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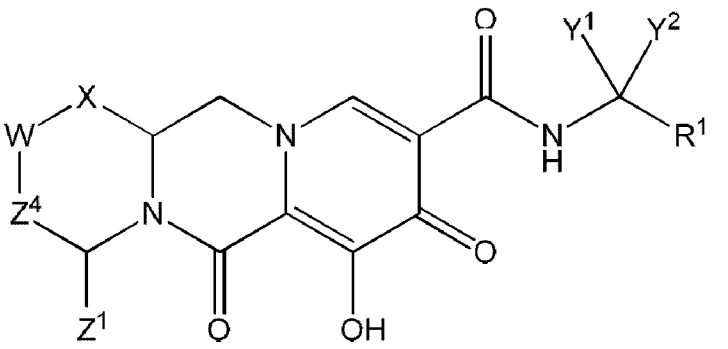
(54) Titre : COMPOSES DE CARBAMOYLPYRIDONE POLYCYCLIQUES ET LEUR UTILISATION PHARMACEUTIQUE

(54) Title: POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE



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(57) Abrégé/Abstract:
Compounds for use in the treatment of human immunodeficiency virus (HIV) infection are disclosed. The compounds have the following Formula (I): (see formula I) including stereoisomers and pharmaceutically acceptable salts thereof, wherein R^1, X, W, Y^1, Y^2, Z^1 and Z^4 are as defined herein. Methods associated with preparation and use of such compounds, as well as pharmaceutical compositions comprising such compounds, are also disclosed.

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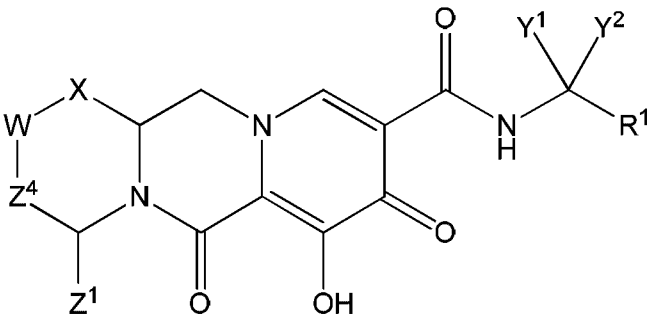
ABSTRACT

Compounds for use in the treatment of human immunodeficiency virus (HIV) infection are disclosed. The compounds have the following Formula (I):



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including stereoisomers and pharmaceutically acceptable salts thereof, wherein R^1, X, W, Y^1, Y^2, Z^1, and Z^4 are as defined herein. Methods associated with preparation and use of such compounds, as well as pharmaceutical compositions comprising such compounds, are also disclosed.

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POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application No. 61/745,375, filed December 21, 2012, U.S. Provisional Patent Application No. 61/788,397, filed March 15, 2013, and U.S. Provisional Patent Application No. 61/845,803, filed July 12, 2013. The foregoing applications are incorporated herein by reference in their entireties.

BACKGROUND

Field

Compounds, compositions, and methods for the treatment of human immunodeficiency virus (HIV) infection are disclosed. In particular, novel polycyclic carbamoylpyridone compounds and methods for their preparation and use as therapeutic or prophylactic agents are disclosed.

Description of the Related Art

Human immunodeficiency virus infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus type 1 (HIV-1) 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 have limited their usefulness (Palella, et al. *N. Engl. J Med.* (1998) 338:853–860; Richman, D. D. *Nature* (2001) 410:995–1001).

Pregnane X receptor (PXR) is a nuclear receptor that is one of the key regulators of enzymes involved in metabolism and elimination of small molecules from the body. Activation of PXR is known to up-regulate or induce the production of metabolic enzymes such as cytochrome P450 3A4 (CYP3A4) as well as enzymes involved in transport such as OATP2 in the liver and intestine (*Endocrine Reviews*

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(2002) 23(5):687–702). When one drug causes the up-regulation of these and other enzymes by activation of PXR, this can reduce the absorption and/or exposure of a co-administered drug that is susceptible to the up-regulated enzymes. To minimize the risk of this type of drug-drug interaction, it is desirable to minimize PXR activation. Further, it is known that PXR is activated by many different classes of molecules (*Endocrine Reviews* (2002) 23(5):687–702). Thus for drugs that will be co-administered with other drugs, it is important to test for and minimize PXR activation.

Transporters have been identified as playing a role in the pharmacokinetic, safety and efficacy profile or drugs, and certain drug-drug interactions are mediated by transporters. See, Giacomini KM, *et al*. ""Membrane transporters in drug development," *Nat.Rev Drug Discov*. 9: 215-236, 2010; Zhang L, *et al.* "Transporter-Mediated Drug-Drug Interactions," *Clin. Pharm. Ther.* 89(4):481-484 (2011). -One tranporter, the organic cation transporter 2 (OCT2; SLC22A2), is a member of the solute carrier (SLC) super-family of transporters and is primarily localized on the basolateral membrane of the renal proximal tubule. OCT2, in concert with apical expressed multidrug and toxin extrusion (MATE) transporters 1 and 2-K, is believed to form the major cationic secretion pathway in the kidney and has been shown to transport endogenous compounds including creatinine and xenobiotics including metformin. Inhibition of OCT2 can thus lead to increased levels of serum creatinine and the potential for increased levels of other OCT2 substrates. It is important as well to test and reduce OCT2 inhibition of drugs.

A goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient. 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 HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Section accessed March 14, 2013.) In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions (Id. at E-12). Because the standard of care requires the use of multiple different drugs to

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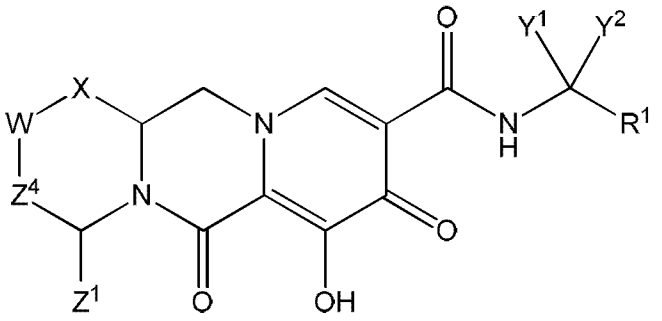
suppress HIV, as well as to treat other conditions the patient may be experiencing, the potential for drug interaction is a criterion for selection of a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for drug interactions.

Accordingly, there is a need for new agents that inhibit the replication of HIV and that minimize PXR activation when co-administered with other drugs.

BRIEF SUMMARY

The present invention is directed to novel polycyclic carbamoylpyridone compounds, having antiviral activity, including stereoisomers and pharmaceutically acceptable salts thereof, and the use of such compounds in the treatment of HIV infections. The compounds of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication.

In one embodiment of the present invention, compounds having the following Formula (I) are provided:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or $-NZ^3-$ or $-CHZ^3-$;

W is $-CHZ^2-$;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, or $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, wherein at least one of Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-;

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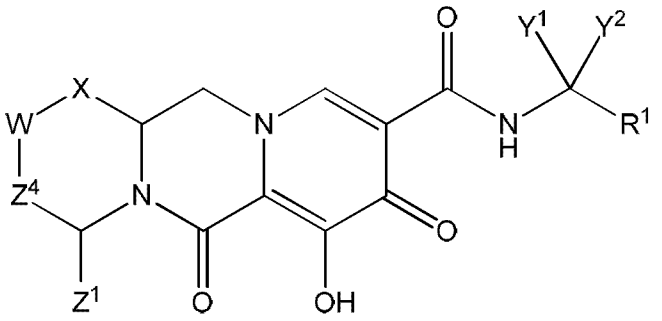
Z^4 is a bond, -CH_2-, or -CH_2CH_2-;

Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl;

R^1 is phenyl substituted with one to three halogens; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl.

In another embodiment of the present invention, compounds having the following Formula (I) are provided:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or -NZ^3- or -CHZ^3-;

W is -O- or –NZ^2- or –CHZ^2-;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is -$C(R^a)_2$-, -$C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2SO_2NR^aC(R^a)_2$- or -$C(R^a)_2NR^aSO_2C(R^a)_2$-;

Z^4 is a bond or -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -CH_2OCH_2-, -$CH_2NR^aCH_2$-, -CH_2SCH_2-,-$CH_2S(O)CH_2$- or -$CH_2SO_2CH_2$-;

Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, or Y^1 and Y^2, together with the carbon atom to which they are attached, form a

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carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms, wherein the carbocyclic or heterocyclic ring is optionally substituted with one or more R^a;

R^1 is optionally substituted aryl or optionally substituted heteroaryl; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl, or wherein two R^a groups, together with the carbon atom to which they are attached, form =O, and

wherein at least one of: (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-; or (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

In another embodiment, a pharmaceutical composition is provided comprising a compound having Formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of an HIV infection in a human being having or at risk of having the infection.

In another embodiment, a method of using a compound having Formula (I) 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 having Formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In another embodiment, use of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the treatment of an HIV infection in a human being having or at risk of having the infection is disclosed.

In another embodiment, the use of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an HIV infection in a human being having or at risk of having the infection is disclosed.

In another embodiment, an article of manufacture comprising a composition effective to treat an HIV infection; and packaging material comprising a

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label which indicates that the composition can be used to treat infection by HIV is disclosed. Exemplary compositions comprise a compound of Formula (I) according to this invention or a pharmaceutically acceptable salt thereof.

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), or a salt thereof, under conditions where replication of HIV is inhibited.

In another embodiment, the use of a compound of Formula (I) to inhibit the activity of the HIV integrase enzyme is disclosed.

In another embodiment, the use of a compound of Formula (I), or a salt thereof, to inhibit the replication of HIV is disclosed.

Other embodiments, objects, features and advantages will be set forth in the detailed description of the embodiments that follows, and in part will be apparent from the description, or may be learned by practice, of the claimed invention. These objects and advantages will be realized and attained by the processes and compositions particularly pointed out in the written description and claims hereof. The foregoing Summary has been made with the understanding that it is to be considered as a brief and general synopsis of some of the embodiments disclosed herein, is provided solely for the benefit and convenience of the reader, and is not intended to limit in any manner the scope, or range of equivalents, to which the appended claims are lawfully entitled.

DETAILED DESCRIPTION

In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention. However, one skilled in the art will understand that the invention 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.

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Definitions

Unless the context requires otherwise, throughout the present specification 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".

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 of the present invention. 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.

Unless the context requires otherwise, reference throughout this specification to "a compound of Formula (I)" or "compounds of Formula (I)" refers to all embodiments of Formula (I), including, for example, compounds of Formulas (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as well as the specific compounds disclosed herein.

"Amino" refers to the $-NH_2$ radical.

"Cyano" refers to the -CN radical.

"Hydroxy" or "hydroxyl" refers to the -OH radical.

"Imino" refers to the =NH substituent.

"Nitro" refers to the $-NO_2$ radical.

"Oxo" refers to the =O substituent.

"Thioxo" refers to the =S substituent.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which is saturated or unsaturated (*i.e.*, contains one or more double and/or triple bonds), having from one to twelve carbon atoms (C_1-C_{12} alkyl), preferably one to eight carbon atoms (C_1-C_8 alkyl) or one to six carbon atoms (C_1-C_6 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, *n*-pentyl,

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1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted.

"Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, which is saturated or unsaturated (*i.e.*, contains one or more double and/or triple bonds), and having from one to twelve carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene, ethenylene, propenylene, *n*-butenylene, propynylene, *n*-butynylene, and the like. The alkylene chain is attached to the rest of the molecule through a single or double bond and to the radical group through a single or double bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain may be optionally substituted.

"Alkoxy" refers to a radical of the formula $-OR_A$ where R_A is an alkyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted.

"Alkylamino" refers to a radical of the formula $-NHR_A$ or $-NR_AR_A$ where each R_A is, independently, an alkyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkylamino group may be optionally substituted.

Thioalkyl" refers to a radical of the formula $-SR_A$ where R_A is an alkyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, a thioalkyl group may be optionally substituted.

"Aryl" refers to a monocylic hydrocarbon ring system radical comprising hydrogen and 6 to 18 carbon atoms. Aryl radicals include, but are not limited to, aryl radicals derived from benzene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted.

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"Aralkyl" refers to a radical of the formula $-R_B-R_C$ where R_B is an alkylene chain as defined above and R_C is one or more aryl radicals as defined above, for example, benzyl. Unless stated otherwise specifically in the specification, an aralkyl group may be optionally substituted.

"Cycloalkyl" or "carbocyclic ring" refers to a stable non-aromatic monocyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted.

"Cycloalkylalkyl" refers to a radical of the formula $-R_BR_D$ where R_B is an alkylene chain as defined above and R_D is a cycloalkyl radical as defined above. Unless stated otherwise specifically in the specification, a cycloalkylalkyl group may be optionally substituted.

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

"Haloalkyl" refers to an alkyl radical, 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. Unless stated otherwise specifically in the specification, a haloalkyl group may be optionally substituted.

"Heterocyclyl" or "heterocyclic ring" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. In the embodiments disclosed herein, the heterocyclyl radical is a monocyclic ring system; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl, [1,3]dithianyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl,

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1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocyclyl group may be optionally substituted.

"*N*-heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. Unless stated otherwise specifically in the specification, an *N*-heterocyclyl group may be optionally substituted.

"Heterocyclylalkyl" refers to a radical of the formula $-R_BR_E$ where R_B is an alkylene chain as defined above and R_E is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkyl radical at the nitrogen atom. Unless stated otherwise specifically in the specification, a heterocyclylalkyl group may be optionally substituted.

"Heteroaryl" refers to a 5- to 14-membered monocyclic ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Examples include, but are not limited to, azepinyl, furanyl, furanonyl, isothiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thiophenyl, and thienyl. Unless stated otherwise specifically in the specification, a heteroaryl group may be optionally substituted.

"*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. Unless stated otherwise specifically in the specification, an *N*-heteroaryl group may be optionally substituted.

"Heteroarylalkyl" refers to a radical of the formula $-R_BR_F$ where R_B is an alkylene chain as defined above and R_F is a heteroaryl radical as defined above. Unless stated otherwise specifically in the specification, a heteroarylalkyl group may be optionally substituted.The term "substituted" used herein means any of the above groups (*i.e.,* alkyl, alkylene, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl,

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N-heteroaryl and/or heteroarylalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_GR_H$, $-NR_GC(=O)R_H$, $-NR_GC(=O)NR_GR_H$, $-NR_GC(=O)OR_H$, $-NR_GC(=NR_g)NR_GR_H$, $-NR_GSO_2R_H$, $-OC(=O)NR_GR_H$, $-OR_G$, $-SR_G$, $-SOR_G$, $-SO_2R_G$, $-OSO_2R_G$, $-SO_2OR_G$, $=NSO_2R_G$, and $-SO_2NR_GR_H$. "Substituted also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_G$, $-C(=O)OR_G$, $-C(=O)NR_GR_H$, $-CH_2SO_2R_G$, $-CH_2SO_2NR_GR_H$. In the foregoing, R_G and R_H are the same or different and independently hydrogen, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents may also be optionally substituted with one or more of the above substituents.

The term "protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect reactive groups including without limitation, hydroxyl and amino groups, against undesired reactions during synthetic procedures.

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Hydroxyl and amino groups protected with a protecting group are referred to herein as "protected hydroxyl groups" and "protected amino groups", respectively. Protecting groups are typically used selectively and/or orthogonally to protect sites during reactions at other reactive sites and can then be removed to leave the unprotected group as is or available for further reactions. Protecting groups as known in the art are described generally in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Generally, groups are protected or present as a precursor that will be inert to reactions that modify other areas of the parent molecule for conversion into their final groups at an appropriate time. Further representative protecting or precursor groups are discussed in Agrawal, et al., Protocols for Oligonucleotide Conjugates, Eds, Humana Press; New Jersey, 1994; Vol. 26 pp. 1–72. Examples of "hydroxyl protecting groups" include, but are not limited to, t-butyl, t-butoxymethyl, methoxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-trimethylsilylethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, 2,6-dichlorobenzyl, diphenylmethyl, p-nitrobenzyl, triphenylmethyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl (TBDPS), triphenylsilyl, benzoylformate, acetate, chloroacetate, trichloroacetate, trifluoroacetate, pivaloate, benzoate, p-phenylbenzoate, 9-fluorenylmethyl carbonate, mesylate and tosylate. Examples of "amino protecting groups" include, but are not limited to, carbamate-protecting groups, such as 2-trimethylsilylethoxycarbonyl (Teoc), 1-methyl-1-(4-biphenylyl)ethoxycarbonyl (Bpoc), t-butoxycarbonyl (BOC), allyloxycarbonyl (Alloc), 9-fluorenylmethyloxycarbonyl (Fmoc), and benzyloxycarbonyl (Cbz); amide protecting groups, such as formyl, acetyl, trihaloacetyl, benzoyl, and nitrophenylacetyl; sulfonamide-protecting groups, such as 2-nitrobenzenesulfonyl; and imine and cyclic imide protecting groups, such as phthalimido and dithiasuccinoyl.

The invention disclosed herein is 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. These radiolabeled compounds could be useful to

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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), 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.

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.

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) can generally be prepared by conventional 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.

The invention disclosed herein is 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 invention includes compounds produced by a process comprising administering a compound of this invention 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 of the invention 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.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

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"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.

"Optional" or "optionally" means that the subsequently described event of 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 aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

"Pharmaceutically acceptable carrier, diluent or 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, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. 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–C_4 alkyl). Pharmaceutically acceptable salts of a nitrogen atom or an amino group include for example salts of organic carboxylic acids such as acetic, benzoic, camphorsulfonic, citric, glucoheptonic, gluconic, lactic, fumaric, tartaric, maleic, malonic, malic, mandelic, isethionic, lactobionic, succinic, 2-napththalenesulfonic, oleic, palmitic, propionic, stearic, and trimethylacetic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric 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–C_4 alkyl group). Pharmaceutically acceptable salts also include salts formed when an acidic proton

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present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

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 invention. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. 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.

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, and combinations with stoichiometric amounts of water as in hydrates.

Often crystallizations produce a solvate of the compound of the invention. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present invention may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the

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corresponding solvated forms. The compound of the invention may be true solvates, while in other cases, the compound of the invention may merely retain adventitious water or be a mixture of water plus some adventitious solvent.

A "pharmaceutical composition" refers to a formulation of a compound of the invention 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 carriers, diluents or excipients therefor.

"Effective amount" or "therapeutically effective amount" refers to an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. 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 invention 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 with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

The term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention 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 detectible levels in the blood, and the administration of a compound or composition according to the present invention 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.

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The term "antiviral agent" as used herein is intended to mean an agent (compound or biological) that is effective to inhibit the formation and/or replication of a virus in a human being, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a human being.

The term "inhibitor of HIV replication" as used herein is intended to mean an agent capable of reducing or eliminating the ability of HIV to replicate in a host cell, whether *in vitro, ex vivo* or *in vivo.*

The compounds of the invention, 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 invention is meant to include all such possible isomers, as well as their racemic 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 conventional techniques, for example, chromatography and fractional crystallization. Conventional 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 centres 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.

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 invention contemplates various stereoisomers and mixtures thereof and includes “enantiomers”, which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

A “tautomer” refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

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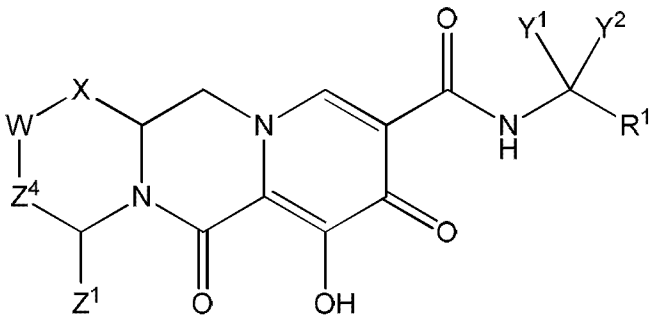
A "prodrug" refers to a compound that is chemically designed to efficiently liberate the parent drug after overcoming biological barriers to oral delivery. In certain embodiments, the present invention includes prodrugs of the compounds of Formula (I).

Compounds

As noted above, in one embodiment of the present invention, compounds having antiviral activity are provided, the compounds having the following Formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or $-NZ^3-$ or $-CHZ^3-$;

W is $-CHZ^2-$;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, or $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, wherein at least one of Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-;

Z^4 is a bond, $-CH_2-$, or $-CH_2CH_2-$;

Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl;

R^1 is phenyl substituted with one to three halogens; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl.

In another embodiment, compounds are provided having the following Formula (II-A):

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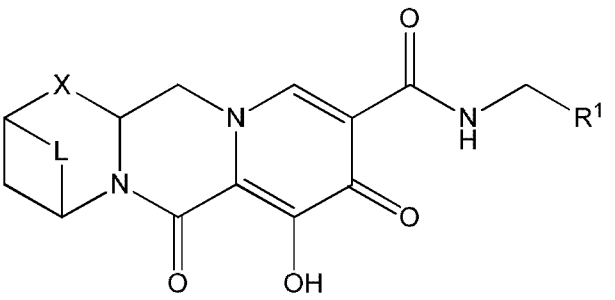
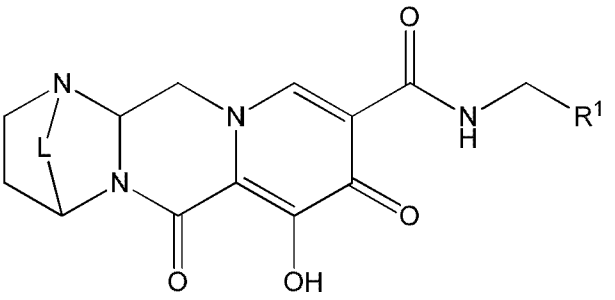


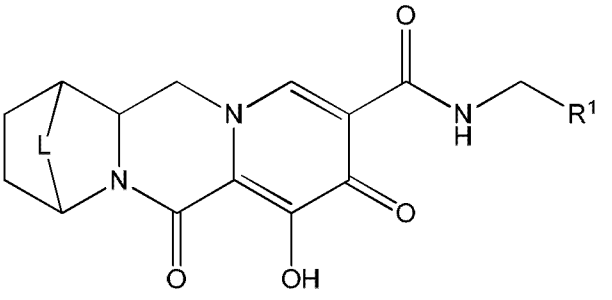
(II-A)

In another embodiment, compounds are provided having the following Formula (II-B):



(II-B)

In another embodiment, compounds are provided having the following Formula (II-C):



(II-C)

In another embodiment, L is $-C(R^a)_2-$. In a further embodiment, L is $-C(R^a)_2C(R^a)_2-$. In still a further embodiment, L is $-C(R^a)_2C(R^a)_2C(R^a)_2-$. In still a

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further embodiment, each R^a is hydrogen. In still a further embodiment, one R^a is methyl and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen. In still a further embodiment, two R^a are halogen and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen.

In another embodiment, X is -O-. In another embodiment, X is $-NZ^3-$. In another embodiment, X is -NH-. 16. In another embodiment, X is $-CHZ^3-$ and Z^1 and Z^3, taken together, form -L-. In a further embodiment, Z^2 is hydrogen. In another embodiment, X is $-CH_2-$.

In another embodiment, Z^4 is a bond or $-CH_2-$. In another embodiment, Z^4 is $-CH_2-$. In another embodiment, Z^4 is a bond.

In another embodiment, Y^1 and Y^2 are each independently hydrogen, methyl or trifluoromethyl.

In another embodiment, R^1 is substituted with one halogen. In a further embodiment, R^1 is 4-fluorophenyl or 2-fluorophenyl.

In another embodiment, R^1 is substituted with two halogens. In a further embodiment, R^1 is 2,4-difluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-chlorophenyl, 3,4-difluorophenyl, 2-fluoro-4-chlorophenyl, or 3,5-difluorophenyl. In still a further embodiment, R^1 is 2,4-difluorophenyl.

In another embodiment, R^1 is substituted with three halogens. In a further embodiment, R^1 is 2,4,6-trifluorophenyl or 2,3,4-trifluorophenyl. In still a further embodiment, R^1 is 2,4,6-trifluorophenyl.

In one embodiment, a pharmaceutical composition is provided comprising a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

Another embodiment is provided comprising a method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof. Another embodiment is provided comprising a method of treating or preventing an HIV infection in a human having or at risk of having the infection by

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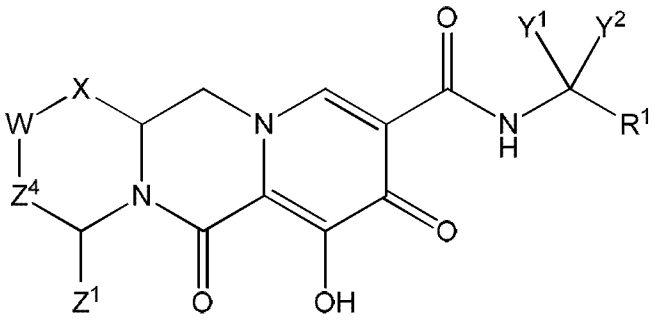
administering to the human a therapeutically effective amount of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof.

In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, for the treatment of an HIV infection in a human having or at risk of having the infection is provided. In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, for the treatment or prevention of an HIV infection in a human having or at risk of having the infection is provided.

In another embodiment, the use in medical therapy of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, is provided.

In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, for use in the therapeutic treatment of an HIV infection is provided. In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, for use in the prophylactic or therapeutic treatment of an HIV infection is provided.

As further noted above, in another embodiment of the present invention, compounds having antiviral activity are provided, the compounds having the following Formula (I):



(I)

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or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or -NZ^3- or -CHZ^3-;

W is -O- or –NZ^2- or -CHZ^2-;

Z^1, Z^2 and Z^3 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is -$C(R^a)_2$-, -$C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2SO_2NR^aC(R^a)_2$- or -$C(R^a)_2NR^aSO_2C(R^a)_2$-;

Z^4 is a bond or -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -CH_2OCH_2-, -$CH_2NR^aCH_2$-, -CH_2SCH_2-,-$CH_2S(O)CH_2$- or -$CH_2SO_2CH_2$-;

Y^1 and Y^2 are each, independently, hydrogen or C_{1-3}alkyl, or Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms, wherein the carbocyclic or heterocyclic ring is optionally substituted with one or more R^a;

R^1 is optionally substituted aryl or optionally substituted heteroaryl; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl, or wherein two R^a groups, together with the carbon atom to which they are attached, form =O, and

wherein at least one of: (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-; or (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

In another embodiment, W is -CHZ^2-.

In another embodiment, Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-.

In another embodiment, compounds are provided having one of the following Formulas (II-A), (II-B), or (II-C):

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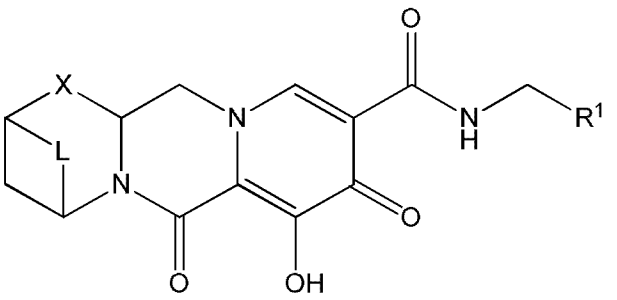
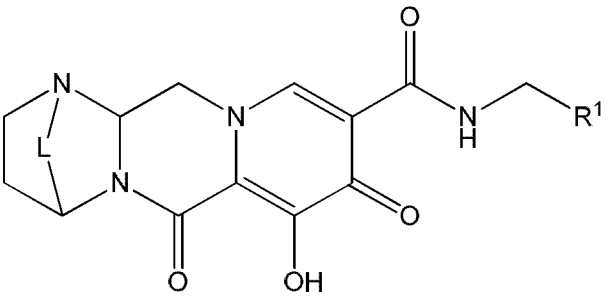


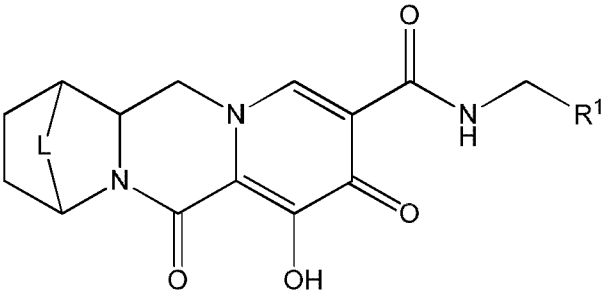
;

(II-A)



; or

(II-B)



,

(II-C)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

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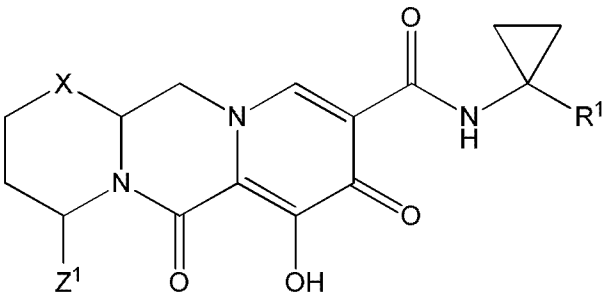
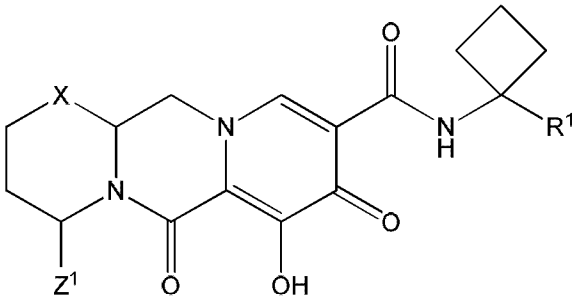
In another embodiment, Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

In another embodiment, compounds are provided having one of the following Formulas (III-A), (III-B), (III-C) or (III-D):



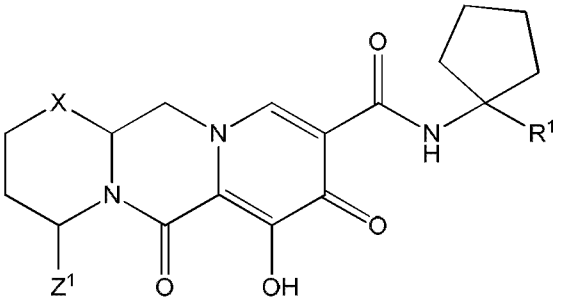
;

(III-A)



;

(III-B)



; or

(III-C)

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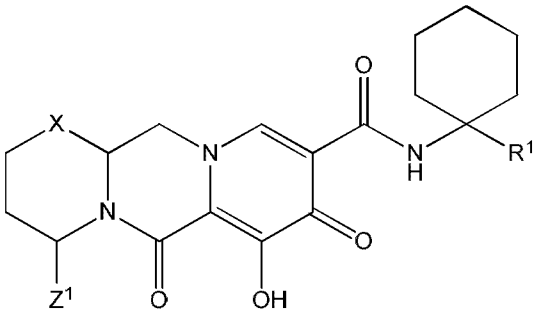
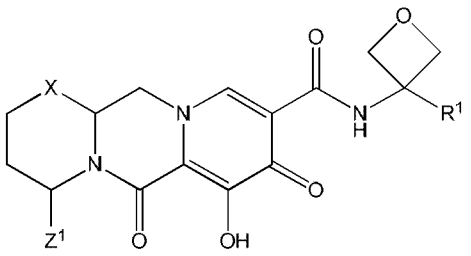


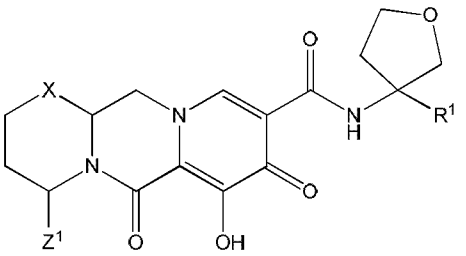
(III-D)

wherein Z^1 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl.

In another embodiment, compounds are provided having one of the following Formulas (III-E), (III-F), (III-G) or (III-H):



(III-E)



(III-F)

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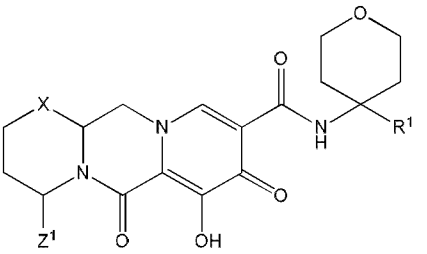
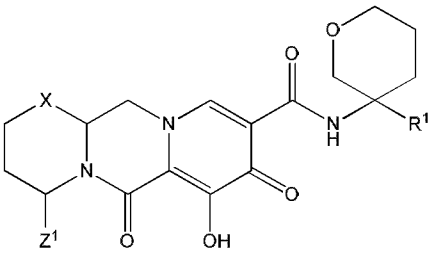


; or

(III-G)



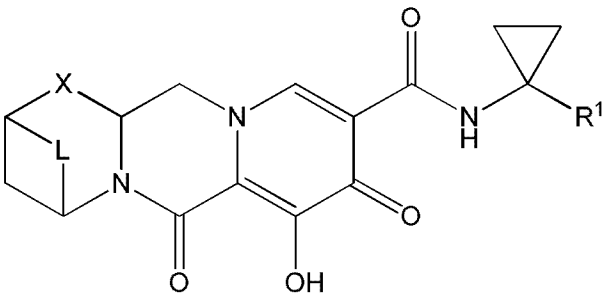
,

(III-H)

wherein Z^1 and Z^3 are each, independently, hydrogen or $C_{1\text{-}3}$alkyl.

In another embodiment, both (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-, and (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

In another embodiment, compounds are provided having one of the following Formulas (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG) or (IV-AH):



;

(IV-AA)

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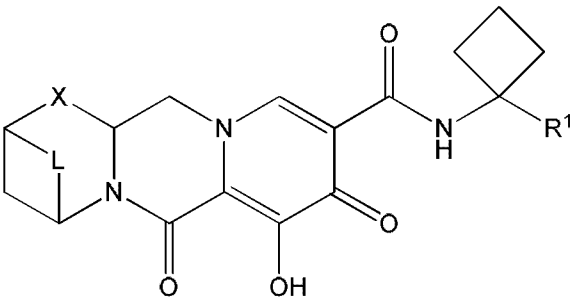
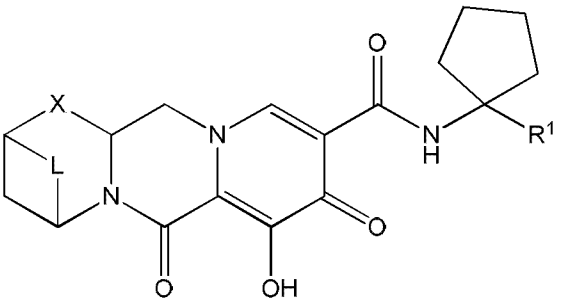


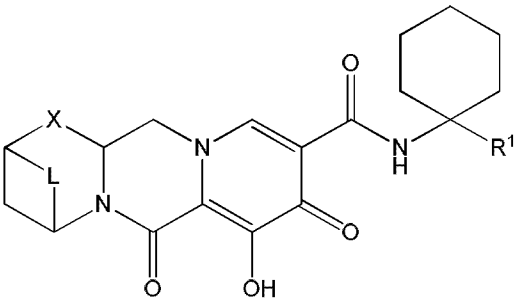
;

(IV-AB)



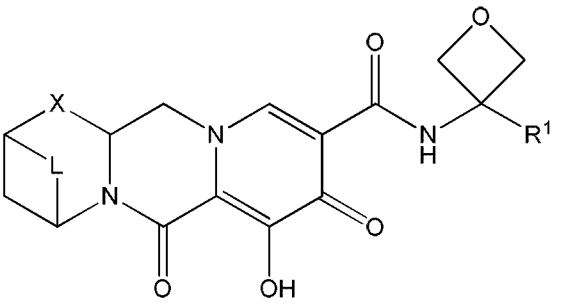
;

(IV-AC)



5 ;

(IV-AD)



;

(IV-AE)

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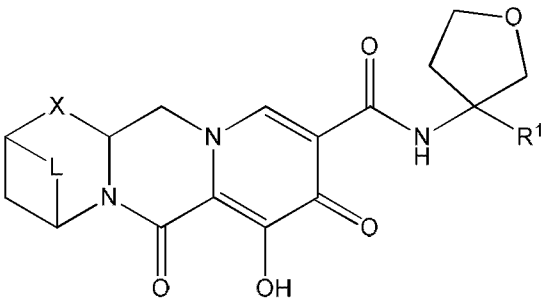
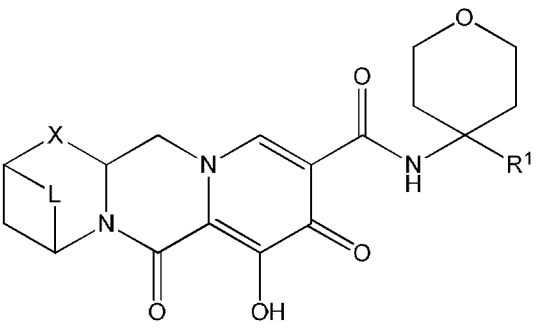


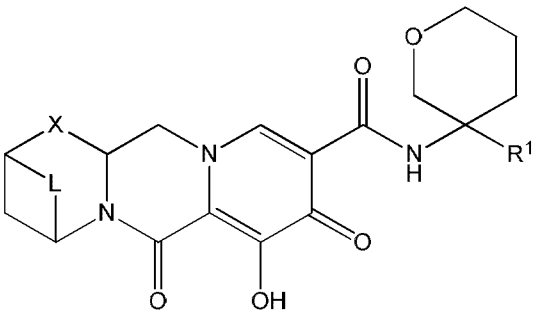
;

(IV-AF)



; or

(IV-AG)



,

(IV-AH)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

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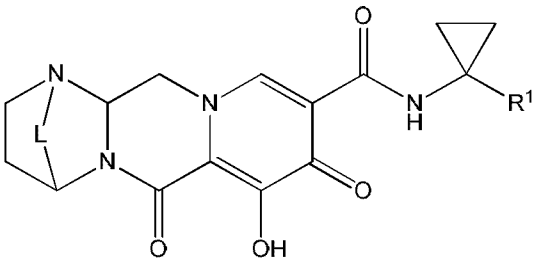
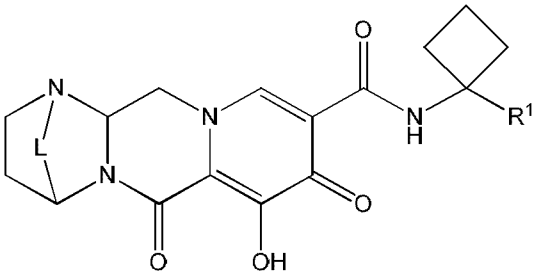
In another embodiment, compounds are provided having one of the following Formulas (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG) or (IV-BH):



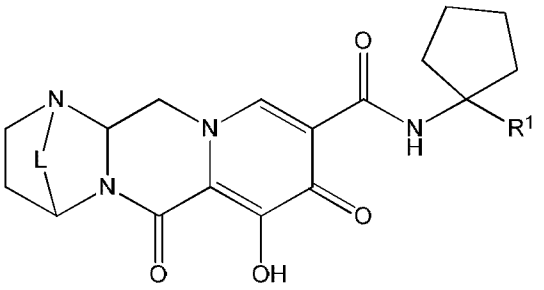
;

(IV-BA)



;

(IV-BB)



;

(IV-BC)

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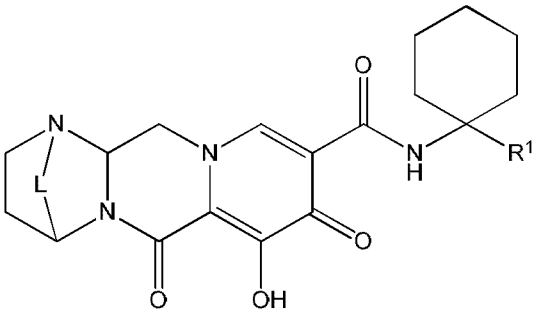
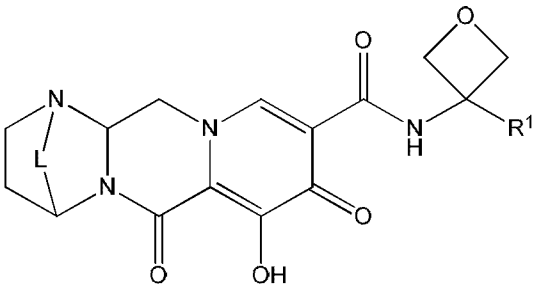


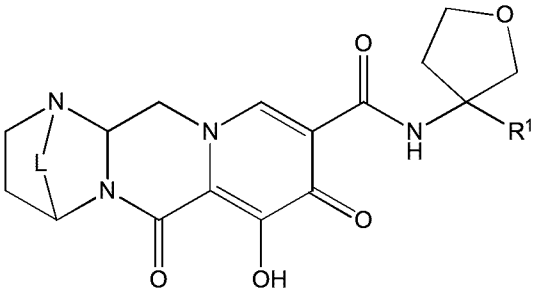
;

(IV-BD)



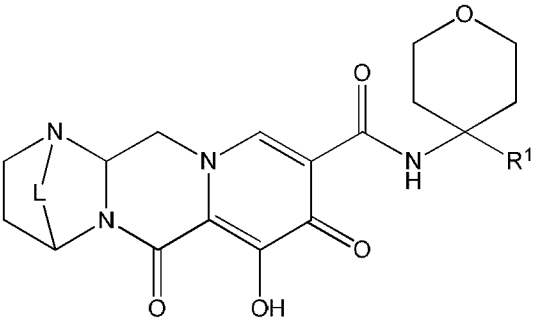
;

(IV-BE)



;

(IV-BF)



; or

(IV-BG)

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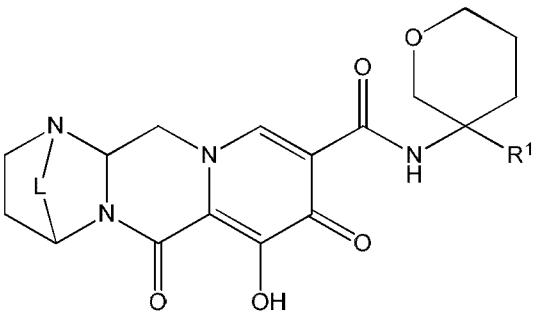

(IV-BH)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

In another embodiment, L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, or $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$. In a further embodiment, L is $-C(R^a)_2-$. In still a further embodiment, L is $-C(R^a)_2C(R^a)_2-$. In still a further embodiment, L is $-C(R^a)_2C(R^a)_2C(R^a)_2-$. In still a further embodiment, each R^a is hydrogen. In still a further embodiment, one R^a is methyl and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen. In still a further embodiment, two R^a are halogen and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen.

In another embodiment, L is $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, or $-C(R^a)_2SO_2C(R^a)_2-$. In a further embodiment, L is $-C(R^a)_2OC(R^a)_2-$. In still a further embodiment, each R^a is hydrogen. In still a further embodiment, one R^a is methyl and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen. In still a further embodiment, two R^a are halogen and

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each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen.

In another embodiment, X is -O-. In a further embodiment, Z^2 is hydrogen. In another embodiment, X is $-NZ^3-$. In another embodiment, X is -NH-. In another embodiment, X is $-CHZ^3-$. In another embodiment, X is $-CH_2-$.

In another embodiment, Z^4 is a bond or $-CH_2-$. In another embodiment, Z^4 is $-CH_2-$. In another embodiment, Z^4 is a bond.

In another embodiment, Y^1 and Y^2 are each independently hydrogen, methyl or trifluoromethyl.

In another embodiment, R^1 is substituted with one halogen. In a further embodiment, R^1 is 4-fluorophenyl or 2-fluorophenyl.

In another embodiment, R^1 is phenyl. In another embodiment, R^1 is pyridinyl.

In another embodiment, R^1 is substituted with at least one halogen.

In another embodiment, R^1 is substituted with one halogen. In a further embodiment, R^1 is 4-fluorophenyl or 2-fluorophenyl.

In another embodiment, R^1 is substituted with two halogens. In a further embodiment, R^1 is 2,4-difluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-chlorophenyl, 3,4-difluorophenyl, 2-fluoro-4-chlorophenyl, or 3,5-difluorophenyl. In still a further embodiment, R^1 is 2,4-difluorophenyl.

In another embodiment, R^1 is substituted with three halogens. In a further embodiment, R^1 is 2,4,6-trifluorophenyl or 2,3,4-trifluorophenyl. In still a further embodiment, R^1 is 2,4,6-trifluorophenyl.

In another embodiment, R^1 is 3-trifluoromethyl-4-fluorophenyl or 2-cyclopropoxy-4-fluorophenyl.

In one embodiment, a pharmaceutical composition is provided comprising a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

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Another embodiment is provided comprising a method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof. Another embodiment is provided comprising a method of treating or preventing an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof.

In another embodiment, the use of a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof for the treatment of an HIV infection in a human having or at risk of having the infection. In another embodiment, the use of a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof for the treatment or prevention of an HIV infection in a human having or at risk of having the infection.

In another embodiment, the use in medical therapy of a compound of any one of the Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof, is provided.

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In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof, for use in the therapeutic treatment of an HIV infection is provided. In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof, for use in the prophylactic or therapeutic treatment of an HIV infection is provided.

It is understood that any embodiment of the compounds of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as set forth above, and any specific substituent set forth herein for a R^1, R^a, X, W, Y^1, Y^2, L, Z^1, Z^2, Z^3, or Z^4 group in the compounds of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as set forth above, may be independently combined with other embodiments and/or substituents of compounds of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), to form embodiments of the inventions not specifically set forth above. In addition, in the event that a list of substitutents is listed for any particular R^1, R^a, X, W, Y^1, Y^2, L, Z^1, Z^2, Z^3, or Z^4 in a particular embodiment and/or claim, it is understood that each individual substituent may be deleted from the particular embodment and/or claim and that the remaining list of substituents will be considered to be within the scope of the invention.

As one of skill in the art will appreciate, compounds of Formulas (I), (II-A), (II-B), (II-C), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF),

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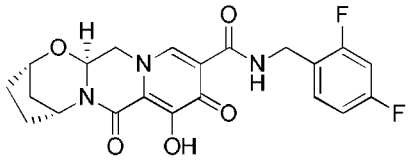
(IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- may be shown in several different ways. For example, the Compound 3 of Example 3 may be shown as:



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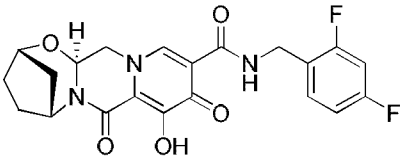

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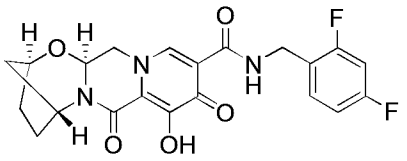
or



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Pharmaceutical Compositions

For the purposes of administration, in certain embodiments, the compounds described herein are administered as a raw chemical or are formulated as pharmaceutical compositions. Pharmaceutical compositions disclosed herein include a compound of Formula (I) and one or more of: a pharmaceutically acceptable carrier, diluent or excipient. The compound of Formula (I) is present in the composition in an amount which is effective to treat a particular disease or condition of interest. The activity of compounds of Formula (I) can be determined by one skilled in the art, for example, as described in the Examples below. Appropriate concentrations and dosages can be readily determined by one skilled in the art. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount from about 25 mg to about 500 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg.

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Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, is carried out via any of the accepted modes of administration of agents for serving similar utilities. The pharmaceutical compositions of the invention are prepared by combining a compound of the invention with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and in specific embodiments are formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Exemplary routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal. Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold a plurality of dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 20th Edition (Philadelphia College of Pharmacy and Science, 2000). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease or condition of interest in accordance with the teachings described herein.

The pharmaceutical compositions disclosed herein are prepared by methodologies well known in the pharmaceutical art. For example, in certain embodiments, a pharmaceutical composition intended to be administered by injection is prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. In some embodiments, a surfactant is added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

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The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy.

Combination Therapy

In one embodiment, 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 additional therapeutic agents.

In one embodiment, pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided.

In one embodiment, combination pharmaceutical agents comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents are provided.

In the above embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, compounds that target the HIV capsid ("capsid inhibitors"; e.g., capsid polymerization inhibitors or capsid disrupting compounds such as those disclosed in WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), and WO 2013/006792

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(Pharma Resources), pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof. In further embodiments, the additional therapeutic agent is selected from one or more of:

(1) HIV protease inhibitors selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, rilpivirene, BILR 355 BS, VRX 840773, lersivirine (UK-453061), RDEA806, KM023 and MK-1439;

(3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS-9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003);

(4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix);

(5) HIV integrase inhibitors selected from the group consisting of 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, S-1360, AR-177, L-870812, and L-870810, raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, elvitegravir, dolutegravir and GSK-744;

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) including, but not limited to, BI-224436, CX0516, CX05045, CX14442, compounds

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disclosed in WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences) each of which is incorporated by references in its entirety herein;

(7) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, albuvirtide, FB006M, and TRI-1144;

(8) the CXCR4 inhibitor AMD-070;

(9) the entry inhibitor SP01A;

(10) the gp120 inhibitor BMS-488043;

(11) the G6PD and NADH-oxidase inhibitor immunitin;

(12) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(13) CD4 attachment inhibitors selected from the group consisting of ibalizumab (TMB-355) and BMS-068 (BMS-663068);

(14) pharmacokinetic enhancers selected from the group consisting of cobicistat and SPI-452; and

(15) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040),

and combinations thereof

In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 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 two, three four or more additional therapeutic agents can be different therapeutic agents selected from the

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same class of therapeutic agents, or they can be selected from different classes of therapeutic agents. In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV 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 nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In a further embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside 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 nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer.

In certain embodiments, when a compound disclosed herein is combined with one or more additional therapeutic agents as described above, the components of the composition are administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

In certain embdoiments, 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.

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 one or more additional therapeutic agents are both present in the body of the patient.

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, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more

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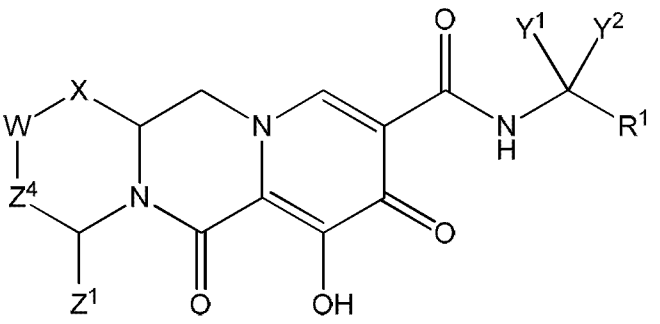
additional therapeutic agents. For example, in some embodiments, a unit dose of a compound disclosed herein is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one 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 some 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 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.

The following Examples illustrate various methods of making compounds of this invention, *i.e.*, compound of Formula (I):



(I)

wherein R^1, X, W, Y^1, Y^2, Z^1, Z^2, or Z^4 are as defined above. It is understood that one skilled in the art may be able to make these compounds by similar methods or by combining other methods known to one skilled in the art. It is also understood that one skilled in the art would be able to make, in a similar manner as described below, other compounds of Formula (I) not specifically illustrated below by using the appropriate starting components and modifying the parameters of the synthesis as needed. In general, starting components may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, etc. or synthesized according to sources known to those skilled in the art (see, for

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example, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th edition (Wiley, December 2000)) or prepared as described herein.

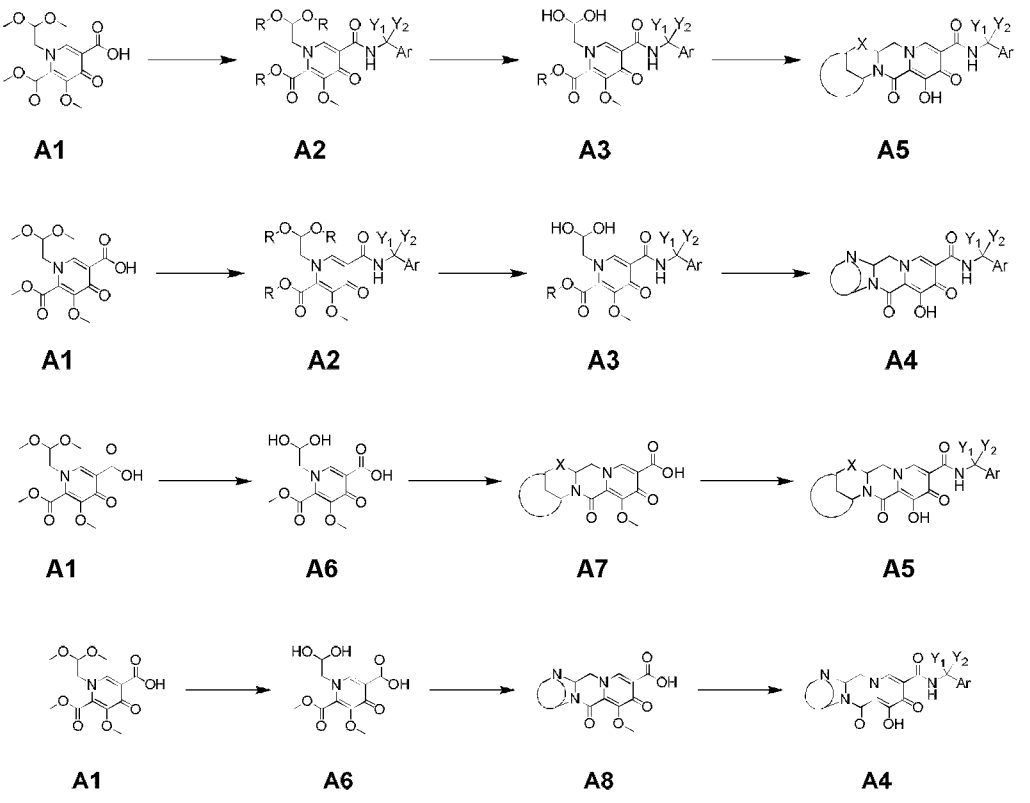
The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

GENERAL SYNTHETIC SCHEMES

Schemes 1–3 are provided as further embodiments of the invention and illustrate general methods which were used to prepare compounds having Formula (I) and which can be used to prepare additional compound having Formula (I).

Scheme 1



A1 can be converted to amide **A2** with an appropriate amine and a coupling reagent such as HATU or EDCI. **A2** can be converted to **A3** with a strong acid

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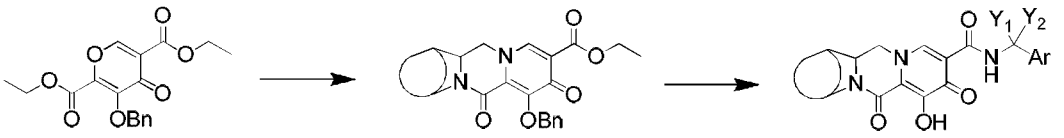
such as methanesulfonic acid. **A3** can be converted to either **A5** or **A4** by heating with an appropriate cyclic diamine or cyclic aminoalcohol followed by methyl deprotection with a reagent such as magnesium bromide.

Alternatively, **A1** can be converted to **A6** by treatment with a strong acid such as methanesulfonic acid. **A6** can be condensed with an appropriate cyclic diamine or cyclic aminoalcohol followed by methyl deprotection with a reagent such as magnesium bromide to form either **A7** or **A8** respectively. **A7** or **A8** can be converted into amides **A5** and **A4** by treatment with an appropriate amine and a coupling reagent such as HATU or EDCI followed by methyl deprotection with a reagent such as magnesium bromide.

Scheme 2



B1 **B2** **B3**

B1 (as described in WO2012/018065) is condensed with diamine under reflux condition to give **B2**. **B2** is hydrolyzed and coupled with an amine by an amide-forming method to afford product **B3** upon removal of a benzyl protecting group.

REPRESENTATIVE COMPOUNDS

Example 1

Preparation of Compound **1**

N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

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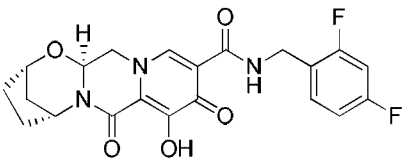

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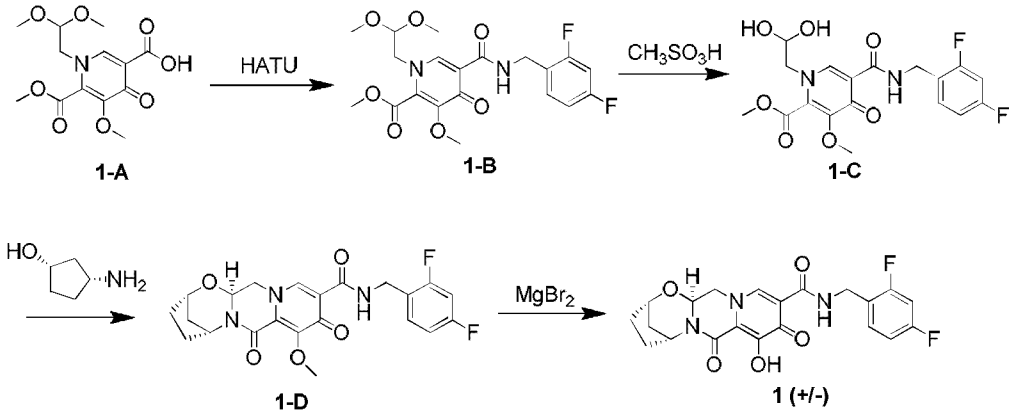

Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1-A**, 0.300 g, 0.95 mmol), prepared as described in WO2011/119566 A1, was evaporated once from dry toluene, suspended in acetonitrile (4 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.329 mL, 1.90 mmol), 2,4-difluorobenzylamine (0.125 mL, 1.05 mmol) and HATU (0.433 g, 1.14 mmol). The reaction mixture was stirred for 10 minutes and concentrated. The residue was purified by flash chromatography on silica gel (10 to 60% ethyl acetate:dichloromethane) to afford the compound methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate, **1-B.** **^{1}H-NMR** (400 MHz, DMSO-d6*)* δ 10.28 (t, *J* = 6.0 Hz, 1H), 8.46 (s, 1H), 7.42 (dd, *J* = 15.4, 8.6 Hz, 1H), 7.24 (m, 1H), 7.06 (m, 1H), 4.52 (m, 3H), 4.22 (d, *J* = 4.4 Hz, 2H), 3.92 (s, 3H), 3.80 (s, 3H),3.29 (d, 6H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{23}F_2N_2O_7$: 441.15; found: 441.2.

Step 2

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-B**, 0.106 g, 0.24 mmol) in

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acetonitrile (0.9 mL) and acetic acid (0.1 mL) was treated with methanesulfonic acid (0.005 mL, 0.072 mmol), sealed with a yellow cap, and heated to 70 °C. After 16 hours, the mixture was cooled to afford a crude solution of methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate, **1-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 413.12; found: 413.1.

Steps 3 and 4

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C,** 0.65 mL of the crude mixture from the previous step, 0.17 mmol) was treated with acetonitrile (0.65 mL) and *cis*-3-aminocyclpentanol (0.06 mL). The reaction mixture was sealed and heated to 90 °C. After 30 minutes, the reaction mixture was cooled and magnesium bromide (0.063 g, 0.34 mmol) was added. The mixture was resealed and heated to 50 °C. After 10 minutes, the reaction mixture was partitioned between dichloromethane and hydrochloric acid (0.2 M aq). The organic layer was removed and the aqueous layer extracted again with dichlormethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Prep-HPLC purification (30-70% acetonitrile:water, 0.1% TFA) afforded Compound **1** as a racemic mixture. **^{1}H-NMR** (400 MHz, DMSO-d6*)* δ 12.45 (br s, 1H), 10.35 (t, *J* = 5.8 Hz, 1H), 8.45 (s, 1H), 7.37 (dd, *J* = 15.4, 8.6 Hz, 1H), 7.23 (dt, *J* = 2.5, 9.9 Hz, 1H), 7.05 (dt, *J* = 2.2, 8.7 Hz, 1H), 5.43 (dd, *J* = 9.6, 4.0 Hz, 1H), 5.09 (br s, 1H), 4.68 (dd, *J* = 13.2, 4.0 Hz, 1H), 4.59 (br s, 1H), 4.53 (m, 2H), 4.02 (dd, *J* = 12.6, 9.4 Hz), 1.93 (br s, 4H), 1.83 (d, *J* = 12.0 Hz), 1.57 (dt, *J* = 12.2, 3.2 Hz). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2.

Examples 2 and 3

Preparation of Compounds **2** and **3**

(2R,5S,13aR)-N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (**2)** and (2S,5R,13aS)-N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-

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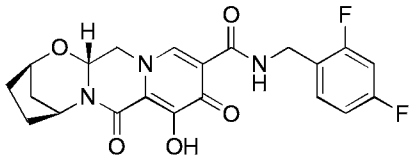
octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (**3**)



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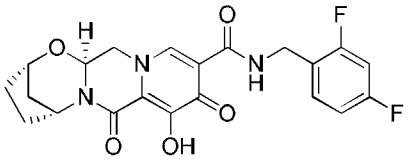

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Compound **1** (16 mg) was separated by chiral HPLC using Chiralpak AS-H with 100% ethanol as eluent to afford Compounds **2** and **3** in enantiomerically enriched form. For Compound **2**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2, **Chiral HPLC** retention time = 4.50 minutes (Chiralpak AS-H, 150 x 4.6 mm, 1 mL/min EtOH). For Compound **3**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2, **Chiral HPLC** retention time = 6.84 minutes (Chiralpak AS-H, 150 x 4.6 mm, 1 mL/min EtOH). **^{1}H-NMR** (400 MHz, DMSO-d6*)* δ 12.45 (br s, 1H), 10.35 (t, *J* = 5.8 Hz, 1H), 8.44 (s, 1H), 7.37 (dd, *J* = 15.2, 8.4 Hz, 1H), 7.23 (m, 1H), 7.05 (dt, *J* = 1.8 Hz, 8.7 Hz, 1H), 5.44 (dd, *J* = 9.6, 4.0 Hz), 5.09 (br s, 1H), 4.68 (dd, *J* = 12.8, 4.0 Hz, 1H), 4.59 (br s, 1H), 4.53 (m, 2H), 4.02 (dd, *J* = 12.6, 9.4 Hz, 1H), 1.93 (br s, 4H), 1.83 (d, *J* = 12.4 Hz, 1H), 1.57 (m, 1H).

