethyl acetate (x 2), and the combined extracts were dried (MgSO4) and concentrated. The residue was purified by preparative HPLC (column, Gemini 5um C18 110A, LC column 100 x 30 mm) eluting 20-100% acetonitrile (0.1% TFA) in water (0.1% TFA) over 30 min to get (3R,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-methoxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. ES/MS m/z: calculated for C29H30F2N3O5 (M+H): 538.22, found: 538.30.

Step 5: Synthesis of (3R,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0339] (3R,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-methoxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (3.1 mg, 5.77 umol) was dissolved in trifluoroacetic acid (1 mL) and stirred at room temperature for 1.5 h. The reaction mixture was concentrated and the residue was purified by preparative HPLC (column, Gemini 5um C18 110A, LC column 100 x 30 mm) eluting 15-70% acetonitrile (0.1% TFA) in water (0.1% TFA) over 20 min to get (3R,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-

a][1,4]diazonine-10-carboxamide. 1H NMR (400 MHz, Acetonitrile-d3) δ 10.41 (s, 1H), 8.29 (s, 1H), 7.41 (q, J = 8.2 Hz, 1H), 7.04 – 6.85 (m, 2H), 4.63 (d, J = 5.7 Hz, 1H), 4.60 – 4.51 (m, 2H), 3.87 (dd, J = 15.0, 2.1 Hz, 1H), 3.76 (td, J = 5.9, 2.9 Hz, 1H), 3.57 (h, J = 7.0 Hz, 1H), 3.45 (dd, J = 15.0, 2.1 Hz, 1H), 3.24 (s, 3H), 1.92 – 1.74 (m, 3H), 1.67 (d, J = 7.2 Hz, 4H); 19F NMR (376 MHz, Acetonitrile-d3) δ -77.29, -114.23 (p, J = 7.4 Hz), -116.68 (q, J = 8.8, 8.2 Hz); ES/MS m/z: calculated for C22H24F2N3O5 (M+H): 448.17, found: 448.22.

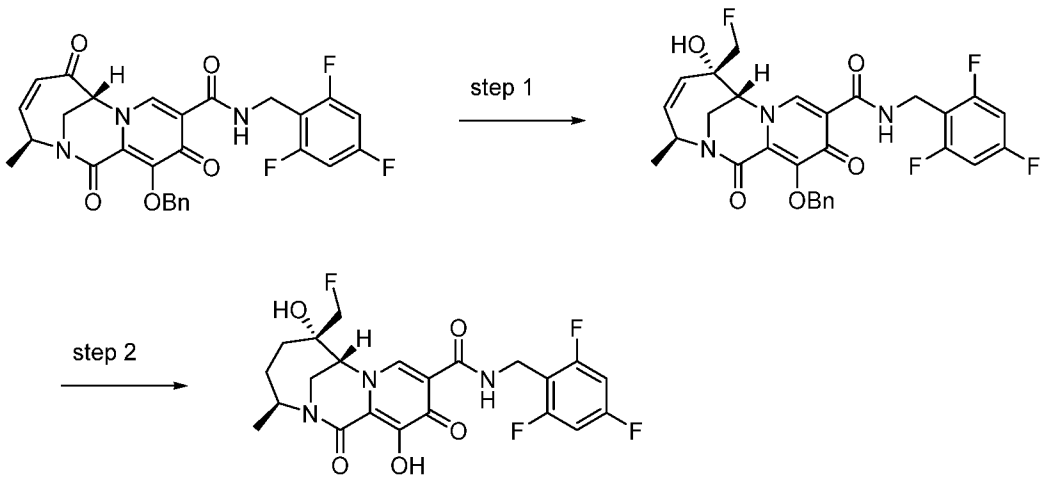
Example 43: Preparation of (3S,6S,7R)-N-(2,4-difluorobenzyl)-6,12-dihydroxy-3,7-dimethyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



[0340] (3S,6S,7R)-N-(2,4-difluorobenzyl)-6,12-dihydroxy-3,7-dimethyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide was made in a similar manner as (3S,6S,7R)-N-(2,4-difluorobenzyl)-6,12-dihydroxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (Example 16) except using benzyl (3S,7S)-3-(((benzyloxy)carbonyl)amino)-3,7-dimethyl-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate instead of benzyl (3S,7S)-3-(((benzyloxy)carbonyl)amino)-7-methyl-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate. MS (*m/z*) 448.27 $[M+H]^+$. 1H NMR (400 MHz, Chloroform-d) δ 10.64 – 10.42 (m, 1H), 8.59 (s, 2H), 7.47 – 7.32 (m, 1H), 6.96 – 6.58 (m, 2H), 4.99 – 4.32 (m, 2H), 3.96 (d, J = 4.7 Hz, 1H), 3.62 (d, J =

14.9 Hz, 1H), 3.38 (dd, J = 14.9, 2.0 Hz, 2H), 2.14 – 1.76 (m, 4H), 1.57 (s, 3H), 1.45 – 1.07 (m, 3H).

Example 44: (3S,6S,7R)-6-(fluoromethyl)-6,12-dihydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide



Step 1: Synthesis of (3S,6S,7R)-12-(benzyloxy)-6-(fluoromethyl)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

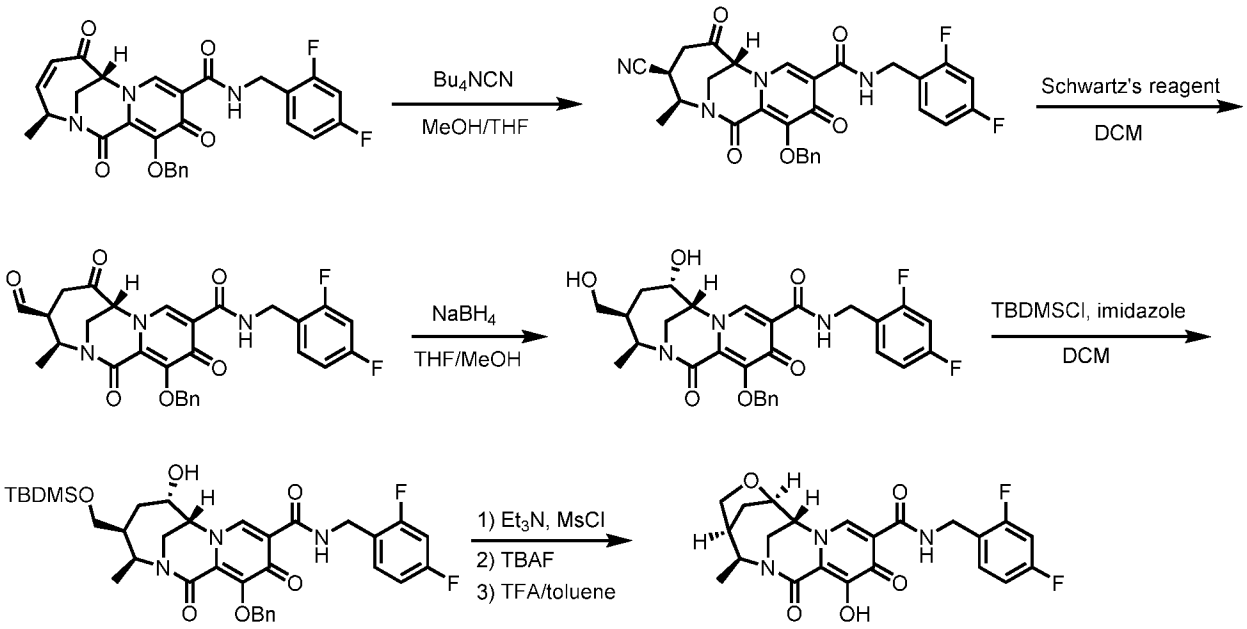
[0341] To a stirred solution of (3S,7R)-12-(benzyloxy)-3-methyl-1,6,11-trioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (220 mg, 0.409 mmol) in dry mixture of THF:Et_2O (12 ml, 1:1, v/v) cooled at -78 °C, fluoroiodomethane (164 mg, 2.5 eq.) was added. Then, a solution of MeLi-LiBr complex (1.5 M, in Et2O, 2 eq.) was added dropwise. After stirring for 5 min at -78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 ml). The mixture was poured into water (50 ml) and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. Flash chromatography on the crude afforded (3S,6S,7R)-12-(benzyloxy)-6-(fluoromethyl)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-

1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide. MS (*m/z*) 572.157$[M+H]^+$.

Step 2: Synthesis of (3S,6S,7R)-6-(fluoromethyl)-6,12-dihydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0342] (3S,6S,7R)-12-(benzyloxy)-6-(fluoromethyl)-6-hydroxy-3-methyl-1,11-dioxo-N-(2,4,6-trifluorobenzyl)-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (5.8 mg, 0.0102 mmol) was dissolved in MeOH (5.0 mL) at room temperature and treated with 2 mg of 20% $Pd(OH)_2/C$ (50 wt% water). The mixture was degassed and flushed with hydrogen 3 times before it was hydrogenated under hydrogen balloon for overnight. The reaction was then degassed and flushed with nitrogen, filtered through a pad of Celite, concentrated, the resulting residue was redissolved in DMF, filtered and purified by reverse phase HPLC. MS (*m/z*) 484.227 $[M+H]^+$. 1H NMR (400 MHz, Chloroform-d) δ 11.12 (s, 1H), 10.22 (t, J = 5.7 Hz, 1H), 8.35 (s, 1H), 6.65 (dd, J = 8.7, 7.5 Hz, 2H), 4.81 – 4.60 (m, 4H), 4.60 – 4.49 (m, 1H), 4.45 (dd, J = 14.5, 5.1 Hz, 1H), 4.26 (s, 1H), 3.79 – 3.62 (m, 2H), 2.15 – 2.05 (m, 1H), 2.00 – 1.92 (m, 1H), 1.80 (s, 1H), 1.65 (s, 1H), 1.29 (d, J = 6.8 Hz, 3H).

Example 45: Preparation (3S,4S,7R,8R)-N-(2,4-difluorobenzyl)-13-hydroxy-3-methyl-1,12-dioxo-1,4,5,7,8,12-hexahydro-3H-2,8:4,7-dimethanopyrido[1,2-d][1,4,7]oxadiazecine-11-carboxamide



Step 1: Preparation of (3S,4S,7R)-12-(benzyloxy)-4-cyano-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0343] To a solution of (3S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (512 mg, 0.985 mmol, 1 Eq) in THF/MeOH (1:1) (18 mL) was added tetrabutylammonium cyanide (397 mg, 1.48 mmol, 1.5 Eq) and the resulting solution was stirred at room temperature for 2 days. EtOAc (20 mL) was added and the resulting mixture was washed with saturated aqueous sodium carbonate and brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel using a gradient of MeOH in DCM (0 to 10%) to afford the desired product as a mixture of the parent ketone as well as the ketone hydrate and hemiketal with methanol. The

stereochemistry at the position alpha to the cyano group was assigned by 2D NMR spectroscopy using Nuclear Overhauser Effect correlation of the diol product obtained after step 3.

Step 2: Preparation of (3S,4S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-4-formyl-3-methyl-1,6,11-trioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0344] A solution of (3S,4S,7R)-12-(benzyloxy)-4-cyano-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (179 mg, 0.317 mmol, 1 Eq) in DCM (5 mL) was cooled to 0 °C under N_2. Bis(cyclopentadienyl)zirconium(IV) chloride hydride (Schwartz's reagent, 425 mg, 0.159 mmol, 5 Eq.) was added and the resulting mixture was stirred for 1 h at 0 °C and then 15 minutes at rt. Water was added and the mixture was extracted 3x with DCM. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The resulting residue was filtered through a plug of silica to remove any Zr species using a gradient of MeOH in DCM (0 to 20%) to afford the desired product as a mixture of the parent carbonyl as well as carbonyl hydrates, hemiketals with MeOH and overreduction products. The mixture was use directly in Step 3 below.