Alternatively, Compound **3** was prepared as follows:

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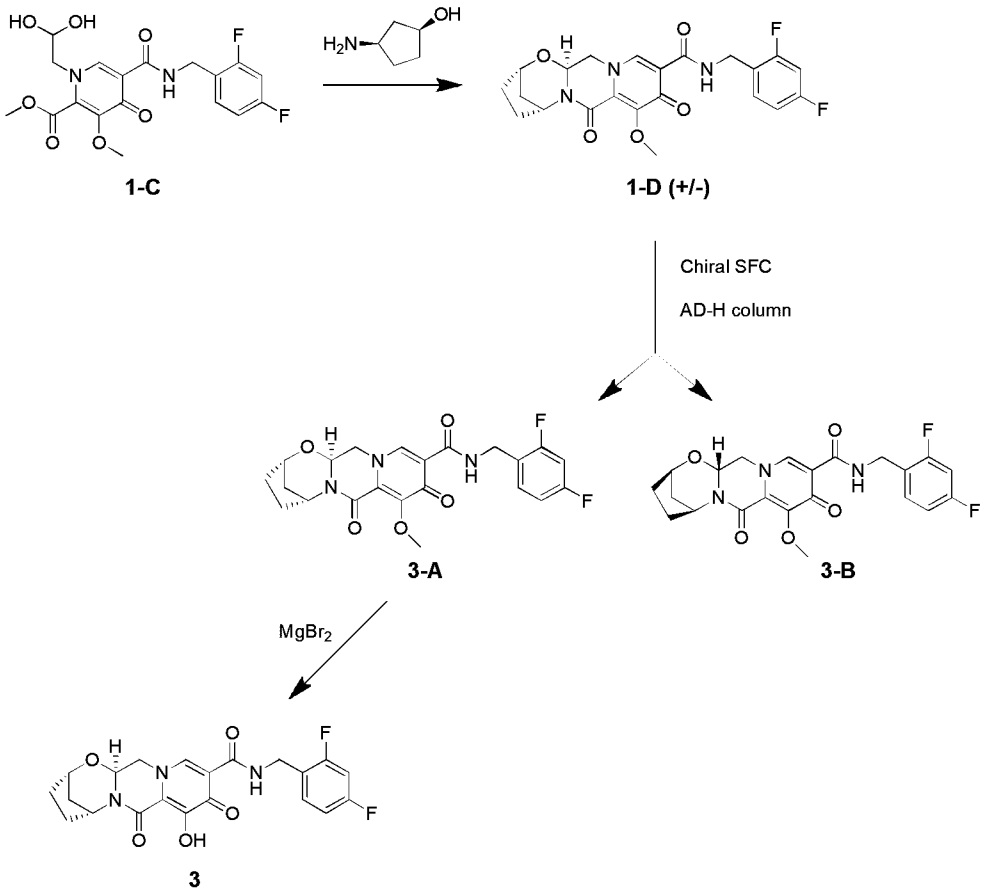

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C,** 1.2 mmol in 5 mL of 9:1 acetonitrile:acetic acid containing 0.026 mL methanesulfonic acid) was treated with acetonitrile (5.0 mL) and *cis*-3-aminocyclpentanol (0.24 g, 2.4 mmol). The reaction mixture was sealed and heated to 90 °C. After 30 minutes, the reaction mixture was cooled, treated with potassium carbonate (0.332 g, 2.4 mmol), sealed and reheated to 90 °C. After 15 minutes, the mixture was cooled and partitioned between dichlormethane and hydrochloric acid (0.2 M aqueous). The organic layer was removed and the aqueous solution was extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate (anhydrous), filtered and concentrated. The residue was purified by flash chromatography (0-8% ethanol (containing 11% saturated aqueous ammonium hydroxide) in dichloromethane) to afford Intermediate **1-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2

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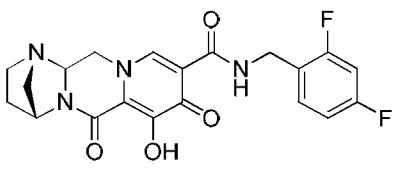
Intermediate **1-D** (270 mg) was separated by chiral SFC on a 50 mm Chiralpak AD-H column using 50% (1:1 methanol:acetonitrile) in supercritical carbon dioxide as eluent to afford Intermediates **3-A** (first eluting peak) and **3-B** (second eluting peak) in enantioenriched form. For **3-A: LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2. For **3-B**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Intermediate **3-A** (0.110 g, 0.247 mmol) in acetonitrile (5 mL) was treated portion wise with magnesium bromide (0.091 g, 0.494 mmol), sealed and heated to 50 °C. After 10 minutes the mixture was cooled and partitioned between dichloromethane and hydrochloric acid (0.2 M aqueous). The organic layer was separated and the aqueous extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Preparative HPLC purification (30-70% acetonitrile:water, 0.1% TFA) afforded Compound **3** in enantioenriched form. **Chiral HPLC** retention time = 6.51 minutes (Chiralpak AS-H, 150 x 4.6 mm, 1 mL/min EtOH). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2. **^{1}H-NMR** (400 MHz, DMSO-d6*)* δ 12.45 (br s, 1H), 10.35 (t, *J* = 5.8 Hz, 1H), 8.44 (s, 1H), 7.37 (dd, *J* = 15.2, 8.4 Hz, 1H), 7.23 (m, 1H), 7.05 (dt, *J* = 1.8 Hz, 8.7 Hz, 1H), 5.44 (dd, *J* = 9.6, 4.0 Hz), 5.09 (br s, 1H), 4.68 (dd, *J* = 12.8, 4.0 Hz, 1H), 4.59 (br s, 1H), 4.53 (m, 2H), 4.02 (dd, *J* = 12.6, 9.4 Hz, 1H), 1.93 (br s, 4H), 1.83 (d, *J* = 12.4 Hz, 1H), 1.57 (m, 1H).

Example 4

Preparation of Compound **4**

(1S,4R)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-1,4-methanopyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide



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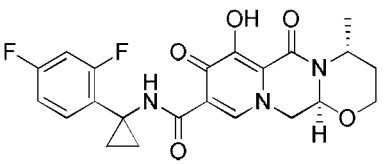
Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C,** 0.12 mmol in 0.53 mL of 9:1 acetonitrile:acetic acid containing 0.002 mL methanesulfonic acid) was treated with acetonitrile then (R)-pyrrolidin-3-amine (0.032 mL, 0.36 mmol). The reaction mixture was capped and heated to 90 °C for 5.5 hours. After cooling, the mixture was partitioned between dichloromethane and sodium bicarbonate (1M aqueous). The organic layer was separated and the aqueous was extracted again with ethyl acetate. The combined organic layers were dried over sodium sulfate (anhydrous), filtered and concentrated. The residue was dissolved in acetonitrile (1 mL), treated with magnesium bromide (0.022 g, 0.12 mmol), capped and heated to 50 °C for 10 minutes. After cooling the mixture was partitioned between dichloromethane and ammonium chloride (sat). The organic layer was separated and the aqueous was extracted again with dichloromethane. The aqueous layer was adjusted to pH = 1 with HCl (aq) and extracted again with dichloromethane. The aqueous solution was adjusted to pH = 3 with NaOH (aq) and extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Preparative HPLC purification (10-55% acetonitrile:water, 0.1% TFA) afforded Compound **4**. **^{1}H-NMR** (400 MHz, CD_3OD-d4*)* δ 8.42 (s, 1H), 7.42, (q, *J* = 7.7 Hz, 1H), 6.99 – 6.90 (m, 2H), 5.07 (br s, 1H), 4.73 (br d, *J* = 10.8 Hz, 1H), 4.62 (s, 2H), 4.51 (br d, *J* = 12.8 Hz, 1H), 4.07 (t, *J* = 11.8 Hz, 1H), 3.4- 3.0 (m, 3H), 2.76 (br d, *J* = 8.8 Hz, 1H), 2.15-2.0 (m, 1H), 1.9-1.8 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{19}F_2N_4O_4$: 417.14; found: 417.2.

Example 5

Preparation of Compound **5**

(4R,12aS)-N-(1-(2,4-difluorophenyl)cyclopropyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-[1,3]oxazino[3,2-d]pyrido[1,2-a]pyrazine-9-carboxamide



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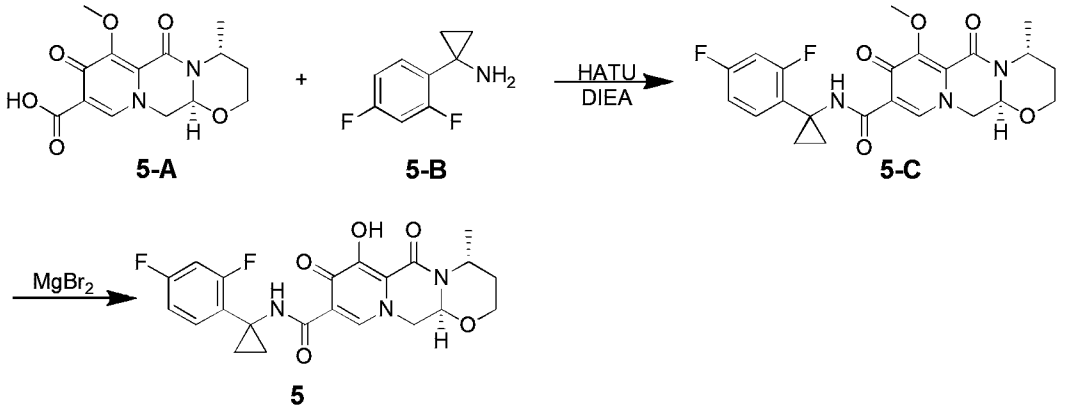

Step 1

(4R,12aS)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-[1,3]oxazino[3,2-d]pyrido[1,2-a]pyrazine-9-carboxylic acid (Intermediate **5-A**) was prepared in an analogous manner to (3S,11aR)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo[3,2-d]pyrido[1,2-a]pyrazine-8-carboxylic acid as described in WO2011/119566, substituting (R)-3-aminobutan-1-ol for (S)-2-aminopropan-1-ol. WO2011/119566 is incorporated herein by reference in its entirety. A suspension of Intermediate **5-A** (24.8 mg, 0.080 mmol), 1-(2,4-difluorophenyl)cyclopropanamine HCl salt (**5-B**, 21.9 mg, 0.107 mmol), and HATU (48 mg, 0.126 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature as N,N-diisopropylethylamine (DIPEA) (0.1 mL, 0.574 mmol) was added. After 30 minutes, the reaction mixture was diluted with ethyl acetate before washing with 10% aqueous citric acid solution (x1) and saturated aqueous $NaHCO_3$ solution (x1). After the aqueous fractions were extracted with ethyl acetate (x1), the organic fractions were combined, dried ($MgSO_4$), and concentrated. The residue was purified by combiflash (12 g column) using hexanes, ethyl acetate, and 20% methanol in ethyl acetate to obtain (4R,12aS)-N-(1-(2,4-difluorophenyl)cyclopropyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-[1,3]oxazino[3,2-d]pyrido[1,2-a]pyrazine-9-carboxamide, Intermediate **5-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{24}F_2N_3O_5$: 460.17; found 460.2.

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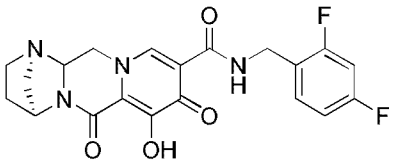
Step 2

A suspension of Intermediate **5-C** (39 mg, 0.080 mmol) and magnesium bromide (42 mg, 0.2282 mmol) in acetonitrile (2 mL) was stirred at 50 °C. After 1 hour, the reaction mixture was stirred at 0 °C bath when 1 N HCl (2 mL) was added. After the resulting mixture was diluted with water (~20 mL), the product was extracted with dichloromethane (x3) and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by preparative HPLC to obtain (4R,12aS)-N-(1-(2,4-difluorophenyl)cyclopropyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-[1,3]oxazino[3,2-d]pyrido[1,2-a]pyrazine-9-carboxamide, compound **5,** as TFA salt. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.72 (br s, 1H), 8.37 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 6.71-6.81 (m, 2H), 5.23 (dd, J = 5.6 and 4.4 Hz, 1H), 4.98 (br quint, J = ~6.5 Hz, 1H), 4.26 (dd, J = 13.6 and 4.4 Hz, 1H), 4.12 (dd, J = 13.6 and 5.6 Hz, 1H), 4.00-4.06 (m, 2H), 2.16-2.25 (m, 1H), 1.55 (br dd, J = 13.8 and 1.8 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H), 1.22-1.31 (m, 4H). **^{19}F NMR** (376.1 MHz, $CDCl_3$) δ -76.38 (s, 3F), -111.69 ~ -111.645 (m, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found**:** 446.2.

Example 6

Preparation of Compound 6

(1R,4S)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-1,4-methanopyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide



6

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C,** 0.100 g, 0.243 mmol), (S)-pyrrolidin-3-amine (0.043 mL, 0.485 mmol) and potassium carbonate (0.067 g, 0.485 mmol) were suspended in acetonitrile (1.9 mL) and acetic acid (0.1 mL) and heated to 90 °C for 1.5 hours. After cooling, the mixture was treated with magnesium bromide

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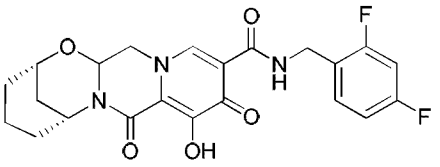
(0.090 g) and heated to 50 °C for 30 minutes. After cooling, the mixture partitioned between dichloromethane and 0.2 M HCl. The organic layer was separated and the aqueous was extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate (anhydrous), filtered and concentrated. Preparative HPLC purification (25-50% acetonitrile:water, 0.1% TFA) afforded Compound **6**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.33 (t, J = 6.0 Hz, 1H), 8.44 (s, 1H), 7.48 – 7.32 (m, 1H), 7.31 – 7.15 (m, 1H), 7.14 – 6.97 (m, 1H), 4.86 (d, J = 2.9 Hz, 1H), 4.62 – 4.54 (m, 1H), 4.52 (d, J = 5.9 Hz, 1H), 4.01 (d, J = 13.0 Hz, 1H), 2.99 – 2.76 (m, 3H), 1.96 – 1.81 (m, 1H), 1.71 – 1.53 (m, 1H). **LCMS-ESI$^+$** (m/z): $[M+H]^+$ calculated for $C_{20}H_{19}F_2N_4O_4$: 417.14; found: 417.2.

Example 7

Preparation of Compound **7**

(2S,6R)-N-(2,4-difluorobenzyl)-9-hydroxy-8,10-dioxo-3,4,5,6,8,10,14,14a-octahydro-2H-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazocine-11-carboxamide



7

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C,** 0.050 g, 0.121 mmol), (1S,3R)-3-aminocyclohexanol (0.028 g, 0.243 mmol) and potassium carbonate (0.034 g, 0.243 mmol) were suspended in acetonitrile (0.95 mL) and heated to 90 °C for 0.5 hour. After cooling, acetic acid (0.050 mL) was added and the mixture was reheated to 90 °C for 2h. After cooling the mixture was treated with magnesium bromide (0.044 g) and heated to 50 °C for 1 hour. After cooling, a second portion of magnesium bromide (0.044 g) was added and the mixture was reheated to 50 °C for 15 minutes. After cooling, the mixture partitioned between dichloromethane and 0.2 M HCl. The organic layer was separated and the aqueous was extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate (anhydrous), filtered and

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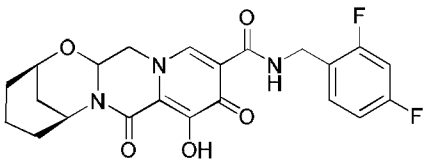
concentrated. Preparative HPLC purification (40-80% acetonitrile:water, 0.1% TFA) afforded Compound **7**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 10.36 (t, J = 6.1 Hz, 1H), 8.45 (s, 1H), 7.48 – 7.29 (m, 1H), 7.31 – 7.13 (m, 1H), 7.13 – 6.97 (m, 1H), 5.56 (dd, J = 10.0, 4.1 Hz, 1H), 4.70 (dd, J = 12.7, 4.1 Hz, 1H), 4.52 (d, J = 5.5 Hz, 2H), 4.40 – 4.29 (m, 2H), 4.06 (dd, J = 12.5, 10.2 Hz, 1H), 2.46 – 2.36 (m, 1H), 1.98 – 1.63 (m, 4H), 1.57 – 1.30 (m, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Example 8

Preparation of Compound **8**

(2R,6S)-N-(2,4-difluorobenzyl)-9-hydroxy-8,10-dioxo-3,4,5,6,8,10,14,14a-octahydro-2H-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazocine-11-carboxamide



8

Compound **8** was prepared in a similar manner to compound **7** using (1R,3S)-3-aminocyclohexanol in place of (1S,3R)-3-aminocyclohexanol. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 10.36 (t, J = 6.1 Hz, 1H), 8.45 (s, 1H), 7.48 – 7.30 (m, 1H), 7.23 (td, J = 10.6, 2.7 Hz, 1H), 7.05 (td, J = 8.3, 2.3 Hz, 1H), 5.56 (dd, J = 10.1, 4.1 Hz, 1H), 4.70 (dd, J = 12.8, 3.9 Hz, 1H), 4.52 (d, J = 5.6 Hz, 2H), 4.39 – 4.27 (m, 2H), 4.06 (dd, J = 12.6, 10.0 Hz, 1H), 2.47 – 2.35 (m, 1H), 2.00 – 1.64 (m, 4H), 1.58 – 1.30 (m, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Examples 9 and 10

Preparation of Compounds **9** and **10**

(2S,5R,13aS)-N-((R)-1-(4-fluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide **9** and (2R,5S,13aR)-N-((R)-1-(4-fluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-

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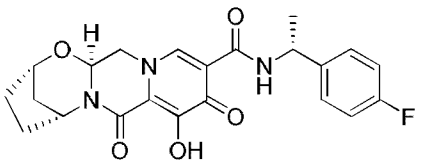
2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide **10**



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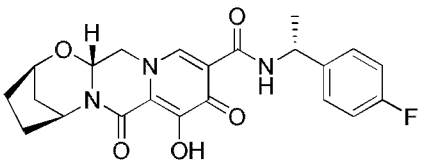

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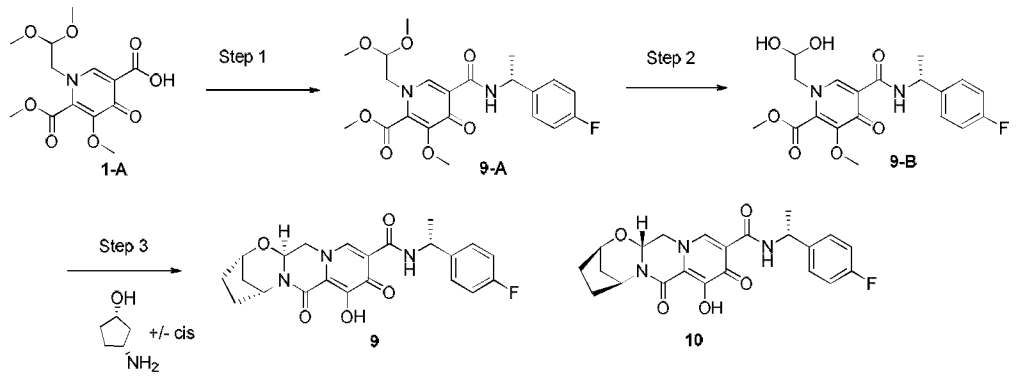

Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1-A,** 0.500 g, 1.59 mmol), was suspended in acetonitrile (6 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.550 mL, 3.17 mmol), (R)-1-(4-fluorophenyl)ethanamine (0.242 mg, 1.74 mmol) and HATU (0.661 g, 1.74 mmol). The reaction mixture was stirred for 2 hours and partitioned between ethyl acetate and water. The organic layer was separated and washed with HCl (10% aq), sodium bicarbonate (1M aq), dried over sodium sulfate, filtered and concentrated to afford crude (R)-methyl 1-(2,2-dimethoxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate which was used without purification in the next step: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{26}FN_2O_7$: 437.17; found: 437.1.

Step 2

(R)-methyl 1-(2,2-dimethoxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate

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was suspended in acetonitrile (5.7 mL) and acetic acid (0.6 mL) and treated with methane sulfonic acid (0.031 mL, 0.477 mmol). The mixture was capped and heated to 75 °C. After 7h, the mixture was cooled and used without purification in the next step: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{19}H_{22}FN_2O_7$: 409.14; found: 409.0.

Step 3

(R)-methyl 1-(2,2-dihydroxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (3.6 mL of the crude mixture from Step 2, 0.8 mmol) was diluted with acetonitrile (3.6 mL) and treated with *cis*-3-aminocyclpentanol, HCl salt (0.219 g, 1.6 mmol) and potassium carbonate (0.276 g, 2.0 mmol). The mixture was capped and heated to 90 °C. After 20 minutes, the reaction mixture was cooled and partitioned between dichloromethane and HCl (0.2 M aq). The layers were separated and the aqueous layer was extracted again with dichloromethane. The combined organic layers were treated with a small amount of acetonitrile, dried over sodium sulfate, filtered and concentrated.

The residue was suspended in acetonitrile (4 mL) and treated with magnesium bromide (0.177 g). The mixture was capped and heated to 50 °C. After 10 minutes, the reaction mixture was cooled and partitioned between dichloromethane and HCl (0.2 M aq). The layers were separated and the aqueous layer was extracted again with dichlormethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (0-8% ethanol:DCM) to afford a diastereomeric mixture of desired **9** and **10**.

The mixture was separated by chiral HPLC using Chiralpak AD-H with 100% ethanol as eluent to afford Compounds **9** and **10** in enantiomerically enriched form:

For Compound **9**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{23}FN_3O_5$: 428.16; found: 428.1. **Chiral HPLC** retention time = 10.177 minutes (Chiralpak AD-H, 150 x 4.6 mm, 1 mL/min EtOH). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 10.45 (d, J = 7.7 Hz, 1H), 8.40 (s, 1H), 7.37 (dd, J = 8.6, 5.6 Hz, 2H), 7.15 (t, J = 8.9 Hz, 2H), 5.44 (dd, J = 9.5, 4.2 Hz, 1H), 5.17 – 5.04 (m, 2H), 4.73 – 4.62

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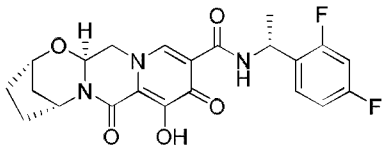
(m, 1H), 4.59 (s, 1H), 4.00 (dd, J = 12.7, 9.5 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 11.8 Hz, 1H), 1.56 (dt, J = 12.1, 3.4 Hz, 1H), 1.44 (d, J = 6.9 Hz, 3H).

For Compound **10**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{23}FN_3O_5$: 428.16; found: 428.1. **Chiral HPLC** retention time = 14.061 minutes (Chiralpak AD-H, 150 x 4.6 mm, 1 mL/min EtOH). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.46 (d, J = 7.8 Hz, 1H), 8.41 (s, 1H), 7.37 (dd, J = 8.6, 5.6 Hz, 2H), 7.15 (t, J = 8.9 Hz, 2H), 5.42 (dd, J = 9.6, 4.1 Hz, 1H), 5.18 – 5.02 (m, 2H), 4.67 (dd, J = 12.8, 4.2 Hz, 1H), 4.59 (s, 1H), 4.02 (dd, J = 12.7, 9.6 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.0 Hz, 1H), 1.57 (dt, J = 13.0, 3.5 Hz, 1H), 1.44 (d, J = 6.9 Hz, 3H).

Example 11

Preparation of Compound **11**

(2S,5R,13aS)-N-((R)-1-(2,4-difluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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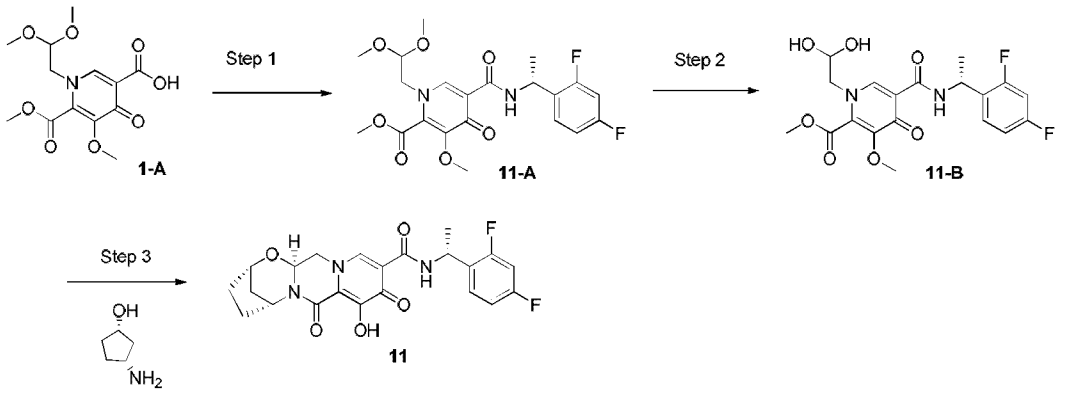

Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1-A**, 0.315 g, 1.00 mmol), was suspended in acetonitrile (4 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.348 mL, 2.00 mmol), (R)-1-(2,4-difluorophenyl)ethanamine HCl salt (0.213 mg, 1.10 mmol) and HATU (0.418 g, 1.10 mmol). The reaction mixture was stirred for 1 hour and partitioned between dichloromethane and HCl (10% aq). The organic layer was separated and washed sodium bicarbonate (1M aq), dried over sodium sulfate, filtered and concentrated to afford crude (R)-methyl 5-(1-(2,4-difluorophenyl)ethylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate which was used without purification in the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{25}F_2N_2O_7$: 455.16; found: 455.1.

Step 2

(R)-methyl 5-(1-(2,4-difluorophenyl)ethylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate was suspended in acetonitrile (3.6 mL) and acetic acid (0.4 mL) and treated with methane sulfonic acid (0.020 mL). The mixture was capped and heated to 75 °C. After 16 hours, the crude mixture was cooled and used without purification in the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{19}H_{21}F_2N_2O_7$: 427.13; found: 427.1.

Step 3

(R)-methyl 5-(1-(2,4-difluorophenyl)ethylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (half of the crude

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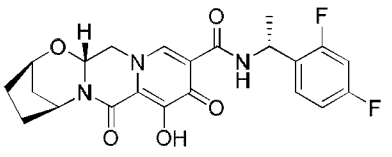
mixture from Step 2, approx 0.5 mmol) was diluted with acetonitrile (2.5 mL) and treated with (1S,3R)-3-aminocyclopentanol (0.110 g, 1.09 mmol) and potassium carbonate (0.069 g, 0.50 mmol). The mixture was capped and heated to 90 °C. After 15 minutes, the reaction mixture was cooled and magnesium bromide (0.184 g) was added. The reaction mixture was heated to 50 °C. After 10 minutes, the mixture was cooled and treated with an additional portion of magnesium bromide (0.184 g). The reaction mixture was reheated to 50 °C and stirred for 10 minutes. After cooling, the mixture was partitioned between dichloromethane and HCl (0.2 M aq). The layers were separated and the aqueous layer was extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Preparative HPLC purification (30-60% acetonitrile:water, 0.1% TFA) afforded desired Compound **11**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.1. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.53 (d, J = 7.5 Hz, 1H), 8.38 (s, 1H), 7.39 (q, J = 8.5 Hz, 1H), 7.29 – 7.12 (m, 1H), 7.13 – 6.93 (m, 1H), 5.44 (dd, J = 9.8, 4.2 Hz, 1H), 5.28 (p, J = 7.3, 6.8 Hz, 1H), 5.09 (s, 1H), 4.66 (dd, J = 13.2, 4.3 Hz, 1H), 4.59 (s, 1H), 3.99 (dd, J = 13.1, 9.6 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.4 Hz, 1H), 1.56 (dt, J = 12.5, 2.9 Hz, 1H), 1.45 (d, J = 6.9 Hz, 3H).

Example 12

Preparation of Compound **12**

(2R,5S,13aR)-N-((R)-1-(2,4-difluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



12

Compound **12** was prepared in a similar manner to compound **11** using (1R,3S)-3-aminocyclopentanol in place of (1S,3R)-3-aminocyclopentanol. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 10.52 (d, J = 8.2 Hz, 1H), 8.38 (s, 1H), 7.39 (q,

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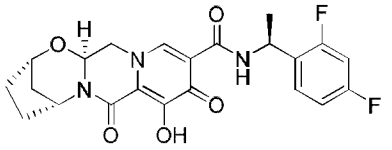
J = 8.4 Hz, 1H), 7.28 – 7.12 (m, 1H), 7.11 – 6.97 (m, 1H), 5.41 (dd, J = 10.0, 4.0 Hz, 1H), 5.35 – 5.20 (m, 1H), 5.08 (s, 1H), 4.65 (dd, J = 13.1, 3.8 Hz, 1H), 4.58 (s, 1H), 4.01 (dd, J = 12.8, 9.5 Hz, 1H), 1.92 (s, 4H), 1.83 (d, J = 11.5 Hz, 1H), 1.61 – 1.51 (m, 1H), 1.44 (d, J = 6.9 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.1.

Example 13

Preparation of Compound **13**

(2S,5R,13aS)-N-((S)-1-(2,4-difluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



13

Compound **13** was prepared in a similar manner to compound **11** using (S)-1-(2,4-difluorophenyl)ethanaminein place of (R)-1-(2,4-difluorophenyl)ethanamine, and using only a single portion of magnesium bromide (0.184 g). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.53 (d, J = 7.8 Hz, 1H), 8.39 (s, 1H), 7.39 (q, J = 8.5 Hz, 1H), 7.32 – 7.14 (m, 1H), 7.05 (t, J = 9.1 Hz, 1H), 5.42 (dd, J = 9.5, 4.2 Hz, 1H), 5.29 (p, J = 6.9 Hz, 1H), 5.09 (s, 1H), 4.65 (dd, J = 12.9, 4.3 Hz, 1H), 4.59 (s, 1H), 4.02 (dd, J = 12.6, 9.8 Hz, 1H), 1.92 (s, 4H), 1.83 (d, J = 12.1 Hz, 1H), 1.61 – 1.52 (m, 1H), 1.44 (d, J = 6.9 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Example 14

Preparation of Compound **14**

(2R,5S,13aR)-N-((S)-1-(2,4-difluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

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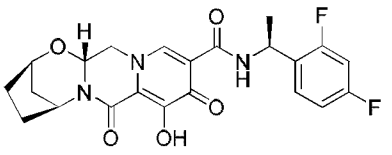


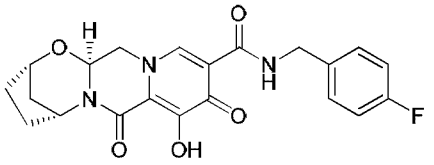
14

Compound **14** was prepared in a similar manner to compound **11** using (S)-1-(2,4-difluorophenyl)ethanamine in place of (R)-1-(2,4-difluorophenyl)ethanamine and using (1R,3S)-3-aminocyclopentanol in place of (1S,3R)-3-aminocyclopentanol. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.53 (d, J = 7.6 Hz, 1H), 8.38 (s, 1H), 7.39 (q, J = 8.6 Hz, 1H), 7.28 – 7.14 (m, 1H), 7.05 (t, J = 8.5 Hz, 1H), 5.44 (dd, J = 9.8, 3.8 Hz, 1H), 5.28 (p, J = 8.0 Hz, 1H), 5.09 (s, 1H), 4.66 (dd, J = 12.9, 4.0 Hz, 1H), 4.59 (s, 1H), 3.99 (dd, J = 12.5, 9.6 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.6 Hz, 1H), 1.56 (dt, J = 13.0, 3.3 Hz, 1H), 1.45 (d, J = 6.9 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.1.

Example 15

Preparation of Compound **15**

(2S,5R,13aS)-N-(4-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



15

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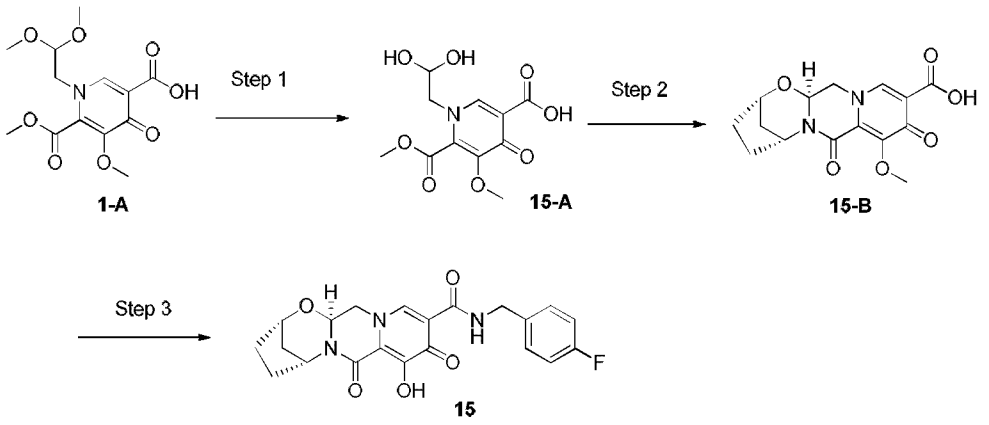

Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1-A**, 3.15 g, 10.0 mmol), suspended in acetonitrile (36 mL) and acetic acid (4 mL) was treated with methane sulfonic acid (0.195 mL). The mixture heated to 75 °C. After 7 hours, the crude mixture was cooled and stored in a -10°C for three days. The crude mixture was reheated to 75 °C for 2 hours, cooled used without purification in the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{19}H_{21}F_2N_2O_7$: 288.07; found: 288.1.

Step 2

Crude 1-(2,2-dihydroxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (16.8 mL of crude mixture from Step 1, approx 4 mmol) was combined with (1S,3R)-3-aminocyclopentanol (0.809 g, 8 mmol), diluted with acetonitrile (16.8 mL), and treated with potassium carbonate (0.553 g, 4 mmol). The reaction mixture was heated to 85 °C, stirred for 15 minutes, cooled to ambient temperature and stirred an additional 16 hours. HCl (50 mL, 0.2M aq) was added and the clear yellow solution was extracted three times with dichloromethane. The combined organics were dried over sodium sulfate, filtered and concentrated to a yellow solid. This crude material was precipitated from dichloromethane/hexanes to afford desired intermediate **15-B** as a light beige powder. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 5.42 (dd, J = 9.6, 4.1 Hz, 1H), 5.09 (s, 1H), 4.72 (dd, J = 13.0, 3.7 Hz, 1H), 4.57 (s, 1H), 4.09 (dd, J = 12.5, 9.6 Hz, 1H), 3.83 (s, 3H), 1.92 (s, 3H), 1.78

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(m, 2H), 1.62 – 1.47 (m, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{17}N_2O_6$: 321.11; found: 321.2.

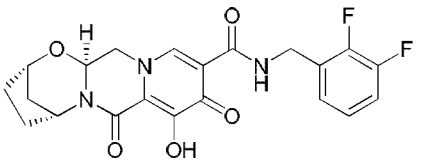
Step 3

Intermediate **15-B** (0.040 g, 0.125 mmol) and (4-fluorophenyl)methanamine (0.017 g, 0.137 mmol) were suspended in acetonitrile (1 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.033 mL, 0.187 mmol) and HATU (0.052 g, 0.137 mmol). After stirring for 30 minutes, the reaction mixture was treated with magnesium bromide (0.046 g, 0.25 mmol) and heated to 50 °C. After 10 minutes, the reaction mixture was cooled and treated with HCl (2 mL, 10% aq). After a few minutes, the precipitate was filtered and washed with HCl (10% aq) and water. Preparative HPLC purification of the precipitate (20-65% acetonitrile:water, 0.1% TFA) afforded desired Compound **15.** **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.36 (t, J = 6.0 Hz, 1H), 8.46 (s, 1H), 7.37 – 7.28 (m, 2H), 7.19 – 7.09 (m, 2H), 5.43 (dd, J = 9.6, 4.0 Hz, 1H), 5.08 (s, 1H), 4.68 (dd, J = 12.8, 4.1 Hz, 1H), 4.59 (s, 1H), 4.58 – 4.42 (m, 3H), 4.02 (dd, J = 12.7, 9.6 Hz, 1H), 1.92 (s, 5H), 1.83 (d, J = 12.2 Hz, 1H), 1.56 (dt, J = 12.0, 3.4 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{21}FN_3O_5$: 414.15; found: 414.2.

Example 16

Preparation of Compound **16**

(2S,5R,13aS)-N-(2,3-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



16

Compound **16** was prepared in a similar manner to compound **15** using (2,3-difluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.41 (t, J = 6.1 Hz, 1H), 8.45 (s, 1H), 7.43 –

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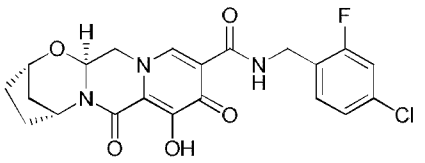
7.25 (m, 1H), 7.25 – 7.05 (m, 2H), 5.44 (dd, J = 9.5, 3.9 Hz, 1H), 5.09 (s, 1H), 4.68 (dd, J = 12.8, 4.0 Hz, 1H), 4.65 – 4.53 (m, 3H), 4.02 (dd, J = 12.7, 9.8 Hz, 1H), 3.56 (s, 1H), 1.93 (s, 4H), 1.83 (d, J = 11.9 Hz, 1H), 1.57 (dt, J = 11.5, 3.0 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2.

Example 17

Preparation of Compound **17**

(2S,5R,13aS)-N-(4-chloro-2-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



17

Compound **17** was prepared in a similar manner to compound **15** using (4-chloro-2-fluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.45 – 10.29 (m, 1H), 8.44 (s, 1H), 7.42 (dd, J = 10.0, 2.0 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.26 (dd, J = 8.4, 1.8 Hz, 1H), 5.50 – 5.38 (m, 1H), 5.09 (s, 1H), 4.68 (dd, J = 13.0, 4.0 Hz, 1H), 4.59 (s, 1H), 4.54 (m, 2H), 4.02 (dd, J = 12.8, 9.7 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.0 Hz, 1H), 1.57 (dt, J = 11.9, 3.4 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}ClFN_3O_5$: 448.11; found: 448.2.

Example 18

Preparation of Compound **18**

(2S,5R,13aS)-N-(3,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

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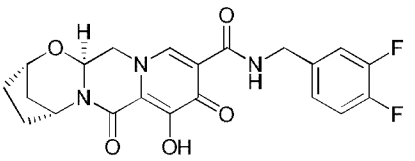


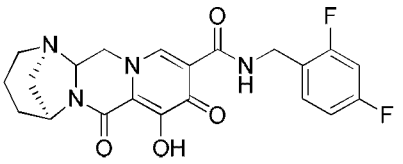
18

Compound **18** was prepared in a similar manner to compound **15** using (3,4-difluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.51 – 10.27 (m, 1H), 8.46 (s, 1H), 7.50 – 7.23 (m, 2H), 7.23 – 7.03 (m, 1H), 5.44 (dd, J = 9.5, 3.6 Hz, 1H), 5.09 (s, 1H), 4.75 – 4.63 (m, 1H), 4.60 (s, 1H), 4.57 – 4.44 (m, 2H), 4.02 (dd, J = 12.6, 9.8 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.0 Hz, 1H), 1.57 (dt, J = 12.0, 3.4 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2.

Example 19

Preparation of Compound **19**

(1R,5S)-N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-1,5-methanopyrido[1',2':4,5]pyrazino[1,2-a][1,3]diazepine-10-carboxamide



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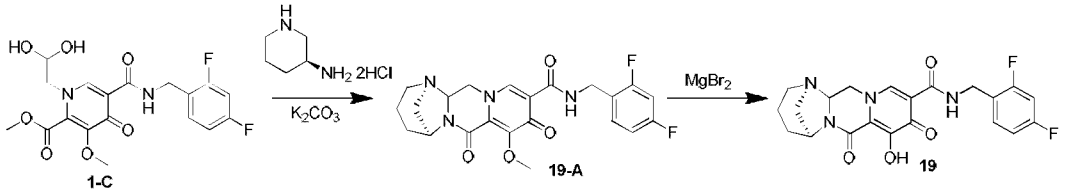

Steps 1 and 2

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C,** 97.5 mg, 0.236 mmol) was treated with acetonitrile (1.9 mL), acetic acid (0.1 mL), potassium carbonate (145 mg,

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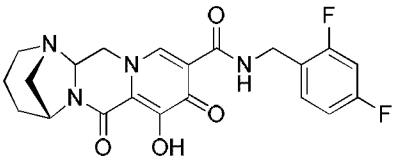
1.05 mmol), and (S)-piperidin-3-amine dihydrochloride (82 mg, 0.472 mmol). The reaction mixture was sealed and heated to 90 °C. After 60 minutes, the reaction mixture was cooled partitioned between brine and dichloromethane. The aqueous phase was thrice extracted into dichloromethane and the combined organic phases were combined, dried over MgSO4, filtered, concentrated. The crude product was dissolved into acetonitrile (2 mL) and magnesium bromide (89.1 mg, 0.48 mmol) was added. The mixture was resealed and heated to 50 °C. After 90 minutes, the reaction mixture was quenched with ~5 mL of 0.2M HCl(aq), the pH adjusted to ~10, diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **19.** **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.43 (t, J = 5.9 Hz, 1H), 8.43 (s, 1H), 7.39 – 7.30 (m, 1H), 6.81 (q, J = 8.1 Hz, 2H), 4.89 (dd, J = 11.6, 3.8 Hz, 1H), 4.69 (s, 1H), 4.64 (d, J = 5.8 Hz, 2H), 4.26 (dd, J = 12.6, 3.8 Hz, 1H), 3.91 (t, J = 12.1 Hz, 1H), 3.20 – 3.10 (m, 2H), 3.06 (s, 2H), 2.14 – 2.02 (m, 1H), 1.96 – 1.81 (m, 2H), 1.81 – 1.70 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_4O_4$: 431.15; found: 431.2.

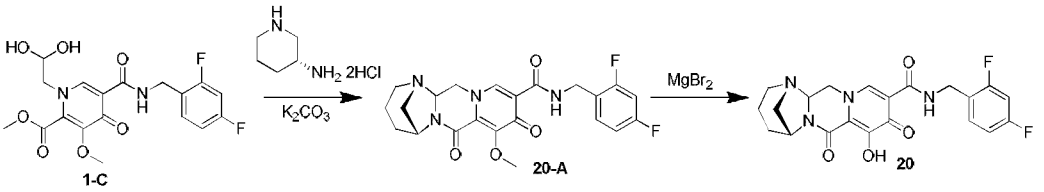
Example 20

Preparation of Compound **20**

(1S,5R)-N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-1,5-methanopyrido[1',2':4,5]pyrazino[1,2-a][1,3]diazepine-10-carboxamide



20



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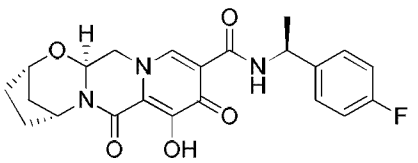
Steps 1 and 2

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C,** 103.3 mg, 0.25 mmol) was treated with acetonitrile (1.9 mL), acetic acid (0.1 mL), potassium carbonate (159.8 mg, 1.16 mmol), and (R)-piperidin-3-amine dihydrochloride (90 mg, 0.52 mmol). The reaction mixture was sealed and heated to 90 °C. After 40 minutes, the reaction mixture was cooled partitioned between brine and dichloromethane. The aqueous phase was thrice extracted into dichloromethane and the combined organic phases were combined, dried over $MgSO_4$, filtered, concentrated. The crude product was dissolved into acetonitrile (2 mL) and magnesium bromide (96.5 mg, 0.52 mmol) was added. The mixture was resealed and heated to 50 °C. After 80 minutes, the reaction mixture was quenched with ~5 mL of 0.2M HCl (aq), the pH adjusted to ~10, diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **20.** **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.35 (t, J = 6.0 Hz, 1H), 8.48 (s, 1H), 7.45 – 7.33 (m, 1H), 7.29 – 7.18 (m, 1H), 7.05 (td, J = 8.5, 2.4 Hz, 1H), 5.06 (dd, J = 11.4, 3.5 Hz, 1H), 4.56 – 4.47 (m, 3H), 4.44 (s, 1H), 4.05 (t, J = 11.8 Hz, 1H), 3.07 – 2.89 (m, 4H), 1.85 – 1.73 (m, 3H), 1.54 – 1.46 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_4O_4$: 431.15; found: 431.2.

Example 21

Preparation of Compound **21**

(2S,5R,13aS)-N-((S)-1-(4-fluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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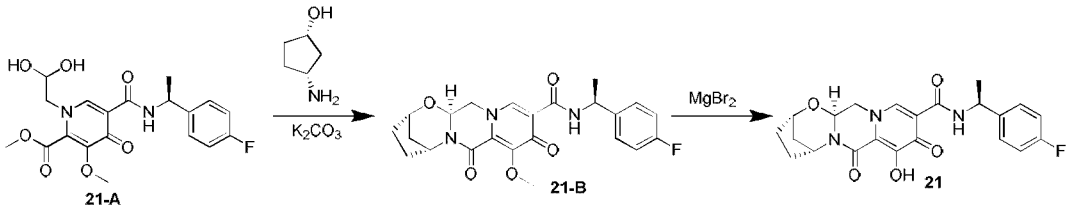

Steps 1 and 2

(S)-Methyl 1-(2,2-dihydroxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**21-A**, 1 mL, 0.23 M solution in 19:1 acetonitrile:acetic acid, prepared as per (R)-methyl 1-(2,2-dihydroxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate **9-A** from Example 9 using (S)-1-(4-fluorophenyl)ethanamine in place of (R)-1-(4-fluorophenyl)ethanamine) was treated with (1S,3R)-3-aminocyclopentanol (62 mg, 0.61 mmol) and potassium carbonate (34 mg, 0.25 mmol). The reaction mixture was sealed and heated to 90 °C. After 60 minutes, the reaction mixture was cooled partitioned between brine and dichloromethane. The aqueous phase was thrice extracted into dichloromethane and the combined organic phases were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product was dissolved into acetonitrile (2 mL) and magnesium bromide (74 mg, 0.4 mmol) was added. The mixture was resealed and heated to 50 °C. After 100 minutes, the reaction mixture was quenched with 0.2M HCl (aq), diluted with brine, and thrice extracted into DCM. HPLC purification (acetonitrile:water, 0.1% TFA) afforded Compound **21.** **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.42 (br s, 1H), 10.45 (d, J = 7.9 Hz, 1H), 8.40 (s, 1H), 7.36 (dd, J = 8.6, 5.5 Hz, 2H), 7.14 (t, J = 8.9 Hz, 2H), 5.42 (dd, J = 9.6, 4.2 Hz, 1H), 5.15 – 5.04 (m, 2H), 4.72 – 4.55 (m, 2H), 4.02 (dd, J = 12.7, 9.7 Hz, 1H), 1.97 – 1.89 (m, 4H), 1.82 (d, J = 12.2 Hz, 1H), 1.56 (dt, J = 11.9, 3.3 Hz, 1H), 1.43 (d, J = 6.9 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}FN_3O_5$: 428.16; found: 428.1.

Example 22

Preparation of Compound **22**

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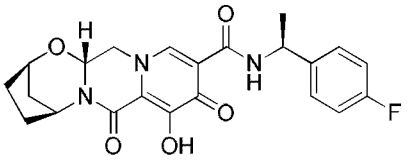
(2R,5S,13aR)-N-((S)-1-(4-fluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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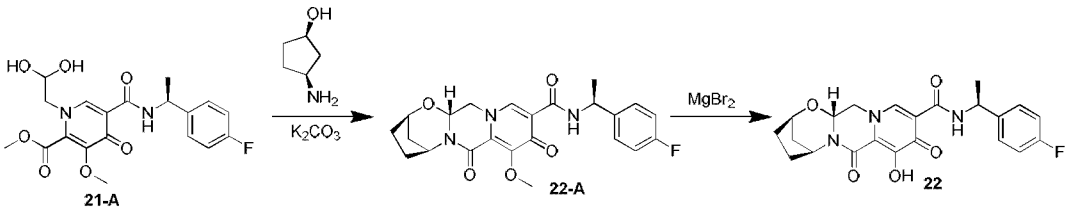

Steps 1 and 2

(S)-methyl 1-(2,2-dihydroxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**21-A**, 1 mL, 0.23 M solution in 19:1 acetonitrile:acetic acid) was treated with (1R,3S)-3-aminocyclopentanol (52 mg, 0.51 mmol) and potassium carbonate (31 mg, 0.22 mmol). The reaction mixture was sealed and heated to 90 °C. After 60 minutes, the reaction mixture was cooled partitioned between brine and dichloromethane. The aqueous phase was thrice extracted into dichloromethane and the combined organic phases were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product was dissolved into acetonitrile (2 mL) and magnesium bromide (91 mg, 0.49 mmol) was added. The mixture was resealed and heated to 50 °C. After 100 minutes, the reaction mixture was quenched with 0.2M HCl(aq), diluted with brine, and thrice extracted into DCM. HPLC purification (acetonitrile:water, 0.1% TFA) afforded Compound **22.** **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (br s, 1H), 10.45 (d, J = 7.7 Hz, 1H), 8.39 (s, 1H), 7.36 (dd, J = 8.5, 5.6 Hz, 2H), 7.14 (t, J = 8.9 Hz, 2H), 5.43 (dd, J = 9.6, 4.0 Hz, 1H), 5.15 – 5.06 (m, 2H), 4.66 (dd, J = 12.8, 3.9 Hz, 1H), 4.58 (s, 1H), 3.99 (dd, J = 12.6, 9.5 Hz, 1H), 1.93 (s, 4H), 1.82 (d, J = 12.0 Hz, 1H), 1.56 (dt, J = 12.0, 3.0 Hz, 1H), 1.44 (d, J = 6.9 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}FN_3O_5$: 428.16; found: 428.1.

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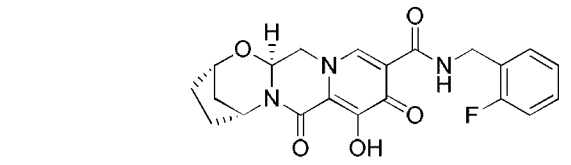
Example 23

Preparation of Compound **23**

(2S,5R,13aS)-N-(2-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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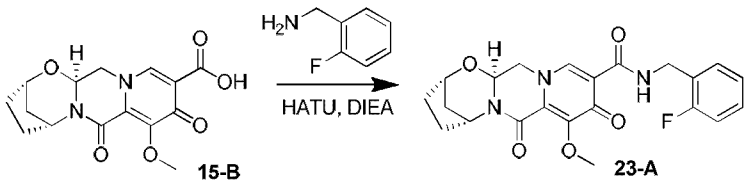

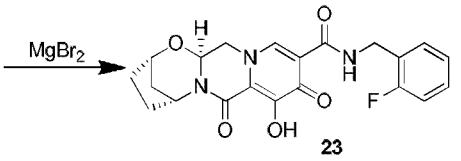

Steps 1 and 2

15-B (41 mg, 0.13 mmol) was treated with acetonitrile (1 mL), (2-fluorophenyl)methanamine (17 mg, 0.14 mmol), HATU (67 mg, 0.18 mmol), and N,N-diisopropylethylamine (DIPEA) (24 mg, 0.19 mmol). The reaction mixture was stirred at room temperature for one hour and magnesium bromide (47 mg, 0.26 mmol) was added. The mixture was sealed and heated to 50 °C. After 60 minutes, the reaction mixture was quenched with 0.2M HCl (aq), diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **23.** **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.42 (s, 1H), 8.34 (s, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.12 – 6.97 (m, 2H), 5.40 – 5.32 (m, 1H), 5.29 (t, J = 3.5 Hz, 1H), 4.67 (s, 3H), 4.28 – 4.20 (m, 1H), 4.06 – 3.95 (m, 1H), 2.20 – 1.96 (m, 4H), 1.95 – 1.84 (m, 1H), 1.59 (dt, J = 12.4, 3.3 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}FN_3O_5$: 414.15; found: 414.2.

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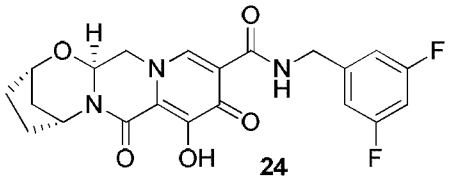
Example 24

Preparation of Compound **24**

(2S,5R,13aS)-N-(3,5-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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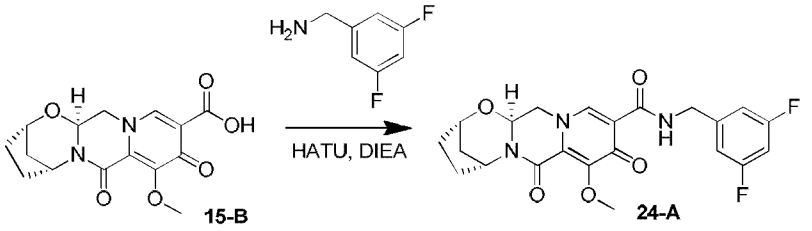
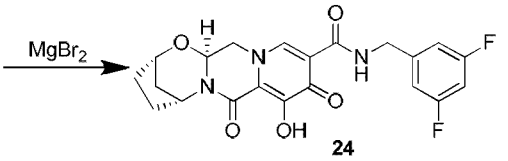


15-B **24-A**



24

Steps 1 and 2

15-B (44 mg, 0.14 mmol) was treated with acetonitrile (1 mL), (3,5-difluorophenyl)methanamine (32 mg, 0.23 mmol), HATU (54 mg, 0.14 mmol), and N,N-diisopropylethylamine (37 mg, 0.29 mmol). The reaction mixture was stirred at room temperature for one hour and magnesium bromide (57 mg, 0.31 mmol) was added. The mixture was sealed and heated to 50 °C. After 60 minutes, the reaction mixture was quenched with 0.2M HCl (aq), diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **24.** **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.39 (s, 1H), 8.42 (s, 1H), 6.82 (d, J = 7.9 Hz, 2H), 6.65 (t, J = 8.8 Hz, 1H), 5.38 (d, J = 7.7 Hz, 1H), 5.28 (s, 1H), 4.78 – 4.41 (m, 3H), 4.32 (d, J = 12.1 Hz, 1H), 4.02 (t, J = 10.9 Hz, 1H), 2.30 – 1.97 (m, 4H), 1.97 – 1.81 (m,

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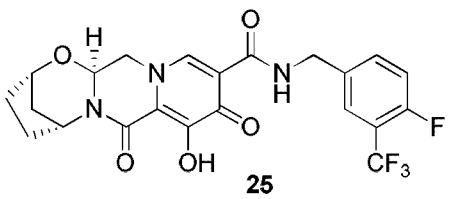
1H), 1.59 (d, J = 12.3 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_2N_3O_5$: 432.14; found: 432.2.

Example 25

Preparation of Compound **25**

(2S,5R,13aS)-N-(4-fluoro-3-(trifluoromethyl)benzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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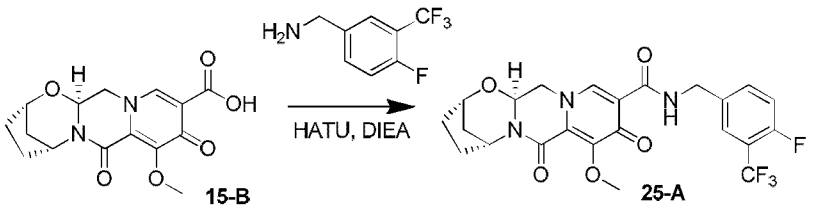
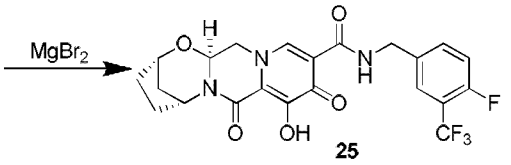


15-B **25-A**



25

Steps 1 and 2

15-B (43 mg, 0.13 mmol) was treated with acetonitrile (1 mL), (4-fluoro-3-(trifluoromethyl)phenyl)methanamine (29 mg, 0.15 mmol), HATU (62 mg, 0.16 mmol), and N,N-diisopropylethylamine (26 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for one hour and magnesium bromide (62 mg, 0.34 mmol) was added. The mixture was sealed and heated to 50 °C. After 60 minutes, the reaction mixture was quenched with 0.2M HCl(aq), diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **25.** **^{1}H-**

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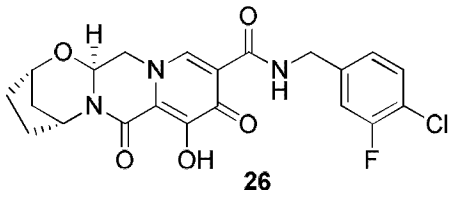
NMR (400 MHz, Chloroform-d) δ 10.44 (s, 1H), 8.29 (s, 1H), 7.56 – 7.38 (m, 2H), 7.06 (t, J = 9.2 Hz, 1H), 5.30 (dd, J = 9.3, 3.5 Hz, 1H), 5.21 (s, 1H), 4.65 – 4.45 (m, 3H), 4.21 (dd, J = 12.8, 3.4 Hz, 1H), 3.95 (dd, J = 12.4, 9.7 Hz, 1H), 2.11 – 1.89 (m, 4H), 1.89 – 1.74 (m, 1H), 1.53 (dt, J = 12.4, 3.2 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{19}F_4N_3O_5$: 482.14; found: 482.2.

Example 26

Preparation of Compound **26**

(2S,5R,13aS)-N-(4-chloro-3-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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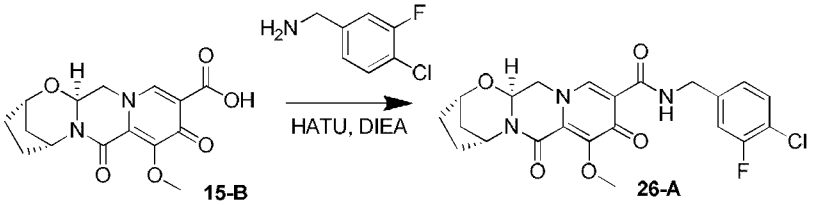
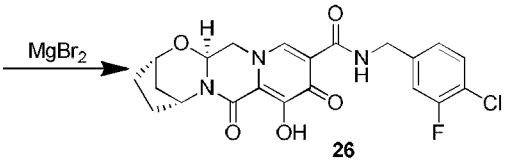


15-B **26-A**



26

Steps 1 and 2

15-B (41 mg, 0.13 mmol) was treated with acetonitrile (1 mL), (4-chloro-3-fluorophenyl)methanamine (40 mg, 0.25 mmol), HATU (60 mg, 0.16 mmol), and N,N-diisopropylethylamine (28 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for one hour and magnesium bromide (48 mg, 0.26 mmol) was added. The mixture was sealed and heated to 50 °C. After 60 minutes, the reaction mixture was quenched with 0.2M HCl (aq), diluted with brine, and thrice extracted into

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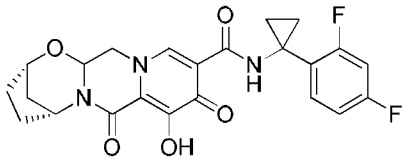
DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **26.** **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.41 (s, 1H), 8.30 (s, 1H), 7.24 (t, J = 6.1 Hz, 1H), 7.13 – 6.90 (m, 2H), 5.30 (dd, J = 9.1, 3.2 Hz, 1H), 5.22 (s, 1H), 4.61 (s, 1H), 4.51 (s, 2H), 4.20 (d, J = 9.4 Hz, 1H), 3.95 (d, J = 12.0 Hz, 1H), 2.11 – 1.90 (m, 4H), 1.90 – 1.76 (m, 1H), 1.53 (d, J = 12.2 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClFN_3O_5$: 448.11; found: 448.2.

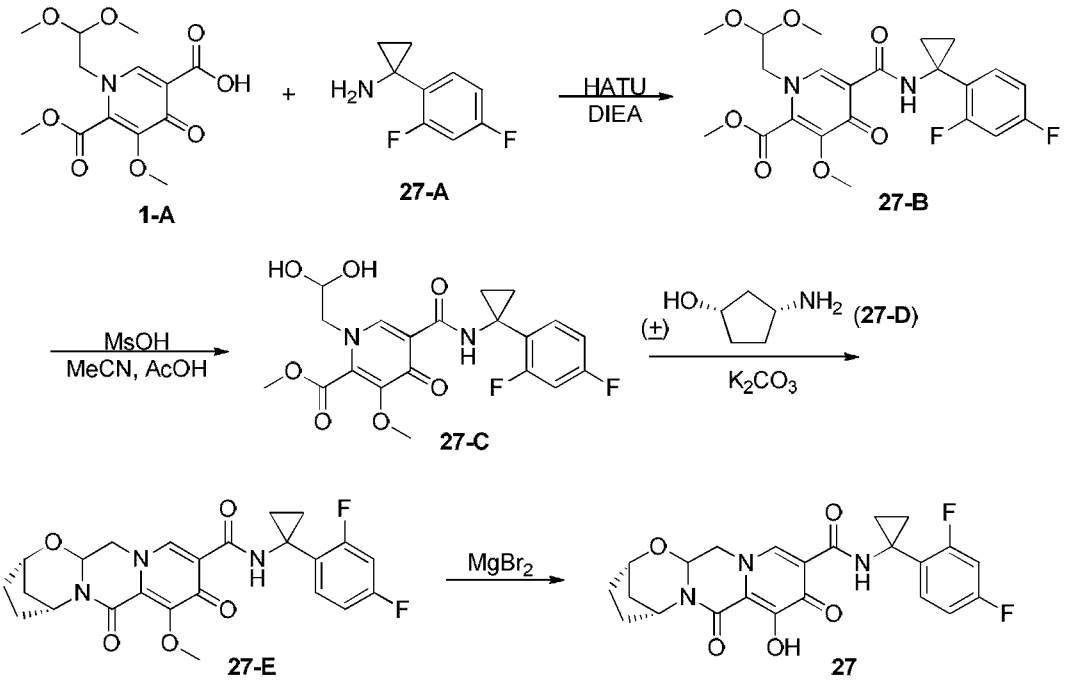
Example 27

Preparation of Compound **27**

(2S,5R)-N-(1-(2,4-difluorophenyl)cyclopropyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



27



1-A **27-A** **27-B** **27-C** **27-E** **27**

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Step 1

A suspension of the compound **1-A** (1.004 g, 3.19 mmol), the amine **27-A** (688 mg, 3.35 mmol), and HATU (1.453 g 3.82 mmol) in CH_2Cl_2 (20 mL) was stirred in 0 °C bath as N,N-diisopropylethylamine (DIPEA) (2 mL, 11.48 mmol) was added. After 1 hour at 0 °C, the reaction mixture was concentrated to a syrup, diluted with ethyl acetate, and washed with water (x 2). After the aqueous fractions were extracted with ethyl acetate (x 1), the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by CombiFlash (120 g column) using hexanes- ethyl acetate as eluents. The major peak was combined and concentrated to afford 1.082 g (73%) of the product **27-B**. After the minor peak was combined and concentrated, the concentrated residue was dissolved in CH_2Cl_2 and some insoluble materials were filtered. The filtrate was concentrated to get 361 mg (24%) of the additional product **27-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{25}F_2N_2O_7$: 467.16; found**:** 467.1.

Step 2 and 3

Compound **27-B** (81 mg, 0.174 mmol) was dissolved in a mixture (1 mL) of acetonitrile (22 mL), AcOH (2 mL), and methanesulfonic acid (0.14 mL, 2.16 mmol) at room temperature and the resulting solution was stirred at 65 °C for 20 hours.