Step 3: Preparation of (3S,4S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-4-(hydroxymethyl)-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

[0345] To a solution of the product mixture from Step 2 (above) (169 mg, 0.298 mmol, 1 Eq) in THF/MeOH (1:1) (12 mL) at 0 °C was added sodium borohydride (22.5 mg, 0.596 mmol, 2 Eq) and the resulting mixture was stirred for 10 minutes at room temperature then concentrated in vacuo. Water was added and the pH was adjusted to ~5 by addition of dilute acetic acid. The mixture was extracted twice with DCM and the combined organic layers were

washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by reverse phase preparative high performance liquid chromatography using a gradient of MeCN in H_2O (40% to 80% with 0.1% TFA) to afford the desired product.

Step 4: Preparation of (3S,4S,6S,7R)-12-(benzyloxy)-4-(((tert-butyldimethylsilyl)oxy)methyl)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide:

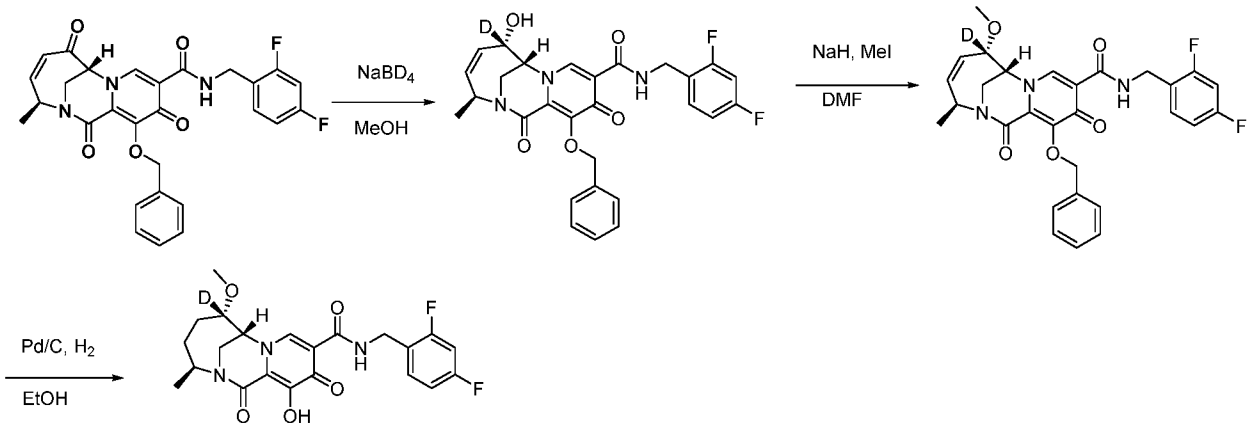
[0346] To a solution of (3S,4S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-4-(hydroxymethyl)-3-methyl-1,11-dioxo-1,4,5,6,7,11-hexahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (15 mg, 0.027 mmol, 1 Eq) in DMF (1.0 mL) was added tert-butylchlorodimethylsilane (22.7 mg, 0.135 mmol, 5 Eq) and imidazole (10 mg, 0.149 mmol, 5.5 Eq) and the resulting mixture was stirred for 30 minutes at 60 °C. The reaction mixture was partitioned between water and EtOAc and the layers were separated. The aqueous layer was extracted twice with EtOAc and the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was used directly in Step 5 without further purification.

Step 5: Preparation of (3S,4S,7R,8R)-N-(2,4-difluorobenzyl)-13-hydroxy-3-methyl-1,12-dioxo-1,4,5,7,8,12-hexahydro-3H-2,8:4,7-dimethanopyrido[1,2-d][1,4,7]oxadiazecine-11-carboxamide:

[0347] To a solution of the crude residue from step 5 (assumed to be 0.0271 mmol, 1 Eq) in DCM (6 mL) was added triethylamine (22.7 uL, 0.163 mmol, 6 Eq) and MsCl (6.29 uL, 0.0813 mmol, 3 Eq) under N_2 atmosphere and the resulting solution was stirred at room temperature for 5 minutes. Tetrabutylammonium fluoride (1.0 M in THF, 0.569 mL, 0.569 mmol, 21 Eq) was added directly to the reaction and the resulting solution was stirred in a sealed vial at 45 °C for 2 days. The reaction mixture was concentrated in vacuo and partitioned between water and

EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The resulting residue was taken up into TFA/toluene (1:1) (2 mL) and stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo and purified by reverse phase preparative high performance liquid chromatography using a gradient of MeCN in H_2O (10% to 90% with 0.1% TFA) and normal phase silica gel column chromatography using a gradient of MeOH in DCM (0 to 20%) to afford the desired compound. MS (*m/z*) 446.200 $[M+H]^+$ ^1H NMR (400 MHz, CD_3CN) δ 10.63 (s, 1H), 10.32 (s, 1H), 8.43 (s, 1H), 7.40 (td, *J* = 8.8, 6.5 Hz, 1H), 7.00 – 6.88 (m, 2H), 4.65 (p, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 6.0 Hz, 2H), 4.54 – 4.47 (m, 1H), 4.31 (dt, *J* = 4.9, 2.3 Hz, 1H), 4.23 (dd, *J* = 9.9, 1.5 Hz, 1H), 3.85 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.60 – 3.38 (m, 2H), 2.71 (q, *J* = 6.2 Hz, 1H), 2.02 (dt, *J* = 14.7, 7.4 Hz, 1H), 1.59 (d, *J* = 14.7 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H).

Example 46: (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-6-d-10-carboxamide



[0348] Step 1: Preparation of (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-6-d-10-carboxamide:

[0349] To a solution of (3S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-3-methyl-1,6,11-trioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-10-carboxamide (100

mg, 0.192 mmol) in MeOH (5 mL) was added cerium (III) chloride heptahydrate (717 mg, 0.192 mmol). Then to the mixture was added sodium borodeuteride (4 mg, 0.096 mol) slowly. The reaction mixture was stirred at 0 °C. After the reaction was finished, the reaction was quenched by adding sat. NaHCO3, extracted with DCM, the organic phase was separated and dried over MgSO4. Then the separated organic phase was filtered, concentrated down and used in next step without purification.

Step 2: Preparation of (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-6-d-10-carboxamide:

[0350] To a solution of (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-hydroxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-6-d-10-carboxamide (90 mg, 0.172 mmol) in DMF (3 mL) was added sodium hydride (8.3 mg, 0.21 mmol, 60%) and iodomethane (12.9 uL, 0.21 mmol). The reaction mixture was stirred at 0°C for 0.5 h. The reaction was quenched by adding sat. $NaHCO_3$, extracted with EtOAc, the organic phase was separated, dried over $MgSO_4$, filtered, concentrated down and the resulting product was used in next step without further purification.

Step 3: Preparation of (3S,6S,7R)-N-(2,4-difluorobenzyl)-12-hydroxy-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-6-d-10-carboxamide:

[0351] To a solution of (3S,6S,7R)-12-(benzyloxy)-N-(2,4-difluorobenzyl)-6-methoxy-3-methyl-1,11-dioxo-1,6,7,11-tetrahydro-3H-2,7-methanopyrido[1,2-a][1,4]diazonine-6-d-10-carboxamide (60 mg, 0.112 mmol) in EtOH (3 mL) was added Pd/C (38 mg). The reaction mixture was stirred at rt with H2 balloon attached. After the reaction was finished, the reaction mixture was filtered through celite. The filtrate was concentrated down and the residue was purified by reverse phase HPLC, eluting with 4-100% ACN in water, containing 0.1% TFA, to afford the title compound. MS (*m/z*) 449.2 $[M+H]^+$. 1H NMR (400 MHz, Methanol-d4) δ 8.36

(s, 1H), 7.44 (td, J = 8.4, 6.3 Hz, 1H), 7.03 – 6.90 (m, 2H), 4.89 (s, 1H), 4.73 (s, 1H), 4.69 – 4.57 (m, 3H), 3.83 – 3.68 (m, 2H), 3.46 (s, 3H), 2.18 – 1.97 (m, 2H), 1.54 (dt, J = 14.6, 11.3 Hz, 1H), 1.28 (d, J = 6.7 Hz, 3H), 1.00 (dd, J = 14.7, 11.6 Hz, 1H).

Example 47: HIV MT-4 Antiviral and Cytotoxicity Assay

Antiviral assay in MT-4 cells

[0352] Compounds were tested in a high-throughput 384-well assay format for their ability to inhibit the replication of HIV-1 (IIIB) in MT-4 cells. Compounds were serially diluted (1:3) in DMSO on 384-well polypropylene plates and further diluted 200-fold into complete RPMI media (10% FBS, 1% P/S) using the Biotek Micro Flow and Labcyte ECHO acoustic dispenser. Each plate contained up to 8 test compounds, with negative (No Drug Control) and 5 μM AZT positive controls. MT-4 cells were pre-infected with 10 μL of either RPMI (mock-infected) or a fresh 1:250 dilution of HIV-1 IIIB concentrated virus stock. Infected and uninfected MT-4 cells were further diluted in complete RPMI media and added to each plate using a Micro Flow dispenser. After 5 days incubation in a humidified and temperature controlled incubator (37 °C), Cell Titer Glo (Promega) was added to the assay plates and chemiluminescence read using an Envision plate-reader. EC_{50} values were defined as the compound concentration that causes a 50% decrease in luminescence signal, and were calculated using a sigmoidal dose-response model to generate curve fits.

Cytotoxicity assay in MT-4 cells

[0353] Assays were performed as above except uninfected MT-4 cells were added to each well containing test compound. In addition, 10 μM puromycin was added to the last column of each assay plate to assess a base level of cytotoxicity.

Example 48: HIV MT-4 Serum Shift Antiviral Reporter Assay

[0354] To quantify the amount of protein binding to human serum, compounds were serially diluted (1:3) in DMSO and acoustically transferred onto 384-well assay plates via a Labcyte ECHO robot. Each plate contained up to 8 test compounds, including negative and positive controls, (DMSO, 5 μM AZT respectively). Assay plates were prepared in duplicate, and tested in either CCM (cell culture media) or HS/CCM (human serum/cell culture media). MT-4 cells were first pre-infected with pLai RLuc reporter virus for 2 h at 37 °C, then further diluted in either CCM (RPMI media, 10% FBS, 1% P/S) or HS/CCM (RPMI media, 10% FBS, 50% HS, 1% P/S), and subsequently added to each plate using a Biotek Micro Flow dispenser. After a 72-h incubation in a humidified and temperature controlled incubator (37 °C), Renilla Glo (Promega) was added to all assay plates and chemiluminescence read using an Envision plate-reader. EC_{50} values were defined as the compound concentration that causes a 50% decrease in luminescence signal, and were calculated using a sigmoidal dose-response model to generate curve fits. To determine the amount of protein binding, EC_{50} fold shifts (or EC_{50} shifts) were calculated by dividing EC_{50} (HS/CCM) / EC_{50} (CCM).

[0355] Compounds of the present disclosure demonstrate antiviral activity in this assay as depicted in Table 1 below. Accordingly, the compounds of the embodiments disclosed herein may be useful for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.

Example 49: High Throughput Microsomal Stability Assay

[0356] Metabolic stability of compounds was assessed using Human, or Rat Liver Microsomal assays (Corning). In this assay, 10 nL compounds at concentration of 1 mM in 100% DMSO were dispensed into 384-well polypropylene plates using the Echo 550 acoustic

liquid dispenser (Labcyte®). Each plate contained 384 wells with a single test compound in each well.

[0357] A solution of human (Corning® Gentest™ Human Mixed Pooled Microsomes), or rat (Corning® Gentest™ Rat [Sprague-Dawley] Pooled Liver Microsomes) liver microsomes at 2 mg/ml in 100 mM K_2HPO_4/KH_2PO_4 pH 7.4 with Alamethicin from *Trichoderma viride* (Sigma-Aldrich) 0.0225 mg/ml were incubated on ice for 15 minutes. 5 uL of this solution was added to individual wells following 15 minute incubation at room temperature; and supplemented with 5 uL NADPH Regenerating Solution of cofactors (Corning® Gentest™ UGT Reaction Mix) containing 100 mM K_2HPO_4/KH_2PO_4 pH 7.4, 2.6 mM NADP+, 6.6 mM glucose-6-phosphate, 6.6 mM $MgCl_2$, 0.8 U/mL glucose-6-phosphate dehydrogenase, 0.1 mM Sodium Citrate, 6.8 mM uridine diphosphate-glucuronic acid. Final concentration of analyte compounds at the beginning of the reaction was 1 uM. The reactions were incubated at 37 °C and time points of 0, 5, 15, 30, 40, 50, 60, and 70 minutes were collected for further analysis. Background data were collected using reactions without analyte compounds.

[0358] Upon collection of the reaction time points, samples were quenched with 30 uL of a solution of 72% acetonitrile, 8% methanol, 0.1% formic acid, 19.9% water, and internal standard (IS). Reaction plates were span in a centrifuge at speed of 4,000 rcf for 30 minutes and 4 °C, following a dilution of the 10 uL quenched reaction into 40 uL de-ionized water, yielding assay plates.

[0359] Assay plates were analyzed using solid-state extraction coupled with quadrupole time-of-flight mass spectrometer, using Agilent QToF 6530 RapidFire 360 system, with C4 type A solid state cartridges. Analysis was performed in either positive or negative ionization modes. Mobile phases contained 0.1% formic acid in water for loading analytes onto solid state extraction cartridges, and 0.1% formic acid in acetonitrile for elution into mass spectrometer in positive ionization mode, or 0.1% acetic acid in water for loading and 0.1% acetic acid in

acetonitrile for extraction in negative ionization mode. Peak-area ratios of integrated counts for individual compounds to IS were plotted as semi-logarithmic chart of log vs time. Initial, linear portion of decay was fitted to a linear regression equation to derive half time of a compound decay.

[0360] Pharmacological parameters for an analyte compound metabolism were calculated using the following equations:

Parameter	Equation
Half Life	$T_{1/2} = \frac{Ln(2)}{-1 * Slope}$
Intrinsic Clearance (*in vitro*)	$Cl_{int,\,in\,vitro} = \frac{\ln 2}{T_{1/2} * Conc}$
Intrinsic Clearance	$Cl_{int} = \frac{Cl_{int,\,in\,vitro} * Liver\ Mass * Yield}{Body\ Weight}$
Predicted Hepatic Clearance	$Cl = \frac{Cl_{int} * Q_H}{Cl_{int} + Q_H}$
Hepatic Extraction	$E = \frac{Cl}{Q_H} * 100\%$

Where:

Calculation of in vitro intrinsic clearance

$$CL_{int,\,in\,vitro} = \frac{\ln 2}{Half\text{-}Life * Concentration}$$

[0361] Concentration refers to the protein concentration (mg/mL) in the reaction.

System	Concentration
"Mixed cofactor" Hepatic microsomes (+UDPGA +NADPH)	1.0 mg protein/mL

Calculation of in vivo intrinsic clearance

[0362] This scales the in vitro intrinsic clearance up to the value that would be predicted for the entire mass of liver tissue (but with no restriction by blood flow). The value depends upon the size of the liver (species-dependent) and the yield of microsomal protein as appropriate (assumed to be species-independent).

$$CL_{int} = \frac{CL_{int,\ in\ vitro} * Liver\ mass * Yield}{Body\ weight}$$

Matrix	Yield
Microsomal fraction	45 mg/g liver

Species	Body weight	Liver weight
	kg	**g**
Human	70	1800

Calculation of predicted clearance

[0363] Hepatic clearance will depend upon the inter-relationship of intrinsic clearance and hepatic blood flow and can be predicted from *in vitro* data using a variety of approaches.

$$CL = \frac{CL_{int} * Q_H}{CL_{int} + Q_H}$$

Species	Hepatic blood flow
	L/hr/kg
Human	1.3

Calculation of hepatic extraction

[0364] This is simply the predicted clearance expressed as a proportion of hepatic blood flow.

$E = CL / Q_H * 100\%$

[0365] Intrinsic clearance of the instant compounds, as well as for reference compounds A-F, were calculated following the procedure above. The results of these compounds are shown in Table 2 below. As seen, the instant compounds are 1.5 to 3.6 times more stable than the Reference compounds A-F.

Table 1

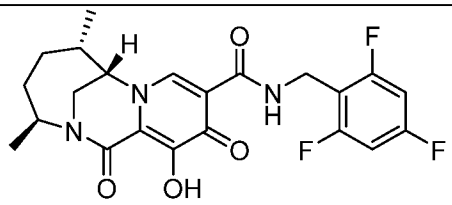
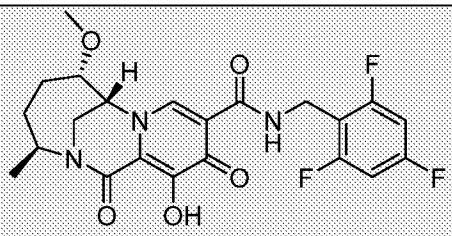
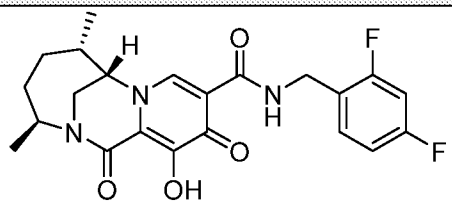
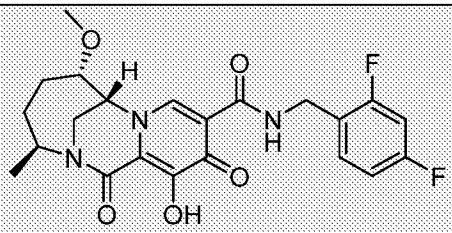
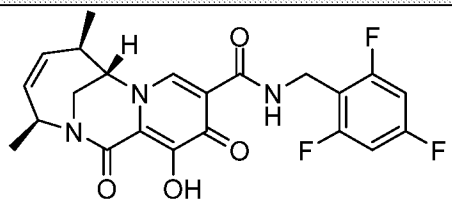
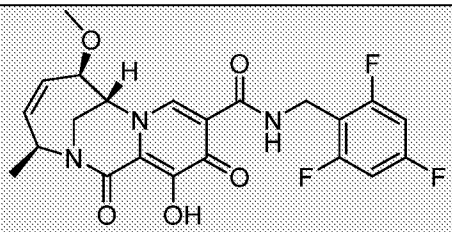
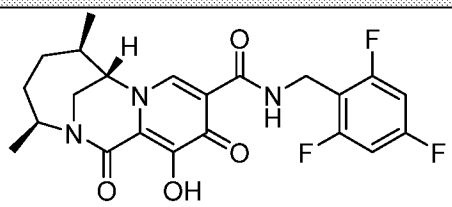
	MT4 EC_{50} (nM)	CC_{50} (nM)	RLUC CCM (nM)	RLUC 50% HS (nM)	RLUC Shift	HLM stability L/h/Kg
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2	1.8	50000	0.53	40	76	0.15
3	1.5	16498	0.42	13	30	0.15
4	1.1	11167	0.34	7.5	22	0.14

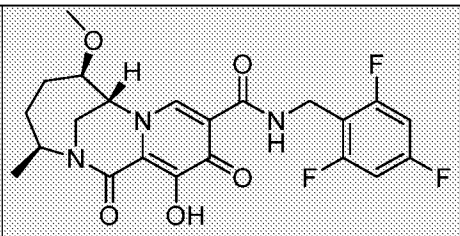
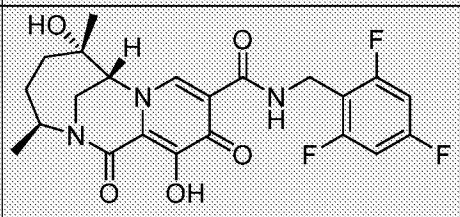
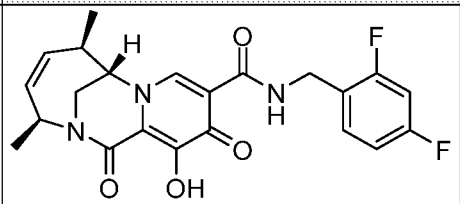
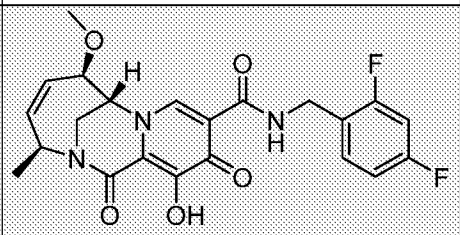
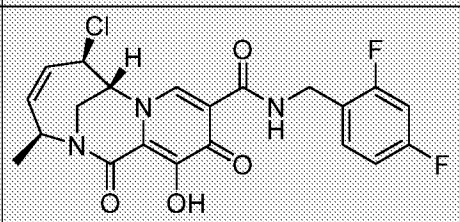
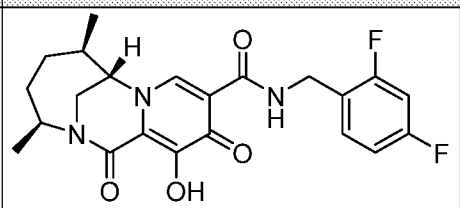
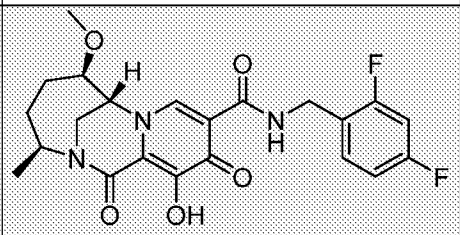
	MT4 EC_{50} (nM)	CC_{50} (nM)	RLUC CCM (nM)	RLUC 50% HS (nM)	RLUC Shift	HLM stability L/h/Kg
5	1.8	50000	0.71	17	24	0.20
6	1.4	13013	0.50	87	174	0.29
7	1.2	9906	0.29	4.8	16	0.20
8	1.4	10671	0.34	34	100	0.22
9	1.0	4272	0.42	30	72	0.48
10	1.2	4015	0.28	22	79	0.40
11	1.5	38651	0.84	72	86	0.25
12	1.4	41294	0.61	47	76	0.15
13	1.5	15605	0.55	22	41	0.26
14	4.2	50000				0.16
15	7.9	28431	1.64	47	29	0.19
16	2.6	41407	1.14	52	46	0.11
17	3.0	31379	1.33	34	26	0.17
18	1.4	13441	0.55	5.3	10	0.73
19	1.1	20000	0.38	2.4	6	0.47