After the resulting solution was cooled to room temperature, the aminoalcohol **27-D** (50 mg, racemic, 0.363 mmol), K_2CO_3 (50 mg, 0.362 mmol), and acetonitrile (2 mL) were added to the solution. The resulting mixture was stirred at 65 °C bath for 1 hour. After the reaction mixture was cooled to room temperature, it was acidified with 1 N HCl (~2 mL), diluted with water (~8 mL), and extracted with CH_2Cl_2 (x 3). Combined extracts were dried (Na_2SO_4), concentrated, and purified by CombiFlash to obtain 67 mg (82%) of compound **27-E**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.25 (s, 1H), 7.60 (td, *J* = 8.5, 6.5 Hz, 1H), 6.85 – 6.57 (m, 2H), 5.33 (br, 1H), 5.26 (dd, *J* = 9.6, 3.9 Hz, 1H), 4.60 (t, *J* = 3.0 Hz, 1H), 4.18 – 4.06 (m, 1H), 4.01 (s, 3H), 3.92 (dd, *J* = 12.7, 9.6 Hz, 1H) , 2.11 – 1.91 (m, 4H), 1.88 – 1.71 (m, 1H), 1.60 – 1.49 (m, 1H), 1.31 – 1.10 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.80 (q, *J* =

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8.8 Hz, 1F), -112.05 (p, J = 7.9 Hz, 1F). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{24}F_2N_3O_5$: 472.17; found**:** 472.1.

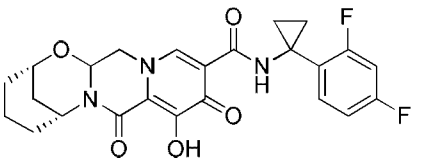
Step 4

A mixture of compound **27-E** (67 mg, 0.142 mmol) and $MgBr_2$ (66 mg, 0.358 mmol) in MeCN (3 mL) was stirred at 50 °C for 30 minutes and cooled to 0 °C before treating with 1 N HCl (3 mL). After the mixture was diluted with water (~30 mL), the product was extracted with CH_2Cl_2 (x 3), and the combined extracts were dried (Na_2SO_4) and concentrated. The product was purified by preparative HPLC and freeze-dried to obtain product **27** as a 1:1 mixture with trifluoroacetic acid. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.35 (s, 1H), 7.57 (q, J = 8.2 Hz, 1H), 6.91 – 6.56 (m, 2H), 5.31 (dt, J = 14.3, 4.0 Hz, 2H), 4.68 (s, 1H), 4.22 (dd, J = 13.2, 3.9 Hz, 1H), 3.99 (dd, J = 12.8, 9.3 Hz, 1H), 2.28 – 1.96 (m, 5H), 1.88 (ddt, J = 12.1, 8.6, 3.7 Hz, 1H), 1.71 – 1.49 (m, 1H), 1.38 – 1.11 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -76.37 (s, 3F), -111.6 ~ -111.75 (m, 2F). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_3O_5$: 458.15; found**:** 458.1.

Example 28

Preparation of Compound **28**

(2S,6R)-N-(1-(2,4-difluorophenyl)cyclopropyl)-9-hydroxy-8,10-dioxo-3,4,5,6,8,10,14,14a-octahydro-2H-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazocine-11-carboxamide



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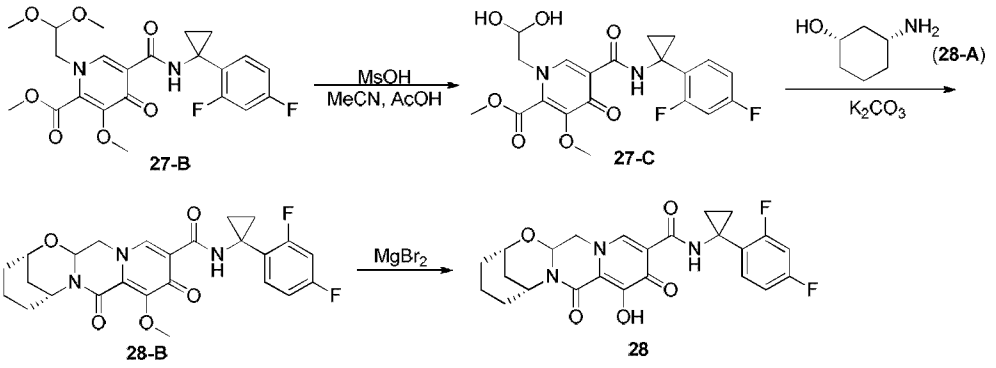

Step 1 and 2

Compound **27-B** (87 mg, 0.187 mmol) was dissolved in a mixture (2 mL) of acetonitrile (22 mL), AcOH (2 mL), and methanesulfonic acid (0.14 mL, 2.16 mmol) at room temperature and the resulting solution was stirred at 65 °C for 20 hours.

After the resulting solution was cooled to room temperature, the aminoalcohol **28-A** (44 mg, racemic, 0.382 mmol) and acetonitrile (2 mL) were added to the solution. After the resulting mixture was stirred at 65 °C bath for 30 minutes, K_2CO_3 (41 mg, 0.297 mmol) was added and the mixture was stirred at 65 °C for 21 hours. The reaction mixture was cooled to room temperature, it was acidified with 1 N HCl (~2 mL), diluted with water (~8 mL), and extracted with CH_2Cl_2 (x 3). Combined extracts were dried (Na_2SO_4), concentrated, and purified by preparative HPLC and the fraction containing the product was freeze-dried. After the residue was dissolved in ethyl acetate, the solution was washed with saturated $NaHCO_3$ (x 1), dried (Na_2SO_4), and concentrated to obtain 18 mg (20%) of compound **28-B** as a 1:1 mixture with trifluoroacetic acid. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.26 (s, 1H), 7.63 (td, J = 8.6, 6.6 Hz, 1H), 6.76 (dddd, J = 21.9, 11.2, 8.7, 2.3 Hz, 2H), 5.39 (dd, J = 9.6, 3.7 Hz, 1H), 4.53 – 4.36 (m, 2H), 4.09 (dd, J = 12.8, 3.7 Hz, 1H), 4.03 (s, 3H), 3.99 (dd, J = 12.7, 9.7 Hz, 1H), 2.41 – 2.20 (m, 2H), 1.84 (dtd, J = 19.7, 9.3, 8.8, 4.4 Hz, 2H), 1.74 (dd, J = 14.6, 2.5 Hz, 1H), 1.62 – 1.35 (m, 2H), 1.34 – 1.14 (m, 5H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.75 (q, J = 8.9 Hz, 1F), -112.01 (p, J = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{26}F_2N_3O_5$: 486.18; found**:** 486.2.

Step 3

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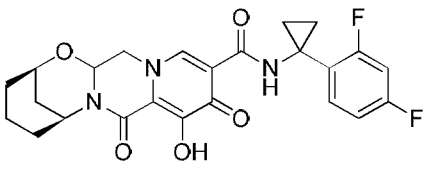
Compound **28-B** (18 mg, 0.037 mmol) was treated with $MgBr_2$ as described in step4 in the synthesis of compound **27-E** to obtain compound **28**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.29 (s, 1H), 7.59 (td, *J* = 8.5, 6.6 Hz, 1H), 6.89 – 6.60 (m, 2H), 5.51 (dd, *J* = 9.9, 4.0 Hz, 1H), 4.55 (s, 1H), 4.48 (t, *J* = 4.2 Hz, 1H), 4.21 (dd, *J* = 12.9, 4.1 Hz, 1H), 3.99 (dd, *J* = 12.8, 9.8 Hz, 1H), 2.56 – 2.35 (m, 1H), 2.14 (dd, *J* = 16.1, 5.9 Hz, 1H), 1.96 – 1.74 (m, 3H), 1.66 – 1.37 (m, 3H), 1.28 (d, *J* = 4.4 Hz, 2H), 1.26 – 1.19 (m, 2H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -76.41 (s, 3F, -111.79 (m, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{23}F_2N_3O_5$: 472.17; found**:** 472.1.

Example 29

Preparation of Compound **29**

(2R,6S)-N-(1-(2,4-difluorophenyl)cyclopropyl)-9-hydroxy-8,10-dioxo-3,4,5,6,8,10,14,14a-octahydro-2H-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazocine-11-carboxamide



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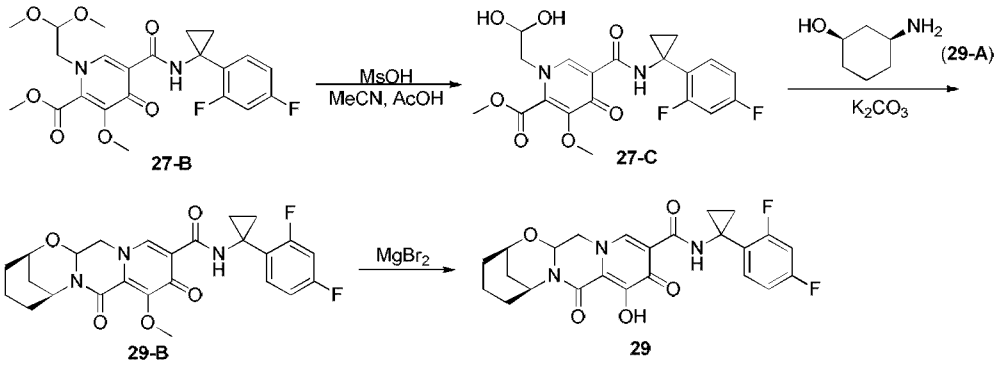

Step 1 and 2

Compound **29-B** (13 mg, 14%) was prepared from compound **27-B** (87 mg, 0.187 mmol) and the aminoalcohol **29-A** (45 mg, 0.391 mmol) in a manner similar

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to that described in step 1 of the synthesis of compound **28-B**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.26 (s, 1H), 7.63 (td, *J* = 8.6, 6.6 Hz, 1H), 6.76 (dddd, *J* = 21.9, 11.2, 8.7, 2.3 Hz, 2H), 5.39 (dd, *J* = 9.6, 3.7 Hz, 1H), 4.53 – 4.36 (m, 2H), 4.09 (dd, *J* = 12.8, 3.7 Hz, 1H), 4.03 (s, 3H), 3.99 (dd, *J* = 12.7, 9.7 Hz, 1H), 2.41 – 2.20 (m, 2H), 1.84 (dtd, *J* = 19.7, 9.3, 8.8, 4.4 Hz, 2H), 1.74 (dd, *J* = 14.6, 2.5 Hz, 1H), 1.62 – 1.35 (m, 2H), 1.34 – 1.14 (m, 5H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.75 (q, *J* = 8.9 Hz, 1F), -112.01 (p, *J* = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{26}F_2N_3O_5$: 486.18; found**:** 486.2.

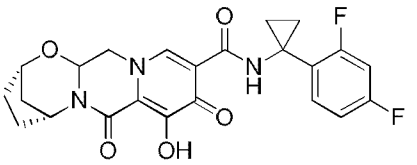
Step 3

Compound **29** was prepared from compound **29-B** in a manner similar to that described in step 2 of the synthesis of compound **16**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.29 (s, 1H), 7.59 (td, *J* = 8.5, 6.6 Hz, 1H), 6.89 – 6.60 (m, 2H), 5.51 (dd, *J* = 9.9, 4.0 Hz, 1H), 4.55 (s, 1H), 4.48 (t, *J* = 4.2 Hz, 1H), 4.21 (dd, *J* = 12.9, 4.1 Hz, 1H), 3.99 (dd, *J* = 12.8, 9.8 Hz, 1H), 2.56 – 2.35 (m, 1H), 2.14 (dd, *J* = 16.1, 5.9 Hz, 1H), 1.96 – 1.74 (m, 3H), 1.66 – 1.37 (m, 3H), 1.28 (d, *J* = 4.4 Hz, 2H), 1.26 – 1.19 (m, 2H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -76.41 (s, 3F, -111.79 (m, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{23}F_2N_3O_5$: 472.17; found**:** 472.1.

Example 30

Preparation of Compound **30**

(2S,5R,13aS)-N-(1-(2,4-difluorophenyl)cyclopropyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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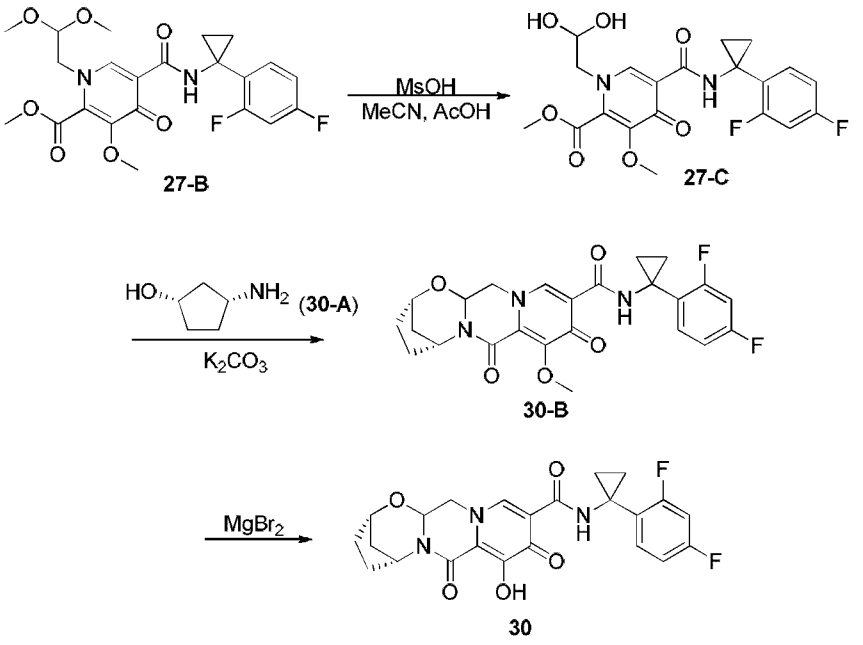

Step 1 and 2

Compound **27-B** (150 mg, 0.322 mmol) was dissolved in acetonitrile (2 mL), AcOH (0.2 mL), and methanesulfonic acid (0.007 mL, 0.108 mmol) at room temperature and the resulting solution was stirred at 65 °C for 20 hours. After the resulting solution was cooled to room temperature, the aminoalcohol **30-A** (72.1 mg, chiral, 0.713 mmol), K_2CO_3 (89.4 mg, 0.647 mmol), and acetonitrile (2 mL) were added to the solution. The resulting mixture was stirred at 65 °C bath for 0.5 hour. After the reaction mixture was cooled to room temperature, it was acidified with 1 N HCl (~3 mL), diluted with water (~12 mL), and extracted with CH_2Cl_2 (x 3). Combined extracts were dried (Na_2SO_4), concentrated, and purified by CombiFlash to obtain 128 mg (84%) of compound **30-B**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.24 (s, 1H), 7.61 (td, J = 8.6, 6.6 Hz, 1H), 6.85 - 6.65 (m, 2H), 5.33 (t, J = 4.1 Hz, 1H), 5.25 (dd, J = 9.5, 3.9 Hz, 1H), 4.61 (d, J = 3.4 Hz, 1H), 4.18 - 4.08 (m, 1H), 4.02 (s, 3H), 3.99 - 3.87 (m, 1H), 2.12 - 1.91 (m, 4H), 1.85 - 1.69 (m, 1H), 1.55 (ddd, J = 12.3, 4.1, 2.8 Hz, 1H), 1.31 - 1.14 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.79 (q, J = 8.8 Hz, 1F), -112.05 (p, J = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{24}F_2N_3O_5$: 472.17; found**:** 472.2.

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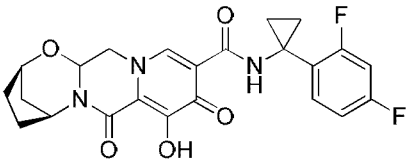
Step 3

A mixture of compound **30-B** (128 mg, 0.272 mmol) and $MgBr_2$ (130 mg, 0.706 mmol) in MeCN (5 mL) was stirred at 50 °C for 30 minutes and cooled to 0 °C before treating with 1 N HCl (4 mL). After the mixture was diluted with water, the product was extracted with CH_2Cl_2 (x 3), and the combined extracts were dried (Na_2SO_4) and concentrated. The product was purified by CombiFlash to obtain product **30**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 12.27 (s, 1H), 10.52 (s, 1H), 8.16 (s, 1H), 7.61 (td, *J* = 8.6, 6.6 Hz, 1H), 6.96 – 6.54 (m, 2H), 5.36 – 5.23 (m, 2H), 4.66 (t, *J* = 3.1 Hz, 1H), 4.18 – 4.06 (m, 1H), 3.94 (dd, *J* = 12.8, 9.4 Hz, 1H), 2.20 – 1.95 (m, 4H), 1.89 (td, *J* = 11.4, 9.8, 6.7 Hz, 1H), 1.70 – 1.54 (m, 1H), 1.32 – 1.15 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.87 (q, J = 8.9 Hz, 1F), -112.21 (p, J = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_3O_5$: 458.15; found**:** 458.2.

Example 31

Preparation of Compound **31**

(2R,5S)-N-(1-(2,4-difluorophenyl)cyclopropyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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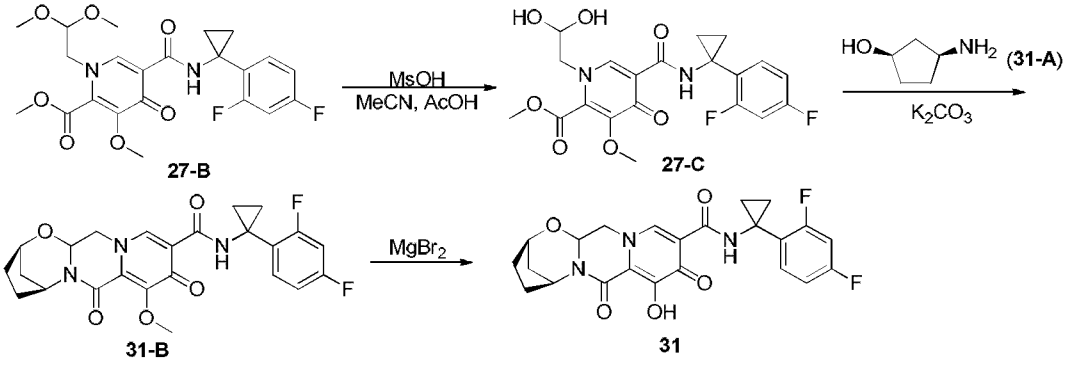

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Step 1 and 2

Compound **31-B** (123 mg, 81%) was prepared from compound **27-B** (150 mg, 0. 322 mmol) and the aminoalcohol **31-A** (70.3 mg, 0.695 mmol) in a manner similar to that described in step 1 and 2 of the synthesis of compound **30-B**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.24 (s, 1H), 7.62 (td, *J* = 8.6, 6.6 Hz, 1H), 6.91 - 6.63 (m, 2H), 5.33 (t, *J* = 4.1 Hz, 1H), 5.25 (dd, *J* = 9.5, 3.9 Hz, 1H), 4.61 (d, *J* = 3.4 Hz, 1H), 4.14 - 4.07 (m, 1H), 4.03 (s, 3H), 3.93 (dd, *J* = 12.7, 9.5 Hz, 1H), 2.12 - 1.91 (m, 4H), 1.85 - 1.69 (m, 1H), 1.55 (ddd, *J* = 12.3, 4.1, 2.8 Hz, 1H), 1.31 - 1.14 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.79 (q, *J* = 9.2, 8.7 Hz, 1F), -112.03 (h, *J* = 8.1, 7.5 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{24}F_2N_3O_5$: 472.17; found**:** 472.1.

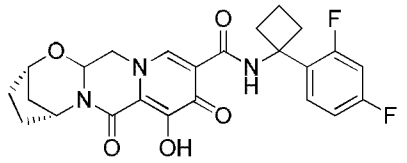
Step 3

Compound **31** was prepared from compound **31-B** in a manner similar to that described in step 3 of the synthesis of compound **30**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 10.49 (s, 1H), 8.13 (s, 1H), 7.58 (td, *J* = 8.6, 6.5 Hz, 1H), 6.90 - 6.56 (m, 2H), 5.32 (dd, *J* = 9.4, 4.1 Hz, 1H), 5.27 - 5.22 (m, 1H), 4.64 (t, *J* = 3.1 Hz, 1H), 4.11 (dd, *J* = 12.8, 4.0 Hz, 1H), 4.01 - 3.79 (m, 1H), 2.28 - 1.95 (m, 4H), 1.95 - 1.80 (m, 1H), 1.71 (m, 1H), 1.56 (m, 1H), 1.42 - 1.08 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.95 (q, *J* = 8.9 Hz, 1F), -112.22 (p, *J* = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_3O_5$: 458.15; found**:** 458.1.

Example 32

Preparation of Compound **32**

(2S,5R)-N-(1-(2,4-difluorophenyl)cyclobutyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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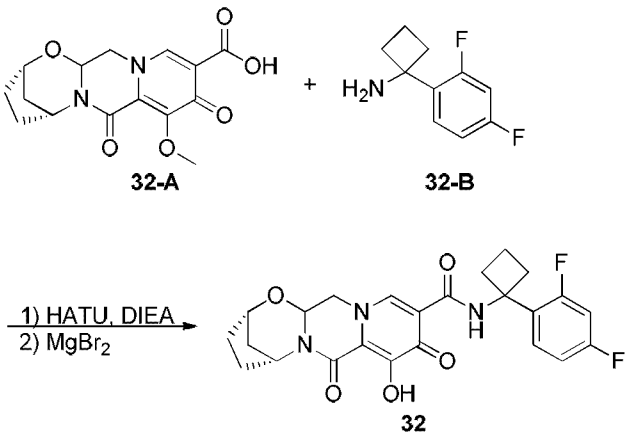

32-A 32-B 32

A solution of compound **32-A** (22.2 mg, 0.069 mmol), compound **32-B** (18.7 mg, 0.102 mmol), and HATU (43 mg, 0.113 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (0.075 mL, 0.431 mmol) was added. After 30 minutes, the reaction mixture was diluted with ethyl acetate and washed with water (x 2). After the aqueous fractions were extracted with EA (x 1), the organic fractions were combined, dried, concentrated, and dried in vacuum.

A mixture of the above crude product and $MgBr_2$ (35 mg, 0.190 mmol) in MeCN (2 mL) was stirred at 50 °C bath for 1 hour and cooled to 0 °C before being treated with 1 N HCl (~ 1 mL). The resulting solution was diluted with water, and extracted with CH_2Cl_2 (x 3). The combined extracts were dried (Na_2SO_4), and concentrated. The product was purified by preparative HPLC and freeze-dried to obtain compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), ~9.3 (br, 1H), 8.35 (s, 1H), 7.50 (td, *J* = 8.7, 6.3 Hz, 1H), 6.89 - 6.78 (m, 1H), 6.72 (ddd, *J* = 11.2, 8.9, 2.6 Hz, 1H), 5.48 - 5.12 (m, 2H), 4.72 - 4.60 (m, 1H), 4.22 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.98 (dd, *J* = 12.9, 9.4 Hz, 1H), 2.68 (m, 4H), 2.33 - 1.98 (m, 6H), 1.90 (m, 2H), 1.60 (ddd, *J* = 12.4, 4.1, 2.7 Hz, 1H). **^{19}F-NMR** (376.1 MHz, CD_3CN) δ -76.39 (s, 3F), -110.50 (q, *J* = 9.2 Hz, 1F), -112.65 (p, *J* = 7.8 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{24}F_2N_3O_5$: 472.17; found**:** 472.0.

Example 33

Preparation of Compound **33**

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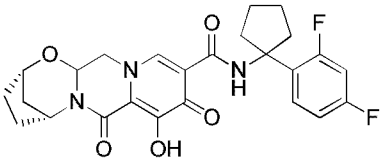
(2S,5R)-N-(1-(2,4-difluorophenyl)cyclopentyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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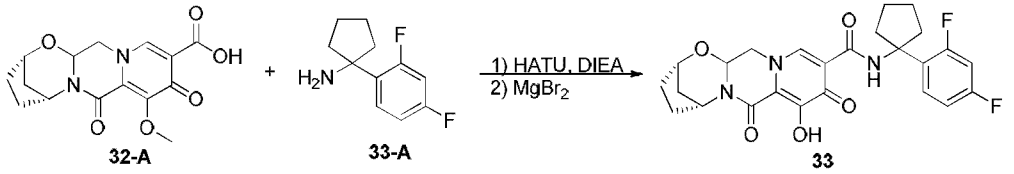


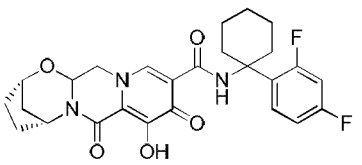
32-A **33-A** **33**

Compound **33** was obtained from compound **32-A** and compound **33-A** as described in the synthesis of compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), ~9.5 (br, 1H), 8.41 (s, 1H), 7.43 (td, *J* = 8.9, 6.4 Hz, 1H), 6.85 - 6.76 (m, 1H), 6.72 (ddd, *J* = 11.5, 8.8, 2.6 Hz, 1H), 5.48 - 5.18 (m, 2H), 4.68 (t, *J* = 3.2 Hz, 1H), 4.26 (dd, *J* = 13.0, 4.1 Hz, 1H), 4.00 (dd, *J* = 13.0, 9.4 Hz, 1H), 2.72 - 2.45 (m, 2H), 2.22 - 1.96 (m, 6H), 1.96 - 1.75 (m, 5H), 1.60 (ddd, *J* = 12.5, 4.1, 2.7 Hz, 1H). **^{19}F-NMR** (376.1 MHz, CD_3CN) δ -76.41 (s, 3F), -107.86 (q, J = 9.4 Hz, 1F), -113.13 (p, J = 8.0 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{26}F_2N_3O_5$: 486.18; found**:** 485.9.

Example 34

Preparation of Compound **34**

(2S,5R)-N-(1-(2,4-difluorophenyl)cyclohexyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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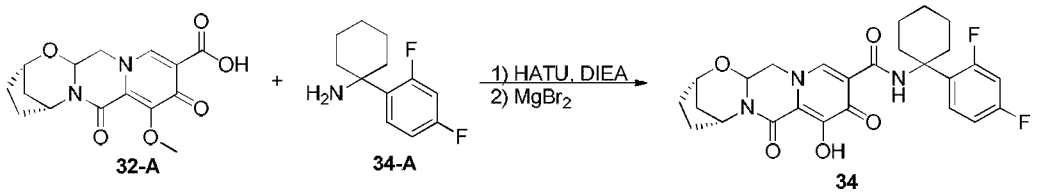


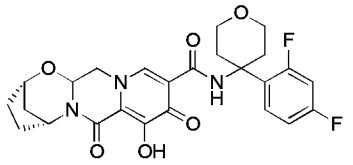
32-A 34-A 34

Compound **34** was obtained from compound **32-A** and compound **34-A** as described in the synthesis of compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), ~9.6 (br, 1H), 8.44 (s, 1H), 7.37 (td, *J* = 9.0, 6.4 Hz, 1H), 6.97 - 6.76 (m, 1H), 6.69 (ddd, *J* = 11.9, 8.8, 2.7 Hz, 1H), 5.48 - 5.18 (m, 2H), 4.68 (t, *J* = 3.0 Hz, 1H), 4.28 (dd, *J* = 13.1, 4.1 Hz, 1H), 4.03 (dd, *J* = 13.0, 9.4 Hz, 1H), 2.60 (d, *J* = 13.1 Hz, 2H), 2.29 - 1.96 (m, 4H), 1.95 - 1.77 (m, 4H), 1.77 - 1.65 (m, 4H), 1.61 (ddd, *J* = 12.5, 4.1, 2.7 Hz, 1H), 1.30 (br, 1H). **^{19}F-NMR** (376.1 MHz, CD_3CN) δ -76.41 (s, 3F), -107.86 (q, *J* = 9.4 Hz, 1F), -113.13 (p, *J* = 8.0 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{26}H_{28}F_2N_3O_5$: 500.20; found**:** 500.0.

Example 35

Preparation of Compound **35**

(2S,5R)-N-(4-(2,4-difluorophenyl)tetrahydro-2H-pyran-4-yl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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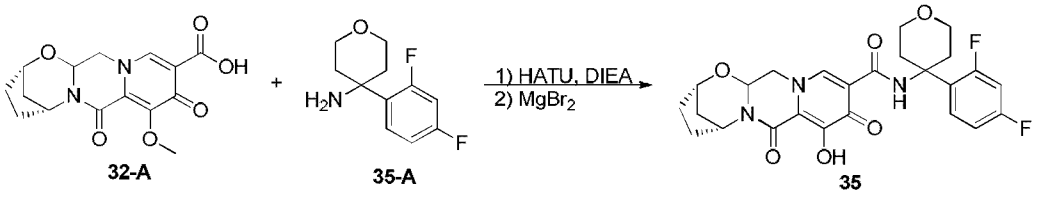

32-A 35-A 35

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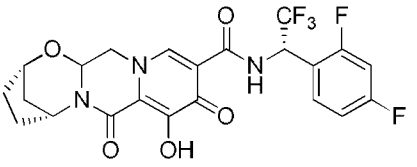
Compound **35** was obtained from compound **32-A** and compound **35-A** as described in the synthesis of compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.33 (s, 1H), ~7.6 (br, 1H), 7.38 (td, *J* = 9.0, 6.3 Hz, 1H), 6.85 (td, *J* = 8.4, 2.6 Hz, 1H), 6.73 (ddd, *J* = 11.7, 8.6, 2.6 Hz, 1H), 5.32 (dt, *J* = 14.4, 4.0 Hz, 2H), 4.68 (t, *J* = 3.1 Hz, 1H), 4.24 (dd, *J* = 13.0, 3.9 Hz, 1H), 4.11 - 3.81 (m, 5H), 2.60 (d, *J* = 13.7 Hz, 2H), 2.33 - 2.17 (m, 2H), 2.18 - 1.97 (m, 4H), 1.87 (m, 1H), 1.61 (dt, *J* = 12.5, 3.3 Hz, 1H). **^{19}F-NMR** (376.1 MHz, CD_3CN) δ -76.40 (s, 3F), -108.78 (q, *J* = 10.3, 9.8 Hz, 1F), -112.63 (p, *J* = 8.0 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{26}F_2N_3O_6$: 502.18; found**:** 502.0.

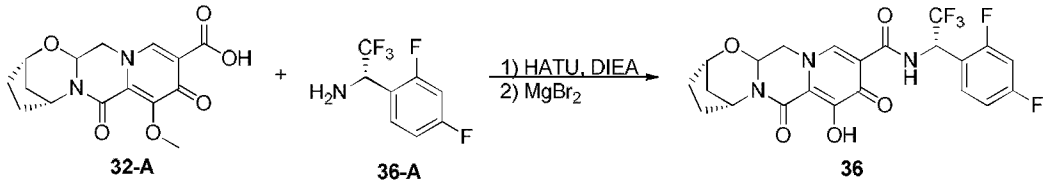
Example 36

Preparation of Compound **36**

(2S,5R)-N-((S)-1-(2,4-difluorophenyl)-2,2,2-trifluoroethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



36



32-A **36-A** **36**

Compound **36** was obtained from compound **32-A** and compound **36-A** as described in the synthesis of compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 11.31 (d, *J* = 9.4 Hz, 1H), 8.41 (s, 1H), 7.65 - 7.44 (m, 1H), 6.95 (ddd, *J* = 9.6, 5.6, 2.0 Hz, 1H), 6.92 - 6.79 (m, 1H), 6.15 (h, *J* = 7.4 Hz, 1H), ~6 (br, 1H), 5.41 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.31 (t, *J* = 4.0 Hz, 1H), 4.70 (s, 1H), 4.34 (dd, *J* = 12.8, 3.9 Hz, 1H), 4.05 (dd, *J* = 12.9, 9.4 Hz, 1H), 2.26 - 1.99 (m, 4H), 1.99 - 1.87 (m, 1H), 1.62 (dt, *J* = 12.6, 3.4 Hz,

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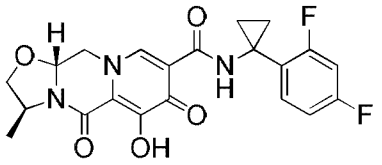
1H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -75.23 (t, *J* = 6.9 Hz, 3F), -76.33 (s, 3F), -108.31 (m, 1F), -112.30 (p, *J* = 8.0 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{19}F_5N_3O_5$: 500.12; found**:** 500.1.

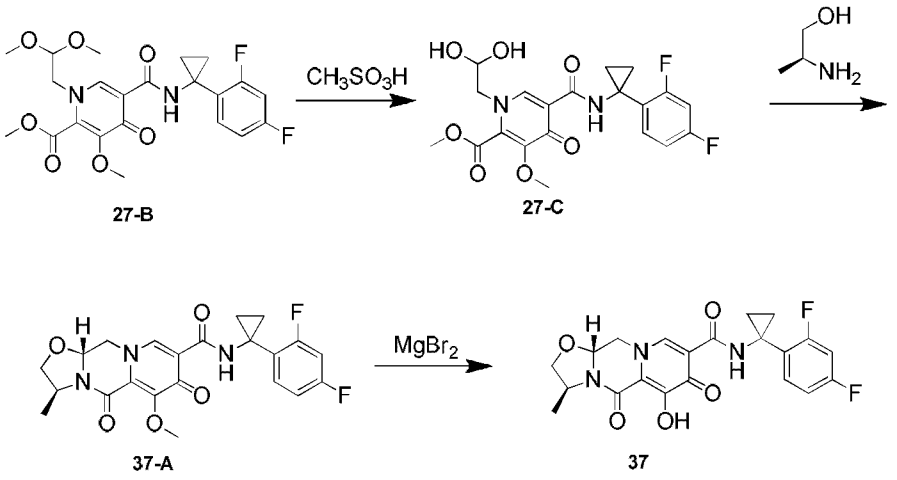
Example 37

Preparation of Compound 37

(3S,11aR)-N-(1-(2,4-difluorophenyl)cyclopropyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide



37



Step 1

Methyl 5-(1-(2,4-difluorophenyl)cyclopropylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**27-B**, 0.150 g, 0.32 mmol) in acetonitrile (1.5 mL) and acetic acid (0.2 mL) was treated with methanesulfonic acid (0.05 mL), sealed with a yellow cap, and heated to 70 °C. After 16 hours, the mixture was cooled to afford a crude solution of methyl 5-(1-(2,4-difluorophenyl)cyclopropylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-

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dihydropyridine-2-carboxylate **27-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 439; found: 439.

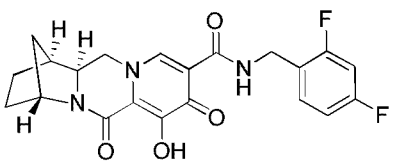
Steps 2 and 3

Methyl 5-(1-(2,4-difluorophenyl)cyclopropylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**27-C,** 0.32 mmol, the crude mixture from the previous step) was dissolved in acetonitrile (1.5 mL) and acetic acid (0.2 mL). (S)-2-aminopropan-1-ol (0.048 g, 0.64 mmol) and K_2CO_3 (0.088 g, 0.64 mmol) were added to the reaction mixture. The reaction mixture was sealed and heated to 70 °C. After 3 hours, the reaction mixture was cooled and magnesium bromide (0.081 g, 0.44 mmol) was added. The mixture was resealed and heated to 50 °C. After 10 minutes, the reaction mixture was cooled to 0 °C and 1 N hydrochloric acid (0.5 mL) was added in. Then the reaction mixture was diluted with MeOH (2 mL). After filtration, the crude was purified by Prep-HPLC (30-70% acetonitrile:water, 0.1% TFA) to afford Compound **37** as a TFA salt. **^{1}H-NMR** (400 MHz, Methanol-d_4) δ 8.31 (s, 1H), 7.62 (td, J = 9.2, 8.7, 6.5 Hz, 1H), 7.02 – 6.78 (m, 2H), 5.53 – 5.20 (m, 1H), 4.68 (dd, J = 12.3, 4.2 Hz, 1H), 4.40 (dq, J = 19.1, 6.7 Hz, 2H), 3.98 (dd, J = 12.2, 10.0 Hz, 1H), 3.71 (dd, J = 8.3, 6.3 Hz, 1H), 1.41 (d, J = 6.1 Hz, 3H), 1.22 (s, 4H). **^{19}F-NMR** (376 MHz, Methanol-d_4) δ -113.66 – -113.95 (m, 1F), -113.94 – -114.29 (m, 1F). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.; found: 432.

Example 38

Preparation of Compound **38**

(1S,4R,12aR)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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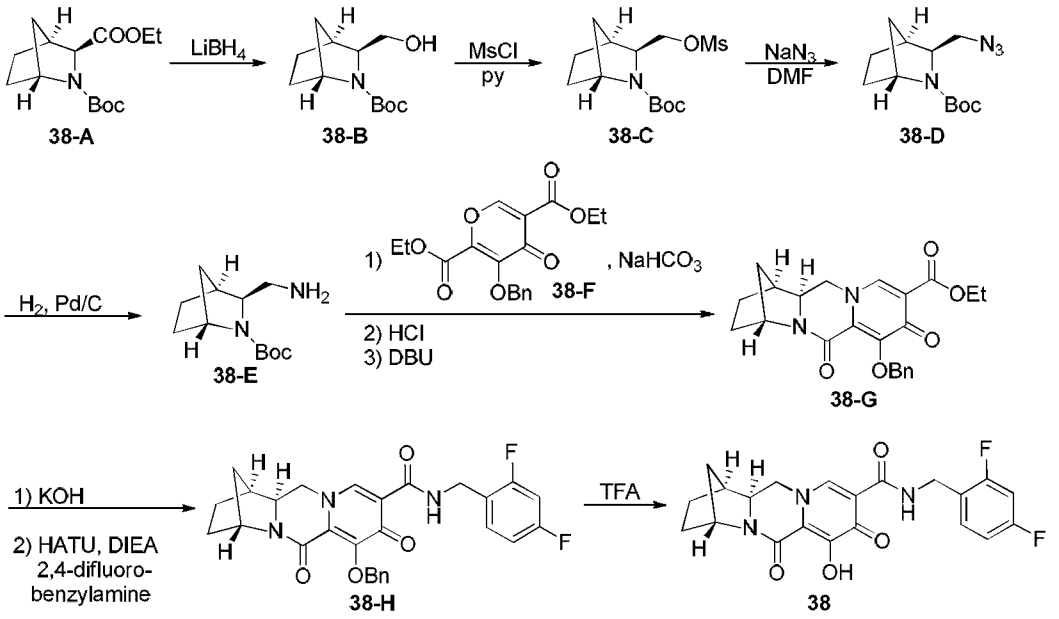

Step 1

A solution of compound **38-A** (1562 mg, 5.799 mmol) (see Example 41b in WO 97/05139) in THF (10 mL) was stirred at -78 °C as 2.0 M $LiBH_4$ in THF (3.2 mL) was added and the resulting mixture was stirred at room temperature. After 3 hours, additional 2.0 M $LiBH_4$ in THF (3.2 mL) was added and the solution was stirred at room temperature for 17.5 hours. After the reaction mixture was diluted with ethyl acetate and added water slowly, two phases were separated, and the separated aqueous fraction was extracted with ethyl acetate (x 1). Two organic fractions were washed with water (x 1), combined, dried (Na_2SO_4), and concentrated. The residue was purified by CombiFlash (40 g column) using hexanes - ethyl acetate as eluents to afford compound **38-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.11 (s, 1H), 3.65 - 3.52 (m, 2H), 3.45 (m, 1H), 2.32 (d, J = 4.1 Hz, 1H), 2.20 (s, 1H), 1.75 - 1.64 (m, 2H), 1.61 (m, 2H), 1.49 – 1.41 (m, 1H), 1.47 (s, 9H), 1.28 - 1.23 (d, J = 10 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{22}NO_3$: 228.16; found**:** 227.7.

Step 2

A solution of compound **38-B** (589 mg, 2.591 mmol) and NEt_3 (0.47 mL, 3.369 mmol) in CH_2Cl_2 (6 mL) was stirred at 0 °C as MsCl (0.22 mL, 2.842 mmol) was added. After 1 hour at room temperature, the mixture was diluted with ethyl acetate

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and washed with water (x 2). The aqueous fractions were extracted with ethyl acetate (x 1), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by Combi Flash (40 g column) using hexanes - ethyl acetate as eluents to afford compound **38-C**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 4.39 – 4.28 (m, 1H), 4.16 (s, 0.4H), 4.06 (s, 0.6H), 3.98 (dd, *J* = 10.0, 8.7 Hz, 0.6H), 3.86 (t, *J* = 9.6 Hz, 0.4H), 3.51 (dd, *J* = 9.3, 3.7 Hz, 0.6H), 3.43 (dd, *J* = 9.3, 3.6 Hz, 0.4H), 3.02 (s, 3H), 2.59 (m, 1H), 1.82 – 1.58 (m, 4H), 1.51 – 1.44 (m, 9H), 1.41 (d, *J* = 14.8 Hz, 1H), 1.31 (s, 0.6H), 1.29 (s, 0.4H).

Step 3

To a solution of compound **38-C** (769 mg, 2.518 mmol,) in DMF (5 mL) was added sodium azide (819 mg, 12.6 mmol). The reaction mixture was stirred at 50 °C for 15 hours, at 80 °C for 5 hours, and at 100 °C for 19 hours. The reaction mixture was diluted with 5% LiCl solution and the product was extracted with ethyl acetate (x 2). After the organic fractions were washed with water (x 1), the two organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by CombiFlash (40 g column) using hexanes - ethyl acetate as eluents to afford compound **38-D**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 4.16 (s, 0.4H), 4.06 (s, 0.6H), 3.61 (dd, *J* = 12.2, 3.6 Hz, 0.6H), 3.51 (dd, *J* = 12.1, 3.2 Hz, 0.4H), 3.38 (dd, *J* = 9.4, 3.4 Hz, 0.6H), 3.26 (dd, *J* = 9.8, 3.3 Hz, 0.4H), 3.06 (dd, *J* = 12.2, 9.4 Hz, 0.6H), 3.01 – 2.92 (m, 0.4H), 2.48 (d, *J* = 5.2 Hz, 1H), 1.82 – 1.57 (m, 4H), 1.46 (d, *J* = 3.0 Hz, 9H), 1.42 (m, 1H), 1.28 (m, 0.6H), 1.27 – 1.23 (m, 0.4H).

Step 4

To a solution of compound **38-D** (507 mg, 2.009 mmol,) in ethyl acetate (10 mL) and EtOH (10 mL) was added 10% Pd/C (52 mg). The reaction mixture was stirred under H_2 atmosphere for 1.5 hours. The mixture was filtered through celite and the filtrate was concentrated to afford crude compound **38-E**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{23}N_2O_2$: 227.18; found**:** 226.8.

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Step 5

The mixture of crude compound **38-E** (206 mg, 0.910 mmol), compound **38-F** (330 mg, 0.953 mmol), and $NaHCO_3$ (154 mg, 1.833 mmol) in water (3 mL) and EtOH (3 mL) was stirred at room temperature for 20 hours. After the reaction mixture was diluted with water and extracted with ethyl acetate (x 2), the extracts were washed with water (x 1), combined, dried (Na_2SO_4), and concentrated to afford the crude pyridine product.

The crude residue (388 mg) was dissolved in CH_2Cl_2 (4 mL) and 4 N HCl in dioxane (4 mL). After 1.5 hours, additional 4 N HCl in dioxane (4 mL) was added and stirred for 1 hour at room temperature. The mixture was concentrated to dryness, coevaporated with toluene (x 1) and dried in vacuum for 30 minutes.

The crude residue and 1,8-diazabicycloundec-7-ene (DBU) (1.06 mL, 7.088 mmol) in toluene (10 mL) was stirred at 110 °C bath. After 30 minutes, the mixture was concentrated and the residue was purified by CombiFlash (40 g column) using ethyl acetate - 20% MeOH/ethyl acetate as eluents to obtain compound **38-G**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.03 (s, 1H), 7.68 - 7.58 (m, 2H), 7.36 - 7.27 (m, 3H), 5.53 (d, J = 9.9 Hz, 1H), 5.11 (d, J = 9.9 Hz, 1H), 4.93 (s, 1H), 4.43 - 4.30 (m, 2H), 3.89 (dd, J = 12.2, 3.3 Hz, 1H), 3.73 (t, J = 12.0 Hz, 1H), 3.59 (dd, J = 11.9, 3.3 Hz, 1H), 2.53 (d, J = 2.8 Hz, 1H), 1.87 - 1.67 (m, 4H), 1.55 (d, J = 10.0 Hz, 1H), 1.51 - 1.45 (m, 1H), 1.38 (t, J = 7.1 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{25}N_2O_5$: 409.18; found**:** 409.2.

Step 6

The mixture of compound **38-G** (232 mg, 0.568 mmol) in THF (3 mL) and MeOH (3 mL) was stirred at room temperature as 1 N KOH (3 mL) was added. After 1 hour, the reaction mixture was neutralized with 1 N HCl (~3.1 mL), concentrated, and the residue was concentrated with toluene (x 3). After the residue was dried in vacuum for 30 minutes, a suspension of the crude residue, 2,4-difluorobenzylamine (86 mg, 0.601 mmol), and HATU (266 mg, 0.700 mmol) were in CH_2Cl_2 (4 mL) and DMF (4 mL) was stirred at 0 °C as N,N-diisopropylethylamine (DIPEA) (0.7 mL, 4.019 mmol) was added. After 45 minutes, additional 2,4-difluorobenzylamine (86 mg, 0.559 mmol), HATU (266 mg, 0.700 mmol), and N,N-

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diisopropylethylamine (DIPEA) (0.7 mL, 4.019 mmol) were added at room temperature. After 1.25 hours, the mixture was concentrated to remove most of CH_2Cl_2, diluted with ethyl acetate, and washed with 5% LiCl (x 2). After the aqueous fractions were extracted with ethyl acetate (x 1), the organic fractions were combined, dried (Na2SO4), and concentrated. The residue was purified by Combiflash (40 g column) using ethyl acetate -20%MeOH/ethyl acetate as eluents to afford compound **38-H**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.48 (t, J = 6.0 Hz, 1H), 8.33 (s, 1H), 7.62 - 7.51 (m, 2H), 7.40 - 7.27 (m, 4H), 6.87 - 6.75 (m, 2H), 5.39 (d, J = 10.0 Hz, 1H), 5.15 (d, J = 10.0 Hz, 1H), 4.92 (s, 1H), 4.68 - 4.53 (m, 2H), 3.97 (dd, J = 12.5, 3.4 Hz, 1H), 3.77 (t, J = 12.2 Hz, 1H), 3.55 (dd, J = 12.1, 3.3 Hz, 1H), 2.53 (d, J = 3.1 Hz, 1H), 1.88 - 1.62 (m, 4H), 1.59 - 1.42 (m, 2H). ^{19}F-NMR (376 MHz, Chloroform-d) δ -112.17 (q, J = 7.6 Hz, 1F), -114.79 (q, J = 8.6 Hz, 1F). **LCMS-ESI$^+$** *(m/z)*: $[M+H]^+$ calculated for C28H26F2N3O4: 506.19; found: 506.2.

Step 7

Compound **38-H** (240 mg, 0.475 mmol) was dissolved in TFA (3 mL) at room temperature for 30 minutes, and the solution was concentrated. The residue was purified by CombiFlash (40 g column) using CH_2Cl_2-20% MeOH in CH_2Cl_2 as eluents. After the collected product fractions were concentrated, the residue was triturated in MeCN (~2 mL) at 0 °C for 15 minutes, and the solids were filtered and washed with MeCN. The collected solids were dried in vacuum to afford compound **38**.

The filtrate was concentrated, and the residue was dissolved in MeCN (~1 mL) and water (~1 mL) by heating. The solution was slowly cooled to room temperature and then in ice bath for 15 minutes. The solids were filtered and washed with MeCN, and dried in vacuum to afford additional compound **38**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.68 (s, 1H), 10.42 (s, 1H), 8.27 (s, 1H), 7.41 - 7.31 (m, 1H), 6.86 - 6.73 (m, 2H), 4.90 (d, J = 2.5 Hz, 1H), 4.71 - 4.53 (m, 2H), 4.07 (d, J = 10.6 Hz, 1H), 3.90 - 3.67 (m, 2H), 2.68 (s, 1H), 2.01 (s, 1H), 1.97 - 1.80 (m, 3H), 1.80 - 1.62 (m, 2H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -112.28 (m, 1F), -114.74 (m, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_2N_3O_4$: 416.14; found**:** 416.3.

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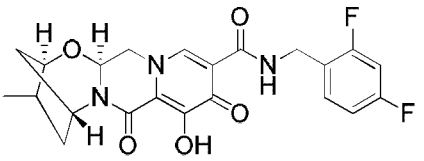
Examples 39 and 40

Preparation of Compounds **39** and **40**

(2R,3S,5R,13aS)-N-(2,4-difluorobenzyl)-8-hydroxy-3-methyl-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide **39** and (2S,3R,5S,13aR)-N-(2,4-difluorobenzyl)-8-hydroxy-3-methyl-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide **40**



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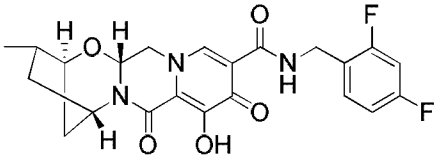

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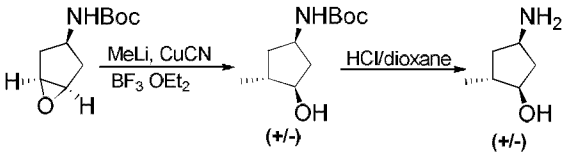

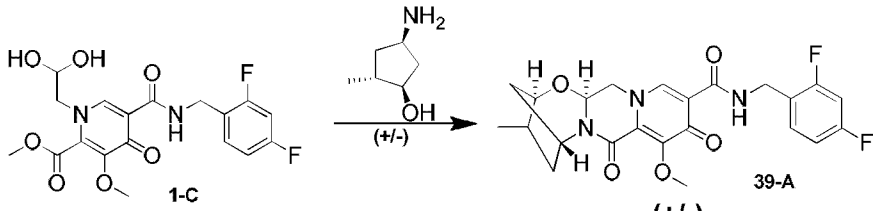

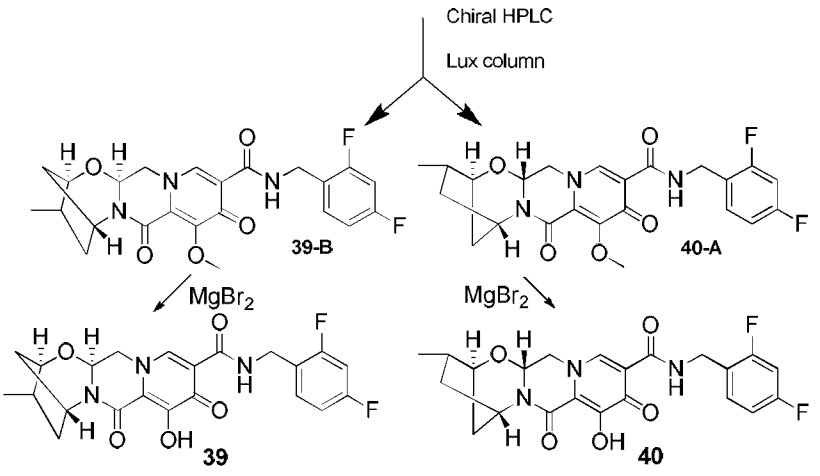

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Step 1

Cuprous cyanide (290 mg, 3.27 mmol) was suspended in 3.3 mL THF and cooled to -78 °C. A 1.6M solution of MeLi (4.1 mL, 6.56 mmol) in diethyl ether was added dropwise, the reaction solution was allowed to warm to room temperature over the course of 2 hours, and recooled to -78 °C. Tert-butyl (1R,3R,5S)-6-oxabicyclo[3.1.0]hexan-3-ylcarbamate (330 mg, 1.66 mmol) was added dropwise in 3.3 mL THF, followed by boron trifluoride diethyl etherate (0.25 mL, 1.99 mmol), allowed to warm to -30 °C over 30 minutes, and stirred between -35 °C and -25 °C for one hour. The reaction solution was then warmed to room temperature and quenched with a mixture of saturated NH_3(aq)/NH_4(aq), extracted to EtOAc, washed with brine, dried over MgSO4, filtered, concentrated, and purified by SGC (0-10% EtOH/DCM) to afford racemic tert-butyl (1S,3S,4S)-3-hydroxy-4-methylcyclopentylcarbamate. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 5.16 (s, 1H), 3.98 (s, 1H), 3.74 (q, *J* = 4.3 Hz, 1H), 3.65 (q, *J* = 7.0 Hz, 1H), 2.23 (dt, *J* = 14.0, 7.0 Hz, 1H), 1.98 (dt, *J* = 13.3, 7.0 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.58 – 1.44 (m, 1H), 1.38 (s, 9H), 1.18 (t, *J* = 7.0 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H).

Step 2

3 mL HCl/dioxane (4M, 12 mmol) was added to a solution of racemic tert-butyl (1S,3S,4S)-3-hydroxy-4-methylcyclopentylcarbamate (182 mg, 0.85 mmol) in 3 mL dioxane. The reaction mixture was stirred at room temperature for 2 hours, concentrated and twice chased with toluene to afford racemic (1S,2S,4S)-4-amino-2-methylcyclopentanol.

Step 3

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 310 mg, 0.75 mmol), racemic (1S,2S,4S)-4-amino-2-methylcyclopentanol (115 mg, 0.76 mmol), and potassium carbonate (232 mg, 1.68 mmol) were taken up in 3.8 mL acetonitrile/0.2 mL acetic acid and stirred at 90 °C for 2 hours, after which the reaction mixture was partitioned between DCM and brine, the aqueous phase extracted to DCM, combined organic

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phases dried over $MgSO_4$, filtered, concentrated, and purified by SGC (0-10% EtOH/DCM) to afford intermediate **39-A**.

Step 4

Intermediate **39-A** (190 mg) was separated by chiral Prep-HPLC on a Lux Cellulose-2 column using 9:1 ACN:MeOH as eluent to afford Intermediates **39-B** (first eluting peak) and **40-A** (second eluting peak) in enantioenriched form. For intermediate **39-B**: (absolute stereochemistry confirmed by XRay crystallography), **Chiral HPLC** retention time = 3.98 minutes (Lux Cellulose-2 IC, 150 x 4.6 mm, 2 mL/min 9:1 ACN:MeOH). For intermediate **40-A**: (absolute stereochemistry confirmed by XRay crystallography), **Chiral HPLC** retention time = 6.35 minutes (Lux Cellulose-2 IC, 150 x 4.6 mm, 2 mL/min 9:1 ACN:MeOH).

Step 5a

Magnesium bromide (68 mg, 0.37 mmol) was added to a solution of intermediate **39-B** (83 mg, 0.18 mmol) in 2 mL acetonitrile. The reaction mixture was stirred at 50 °C for 1 hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted to dichloromethane. The combined organic phases were dried over MgSO4, filtered, concentrated, and purified by silica gel chromatography (0-10% EtOH/DCM) to afford compound **39**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.32 (s, 1H), 10.36 (s, 1H), 8.29 (s, 1H), 7.44 – 7.33 (m, 1H), 6.88 – 6.76 (m, 2H), 5.37 (dd, J = 9.5, 4.1 Hz, 1H), 5.28 (t, J = 5.3 Hz, 1H), 4.63 (d, J = 5.9 Hz, 2H), 4.23 (d, J = 23.0 Hz, 2H), 3.99 (dd, J = 12.7, 9.5 Hz, 1H), 3.72 (q, J = 7.0 Hz, 1H), 2.51 (dq, J = 13.7, 6.8, 6.1 Hz, 1H), 2.15 (ddd, J = 14.7, 8.3, 2.3 Hz, 1H), 1.94 (d, J = 12.7 Hz, 1H), 1.77 (ddd, J = 12.7, 4.0, 2.9 Hz, 1H), 1.61 (dt, J = 14.6, 5.2 Hz, 2H), 1.24 (t, J = 7.0 Hz, 1H), 1.09 (d, J = 7.2 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Step 5b

Magnesium bromide (59 mg, 0.32 mmol) was added to a solution of intermediate **40-A** (70 mg, 0.15 mmol) in 2 mL acetonitrile. The reaction mixture was stirred at 50 °C for 1 hour, acidified with 10% aqueous HCl, partitioned between the

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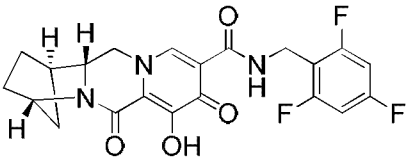
aqueous and dichloromethane, and the aqueous phase extracted to dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (0-10% EtOH/DCM) to afford compound **40**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 12.32 (s, 1H), 10.36 (s, 1H), 8.29 (s, 1H), 7.44 – 7.33 (m, 1H), 6.88 – 6.76 (m, 2H), 5.37 (dd, *J* = 9.5, 4.1 Hz, 1H), 5.28 (t, *J* = 5.3 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 4.23 (d, *J* = 23.0 Hz, 2H), 3.99 (dd, *J* = 12.7, 9.5 Hz, 1H), 3.72 (q, *J* = 7.0 Hz, 1H), 2.51 (dq, *J* = 13.7, 6.8, 6.1 Hz, 1H), 2.15 (ddd, *J* = 14.7, 8.3, 2.3 Hz, 1H), 1.94 (d, *J* = 12.7 Hz, 1H), 1.77 (ddd, *J* = 12.7, 4.0, 2.9 Hz, 1H), 1.61 (dt, *J* = 14.6, 5.2 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 1H), 1.09 (d, *J* = 7.2 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Example 41

Preparation of Compound **41**

(1R,4S,12aR)-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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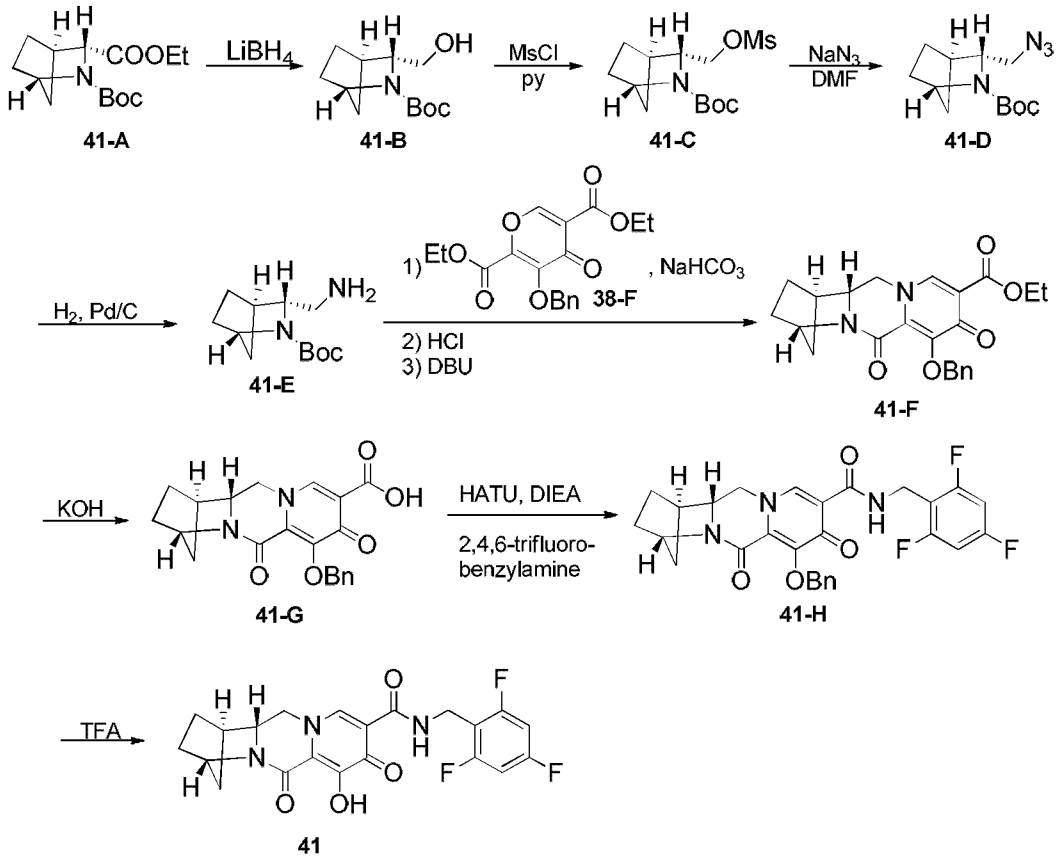

Step 1

A solution of the **41-A** (2020 mg, 7.463 mmol) (prepared by the same method as **38-A**) in THF (14 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (7.5 mL, 15 mmol) was added. After the resulting mixture was stirred at rt for 21 h, it was cooled at 0 °C and diluted with EA before water was added slowly to quench. After two phases were separated, the aqueous fraction was extracted with EA (x 1) and the two organic fractions were washed with water (x 1), combined, dried (Na_2SO_4), and concentrated. The residue was purified by CombiFlash (120 g column) using hexanes - EA as eluents to get **41-B**. **LCMS-ESI**$^+$ (*m/z*): $[M-C_4H_8+H]^+$ calculated for $C_8H_{14}NO_3$: 172.10; found: 171.95.

Step 2

A 100-mL round bottom flask was charged with reactant **41-B** (1.6 g, 7.05 mmol) and triethylamine (0.94 g, 9.3 mmol) in DCM (20 mL). Methanesulfonyl

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chloride (0.91 g, 8.0 mmol) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 3 hours. The mixture was diluted with EA (100 mL) and washed with water (2x). The aqueous fractions were extracted with EA (1x), and the organic fractions were combined, dried (Na2SO4), and concentrated. The residue was purified by Combi Flash (120 g column, cartridge used) using hexanes - EA as eluents to afford **41-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 306; found: 306.

Step 3

A 100-mL round bottom flask was charged with reactant **41-C** (2.1 g, 6.9 mmol) and sodium azide (2.3 g, 34.5 mmol) in DMF (10 mL). Then the reaction mixture was stirred at 100 °C for overnight. The mixture was diluted with EA (100 mL) and washed with water (2x). The aqueous fractions were extracted with EA (1x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by Combi Flash (120 g column, cartridge used) using hexanes - EA as eluents to afford **41-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 253; found: 253.

Step 4

To a solution (purged with N_2) of reactant **41-D** (1.3 g) in EA (20 mL) and EtOH (20 mL) was added Pd/C (130 mg). The mixture was stirred under H_2 for 3 hours. The mixture was filtered through celite and the filtrate was concentrated to afford compound **41-E**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 227; found: 227.

Step 5

A 100-mL round bottom flask was charged with reactant **41-E** (1.05 g, 4.62 mmol) and reactant **38-F** (1.6 g, 4.62 mmol) in Ethanol (20 mL). Sodium bicarbonate (0.77 g, 9.2 mmol) in water (20 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature overnight. The mixture was diluted with EA (100 mL) and washed with water (2x). The aqueous fractions were extracted with EA (1x), and the organic fractions were combined, dried (Na2SO4), and

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concentrated. The crude product (2.4 g) was used for next step without further purification. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 556; found: 556.

A 100-mL round bottom flask was charged with the crude product from the previous reaction in 4 N HCl /dioxane (24.7 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, the intermediate (2.1 g) and DBU (3.27 g, 21.5 mmol) in toluene (30 mL) was heated to 110 °C with stirring for 1 hour. After concentration, the residue was purified by CombiFlash (120 g column) using hexanes - ethyl acetate as eluents to afford **41-F**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 409; found: 409.

Step 6

A 100-mL round bottom flask was charged with reactant **41-F** (0.5 g, 1.22 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (3.7 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (3.7 mL), concentrated to remove most of organic solvents, and extracted with EtOAc (2 X). The organic layers were combined, dried (Na_2SO_4), and concentrated to afford compound **41-G**.

Step 7

A 100-mL round bottom flask was charged with reactant **41-G** (0.14 g, 0.37 mmol), (2,4,6-trifluorophenyl)methanamine (0.12 g, 0.73 mmol), N,N-diisopropylethylamine (DIPEA) (0.24 g, 1.84 mmol) and HATU (0.28 g, 0.74 mmol) were dissolved in DCM (5 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford compound **41-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 524.5; found: 524.5.

Step 8

A 50-mL round bottom flask was charged with reactant **41-H** (0.13 g, 0.25 mmol) in TFA (2 mL). The reaction mixture was stirred at room temperature for

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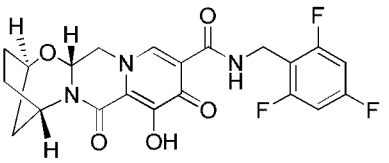
30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **41**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.61 (s, 1H), 10.70 - 10.01 (m, 1H), 8.26 (s, 1H), 6.65 (t, J = 8.1 Hz, 2H), 4.88 (s, 1H), 4.65 (dd, J = 6.1, 2.4 Hz, 2H), 4.07 (d, J = 10.9 Hz, 1H), 3.93 - 3.58 (m, 2H), 2.67 (d, J = 3.1 Hz, 1H), 2.08 - 1.41 (m, 7H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -109.22 (d, J = 11.6 Hz, 1F), -111.04 - -112.79 (m, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 434.; found: 434.

Example 42

Preparation of Compound **42**

(2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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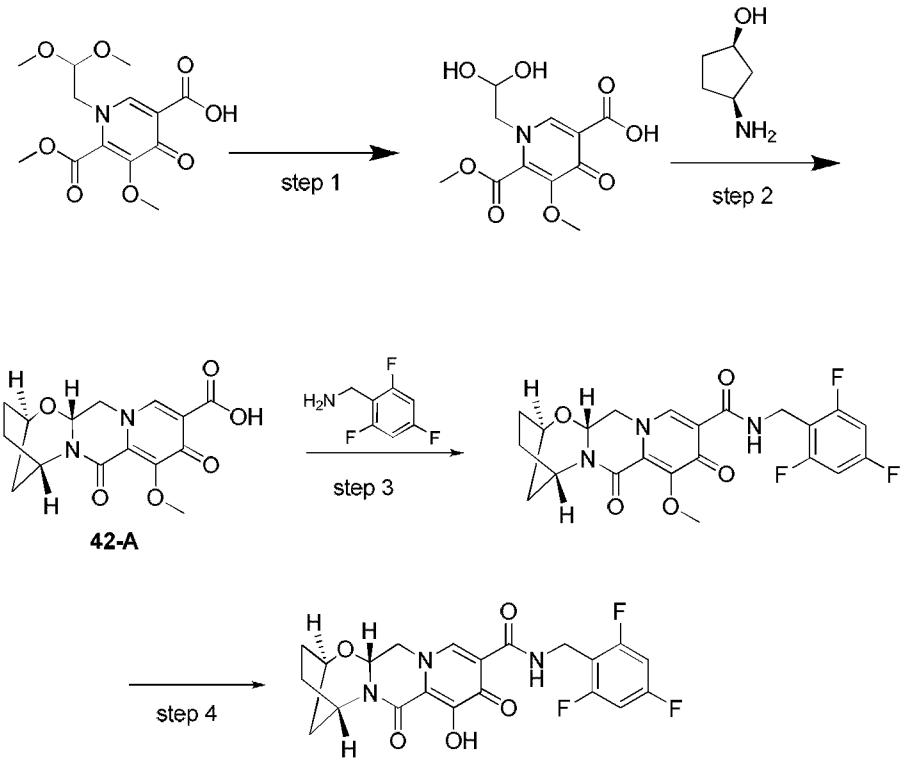

Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (3.15 g, 10 mmol) in acetonitrile (36 mL) and acetic acid (4 mL) was treated with methanesulfonic acid (0.195 mL, 3 mmol) and placed in a 75 deg C bath. The reaction mixture was stirred for 7 h, cooled and stored at -10 °C for 3 days and reheated to 75 °C for an additional 2 h. This material was cooled and carried on crude to the next step.

Step 2

Crude reaction mixture from step 1 (20 mL, 4.9 mmol) was transferred to a flask containing (1R,3S)-3-aminocyclopentanol (0.809 g, 8 mmol). The mixture was diluted with acetonitrile (16.8 mL), treated with potassium carbonate (0.553 g, 4 mmol) and heated to 85 °C. After 2 h, the reaction mixture was cooled to ambient temperature and stirred overnight. 0.2M HCl (50 mL) was added, and the clear yellow solution was extracted with dichloromethane (2x150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to 1.49 g of a light

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orange solid. Recrystallization from dichlormethane:hexanes afforded the desired intermediate **42A**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{17}N_2O_6$: 321.11; found: 321.3.

Step 3

Intermediate **42-A** (0.225 g, 0.702 mmol) and (2,4,6-trifluorophenyl)methanamine (0.125 g, 0.773 mmol) were suspended in acetonitrile (4 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.183 mmol, 1.05 mmol). To this suspension was added (dimethylamino)-*N*,*N*-dimethyl(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methaniminium hexafluorophosphate (HATU, 0.294 g, 0.774 mmol). After 1.5 hours, the crude reaction mixture was taken on to the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{21}F_3N_3O_5$: 464.14; found: 464.2.

Step 4

To the crude reaction mixture of the previous step was added $MgBr_2$ (0.258 g, 1.40 mmol). The reaction mixture was stirred at 50 °C for 10 minutes, acidified with 10% aqueous HCl, and extract twice with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (EtOH/dichlormethane) followed by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **42**: **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 10.34 (t, J = 5.7 Hz, 1H), 8.42 (s, 1H), 7.19 (t, J = 8.7 Hz, 2H), 5.43 (dd, J = 9.5, 4.1 Hz, 1H), 5.08 (s, 1H), 4.66 (dd, J = 12.9, 4.0 Hz, 1H), 4.59 (s, 1H), 4.56 – 4.45 (m, 2H), 4.01 (dd, J = 12.7, 9.7 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.0 Hz, 1H), 1.56 (dt, J = 12.0, 3.4 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_3N_3O_5$: 450.13; found: 450.2.

Example 43

Preparation of Compound **43**

(12aR)-N-((R)-1-(2,4-difluorophenyl)ethyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

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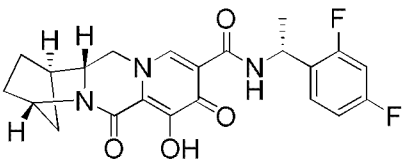

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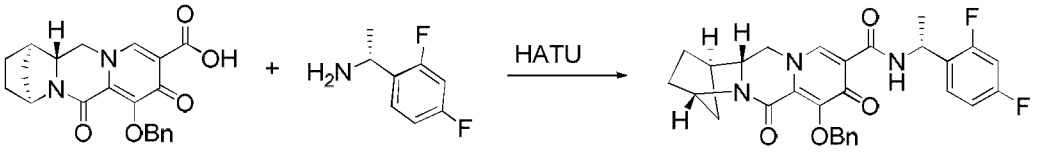
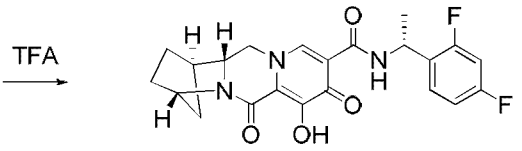


41-G

43-A



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Step 1

A 100-mL round bottom flask was charged with reactant **41-G** (0.14 g, 0.37 mmol), (R)-1-(2,4-difluorophenyl)ethanamine (0.12 g, 0.74 mmol), *N,N*-diisopropylethylamine (0.24 g, 1.84 mmol) and HATU (0.28 g, 0.74 mmol) and were dissolved in DCM (5 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford compound **43-A**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 520; found: 520.

Steps 2

A 50-mL round bottom flask was charged with reactant **43-A** (0.14 g, 0.27 mmol) in TFA (2 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **43**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.65 (s, 1H), 10.57 (s, 1H), 8.22 (s, 1H), 7.31 (m, 1H), 6.99 - 6.62 (m, 2H), 5.64 - 5.32 (m, 1H), 4.90 (d, J = 2.7 Hz, 1H), 4.04 (d, J = 11.5 Hz, 1H), 3.93 - 3.63

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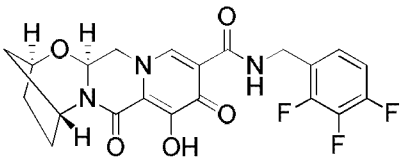
(m, 2H), 2.67 (s, 1H), 2.08 - 1.40 (m, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -113.09 (m, 1F), -115.01 (m, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 430.; found: 430.

Example 44

Preparation of Compound **44**

(13aS)-8-hydroxy-7,9-dioxo-N-(2,3,4-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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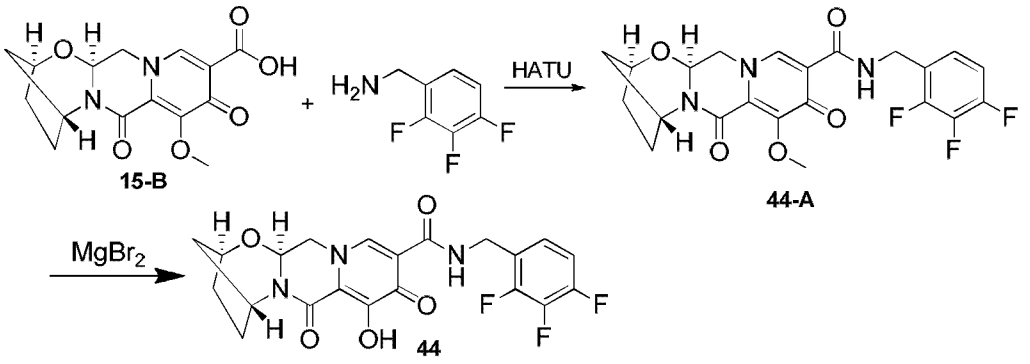

Step 1

Compound **15-B** (40 mg, 0.12 mmol) was taken up in 1 mL acetonitrile and treated with 2,3,4-trifluorobenzylamine (29 mg, 0.18 mmol), HATU (53 mg, 0.14 mmol), N,N-diisopropylethylamine (DIPEA) (20 mg, 0.16 mmol), and stirred at room temperature for 2 hours, after which LCMS analysis revealed complete consumption of compound **15-B** and formation of intermediate **44-A**. The reaction mixture was carried onto the next step.

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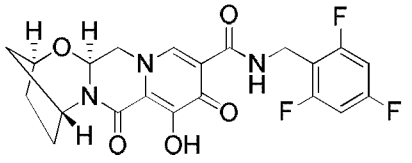
Step 2

To the crude reaction solution of the previous step was added $MgBr_2$ (63 mg, 0.34 mmol). The reaction mixture was stirred at 50 °C for one hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted to dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to compound **44**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 10.38 (t, J = 6.0 Hz, 1H), 8.43 (s, 1H), 7.27 (q, J = 9.2 Hz, 1H), 7.16 (q, J = 8.5 Hz, 1H), 5.42 (dd, J = 9.5, 4.0 Hz, 1H), 5.08 (s, 1H), 4.76 – 4.47 (m, 4H), 4.01 (dd, J = 12.8, 9.7 Hz, 1H), 1.92 (s, 4H), 1.82 (d, J = 12.1 Hz, 1H), 1.55 (dt, J = 12.2, 2.9 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_3N_3O_5$: 450.13; found: 450.2.

Example 45

Preparation of Compound **45**

(13aS)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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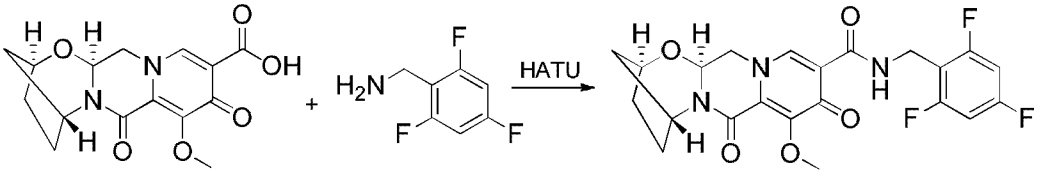
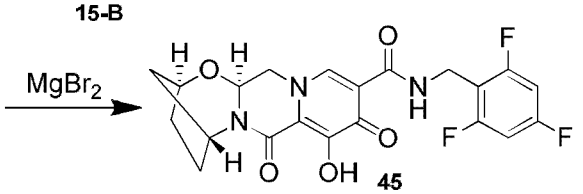


15-B **45-A**



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Step 1

Compound **15-B** (38 mg, 0.12 mmol) was taken up in 1 mL acetonitrile and treated with 2,4,6-trifluorobenzylamine (34 mg, 0.21 mmol), HATU (50 mg, 0.13 mmol), N,N-diisopropylethylamine (DIPEA) (23 mg, 0.18 mmol), and stirred at room temperature for 2 hours, after which LCMS analysis revealed complete consumption of compound **15-B** and formation of intermediate **45-A**. The reaction mixture was carried onto the next step.

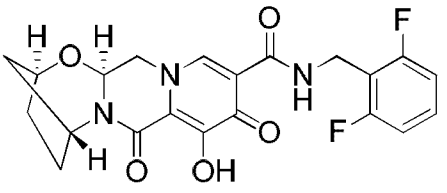
Step 2

To the crude reaction solution of the previous step was added $MgBr_2$ (55 mg, 0.30 mmol). The reaction mixture was stirred at 50 °C for one hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **45**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 10.37 – 10.25 (m, 1H), 8.37 (s, 1H), 7.14 (t, J = 8.7 Hz, 2H), 5.37 (dd, J = 9.5, 4.0 Hz, 1H), 5.02 (s, 1H), 4.66 – 4.40 (m, 4H), 3.95 (dd, J = 12.8, 9.6 Hz, 1H), 1.87 (s, 4H), 1.77 (d, J = 11.9 Hz, 1H), 1.50 (dt, J = 11.8, 3.2 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_3N_3O_5$: 450.13; found: 450.2.

Example 46

Preparation of Compound **46**

(13aS)-N-(2,6-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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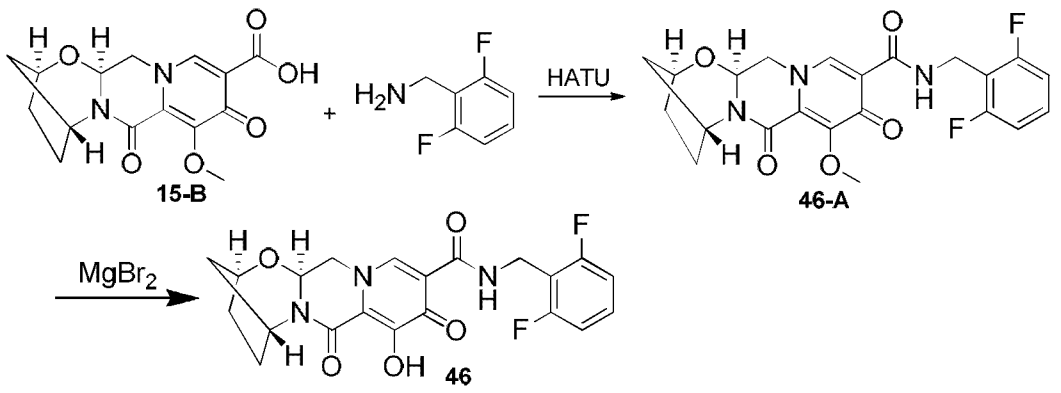

Step 1

Compound **15-B** (38 mg, 0.12 mmol) was taken up in 1 mL acetonitrile and treated with 2,6-difluorobenzylamine (19 mg, 0.14 mmol), HATU (56 mg, 0.15 mmol), N,N-diisopropylethylamine (DIPEA) (20 mg, 0.15 mmol), and stirred at room temperature for 90 minutes, after which LCMS analysis revealed complete consumption of compound **A** and formation of intermediate **46-A**. The reaction mixture was carried onto the next step.

Step 2

To the crude reaction solution of the previous step was added $MgBr_2$ (50 mg, 0.27 mmol). The reaction mixture was stirred at 50 °C for one hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **46**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 10.33 – 10.26 (m, 1H), 8.37 (s, 1H), 7.39 – 7.29 (m, 1H), 7.05 (t, J = 7.9 Hz, 2H), 5.37 (dd, J = 9.5, 4.1 Hz, 1H), 5.02 (s, 1H), 4.66 – 4.45 (m, 4H), 3.95 (dd, J = 12.7, 9.6 Hz, 1H), 1.87 (s, 4H), 1.77 (d, J = 12.0 Hz, 1H), 1.50 (dt, J = 12.2, 3.5 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2.

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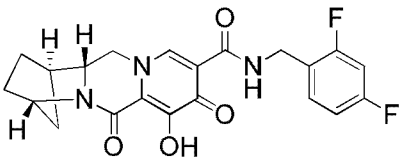
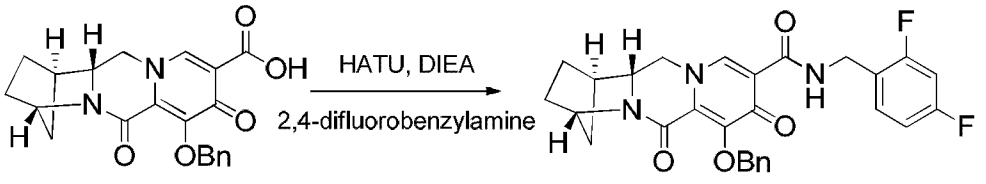
Example 47

Preparation of Compound **47**

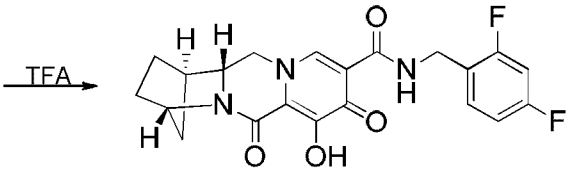
(1R,4S,12aR)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



47



41-G **47-A**



47

Step 1

The crude acid **41-G** (0.45 g, 1.18 mmol), 2,4-difluobenzylamine (0.35 g, 2.44 mmol), N,N-diisopropylethylamine (DIPEA) (0.79 g, 6.11 mmol) and HATU (0.93 g, 2.44 mmol) were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford compound **47-A**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 506; found: 506.

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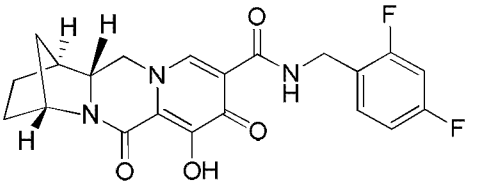
Step 2

A 50-mL round bottom flask was charged with reactant **47-A** (0.5 g, 0.99 mmol) in TFA (6 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **47**. **^{1}H NMR** (400 MHz, Chloroform-d) δ 11.70 (s, 1H), 10.44 (s, 1H), 8.29 (s, 1H), 7.60 - 7.29 (m, 1H), 6.95 - 6.58 (m, 2H), 4.10 (s, 1H), 4.02 - 3.54 (m, 3H), 2.68 (d, J = 3.1 Hz, 1H), 2.00 - 1.40 (m, 8H). **^{19}F NMR** (376 MHz, Chloroform-d) δ -112.31 (d, J = 8.0 Hz, 1F), -114.77 (d, J = 8.4 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 416.; found: 416.

Example 48

Preparation of Compound **48**

(1S,4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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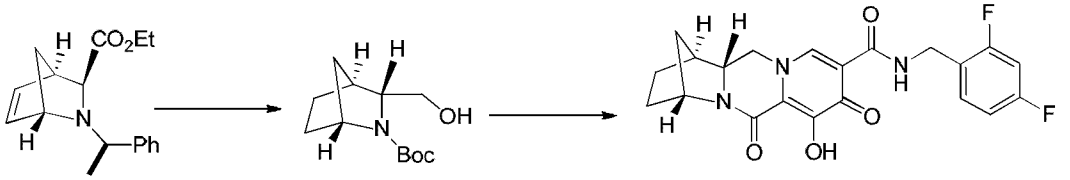

48-A **48-B** **48**

48-B was prepared analogously to **55-H** in Example 55, substituting **48-A** for **55-A**. Compound **48** was prepared as described for compound **38** in Example 38, substituting **48-B** for **38-B** to afford compound **48**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.79 (s, 1H), 10.44 (m, 1H), 8.33 (s, 1H), 7.42 – 7.31 (m, 1H), 6.86 – 6.74 (m,

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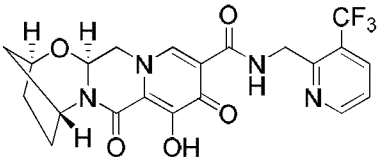
2H), 4.74 (s, 1H), 4.63 (d, J = 5.8 Hz, 2H), 4.19 (m, 1H), 4.07 – 4.03 (m, 2H), 2.83 (s, 1H), 1.92 – 1.68 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-d) δ -112.3 (m, 1F), -114.8 (m, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_4$: 416.14.; found: 416.07.

Example 49

Preparation of Compound **49**

(2S,5R,13aS)-8-hydroxy-7,9-dioxo-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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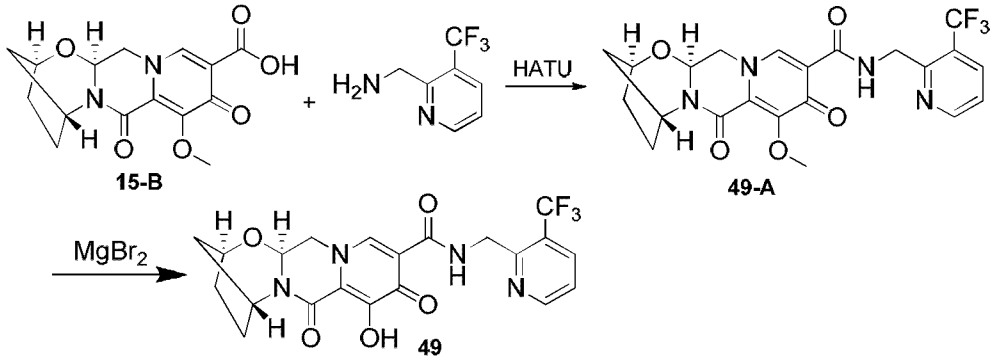

Step 1

Compound **15-B** (44 mg, 0.14 mmol) was taken up in 1 mL acetonitrile and treated with (3-(trifluoromethyl)pyridin-2-yl)methanamine (38 mg, 0.18 mmol, HCl salt), HATU (69 mg, 0.18 mmol), N,N-diisopropylethylamine (DIPEA) (0.07 mL, 0.40 mmol), and stirred at room temperature for 1 hour, after which LCMS analysis revealed complete consumption of compound **15-B** and formation of intermediate **49-A**. The reaction mixture was carried onto the next step.

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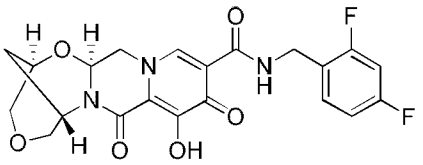
Step 2

To the crude reaction solution of the previous step was added $MgBr_2$ (51 mg, 0.28 mmol). The reaction mixture was stirred at 50 °C for 90 minutes, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and triturated by methanol followed by diethyl ether to afford compound **49**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 10.80 – 10.70 (m, 1H), 8.83 (d, J = 5.0 Hz, 1H), 8.44 (s, 1H), 8.19 (d, J = 8.6 Hz, 1H), 7.56 (dd, J = 7.7, 5.2 Hz, 1H), 5.43 (dd, J = 9.5, 4.0 Hz, 1H), 5.08 (s, 1H), 4.86 – 4.80 (m, 2H), 4.67 (dd, J = 12.9, 4.0 Hz, 1H), 4.59 (s, 1H), 4.02 (dd, J = 12.6, 9.8 Hz, 1H), 1.93 (s, 4H), 1.82 (d, J = 12.1 Hz, 1H), 1.60 – 1.52 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_3N_4O_5$: 465.14; found: 465.2.

Examples 50 and 51

Preparation of Compounds **50** and **51**

N-(2,4-difluorobenzyl)-9-hydroxy-8,10-dioxo-2,3,5,6,8,10,14,14a-octahydro-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,6,3]dioxazocine-11-carboxamide **50** and **51**



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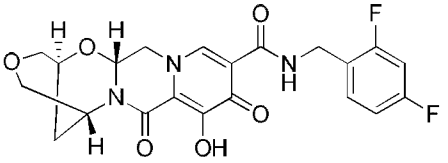

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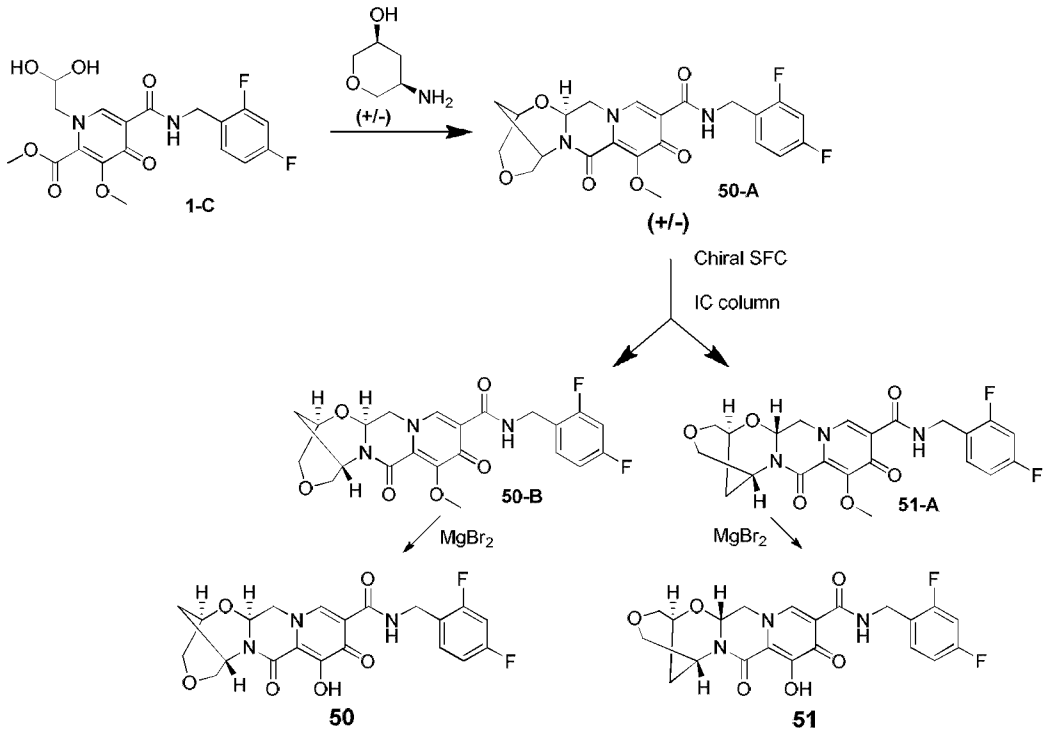

Step 1

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 392 mg, 0.95 mmol) (Example 87), racemic *cis*-5-aminotetrahydro-2H-pyran-3-ol (WO 2012/145569 Bennett, B. L. et al, filed April 20, 2012) (112 mg, 0.95 mmol), and potassium carbonate (134 mg, 0.97 mmol) were taken up in 3.8 mL acetonitrile/0.2 mL acetic acid and stirred at 90 °C for 90 minutes, after which the reaction mixture was partitioned between DCM and brine, the aqueous phase extracted with DCM, combined organic phases dried over $MgSO_4$, filtered, concentrated, and purified by SGC (0-10% EtOH/DCM) to afford intermediate **50-A**.

Step 2

Intermediate **50-A** (40 mg) was separated by chiral SFC on a Chiralpak IC column using 10% DMF in supercritical carbon dioxide as eluent to afford Intermediates **50-B** (first eluting peak) and **51-A** (second eluting peak) in enantioenriched form. For intermediate **50-B**: (absolute stereochemistry unknown), **Chiral HPLC** retention time = 11.48 minutes (Chiralpak IC, 150 x 4.6 mm, 1 mL/min

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MeOH). For intermediate **51-A**: (absolute stereochemistry unknown), **Chiral HPLC** retention time = 14.35 minutes (Chiralpak IC, 150 x 4.6 mm, 1 mL/min MeOH).

Step 3a

Magnesium bromide (12 mg, 0.06 mmol) was added to a solution of intermediate **50-B** (10.5 mg, 0.02 mmol, absolute stereochemistry unknown) in 1 mL acetonitrile. The reaction mixture was stirred at 50 °C for 1 hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **50**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.47 (t, *J* = 5.8 Hz, 1H), 8.42 (s, 1H), 7.35 (q, *J* = 8.6, 8.2 Hz, 1H), 6.81 (q, *J* = 8.7, 8.0 Hz, 2H), 6.41 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.79 (s, 1H), 4.65 (s, 2H), 4.36 – 4.26 (m, 2H), 4.20 – 4.08 (m, 2H), 3.98 (dd, *J* = 12.4, 10.2 Hz, 1H), 3.88 (t, *J* = 11.8 Hz, 2H), 2.27 (dt, *J* = 13.3, 3.1 Hz, 1H), 2.15 – 2.06 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_6$: 448.40; found: 448.2.

Step 3b

Magnesium bromide (13 mg, 0.07 mmol) was added to a solution of intermediate **51-A** (13.2 mg, 0.03 mmol, absolute stereochemistry unknown) in 1 mL acetonitrile. The reaction mixture was stirred at 50 °C for 1 hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **51**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.47 (t, *J* = 5.8 Hz, 1H), 8.42 (s, 1H), 7.35 (q, *J* = 8.6, 8.2 Hz, 1H), 6.81 (q, *J* = 8.7, 8.0 Hz, 2H), 6.41 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.79 (s, 1H), 4.65 (s, 2H), 4.36 – 4.26 (m, 2H), 4.20 – 4.08 (m, 2H), 3.98 (dd, *J* = 12.4, 10.2 Hz, 1H), 3.88 (t, *J* = 11.8 Hz, 2H), 2.27 (dt, *J* = 13.3, 3.1 Hz, 1H), 2.15 – 2.06 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_6$: 448.40; found: 448.2.

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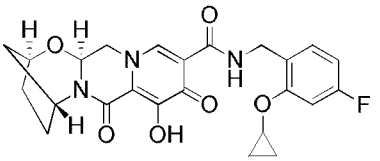
Example 52

Preparation of Compound **52**

(2S,5R,13aS)-N-(2-cyclopropoxy-4-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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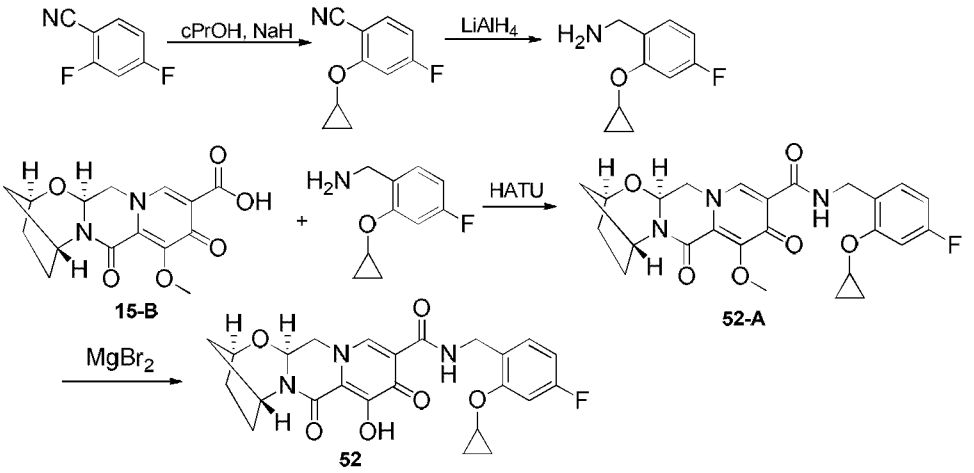

Step 1

A solution cyclopropanol (1.9 g, 29 mmol) in 20 mL dioxane was added dropwise to a 0 °C solution of Sodium hydride (60% dispersion in mineral oil, 1.04 g, 26 mmol) in 80 mL dioxane. The reaction mixture was allowed to warm to room temperature, 2,4-difluorobenzonitrile (3.48 g, 25 mmol) was added portionwise, and reaction temperature raised to 95 °C. The reaction solution was cooled to room temperature after stirring for 18 hours, diluted with ethyl acetate, washed twice with water and twice with brine, dried over $MgSO_4$, filtered, and concentrated onto silica gel. Purification by silica gel chromatography (0-10% EtOAc/hexanes) afforded 2-cyclopropoxy-4-fluorobenzonitrile. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.52 (dd, *J* =

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8.6, 6.2 Hz, 1H), 7.05 (dd, J = 10.5, 2.3 Hz, 1H), 6.73 (td, J = 8.2, 2.3 Hz, 1H), 3.87 – 3.76 (m, 1H), 0.87 (m, 4H).

Step 2

To a 0 °C suspension of lithium aluminum hydride in THF (1M, 15 mL, 15 mmol) was added 2-cyclopropoxy-4-fluorobenzonitrile in 14 mL diethyl ether dropwise. The reaction solution was stirred for 3 hours, gradually warming to room temperature, at which point it was recooled to 0 °C, an additional 8 mL lithium aluminum hydride in THF (1M, 8 mmol) added, and stirred for an additional 90 minutes. The reaction was quenched by sequential addition of 0.9 mL water, 0.9 mL 15% $NaOH_{(aq)}$, and 2.7 mL water. The reaction was filtered through celite with diethyl ether rinses, dried over $MgSO_4$, and concentrated to afford 2-cyclopropoxy-4-fluorobenzylamine of sufficient purity to carry on as crude. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.17 – 7.08 (m, 1H), 6.96 (dd, J = 10.9, 2.4 Hz, 1H), 6.61 (td, J = 8.3, 2.5 Hz, 1H), 3.78 – 3.66 (m, 3H), 0.89 – 0.72 (m, 4H).

Step 3

Compound **15-B** (46 mg, 0.14 mmol) was taken up in 1 mL acetonitrile and treated with 2-cyclopropoxy-4-fluorobenzylamine (32 mg, 0.18 mmol), HATU (62 mg, 0.16 mmol), N,N-diisopropylethylamine (DIPEA) (0.04 mL, 0.22 mmol), and stirred at room temperature for 2 hours, after which LCMS analysis revealed complete consumption of compound **15-B** and formation of intermediate **52-A**. The reaction mixture was carried onto the next step.

Step 4

To the crude reaction solution of the previous step was added $MgBr_2$ (56 mg, 0.30 mmol). The reaction mixture was stirred at 50 °C for 90 minutes, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **52**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.21 (t, J = 5.8 Hz, 1H), 8.41 (s, 1H), 7.22 – 7.15 (m, 1H), 7.12 (dd, J = 11.2, 2.5

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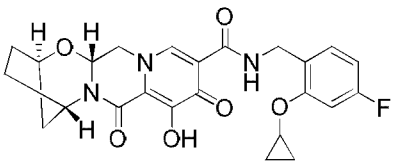
Hz, 1H), 6.72 (td, J = 8.5, 2.5 Hz, 1H), 5.42 (dd, J = 9.6, 4.1 Hz, 1H), 5.07 (s, 1H), 4.66 (dd, J = 12.8, 4.1 Hz, 1H), 4.58 (s, 1H), 4.34 (dd, J = 5.6, 2.4 Hz, 2H), 4.04 – 3.91 (m, 2H), 1.92 (s, 4H), 1.82 (d, J = 11.9 Hz, 1H), 1.55 (dt, J = 12.4, 3.5 Hz, 1H), 0.80 (q, J = 6.3, 5.7 Hz, 2H), 0.72 (q, J = 6.0, 4.9 Hz, 2H). **LCMS-ESI**$^+$ (m/z): $[M+H]^+$ calculated for $C_{24}H_{25}FN_3O_6$: 470.17; found: 470.1.

Example 53

Preparation of Compound **53**

(2R,5S,13aR)-N-(2-cyclopropoxy-4-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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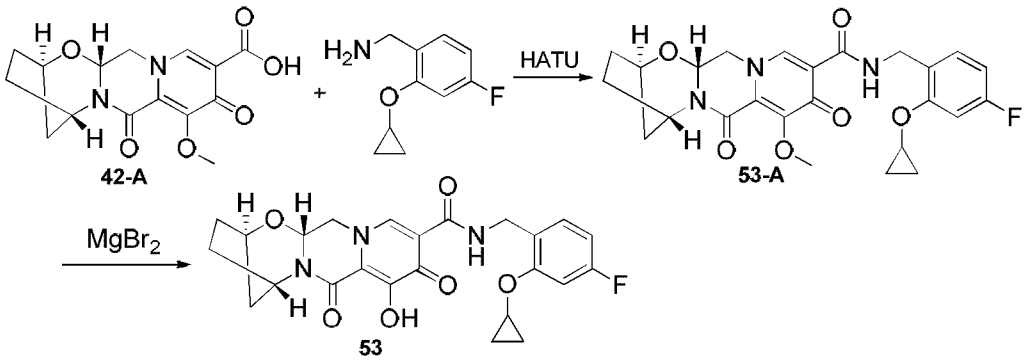

Step 1

Compound **42-A** (46 mg, 0.14 mmol) was taken up in 1 mL acetonitrile and treated with 2-cyclopropoxy-4-fluorobenzylamine (33 mg, 0.18 mmol), HATU (61 mg, 0.16 mmol), N,N-diisopropylethylamine (DIPEA) (0.04 mL, 0.24 mmol), and stirred at room temperature for 2 hours, after which LCMS analysis revealed complete consumption of compound **42-A** and formation of intermediate **53-A**. The reaction mixture was carried onto the next step.

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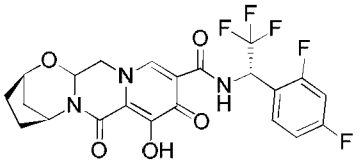
Step 2

To the crude reaction solution of the previous step was added $MgBr_2$ (55 mg, 0.30 mmol). The reaction mixture was stirred at 50 °C for 90 minutes, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **53**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.21 (t, J = 5.8 Hz, 1H), 8.41 (s, 1H), 7.22 – 7.15 (m, 1H), 7.12 (dd, J = 11.2, 2.5 Hz, 1H), 6.72 (td, J = 8.5, 2.5 Hz, 1H), 5.42 (dd, J = 9.6, 4.1 Hz, 1H), 5.07 (s, 1H), 4.66 (dd, J = 12.8, 4.1 Hz, 1H), 4.58 (s, 1H), 4.34 (dd, J = 5.6, 2.4 Hz, 2H), 4.04 – 3.91 (m, 2H), 1.92 (s, 4H), 1.82 (d, J = 11.9 Hz, 1H), 1.55 (dt, J = 12.4, 3.5 Hz, 1H), 0.80 (q, J = 6.3, 5.7 Hz, 2H), 0.72 (q, J = 6.0, 4.9 Hz, 2H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{25}FN_3O_6$: 470.17; found: 470.1.

Example 54

Preparation of Compound **54**

(2R,5S)-N-((S)-1-(2,4-difluorophenyl)-2,2,2-trifluoroethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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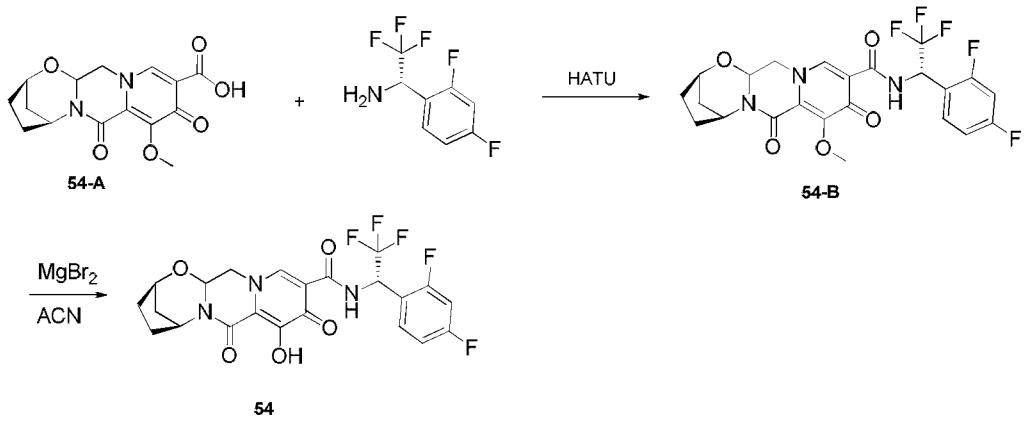

54-A

54-B

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Step 1

A 50-mL round bottom flask was charged with reactant **54-A** (0.02 g, 0.06 mmol), (S)-1-(2,4-difluorophenyl)-2,2,2-trifluoroethanamine (0.019 g, 0.09 mmol), N,N-diisopropylethylamine (DIPEA) (0.048 g, 0.38 mmol) and HATU (0.036 g, 0.09 mmol) in DCM (2 ml). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain **54-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 514; found: 514.

Step 2

A 50-mL round bottom flask was charged with reactant **54-B** (0.03 g, 0.058 mmol) and magnesium bromide (0.03 g, 0.15mmol) in acetonitrile (2 mL). The reaction mixture was heated to 50 °C. After 10 minutes, the reaction mixture was cooled to 0 °C and 1 N hydrochloric acid (0.5 mL) was added in. Then the reaction mixture was diluted with MeOH (2 mL). After filtration, the crude was purified by Pre-HPLC purification (30-70% acetonitrile:water, 0.1% TFA) afforded compound **54** as TFA salt. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.28 (d, J = 9.4 Hz, 1H), 8.39 (s, 1H), 7.54 (q, J = 7.8 Hz, 1H), 7.12 - 6.76 (m, 2H), 6.40 - 5.98 (m, 1H), 5.57 - 5.18 (m, 2H), 4.68 (s, 1H), 4.29 (dd, J = 13.1, 4.0 Hz, 1H), 4.05 (dd, J = 12.9, 9.3 Hz, 1H), 2.39 - 1.94 (m, 4H), 1.86 (t, J = 10.5 Hz, 1H), 1.60 (dt, J = 12.6, 3.4 Hz, 1H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -75.30 (t, J = 6.8 Hz, 3 F), -108.33 (dd, J = 8.6, 6.3 Hz, 1F), -111.56 - -

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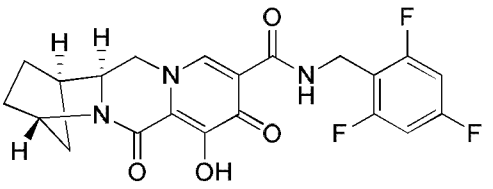
113.23 (m, 1 F). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 500.; found: 500.

Example 55

Preparation of Compound **55**

(1R,4S,12aS)-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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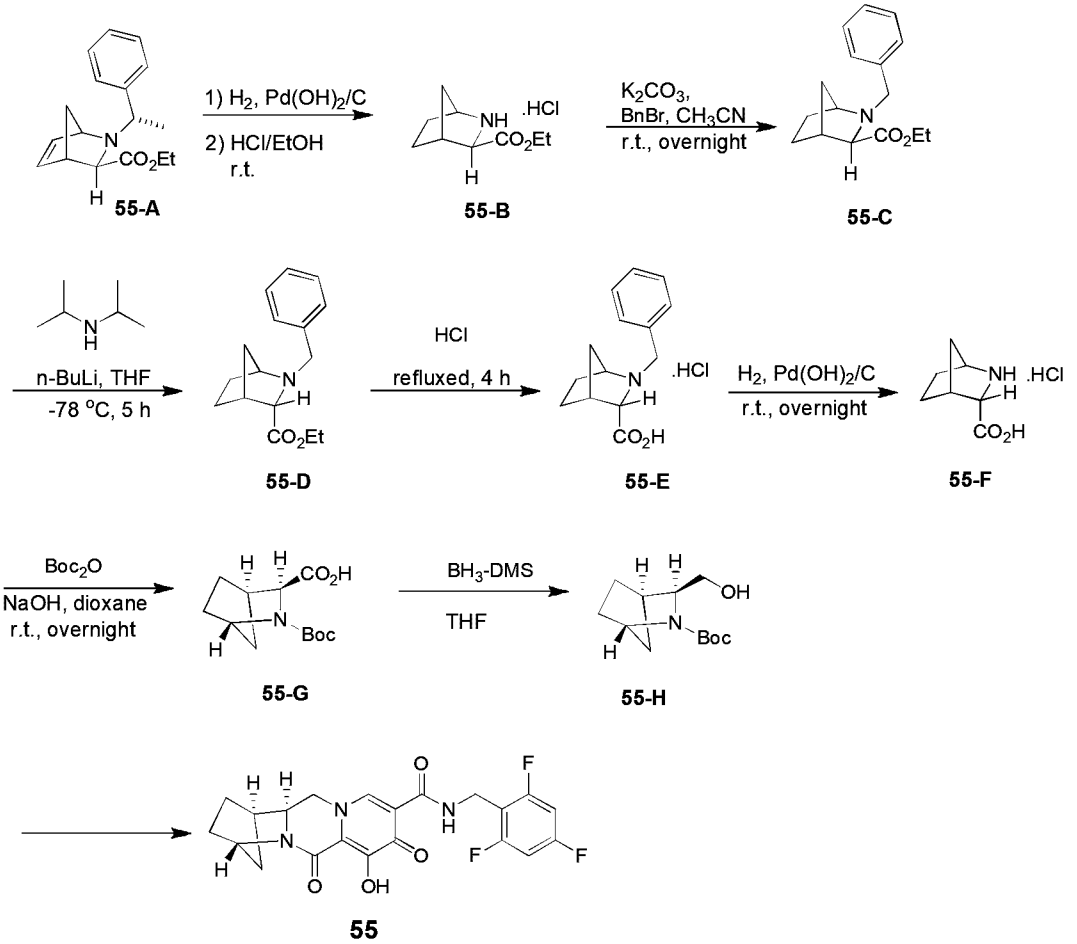

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Step 1

A mixture of compound **55-A** (40.60 g, 150 mmol) and $Pd(OH)_2/C$ (12 g) in EtOH (400 mL) under an atmosphere of H_2 was stirred at room temperature overnight. The reaction mixture was filtered and treated with HCl/EtOH (400 ml). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated to give compound **55-B**, which was used in next step without purification. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_9H_{16}NO$: 170.1.; found: 170.2.

Step 2

To a solution of compound **55-B** (92.25 g, 0.45 mol) and K_2CO_3 (186.30 g, 1.35 mol) in CH_3CN (1 L) was added benzyl bromide (76.50 g, 0.45 mol) at 0 °C. The mixture was stirred at room temperature overnight. The reaction mixture was filtered, concentrated and the residue was purified by chromatography on silica gel to give compound **55-C**.

Step 3

To a mixture of diisopropylamine (50 g, 0.50 mol) in THF (400 mL) was added n-BuLi (200 mL, 0.50 mol) at -78 °C at N_2 atmosphere. After 0.5 h, the reaction mixture was warmed to 20 °C and stirred for 0.5 h. The mixture was cooled to -78 °C and added a solution of compound **55-C** (64.75 g, 0.25 mol) in THF (600 mL) under N_2 atmosphere. The mixture was stirred for 4 h and quenched with saturated NH_4Cl solution. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel to give compound **55-D**.

Step 4

A mixture of compound **55-D** (129.50 g 0.50 mol) in 4N HCl (1.30 L) was refluxed for 4 h. the mixture was concentrated. The residue was purified by HPLC to give compound **55-E**.

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Step 5

To a mixture of compound **55-E** (47 g, 176 mmol) and $Pd(OH)_2/C$ (9 g) in EtOH (400 mL) under an atmosphere of H_2 was stirred at room temperature overnight. The reaction mixture was concentrated to give compound **55-F**, which was used in next step without purification. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.22 (s, 1H), 4.06 (s, 1H), 2.98-2.95 (d, J = 11.2 Hz, 1H), 1.96-1.93 (d, J = 11.2 Hz, 1H), 1.86-1.82 (m, 2H), 1.76-1.74 (d, J = 9.2 Hz, 2H), 1.49 (s, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_7H_{12}NO_2$: 142.1.; found: 142.1.

Step 6

To a mixture of compound **55-F** (29.20 g, 165 mmol) and 2N NaOH solution (330 mL, 0.66 mol) in dioxane (120 mL) was added Boc_2O (39.60 g, 181 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The mixture was adjusted with 3N HCl to pH=5~6 and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated to give **55-G**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.40 (s, 1H), 4.26 (s, 1H), 2.89 (s, 1H), 1.76-1.74 (s, 1H), 1.69-1.59 (m, 4H), 1.50 (s, 1H), 1.47 (s, 9H). **LCMS-ESI$^+$** (*m/z*): $[M+Na]^+$ calculated for $C_{12}H_{19}NNaO_4$: 264.1.; found: 264.1.

Step 7

To a mixture of compound **55-G** (500 mg, 2.07 mmol) in THF (10 mL) chilled to 0 °C was added BH_3-DMS THF complex (2N in THF, 8.23 mmol, 4.1 mL) slowly. Gas evolution occured. Internal temperature was monitored to ensure no major exotherm. Reaction was allowed to warm to r.t. overnight. Some starting material remained by LC/MS, additional 2 mL BH_3-DMS THF complex was added and the mixture was stirred for additional 3 hr then cooled reaction to 0 ^{0}C and slowly quenched with methanol (gas evolution occurs). Internal temperature monitored to ensure exotherm below 25 ^{0}C. The mixture was concentrated then purified by silica gel chromotography (20-40% EtOAc/Hexanes) to afford **55-H**.

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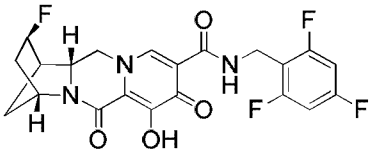
Step 8

Compound **55** was prepared as described for Example 41, substituting **55-H** for **41-B** to afford compound **55**. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.81 (s, 1H), 10.40 (t, J = 5.8 Hz, 1H), 8.39 (s, 1H), 7.19 (t, J = 8.6 Hz, 2H), 4.59 – 4.48 (m, 4H), 4.16 (t, J = 12.2 Hz, 1H), 4.03 (d, J = 12.2 Hz, 1H), 2.69 (s, 1H), 1.75 (d, J = 10.1 Hz, 1H), 1.69 – 1.55 (m, 5H). ^{19}F NMR (376 MHz, DMSO-d6) δ -109.3 (m, 1F), -112.5 (m, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_3N_3O_4$: 434.13.; found: 434.32.

Example 56

Preparation of Compound **56**

(1R,2S,4R,12aR)-2-fluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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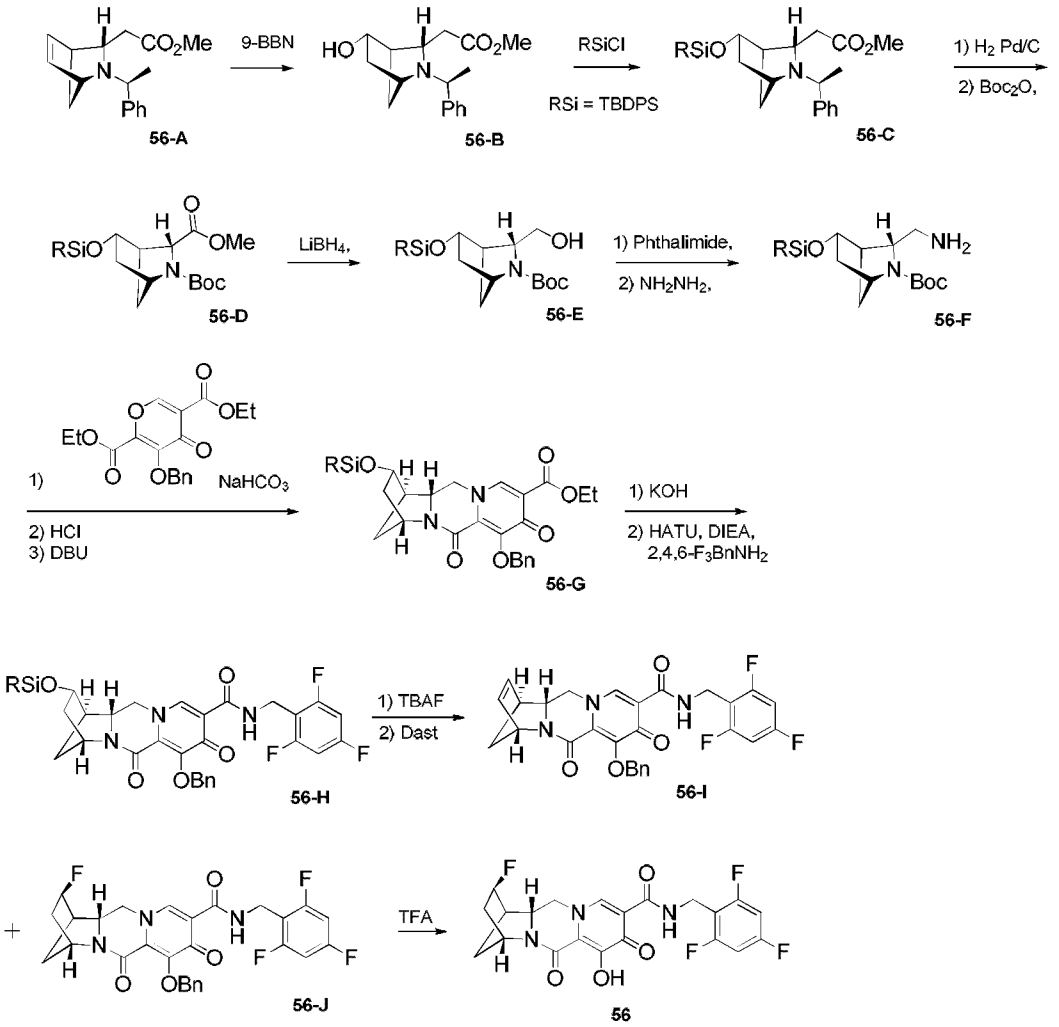

Step 1

A solution of **56-A** (5 g, 19.43 mmol) in tetrahydrofuran (65 ml) was cooled in an ice bath as 0.5 M 9-borabicyclo[3.3.1]nonane (48.58 ml) was added dropwise. The reaction mixture was warmed up to room temperature. After 18 hours, the reaction was cooled to 0 ºC and a mixture of 2M sodium hydroxide (34 ml) and hydrogen peroxide (9.34 ml, 97.15 mmol) was added dropwise. After 2 hours at 0 °C, the reaction was warmed up to room temperature and stirred for 1 hour. The mixture was diluted with EtOAc and washed with water. The aqueous fractions were extracted with EtOAc, and the organic fractions combined were dried (Na_2SO_4) and concentrated. The residue was purified by silica column chromatography (50-70% EtOAc/hexanes) to afford **56-B** (3.05 g, 57%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{21}NO_3$: 275.34; found: 276.122.

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Step 2

To a solution of **56-B** (1.45 g, 5.27 mmol) in N,N-dimethylformamide (12 ml) was added tert-butylchlorodiphenylsilane (1.51 ml, 5.79 mmol) and imidazole (1.08 g, 15.8 mmol). After 18 hours, the mixture was diluted with water, extracted into EtOAc (2x), the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (10-20% EtOAc/hexanes) to afford **56-C** (2.6 g, 96.1%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{32}H_{39}NO_3Si$: 513.74; found: 514.625.

Step 3

To a solution of **56-C** (3.27 g, 6.36 mmol) in EtOH (26 mL) and acetic acid (3 mL) was added 10% PdOH/C (0.52 g, 3.7 mmol) and the suspension was shaken in a Parr apparatus at 50 atm for 20 hours. After filtering through Celite, the cake was washed with EtOH, the filtrate was concentrated under vacuum. The residue was dissolved in ethanol (26 ml) and acetic acid (3 ml, 52.4 mmol), treated with 10% PdOH/C (0.52 g, 3.7 mmol) and shaken in a Parr apparatus at 50 atm for 20 hours. Filtered through Celite, the cake was washed with EtOH, the filtrate was concentrated under vacuum to dryness to afford the crude deprotected product (2.07g, 79.4 %). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{31}NO_3Si$: 409.59; found: 410.485.

To the crude residue (2 g, 4.88 mmol) and di-tert-butyl dicarbonate 97% (2.14 g, 9.79 mmol) in THF (20 ml) was added N,N-diisopropylethylamine (DIPEA) (2.14 ml, 12.27 mmol). After 20 h, the reaction mixture was diluted with water, extracted into EtOAC (2x) and the two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (10-20% EtOAc/Hexanes) to afford **56-D** (2.13 g, 86.14%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{30}H_{41}NO_5Si$: 523.74; found: 523.922.

Step 4

A solution of **56-D** (2.07 g, 4.06 mmol) in THF (20 ml) was stirred in an ice bath as 2.0 M $LiBH_4$ in THF (4.07 ml) was added and the resulting mixture was stirred at room temperature for 18 h. After, the reaction mixture was diluted with ethyl

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acetate and treated slowly with water. The two phases were separated, and the aqueous fraction was extracted again with ethyl acetate. The two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (20-40% EOAc/hexanes) to afford **56-E** (1.59 g, 81.3%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{39}NO_4Si$: 481.7; found: 482.337.

Step 5

A mixture of **56-E** (1.58 g, 3.28 mmol), phthalimide (0.79 g, 5.38 mmol) and triphenylphosphine (1.93 g, 7.37 mmol) in THF (90 ml) was cooled in an ice bath. Diisopropyl azodicarboxylate, 95% (1.46 ml, 7.42 mmol) was added. The mixture was then warmed up to room temperature and stirred for 20 h. After, the reaction mixture was concentrated and the residue dissolved in ether, cooled in an ice bath and stirred for 1.5 h. The solids were filtered off and the filtrate was concentrated. The residue was purified by silica column chromatography (10-30% EtOAc/hexanes) to afford the protected amino compound (1.86 g, 92.8%).

A solution of the protected amino compound **56-F** (1.85 g, 3.03 mmol) and hydrazine hydrate (0.6 ml, 12.39 mmol) in ethanol (19 ml) was stirred at 70 °C for 2 h. The reaction mixture was cooled in an ice bath, ether (10 ml) was added and the mixture was stirred for 30 min. The solid formed was filtered off and the filtrate was concentrated under vacuum to dryness.

Step 6

A mixture of crude amino compound **56-F** (991 mg, 2.06 mmol), compound **38-F** (Example 38) (714 mg, 2.06 mmol) and $NaHCO_3$ (347 mg, 4.12 mmol) in water (15 mL) and EtOH (15 mL) was stirred for 20 h. The reaction mixture was concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue (1.5 g) was dissolved in CH_2Cl_2 (5 mL) and 4N HCl in dioxane (18.6 mL) was added. After 1.5 hours the mixture was concentrated to dryness, co-evaporated with toluene and dried in vacuo.

The crude residue (1.38 g) and DBU (1.4 ml, 9.38 mmol) in toluene (25 ml) was stirred at 110 °C. After 35 minutes the mixture was concentrated and the

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residue was purified by silica column chromatography (5-15% MeOH/EtOAc) to afford **56-G** (450 mg, 72.3%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{39}H_{42}N_2O_6Si$: 662.85; found: 663.766.

Step 7

The mixture of **56-G** (890 mg, 1.34 mmol) in MeOH (14 ml) and THF (14 ml) was stirred at room temperature as 1M KOH (7.09 ml) was added. After 30 min the reaction mixture was neutralized with 1N HCl, extracted into EtOAc (2x) and the combined organic extracts were dried (Na_2SO_4) and concentrated.

A suspension of the crude residue (850 mg), 2,4,6-trifluorobenzylamine (248 mg, 1.54 mmol) and HATU (662 mg, 1.74 mmol) in dichloromethane (5 ml) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (1.63 ml, 9.37 mmol) was added. After 1 h, additional 2,4,6-difluorobenzylamine (32 mg, 0.2 mmol), HATU (153 mg, 0.4 mmol) and N,N-diisopropylethylamine (DIPEA) (0.12 ml, 0.67 mmol) were added. After 30 minutes the mixture was diluted with water, extracted into EtOAc (3x) the combined organic phases were dried (Na_2SO_4), concentrated and the residue was purified by silica column chromatography (50-75% EtOAc/hexanes) to afford **56-H** (919 mg, 88.23%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{44}H_{42}F_3N_3O_5Si$: 777.9; found: 778.409.

Step 8

A solution of **56-H** (915 mg, 1.18 mmol) in THF (5 ml) was stirred in an ice bath as 1.0 M tetrabutylammonium fluoride in THF (1.18 ml) was added dropwise. The resulting mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under vacuum and the residue was diluted with EtOAc, washed with water, dried (Na_2SO_4), concentrated and the residue was purified by silica column chromatography (50-75% EtOAc/hexanes then 5% MeOH/EtOAc). The resulting material (248 mg, 0.46 mmol) was dissolved in dichloromethane (2 ml) cooled to -78ºC as diethylaminosulfur trifluoride (0.07 mL, 0.55 mmol) was added dropwise and the reaction was warmed to room temperature and stirred for 1 h. The reaction was cooled in an ice bath and quenched with saturated $NaHCO_3$, two phases were separated, and the separated aqueous fraction was extracted with CH_2Cl_2. The two organic fractions

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were combined dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (1% MeOH/EtOAc) to afford **56-J** (75 mg) (**LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{23}F_4N_3O_4$: 541.49; found: 542.320) and **56-I** (30 mg) (**LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{22}F_3N_3O_4$: 521.49; found: 522.05).

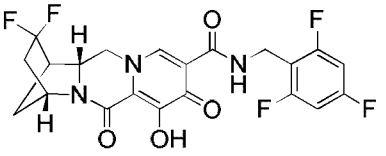
Step 9

Compound **56-J** (75 mg, 139 mmol) was dissolved in TFA (1 mL), stirred at room temperature for 10 minutes, and the solution was concentrated. The residue was purified by reverse phase HPLC (Gemini, 15 to 43% ACN/H_2O + 0.1% TFA) to afford compound **56**. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 10.67 (s, 1H), 7.80 (s, 1H), 7.17 (t, J = 8.6 Hz, 2H), 5.45 – 5.18 (m, 1H), 4.70 – 4.39 (m, 3H), 4.23 (d, J = 11.5 Hz, 1H), 4.11 – 3.85 (m, 2H), 2.85 (dd, J = 4.2, 2.0 Hz, 1H), 2.34 – 2.13 (m, 1H), 1.81 (s, 1H), 1.55 – 1.33 (m, 2H). **^{19}F-NMR** (376 MHz, DMSO-d_6) δ -74.20 (m), -106.95 – -116.45 (m), -190.65 – -194.54 (m).