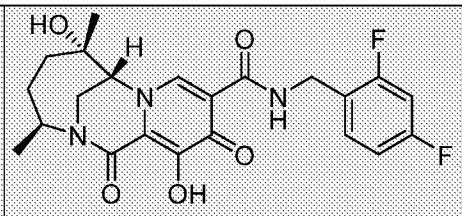
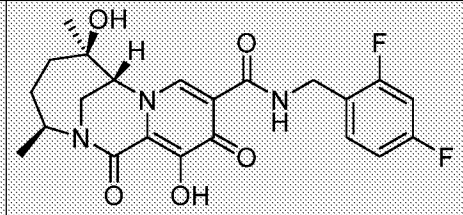
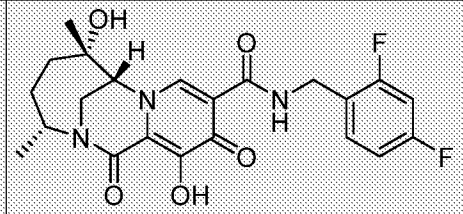
	MT4 EC_{50} (nM)	CC_{50} (nM)	RLUC CCM (nM)	RLUC 50% HS (nM)	RLUC Shift	HLM stability L/h/Kg
20	2.8	30009				0.11
21	1.8	19331	0.52	3.4	7	0.37
22	1.7	8914.7				0.84
23	2.2	9790.3	0.47	22	47	0.7
24	2.2	11101				0.69
25	4.1	43655	0.82	15	18	0.58
26	4.4	44336	0.92	212	231	0.22
27	1.1	13601	0.35	28	80	0.88
28	4.1	24443	0.96	39	40	0.34
29	2.0	12998	0.74	23	30	0.11
30	2.1	7478.2				0.11
31	2.1	8226.7	0.36	16	45	0.18
32	1.9	34620	0.43	3.9	9	0.54
33	2.1	22780	0.36	9.4	26	0.35
34	0.9	15134	0.42	20	47	0.25

	MT4 EC_{50} (nM)	CC_{50} (nM)	RLUC CCM (nM)	RLUC 50% HS (nM)	RLUC Shift	HLM stability L/h/Kg
35	3.2	11712	1.45	4.3	3	0.62
36	2.6	27314	0.33	14	43	0.2
37	1.4	14802	0.65	191	294	0.17
38	1.8	25460	0.34	101	298	0.19
39	1.5	11708	1.5	257	171	0.28
40	1.1	19598	2.87	450	157	0.28
41	1.7	19370	0.56	28	50	0.11
42	1.9	50000	0.61	2.4	4	0.58
43	1.3	23608	0.71	97	137	0.29
44	4	44695	1.9	389	205	0.22
45	1.9	12404	0.46	0.86	2	0.17

Table 2

Compound	GS No.	Structure	MS Cl	MS Cl improvement
A (186)	GS-1074961		0.68	
Example 1	GS-1152221		0.21	3.2 times relative to compound A
B (187)	GS-1075233		0.48	
Example 3	GS-1153195		15	3.2 times relative to compound B
C (176)	GS-1073795		0.51	
Example 4	GS-1153196		0.14	3.6 times relative to compound C
D (174)	GS-1073699		0.68	

Example 6	GS-1155372		0.29	2.3 times relative to compound D
Example 11	GS-1152096		0.25	2.7 times relative to compound D
E (177)	GS-1073796 (lead)		0.39	
Example 7	GS-1156005		0.2	2.0 times relative to compound E
Example 13	GS-1151383		0.26	1.5 times relative to compound E
F (175)	GS-1073701		0.49	
Example 8	GS-1156006		.22	2.2 times relative to compound F

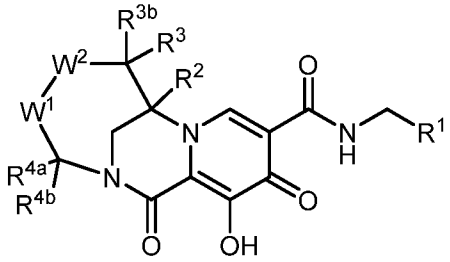
Example 12	GS-1152107		0.15	3.3 times relative to compound F
Example 33	GS-1159776		0.35	
Example 35	GS-1161234		0.62	

[0366] All references, including publications, patents, and patent documents are incorporated are incorporated by reference herein, as though individually incorporated by reference. The present disclosure provides reference to various embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the present disclosure. The description is made with the understanding that it is to be considered an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated.

Claims

What is claimed:

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is C_{6-10}aryl or 5 to 10 membered heteroaryl, wherein the C_{6-10}aryl or 5 to 10 membered heteroaryl is optionally substituted with one to four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkyl–O–C_{1-4}alkyl;

R^2 is H, C_{1-6}alkyl, or C_{1-4}haloalkyl;

R^3 is halo or –OR^{3a}, wherein R^{3a} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{3-6}cycloalkyl; or

R^{3a} and any one of R^2, R^{5a}, and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S;

R^{3b} is H, –C_{1-6}alkyl, –C_{1-4}haloalkyl, or –C_{1-4}alkylene–O–C_{1-4}alkyl;

R^{4a} is –C_{1-6}alkyl or –C_{1-4}haloalkyl;

R^{4b} is H, halo, –C_{1-6}alkyl, or –C_{1-4}haloalkyl;

W^1 is a bond or –$CR^{5a}R^{5b}$–;

R^{5a} and R^{5b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo; or

R^{5a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{5b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo;

W^2 is –$CR^{6a}R^{6b}$– or –CR^{7a}=CR^{7b}–;

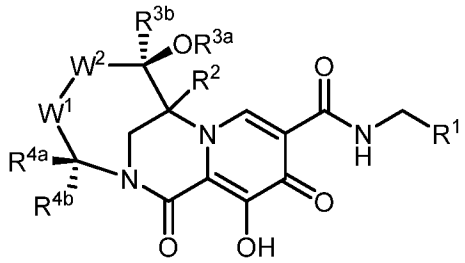
R^{6a} and R^{6b} are independently H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkylene–O–C_{1-4}alkyl; or

R^{6a} and R^{3a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S; and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkylene–O–C_{1-4}alkyl;

R^{7a} and R^{7b} are independently H, halo, C_{1-4}haloalkyl, or C_{1-6}alkyl; or

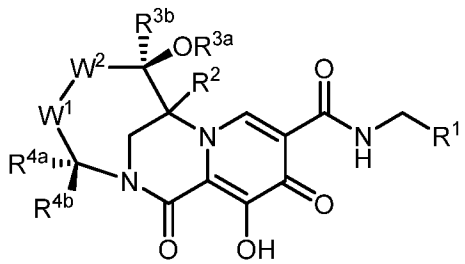
R^{7a} and R^{7b} together with the carbons to which they are attached form a C_{5-10}aryl optionally substituted with one to four R^{A2}, wherein each R^{A2} is independently halo, cyano, or C_{1-4}alkyl.

2. The compound of claim 1, or the pharmaceutically acceptable salt thereof, wherein the compound is of a Formula Ia:



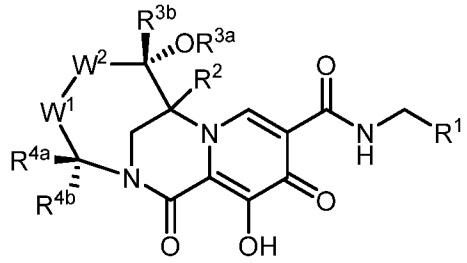
Formula Ia.

3. The compound of claim 1, or the pharmaceutically acceptable salt thereof, wherein the compound is of a Formula Ib:



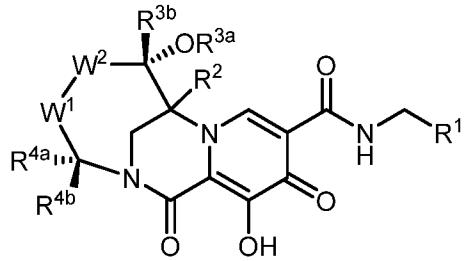
Formula Ib.

4. The compound of claim 1, or the pharmaceutically acceptable salt thereof, wherein the compound is of a Formula Ic:



Formula Ic.

5. The compound claim 1, or the pharmaceutically acceptable salt thereof, wherein the compound is of a Formula Id:



Formula Id.

6. The compound of any one of claims 1-5, or the pharmaceutically acceptable salt thereof, wherein R^1 is phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine, wherein the phenyl, pyridyl, pyridazine, pyrazine, or pyrimidine is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or –C_{1-4}alkyl–O–C_{1-4}alkyl.

7. The compound of any one of claims 1-6, or the pharmaceutically acceptable salt thereof, wherein R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or –C_{1-4}alkyl–O–C_{1-4}alkyl.

8. The compound of any one of claims 1-7, or the pharmaceutically acceptable salt thereof, wherein R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently a halogen.

9. The compound of any one of claims 1-8, or the pharmaceutically acceptable salt thereof, wherein R^1 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with two or three R^{A1}, wherein each R^{A1} is independently selected from chloro and fluoro.

10. The compound of any one of claims 1-7, or the pharmaceutically acceptable salt thereof, wherein R^1 is pyridyl, wherein the pyridyl is optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently wherein each R^{A1} is independently halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}4}$haloalkyl, cyano, –O–$C_{1\text{-}4}$alkyl, or –$C_{1\text{-}4}$alkyl–O–$C_{1\text{-}4}$alkyl.

11. The compound of any one of claims 1-10, or the pharmaceutically acceptable salt thereof, wherein R^1 is pyridyl, wherein the pyridyl is substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently a halogen.

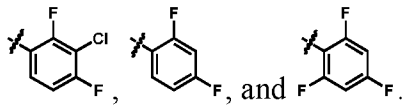
12. The compound of any one of claims 1-11, or the pharmaceutically acceptable salt thereof, wherein R^1 is pyridyl, wherein the pyridyl is substituted with two or three R^{A1}, wherein each R^{A1} is independently selected from chloro and fluoro.

13. The compound of any one of claims 1-7, or the pharmaceutically acceptable salt thereof, wherein R^1 is phenyl, optionally substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently halo, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$haloalkyl, or –O–$C_{1\text{-}4}$alkyl.

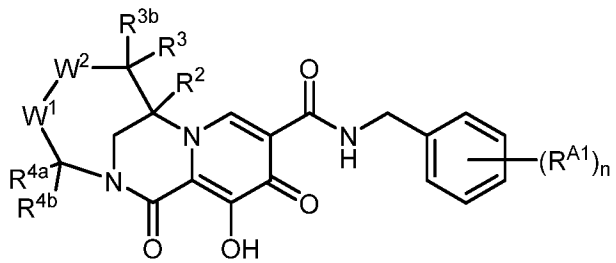
14. The compound of any one of claims 1-7 and 13, or the pharmaceutically acceptable salt thereof, wherein R^1 is phenyl substituted with one, two, three, or four R^{A1}, wherein each R^{A1} is independently a halogen.

15. The compound of any one of claims 1-7, 13, and 14, or the pharmaceutically acceptable salt thereof, wherein R^1 is phenyl substituted with two or three R^{A1}, wherein each R^{A1} is independently selected from chloro and fluoro.

16. The compound of any one of claims 1-15, or the pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of:



17. The compound of any one of claims 1-16, or the pharmaceutically acceptable salt thereof, wherein the compound has a Formula II:



Formula II;

wherein n is 2, 3, or 4; and each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkyl–O–C_{1-4}alkyl.

18. The compound of any one of claims 1-17, or the pharmaceutically acceptable salt thereof, wherein each R^{A1} is independently halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, or –O–C_{1-4}alkyl.

19. The compound of any one of claims 1-18, or the pharmaceutically acceptable salt thereof, wherein each R^{A1} is independently halo.

20. The compound of any one of claims 1-19, or the pharmaceutically acceptable salt thereof, wherein each R^{A1} is independently chloro or fluoro.

21. The compound of any one of claims 1-20, or the pharmaceutically acceptable salt thereof, wherein R^2 is H or C_{1-6}alkyl.

22. The compound of any one of claims 1-20, or the pharmaceutically acceptable salt thereof, wherein R^2 is H or C_{1-4}haloalkyl.

23. The compound of any one of claims 1-20, or the pharmaceutically acceptable salt thereof, wherein R^2 is C_{1-6}alkyl or C_{1-4}haloalkyl.