Example 57

Preparation of Compound **57**

(1R,4R,12aR)-2,2-difluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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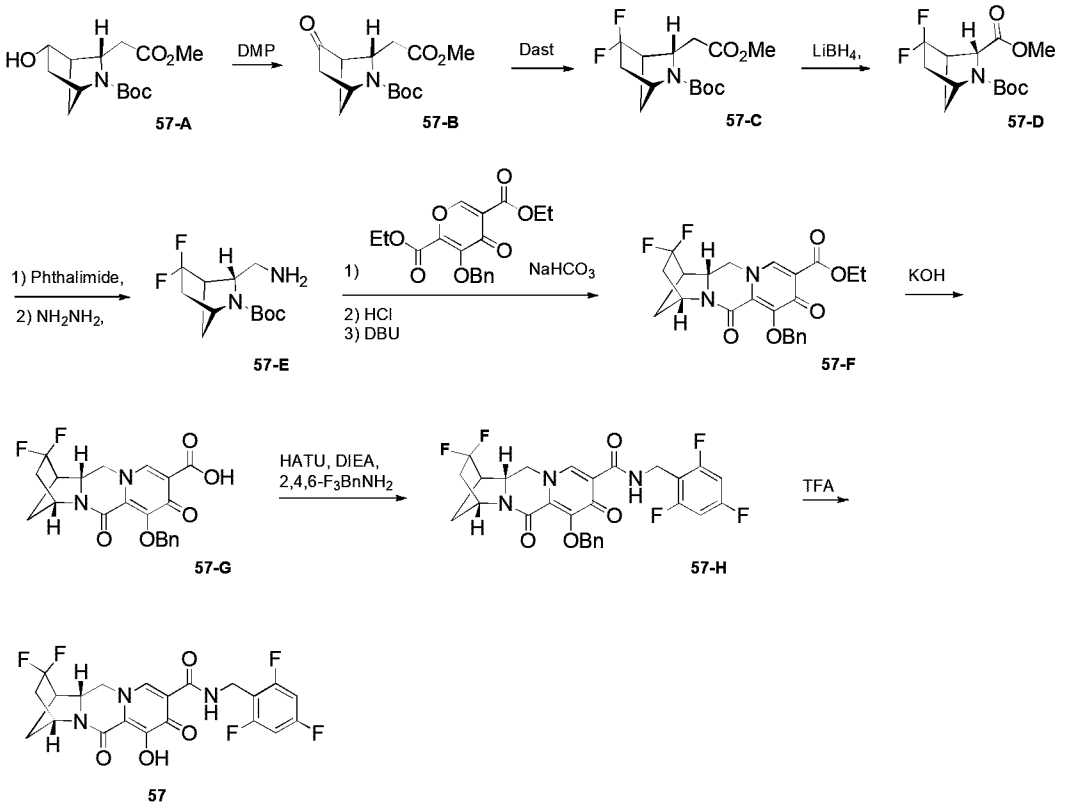

Step 1

A solution of **57-A** (1.45 g, 5.34 mmol) in dichloromethane (30 ml) was cooled in an ice bath as Dess Martin periodinane (4.53 g, 10.69 mmol) was added in portions and the reaction was stirred at room temperature for 18 h. The reaction was quenched by addition of water, the precipitate was filtered off and a saturated solution of $Na_2S_2O_3$ was added. The mixture was stirred until the biphasic solution turned then saturated $NaHCO_3$ was added and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4) and concentrated. The residue was purified by silica column chromatography (30-50% EtOAc/Hexanes) to afford **57-B** (1.13 g, 78.2 %). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{19}NO_5$: 269.29; found: 269.722.

Step 2

A solution of **57-B** (0.5 g, 1.86 mmol) in dichloromethane (10 ml) was cooled to -78ºC as diethylaminosulfur trifluoride (0.52 mL, 3.91 mmol) was added dropwise and the reaction was warmed to room temperature and stirred for 18 h. The

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reaction was cooled in an ice bath and quenched with saturated $NaHCO_3$, two phases were separated, and the separated aqueous fraction was extracted with CH_2Cl_2. The two organic fractions were combined, dried (Na_2SO_4) and concentrated. The residue was purified by silica column chromatography (20-50% EtOAc/hexanes) to afford **57-C** (518 mg, 95.39%). **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.43 (s, 1H), 4.36 – 4.27 (m, 1H), 4.22 (s, 1H), 3.75 (s, 3H), 2.95 (t, J = 8.1 Hz, 1H), 2.30 – 1.98 (m, 2H), 1.85 – 1.71 (m, 1H), 1.44 (m, 9H).

Step 3

A solution of **57-C** (935 mg, 3.21 mmol) in THF (10 ml) was stirred in an ice bath as 2.0 M LiBH4 in THF (3.22 ml) was added and the resulting mixture was stirred at room temperature for 18 h. After, the reaction mixture was diluted with ethyl acetate and water was added slowly. The two phases were separated, and the separated aqueous fraction was extracted with ethyl acetate. The two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (20-40% EtOAc/hexanes) to afford **57-D** (724 mg, 85.67%). **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 4.30 – 3.48 (m, 5H), 2.75 – 2.56 (m, 1H), 2.24 – 1.90 (m, 3H), 1.86 – 1.65 (m, 1H), 1.47 (s, 9H).

Step 4

A mixture of **57-D** (720 mg, 2.74 mmol), phthalimide (402 mg, 2.73 mmol) and triphenylphosphine (1.61 g, 6.15 mmol) in THF (45 ml) was cooled in an ice bath. Diisopropyl azodicarboxylate, 95% (1.22 ml, 6.19 mmol), was added. The mixture was then warmed up to room temperature and stirred for 20 h. After, the reaction mixture was concentrated and the residue dissolved in ether, cooled in an ice bath and stirred for 1.5 h. After the solids were filtered off, the filtrate was concentrated. The residue was purified by silica column chromatography (40-60% EtOAc/hexanes) to afford the phthalimide adduct (1.07 g, 99.7%). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{22}F_2N_2O_4$: 392.4; found: 393.204

A solution of the phthalimide adduct (1.07 g, 2.73 mmol) and hydrazine hydrate (0.54 mL, 11.15 mmol) in ethanol (10 ml) was stirred at 70 °C for 2 hours. The reaction mixture was cooled in an ice bath and ether (10 ml) was added. The mixture

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was stirred for 30 min. The solid formed was filtered off and the filtrate was concentrated under vacuum to dryness to afford crude **57-E**.

Step 5

A mixture of crude **57-E** (709 mg, 2.7 mmol) compound **38-F** (Example 38) (936 mg, 2.7 mmol) and $NaHCO_3$ (454 mg, 5.41 mmol) in water (15 mL) and EtOH (15 mL) was stirred for 20 h. The reaction mixture was concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue (1.5 g) was dissolved in CH_2Cl_2 (7 mL) and 4N HCl in dioxane (26.9 mL) was added. After 1.5 hours the mixture was concentrated to dryness, co-evaporated with toluene and dried in vacuum. The crude residue (1.3 g) and DBU (2 ml, 13.4 mmol) in toluene (25 ml) was stirred at 110 °C. After 35 minutes the mixture was concentrated and the residue was purified by silica column chromatography (5-15% MeOH/EtOAc) to afford **57-F** (426 mg, 36.17%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_2O_5$: 444.43; found: 445.280.

Step 6

The mixture of compound **57-F** (426 mg, 0.96 mmol) in MeOH (7 ml) and THF (7 ml) was stirred at room temperature as 1M KOH (5.06 ml) was added. After 30 minutes the reaction mixture was neutralized with 1N HCl, extracted into EtOAc (2x) and the combined organic extracts were dried (Na_2SO_4) and concentrated to crude **57-G**.

Step 7

A suspension of the crude residue **57-G** (189 mg), 2,4,6-trifluorobenzylamine (95 mg, 0.59 mmol) and HATU (276 mg, 0.73 mmol) in dichloromethane (3 ml) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (0.59 ml, 3.4 mmol) was added. After 1 h he mixture was diluted with water, extracted into EtOAc (3x). The combined organic phases were dried (Na_2SO_4) and concentrated to **57-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{22}F_5N_3O_4$: 559.48; found: 560.24.

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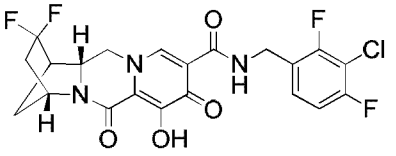
Step 8

Compound **57-H** (150 mg, 0.27 mmol) was dissolved in TFA (2 mL), stirred at room temperature for 10 min, and the solution was concentrated. The residue was purified by reverse phase HPLC (Gemini, 15 to 60% ACN/H_2O + 0.1% TFA), to afford compound **57** (85 mg, 67.5%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{16}F_5N_3O_4$: 469.36; found: 470.229. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.41 (t, J = 5.6 Hz, 1H), 8.20 (s, 1H), 7.12 (t, J = 8.7 Hz, 2H), 4.79 (s, 1H), 4.48 (m, 3H), 4.10 (m, 2H), 3.02 (d, J = 5.7 Hz, 1H), 2.33 (m, 1H), 2.22 – 1.97 (m, 2H), 1.85 (d, J = 11.0 Hz, 1H), 1.21 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -69.88 , -71.77 , -74.09 , -88.33 (dd, J = 222.6, 23.8 Hz), -109.15 – -109.60 (m), -110.04 , -112.44 (t, J = 7.6 Hz).

Example 58

Preparation of Compound **58**

(1R,4R,12aR)-N-(3-chloro-2,4-difluorobenzyl)-2,2-difluoro-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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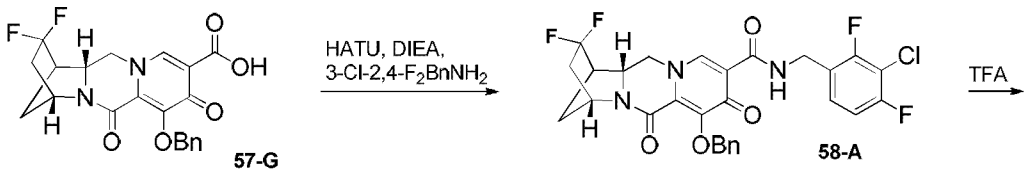
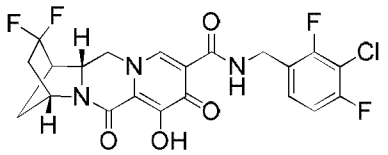


57-G **58-A**



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Step 1

A suspension of the crude residue **57-G** (120 mg), 3-chloro,2,4-difluorobenzylamine (67 mg, 0.38 mmol) and HATU (175 mg, 0.46 mmol) in dichloromethane (3 ml) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (0.38 ml, 0.28 mmol) was added. After 1 h the mixture was diluted with water, extracted into EtOAc (3x) the combined organic phases were dried (Na_2SO_4) and concentrated to yield **58-A**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{22}ClF_4N_3O_4$: 575.94; found: 576.394.

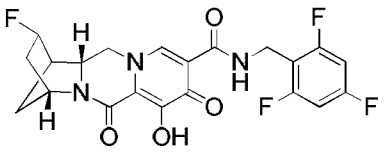
Step 2

Compound **58-A** (166 mg) was dissolved in TFA (2 mL), stirred at room temperature for 10 min, and the solution was concentrated. The residue was purified by reverse phase HPLC (Gemini, 15 to 70% ACN/H_2O + 0.1% TFA), to afford compound **57** (60 mg, 42.8%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{16}ClF_4N_3O_4$: 485.82; found: 486.135. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 10.77 (t, J = 6.0 Hz, 1H), 7.77 (s, 1H), 7.28 (m, 2H), 4.77 (s, 1H), 4.64 – 4.40 (m, 2H), 4.27 (d, J = 9.1 Hz, 1H), 3.93 (m, 2H), 2.95 (d, J = 5.8 Hz, 1H), 2.51 (s, 1H), 2.42 – 2.17 (m, 1H), 2.14 – 1.89 (m, 2H), 1.77 (m, 1H). **^{19}F-NMR** (376 MHz, DMSO-d_6) δ -87.63 , -88.23 , -108.67 , -109.27 , -116.42 (t, J = 7.0 Hz), -118.48 (d, J = 7.8 Hz).

Example 59

Preparation of Compound **59**

(1R,2R,4R,12aR)-2-fluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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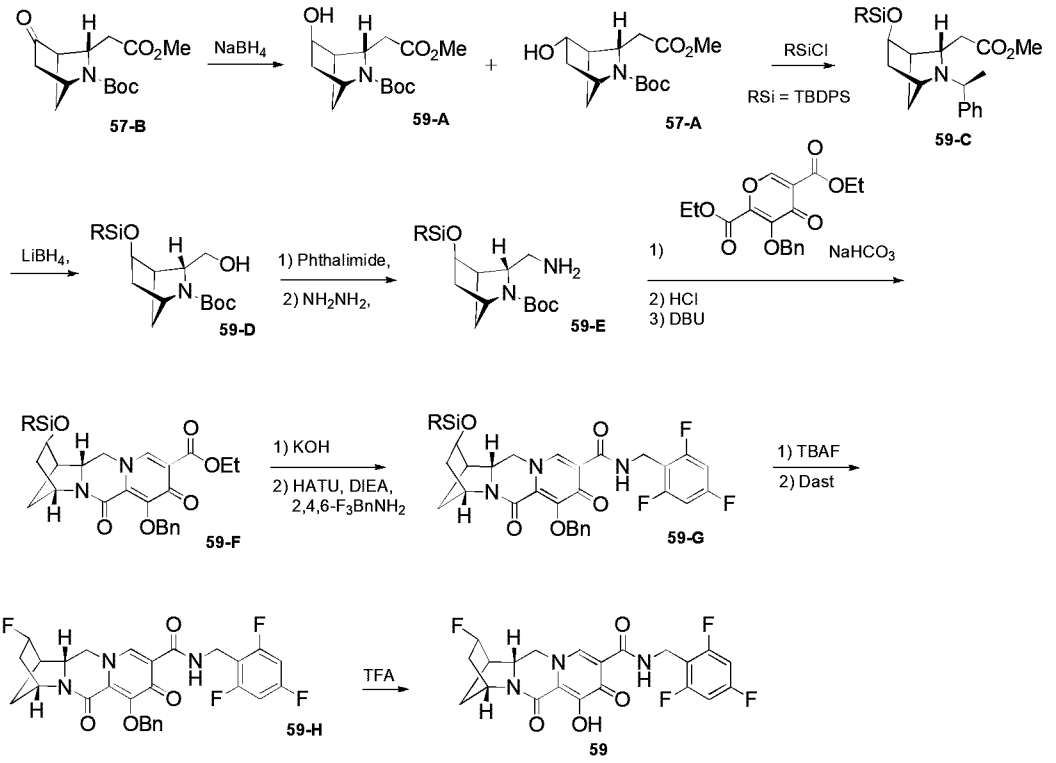

Step 1

A solution of **57-B** (1.9 g, 7.06 mmol) in methanol (35 mL) was stirred at 0 °C as sodium borohydride (667 mg, 17.64 mmol) was added portionwise and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was cooled in an ice bath, quenched by addition of water and concentrated. The residue was partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated The residue was purified by silica column chromatography (30-60% EtOAc/hexanes) to afford **59-A** (1.49 g). **^{1}H-NMR** (400 MHz, chloroform-*d*) δ 4.57 (s, 1H), 4.52 – 4.42 (m, 2H), 4.28 (s, 1H), 4.14 (s, 1H), 3.72 (d, J = 2.1 Hz, 3H), 2.74 (s, 1H), 2.08 – 1.87 (m, 2H), 1.43 (d, J = 23.1 Hz, 10H) and **57-A** (96 mg): **^{1}H-NMR** (400 MHz, chloroform-*d*) δ 4.65 – 4.40 (m, 2H), 4.34 – 4.02 (m, 1H), 3.73 (d, J = 2.3 Hz, 3H), 2.74 (t, J = 5.3 Hz, 1H), 2.12 – 1.55 (m, 3H), 1.52 – 1.18 (m, 11H).

Step 2

To a solution of **59-A** (686 mg, 2.53 mmol) in N,N-dimethylformamide

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(5 ml) was added tert-butylchlorodiphenylsilane (0.723 mL, 2.78 mmol) and imidazole (516 mg, 7.56 mmol). After 18 h, the mixture was diluted with water, extracted into EtOAc (2x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (10-20% EtOAc/hexanes) to afford **59-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{29}H_{39}NO_5Si$: 509.71; found: 510.793.

Step 3

A solution of **59-C** (1.23 g, 2.41 mmol) in THF (13 ml) was stirred in an ice bath as 2.0 M $LiBH_4$ in THF (2.42mL, 4.84 mmol)) was added and the resulting mixture was stirred at room temperature for 18 h. After the reaction mixture was diluted with ethyl acetate water was added slowly, two phases were separated, and the separated aqueous fraction was extracted with ethyl acetate. The two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (20-40% EtOAc/hexanes) to afford **59-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{39}NO_4Si$: 481.7; found: 482.741.

Step 4

A mixture of **59-D** (963 mg, 2.0 mmol), phthalimide (482 mg, 3.28 mmol) and triphenylphosphine (1.18 g, 4.49 mmol) in THF (50 ml) was cooled in an ice bath. Diisopropyl azodicarboxylate, 95% (0.89 mL, 4.52 mmol) was added. The mixture was then warmed up to room temperature and stirred for 20 h. After, the reaction mixture was concentrated and the residue dissolved in ether, cooled in an ice bath and stirred for 1.5 h. After, the solids were filtered off and the filtrate was concentrated. The residue was purified by silica column chromatography (10-30% EtOAc/hexanes) to afford the phthalimide adduct. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{36}H_{42}N_2O_5Si$: 610.81; found: 611.935.

A solution of the phthalimide adduct (1.2 g, 1.97 mmol) and hydrazine hydrate (0.4 ml, 8.03 mmol) in ethanol (12 ml) was stirred at 70 °C for 2h. The reaction mixture was cooled in an ice bath and ether (10 ml) was added, the mixture was stirred for 30 min. The solid formed was filtered off and the filtrate was concentrated under vacuum to dryness to afford **59-E**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for

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$C_{28}H_{40}N_2O_3Si$: 480.71; found: 481.356.

Step 5

A mixture of crude **59-E** (770 mg, 1.60 mmol), compound **38-F** (Example 38) (555 mg, 1.60 mmol) and $NaHCO_3$ (269 mg, 3.20 mmol) in water (12 mL) and EtOH (12 mL) was stirred for 20 h. The reaction mixture was concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated.

The residue (1.29 g) was dissolved in CH_2Cl_2 (4 mL) and 4N HCl in dioxane (15.6 mL) was added. After 1.5 hours the mixture was concentrated to dryness, co-evaporated with toluene and dried in vacuum. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{41}H_{48}N_2O_7Si$: 708.91; found: 709.782.

The crude residue (1.09 mg) and DBU (1.17 ml, 7.8 mmol) in toluene (20 ml) was stirred at 110 °C. After 35 min the mixture was concentrated and the residue was purified by silica column chromatography (5-15% MeOH/EtOAc) to afford **59-F**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{39}H_{42}N_2O_6Si$: 662.85; found: 663.677.

Step 6

A mixture of **59-F** (680 mg, 1.03 mmol) in MeOH (10 ml) and THF (10 ml) was stirred at room temperature as 1M KOH (5.42 ml) was added. After 30 min the reaction mixture was neutralized with 1N HCl, extracted into EtOAc (2x) and the combined organic extracts were dried (Na_2SO_4) and concentrated. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{37}H_{38}N_2O_6Si$: 634.79; found: 635.466.

A suspension of the crude residue (650 mg), 2,4,6-trifluorobenzylamine (214 mg, 1.33 mmol) and HATU (623 mg, 1.64 mmol) in dichloromethane (6 ml) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (1.34 ml, 7.68 mmol) was added. After 2 h, the mixture was diluted with water, extracted into EtOAc (3x) nad the combined organic phases were dried (Na_2SO_4), concentrated and the residue was purified by silica column chromatography (50-75% EtOAc/hexanes) to afford **59-G**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{44}H_{42}F_3N_3O_5Si$: 777.9; found:

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778.566.

Step 7

A solution of **59-G** (648 mg, 0.83 mmol) in THF (10 ml) was stirred in an ice bath as 1.0 M tetrabutylammonium fluoride in THF (0.83 ml) was added dropwise and the resulting mixture was stirred at room temperature for 30 min. Additional 1.0 M tetrabutylammonium fluoride in THF (0.1 ml) was added dropwise. After 30 minutes, the reaction mixture was concentrated under vacuum and the residue was diluted with EtOAc, washed with water, dried (Na_2SO_4), concentrated and the residue was purified by silica column chromatography (5% MeOH/EtOAc). A solution of the residue (290 mg, 0.54 mmol) in dichloromethane (3 ml)was cooled to -78°C as diethylaminosulfur trifluoride (0.09 mL, 0.65 mmol) was added dropwise and the reaction was warmed to room temperature and stirred for 2.5 h. The reaction was cooled in an ice bath, quenched with saturated $NaHCO_3$, two phases were separated, and the separated aqueous fraction was extracted with CH_2Cl_2. The two organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (1% MeOH/EtOAc) to afford **59-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{23}F4N_3O_4$: 541.49; found: 542.320.

Step 8

Compound **59-H** (103 mg, 0.19 mmol) was dissolved in TFA (1.4 mL) at room temperature for 15 min, and the solution was concentrated. The residue was suspended in DMF, filtered off, and the precipitated product was washed with water, dried under vacuum to afford compound **59**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{17}F_4N_3O_4$: 451.37, found: 452.226. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.53 (s, 1H), 10.35 (t, J = 5.8 Hz, 1H), 8.34 (s, 1H), 7.18 (t, J = 8.6 Hz, 2H), 5.15 – 4.88 (m, 1H), 4.73 (d, J = 3.3 Hz, 1H), 4.49 (m, 3H), 4.04 (t, J = 12.4 Hz, 1H), 3.65 (dd, J = 12.4, 3.7 Hz, 1H), 2.95 – 2.76 (m, 1H), 2.26 – 2.03 (m, 1H), 1.96 – 1.64 (m, 3H). **^{19}F-NMR** (376 MHz, DMSO-d_6) δ -73.93 , -74.74 (d, J = 28.8 Hz), -109.31 (m), -112.51 (m), -165.65 (m).

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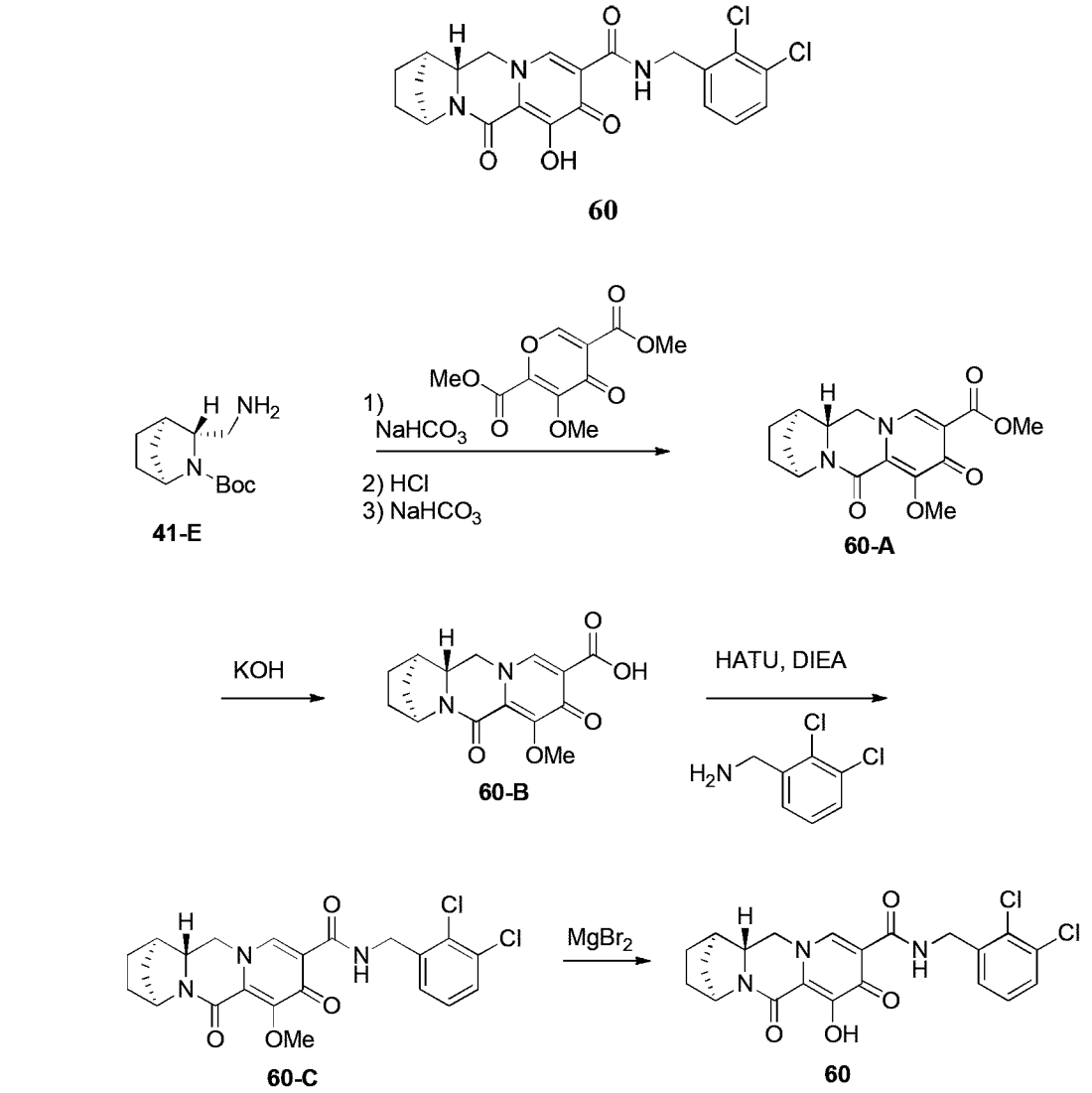
Example 60

Preparation of Compound **60**

(1R,4S,12aR)-N-(2,3-dichlorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



Step 1

To a solution of dimethyl 3-methoxy-4-oxo-4H-pyran-2,5-dicarboxylate (5.5 g, 23 mmol) in MeOH (100 mL) was added **41-E** (Example 41) (5 g, 22 mmol) and sodium bicarbonate (3.6 g, 43 mmol). The solution was stirred at room temperature for 1.5 h. 4M HCl (in dioxane, 55 mL, 221 mmol) was added and the solution was heated

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to 50 °C for 2h. The reaction was cooled to room temperature and concentrated *in vacuo*. The resulting oil was dissolved in sodium bicarbonate and washed with EtOAc. The aqueous layers were then extracted with CH_2Cl_2 (4x). The combined CH_2Cl_2 extractions were dried over Na_2SO_4 and concentrated to provide **60-A**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{19}N_2O_5$: 319.13; found: 319.20.

Step 2

To a suspension of **60-A** (3.7 g, 11.6 mmol) in MeOH (12 mL) and THF (23 mL) was added aqueous KOH (2M, 15.7 mL, 31.4 mmol). The resulting solution was stirred at room temperature for 10 min. Volatiles were removed *in vacuo*, and the resulting aqueous layer was acidified with 1N HCl. The resulting white solid was filtered, washed with water, and dried *in vacuo* to provide **60-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.36 (s, 1H), 5.01 (d, J = 2.7 Hz, 1H), 4.12 (s, 4H), 3.90 (t, J = 12.2 Hz, 1H), 3.78 (dd, J = 12.1, 3.1 Hz, 1H), 2.69 (s, 1H), 1.95 - 1.71 (m, 4H), 1.70 - 1.54 (m, 2H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{17}N_2O_5$: 305.11; found: 305.15.

Step 3

To a solution of **60-B** (0.10 g, 0.33 mmol) in CH_2Cl_2 (3.5 mL) was added (2,3-dichlorophenyl)methanamine (0.12 g, 0.70 mmol), HATU (0.25 g, 0.66 mmol), and N,N-diisopropylethylamine (DIPEA) (0.29 mL, 1.64 mmol). The resulting solution was stirred at room temperature until judged complete by LC/MS. The reaction mixture was diluted with CH_2Cl_2 and washed with 1N HCl. The aqueous layer was back-extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was dissolved in hot DMF and allowed to precipitate upon cooling. Filtration provided **60-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}Cl_2N_3O_4$: 462.10; found: 462.14.

Step 4

To a slurry of **60-C** (0.11 g, 0.24 mmol), in acetonitrile (4.5 mL), was added magnesium bromide (0.089 g, 0.48 mmol). The reaction mixture was heated to 45 °C for 2.5 h and then cooled to room temperature. The slurry was diluted with

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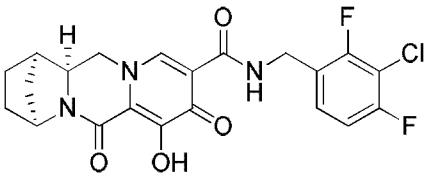
CH_2Cl_2 and washed with 1N HCl and brine. The aqueous layers were back-extracted with CH_2Cl_2 (2x) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was triturated with methanol and filtered to provide **60**. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.72 (s, 1H), 10.50 (t, 1H), 8.34 (s, 1H), 7.55 (dd, 1H), 7.40 – 7.24 (m, 2H), 4.67 (s, 1H), 4.61 (d, 2H), 4.45 (dd, 1H), 3.95 (t, 1H), 3.84 – 3.73 (m, 1H), 1.86 – 1.67 (m, 3H), 1.66 – 1.40 (m, 4H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}Cl_2N_3O_4$: 448.08; found: 448.18.

Example 61

Preparation of Compound **61**

(1R,4S,12aS)-N-(3-chloro-2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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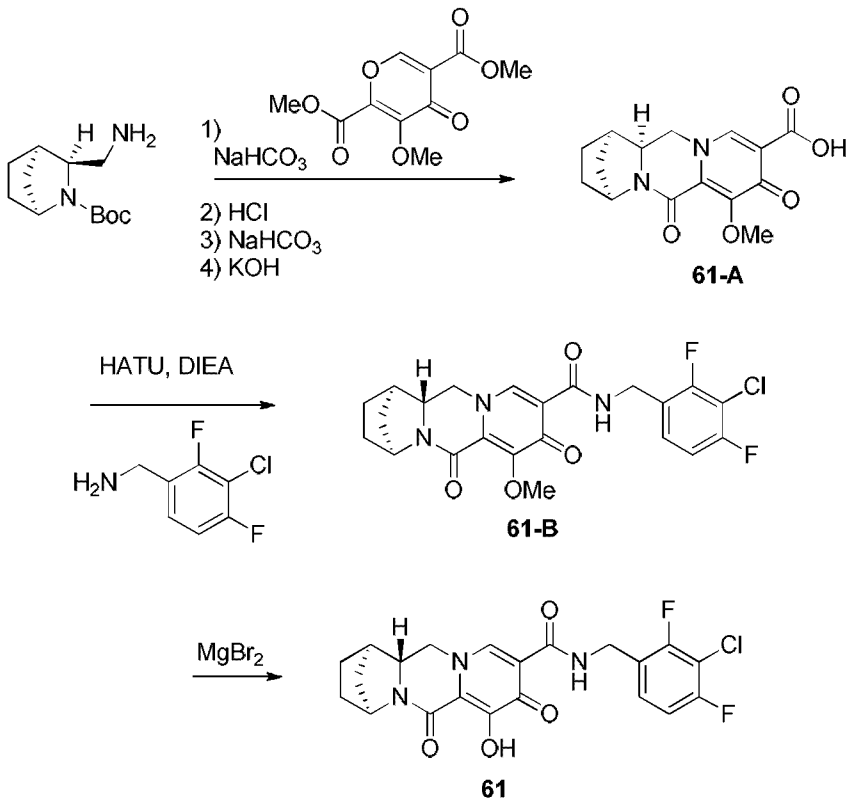

61 was prepared analogously to Example **60**, substituting (1S,3S,4R)-tert-butyl 3-(aminomethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (prepared in Example **55**) for **41-E**, and (3-chloro-2,4-difluorophenyl)methanamine for (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.85 (s, 1H), 10.45 (t, 1H), 8.40 (s, 1H), 7.37 (td, 1H), 7.27 (td, 1H), 4.63 - 4.46 (m, 4H), 4.17 (t, 1H), 4.04 (dt, 1H), 1.76 (d, 1H), 1.73 - 1.54 (m, 5H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClF_2N_3O_4$: 450.10; found: 450.15.

Example 62

Preparation of Compound **62**

'(2R,5S,13aR)-N-(4-fluoro-2-(trifluoromethyl)benzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

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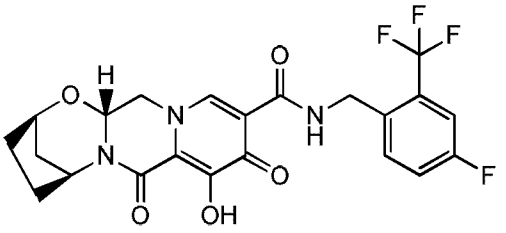


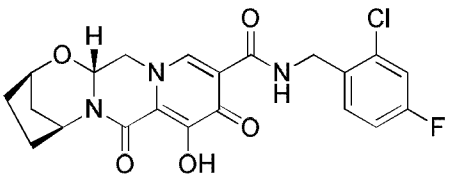
62

Compound **62** was prepared in a similar manner to compound **42** using (4-fluoro-2-(trifluoromethyl)phenyl)methanamine in place of (2,4,6-trifulorophenylphenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.50 (s, 1H), 8.38 (s, 1H), 7.57 (dd, 1H), 7.36 (dd, 1H), 7.19 (td, 1H), 5.40 - 5.28 (m, 2H), 4.79 (t, 2H), 4.69 (s, 1H), 4.25 (dd, 1H), 4.03 (dd, 1H), 2.17 - 1.98 (m, 4H), 1.96 - 1.84 (m, 1H), 1.61 (dt, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{20}F_4N_3O_5$: 482.13; found: 482.145.

Example 63

Preparation of Compound **63**

(2R,5S,13aR)-N-(2-chloro-4-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



63

Compound **63** was prepared in a similar manner to compound **42** using (2-chloro-4-fluorophenyl)methanamine in place of (2,4,6-trifulorophenylphenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.48 (s, 1H), 8.45 (s, 1H), 7.39 (dd, 1H), 7.12 (dd, 1H), 6.93 (td, 1H), 5.37 (d, 1H), 5.31 (t, 1H), 4.68 (s, 3H), 4.29 (d, 1H), 4.04 (t, 1H), 2.21 - 2.01 (m, 4H), 1.97 - 1.82 (m, 1H), 1.67 - 1.56 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}ClFN_3O_5$: 448.10; found: 448.143.

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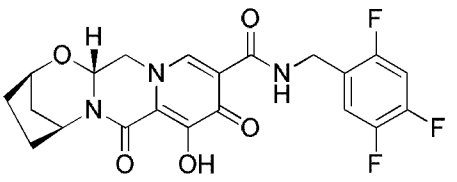
Example 64

Preparation of Compound **64**

(2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,5-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



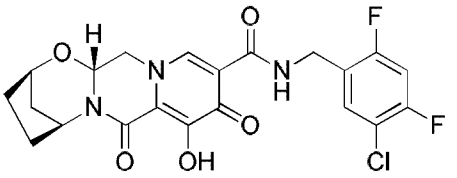
64

Compound **64** was prepared in a similar manner to compound **42** using (2,4,5-trifluorophenyl)methanamine in place of (2,4,6-trifulorophenylphenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.42 (s, 1H), 8.42 (s, 1H), 7.19 (ddd, 1H), 6.91 (td, 1H), 5.38 (dd, 1H), 5.31 (t, 1H), 4.69 (s, 1H), 4.61 (d, 2H), 4.29 (dd, 1H), 4.05 (dd, 1H), 2.18 - 2.02 (m, 4H), 1.96 - 1.84 (m, 1H), 1.66 - 1.56 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_3N_3O_5$: 450.12; found: 450.119.

Example 65

Preparation of Compound **65**

(2R,5S,13aR)-N-(5-chloro-2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



65

Compound **65** was prepared in a similar manner to compound 42 using (5-chloro-2,4-difluorophenyl)methanamine in place of (2,4,6-trifulorophenylphenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.47 (t,

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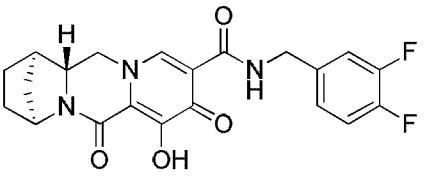
1H), 8.41 (s, 1H), 7.40 (dd, 1H), 6.90 (t, 1H), 5.37 (dd, 1H), 5.31 (t, 1H), 4.69 (s, 1H), 4.62 (d, 2H), 4.28 (d, 1H), 4.04 (dd, 1H), 2.17 - 2.02 (m, 4H), 1.94 - 1.86 (m, 1H), 1.61 (dt, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClF_2N_3O_5$: 466.09; found: 466.107.

Example 66

Preparation of Compound **66**

(1R,4S,12aR)-N-(3,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



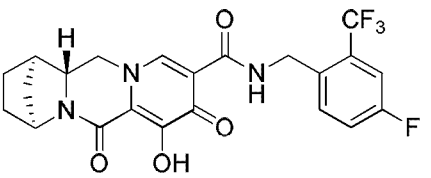
66

Compound **66** was prepared in a similar manner to compound **60** using (3,4-difluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.59 (s, 1H), 7.24 – 7.16 (m, 2H), 7.14 – 7.04 (m, 2H), 4.91 (s, 1H), 4.58 (d, 3H), 3.94 – 3.82 (m, 1H), 3.79 (d, 1H), 1.99 – 1.81 (m, 4H), 1.76 (d, 1H), 1.70 – 1.60 (m, 3H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_4$: 416.13; found: 416.415.

Example 67

Preparation of Compound **67**

(1R,4S,12aR)-N-(4-fluoro-2-(trifluoromethyl)benzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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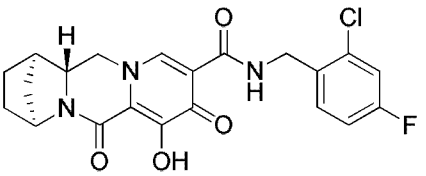
67

Compound **67** was prepared in a similar manner to compound **60** using (4-fluoro-2-(trifluoromethyl)phenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 11.72 (s, 1H), 10.55 (s, 1H), 8.29 (s, 1H), 7.61 (s, 1H), 7.36 (dd, 1H), 7.18 (td, 1H), 4.91 (s, 1H), 4.80 (d, 3H), 4.11 (s, 1H), 1.99 – 1.80 (m, 4H), 1.76 (d, 1H), 1.71 – 1.47 (m, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{20}F_4N_3O_4$: 466.13; found: 466.297.

Example 68

Preparation of Compound **68**

(1R,4S,12aR)-N-(2-chloro-4-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



68

Compound **68** was prepared in a similar manner to compound **60** using (2-chloro-4-fluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 11.68 (s, 1H), 10.52 (s, 1H), 8.27 (s, 1H), 7.44 – 7.37 (m, 1H), 7.11 (dd, 1H), 6.93 (td, 1H), 4.90 (s, 1H), 4.68 (d, 2H), 4.16 – 4.01 (m, 1H), 3.88 – 3.70 (m, 2H), 2.00 – 1.79 (m, 4H), 1.75 (d, 1H), 1.70 – 1.57 (m, 2H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}ClFN_3O_4$: 432.10; found: 432.214.

Example 69

Preparation of Compound **69**

(1R,4S,12aR)-N-(3-chloro-2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

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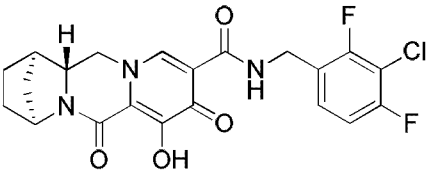


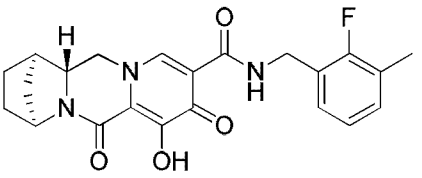
69

Compound **69** was prepared in a similar manner to compound **60** using (3-chloro-2,4-difluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 11.71 (s, 1H), 10.48 (s, 1H), 8.26 (s, 1H), 7.27 (s, 1H), 6.92 (td, 1H), 4.90 (s, 1H), 4.66 (d, 2H), 4.08 (s, 1H), 3.91 – 3.69 (m, 2H), 2.01 – 1.79 (m, 3H), 1.75 (d, 1H), 1.71 – 1.44 (m, 2H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClF_2N_3O_4$: 450.10; found: 450.27.

Example 70

Preparation of Compound **70**

(1R,4S,12aR)-N-(2-fluoro-3-methylbenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



70

Compound **70** was prepared in a similar manner to compound **60** using (2-fluoro-3-methylphenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.62 (s, 1H), 10.39 (s, 1H), 8.30 (s, 1H), 7.19 (t, 1H), 7.07 (t, 1H), 6.96 (t, 1H), 4.89 (d, 1H), 4.67 (d, 2H), 4.08 (s, 1H), 3.88 - 3.67 (m, 2H), 2.26 (d, 3H), 1.97 - 1.79 (m, 3H), 1.78 - 1.39 (m, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{23}FN_3O_4$: 412.16; found: 412.26.

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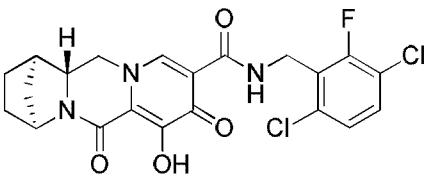
Example 71

Preparation of Compound **71**

(1R,4S,12aR)-N-(3,6-dichloro-2-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



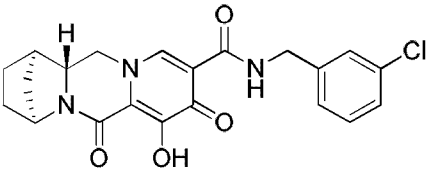
71

Compound **71** was prepared in a similar manner to compound **60** using (3,6-dichloro-2-fluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.62 (s, 1H), 10.47 (t, 1H), 8.29 (s, 1H), 7.13 (dd, 1H), 4.88 (s, 1H), 4.85 - 4.73 (m, 2H), 4.09 (d, 1H), 3.88 - 3.68 (m, 2H), 1.99 - 1.53 (m, 8H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}Cl_2FN_3O_4$: 466.07; found: 466.257.

Example 72

Preparation of Compound **72**

(1R,4S,12aR)-N-(3-chlorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



72

Compound **72** was prepared in a similar manner to compound **60** using (3-chlorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 10.44 (t, 1H), 8.38 (s, 1H), 7.42 - 7.22 (m, 4H), 4.68 (s, 1H), 4.54 (d, 2H), 4.48 (dd, 1H), 3.97 (t, 1H), 3.81 (dd, 1H), 2.58 (s, 1H), 1.87 -

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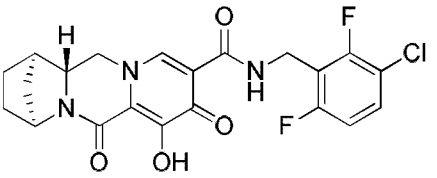
1.69 (m, 3H), 1.68 - 1.51 (m, 2H), 1.46 (d, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{21}ClN_3O_4$: 414.11; found: 414.21.

Example 73

Preparation of Compound **73**

(1R,4S,12aR)-N-(3-chloro-2,6-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



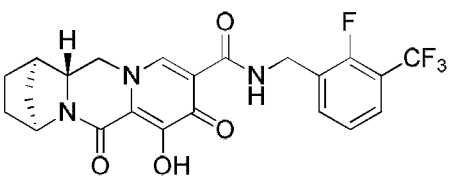
73

Compound **73** was prepared in a similar manner to compound **60** using (3-chloro-2,6-difluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.71 (s, 1H), 10.46 (t, 1H), 8.34 (s, 1H), 7.60 (td, 1H), 7.19 (td, 1H), 4.67 (s, 1H), 4.62 (d, 2H), 4.44 (dd, 1H), 3.95 (t, 1H), 3.78 (dd, 1H), 2.57 (s, 1H), 1.86 - 1.68 (m, 3H), 1.67 - 1.49 (m, 2H), 1.45 (d, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClF_2N_3O_4$: 450.10; found: 450.16.

Example 74

Preparation of Compound **74**

(1R,4S,12aR)-N-(2-fluoro-3-(trifluoromethyl)benzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



74

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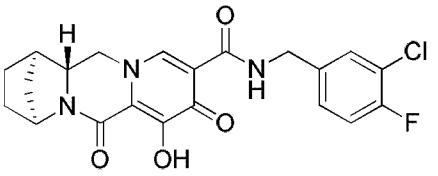
Compound **74** was prepared in a similar manner to compound **60** using (2-fluoro-3-(trifluoromethyl)phenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.76 (s, 1H), 10.48 (t, 1H), 8.36 (s, 1H), 7.68 (q, 2H), 7.38 (t, 1H), 4.68 (s, 1H), 4.65 (d, 2H), 4.47 (dd, 1H), 3.96 (t, 1H), 3.80 (dd, 1H), 2.57 (s, 1H), 1.88 - 1.69 (m, 3H), 1.67 - 1.50 (m, 2H), 1.45 (d, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{20}F_4N_3O_4$: 466.13; found: 466.142.

Example 75

Preparation of Compound **75**

(1R,4S,12aR)-N-(3-chloro-4-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



75

Compound **75** was prepared in a similar manner to compound **60** using (3-chloro-4-fluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 10.43 (t, 1H), 8.38 (s, 1H), 7.51 (dd, 1H), 7.42 - 7.28 (m, 2H), 4.68 (s, 1H), 4.51 (d, 2H), 4.47 (dd, 1H), 3.97 (t, 1H), 3.80 (dd, 1H), 2.58 (s, 1H), 1.86 - 1.68 (m, 3H), 1.68 - 1.52 (m, 2H), 1.46 (d, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}ClFN_3O_4$: 432.10; found: 432.159.

Example 76

Preparation of Compound **76**

(1R,4S,12aR)-N-((3,5-difluoropyridin-2-yl)methyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

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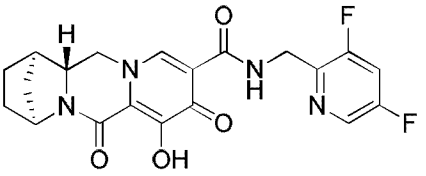


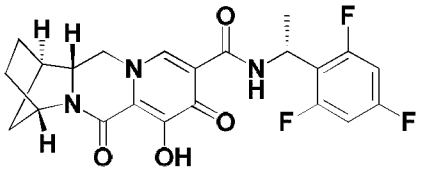
76

Compound **76** was prepared in a similar manner to compound **60** using (3,5-difluoropyridin-2-yl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.80 (s, 1H), 8.81 (s, 1H), 8.33 (d, 1H), 7.20 (td, 1H), 4.90 (s, 1H), 4.82 (s, 2H), 4.28 (d, 1H), 3.92 – 3.75 (m, 2H), 3.48 (s, 2H), 1.98 – 1.80 (m, 3H), 1.77 (d, 1H), 1.71 – 1.58 (m, 2H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{19}F_2N_4O_4$: 417.13; found: 417.189.

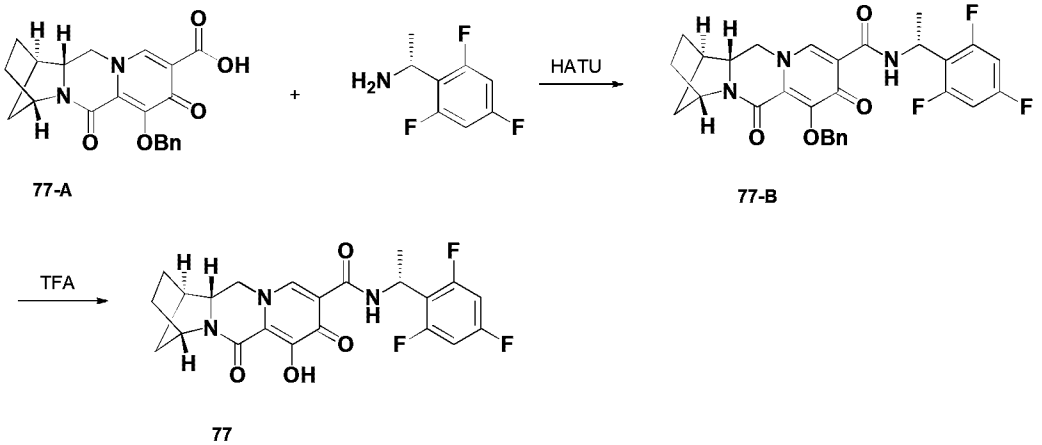
Example 77

Preparation of Compound **77**

(1R,4S,12aR)-7-hydroxy-6,8-dioxo-N-((R)-1-(2,4,6-trifluorophenyl)ethyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



77



77-A

77-B

77

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Step 1

A 50-mL round bottom flask was charged with **77-A** (0.15 g, 0.39 mmol), (*R*)-1-(2,4,6-trifluorophenyl)ethanamine (0.14 g, 0.78 mmol), N,N-diisopropylethylamine (DIPEA) (0.25 g, 1.97 mmol) and HATU (0.29 g, 0.79 mmol) in DCM (10 ml). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain **77-B** as a white solid. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 538.

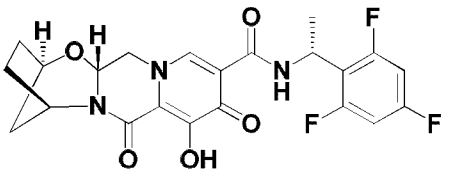
Step 2

A 50-mL round bottom flask was charged with **77-B** (0.20 g, 0.37 mmol) in TFA (2 mL). The reaction mixture was stirred at room temperature for 30 min. The solution was concentrated and the residue was purified by flash chromatography using EtOAc-20% MeOH in EtOAc as eluents to afford compound **77**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.67 (d, J = 8.2 Hz, 1H), 8.22 (s, 1H), 6.61 (t, J = 8.4 Hz, 2H), 5.60 (dd, J = 8.1, 6.9 Hz, 1H), 4.85 (s, 1H), 3.82 (t, J = 12.2 Hz, 1H), 3.71 (dd, J = 12.4, 3.4 Hz, 1H), 2.75 - 2.55 (m, 3H), 1.97 - 1.57 (m, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -109.65 - -111.29 (m), -111.76 - -113.09 (m). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 448.

Example 78

Preparation of Compound **78**

(2R,13aR)-8-hydroxy-7,9-dioxo-N-((R)-1-(2,4,6-trifluorophenyl)ethyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



78

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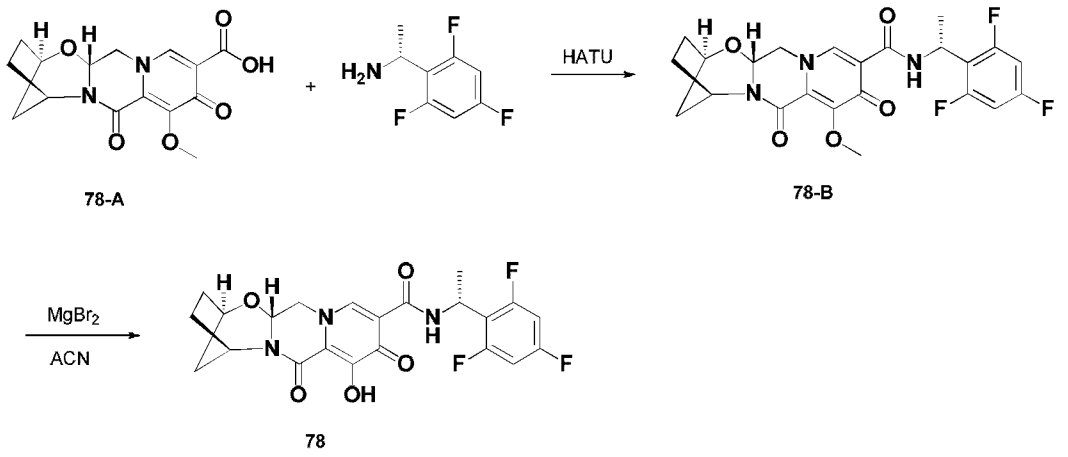

78-A

78-B

78

Step 1

A 50-mL round bottom flask was charged with **78-A** (0.30 g, 0.94 mmol), (R)-1-(2,4,6-trifluorophenyl) ethanamine (0.39 g, 1.87 mmol), N,N-diisopropylethylamine (DIPEA) (0.61 g, 4.87 mmol) and HATU (0.71 g, 1.87 mmol) in DCM (10 ml). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain **78-B** as a white solid. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$; found: 478.

Step 2

A 50-mL round bottom flask was charged with **78-B** (0.4 g, 0.84 mmol) and magnesium bromide (0.4 g, 2.2 mmol) in acetonitrile (5 mL). The reaction mixture was heated to 50 °C. After 10 minutes, the reaction mixture was cooled to 0 ^{0}C and 1 N hydrochloric acid (4 mL) was added in. More water (~ 5 mL) was added and the solid was filtrated and washed with water and dried to afford afford compound **78**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.30 (s, 1H), 10.59 (d, J = 8.3 Hz, 1H), 8.21 (s, 1H), 6.60 (t, J = 8.4 Hz, 2H), 5.59 (t, J = 7.4 Hz, 1H), 5.37 (dd, J = 9.4, 4.1 Hz, 1H), 5.31 - 5.09 (m, 1H), 4.64 (t, J = 3.0 Hz, 1H), 4.20 (dd, J = 12.9, 4.1 Hz, 2H), 3.96 (dd, J = 12.8, 9.4 Hz, 2H), 2.21 - 1.85 (m, 4H), 1.71 - 1.43 (m, 3H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -110.37 (tt, J = 8.7, 6.1 Hz), -112.19 (t, J = 7.2 Hz). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 464.

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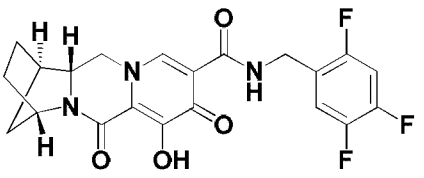
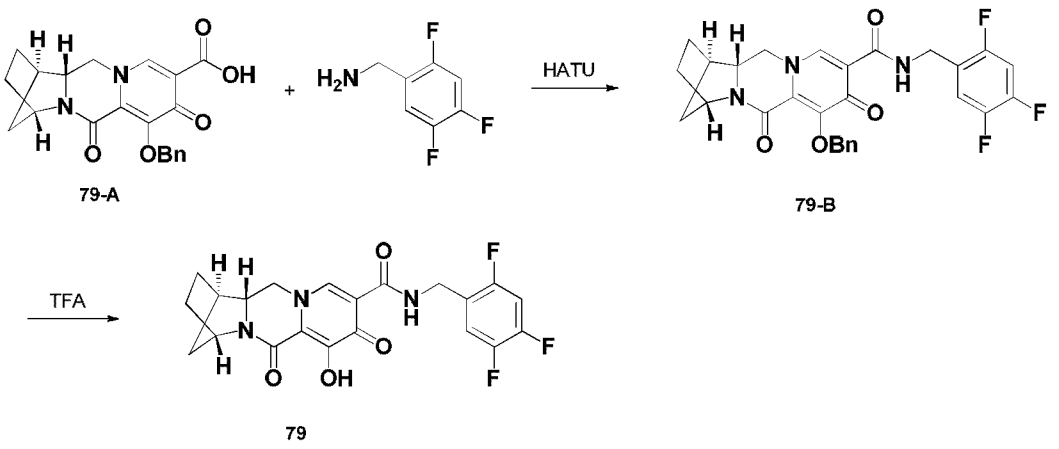
Example 79

Preparation of Compound **79**

(1R,4S,12aR)-7-hydroxy-6,8-dioxo-N-(2,4,5-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



79



Step 1

A 50-mL round bottom flask was charged with **79-A** (0.12 g, 0.32 mmol), (2,4,5-trifluorophenyl)methanamine (0.10 g, 0.63 mmol), N,N-diisopropylethylamine (DIPEA) (0.20 g, 1.58 mmol) and HATU (0.24 g, 0.63 mmol) in DCM (10 ml). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain **79-B** as a white solid. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$; found: 524.

Step 2

A 50-mL round bottom flask was charged with **79-B** (0.15 g, 0.29 mmol)

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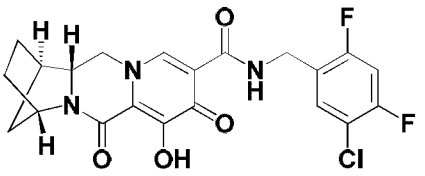
in TFA (2 mL). The reaction mixture was stirred at room temperature for 30 min. The solution was concentrated and the residue was purified by flash chromatography using EtOAc-20% MeOH in EtOAc as eluents to afford compound **79.** **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.70 (s, 1H), 10.65 - 10.18 (m, 1H), 8.27 (s, 1H), 7.26 (m, 1H), 6.90 (td, J = 9.7, 6.4 Hz, 1H), 4.89 (s, 1H), 4.60 (d, J = 6.0 Hz, 2H), 4.09 (dd, J = 11.4, 2.6 Hz, 1H), 3.96 - 3.66 (m, 2H), 2.68 (s, 1H), 2.15 - 1.43 (m, 6H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ 120.53 - -120.85 (m), -134.68 - -136.79 (m), -142.26 - -144.11 (m). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 434.

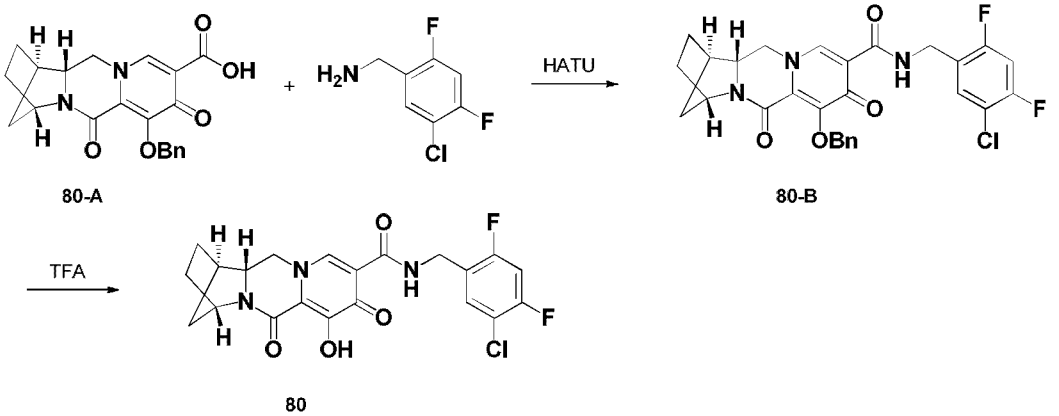
Example 80

Preparation of Compound **80**

(1R,4S,12aR)-N-(5-chloro-2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



80



Step 1

A 50-mL round bottom flask was charged with **80-A** (0.12 g, 0.32 mmol), (5-chloro-2,4-difluorophenyl)methanamine (0.11 g, 0.63 mmol), N,N-diisopropylethylamine (DIPEA) (0.20 g, 1.58 mmol) and HATU (0.24 g, 0.63 mmol) in DCM (10 ml). The reaction mixture was stirred at room temperature for 1 h. The

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reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain **80-B** as a white solid. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$; found: 541.

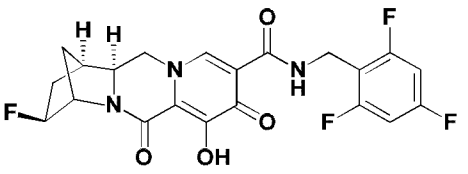
Step 2

A 50-mL round bottom flask was charged with **80-B** (0.14 g, 0.26 mmol) in TFA (2 mL). The reaction mixture was stirred at room temperature for 30 minutes. The solution was concentrated and the residue was purified by flash chromatography using EtOAc-20% MeOH in EtOAc as eluents to afford compound **80.** **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.46 (s, 1H), 8.27 (s, 1H), 7.40 (t, J = 7.8 Hz, 1H), 6.89 (t, J = 9.1 Hz, 1H), 4.90 (s, 1H), 4.78 - 4.48 (m, 2H), 4.08 (dd, J = 11.3, 2.5 Hz, 1H), 3.95 - 3.63 (m, 2H), 2.68 (s, 1H), 2.22 - 1.51 (m, 7H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -113.37 (q, J = 8.1 Hz), -116.37 (q, J = 8.0 Hz). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 451.

Example 81

Preparation of Compound **81**

(1R,3S,4S,12aS)-3-fluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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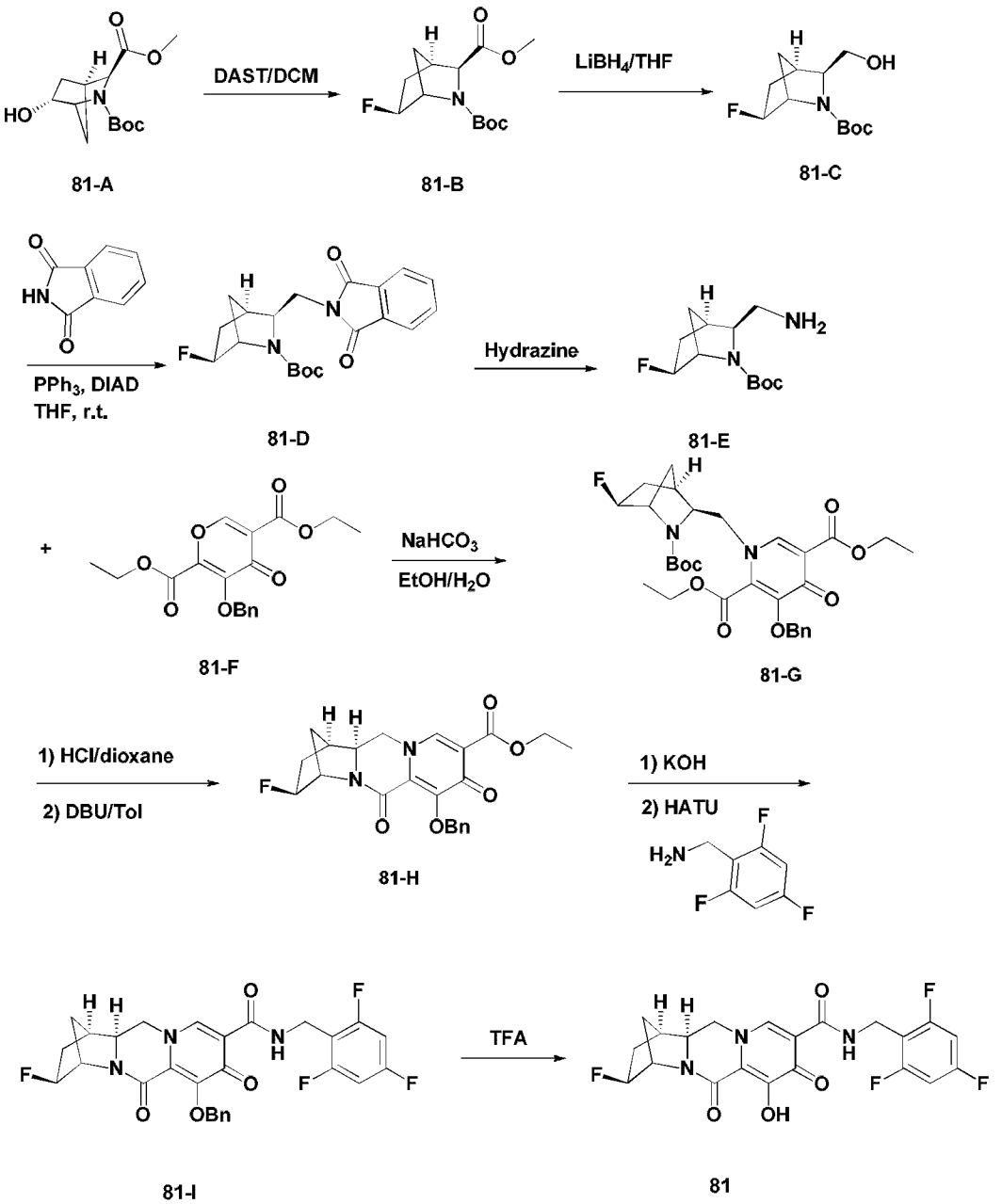

Step 1

A 100-mL round bottom flask was charged with **81-A** (1.0 g, 3.7 mmol) in DCM (10 mL). The reaction mixture was cooled to 0 ^{0}C. Diethylaminosulfur trifluoride (DAST) (0.58 mL, 4.1 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature for one hour. The mixture was cooled back to 0 ^{0}C. Saturated $NaHCO_3$ (5 mL) was added dropwise to quench the reaction. Then the reaction mixture was diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$, brine,

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and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **81-B**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 274.

Step 2

A 100-mL round bottom flask was charged with **81-B** (0.8 g, 3.0 mmol) in THF (10 mL). The reaction mixture was stirred at -78 ^{0}C. 2.0 M $LiBH_4$ in THF (3.2 mL, 6.4 mmol) was slowly added in. Then the reaction mixture was warmed up and stirred at room temperature for 3 hours. Then the reaction mixture was diluted with EtOAc (100 mL) and treated slowly with water (H_2 evolution). After the two phases were separated, the aqueous fraction was extracted with EtOAc and the two organic fractions were combined, washed with water, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **81-C**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 246.

Step 3

A 100-mL round bottom flask was charged with **81-C** (0.57 g, 2.3 mmol), triphenylphosphine (1.3 g, 5.1 mmol) and phthalimide (0.55 g, 3.7 mmol) in THF (15 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. Diisopropyl azodicarboxylate (DIAD) (1.0 mL, 5.1 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **81-D**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 375.

Step 4

To a solution of **81-D** (0.8 g, 2.1 mmol) EtOH (40 mL) was added hydrazine monohydrate (0.6 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **81-E**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 245.

Step 5

A 100-mL round bottom flask was charged with **81-E** (0.49 g, 2.0 mmol)

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and **81-F** (0.7 g, 2.0 mmol) in ethanol (7 mL). Sodium bicarbonate (0.34 g, 4.0 mmol) in water (7 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for overnight. The mixture was diluted with EtOAc (50 mL) and washed with water (2 x). The aqueous fractions were extracted with EtOAc (1 x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **81-G** was used for next step without further purification. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 573.

Step 6

A 100-mL round bottom flask was charged with **81-G** (1.1 g, 1.9 mmol) in 4 N HCl /dioxane (11 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 1.0 g intermediate was obtained. The intermediate and DBU (1.3 g, 8.8 mmol) were dissolved in toluene (10 mL). The reaction mixture was heated to 110 ^{0}C with stirring for 1 hour. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **81-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 413.

Step 7

A 100-mL round bottom flask was charged with **81-H** (0.56 g, 1.4 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (4 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (4 mL). After concentration, the residue was co-evaporated with toluene (3 x). Half of the crude acid, 2,4,6-trifluobenzylamine (0.2 g, 1.3 mmol), N,N-diisopropylethylamine (DIPEA) (0.41 g, 3.1 mmol) and HATU (0.48 g, 1.25 mmol) were dissolved in DMF (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **81-I**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 542.

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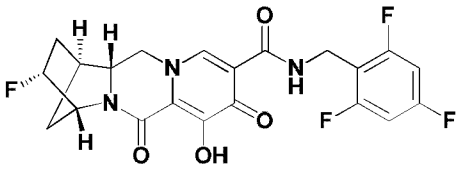
Step 8

A 50-mL round bottom flask was charged with **81-I** (0.31 g, 0.58 mmol) in TFA (3 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **81**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.29 (s, 1H), 8.31 (s, 1H), 6.65 (dd, J = 8.7, 7.5 Hz, 2H), 5.05 - 4.75 (m, 2H), 4.65 (d, J = 5.6 Hz, 2H), 4.11 (d, J = 12.2 Hz, 1H), 3.83 (t, J = 12.3 Hz, 1H), 3.56 (dd, J = 12.3, 3.3 Hz, 1H), 2.77 (s, 1H), 2.25 - 1.97 (m, 2H), 1.95 (d, J = 11.0 Hz, 2H), 1.77 (d, J = 11.2 Hz, 1H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -108.98 (t, J = 8.2 Hz), -112.03 (t, J = 7.2 Hz), -168.00. **LCMS-ESI$^+$** (*m/z*): found: 452.

Example 82

Preparation of Compound **82**

(1S,3R,4R,12aR)-3-fluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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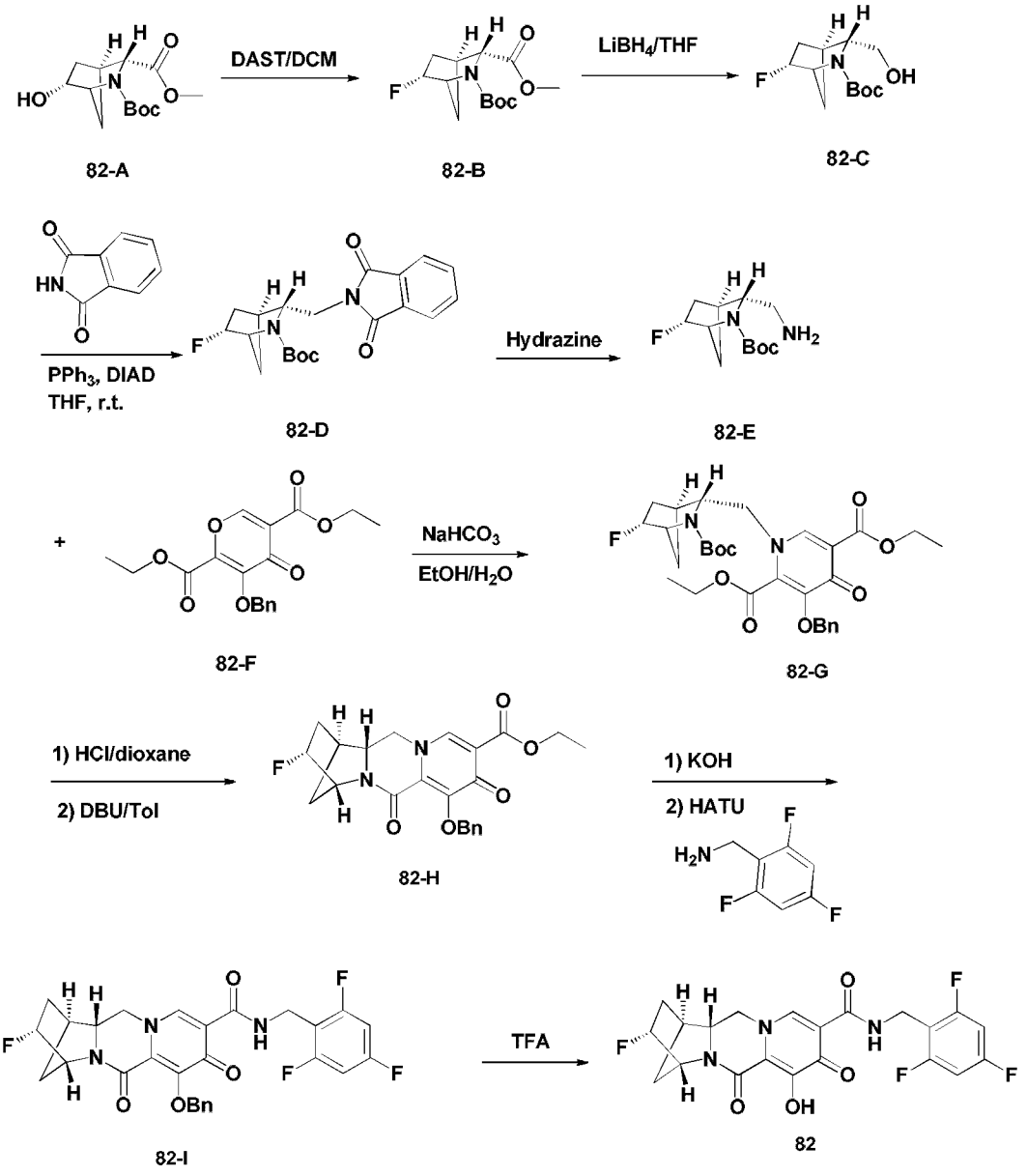

Step 1

A 100-mL round bottom flask was charged with **82-A** (0.6 g, 2.1 mmol) in DCM (6 mL). The reaction mixture was cooled to 0 ^{0}C. DAST (0.35 mL, 3.0 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature for one hour. The mixture was cooled back to 0 ^{0}C. Saturated $NaHCO_3$ (5 mL) was added drop wise to quench the reaction. Then the reaction mixture was diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to

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afford **82-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 274.

Step 2

A 100-mL round bottom flask was charged with **82-B** (0.4 g, 1.5 mmol) in THF (10 mL). The reaction mixture was stirred at -78 ^{0}C. 2.0 M $LiBH_4$ in THF (1.6 mL, 3.2 mmol) was slowly added in. Then the reaction mixture was warmed up and stirred at room temperature for 3 hours. Then the reaction mixture was diluted with EtOAc (100 mL) and added water slowly (H_2 evolution). After the two phases were separated, the aqueous fraction was extracted with EtOAc and the two organic fractions were combined, washed with water and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **82-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 246.

Step 3

A 100-mL round bottom flask was charged with **82-C** (0.25 g, 1.0 mmol), triphenylphosphine (0.59 g, 2.2 mmol) and phthalimide (0.24 g, 1.6 mmol) in THF (10 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (0.44 mL, 2.2 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **82-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 375.

Step 4

To a solution of **82-D** (0.35 g, 0.9 mmol) EtOH (20 mL) was added hydrazine monohydrate (0.3 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **82-E**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 245.

Step 5

A 100-mL round bottom flask was charged with **82-E** (0.21 g, 0.87 mmol) and **82-F** (0.3 g, 0.87 mmol) in ethanol (7 mL). Sodium bicarbonate (0.15 g, 1.7 mmol) in water (7 mL) was added to the reaction mixture. Then the reaction mixture

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was stirred at room temperature for overnight. The mixture was diluted with EtOAc (50 mL) and washed with water (2 x). The aqueous fractions were extracted with EtOAc, and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **82-G** was used for next step without further purification. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 573.

Step 6

A 100-mL round bottom flask was charged with **82-G** (0.49 g, 0.86 mmol) in 4 N HCl /dioxane (5 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 0.4 g intermediate was obtained. The intermediate and DBU (0.6 g, 4.0 mmol) were dissolved in toluene (10 mL). The reaction mixture was heated to 110 ^{0}C with stirring for 1 hour. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **82-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 413.

Step 7

A 100-mL round bottom flask was charged with **82-H** (0.2 g, 0.49 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (1.5 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (1.5 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid, 2,4,6-trifluobenzylamine (0.15 g, 0.95 mmol), N,N-diisopropylethylamine (DIPEA) (0.31 g, 2.4 mmol) and HATU (0.36 g, 0.95 mmol) were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **82-I**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 542.

Step 8

A 50-mL round bottom flask was charged with **82-I** (0.22 g, 0.41 mmol) in TFA (3 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel

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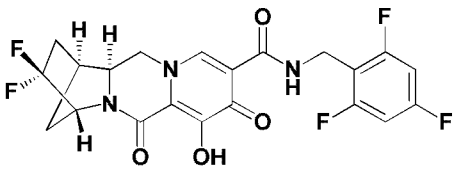
with EtOAc-MeOH to afford compound **82**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.25 (s, 1H), 8.28 (s, 1H), 6.65 (s, 2H), 5.15 - 4.77 (m, 2H), 4.65 (s, 2H), 4.32 - 3.41 (m, 2H), 2.78 (s, 1H), 1.86 (dd, J = 144.8, 72.3 Hz, 6H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -108.98 (t, J = 8.2 Hz), -112.03 (t, J = 7.2 Hz), -168.00. **LCMS-ESI$^+$** (*m/z*): found: 452.

Example 83

Preparation of Compound **83**

(1S,4R,12aS)-3,3-difluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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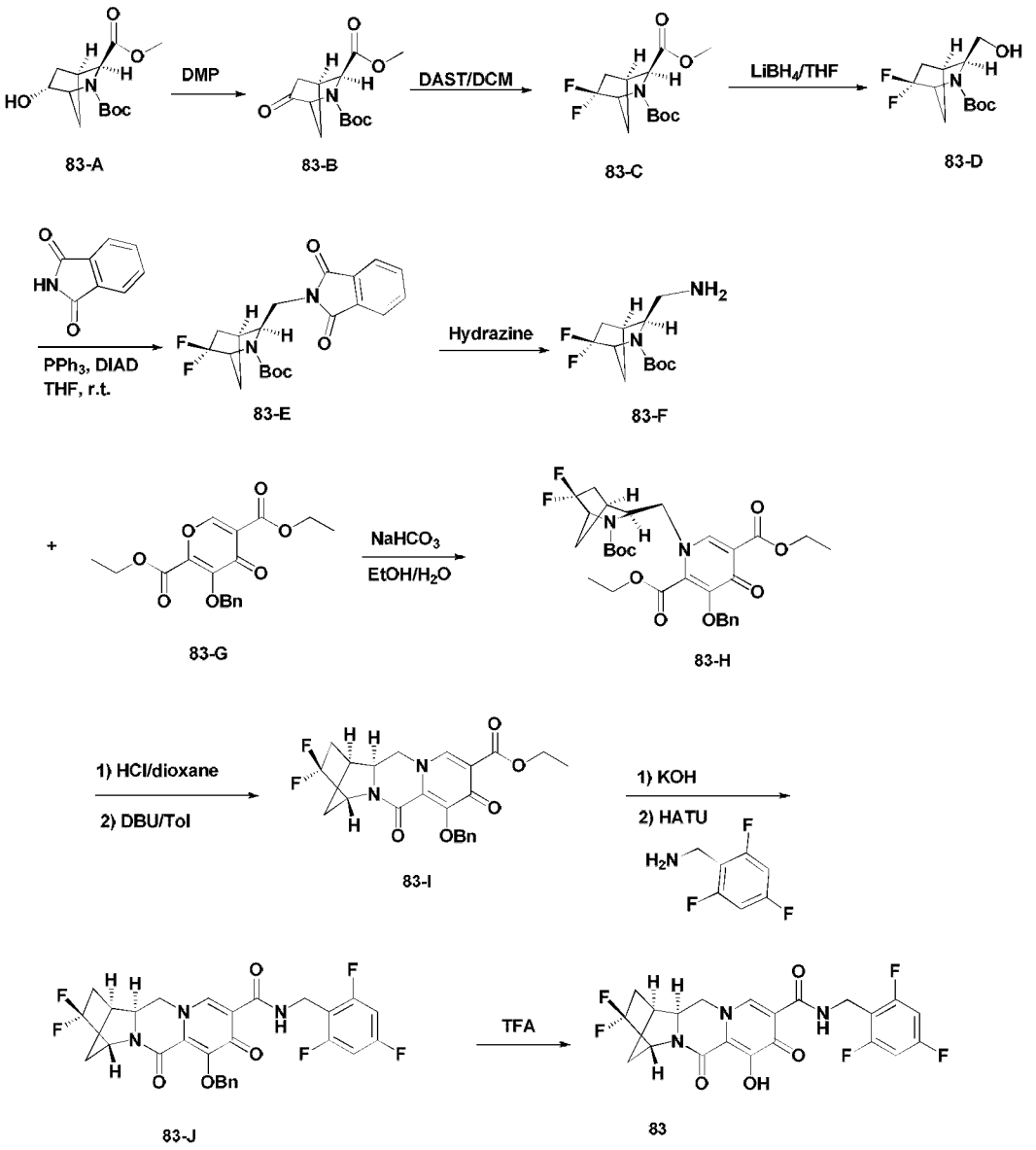

Step 1

A 100-mL round bottom flask was charged with **83-A** (1.0 g, 3.7 mmol) in DCM (20 mL). The reaction mixture was cooled to 0 ^{0}C. Dess-Martin periodinane (1.8 g, 4.2 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature for 3 hours. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 270.

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Step 2

A 100-mL round bottom flask was charged with **83-B** (0.85 g, 3.2 mmol) in DCM (15 mL). The reaction mixture was cooled to 0 ^{0}C. DAST (1.5 mL, 11.3 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature overnight. The mixture was cooled back to 0 ^{0}C. Saturated $NaHCO_3$ (5 mL) was added dropwise to quench the reaction. Then the reaction mixture was diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-C**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 292.

Step 3

A 100-mL round bottom flask was charged with **83-C** (0.44 g, 1.5 mmol) in THF (6 mL). The reaction mixture was stirred at -78 ^{0}C. 2.0 M $LiBH_4$ in THF (1.6 mL, 3.2 mmol) was slowly added in. Then the reaction mixture was warmed up and stirred at room temperature for 3 hours. Then the reaction mixture was diluted with EtOAc (100 mL) and added water slowly (H_2 evolution). After the two phases were separated, the aqueous fraction was extracted with EtOAc and the two organic fractions were combined, washed with water, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-D**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 264.

Step 4

A 100-mL round bottom flask was charged with **83-D** (0.17 g, 0.65 mmol), triphenylphosphine (0.37 g, 1.4 mmol) and phthalimide (0.15 g, 1.0 mmol) in THF (10 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (0.28 mL, 1.4 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-E**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 393.

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Step 5

To a solution of **83-E** (0.25 g, 0.64 mmol) EtOH (20 mL) was added hydrazine monohydrate (0.3 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **83-F**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 263.

Step 6

A 100-mL round bottom flask was charged with **83-F** (0.18 g, 0.69 mmol) and **83-G** (0.324g, 0.69 mmol) in ethanol (7 mL). Sodium bicarbonate (0.12 g, 1.4 mmol) in water (7 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc (50 mL) and washed with water. The aqueous fractions were extracted with EtOAc, and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **83-H** was used for next step without further purification. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 591.

Step 7

A 100-mL round bottom flask was charged with **83-H** (0.4 g, 0.68 mmol) in 4 N HCl /dioxane (3.8 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 0.35 g intermediate was obtained. The intermediate and DBU (0.51 g, 3.3 mmol) were dissolved in toluene (10 mL). The reaction mixture was heated to 110 ^{0}C with stirring for 1 hour. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-I**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 431.

Step 8

A 100-mL round bottom flask was charged with **83-I** (0.2 g, 0.47 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (1.4 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (1.4 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid, 2,4,6-trifluobenzylamine (0.14 g, 0.91 mmol), N,N-diisopropylethylamine (DIPEA) (0.29 g, 2.2 mmol) and

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HATU (0.35 g, 0.91 mmol) were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **83-J**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 560.

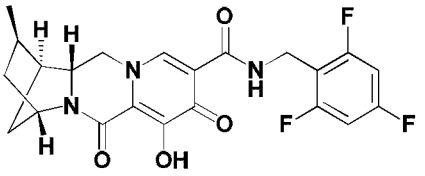
Step 9

A 50-mL rbf was charged with **83-J** (0.18 g, 0.32 mmol) in TFA (3 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **83** as a white solid. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.29 (d, J = 6.1 Hz, 1H), 8.34 (s, 1H), 6.65 (dd, J = 8.7, 7.5 Hz, 2H), 4.83 (s, 1H), 4.72 - 4.58 (m, 2H), 4.36 - 4.10 (m, 2H), 4.05 (t, J = 11.5 Hz, 1H), 2.97 (d, J = 4.4 Hz, 1H), 2.49 - 2.08 (m, 3H), 2.12 - 1.94 (m, 2H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ - 92.32 (ddd, J = 225.6, 22.5, 9.1 Hz), -107.64 - -109.54 (m), -112.05 (t, J = 7.0 Hz), -114.67 (d, J = 226.7 Hz). **LCMS-ESI**$^+$ (*m/z*): found: 470.

Example 84

Preparation of Compound **84**

(1S,2R,4S,12aR)-7-hydroxy-2-methyl-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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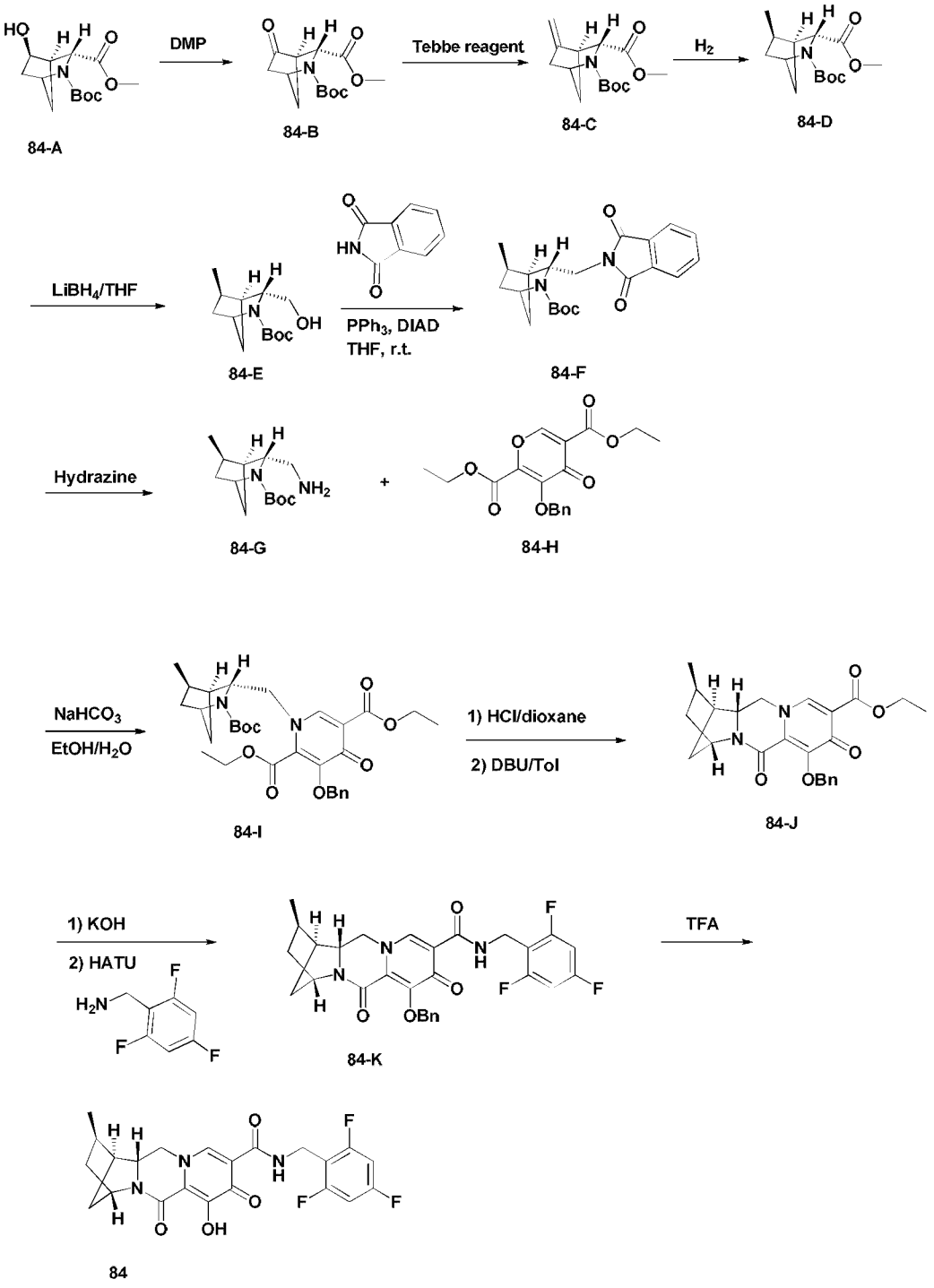

Step 1

A 100-mL round bottom flask was charged with **84-A** (1.6 g, 5.9 mmol) in DCM (20 mL). The reaction mixture was cooled to 0 ^{0}C. Dess-Martin periodinane (4.9 g, 11.7 mmol) was slowly added in. Then the reaction mixture was stirred at room

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temperature for 3 hours. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **84-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 270.

Step 2

A 100-mL round bottom flask was charged with **84-B** (1.3 g, 4.8 mmol) in THF (30 mL). The reaction mixture was cooled to 0 ^{0}C. Tebbe reagent (0.5 M in toluene, 19.4 mL, 9.7 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature for 2 hours. The mixture was cooled back to 0 ^{0}C. Saturated $NaHCO_3$ (5 mL) was added drop wise to quench the reaction. The reaction mixture was stirred at room temperature for another 15 minutes and filtered through celite. The filtered cake was washed with DCM (2 x). The combined filtrates were concentrated in vacuum and the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **84-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 268.

Step 3

To a solution (purged with N_2) of **84-C** (0.9 g, 3.4 mmol) in EtOH (20 mL) was added Pd/C (0.18 g). The mixture was stirred under H_2 for 3 hours. The mixture was filtered through celite and the filtrate was concentrated to afford **84-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 270.

Step 4

A 100-mL round bottom flask was charged with **84-D** (0.9 g, 3.3 mmol) in THF (6 mL). The reaction mixture was stirred at -78 ^{0}C. 2.0 M $LiBH_4$ in THF (13.2 mL, 26.4 mmol) was slowly added in. Then the reaction mixture was warmed up and stirred at room temperature for 3 hours. Then the reaction mixture was diluted with EtOAc (100 mL) and added water slowly (H_2 evolution). After the two phases were separated, the aqueous fraction was extracted with EtOAc and the two organic fractions were combined, washed with water, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **84-E**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 242.

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Step 5

A 100-mL round bottom flask was charged with **84-E** (0.4 g, 1.66 mmol), triphenylphosphine (0.96 g, 3.6 mmol) and phthalimide (0.39 g, 2.7 mmol) in THF (15 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (0.7 mL, 3.6 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **84-F**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 371.

Step 6

To a solution of **84-F** (0.55 g, 1.5 mmol) EtOH (20 mL) was added hydrazine monohydrate (0.3 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **84-G**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 241.

Step 7

A 100-mL round bottom flask was charged with **84-G** (0.35 g, 1.4 mmol) and **84-H** (0.5g, 1.4 mmol) in ethanol (10 mL). Sodium bicarbonate (0.24 g, 2.8 mmol) in water (10 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for overnight. The mixture was diluted with EtOAc (50 mL) and washed with water (2 x). The aqueous fractions were extracted with EtOAc, and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **84-I** was used for next step without further purification. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 583.

Step 8

A 100-mL rbf was charged with **84-I** (0.84 g, 1.4 mmol) in 4 N HCl /dioxane (8.2 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 0.74 g intermediate was obtained. The intermediate and DBU (1.1 g, 7.2 mmol) were dissolved in toluene (10 mL). The reaction mixture was heated to 110 ^{0}C with stirring for 1 hour. After concentration, the residue was purified by flash

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chromatography using hexanes - EtOAc as eluents to afford **84-J**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 409.

Step 9

A 100-mL round bottom flask was charged with **84-J** (0.4 g, 0.98 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (3.0 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (3.0 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid, 2,4,6-trifluobenzylamine (0.32 g, 1.96 mmol), N,N-diisopropylethylamine (DIPEA) (0.63 g, 4.9 mmol) and HATU (0.74 g, 1.9 mmol) were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **84-K**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 538.

Step 10

A 50-mL round bottom flask was charged with **84-K** (0.5 g, 0.93 mmol) in TFA (6 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **84**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.37 (s, 1H), 8.28 (s, 1H), 6.65 (t, J = 8.1 Hz, 2H), 4.80 (s, 1H), 4.77 - 4.52 (m, 3H), 4.08 (d, J = 13.1 Hz, 1H), 3.88 (d, J = 12.3 Hz, 1H), 2.47 (d, J = 3.2 Hz, 1H), 2.35 (s, 1H), 2.16 (ddd, J = 14.3, 11.2, 3.6 Hz, 1H), 1.93 - 1.57 (m, 3H), 1.29 - 1.19 (m, 1H), 1.17 (d, J = 7.0 Hz, 3H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -109.24 , -111.98. **LCMS-ESI**$^+$ (*m/z*): found: 448.

Example 85

Preparation of Compound **85**

(6aS,7R,11S)-1-hydroxy-2,13-dioxo-N-(2,4,6-trifluorobenzyl)-6,6a,7,8,9,10,11,13-octahydro-2H-7,11-methanopyrido[1',2':4,5]pyrazino[1,2-a]azepine-3-carboxamide

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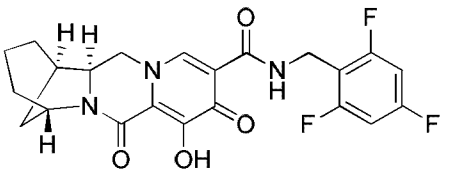

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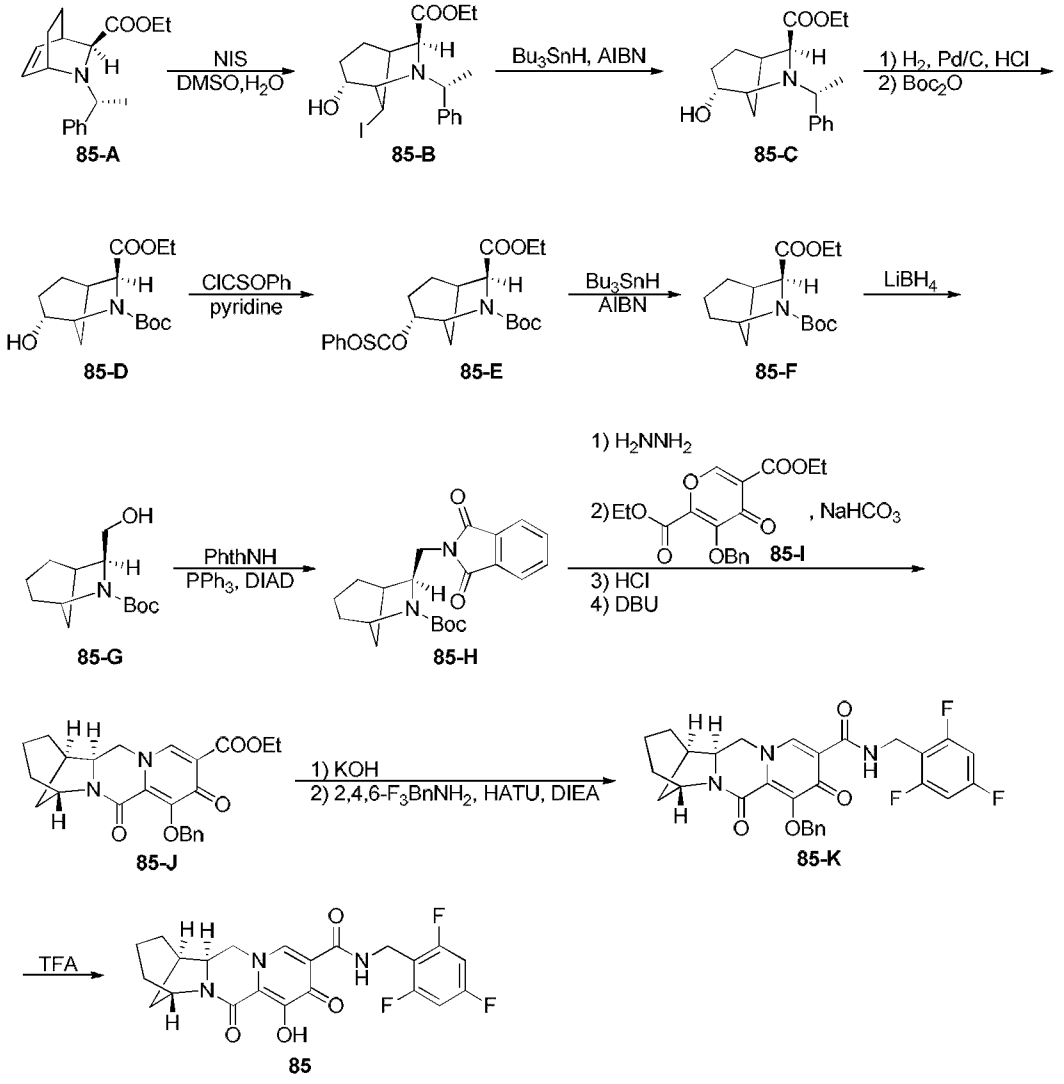

Step 1

A solution of **85-A** (1100 mg, 3.855 mmol) in DMSO (6 mL) and water (0.75 mL) was stirred at room temperature as N-iodosuccinmide (885 mg, 3.934 mmol) was added. After 2 h, additional N-iodosuccinmide (88 mg, 0.391 mmol) was added and the resulting mixture was stirred at room temperature for 1.5 h. The dark brown reaction mixture was diluted with EtOAc, and washed with a mixture of 10 % aq.

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$Na_2S_2O_3$ solution and aq. $NaHCO_3$ solution (~1:4 mixture) and then with water (with some brine). After the aqueous fractions were extracted with EtOAc, the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to obtain **85-B**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.51 - 7.44 (m, 2H), 7.33 - 7.17 (m, 3H), 4.22 - 4.05 (m, 2H), 4.02 - 3.86 (m, 2H), 3.77 (d, J = 5.3 Hz, 1H), 3.54 - 3.44 (m, 1H), 3.27 (t, J = 4.5 Hz, 1H), 2.75 - 2.66 (m, 1H), 2.30 (dddd, J = 14.8, 13.1, 7.2, 5.8 Hz, 1H), 2.14 (dddd, J = 14.8, 13.0, 6.1, 2.1 Hz, 1H), 1.97 (d, J = 8.9 Hz, 1H), 1.58 - 1.46 (m, 1H), 1.45 - 1.34 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{25}INO_3$: 430.1; found**:** 430.0.

Step 2

A solution of **85-B** (993 mg, 2.313 mmol), AIBN (305 mg, 1.857 mmol), and tributyltin hydride (1392 mg, 4.799 mmol) in toluene (15 mL) was stirred at 100 °C. After 2 h, the reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with water and brine. After the aqueous fractions were extracted with EtOAc, the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to obtain **85-C**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.57 - 7.49 (m, 2H), 7.32 - 7.23 (m, 2H), 7.23 - 7.15 (m, 1H), 4.24 - 4.02 (m, 2H), 3.97 (q, J = 6.7 Hz, 1H), 3.83 (d, J = 5.1 Hz, 1H), 3.48 (t, J = 4.6 Hz, 1H), 3.19 - 3.04 (m, 1H), 2.58 (p, J = 4.0 Hz, 1H), 2.30 (dddd, J = 14.7, 13.1, 7.0, 4.5 Hz, 1H), 1.98 (d, J = 11.2 Hz, 1H), 1.64 (tdd, J = 13.3, 6.2, 2.6 Hz, 1H), 1.49 - 1.33 (m, 3H), 1.37 (d, J = 6.7 Hz, 3H), 1.32 - 1.26 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{26}NO_3$: 304.2; found**:** 304.1.

Step 3

A mixture of **85-C** (725 mg, 2.39 mmol) and 20% $Pd(OH)_2/C$ (351 mg) in EtOH (25 mL) and 4 N HCl in dioxane (0.9 mL) was stirred under H_2 atmosphere. After 2 h, the reaction mixture was filtered, and the filtrate was concentrated. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{10}H_{18}NO_3$: 200.13; found**:** 200.1. After the residue was co-evaporated with toluene (x 2), the residue and Boc_2O

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(720 mg, 3.299 mmol) in THF (15 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (1.2 mL, 6.889 mmol) was added. After 1 h, the reaction mixture was diluted with water and extracted with EtOAc (x 2). After the organic extracts were washed with water, the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash using hexanes - EtOAc as eluents to obtain **85-D** which appears to be a mixture of rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.42 - 3.97 (m, 5H), 2.62 (d, J = 5.6 Hz, 1H), 2.45 - 2.26 (m, 1H), 2.25 - 2.15 (m, 1H), 1.80 (td, J = 13.7, 6.7 Hz, 1H), 1.66 (dd, J = 12.3, 6.6 Hz, 2H), 1.55 – 1.70 (m, 2H), 1.47 (s, 2H), 1.42 (s, 7H), 1.28 (dt, J = 9.5, 7.1 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{26}NO_5$: 300.2; found**:** 299.7.

Step 4

To a solution of **85-D** (568 mg, 1.897 mmol) and pyridine (0.25 mL, 3.091 mmol) in THF (5 mL) was added phenyl chlorothionoformate (0.3 mL, 2.169 mmol) at 0 °C, which produced insoluble material quickly. After ~30 min at 0 °C, additional pyridine (0.3 mL, 3.709 mmol) and phenyl chlorothionoformate (0.3 mL, 2.169 mmol) were added. After 1.5 h at 0 °C and 1 h at room temperature, the mixture was concentrated, and the residue was dissolved in EtOAc and water. After separation of two layers, the organic fraction was washed with ~0.1 N HCl, saturated aqueous $NaHCO_3$, and brine . After the aqueous fractions were extracted with EtOAc, the combined organic fractions were dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using EtOAc/hexanes as eluents to afford **85-E**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.47 - 7.37 (m, 2H), 7.30 (t, J = 6.9 Hz, 1H), 7.11 (dd, J = 8.0, 4.0 Hz, 2H), 5.54 (dt, J = 9.0, 4.9 Hz, 1H), 4.50 (dt, J = 9.8, 5.3 Hz, 1H), 4.35 (dd, J = 21.4, 5.0 Hz, 1H), 4.30 - 4.14 (m, 2H), 2.71 (s, 1H), 2.54 (s, 1H), 2.14 - 2.00 (m, 1H), 1.82 (m, 3H), 1.54 (m, 1H), 1.48 (s, 4.5H), 1.45 (s, 4.5H), 1.30 (dt, J = 9.4, 7.1 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{30}NO_6S$: 436.2; found**:** 435.8.

Step 5

A mixture of **85-E** (602 mg, 1.382 mmol), AIBN (182 mg, 1.108 mmol), and tributyltin hydride (608 mg, 2.096 mmol) in toluene (8 mL) was stirred at 100 °C. After 1 h, the reaction mixture was concentrated and the residue was dissolved in

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EtOAc before washing with water and brine. After the aqueous fractions were extracted with EtOAc, the combined organic fractions were dried (Na_2SO_4) and concentrated. The residue was purified with flash chromatography using EtOAc/hexanes as eluents to give **85-F** which appears to be a mixture of rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.37 - 4.06 (m, 4H), 2.69 - 2.53 (m, 1H), 2.11 (m, 1H), 1.97 (m,0.65H), 1.93 - 1.80 (m, 1.35H), 1.54 (s, 5H), 1.46 (s, 3.15H), 1.42 (s, 5.85H), 1.27 (m, 3H). **LCMS-ESI$^+$** (*m/z*): $[M-C_4H_8+H]^+$ calculated for $C_{11}H_{18}NO_4$: 228.1; found**:** 227.9.

Step 6

85-F (420 mg) was repurified and the purified **85-F** in THF (3 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (1.5 mL) was added. After 5 min, the mixture was stirred at room temperature for 17 h and additional 2.0 M $LiBH_4$ in THF (1.5 mL) was added at room temperature. After 23 h at room temperature, additional 2.0 M $LiBH_4$ in THF (3 mL) was added and the resulting mixture was stirred for ~72 h. After the reaction mixture was stirred at 0 °C as water was slowly added and further diluted with water, the product was extracted with EtOAc (x 2). The extracts were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexane - EtOAc as eluents to give **85-G**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.12 (t, J = 5.3 Hz, 1H), 3.99 (dd, J = 12.0, 7.9 Hz, 1H), 3.85 (dd, J = 8.0, 4.7 Hz, 1H), 3.73 (dd, J = 11.9, 1.4 Hz, 1H), 2.28 (d, J = 4.6 Hz, 1H), 1.90 - 1.73 (m, 2H), 1.68 - 1.45 (m, 6H), 1.47 (s, 9H), 1.43 - 1.33 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M-C_4H_8+H]^+$ calculated for $C_9H_{16}NO_3$: 186.1; found**:** 186.0.

Step 7

A solution of **85-G** (198 mg, 0.820 mmol), phthalimide (200 mg, 1.359 mmol), and PPh_3 (488 mg, 1.861 mmol) in THF (10 mL) was stirred at 0 °C bath as DIAD (0.36 mL, 1.828 mmol) was added. After 30 min at 0 °C, the mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated and the residue was purified by flash chromatography using hexane-EtOAc as eluents to **85-H** which appears to be a mixture of rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 5.4, 3.1 Hz, 2H), 7.69 (dd, J = 5.4, 3.1 Hz, 2H), 4.46 (s, 1H), 4.19 (m, 2H), 3.95 (s, 1H),

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2.31 - 2.14 (m, 1H), 2.05 (d, J = 16.5 Hz, 1H), 1.84 (m, 2H), 1.79 - 1.70 (m, 1H), 1.66 (m, 1H), 1.61 - 1.30 (m, 12H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{27}N_2O_4$: 371.2; found**:** 370.8.

Step 8

To a solution of **85-H** (270 mg, 0.729 mmol) in EtOH (12 mL) was added hydrazine hydrate (0.145 mL, 3.083 mmol) at room temperature and the resulting solution was stirred at 70 °C. After 1.5 h, the mixture was cooled to 0 °C and diluted with ether (30 mL) before stirring for 1 h at 0 °C. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 and filtered to remove some insoluble material. The resulting filtrate was concentrated. The residue, combined with **85-I** (257 mg, 0.742 mmol), and $NaHCO_3$ (131 mg, 1.559 mmol) in water (3 mL) and EtOH (3 mL) was stirred at room temperature. After 1 h, the mixture was diluted with water and extracted with EtOAc (x 2). After the extracts were washed with water, the organic extracts were combined, dried (Na_2SO_4), and concentrated. To a solution of the residue in CH_2Cl_2 (2 mL) was added 4 N HCl in dioxane (6 mL). After 1.5 h at room temperature, the solution was concentrated and co-evaporated with toluene. A mixture of the residue and DBU (0.6 mL, 4.012 mmol) in toluene (5 mL) was stirred at 100 °C bath. After 1 h, additional DBU (0.3 mL, 2.006 mmol) was added and the mixture was stirred another 1 h at 100 °C. After the mixture was concentrated, the residue was purified by flash chromatography using EtOAc - 20% MeOH/EtOAc as eluents to give **85-J**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.71 - 7.62 (m, 2H), 7.36 - 7.29 (m, 2H), 7.29 - 7.23 (m, 1H), 5.44 (d, J = 9.8 Hz, 1H), 5.10 (d, J = 9.8 Hz, 1H), 4.44 - 4.28 (m, 3H), 4.23 (t, J = 13.0 Hz, 1H), 3.99 (ddt, J = 10.2, 6.3, 3.6 Hz, 2H), 2.44 - 2.36 (m, 1H), 2.29 (dt, J = 11.6, 5.3 Hz, 1H), 1.84 (dt, J = 10.8, 5.3 Hz, 2H), 1.77 - 1.61 (m, 3H), 1.57 (d, J = 11.7 Hz, 1H), 1.48 (ddd, J = 20.9, 12.3, 5.5 Hz, 1H), 1.38 (t, J = 7.1 Hz, 3H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{27}N_2O_5$: 423.2; found**:** 423.3.

Step 9

A mixture of **85-J** (214 mg, 0.507 mmol) in THF (4 mL) and MeOH (4 mL) was stirred at room temperature as 1 N KOH (1.1 mL) was added. After 30 min,

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the reaction mixture was concentrated to ~1 mL, acidified with 1 N HCl (~1.2 mL), and diluted with brine before extraction with CH_2Cl_2 (20 mL x 2). The combined extracts were dried (Na_2SO_4) and concentrated to obtain the crude acid. **LCMS-ESI$^+$** (*m/z*): [M +H]$^+$ calculated for $C_{22}H_{23}N_2O_5$: 395.2; found**:** 395.3.

A mixture of the crude acid (199 mg, 0.505 mmol), 2,4,6-trifluorobenzyl amine (130 mg, 0.807 mmol), and HATU (304 mg, 0.800 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (0.62 mL, 3.559 mmol) was added. After 30 min, the reaction mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqueous NH_4Cl (x 2), saturated aqueous $NaHCO_3$ (x 2), and brine. After the aqueous fractions were extracted with EtOAc, two organic fractions were combined, dried (Na_2SO_4) and concentrated. The residue was purified by flash using EtOAc-20%MeOH/EA as eluents to obtain **85-K**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.40 (t, J = 5.7 Hz, 1H), 8.42 (s, 1H), 7.68 - 7.54 (m, 2H), 7.33 (ddd, J = 7.7, 6.3, 1.5 Hz, 2H), 7.30 - 7.26 (m, 1H), 6.74 - 6.60 (m, 2H), 5.37 (d, J = 10.0 Hz, 1H), 5.17 (d, J = 10.0 Hz, 1H), 4.76 - 4.57 (m, 2H), 4.46 (dd, J = 6.0, 4.3 Hz, 1H), 4.34 (t, J = 12.4 Hz, 1H), 4.07 (dd, J = 12.4, 3.6 Hz, 1H), 3.91 (dt, J = 12.4, 3.9 Hz, 1H), 2.52 - 2.44 (m, 1H), 2.32 (dd, J = 11.8, 6.2 Hz, 1H), 1.92 (dt, J = 10.7, 5.4 Hz, 1H), 1.83 - 1.70 (m, 3H), 1.67 (d, J = 11.7 Hz, 1H), 1.52 (dddt, J = 25.5, 17.0, 11.8, 5.3 Hz, 2H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -109.15 (dq, J = 15.0, 7.5, 7.1 Hz, 1F), -111.85 (t, J = 6.8 Hz, 2F). **LCMS-ESI$^+$** (*m/z*): [M +H]$^+$ calculated for $C_{29}H_{27}F_3N_3O_4$: 538.2; found**:** 538.3.

Step 10

85-K (187 mg, 0.348 mmol) was dissolved in trifluoroacetic acid (3 mL) at room temperature and stirred at room temperature. After 1 h, the solution was concentrated and the residue was dissolved in CH_2Cl_2. After the solution was washed with 0.1 N HCl, the aqueous fraction was extracted with CH_2Cl_2 (x 2). The organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using CH_2Cl_2-20% MeOH in CH_2Cl_2 as eluents to obtain 150 mg (96%) of compound **85**. Compound **85** was further purified by recrystallization from methanol (10 mL) to give compound **85**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 10.39 (t, J = 5.7 Hz, 1H), 8.36 (s, 1H), 6.74 - 6.48 (m, 2H), 4.64 (d, J = 5.7 Hz,

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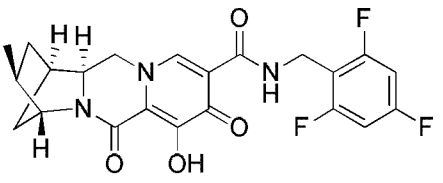
2H), 4.59 (dd, J = 6.1, 4.4 Hz, 1H), 4.36 - 4.18 (m, 2H), 4.12 (dt, J = 12.4, 4.1 Hz, 1H), 2.68 - 2.47 (m, 1H), 2.25 - 2.10 (m, 1H), 2.10 - 1.98 (m, 1H), 1.98 - 1.66 (m, 4H), 1.66 - 1.48 (m, 2H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -109.23 (ddd, J = 15.1, 8.6, 6.0 Hz, 1F), -112.02 (t, J = 6.9 Hz, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{21}F_3N_3O_4$: 448.2; found**:** 448.3.

Example 86

Preparation of Compound **86**

(1R,3S,4R,12aS)-7-hydroxy-3-methyl-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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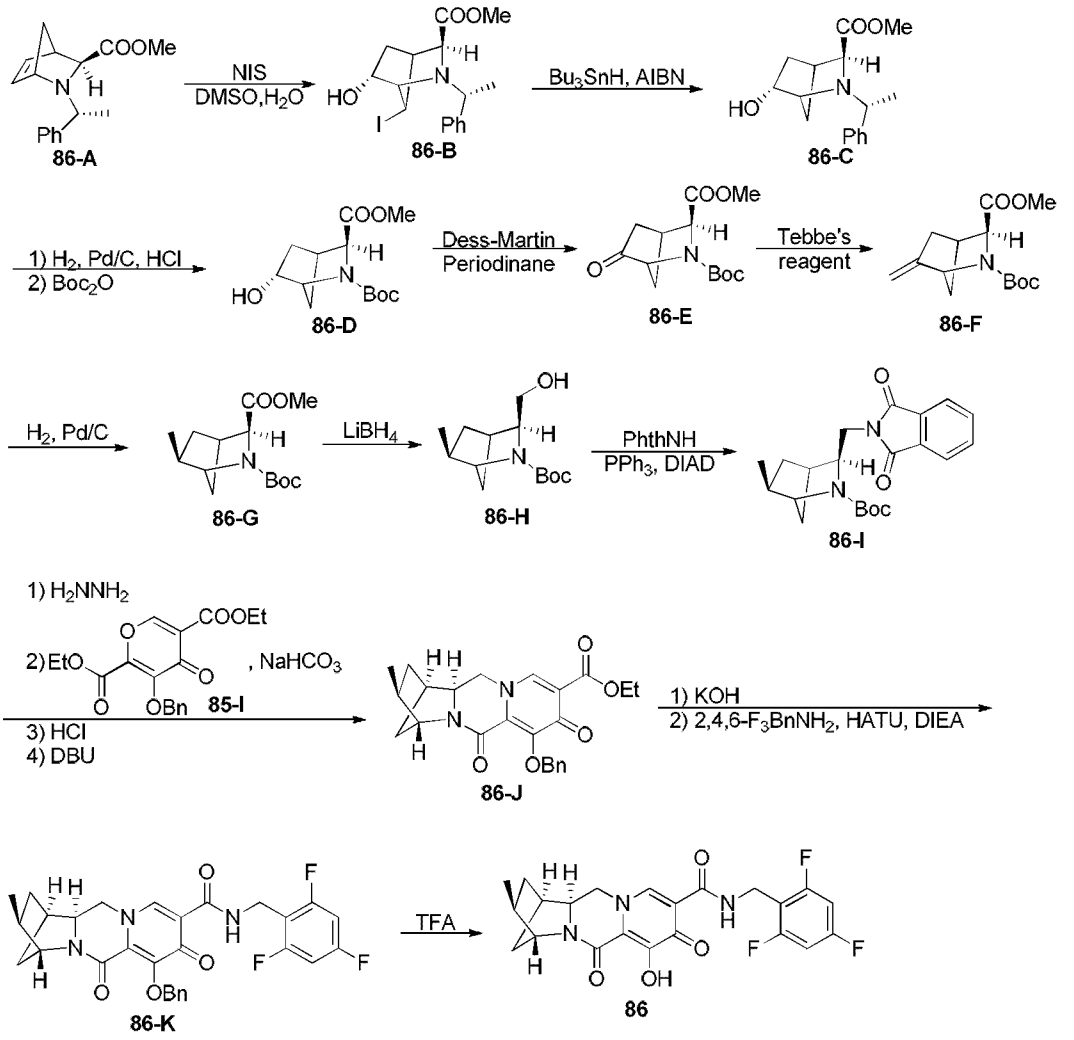

Step 1

A solution of **86-A** (10.160 g, 39.48 mmol) in DMSO (52 mL) and water (6.5 mL) was stirred at room temperature as N-iodosuccinmide (8.888 g, 39.50 mmol) was added. After 30 min, the dark brown reaction mixture was diluted with EtOAc, and washed with saturated aqueous $NaHCO_3$ solution, 10 % aqueous $Na_2S_2O_3$ solution],and brine. After the aqueous fractions were extracted with EtOAc, the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to obtain **86-B** as a white solid. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.33 - 7.19 (m, 5H), 4.25 - 4.12 (m, 1H), 3.79 (q, J = 1.6 Hz, 1H), 3.72 (q, J = 6.5 Hz, 1H), 3.51 (s, 1H), 3.47 (s, 3H), 3.31 (dd, J = 3.9, 1.6 Hz, 1H), 2.76 - 2.69 (m, 1H), 2.13 (ddd, J = 14.3, 7.8, 1.7 Hz, 1H), 2.08 - 1.97 (m, 1H), 1.91

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(dtd, J = 14.1, 4.0, 1.5 Hz, 1H), 1.42 (d, J = 6.5 Hz, 3H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{21}INO_3$: 402.1; found**:** 402.0.

Step 2

A solution of **86-B** (12.468 g, 31.07 mmol), azobisisobutyronitrile (AIBN) (4.082 g, 24.86 mmol), and tributyltin hydride (18.047 g, 62.22 mmol) in toluene (150 mL) was stirred at 100 °C. After 30 min, the reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with water and brine. After the aqueous fractions were extracted with EtOAc, the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography twice using hexanes - EtOAc as eluents to obtain **86-C**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.39 - 7.31 (m, 2H), 7.31 - 7.24 (m, 2H), 7.24 - 7.17 (m, 1H), 4.11 (s, 1H), 3.72 (s, 1H), 3.49 (s, 3H), 3.33 (d, J = 3.4 Hz, 1H), 3.27 (d, J = 6.4 Hz, 1H), 2.65 - 2.51 (m, 1H), 1.92 (ddd, J = 13.6, 6.8, 2.4 Hz, 1H), 1.69 - 1.50 (m, 2H), 1.47 (d, J = 10.1 Hz, 1H), 1.41 (d, J = 6.6 Hz, 3H), 1.21 - 1.07 (m, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{22}NO_3$: 276.2; found**:** 276.1.

Step 3

A mixture of **86-C** (4.187 g, 15.21 mmol) and 20% $Pd(OH)_2/C$ (1.022 g) in EtOH (100 mL) and 4 N HCl in dioxane (5.7 mL) was stirred under H_2 atmosphere. After 1.5 h, the reaction mixture was filtered, and the filtrate was concentrated. After the residue was co evaporated with toluene, the residue was used for the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_8H_{14}NO_3$: 172.1; found**:** 172.1.

After the residue was co-evaporated with toluene, the residue and Boc_2O (5.712 g, 26.17 mmol) in THF (45 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (8 mL, 45.93 mmol) was added. After 30 min, the reaction mixture was diluted with water and extracted with EtOAc (x 2). After the organic extracts were washed with water, the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to obtain **86-D**. ^{1}H NMR spectrum suggests a mixture of rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.20 (d, J = 7.6 Hz, 1H), 4.19 - 4.10 (m, 2H),

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4.08 (d, J = 3.5 Hz, 1H), 3.72 (s, 3H), 2.74 (d, J = 5.6 Hz, 1H), 1.97 (ddd, J = 13.6, 6.9, 2.8 Hz, 1H), 1.88 - 1.78 (m, 1H), 1.79 - 1.50 (m, 1H), 1.46 (s, 3H), 1.38 (s, 6H), 1.31 (d, J = 13.3 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{22}NO_5$: 272.2; found**:** 271.6.

Step 4

A solution of **86-D** (1659 mg, 6.115 mmol) in CH_2Cl_2 (35 mL) was stirred at 0 °C bath as Dess-Martin periodinane (5.183 g, 12.22 mmol) was added in portions. After 5 min, the mixture was stirred at room temperature. After 2 h, the reaction mixture was cooled in an ice bath, quenched with water, and filtered. The filtrate was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to give **86-E**. ^{1}H NMR spectrum suggests two rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.43 (d, J = 3.8 Hz, 0.5H), 4.39 (s, 1H), 4.26 (s, 0.5H), 3.75 (s, 3H), 3.10 (s, 1H), 2.24 (d, J = 4.5 Hz, 0.5H), 2.19 (d, J = 4.4 Hz, 0.5H), 2.12 (d, J = 4.4 Hz, 0.5H), 2.07 (d, J = 4.2 Hz, 0.5H), 2.01 (dd, J = 4.5, 2.2 Hz, 0.5H), 1.98 (dt, J = 4.3, 1.9 Hz, 0.5H), 1.80 (s, 0.5H), 1.77 (s, 0.5H), 1.46 (s, 4.5H), 1.40 (d, J = 2.8 Hz, 4.5H). **LCMS-ESI$^+$** (*m/z*): $[M-C_4H_8+H]^+$ calculated for $C_9H_{12}NO_5$: 214.1; found**:** 213.8.

Step 5

A solution of **86-E** (528 mg, 1.961mmol) in THF (12 mL) was stirred at 0 °C as 0.5 M solution of Tebbe reagent in toluene (7.9 mL, 3.95 mmol) was added dropwise. After addition, the brown solution was allowed to warm to room temperature slowly and was stirred at room temperature for 2.5 h. The reaction mixture was stirred at 0 °C bath as the reaction was quenched carefully by the addition of saturated aqueous $NaHCO_3$ solution. After the mixture was diluted with CH_2Cl_2 and stirred at room temperature for 15 minutes, the resulting mixture was filtered through celite pad and the filter cake was washed with CH_2Cl_2. After the two fractions in the filtrate were separated, the aq. fraction was extracted with CH_2Cl_2, and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to give **86-F**. ^{1}H NMR spectrum suggests two rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.13 (s, 0.6H), 5.04 (s, 0.4H),

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4.82 - 4.71 (m, 1H), 4.55 (s, 0.6H), 4.43 (s, 0.4H), 4.29 (d, J = 3.7 Hz, 0.4H), 4.24 (d, J = 3.7 Hz, 0.6H), 3.71 (s, 3H), 2.84 (s, 1H), 2.14 (m, 2H), 1.75 (s, 0.6H), 1.74 - 1.70 (s, 0.4H), 1.55 (m, 1H), 1.45 (s, 3.6H), 1.37 (s, 5.4H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{22}NO_4$: 268.2; found**:** 267.6.

Step 6

A mixture of **86-F** (333 mg, 1.246 mmol) and 20% $Pd(OH)_2/C$ (53 mg) in EtOH (5 mL) was stirred under H_2 atmosphere. After 30 min, the mixture was filtered and the filtrate was concentrated to give **86-G**. ^{1}H NMR spectrum suggests two rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.20 (m, 1H), 4.08 (m, 1H), 3.71 (two s, 3H), 2.68 (m, 1H), 2.06 (m, 1H), 1.80 - 1.63 (m, 2H), 1.63 - 1.51 (m, 1H), 1.44 (s, 4H), 1.38 (s, 5H), 1.13 (m, 3H), 0.92 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{24}NO_4$: 270.2; found**:** 269.7.

Step 7

A solution of **86-G** (336 mg, 1.482 mmol) in THF (5 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (1.5 mL) was added. After 5 min, the mixture was stirred at room temperature. After 2 h, additional 2.0 M $LiBH_4$ in THF (1.5 mL) was added. After 21 h at room temperature, additional 2.0 M $LiBH_4$ in THF (3 mL) was added. After 3 h at room temperature, the solution was heated at 35 °C for 18 h. The reaction mixture was cooled to 0 °C and quenched carefully with water. After the mixture was extracted with EtOAc (x 2), the two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc to give **86-H**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.95 - 4.09 (br, 1H), 4.05 (s, 1H), 3.82 (dd, J = 11.5, 7.7 Hz, 1H), 3.76 - 3.69 (m, 1H), 3.66 (d, J = 11.5 Hz, 1H), 2.45 (d, J = 4.1 Hz, 1H), 2.03 (dqdd, J = 11.4, 7.0, 4.5, 2.6 Hz, 1H), 1.77 - 1.57 (m, 2H), 1.48 (dd, J = 10.1, 1.8 Hz, 1H), 1.45 (s, 9H), 1.00 (d, J = 6.9 Hz, 3H), 0.93 (ddd, J = 13.2, 4.7, 2.6 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{24}NO_3$: 242.2; found**:** 241.7.

Step 8

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A solution of **86-H** (218 mg, 0.903 mmol), phthalimide (218 mg, 1.482 mmol), and PPh_3 (535 mg, 2.040 mmol) in THF (10 mL) was stirred at 0 °C bath as DIAD (0.40 mL, 2.032 mmol) was added. After 10 min at 0 °C, the mixture was stirred at room temperature for 19 h. The reaction mixture was concentrated and the residue was purified by flash chromatography using hexane-EtOAc as eluents to give **86-I**. ^1H NMR suggests two rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.82 (dt, J = 7.3, 3.6 Hz, 2H), 7.70 (d, J = 5.3 Hz, 2H), 4.53 - 4.26 (m, 1H), 4.26 - 3.89 (m, 2H), 3.89 - 3.65 (m, 1H), 2.28 (m, 1H), 2.04 (m, 1H), 1.82 - 1.65 (m, 2H), 1.66 - 1.43 (m, 7H), 1.38 (s, 4H), 1.19 - 1.01 (m, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{27}N_2O_4$: 371.2; **found:** 370.8.

Step 9

To a solution of **86-I** (319 mg, 0.861 mmol) in EtOH (12 mL) was added hydrazine hydrate (0.17 mL, 3.494 mmol) at room temperature and the resulting solution was stirred at 70 °C bath. After 1.5 h, the mixture was cooled to 0 °C and diluted with ether (25 mL) before stirring for 1 h at 0 °C. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 and filtered to remove some insoluble material. The resulting filtrate was concentrated to give crude amine. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{25}N_2O_2$: 241.2; **found:** 240.9.

After the crude amine was co-evaporated with toluene, a mixture of the crude amine, **85-I** (300 mg, 0.866 mmol), and $NaHCO_3$ (150 mg, 1.845 mmol) in water (3 mL) and EtOH (3 mL) was stirred at room temperature. After 2 h, the mixture was diluted with water and extracted with EtOAc (x 2). After the extracts were washed with water, the organic extracts were combined, dried (Na_2SO_4), and concentrated. To a solution of the residue in CH_2Cl_2 (2 mL) was added 4 N HCl in dioxane (6 mL). After 1.5 h at room temperature, the solution was concentrated and co-evaporated with toluene. A mixture of the residue and DBU (0.65 mL, 4.347 mmol) in toluene (6 mL) was stirred at 100 °C. After 1 h, additional DBU (0.65 mL, 4.347 mmol) was added and the mixture was stirred at 100 °C. Additional DBU (0.65 mL, 4.347 mmol) was added after 1 h and the mixture was stirred another 2.5 h at 100 °C. The mixture was diluted with CH_2Cl_2 and washed with water containing 3 mL of 1 N HCl. The organic fraction was dried (Na_2SO_4) and concentrated. The residue was purified by flash

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chromatography using EtOAc-20% MeOH/EtOAc as eluents to give **86-J**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.70 - 7.62 (m, 2H), 7.37 - 7.27 (m, 3H), 5.48 (d, J = 9.9 Hz, 1H), 5.16 (d, J = 9.9 Hz, 1H), 4.53 (s, 1H), 4.38 (m, 2H), 4.11 (m, 1H), 3.97 (dd, J = 12.2, 3.0 Hz, 1H), 3.88 (dt, J = 12.2, 3.0 Hz, 1H), 2.63 (d, J = 4.2 Hz, 1H), 2.28 (qd, J = 7.2, 3.1 Hz, 1H), 2.00 - 1.88 (m, 1H), 1.80 - 1.56 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 1.04 (dd, J = 5.0, 2.5 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): [M +H]$^+$ calculated for $C_{24}H_{27}N_2O_5$: 423.2; found**:** 423.2.