24. The compound of any one of claims 1-22, or the pharmaceutically acceptable salt thereof, wherein R^2 is H.

25. The compound of any one of claims 1-24, or the pharmaceutically acceptable salt thereof, wherein R^3 is halo.

26. The compound of any one of claims 1-25, or the pharmaceutically acceptable salt thereof, wherein R^3 is chloro.

27. The compound of any one of claims 1-24, or the pharmaceutically acceptable salt thereof, wherein R^3 is OR^{3a}.

28. The compound of any one of claims 1-27, or the pharmaceutically acceptable salt thereof, wherein R^{4a} is $-C_{1-4}$haloalkyl.

29. The compound of any one of claims 1-27, or the pharmaceutically acceptable salt thereof, wherein R^{4a} is $-C_{1-3}$alkyl.

30. The compound of any one of claims 1-27 and 29, or the pharmaceutically acceptable salt thereof, wherein R^{4a} is methyl.

31. The compound of any one of claims 1-30, or the pharmaceutically acceptable salt thereof, wherein R^{4b} is H, $-C_{1-4}$haloalkyl, or $-C_{1-3}$alkyl.

32. The compound of any one of claims 1-31, or the pharmaceutically acceptable salt thereof, wherein R^{4b} is H.

33. The compound of any one of claims 1-32, or the pharmaceutically acceptable salt thereof, wherein:

R^{3a} is $-C_{1-6}$alkyl, $-C_{1-4}$haloalkyl, or $-C_{3-6}$cycloalkyl; and

R^{3b} is H, $-C_{1-6}$alkyl, $-C_{1-4}$haloalkyl, or $-C_{1-4}$alkylene–O–C_{1-4}alkyl.

34. The compound of any one of claims 1-33, or the pharmaceutically acceptable salt thereof, wherein R^{3a} is $-C_{1-6}$alkyl or $-C_{1-4}$haloalkyl.

35. The compound of any one of claims 1-34, or the pharmaceutically acceptable salt thereof, wherein R^{3a} is $-C_{1-6}$alkyl.

36. The compound of any one of claims 1-35, or the pharmaceutically acceptable salt thereof, wherein R^{3a} is methyl or ethyl.

37. The compound of any one of claims 1-36, or the pharmaceutically acceptable salt thereof, wherein R^{3a} is methyl.

38. The compound of any one of claims 1-32, or the pharmaceutically acceptable salt thereof, wherein R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S.

39. The compound of any one of claims 1-32 and 38, or the pharmaceutically acceptable salt thereof, wherein R^{3a} and any one of R^2, R^{5a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom.

40. The compound of any one of claims 1-32, or the pharmaceutically acceptable salt thereof, wherein R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S.

41. The compound of any one of claims 1-32 and 38-40, or the pharmaceutically acceptable salt thereof, wherein R^{3a} and R^2 together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom.

42. The compound of any one of claims 1-32, 38, and 39, or the pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S.

43. The compound of any one of claims 1-32, 38, 39, and 42, or the pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{5a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom.

44. The compound of any one of claims 1-32, 38 and 39, or the pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one or two heteroatoms independently selected from N, O, and S.

45. The compound of any one of claims 1-32, 38, 39, and 44, or the pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{6a} together with the carbons to which they are attached from a 4 to 6 membered heterocyclic ring containing one oxygen atom.

46. The compound of any one of claims 1-45, or the pharmaceutically acceptable salt thereof, wherein R^{3b} is H, $-C_{1-6}$alkyl, $-C_{1-4}$haloalkyl.

47. The compound of any one of claims 1-46, or the pharmaceutically acceptable salt thereof, wherein R^{3b} is H or $-C_{1-6}$alkyl.

48. The compound of any one of claims 1-47, or the pharmaceutically acceptable salt thereof, wherein R^{3b} is H or $-C_{1-3}$alkyl.

49. The compound of any one of claims 1-48, or the pharmaceutically acceptable salt thereof, wherein R^{3b} is H or methyl.

50. The compound of any one of claims 1-49, or the pharmaceutically acceptable salt thereof, wherein R^{3b} is H.

51. The compound of any one of claims 1-50, or the pharmaceutically acceptable salt thereof, wherein W^1 is a bond.

52. The compound of any one of claims 1-50, or the pharmaceutically acceptable salt thereof, wherein W^1 is $-CR^{5a}R^{5b}-$.

53. The compound of any one of claims 1-41 and 44-52, or the pharmaceutically acceptable salt thereof, wherein R^{5a} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo and R^{5b} is H or halo.

54. The compound of any one of claims 1-41 and 44-53, or the pharmaceutically acceptable salt thereof, wherein R^{5a} is H or halo and R^{5b} is H or halo.

55. The compound of any one of claims 1-41 and 44-53, or the pharmaceutically acceptable salt thereof, wherein R^{5a} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, or halo and R^{5b} is H.

56. The compound of any one of claims 1-41 and 44-55, or the pharmaceutically acceptable salt thereof, wherein R^{5a} is H and R^{5b} is H.

57. The compound of any one of claims 1-56, or the pharmaceutically acceptable salt thereof, wherein W^2 is $-CR^{6a}R^{6b}-$.

58. The compound of any one of claims 1-43 and 46-57, or the pharmaceutically acceptable salt thereof, wherein R^{6a} is H and R^{6b} is H, C_{1-6}alkyl, C_{1-4}haloalkyl, halo, hydroxyl, cyano, –O–C_{1-4}alkyl, or C_{1-4}alkylene–O–C_{1-4}alkyl.

59. The compound of any one of claims 1-43 and 46-58, or the pharmaceutically acceptable salt thereof, wherein R^{6a} is H and R^{6b} is H.

60. The compound of any one of claims 1-56, or the pharmaceutically acceptable salt thereof, wherein W^2 is $–CR^{7a}=CR^{7b}–$.

61. The compound of any one of claims 1-60, or the pharmaceutically acceptable salt thereof, wherein R^{7a} and R^{7b} are independently H, halo, C_{1-4}haloalkyl, or C_{1-6}alkyl.

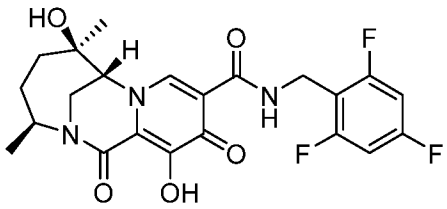
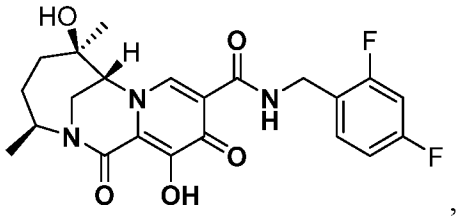
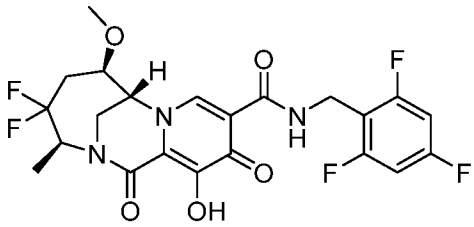
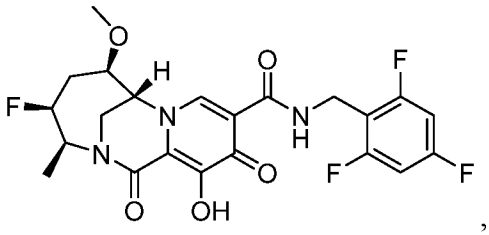
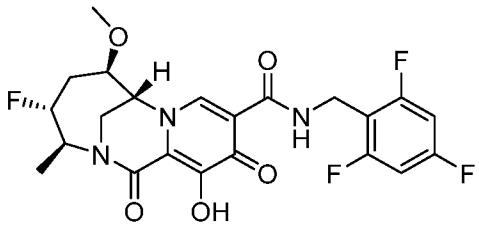
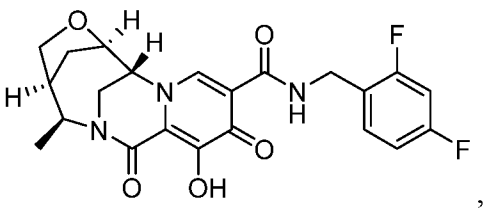
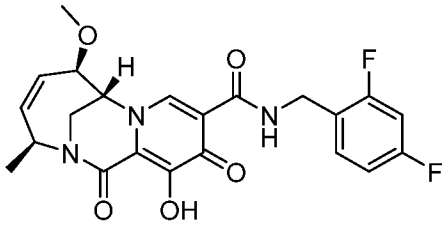
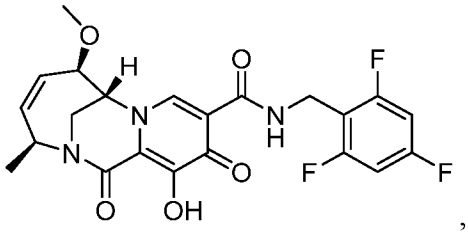
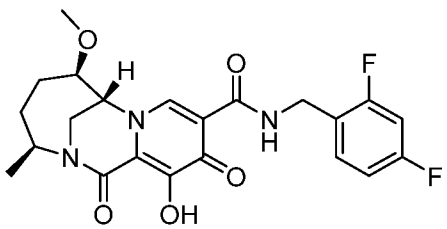
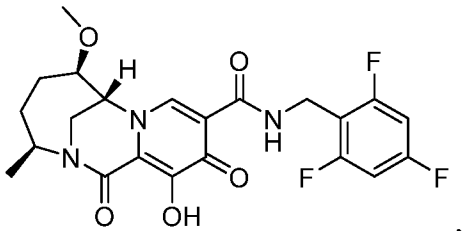
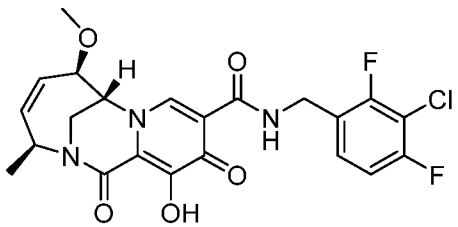
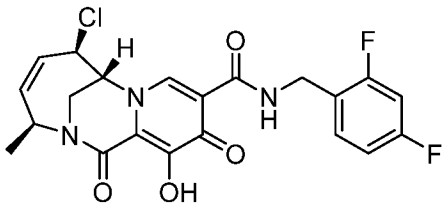
62. The compound of any one of claims 1-61, or the pharmaceutically acceptable salt thereof, wherein R^{7a} is H and R^{7b} is H.

63. The compound of any one of claims 1-60, or the pharmaceutically acceptable salt thereof, wherein R^{7a} and R^{7b} together with the carbon atoms to which they are attached form a C_{5-10}aryl optionally substituted with one to four R^{A2}, wherein each R^{A2} is independently halo, cyano, or C_{1-4}alkyl.