Step 10

A mixture of **86-J** (83 mg, 0.196 mmol) in THF (2 mL) and EtOH (2 mL) was stirred at room temperature as 1 N KOH (0.4 mL) was added. After 30 min, the reaction mixture was diluted with water and washed with CH_2Cl_2. After the aqueous fraction was acidified with 1 N HCl 0.45 mL), the product was extracted with CH_2Cl_2 (x 2). The combined extracts were dried (Na_2SO_4) and concentrated to obtain the crude acid. **LCMS-ESI$^+$** (*m/z*): [M +H]$^+$ calculated for $C_{22}H_{23}N_2O_5$: 395.2; found**:** 395.2.

A mixture of the crude acid (69 mg, 0.175 mmol), 2,4,6-trifluorobenzyl amine (42 mg, 0.261 mmol), and HATU (106 mg, 0.279 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (0.25 mL, 1.435 mmol) was added. After 30 min, the reaction mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqueous NH_4Cl (x 2), saturated aqueous $NaHCO_3$ (x 2), and brine. After the aqueous fractions were extracted with EtOAc, two organic fractions were combined, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using EtOAc-20%MeOH/EtOAc as eluents to obtain **86-K**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.40 (t, J = 5.7 Hz, 1H), 8.40 (s, 1H), 7.66 - 7.51 (m, 2H), 7.36 - 7.29 (m, 2H), 7.29 - 7.23 (m, 1H), 6.71 - 6.61 (m, 2H), 5.36 (d, J = 10.0 Hz, 1H), 5.18 (d, J = 10.0 Hz, 1H), 4.73 - 4.58 (m, 2H), 4.53 (s, 1H), 4.22 - 4.11 (m, 1H), 4.03 (dd, J = 12.4, 3.1 Hz, 1H), 3.81 (dt, J = 12.3, 3.1 Hz, 1H), 2.68 - 2.59 (m, 1H), 2.29 (dddd, J = 11.4, 7.1, 4.7, 2.4 Hz, 1H), 1.94 (ddd, J = 13.5, 11.2, 4.6 Hz, 1H), 1.88 - 1.67 (m, 2H), 1.06 (d, J = 7.0 Hz, 3H), 1.03-1.09 (m, 1H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -109.14 (ddd, J = 15.2, 8.7, 6.2 Hz, 1F), -111.86 (t, J = 7.0 Hz, 2F). **LCMS-ESI$^+$** (*m/z*): [M +H]$^+$ calculated for $C_{29}H_{27}F_3N_3O_4$: 538.2; found**:** 538.1.

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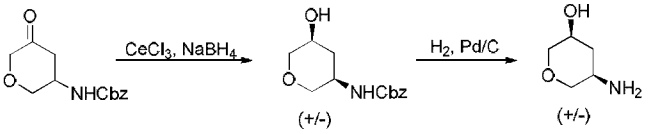
Step 11

86-K (61 mg, 0.113 mmol) was dissolved in trifluoroacetic acid (2 mL) and stirred at room temperature. After 1 h, the solution was concentrated and the residue was dissolved in CH_2Cl_2. After the solution was washed with 0.1 N HCl, the aqueous fraction was extracted with CH_2Cl_2 (x 2). The organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using CH_2Cl_2-20% MeOH in CH_2Cl_2 as eluents to obtain compound **86**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 12.02 (s, 1H), 10.40 (t, J = 5.7 Hz, 1H), 8.35 (s, 1H), 6.63 (t, J = 8.1 Hz, 2H), 4.62 (d, J = 5.7 Hz, 2H), 4.59 (s, 1H), 4.22 (dd, J = 12.2, 3.5 Hz, 1H), 4.13 (t, J = 11.9 Hz, 1H), 4.05 (dt, J = 12.0, 3.1 Hz, 1H), 2.77 - 2.70 (m, 1H), 2.31 m, 1H), 2.09 - 1.93 (m, 1H), 1.93 - 1.81 (m, 2H), 1.10 (ddd, J = 13.9, 5.0, 2.1 Hz, 1H), 1.02 (d, J = 6.9 Hz, 3H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -109.22 (ddd, J = 15.1, 8.7, 6.1 Hz, 1F), -112.05 (t, J = 6.9 Hz, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{21}F_3N_3O_4$: 448.2; found**:** 448.3.

Example 87

Preparation of *cis*-5-aminotetrahydro-2H-pyran-3-ol



Step 1

A solution of benzyl (5-oxotetrahydro-2H-pyran-3-yl)carbamate (740 mg, 3.0 mmol) and cerium(III) chloride heptahydrate (1.12 g, 3.0 mmol) in 20 mL methanol was cooled to 0 °C and sodium borohydride (120 mg, 3.2 mmol) was then added portionwise. The reaction mixture was allowed to stir at 0 °C for 45 minutes and then quenched by slow addition of 1 mL acetone followed by 3 hours stirring at room temperature. The reaction mixture was partitioned between water and dichloromethane and the aqueous phase extracted into dichloromethane followed by 2-butanol. The combined organic phases were dried over magnesium sulfate, filtered, concentrated,

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and the residue purified by flash chromatography (0-100% EtOAc/hexanes) to afford the desired *cis*-benzyl ((3R,5S)-5-hydroxytetrahydro-2H-pyran-3-yl)carbamate. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.39 – 7.26 (m, 5H), 6.06 (br s, 1H), 5.07 (s, 2H), 3.86 – 3.70 (m, 2H), 3.69 – 3.47 (m, 4H), 2.00 – 1.89 (m, 1H), 1.76 (d, J = 13.5 Hz, 1H). The undesired *trans*-isomer was also isolated.

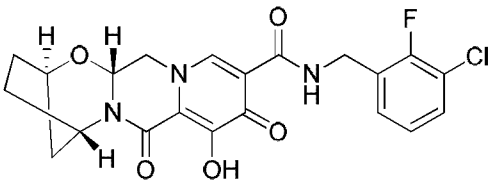
Step 2

To a solution of *cis*-benzyl ((3R,5S)-5-hydroxytetrahydro-2H-pyran-3-yl)carbamate (290 mg, 1.16 mmol) in 5 mL 1:1 DCM:EtOH was added 10wt% Pd/C (255 mg). This mixture was stirred under balloon pressure hydrogen for 18 hours and palladium removed by filtration thru celite with ethanol rinse. Upon concentration of filtrate, the *cis*-5-aminotetrahydro-2H-pyran-3-ol was afforded and carried on as crude.

Example 88

Preparation of Compound **88**

'(2R,5S,13aR)-N-(3-chloro-2-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



88

Compound **88** was prepared in a similar manner to compound **15** using (3-chloro-2-fluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.43 (br s, 1H), 8.34 (br s, 1H), 7.32 – 7.24 (m, 2H), 7.02 (t, J = 7.9 Hz, 1H), 5.36 (d, J = 9.4 Hz, 1H), 5.30 (s, 2H), 4.70 (d, J = 6.0 Hz, 3H), 4.24 (d, J = 12.0 Hz, 1H), 4.00 (dd, J = 12.7, 9.5 Hz, 1H), 2.18 – 1.96 (m, 4H), 1.96 – 1.83 (m, 1H), 1.60 (dt, J = 12.4, 3.1 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClFN_3O_5$: 448.11; found: 448.2.

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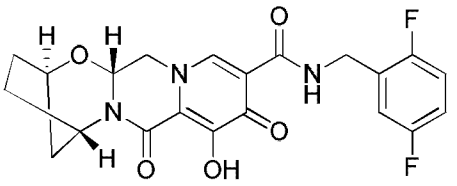
Example 89

Preparation of Compound **89**

(2R,5S,13aR)-N-(2,5-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



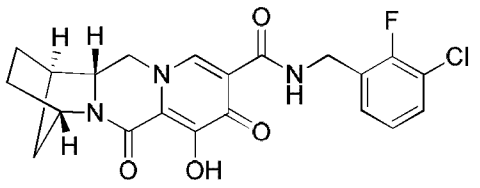
89

Compound **89** was prepared in a similar manner to compound **15** using (2,5-difluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.32 (t, *J* = 5.8 Hz, 1H), 8.31 (br s, 1H), 7.15 – 6.89 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.40 (d, *J* = 9.3 Hz, 1H), 5.24 (s, 1H), 4.67 – 4.51 (m, 3H), 4.35 – 4.28 (m, 1H), 3.99 – 3.90 (m, 1H), 2.16 – 1.85 (m, 5H), 1.60 – 1.50 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_2N_3O_5$: 432.14; found: 432.2.

Example 90

Preparation of Compound **90**

(1R,4S,12aR)-N-(3-chloro-2-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



90

Compound **90** was prepared in a similar manner to compound **41** using (3-chloro-2-fluorophenyl)methanamine in place of (2,4,6-trifluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 9.22 (s, 1H), 8.79 (s, 1H), 7.39 – 7.28 (m, 2H), 7.06 (t, *J* = 8.0 Hz, 1H), 4.89 (s, 1H), 4.70 – 4.56 (m, 3H), 4.06 – 3.83 (m, 2H), 3.04 –

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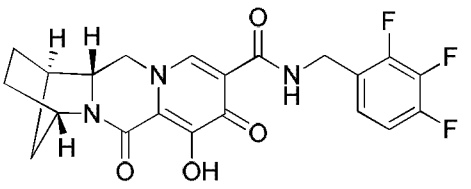
2.88 (m, 1H), 2.77 (s, 1H), 1.97 – 1.58 (m, 6H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClFN_3O_4$: 432.11; found: 432.2.

Example 91

Preparation of Compound **91**

(1R,4S,12aR)-7-hydroxy-6,8-dioxo-N-(2,3,4-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



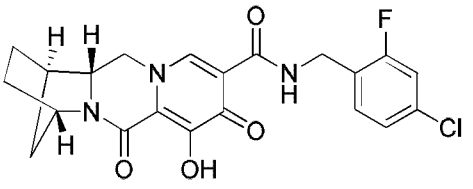
91

Compound **91** was prepared in a similar manner to compound **41** using (2,3,4-trifluorophenyl)methanamine in place of (2,4,6-trifluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.25 (s, 1H), 8.45 (s, 1H), 7.10 (d, *J* = 5.1 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 4.89 (s, 1H), 4.63 (s, 2H), 4.22 (d, *J* = 11.6 Hz, 1H), 3.93 – 3.73 (m, 2H), 2.71 (s, 1H), 1.97 – 1.57 (m, 6H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{18}F_3N_3O_4$: 434.13; found: 434.2.

Example 92

Preparation of Compound **92**

(1R,4S,12aR)-N-(4-chloro-2-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



92

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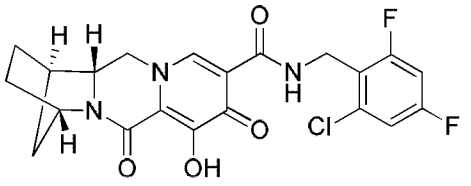
Compound **92** was prepared in a similar manner to compound **41** using (4-chloro-2-fluorophenyl)methanamine in place of (2,4,6-trifluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.28 (s, 1H), 8.41 (s, 1H), 7.29 (s, 1H), 7.11 – 6.95 (m, 2H), 4.85 (s, 1H), 4.57 (s, 2H), 4.22 (d, *J* = 10.2 Hz, 1H), 3.81 (q, *J* = 13.9, 13.1 Hz, 2H), 2.68 (s, 1H), 1.99 – 1.50 (m, 6H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClFN_3O_4$: 432.11; found: 432.2.

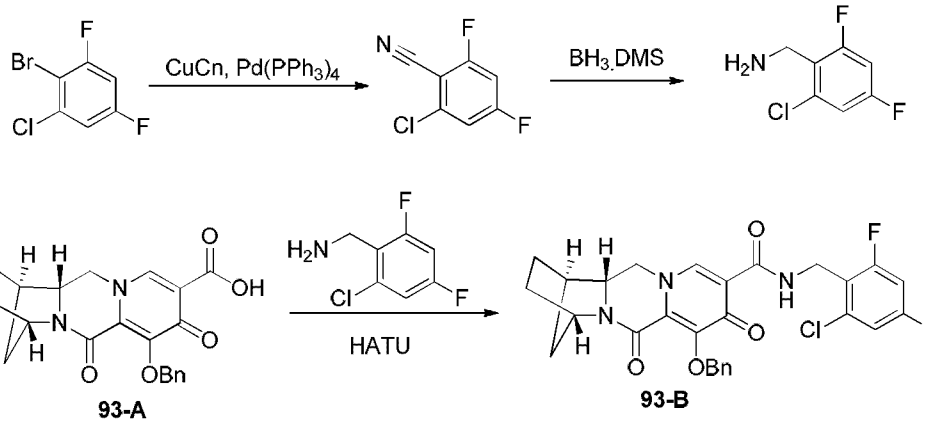
Example 93

Preparation of Compound **93**

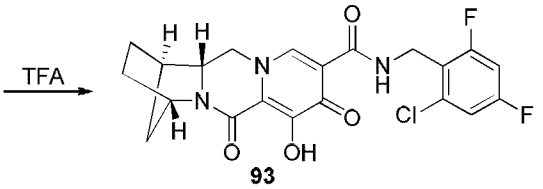
(1R,4S,12aR)-N-(2-chloro-4,6-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



93



93-A **93-B**



93

Step 1

A 5 mL microwave vial was charged with 2-bromo-1-chloro-3,5-difluorobenzene (540 mg, 2.4 mmol), cuprous cyanide (436 mg, 4.87 mmol), tetrakis(triphenylphosphine)palladium (63 mg, 0.05 mmol), sealed, and evacuated/backfilled with nitrogen. To this was added 5 mL degassed DMF. The sealed vessel was heated at 110 °C for 18 hours, diluted with ethyl acetate, and washed sequentially with twice 9:1 NH_4OH:$NH_4Cl_{(aq)}$, twice 5% $LiCl_{(aq)}$, and brine. The organic phase was then dried over magnesium sulfate, filtered, and concentrated. The crude residue was purified by flash chromatography (100% hexanes) to afford 2-chloro-4,6-difluorobenzonitrile. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.13 (dt, *J* = 8.0, 1.9 Hz, 1H), 6.93 (td, *J* = 8.5, 2.3 Hz, 1H).

Step 2

To a solution of 2-chloro-4,6-difluorobenzonitrile (210 mg, 1.2 mmol) in 2.4 mL THF was added a 2M solution of borane-DMS in THF (0.6 mL). This reaction mixture was allowed to stir at refluxing temperature for 18 hours resulting in a loss of all solvent. The residue was re-dissolved in 3 mL THF, cooled to 0 °C, a 6M solution of $HCl_{(aq)}$ was carefully added, and the mixture returned to reflux for 30 minutes. The reaction mixture was once again cooled to 0 °C and treated with 4M $NaOH_{(aq)}$. The aqueous phase was extracted with DCM, combined organic phases dried over magnesium sulfate, filtered, and concentrated. The crude residue was purified by flash chromatography (0-10% MeOH/DCM) to afford (2-chloro-4,6-difluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 6.95 (dt, *J* = 8.3, 2.1 Hz, 1H), 6.76 (td, *J* = 9.4, 2.5 Hz, 1H), 3.94 (d, *J* = 1.9 Hz, 2H).

Steps 3 and 4

A solution of **93-A** (74 mg, 0.11 mmol), (2-chloro-4,6-difluorophenyl)methanamine (48.5 mg, 0.27 mmol), HATU (100 mg, 0.26 mmol), and N,N-diisopropylethylamine (0.1 mL, 0.57 mmol) in 1 mL dichloromethane was stirred at room temperature for one hour at which point complete disappearance of **93-A** and formation of **93-B** was observed by LCMS. TFA (0.65 M) was added and the mixture

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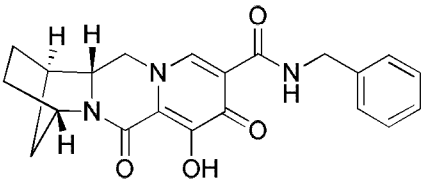
was stirred at room temperature for one hour, at which point 1 mL DMF was added. The reaction mixture and then concentrated and purified by preparative HPLC (ACN/H_2O + 0.1% TFA) to afford compound **93**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.41 (t, J = 5.7 Hz, 1H), 8.33 (s, 1H), 7.41 – 7.26 (m, 2H), 4.72 – 4.57 (m, 3H), 4.43 (dd, J = 12.5, 3.6 Hz, 1H), 3.94 (t, J = 12.4 Hz, 2H), 3.77 (dd, J = 12.4, 3.6 Hz, 3H), 1.87 – 1.67 (m, 3H), 1.67 – 1.45 (m, 2H), 1.43 (d, J = 10.4 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{18}ClF_2N_3O_4$: 450.10; found: 450.2.

Example 94

Preparation of Compound **94**

(1R,4S,12aR)-N-benzyl-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



94

Compound **94** was prepared in a similar manner to compound **41** using phenylmethanamine in place of (2,4,6-trifluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.37 (s, 1H), 8.26 (s, 1H), 7.37 – 7.19 (m, 5H), 4.55 (d, J = 4.8 Hz, 1H), 4.34 (d, J = 5.7 Hz, 1H), 4.23 (d, J = 9.8 Hz, 1H), 4.09 (d, J = 28.2 Hz, 1H), 3.78 (d, J = 10.9 Hz, 1H), 3.64 (d, J = 13.2 Hz, 1H), 3.14 – 3.01 (m, 1H), 1.91 – 1.49 (m, 4H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{21}N_3O_4$: 380.16; found: 380.2.

Example 95

Preparation of chiral tert-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylates **95-A** and **95-B**

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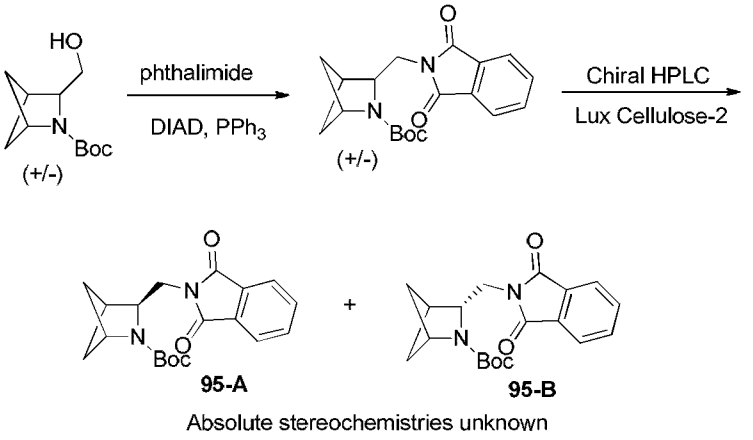

Step 1

To a 0 °C solution of racemic tert-butyl 3-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (285 mg, 1.34 mmol), triphenylphosphine (425 mg, 1.62 mmol), and phthalimide (240 mg, 1.62 mmol) in 9 mL THF was added dropwise a solution of diisopropyl azodicarboxylate (0.35 mL, 1.8 mmol) in 1 ml THF. The reaction mixture was warmed to room temperature, stirred for 90 minutes, concentrated onto silica, and purified by flash chromatography (0-25% EtOAc/hexanes) to afford tert-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate as a racemic mixture. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{19}H_{23}N_2O_4$: 343.2; found: 342.8.

Step 2

Racemic tert-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (655 mg, 1.91 mmol) was separated by chiral HPLC on a Lux Cellulose-2 column using an acetronitrile eluent to afford chiral **95-A** (first eluting peak) and **95-B** (second eluting peak) in enantioenriched form. For **95-A**: 144 mg, 98%ee (absolute stereochemistry unknown). For **95-B**: 242 mg, 49%ee (absolute stereochemistry unknown).

Example 96

Preparation of Compound **96**

(1R,3R,11aS)-6-hydroxy-5,7-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,5,7,11,11a-hexahydro-1H-1,3-methanopyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide

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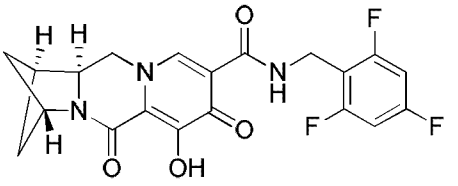
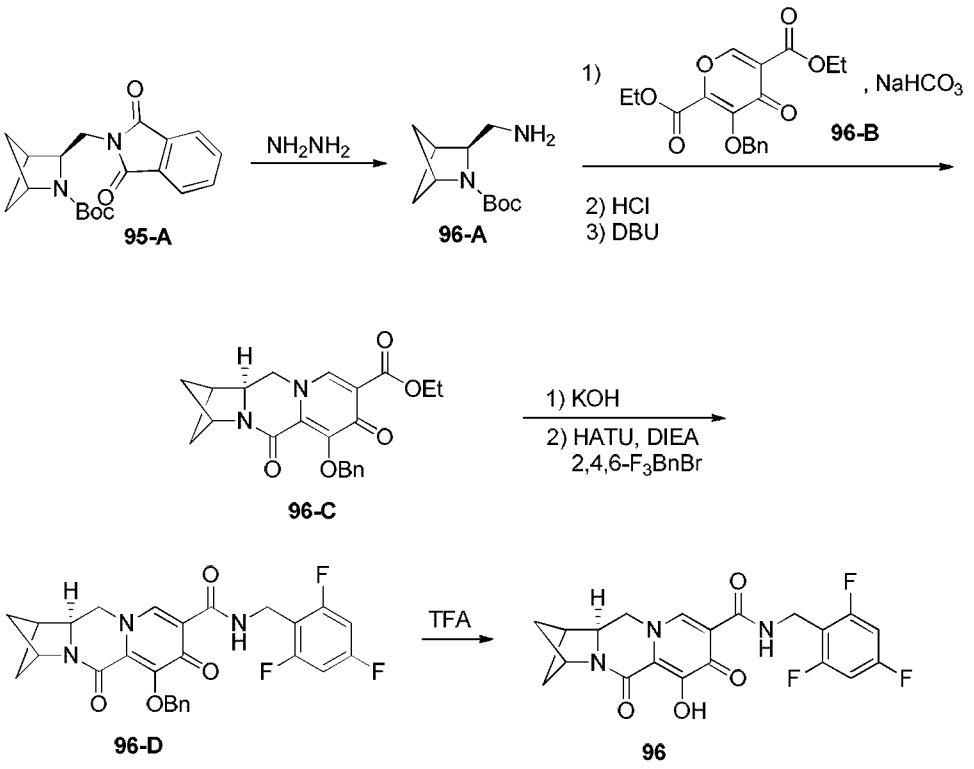


96



95-A **96-A** **96-B** **96-C** **96-D** **96**

(Absolute stereochemistries unknown)

Step 1

To a solution of intermediate **95-A** (141 mg, 0.41 mmol, 98% ee, unknown absolute stereochemistry) in 9 mL ethanol was added hydrazine hydrate (0.5 mL, 10.3 mmol) and stirred at 70 °C for 18 hours to afford **96-A** of unknown absolute stereochemistry. Solids were removed by filtration and the filtrate concentrated and carried on as crude.

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Step 2

A mixture of crude **96-A** (0.41 mmol assumed), **96-B** (430 mg, 1.25 mmol), and sodium bicarbonate (69 mg, 0.82 mmol) in 2 mL water and 2 mL ethanol were stirred at room temperature for 18 hours, after which the reaction mixture was diluted with water and thrice extracted to ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered, concentrated. The crude residue (222 mg) was dissolved in 1.5 mL DCM and 4 N HCl in dioxane (4 mL) was added and stirred for 90 minutes at room temperature. The mixture was concentrated to dryness and coevaporated with toluene. The crude residue and DBU (0.3 mL, 2.0 mmol) in 6 mL methanol was stirred at 50 °C for 90 minutes. The reaction mixture was then concentrated onto silica gel and purified by flash chromatography (0-10% MeOH/DCM) to afford **96-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}N_2O_5$: 395.16; found: 395.2.

Step 3

A mixture of **96-C** (112 mg, 0.28 mmol), 1M aqueous potassium hydroxide (1 mL), 4 mL methanol, and 4 mL THF was stirred at room temperature for 3 hours, at which point the mixture was diluted with dichloromethane, acidified by addition of 1M aqueous hydrogen chloride, and the organic phase extracted to dichloromethane. The combined organics were dried, filtered, and concentrated from toluene. After drying under vacuum, the residue was suspended in 1.5 mL DCM and trifluorobenzylamine (62 mg, 0.38 mmol), HATU (220 mg, 0.58 mmol), and N,N-diisopropylethylamine (DIPEA) (0.15 mL, 0.86 mmol) were added. This reaction mixture was stirred at room temperature for 2 hours to afford **96-D** which was carried forward as crude.

Step 4

Trifluoroacetic acid (1.7 mL, 22.2 mmol) was added to the crude reaction solution containing **96-D** from the prior step and the reaction mixture allowed to stir at room temperature for 90 minutes. 1 mL of DMF was then added, the reaction mixture concentrated down to ~1 mL, filtered, and purified by preparative HPLC

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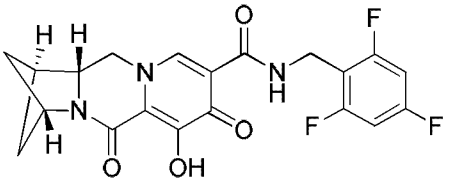
(ACN/water + 0.1% TFA) to afford compound **96** (unknown absolute stereochemistry). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.45 – 10.35 (m, 1H), 8.39 (s, 1H), 7.23 – 7.09 (m, 2H), 4.67 (dd, J = 12.6, 4.8 Hz, 2H), 4.53 (d, J = 5.5 Hz, 2H), 4.20 (dd, J = 11.9, 3.8 Hz, 1H), 4.05 – 3.95 (m, 1H), 2.96 – 2.88 (m, 1H), 2.16 (d, J = 7.0 Hz, 1H), 1.97 (d, J = 7.0 Hz, 1H), 1.68 – 1.60 (m, 1H), 1.53 – 1.45 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{16}F_3N_3O_4$: 420.12; found: 420.2.

Example 97

Preparation of Compound **97**

(1S,3S,11aR)-6-hydroxy-5,7-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,5,7,11,11a-hexahydro-1H-1,3-methanopyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide



(Absolute stereochemistry unknown)

97

Compound **97** (49% ee, unknown absolute stereochemistry) was prepared in a similar manner to compound **96** using intermediate **95-B** (49% ee, unknown absolute stereochemistry) in place of enantiomerically opposite intermediate **95-A**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.39 (t, J = 5.7 Hz, 1H), 8.42 (s, 1H), 7.25 – 7.13 (m, 2H), 4.73 – 4.66 (m, 2H), 4.54 (d, J = 5.7 Hz, 2H), 4.20 (dd, J = 12.3, 3.9 Hz, 1H), 4.01 (t, J = 12.4 Hz, 1H), 2.93 (dd, J = 6.7, 3.4 Hz, 1H), 2.19 – 2.14 (m, 1H), 1.97 (d, J = 8.3 Hz, 1H), 1.65 (dd, J = 10.4, 7.9 Hz, 1H), 1.49 (dd, J = 10.5, 7.7 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{16}F_3N_3O_4$: 420.12; found: 420.2.

Example 98

Preparation of Compound **98**

(1S,4R,12aR)-3,3-difluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

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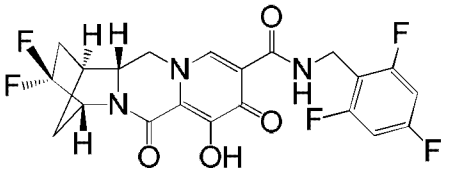
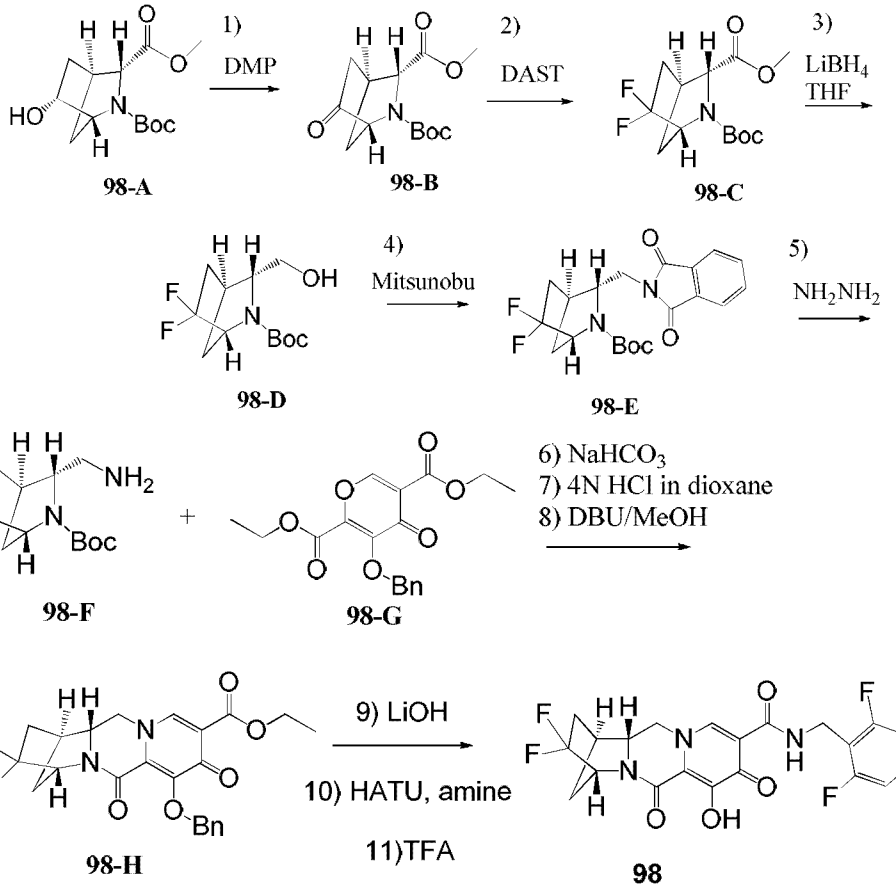


98



98-A **98-B** **98-C** **98-D** **98-E** **98-F** **98-G** **98-H** **98**

Step 1

98-A (0.5g, 1.87mmol) was dissolved in DCM (20 mL) and cooled to 0 °C under Nitrogen. Dess-Martin Periodinane (1.59 g, 3.74 mmol) was added slowly. The mixture was stirred for 2 h at room temperature, quenched with $Na_2S_2O_3/NaHCO_3$ (7:1) aqueous saturated solution (160 mL) and stirred vigorously until two layers were separated. The crude product was twice extracted with DCM. The combined organic layers was dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography on silica gel with 0-20%MeOH/DCM to afford **98-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.34 - 4.05 (m, 1H), 3.97 - 3.75 (m, 1H), 3.69 (s,

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3H), 2.89 (dd, J = 4.4, 2.1 Hz, 1H), 2.30 - 1.97 (m, 3H), 1.56 (d, J = 11.3 Hz, 1H), 1.35 (s, 9H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{19}NO_5$: 269.13; found: 270.78.

Step 2

A solution of **98-B** (504 mg, 1.87mmol) in DCM (15 mL) was stirred at 0 °C. DAST (1ml) was added drop wise to the reaction mixture. After overnight stirring at room temperature, the reaction mixture was cooled back to 0 °C. Saturated $NaHCO_3$ (10 mL) was added slowly. The mixture was extracted with twice with DCM and dried over Na_2SO_4. After concentrating, the residue was purified by flash chromatography 0-50% EtOAc/hexanes to give **98-C**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.45 - 4.18 (m, 1H), 3.85 (m, 1H), 3.72 (d, J = 1.5 Hz, 3H), 2.72 (ddd, J = 5.1, 3.2, 1.6 Hz, 1H), 2.27 - 1.52 (m, 4H), 1.41 (d, J = 21.9 Hz, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -91.72 - -93.99 (m), -113.65 - -115.98 (m). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{19}F_2NO_4$: 291.13; found: 291.55.

Step 3

98-C (476 mg, 1.634mmol) in THF (20 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (2.4 mL, 4.8mmol) was added. The mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was quenched with ice and diluted with EtOAc and saturated NH_4Cl (some H_2 evolution). After the two phases were separated, the organic fraction was washed with brine, dried (Na_2SO_4), and concentrated. The crude product of **98-D** was used as is for the next step. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{19}F_2NO_3$: 263.13; found: 164.10.

Step 4

98-D (1.634mmol), phthalimide (0.36 g, 2.4 5mmol), and PPh_3 (0.855 g, 3.26mmol) in THF (10 mL) was stirred at 0 °C bath as DIAD (0.642 mL, 3.26mmol) was added. After addition, the mixture was stirred at 0 °C for 30 min and then at room temperature for 16 h. It was diluted with EtOAc, and saturated NH_4Cl. After stirring for 5 min, a solid was filtered off and the two phases were separated. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography with 0-50%EA/Hex as eluents to give **98-E**. **^{1}H-**

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NMR suggests a mixture of two rotamers. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 7.89 - 7.80 (m, 2H), 7.78 - 7.66 (m, 2H), 5.02 (ddt, J = 16.6, 12.5, 6.3 Hz, 1H), 4.24 (d, J = 71.8 Hz, 1H), 4.10 - 3.92 (m, 1H), 3.83 - 3.51 (m, 2H), 2.46 (s, 1H), 2.21 - 1.98 (m, 2H), 1.87 - 1.62 (m, 2H),1.31 (d, J = 8.5 Hz, 9H); **^{19}F-NMR** (376 MHz, Chloroform-d) δ -91.22 - -93.58 (m), -113.20 - -115.45 (m). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{22}F_2N_2O_4$: 392.15; found: 393.3.

Step 5

To a solution of **98-E** (696 mg, 1.774mmol) in EtOH (10mL) was added hydrazine hydrate (1mL) at room temperature and the resulting solution was stirred at room temperature for 2 h. The mixture was diluted with ethyl ether (30 mL) and stirred at 0 °C for 60 min before filtration. The filtrate was concentrated and the residue was dissolved in CH_2Cl_2 and filtered. The filtrate was concentrated and purified by flash chromatography on silica gel with 0-20% MeOH (0.2% TEA) /DCM to give **98-F**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.91 (p, J = 6.2 Hz, 1H), 4.29 - 3.97 (m, 1H), 3.36 - 2.93 (m, 2H), 2.49 (qt, J = 8.8, 5.2 Hz, 2H), 2.08 (dddd, J = 25.5, 14.0, 7.1, 4.9 Hz, 1H), 1.89 - 1.49 (m, 4H), 1.41 and 1.21 (d, J = 6.2 Hz, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -91.63 - -93.16 (m), -113.11 - -115.08 (m). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{20}F_2N_2O_2$: 262.15; found: 262.8.

Step 6, 7 and 8

The mixture of **98-G** (375.8 mg, 1.55 mmol), **98-E** (370 mg, 1.41 mmol), and $NaHCO_3$ (261 mg, 3.10 mmol) in water (5 mL) and EtOH (5 mL) was stirred at room temperature for 2 h. The mixture was diluted with brine and extracted with EtOAc (x 2). The extracts were combined, dried (Na_2SO_4), concentrated, and dried in vacuo to afford crude **A**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ 591.59. Crude **A** (1.38mmol) in CH_2Cl_2 (5 mL) was added 4 N HCl in dioxane (5 mL). After 2 h at room temperature, mixture was concentrated to dryness. It was co-evaporated with toluene once and dried in vacuo to afford crude **B**. **B** (1.38mmol + 0.442mmol) and DBU (3 mL, 11mmol) in anhydrous MeOH (15 mL) were stirred at 50 °C bath for 40 min. The mixture was concentrated. The residue was purified by flash chromatography (80 g

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column) using 0 - 20% MeOH/DCM as eluents to give **98-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_2O_5$: 444.15; found: 445.36 (90%), 431.18 (10%).

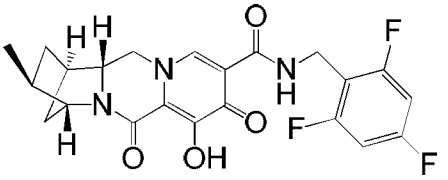
Steps 9,10 and 11

The remaining steps were performed using procedures similar to Example **41** to afford desired compound **98**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.29 (d, J = 6.1 Hz, 1H), 8.34 (s, 1H), 6.65 (dd, J = 8.7, 7.5 Hz, 2H), 4.83 (s, 1H), 4.72 - 4.58 (m, 2H), 4.36 - 4.10 (m, 2H), 4.05 (t, J = 11.5 Hz, 1H), 2.97 (d, J = 4.4 Hz, 1H), 2.49 - 2.08 (m, 3H), 2.12 - 1.94 (m, 1H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -92.08 - -93.57 (m, 1F), -108.92 (ddd, J = 15.1, 8.8, 6.3 Hz, 1F), -109.30 - -110.65 (m, 1F), -112.16 (p, J = 7.3 Hz, 2F). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{16}F_5N_3O_4$: 469.11; found: 470.23.

Example 99

Preparation of Compound **99**

(1R,3S,4R,12aR)-7-hydroxy-3-methyl-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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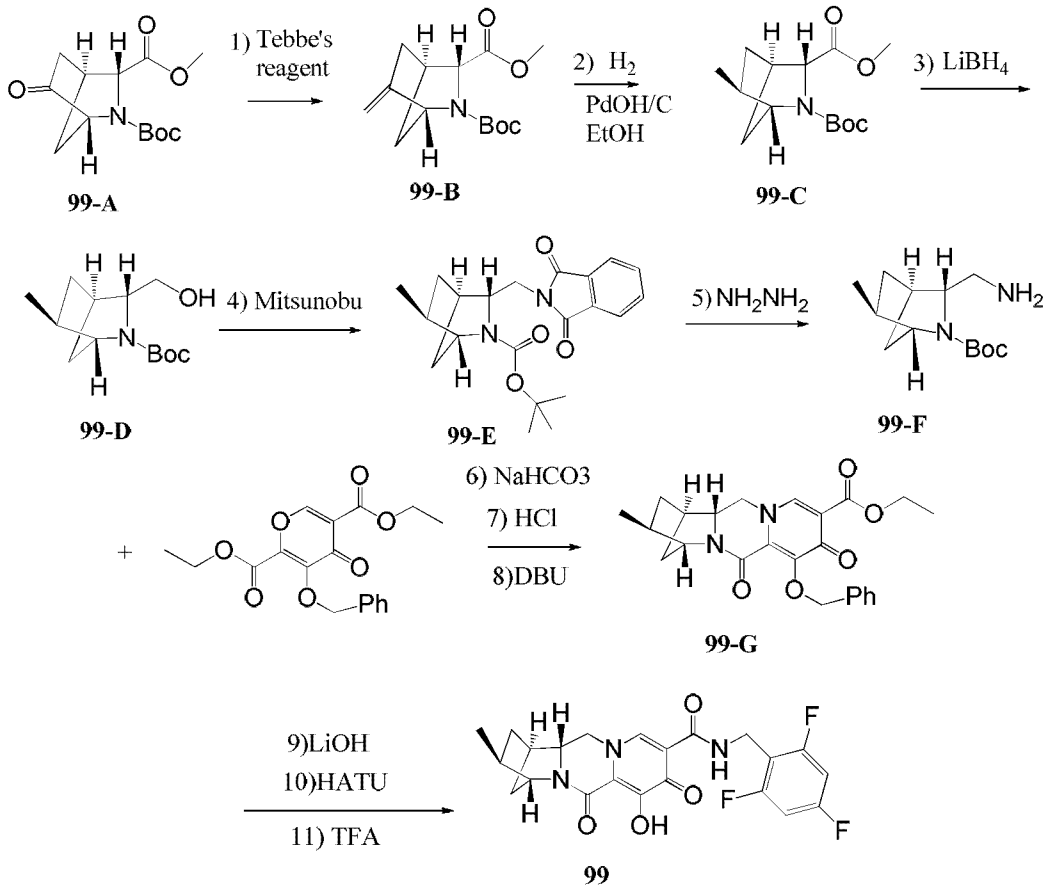

Step 1

To a stirred solution of **99-A** (1 g, 3.71 mmol) in THF (20 mL) was added dropwise a solution of the Tebbe reagent (0.5 M in toluene, 14.85mL, 7.42 mmol) at 0 °C. After addition, the brown solution was allowed to warm to room temperature slowly and was stirred at room temperature for 2 h. The reaction was quenched carefully by the addition of saturated $NaHCO_3$ solution at 0 °C, and the mixture was stirred at room temperature for 15 minutes. The mixture was filtered through celite, and the filter cake was washed with ether and DCM (1:1) twice. After separated layers, the organics were combined and concentrated in vacuo, and the residue was purified by column chromatography on silica gel column with 0-50% EtOAc/hexanes to afford **99-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 5.06 (dt, J = 48.6, 2.6 Hz, 1H), 4.73 (d, J = 7.0 Hz, 1H), 4.42 (d, J = 61.8 Hz, 1H), 3.81 (d, J = 48.2 Hz, 1H), 3.73 (d, J = 1.6 Hz, 3H), 2.74 (dd, J = 9.4, 4.4 Hz, 1H), 2.38 (ddt, J = 13.5, 4.5, 2.5 Hz, 1H), 2.18 - 2.06 (m, 1H), 1.99 (dt, J = 10.2, 2.4 Hz, 1H), 1.58 (s, 1H), 1.42 (d, J

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= 25.5 Hz, 9H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{21}NO_4$: 267.15; found: 267.65.

Step 2

A mixture of **99-B** (675 mg, 2.506 mmol) and 20% $Pd(OH)_2/C$ (500 mg) in EtOH (50 mL) was stirred under H_2 atmosphere. The mixture was filtered through Celite and the filtrate was concentrated to give **99-C**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.23 - 3.99 (m, 1H), 3.77 - 3.64 (m, 4H), 2.55 (d, J = 4.8 Hz, 1H), 2.14 - 1.86 (m, 3H), 1.42 (d, J = 24.2 Hz, 9H), 0.96 (d, J = 6.6 Hz, 3H), 0.85 (ddd, J = 12.5, 4.8, 2.4 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{23}NO_4$: 269.16; found: 269.69.

Step 3

99-C (670 mg, 2.488 mmol) in THF (20 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (3.7mL, 7.46 mmol) was added. The mixture was warmed to room temperature and stirred for 4h. The reaction mixture was quenched with ice and diluted with EtOAc and saturated NH_4Cl (some H_2 evolution). After two phases were separated, the organic fraction was washed with brine, dried (Na_2SO_4), and concentrated. The crude alcohol **99-D** was used as is for the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{23}NO_3$: 241.17; found: 241.76.

Steps 4 and 5

Steps 4 and 5 were performed using procedures similar to those in Example **41** to afford **99-F**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{24}N_2O_2$: 240.18; found: 241.2.

Step 6, 7 and 8

Steps 6, 7 and 8 were performed using procedures similar to that of Example **41** to give **99-G**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{26}N_2O_5$: 422.18; found: 423.21.

Step 9, 10 and 11

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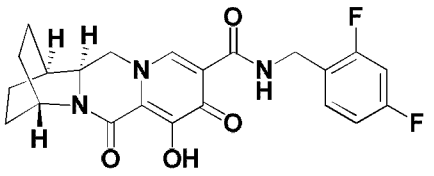
The remaining steps were performed using procedures similar to Example **41** to afford compound **99**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.71 (s, 1H), 10.36 (t, J = 5.7 Hz, 1H), 8.28 (s, 1H), 6.63 (t, J = 8.1 Hz, 2H), 4.63 (t, J = 5.4 Hz, 3H), 4.12 (dd, J = 12.3, 3.5 Hz, 1H), 3.83 (t, J = 12.3 Hz, 1H), 3.67 (dd, J = 12.3, 3.4 Hz, 1H), 2.64 - 2.52 (m, 1H), 2.30 (ddq, J = 10.5, 7.2, 3.6 Hz, 1H), 2.13 (td, J = 12.1, 4.4 Hz, 1H), 1.82 - 1.63 (m, 2H), 1.24 (d, J = 3.3 Hz, 1H), 1.04 (d, J = 6.9 Hz, 4H), 0.90 - 0.79 (m, 1H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -109.20 (ddd, J = 15.0, 8.8, 6.2 Hz), -112.03 (t, J = 7.0 Hz). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{20}F_3N_3O_4$: 447.14; found: 448.32.

Example 100

Preparation of Compound **100**

(1R,4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-ethanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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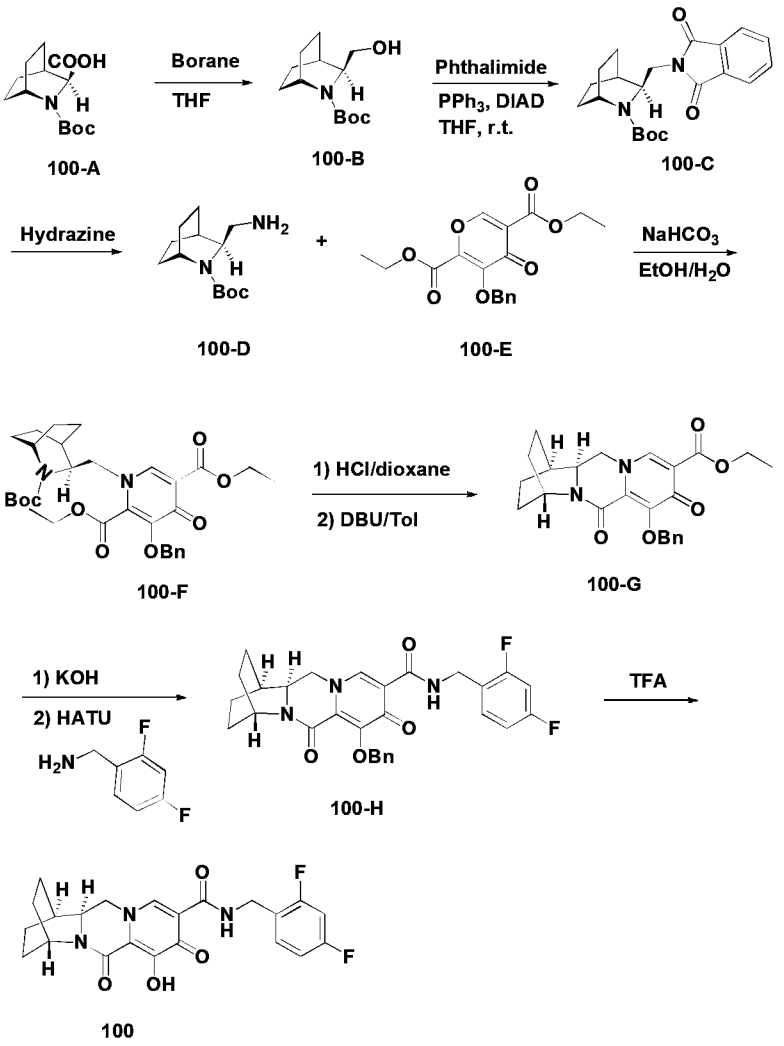

Step 1

A 100-mL rbf was charged with **100-A** (2.0 g, 7.8 mmol) in THF (20 mL). The reaction mixture was cooled to 0 ^{0}C. Borane dimethyl sulfide (2 N in THF, 17.6 mL) was slowly added in. Then the reaction mixture was stirred at room temperature for overnight. The reaction mixture was cooled back to 0 ^{0}C. Methanol (8 mL) was added drop wise to quench the reaction. After concentration, the residue was purified by Combi Flash (40 g column, cartridge used) using hexanes - EA as eluents to afford **100-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 242.

Step 2

A 100-mL rbf was charged with **100-B** (1.8 g, 7.4 mmol),

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triphenylphosphine (4.3 g, 16.2 mmol) and phthalimide (1.8 g, 12.2 mmol) in THF (30 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (3.2 mL, 16.2 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by Combi Flash (80 g column, cartridge used) using hexanes - EA as eluents to afford **100-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 371.

Step 3

To a solution of **100-C** (2.5 g, 6.8 mmol) in EtOH (50 mL) was added hydrazine monohydrate (1.7 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **100-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 241.

Step 4

A 100-mL rbf was charged with **100-D** (1.6 g, 6.7 mmol) and **100-E** (2.3 g, 6.7 mmol) in ethanol (30 mL). Sodium bicarbonate (1.2 g, 1.4 mmol) in water (30 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for overnight. The mixture was diluted with EA (200 mL) and washed with water (2 x). The aqueous fractions were extracted with EA (1 x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **100-F** was used for next step without further purification. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 569.

Step 5

A 100-mL rbf was charged with **100-F** (3.7 g, 6.5 mmol) in 4 N HCl /dioxane (38 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 3.2 g intermediate was obtained. The intermediate and DBU (5.1 g, 33.8 mmol) were dissolved in toluene (100 mL). The reaction mixture was heated to 110^{0}C with stirring for 1 hour. After concentration, the residue was purified by Combi Flash (80 g column, cartridge used) using hexanes - EA as eluents to afford **100-G**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 423.

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Step 6

A 100-mL rbf was charged with **100-G** (2.0 g, 4.7 mmol) in THF (20 mL) and MeOH (20 mL). 1 N KOH (18.9 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (18.9 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid (0.28 g, 0.72 mmol), 2, 4-difluobenzylamine (0.2 g, 1.44 mmol), N,N-diisopropylethylamine (DIPEA) (0.47 g, 3.6 mmol) and HATU (0.55 g, 1.44 mmol) were dissolved in DCM (20 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **100-H**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 520.

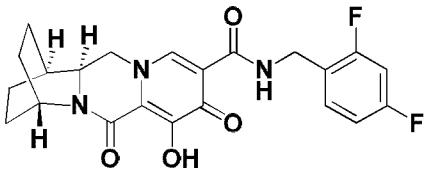
Step 7

A 50-mL rbf was charged with **100-H** (0.36 g, 0.69 mmol) in TFA (5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **100**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.25 (m, 1H), 10.47 (t, J = 5.9 Hz, 1H), 8.30 (s, 1H), 7.58 - 7.29 (m, 1H), 6.98 - 6.50 (m, 2H), 4.62 (dd, J = 14.8, 4.9 Hz, 3H), 4.22 (t, J = 12.2 Hz, 1H), 4.14 - 4.07 (m, 1H), 3.96 (dd, J = 12.2, 3.1 Hz, 1H), 2.26 - 1.44 (m, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -112.38 (t, J = 7.7 Hz), -114.78 (q, J = 8.5 Hz). **LCMS-ESI$^+$** (*m/z*): found: 430.

Example 101

Preparation of Compound **101**

(1R,4R,12aS)-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-ethanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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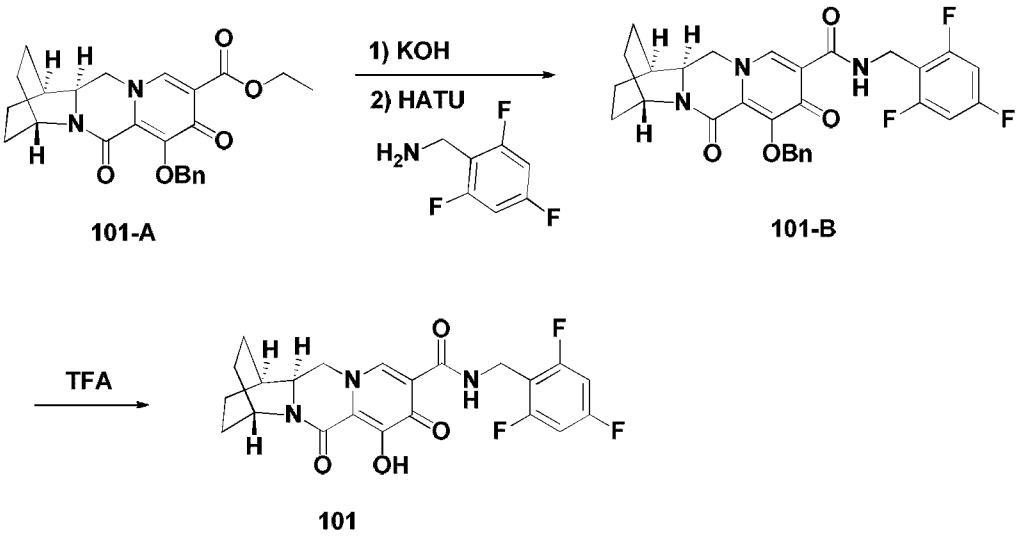

101-A **101-B** **101**

Step 1

A 100-mL rbf was charged with **101-A** (0.3 g, 0.72 mmol) in THF (2 mL) and MeOH (2 mL). 1 N KOH (2.1 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (2.1 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid (0.72 mmol), 2, 4, 6-trifluobenzylamine (0.23 g, 1.44 mmol), N,N-diisopropylethylamine (DIPEA) (0.47 g, 3.6 mmol) and HATU (0.55 g, 1.44 mmol) were dissolved in DCM (20 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **101-B**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 538.

Step 2

A 50-mL rbf was charged with **101-B** (0.36 g, 0.67 mmol) in TFA (5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **101**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.11 (s, 1H), 10.40 (t, J = 5.8 Hz, 1H), 8.28 (s, 1H), 6.91 - 6.39 (m, 2H), 4.62 (ddd, J = 25.0,

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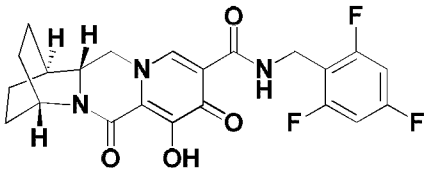
6.5, 2.8 Hz, 3H), 4.21 (t, J = 12.2 Hz, 1H), 4.09 (dd, J = 12.5, 3.0 Hz, 1H), 3.93 (dd, J = 12.2, 3.1 Hz, 1H), 2.35 - 1.39 (m, 9H). **^{19}F NMR** (376 MHz, Chloroform-d) δ -112.38 (t, J = 7.7 Hz), -114.78 (q, J = 8.5 Hz). **LCMS-ESI$^+$** (*m/z*): found: 448.

Example 102

Preparation of Compound **102**

(1S,4S,12aR)-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-ethanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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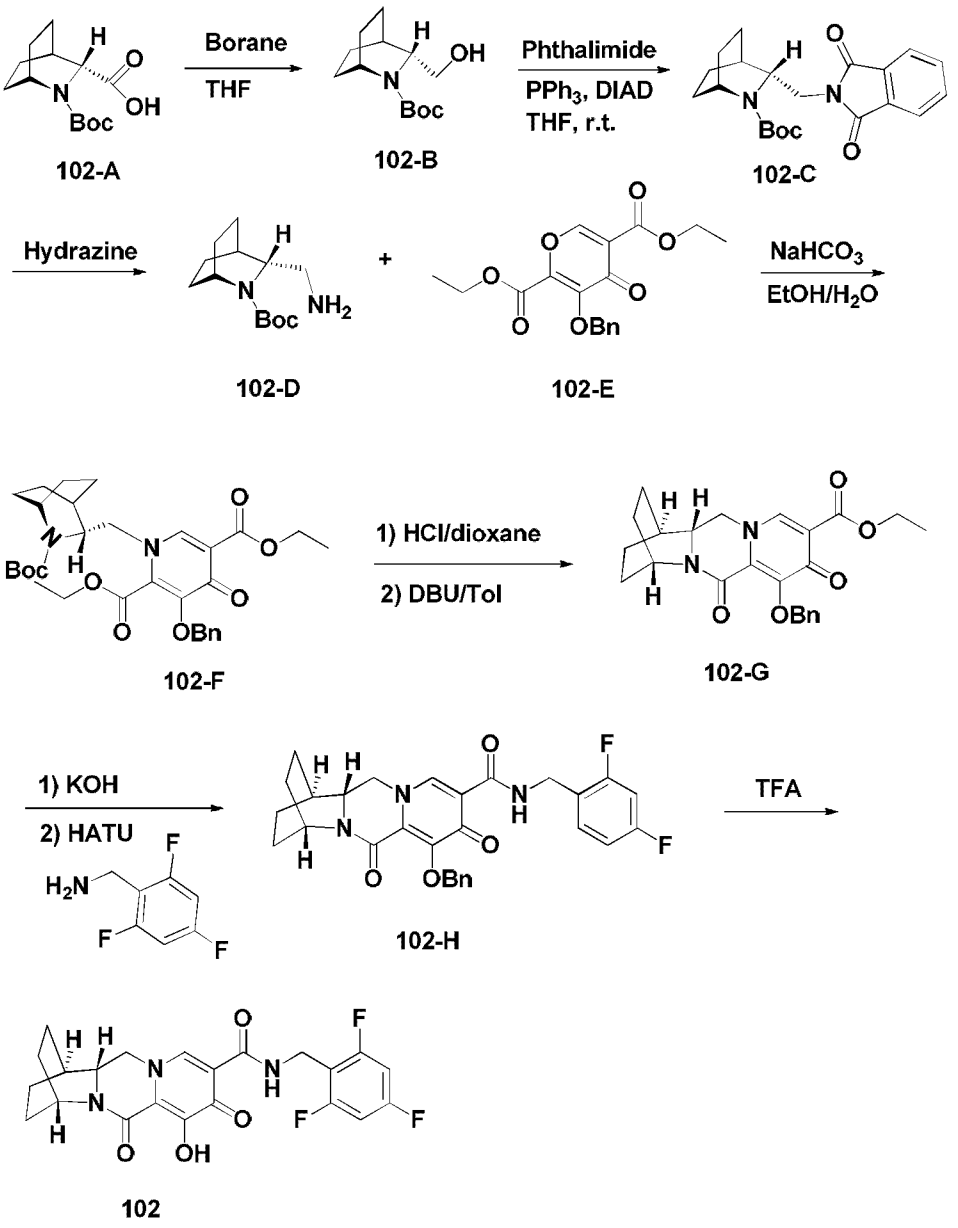

Step 1

A 100-mL rbf was charged with **102-A** (2.0 g, 7.8 mmol) in THF (20 mL). The reaction mixture was cooled to 0 ^{0}C. Borane dimethyl sulfide (2 N in THF, 17.6 mL) was slowly added in. Then the reaction mixture was stirred at room temperature for overnight. The reaction mixture was cooled back to 0 ^{0}C. Methanol (8 mL) was added drop wise to quench the reaction. After concentration, the residue was purified by Combi Flash (40 g column, cartridge used) using hexanes - EA as eluents to afford **102-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 242.

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Step 2

A 100-mL rbf was charged with **102-B** (1.8 g, 7.4 mmol), triphenylphosphine (4.3 g, 16.2 mmol) and phthalimide (1.8 g, 12.2 mmol) in THF (30 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (3.2 mL, 16.2 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by Combi Flash (80 g column, cartridge used) using hexanes - EA as eluents to afford **102-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 371.

Step 3

To a solution of **102-C** (2.5 g, 6.8 mmol) in EtOH (50 mL) was added hydrazine monohydrate (1.7 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **102-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 241.

Step 4

A 100-mL rbf was charged with **102-D** (1.6 g, 6.7 mmol) and **102-E** (2.3 g, 6.7 mmol) in ethanol (30 mL). Sodium bicarbonate (1.2 g, 1.4 mmol) in water (30 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for overnight. The mixture was diluted with EA (200 mL) and washed with water (2 x). The aqueous fractions were extracted with EA (1 x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **102-F** was used for next step without further purification. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 569.

Step 5

A 100-mL rbf was charged with **102-F** (3.7 g, 6.5 mmol) in 4 N HCl /dioxane (38 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 3.2 g intermediate was obtained. The intermediate and DBU (5.1 g, 33.8 mmol) were dissolved in toluene (100 mL). The reaction mixture was heated to 110^{0}C with stirring for 1 hour. After concentration, the residue was purified by Combi Flash (80 g column, cartridge used) using hexanes - EA as eluents to afford **102-G**.

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LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ found: 423.

Step 6

A 100-mL rbf was charged with **102-G** (0.3 g, 0.72 mmol) in THF (2 mL) and MeOH (2 mL). 1 N KOH (2.1 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (2.1 mL). After concentration, the residue was co-evaporated with toluene (3x). The crude acid (0.72 mmol), 2, 4, 6-trifluobenzylamine (0.23 g, 1.44 mmol), N,N-diisopropylethylamine (DIPEA) (0.47 g, 3.6 mmol) and HATU (0.55 g, 1.44 mmol) were dissolved in DCM (20 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **102-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 538.

Step 7

A 50-mL rbf was charged with **102-H** (0.36 g, 0.67 mmol) in TFA (5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **102**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.13 (s, 1H), 10.40 (t, J = 5.8 Hz, 1H), 8.28 (s, 1H), 6.64 (t, J = 8.1 Hz, 2H), 4.89 - 4.41 (m, 3H), 4.22 (t, J = 12.2 Hz, 1H), 4.09 (dd, J = 12.3, 3.1 Hz, 1H), 3.95 (dd, J = 12.1, 4.1 Hz, 1H), 2.45 - 1.60 (m, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ - 109.26 (ddd, J = 15.1, 8.8, 6.3 Hz), -111.99 (t, J = 6.9 Hz). **LCMS-ESI**$^+$ (*m/z*): found: 448.

Example 103

Preparation of Compound **103**

(1R,4R,12aR)-2,3-difluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

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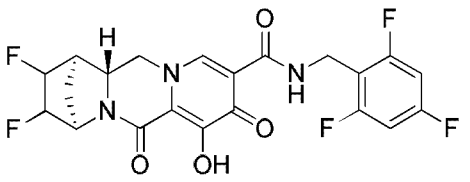
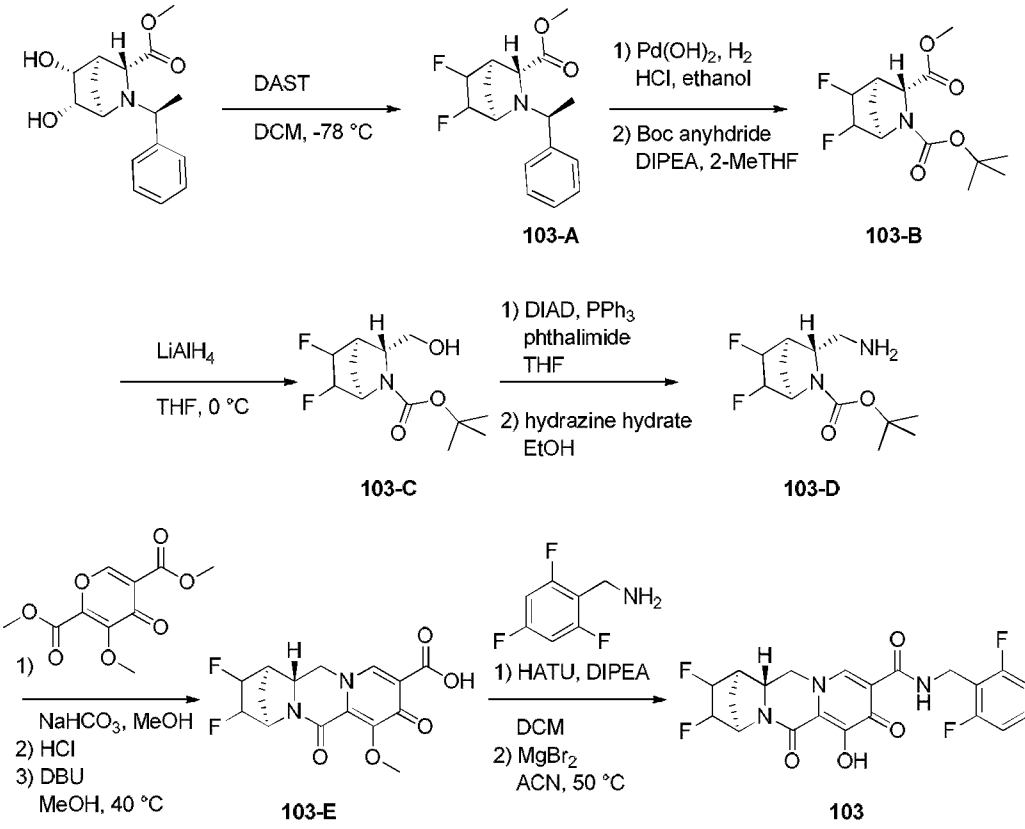


103



103-A **103-B** **103-C** **103-D** **103-E** **103**

Step 1

A solution of (1R,3R,4R,5R,6S)-methyl 5,6-dihydroxy-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (2.0g, 6.9mmol) in DCM (27mL) was cooled to -78 °C in a dry ice/acetone bath. To this solution was added DAST (2.18 ml, 16.48 mmol) via plastic tipped pipette. The solution was stirred at -78 °C for 30 minutes after which time it was removed from the bath, let warm slowly to room temperature, and stirred at room temperature for one hour. The reaction was quenched by slow addition of the reaction mixture to a stirring solution of saturated sodium bicarbonate (150mL) via plastic tipped pipette. The layers were separated and

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the aqueous layer was back-extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (7-28% ethyl acetate/hexane) to provide **103-A**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.43 – 7.16 (m, 5H), 5.01 – 4.60 (m, 2H), 3.85 (q, *J* = 7.1, 6.6 Hz, 1H), 3.55 (s, 2H), 3.53 – 3.42 (m, 2H), 2.76 (dq, *J* = 5.1, 2.0 Hz, 1H), 2.19 – 2.07 (m, 1H), 2.03 – 1.88 (m, 1H), 1.39 (d, *J* = 6.7 Hz, 3H).