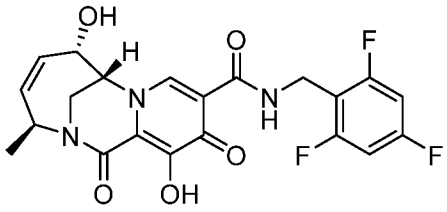
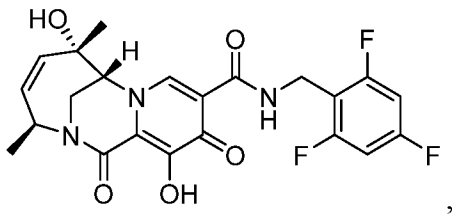
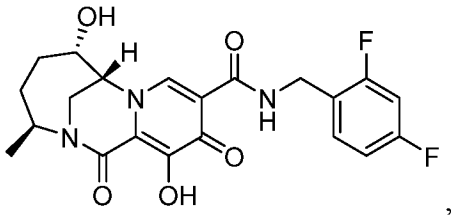
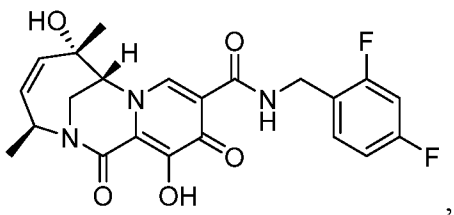
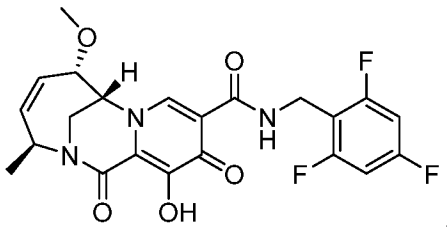
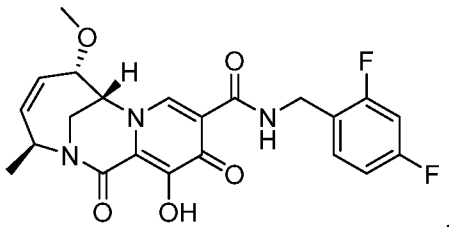
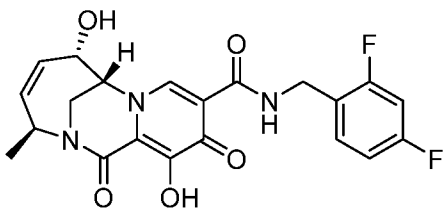
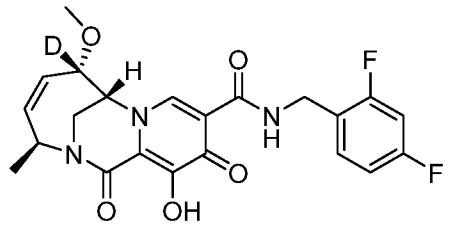
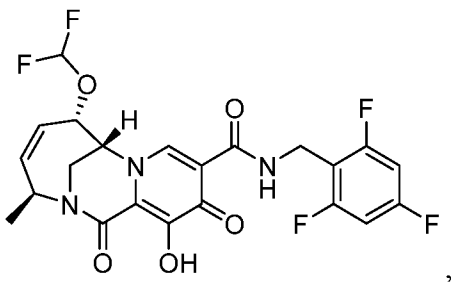
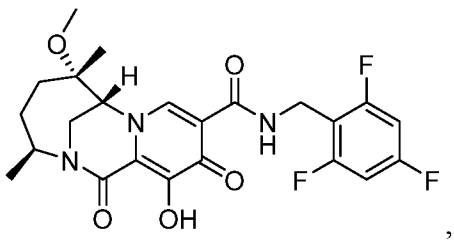
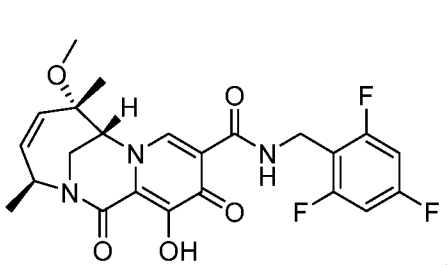
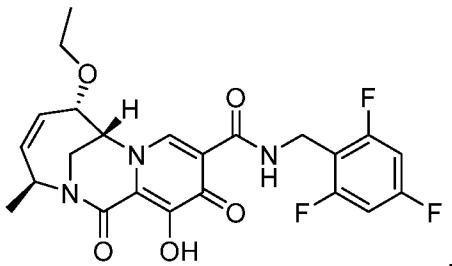
64. The compound of any one of claims 1-60, and 63, or the pharmaceutically acceptable salt thereof, wherein R^{7a} and R^{7b} together with the carbon atoms to which they are attached form a fused phenyl optionally substituted with one to four R^{A2}, wherein each R^{A4} is independently halo, cyano, or C_{1-4}alkyl.

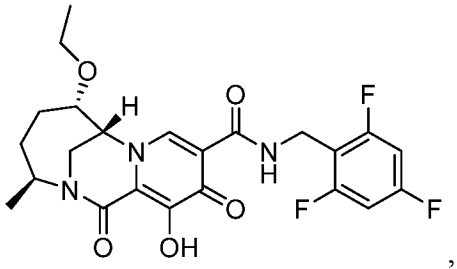
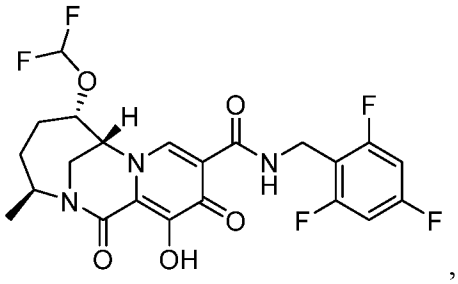
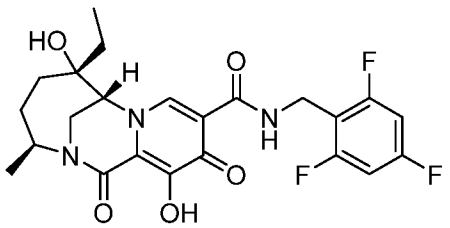
65. The compound of any one of claims 1-60, 63, and 64, or the pharmaceutically acceptable salt thereof, wherein R^{7a} and R^{7b} together with the carbon atoms to which they are attached form an unsubstituted fused phenyl.

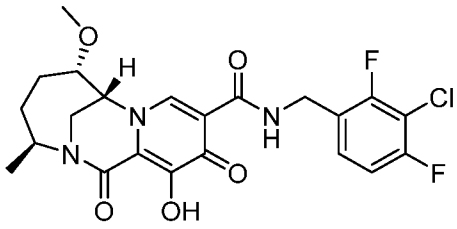
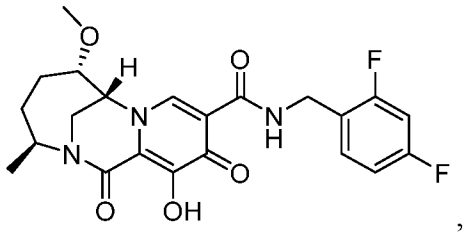
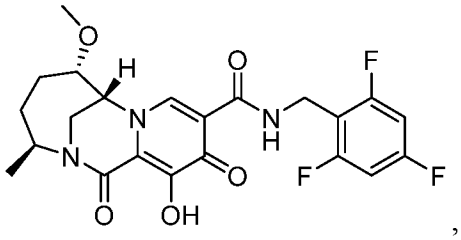
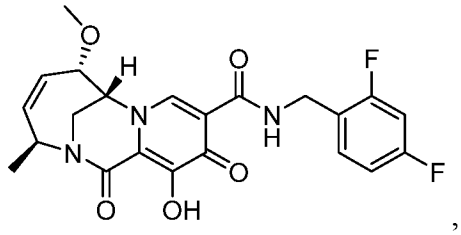
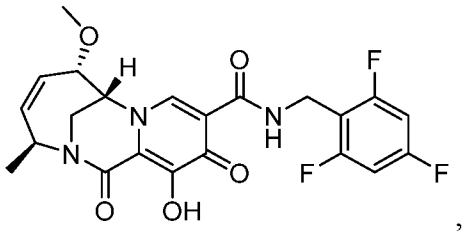
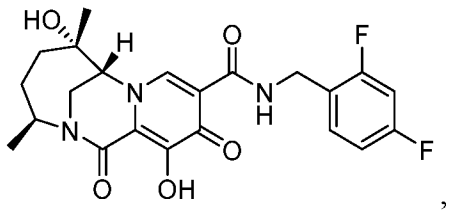
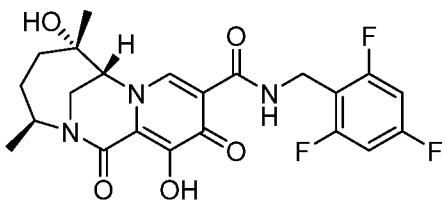
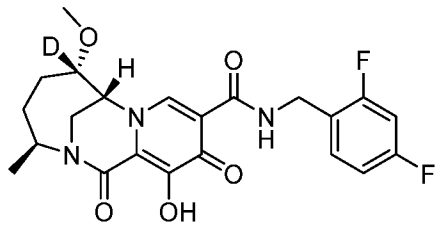
66. A compound selected from the group consisting of


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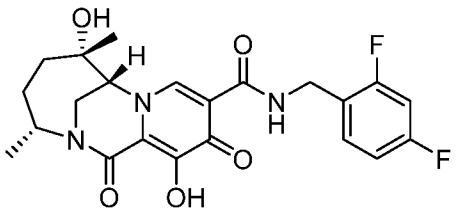
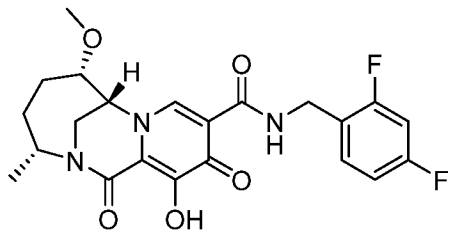
67. A compound selected from the group consisting of


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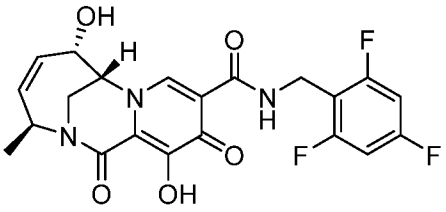
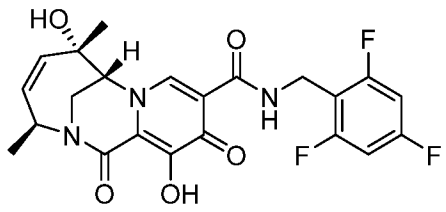
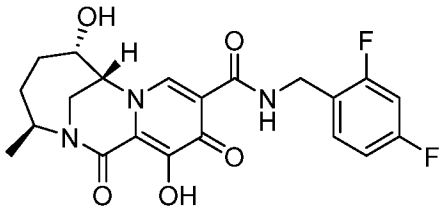
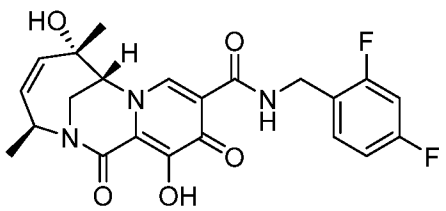
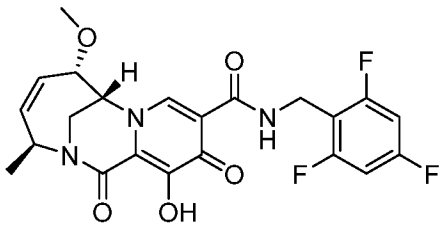
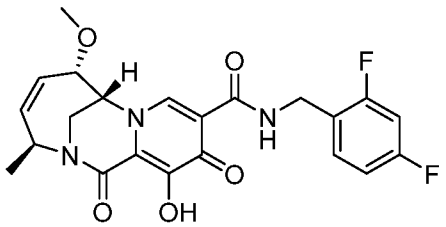
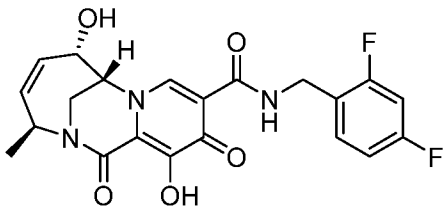
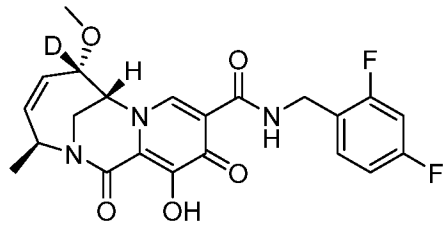
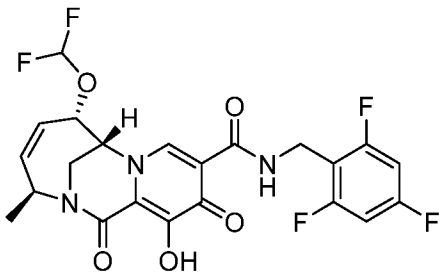
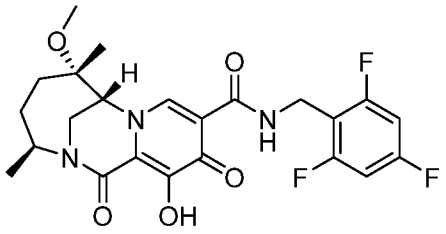
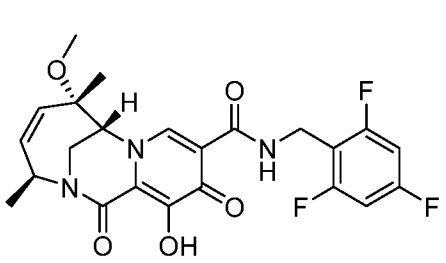
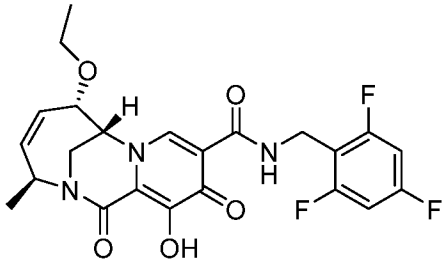

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68. A compound selected from the group consisting of

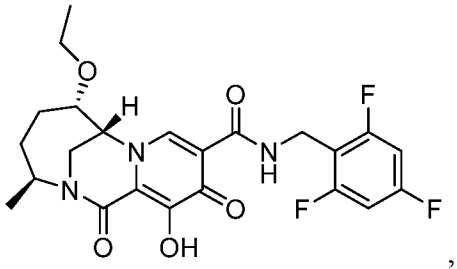
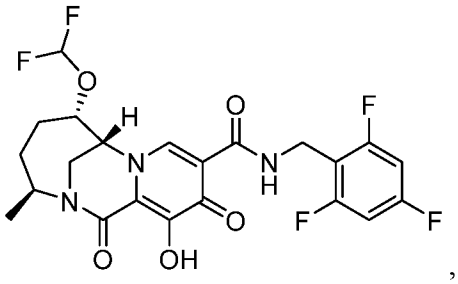
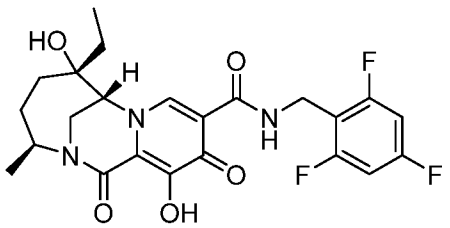
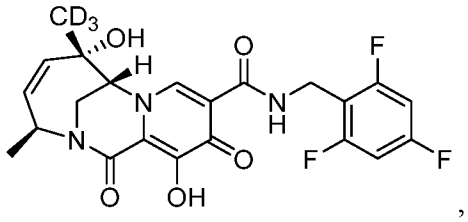
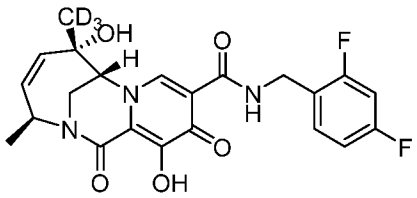
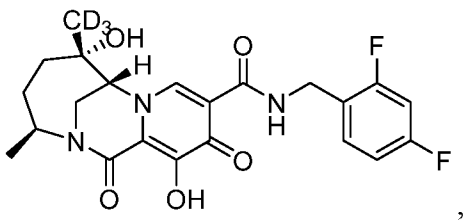
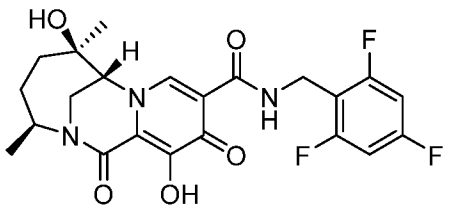
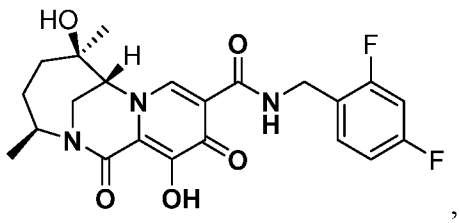
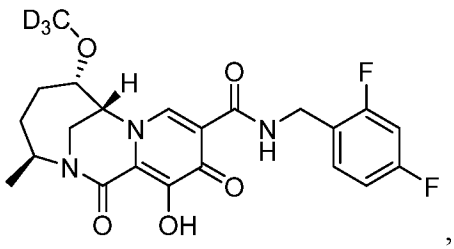
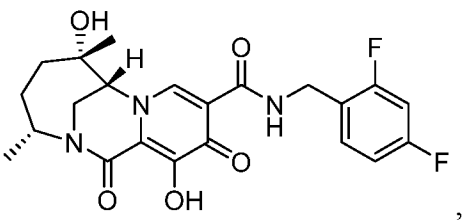
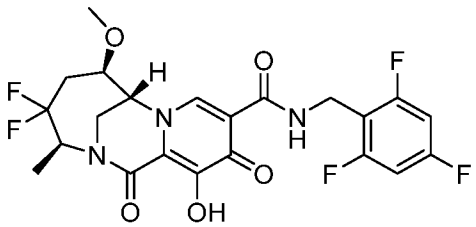
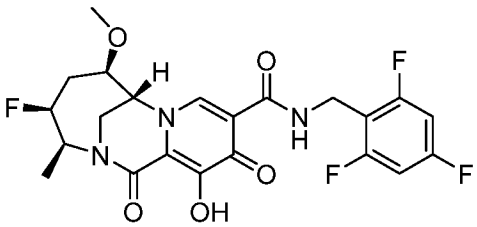
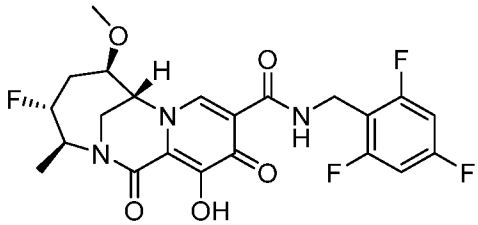
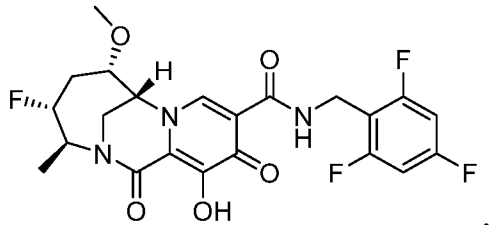

and

; or a pharmaceutically acceptable salt thereof.

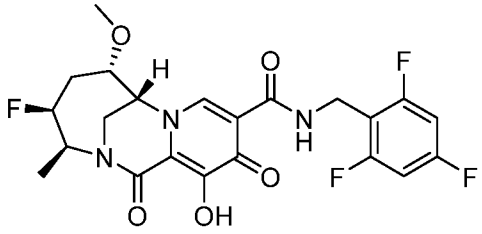
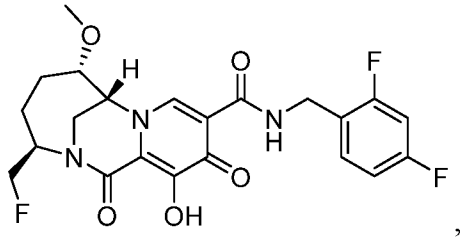
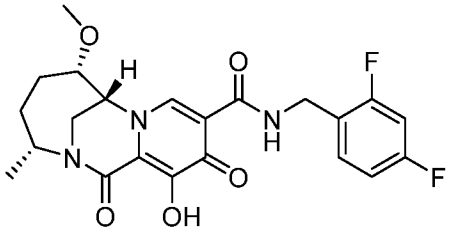
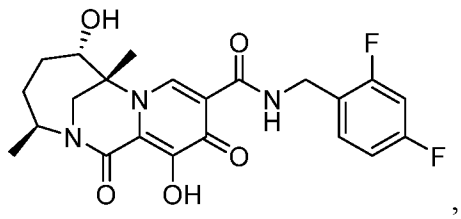
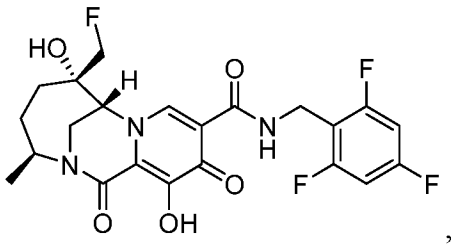
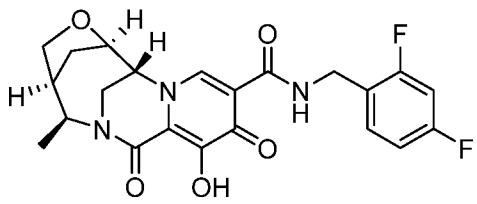
69. A compound selected form a group consisting of:


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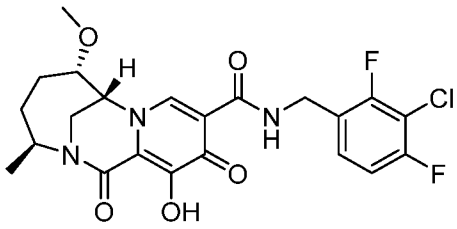
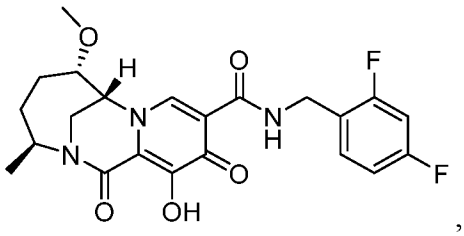
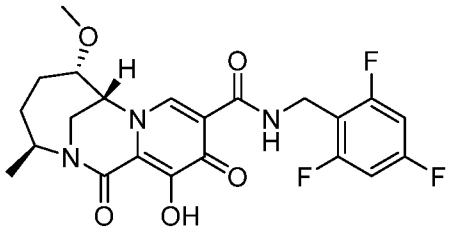
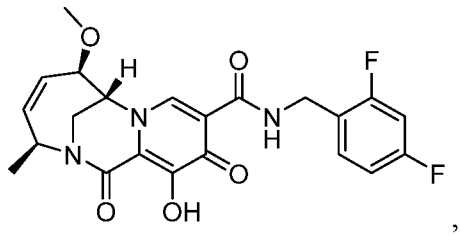
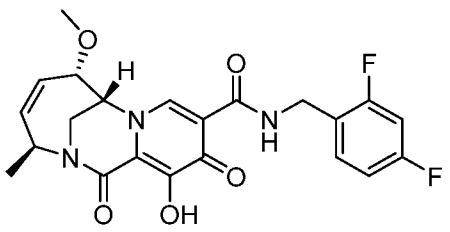
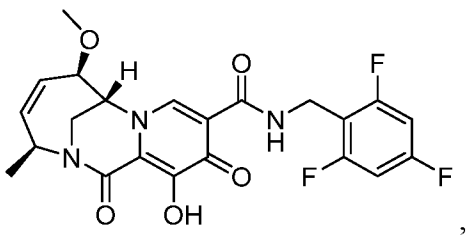
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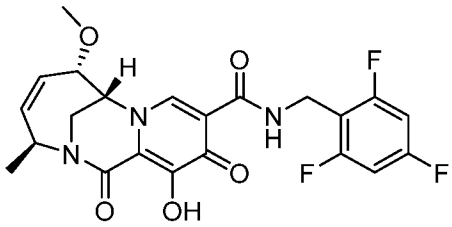
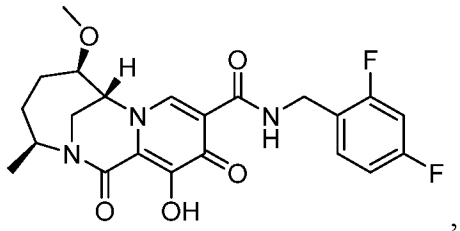
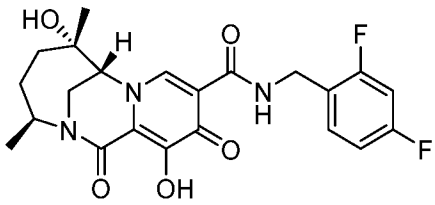
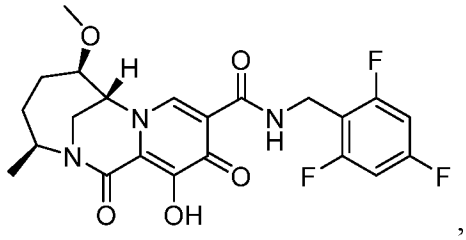
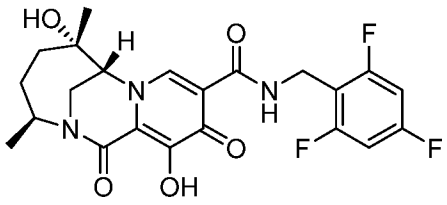
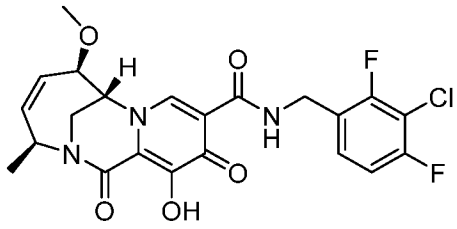
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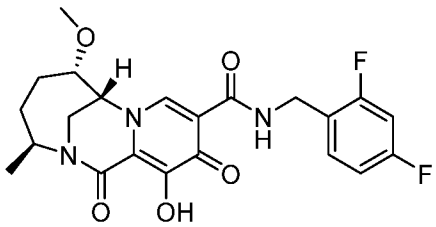

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; or a pharmaceutically acceptable salt thereof.

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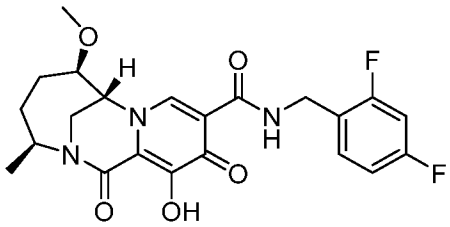

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, and

, or a pharmaceutically acceptable salt thereof.

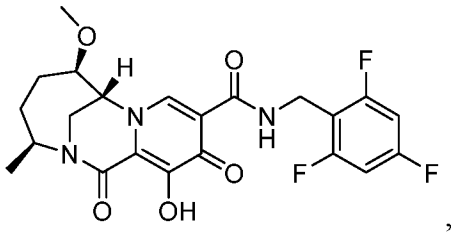
71. A compound of Formula :


, or a pharmaceutically acceptable salt thereof.

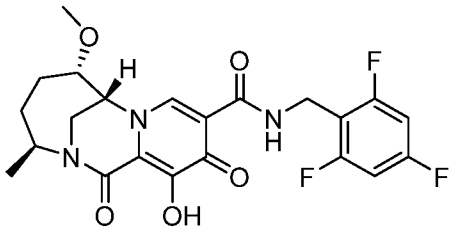
72. A compound of Formula:


, or a pharmaceutically acceptable salt thereof.

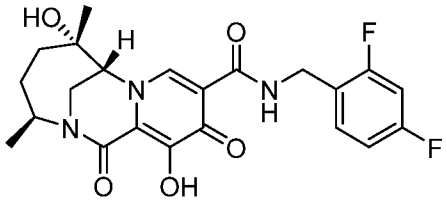
73. A compound of Formula:


, or a pharmaceutically acceptable salt thereof.

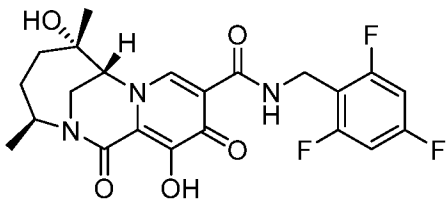
74. A compound of Formula:


, or a pharmaceutically acceptable salt thereof.

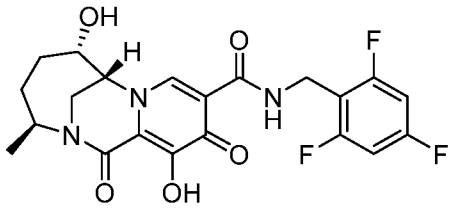
75. A compound of Formula:


, or a pharmaceutically acceptable salt thereof.

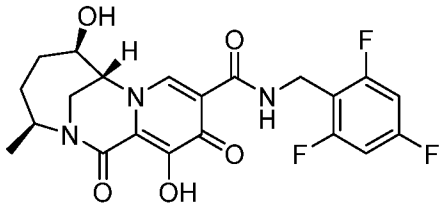
76. A compound of Formula:


, or a pharmaceutically acceptable salt thereof.

77. A compound of Formula:

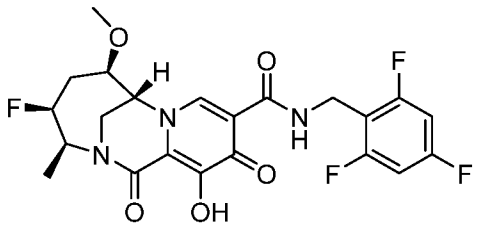

, or a pharmaceutically acceptable salt thereof.

78. A compound of Formula:



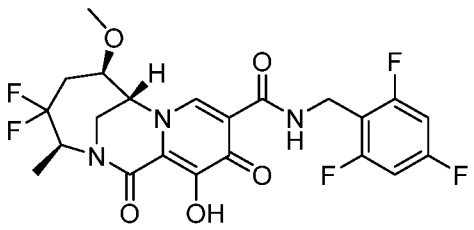
, or a pharmaceutically acceptable salt thereof.

79. A compound of Formula:



, or a pharmaceutically acceptable salt thereof.

80. A compound of Formula:



, or a pharmaceutically acceptable salt thereof.

81. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-80, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

82. The pharmaceutical composition of claim 81, further comprising one, two, three, or four additional therapeutic agents.

83. The pharmaceutical composition of claim 82, wherein the additional therapeutic agent or agents are anti-HIV agents.

84. The pharmaceutical composition of claim 82 or 83, wherein the additional therapeutic agent or agents are HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse

transcriptase, HIV capsid inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, latency reversing agents, capsid polymerization inhibitors, Maturation inhibitors, HIV bNAbs, TLR7 agonists, pharmacokinetic enhancers, other drugs for treating HIV, or combinations thereof.

85. The pharmaceutical composition of any one of claims 82-84, wherein the additional therapeutic agent or agents are abacavir, tenofovir alafenamide, tenofovir disoproxil, N-((*S*)-l-(3-(4-chloro-3-(methylsulfonamido)-l-(2,2,2-trifluoroethyl)-l*H*-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-l-yn-l-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-l*H*-cyclopropa[3,4]cyclopenta[l,2-*c*]pyrazol-l-yl)acetamide, or a pharmaceutically acceptable salt thereof.

86. The pharmaceutical composition of any one of claims 81-85, wherein the pharmaceutical composition is for oral or parenteral administration.

87. A kit comprising a compound of any one of claims 1-80, or a pharmaceutically acceptable salt thereof, and instructions for use.

88. The kit of claim 87, further comprising one, two, three, or four additional therapeutic agent or agents.

89. The kit of claim 88, wherein the additional therapeutic agent or agents are anti-HIV agents.

90. The kit of any one of claim 88 or 89, wherein the additional therapeutic agent or agents are HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV capsid inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors,

latency reversing agents, capsid polymerization inhibitors, HIV bNAbs, TLR7 agonists, pharmacokinetic enhancers, other drugs for treating HIV, or combinations thereof.

91. The kit of any one of claims 88-90, wherein the additional therapeutic agent or agents are abacavir, tenofovir alafenamide, tenofovir disoproxil, N-((*S*)-l-(3-(4-chloro-3-(methylsulfonamido)-l-(2,2,2-trifluoroethyl)-l*H*-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-l-yn-l-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-l*H*-cyclopropa[3,4]cyclopenta[l,2-*c*]pyrazol-l-yl)acetamide, or a pharmaceutically acceptable salt thereof.

92. A method of treating an HIV infection in a human having or at risk of having the infection, comprising administering to the human a therapeutically effective amount of a compound of any one of claims 1-80, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 81-86.

93. The method of claim 92, further comprising administering to the human a therapeutically effective amount of one, two, three, or four additional therapeutic agents.

94. The method of claim 93, wherein the additional therapeutic agent or agents are anti-HIV agents.

95. The method of claim 93 or 94, wherein the additional therapeutic agent or agents are HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV capsid inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, latency reversing agents, capsid polymerization inhibitors, HIV bNAbs, TLR7 agonists, pharmacokinetic enhancers, other drugs for treating HIV, or combinations thereof.

96. The method of any one of claims 93-95, wherein the additional therapeutic agent or agents are abacavir, tenofovir alafenamide, tenofovir disoproxil, lenacapavir, or a pharmaceutically acceptable salt thereof.

97. The method of any one of claim 92-96, wherein the administration is oral, intravenous, subcutaneous, or intramuscular.

98. Use of a compound of any one of claims 1-80, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 81-86, for treating an HIV infection in a human having or at risk of having the infection.

99. A compound of any one of claims 1-80, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 81-86, for use in medical therapy.

100. A compound of any one of claims 1-80, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 81-86, for use in treating an HIV infection.

101. The compound for the use of claim 100, wherein the compound is used with therapeutically effective amount of one, two, three, or four additional therapeutic agents.

102. The compound for the use of claim 101, wherein the additional therapeutic agent or agents are anti-HIV agents.

103. The compound for the use of claim 101 or 102, wherein the additional therapeutic agent or agents are HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV capsid inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, latency reversing agents, capsid polymerization inhibitors, HIV bNAbs, TLR7

agonists, pharmacokinetic enhancers, other drugs for treating HIV, or combinations thereof.

104. The compound for the use of any one of claims 101-103, wherein the additional therapeutic agent or agents are abacavir, tenofovir alafenamide, tenofovir disoproxil, lenacapavir, or a pharmaceutically acceptable salt thereof.

105. The compound for the use of any one of claims 101-104, wherein the compound is for oral, intravenous, subcutaneous, or intramuscular administration.

106. Use of a compound of any one of claims 1-80, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 81-86, in the manufacture of a medicament for treating an HIV infection in a human having or at risk of having the infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/052683

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61P31/18 A61K31/495
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/161382 A1 (GILEAD SCIENCES INC [US]) 6 October 2016 (2016-10-06) claim 1	1-106
X	WO 2014/100323 A1 (GILEAD SCIENCES INC [US]) 26 June 2014 (2014-06-26) cited in the application claim 1	1-106
X,P	WO 2020/197991 A1 (GILEAD SCIENCES INC [US]) 1 October 2020 (2020-10-01) Examples	1-106
X,P	WO 2020/221294 A1 (TUOJIE BIOTECH SHANGHAI CO LTD [CN]) 5 November 2020 (2020-11-05) Examples	1-106

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2021	04/01/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Baston, Eckhard

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/052683

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Information on patent family members

International application No
PCT/US2021/052683

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