Steps 2 and 3

To a solution of **103-A** (0.96 g, 3.24 mmol) in Ethanol (36.01 ml) and 1.25M HCl-ethanol (4.09 ml) was added 20% PdOH/C (1.14 g, 1.62 mmol) the suspension was stirred under an atmosphere of hydrogen for 22 hours. After filtering through Celite, the cake was washed with EtOH, the filtrate was concentrated under vacuum to dryness to afford the crude deprotected product which was assumed to be 3.24mmol for next step. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_8H_{12}F_2NO_2$: 192.08; found: 192.110.

To the crude residue (0.62 g, 3.24 mmol) and Di-tert-butyl dicarbonate (1.06 g, 4.86 mmol) in 2-Methyltetrahydrofuran (32.43 ml) was added N,N-diisopropylethylamine (0.56 ml, 0 mol). Upon completion, the reaction mixture was diluted with water, extracted into EtOAC (2x) and the organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (0-55% EtOAc/Hexanes) to afford **103-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 5.12 - 5.01 (m, 1H), 4.92 (s, 1H), 4.49 (s, 1H), 4.14 (d, J = 14.7 Hz, 1H), 3.75 (s, 3H), 2.91 (s, 1H), 2.24 - 1.98 (m, 2H), 1.47 (s, 5H), 1.38 (s, 5H). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{20}F_2NO_4$: 292.13; found: 291.75.

Step 4

A solution of **103-B** (0.68 g, 2.33 mmol) in THF (15 ml) was stirred in an ice bath as 1.0 M $LiBH_4$ in THF (4.65 ml) was added and the resulting mixture was stirred at 0 °C for 30 minutes at which time it was shown to be complete by TLC. The reaction mixture was carefully treated with water (0.3 mL), then with NaOH (~15%, 3.5M, 0.3 mL), then finally with additional water (0.9 mL). The mixture was stirred at

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room temperature for 15 minutes, and the ppt that formed was filtered, washed with diethyl ether and the supernate was concentrated to afford **103-C**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.83 (s, 1H), 4.56 (d, J = 10.5 Hz, 1H), 4.37 (s, 1H), 3.78 - 3.47 (m, 3H), 2.76 (s, 1H), 2.36 - 2.18 (m, 1H), 2.17 - 1.98 (m, 1H), 1.55 (s, 1H), 1.48 (s, 9H).

Steps 5 and 6

A mixture of **103-C** (0.59 g, 2.25 mmol), phthalimide (0.53 g, 3.6 mmol) and triphenylphosphine (1.3 g, 4.95 mmol) in THF (11 ml) was cooled in an ice bath. Diisopropyl Azodicarboxylate (0.97 ml, 4.95 mmol) was added. The mixture was then warmed up to room temperature and stirred for 14h and then concentrated in vacuo. The residue was dissolved in ether, stirred for 1 h, then the solids were filtered off and the filtrate was concentrated. The residue was purified by silica column chromatography (10-31-91% EtOAc/hexanes) to afford the protected amino compound (assumed 2.25mmol of product). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{23}F_2N_2O_4$: 393.15; found: 392.77.

A solution of the protected amino compound (0.88 g, 2.25 mmol) and hydrazine hydrate (0.46 ml, 9.52 mmol) in ethanol (22 ml) was stirred at 60 °C for 2 h. The reaction mixture was cooled in an ice bath, ether (10 ml) was added and the mixture was stirred for 30 min. The solid formed was filtered off and the filtrate was concentrated under vacuum to dryness to give **103-D**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 5.17 - 4.61 (m, 2H), 4.37 (s, 1H), 3.80 (s, 1H), 3.11 - 2.77 (m, 1H), 2.01 (s, 2H), 1.87 (s, 1H), 1.83 (d, J = 7.4 Hz, 1H), 1.46 (s, 9H), 1.30 (d, J = 6.4 Hz, 1H), 1.27 (d, J = 6.3 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{20}F_2N_2O_2$: 263.15; found: 262.86.

Steps 7, 8 and 9

Compound **103** was prepared in a similar manner to compound **60** using **103-D** in place of **41-E** and using (2,4,6-trifluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. A single diastereomer resulted. The stereochemistry of the fluorines is unknown. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.08 (s, 1H), 6.46 - 6.27 (m, 2H), 4.95 (d, J = 53.5 Hz, 1H), 4.65 (d, J = 54.9 Hz, 1H), 4.45 (s, 1H), 4.33 (d,

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J = 5.6 Hz, 2H), 3.84 (t, J = 3.6 Hz, 2H), 2.75 (s, 1H), 2.28 (p, J = 1.9 Hz, 2H), 2.20 (s, 1H), 1.91 (dd, J = 33.3, 15.2 Hz, 1H), 0.95 (s, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{17}F_5N_3O_4$: 470.11; found: .470.13.

ANTIVIRAL ASSAY

Example 104

Antiviral Assays in MT4 Cells

For the antiviral assay utilizing MT4 cells, 0.4 µL of 189X test concentration of 3-fold serially diluted compound in DMSO was added to 40 µL of cell growth medium (RPMI 1640, 10% FBS, 1% penicilline/Streptomycine, 1% L-Glutamine, 1% HEPES) in each well of 384-well assay plates (10 concentrations) in quidruplicate.

1 mL aliquots of 2×10^6 MT4 cells are pre-infected for 1 and 3 hours respectively at 37 °C with 25 µL (MT4) or of either cell growth medium (mock-infected) or a fresh 1:250 dilution of an HIV-IIIb concentrated ABI stock (0.004 m.o.i. for MT4 cells). Infected and uninfected cells are diluted in cell growth medium and 35 µL of 2000 (for MT4) cells is added to each well of the assay plates.

Assay plates were then incubated in a 37 °C incubator. After 5 days of incubation, 25 µL of 2X concentrated CellTiter-Glo™ Reagent (catalog # G7573, Promega Biosciences, Inc., Madison, WI) was added to each well of the assay plate. Cell lysis was carried out by incubating at room temperature for 2–3 minutes, and then chemiluminescence was read using the Envision reader (PerkinElmer).

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

Table 1

Compound Number	nM in MT-4	
	EC_{50}	CC_{50}

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Compound Number	nM in MT-4	
	EC_{50}	CC_{50}
1	2.6	5819
2	2.2	3111
3	2.0	38446
4	14.8	45769
5	8.1	10452
6	5.3	53192
7	3.5	15610
8	2.5	13948
9	5.1	13451
10	6.1	3670
11	4.9	10274
12	5.9	3337
13	46.0	12666
14	65.5	4939
15	2.2	16268
16	1.5	13633
17	5.9	6613
18	4.1	10263
19	2.8	38690
20	3.3	27990
21	38.3	13010
22	64.3	4433
23	2.3	13444
24	6.1	12074
25	26.2	5233
26	10.3	8836
27	4.4	8751
28	15.6	18687

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Compound Number	nM in MT-4	
	EC_{50}	CC_{50}
29	13.9	9446
30	4.0	6828
31	9.0	4525
32	14.0	4684
33	43.5	3971
34	422.1	3585
35	157.0	15546
36	7.6	11424
37	10.2	19486
38	1.7	10223
39	3.6	12174
40	2.4	9560
41	2.1	15675
42	2.5	3544
43	6.9	10321
44	2.3	9869
45	2.4	15765
46	2.6	19295
47	1.9	11301
48	2.7	13967
49	33.3	52219
50/51 (racemic mixture)	1.9	37173
52	15.0	12943
53	14.3	3347
54	15.6	3236
55	1.5	11100
56	3.1	17238

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Compound Number	nM in MT-4	
	EC_{50}	CC_{50}
57	2.3	11751
58	1.5	7694
59	3.1	22200
60	2.1	3308
61	1.8	25881
62	9.2	3492
63	2.5	3164
64	3.5	3332
65	2.4	2508
66	9.4	11848
67	10.7	2981
68	2.7	4175
69	1.9	4767
70	5.1	8413
71	2.6	4660
72	4.3	6255
73	1.8	9194
74	29.3	4340
75	2.8	5292
76	17.8	34581
77	5.6	10145
78	5.6	3198
79	3.4	12092
80	4.6	5045
81	1.9	12298
82	2.9	30434
83	1.9	27501
84	2.9	9727

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Compound Number	nM in MT-4	
	EC_{50}	CC_{50}
85	2.0	10378
86	2.3	22405
88	2.9	3230
89	8.4	4629
90	5.7	8086
91	5.0	7183
92	18.6	4553
93	2.2	6158
94	11.5	51173
96	2.6	26586
97	2.1	17341
98	2.4	17947
99	2.0	8475
100	2.2	11580
101	2.1	11585
102	2.3	12042
103	10.3	35127

Example 105

Human PXR Activation Assay

Luciferase Reporter Gene Assay. A stably transformed tumor cell line (DPX2) was plated on 96-well microtiter plates. DPX2 cells harbor the human PXR gene (NR1I2) and a luciferase reporter gene linked to two promoters identified in the human CYP3A4 gene, namely XREM and PXRE. The cells were treated with six concentrations of each compound (0.15 ~ 50 μM) and incubated for 24 hours. The number of viable cells was determined and the reporter gene activity was assessed. Positive control: Rifampicin at 6 concentrations (0.1 ~ 20 μM). $\%E_{max}$ relative to the maximum fold induction by 10 or 20 μM RIF was calculated for test compounds

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according to the following equation which adjusts for the DMSO background: $\%E_{max}$ = (Fold induction – 1)/(Maximum fold induction by RIF – 1) x 100%.

Table 2

Compound Number	$\%E_{max}$ at 15 µM
2	4.5
3	7.5
4	3
5	32
6	0
7	6
8	7
9	7
10	19
15	20
16	17
17	7
18	4
19	2
20	2
23	45
28	6
29	3
32	14
33	17
36	3
37	2
38	7
39	6

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Compound Number	$\%E_{max}$ at 15 μM
40	0
41	11.5
42	21
43	18
44	4
45	19
46	34
47	11
48	5
54	2
55	24
56	3
57	3
58	1
59	4
60	3
61	1
63	13
64	8
66	0
67	0
68	6
69	5
70	10
71	3
72	4
73	7
75	0

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Compound Number	$\%E_{max}$ at 15 μM
77	11
79	0
80	2
81	1
82	1
83	1
84	21
85	77
86	30
88	27
89	5
90	11
91	3
92	3
93	9
96	11
97	9
98	0
99	17
100	45
102	123
103	0

Example 106

OCT2 Inhibition Assay

The dose dependent inhibition of OCT2 mediated uptake of a model substrate ^{14}C-Tetraethylammonium (TEA) by test compounds was studied in wild-type and OCT2-transfected MDCKII cells at 7 concentrations from 0.014 μM to 10 μM.

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MDCKII cells were maintained in minimal essential medium (MEM) with 1% Pen/Strep, 10% fetal bovine serum, and 0.25 mg/mL hygromycin B in an incubator set at 37 ºC, 90% humidity and 5% CO_2. 24 hours prior to assay, media containing 5 mM sodium butyrate were added to MDCKII cells in flasks, and cells were grown to 80-90% confluence. On assay day, cells were trypsinized and resuspended in Krebs-Henseleit Buffer (KHB), pH 7.4 at 5 x 10^6 million cells/mL. Cells were preincubated for 15 min in assay plate before addition of test compound or substrate.

Test compounds were serially diluted in DMSO and then spiked (2 µL) into in 0.4 mL KHB buffer containing wild-type or OCT2-transfected cells and incubated for 10 minutes. Assay was initiated with the addition of 0.1 mL of 100 µM ^{14}C-TEA in KHB buffer (20 µM final concentration after mixing). The concentration of TEA is based on the K_m. After 10 minutes of incubation, the assay mixture was quenched with addition of 0.5 mL of ice-cold 1X PBS buffer. Samples were then centrifuged at 1000 rpm for 5 min and supernatants were removed. Wash steps were repeated four times with ice-cold PBS. Finally, the cell pellets were lysed with 0.2N NaOH and let sit at room temperature for at least 30 min to ensure complete lysis. Samples were then counted on liquid scintillation counter and dpm counts were used to perform the following calculations. The % inhibition was calculated as follows: % inhibition = $[1- \{ [OCT2]_i - [WT]_{ni} \} / \{[OCT2]_{ni}-[WT]_{ni}\}]*100$ where, $[OCT2]_i$ represents the dpm count in the presence of test compound for either OCT2 cells, $[OCT2]_{ni}$ represents the dpm count in the absence of test compound for OCT2 cells and $[WT]_{ni}$ represents the dpm count in the absence of test compound for wild type cells, respectively.

Table 3

Compound Number	IC_{50} (nM)
2	240
3	250
5	2230
11	10000

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Compound Number	IC_{50} (nM)
13	610
36	10000
39	358
40	204
41	2823
42	487
45	137
47	6200
48	4909
55	476
63	42
64	94
77	3830
82	10000
83	10000
96	1357
98	3726
99	1506
100	450

The data in Tables 1, 2 and 3 represent an average over time of each assays for each compound. For certain compounds, multiple assays have been conducted over the life of the project. Thus, the data reported in Tables 1, 2 and 3 include the data reported in the priority documents, as well as data from assays run in the intervening period.

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Example 107

Pharmacokinetic Analysis Following Oral or Intravenous Administration to Beagle Dogs

Pharmacokinetic analysis was performed on various test compounds following intravenous or oral administration to beagle dogs.

For pharmacokinetic analysis of intravenously administered compounds, the test compounds were formulated in 5% Ethanol, 55% PEG 300, and 40% water at 0.1 mg/mL for IV infusion. For pharmacokinetic analysis of orally administered compounds, the test compounds were formulated as an aqueous suspension in 0.1% Tween 20, 0.5% HPMC LV100 in Di Water at 1 mg/kg.

Each dosing group consisted of 3 male, non-naïve purebred beagle dogs. At dosing, the animals weighed between 10 to 13 kg. The animals were fasted overnight prior to dose administration and up to 4 hr after dosing. For studies of intravenous administration, the test article was administered to the animals by intravenous infusion over 30 min. The rate of infusion was adjusted according to the body weight of each animal to deliver a dose of 0.5 mg/kg. For studies of oral administration, the test article was administered according to the body weight of each animal to deliver a dose of 1 mg/kg.

For pharmacokinetic analysis of intravenously administered compounds, serial venous blood samples (approximately 1 mL each) were taken from each animal at 0, 0.250, 0.483, 0.583, 0.750, 1.00, 1.50, 2.00, 4.00, 8.00, 12.0, and 24.0 hours after dosing. The blood samples were collected into Vacutainer™ tubes containing EDTA-K2 as the anti-coagulant and were immediately placed on wet ice pending centrifugation for plasma. An LC/MS/MS method was used to measure the concentration of the test compound in plasma. An aliquot of 100 µL of each plasma sample was added to a clean 96 well plate, and 400 µL of cold acetonitrile/internal standard solution (ACN)/(ISTD) was added. After protein precipitation, an aliquot of 110 µL of the supernatant was transferred to a clean 96-well plate and diluted with 300 µL of water. An aliquot of 25 µL of the above solution was injected into a TSQ Quantum Ultra LC/MS/MS system utilizing a Hypersil Gold C_{18} HPLC column (50 X 3.0 mm, 5 µm; Thermo-Hypersil Part # 25105-053030). An Agilent 1200 series binary

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pump (P/N G1312A Bin Pump) was used for elution and separation, and an HTS Pal autosampler (LEAP Technologies, Carrboro, NC) was used for sample injection. A TSQ Quantum Ultra triple quadrupole mass spectrometer was utilized in selective reaction monitoring mode (Thermo Finnigan, San Jose, CA). Liquid chromatography was performed using two mobile phases: mobile phase A contained 1% acetonitrile in 2.5 mM ammonium formate aqueous solution with pH of 3.0, and mobile phase B contained 90% acetonitrile in 10 mM ammonium formate with pH of 4.6. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data. The resulting data are shown in the first three columns of Table 4. In Table 4, **CL** refers to clearance, which characterizes the rate at which drug is removed from plasma. The lower the clearance of a drug is, the longer the elimination half-life is in the body. **V_{ss}** refers to the steady state volume of distribution and indicates how well a drug is distributed into the tissues. The larger the V_{ss} is, the longer the elimination half-life is in the body. **MRT** refers to mean residence time, which is a measure of the average time molecules exist in the body.

For pharmacokinetic analysis of orally administered compounds, serial venous blood samples (approximately 0.3 mL each) were taken from each animal at time points of 0, 0.25, 0.50, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hours after dosing. Blood samples were collected, prepared and analyzed in a similar way to the intranveous studies described above. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data. The resulting data are shown in the last three columns of Table 4. In Table 4, F (%) refers to oral bioavailability. C_{max} refers to the peak plasma concentration of the compound after administration. AUC refers to area under the curve and is a measure of total plasma exposure of the indicated compound.

Table 4

Compound #	**CL (L/h/kg)**	**V_{ss} (L/kg)**	**MRT (h)**	**F (%) aqueous suspension**	**C_{max} (µM) aqueous suspension**	**AUC (µM*h) aqueous suspension**

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98	0.047	0.16	3.3	n/a	n/a	n/a
83	0.161	0.38	2.4	n/a	n/a	n/a
55	0.058	0.24	4.2	n/a	n/a	n/a
77	0.300	0.64	2.2	n/a	n/a	n/a
41	0.015	0.11	7.5	10.7	2.4	16.3
42	0.020	0.15	7.1	28.0	4.5	28.6
47	0.014	0.10	7.4	12.6	2.8	20.4
8	0.498	0.87	1.8	n/a	n/a	n/a
7	0.510	1.20	2.3	n/a	n/a	n/a
3	0.047	0.23	4.9	18.7	1.2	9.2
2	0.030	0.20	6.5	40.7	7.8	66.1

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification are incorporated herein by reference, in their entirety to the extent not inconsistent with the present description.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

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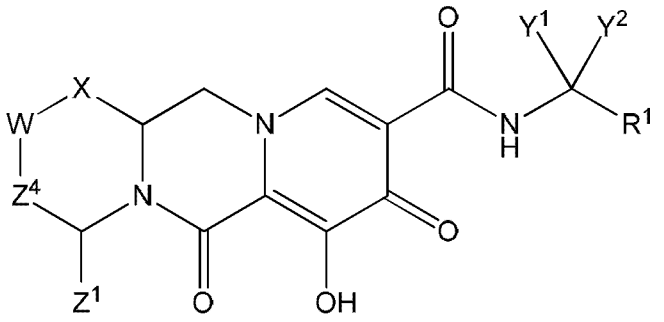
CLAIMS

What is claimed is:

1. A compound having the following Formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or -NZ^3- or -CHZ^3-;

W is -CHZ^2-;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is -$C(R^a)_2$-, -$C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2$-, or -$C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2$-, wherein at least one of Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-;

Z^4 is a bond, -CH_2-, or -CH_2CH_2-;

Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl;

R^1 is phenyl substituted with one to three halogens; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl.

2. A compound of claim 1 having the following Formula (II-A):

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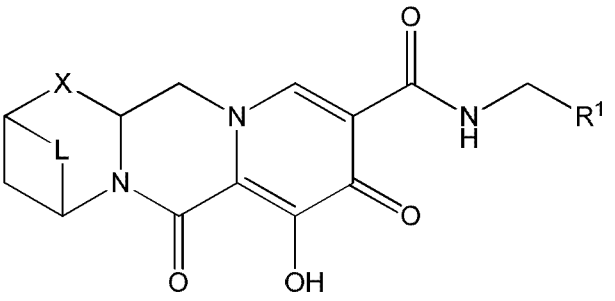
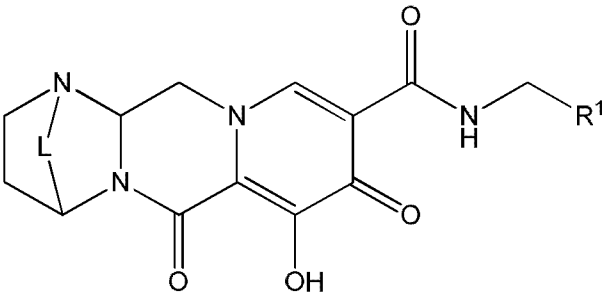


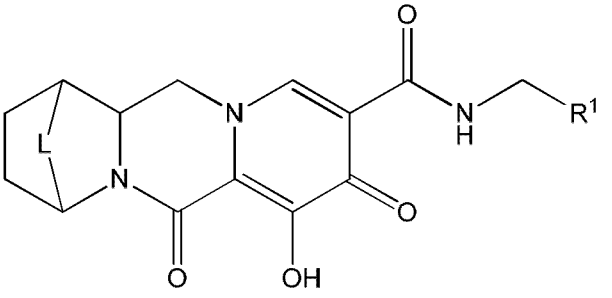
(II-A)

3. A compound of claim 1 having the following Formula (II-B):



(II-B)

4. A compound of claim 1 having the following Formula (II-C):



(II-C)

5. A compound of any one of claims 1–4 wherein L is $-C(R^a)_2-$.

6. A compound of any one of claims 1–4 wherein L is $-C(R^a)_2C(R^a)_2-$.

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7. A compound of any one of claims 1–4 wherein L is $-C(R^a)_2C(R^a)_2C(R^a)_2-$.

8. A compound of any one of claims 1–7 wherein each R^a is hydrogen.

9. A compound of any one of claims 1–7 wherein one R^a is methyl and each remaining R^a is hydrogen.

10. A compound of any one of claims 1-7 wherein at least one R^a is halogen and each remaining R^a is hydrogen.

11. A compound of any one of claims 1-7 wherein two R^a are halogen and each remaining R^a is hydrogen.

12. A compound of any one of claims 1-7 wherein one R^a is halogen and each remaining R^a is hydrogen.

13. A compound of any one of claims 1–2 or 5–12 wherein X is -O-.

14. A compound of any one of claims 1–2 or 5–12 wherein X is $-NZ^3-$.

15. A compound of any one of claims 1–2 or 5–12 wherein X is -NH-.

16. A compound of any one of claims 1–2 or 5–12 wherein X is $-CHZ^3-$ and Z^1 and Z^3, taken together, form -L-.

17. A compound of claim 16 wherein Z^2 is hydrogen.

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18. A compound of any one of claims 1–2 or 5–12 wherein X is $-CH_2-$.

19. A compound of any one of claims 1 or 5-18 wherein Z^4 is a bond or $-CH_2-$.

20. A compound of any one of claims 1 or 5-18 wherein Z^4 is $-CH_2-$.

21. A compound of any one of claims 1 or 5-18 wherein Z^4 is a bond.

22. A compound of any one of claims 1 or 5-21 wherein Y^1 and Y^2 are each independently hydrogen, methyl or trifluoromethyl.

23. A compound of any one of claims 1–22 wherein R^1 is substituted with one halogen.

24. A compound of claim 23 wherein R^1 is 4-fluorophenyl or 2-fluorophenyl.

25. A compound of any one of claims 1–22 wherein R^1 is substituted with two halogens.

26. A compound of claim 25 wherein R^1 is 2,4-difluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-chlorophenyl, 3,4-difluorophenyl, 2-fluoro-4-chlorophenyl, or 3,5-difluorophenyl.

27. A compound of claim 26 wherein R^1 is 2,4-difluorophenyl.

28. A compound of any one of claims 1–22 wherein R^1 is substituted with three halogens.

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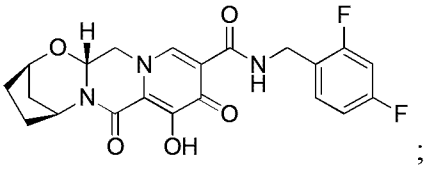
29. A compound of claim 28 wherein R^1 is 2,4,6-trifluorophenyl or 2,3,4-trifluorophenyl.

30. A compound of claim 29 wherein R^1 is 2,4,6-trifluorophenyl.

31. A compound of claim 1 selected from: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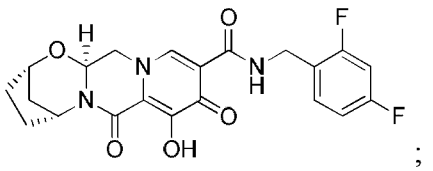
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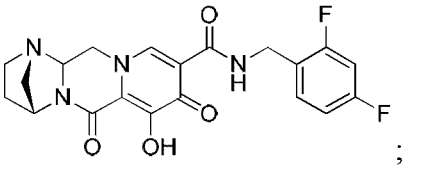
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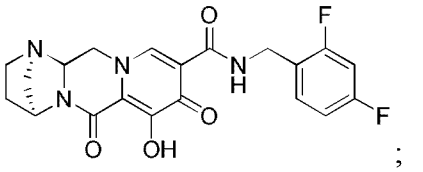
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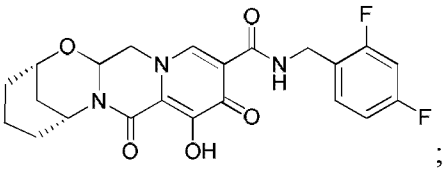
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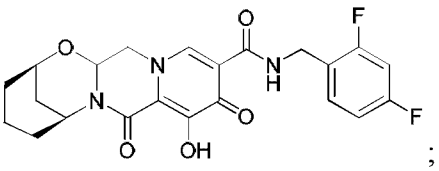
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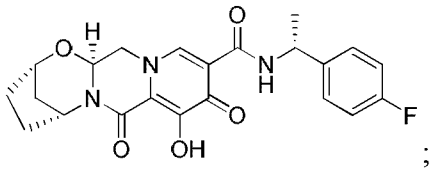
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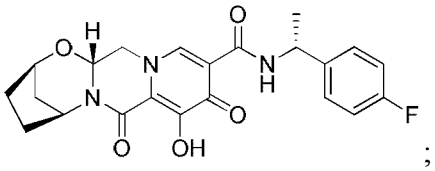
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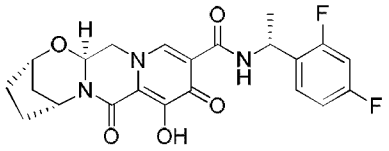
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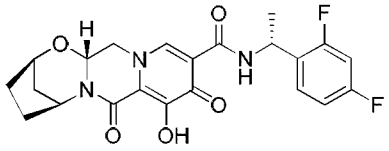
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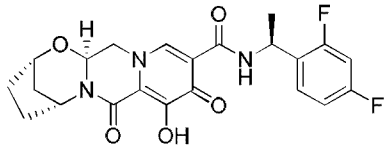
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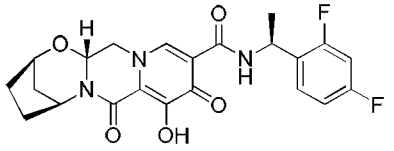
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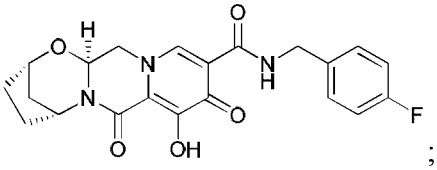
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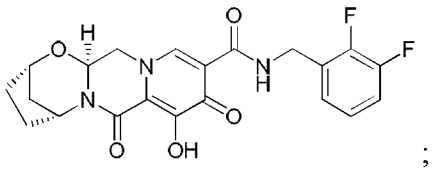
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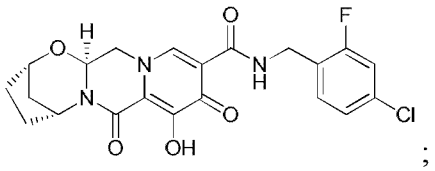
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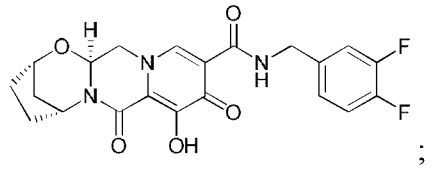
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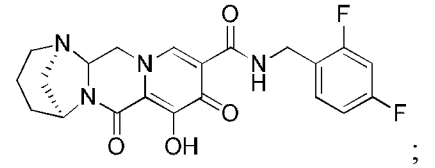
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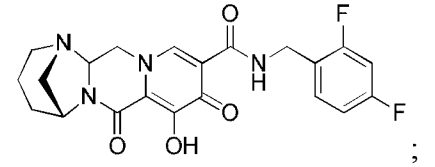
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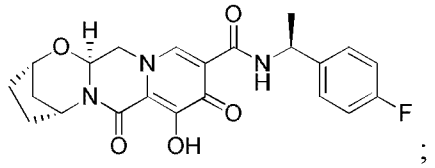
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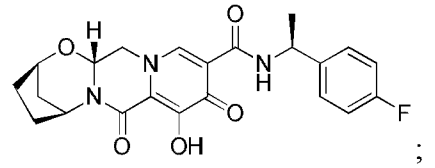
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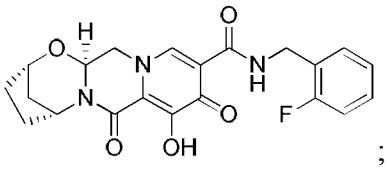
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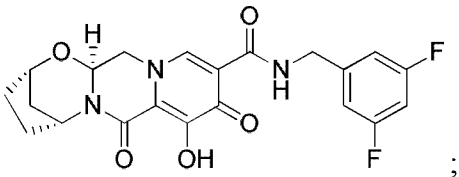
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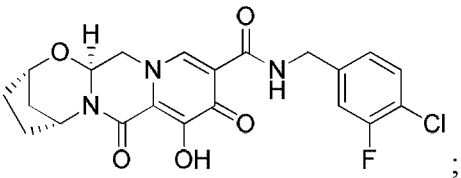
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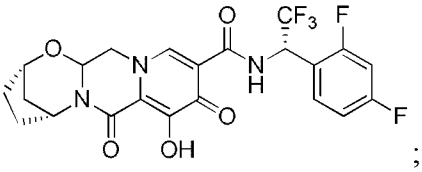
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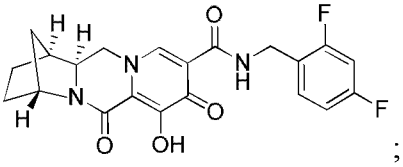
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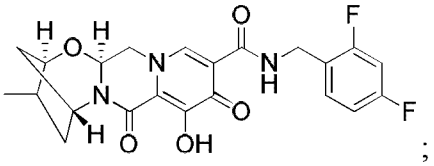
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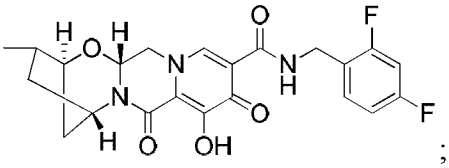
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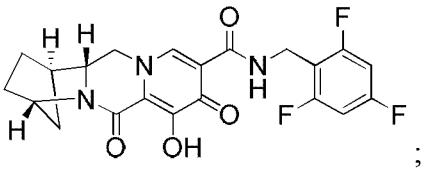
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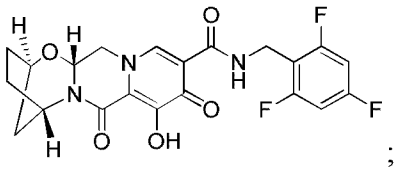
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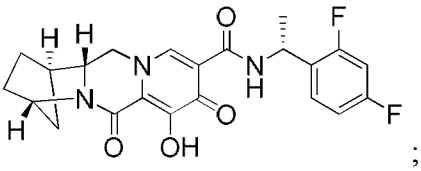
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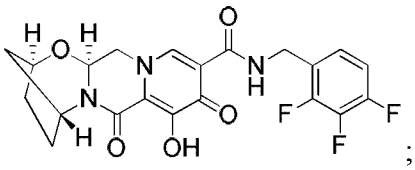
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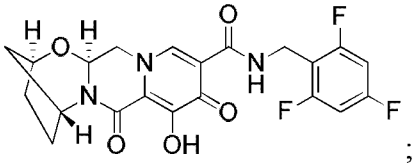
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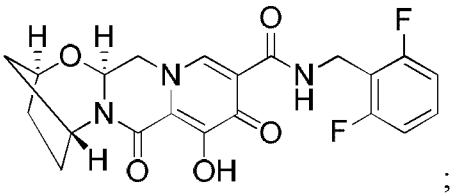
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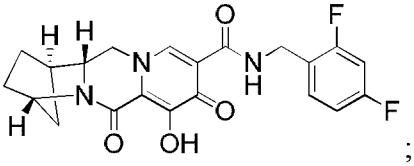
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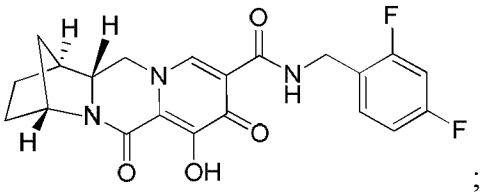
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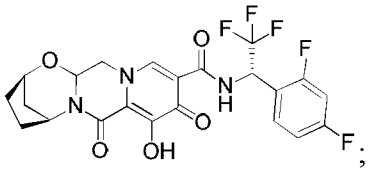
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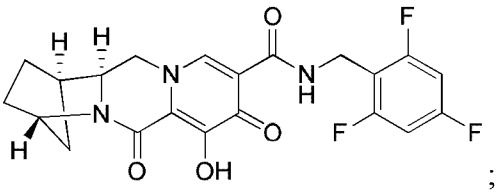
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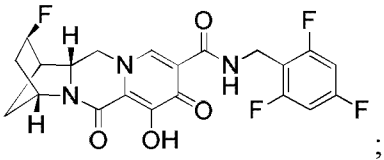
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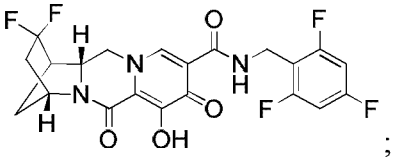
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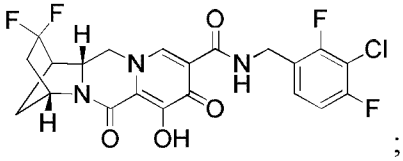
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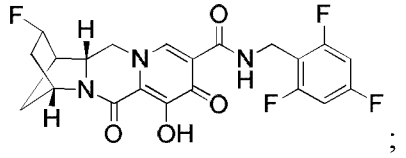
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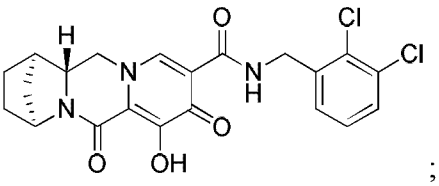
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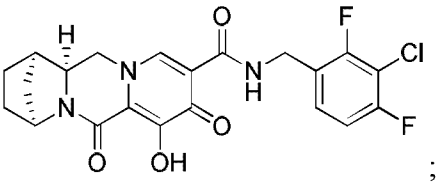
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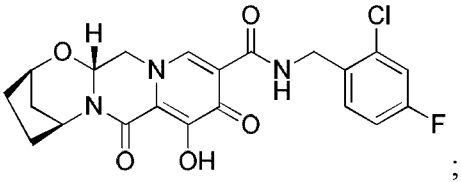
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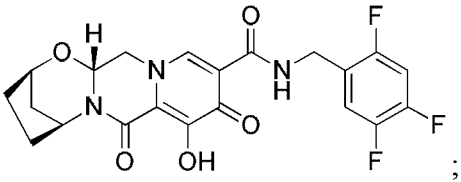
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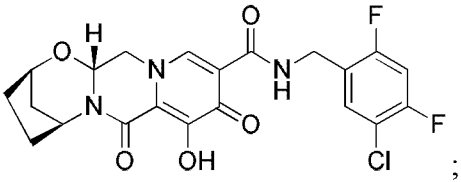
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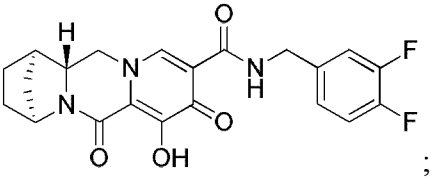
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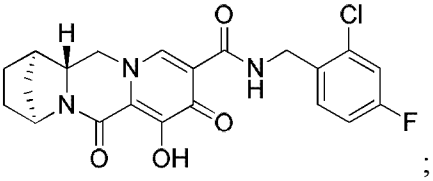
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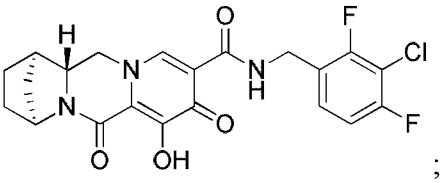
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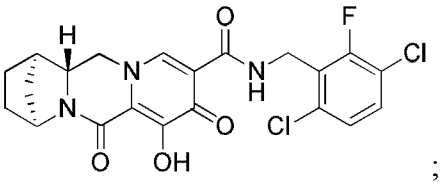
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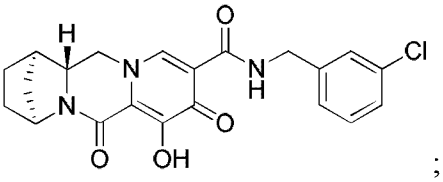
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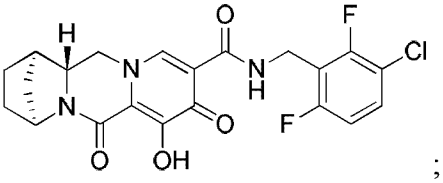
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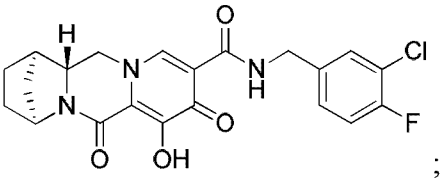
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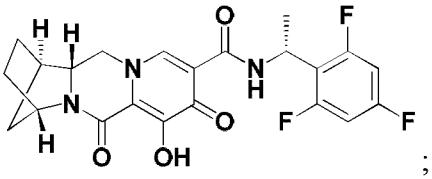
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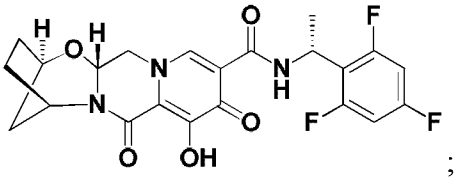
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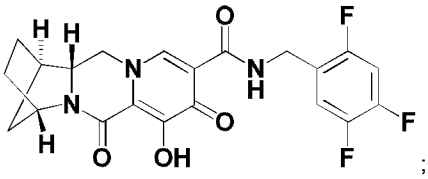
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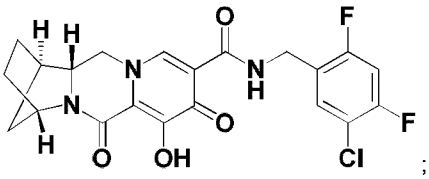
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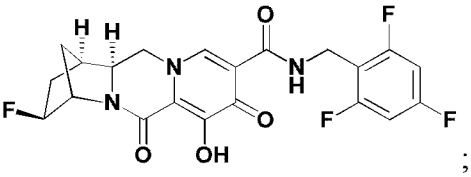
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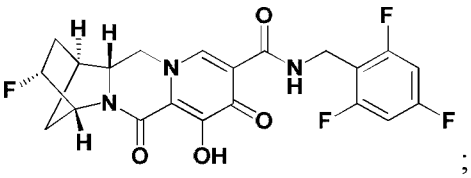
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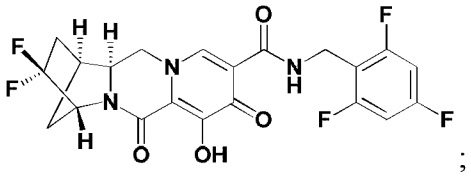
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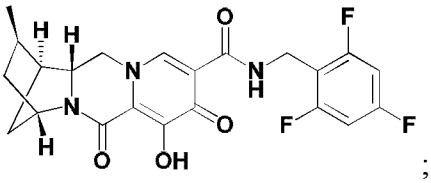
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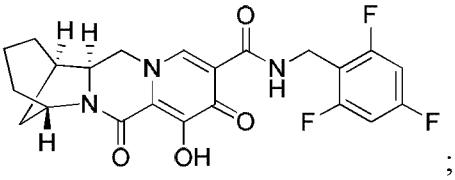
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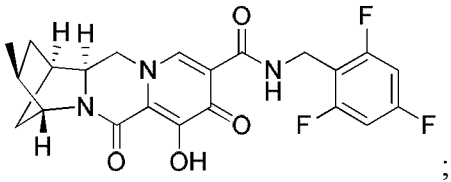
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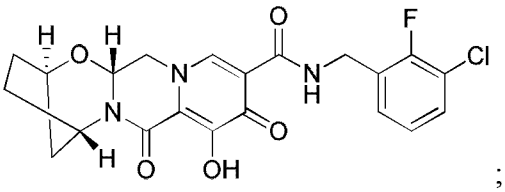
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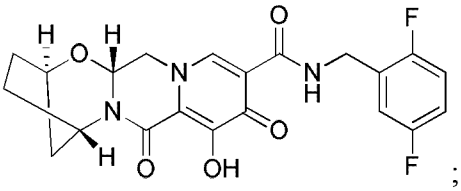
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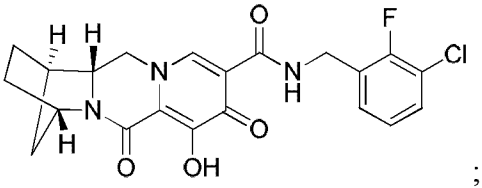
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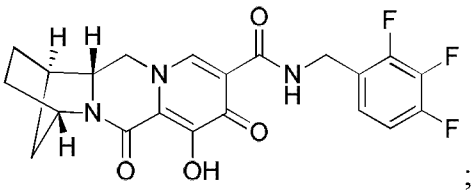
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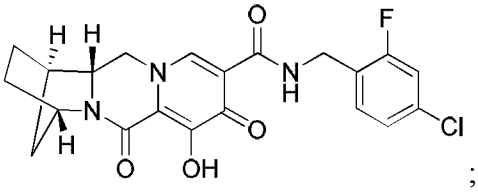
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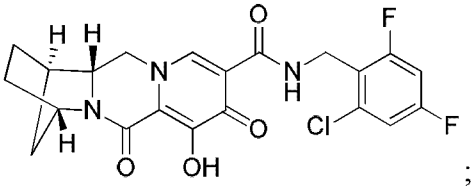
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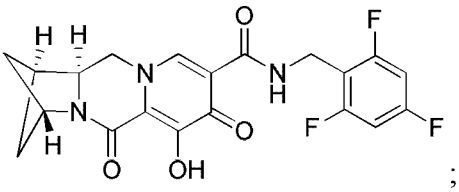
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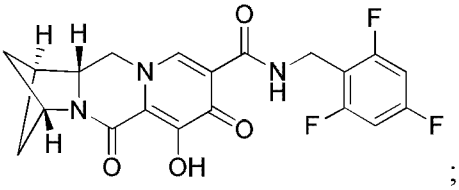
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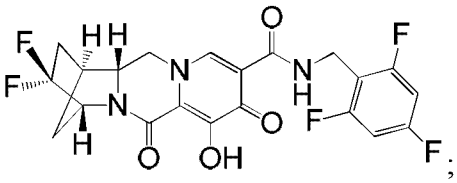
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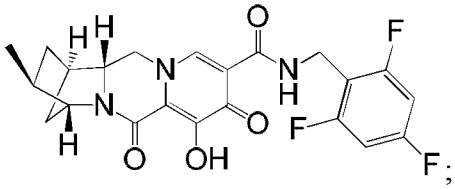
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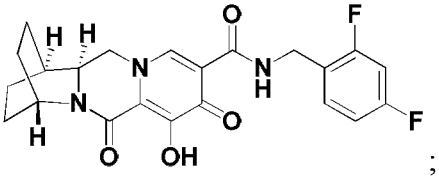
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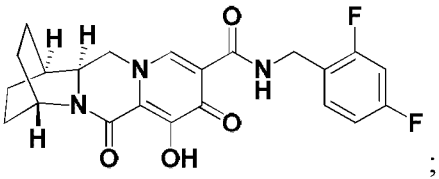
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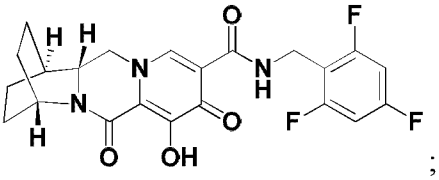
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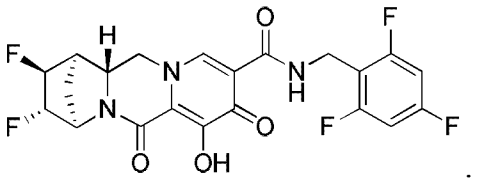
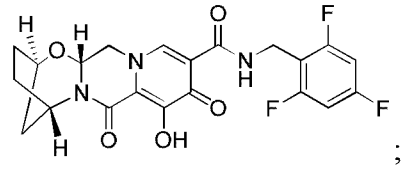


.

32. A compound of claim 1 selected from:



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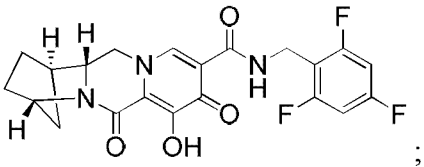

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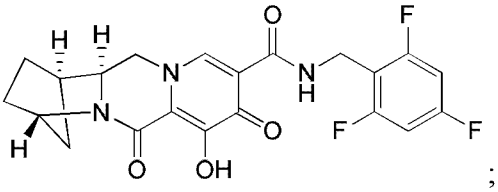

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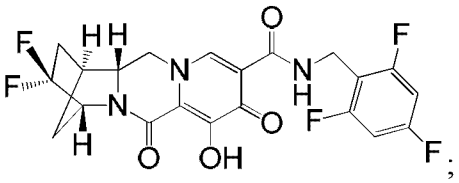

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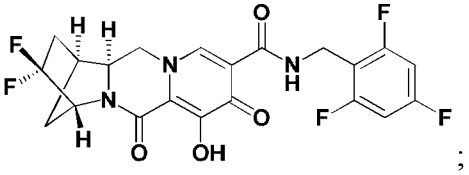

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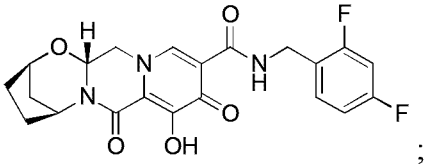

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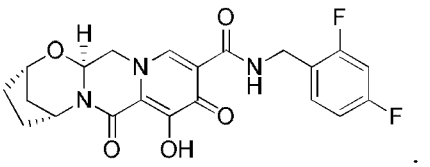

33. A pharmaceutical composition comprising a compound of any one of claims 1–32, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

34. A pharmaceutical composition of claim 33 further comprising one or more additional therapeutic agents.

35. A pharmaceutical composition of claim 34 wherein the one or more one additional therapeutic agents is an anti-HIV agent.

36. A pharmaceutical composition of claim 35 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and combinations thereof.

37. A method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of claims 1–32 or a pharmaceutical composition of claim 33.

38. A method of claim 37 further comprising administering to the human a therapeutically effective amount of one or more additional therapeutic agents.

39. A method of claim 38 wherein the one or more additional therapeutic agents is an anti-HIV agent.

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40. A method of claim 39 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and combinations thereof.

41. Use of a compound of any one of claims 1–32 or a pharmaceutical composition of claim 33 for the treatment of an HIV infection in a human having or at risk of having the infection.

42. A use of claim 41 further comprising administering to the human a therapeutically effective amount of one or more additional therapeutic agents.

43. A use of claim 42 wherein the one or more additional therapeutic agents is an anti-HIV agent.

44. A use of claim 43 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and combinations thereof.

45. A compound as described in any one of claims 1–32, or a pharmaceutically acceptable salt thereof for use in medical therapy.

46. A compound as described in any one of claims 1–32, or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment of an HIV infection.

47. A compound having the following Formula (I):

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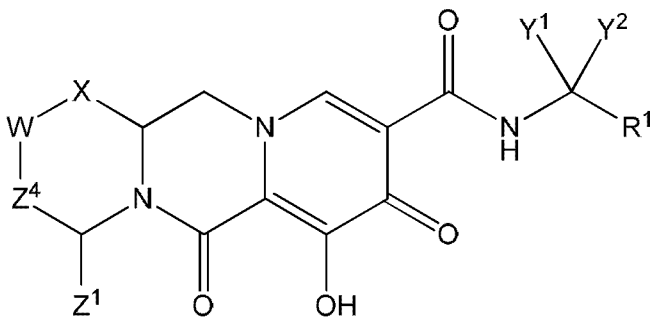

(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or -NZ^3- or -CHZ^3-;

W is -O- or –NZ^2- or –CHZ^2-;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is -$C(R^a)_2$-, -$C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2SO_2NR^aC(R^a)_2$- or -$C(R^a)_2NR^aSO_2C(R^a)_2$-;

Z^4 is a bond or -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -CH_2OCH_2-, -$CH_2NR^aCH_2$-, -CH_2SCH_2-,-$CH_2S(O)CH_2$- or -$CH_2SO_2CH_2$-;

Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, or Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms, wherein the carbocyclic or heterocyclic ring is optionally substituted with one or more R^a;

R^1 is optionally substituted aryl or optionally substituted heteroaryl; and

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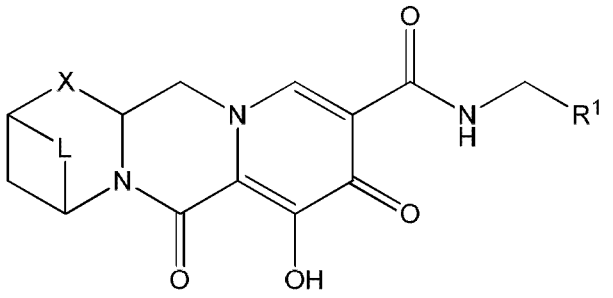
each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl, or wherein two R^a groups, together with the carbon atom to which they are attached, form C=O, and

wherein at least one of: (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-; or (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

48. A compound of claim 47 wherein W is $-CHZ^2-$

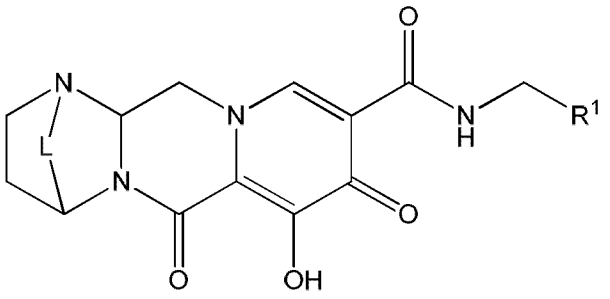
49. A compound of claim 47 or 48 wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-.

50. A compound of claim 49 having one of the following Formulas (II-A), (II-B), or (II-C):



;

(II-A)



; or

(II-B)

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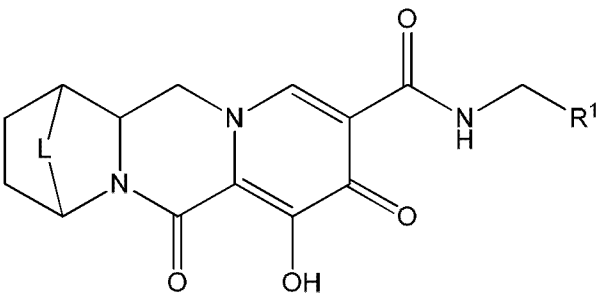
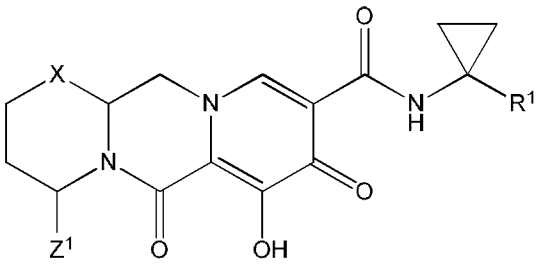


(II-C)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

51. A compound of claim 47 or 48 wherein Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

52. A compound of claim 51 having one of the following Formulas (III-A), (III-B), (III-C) or (III-D):



(III-A)

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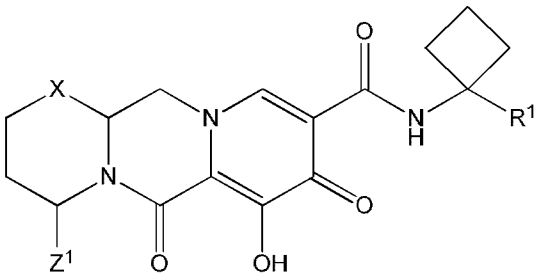

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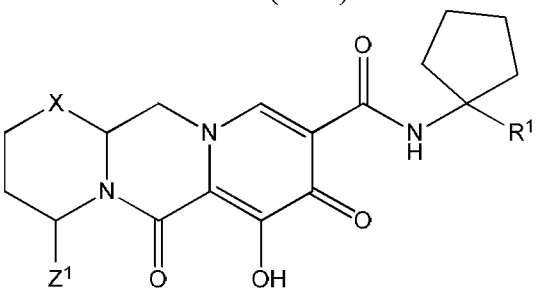
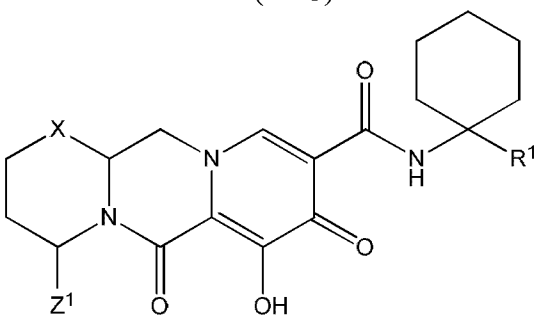
(III-B)



; or

(III-C)



,

(III-D)

wherein Z^1 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl.

53. A compound of claim 51 having one of the following Formulas (III-E), (III-F), (III-G) or (III-H):

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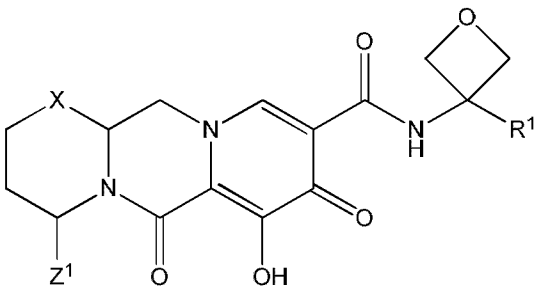
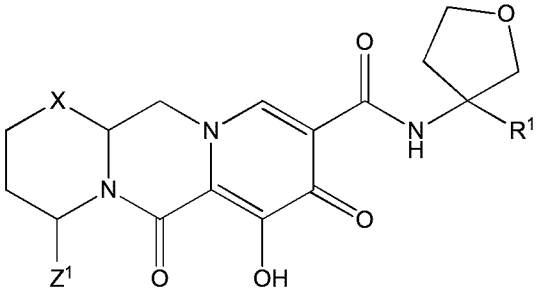


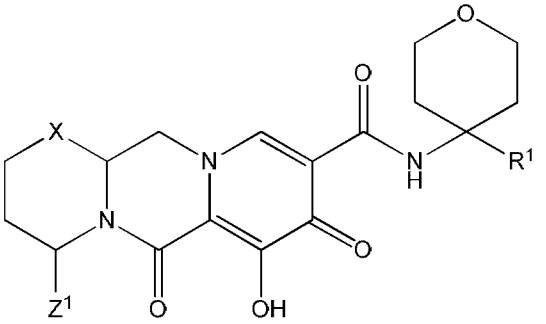
;

(III-E)



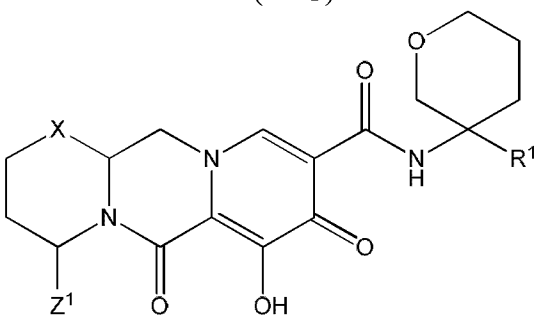
;

(III-F)



; or

(III-G)



,

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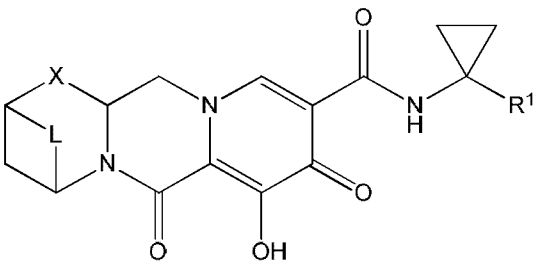
(III-H)

wherein Z^1 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl.

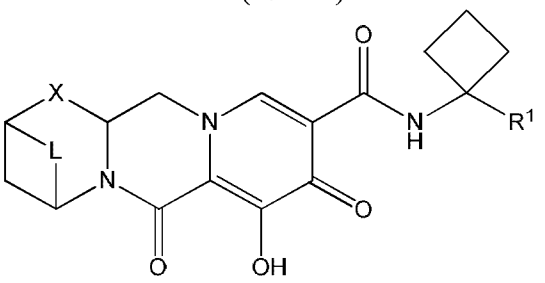
54. A compound of claim 47 or 48 wherein both (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-, and (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

55. A compound of claim 54 having one of the following Formulas (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG) or (IV-AH):



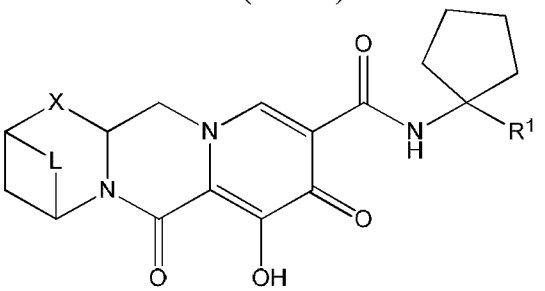
;

(IV-AA)



;

(IV-AB)



;

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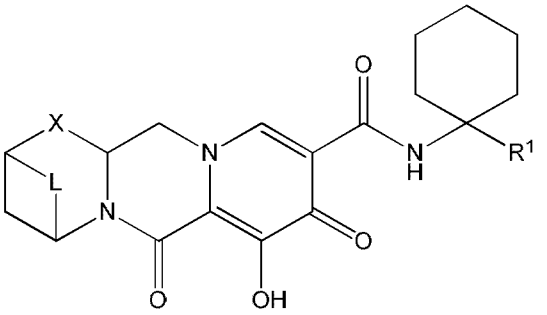
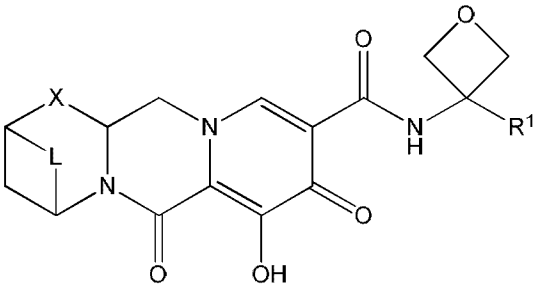
(IV-AC)



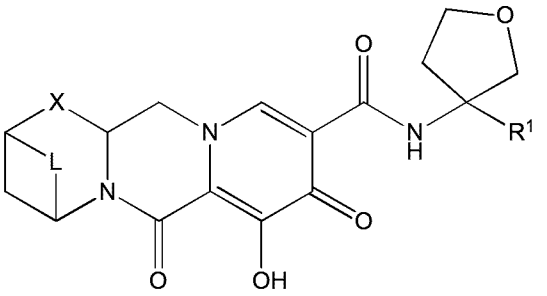
;

(IV-AD)



;

(IV-AE)



;

(IV-AF)

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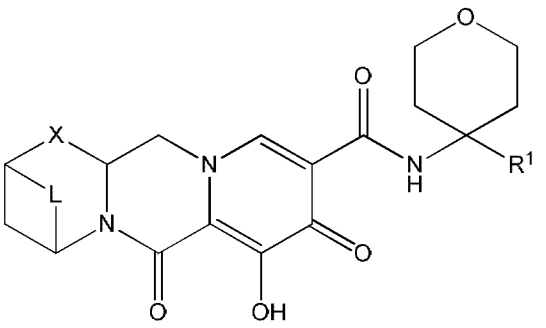
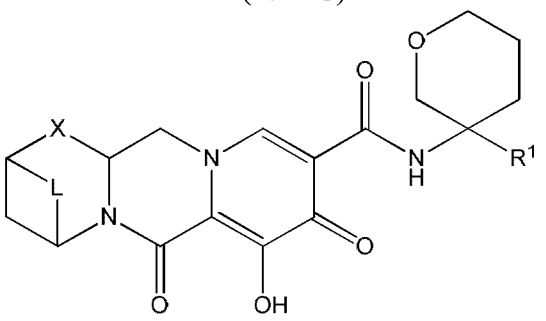


; or

(IV-AG)



,

(IV-AH)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

56. A compound of claim 54 having one of the following Formulas (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG) or (IV-BH):

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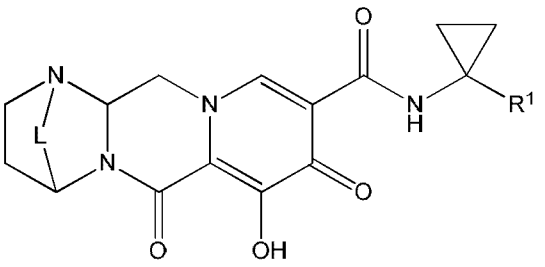
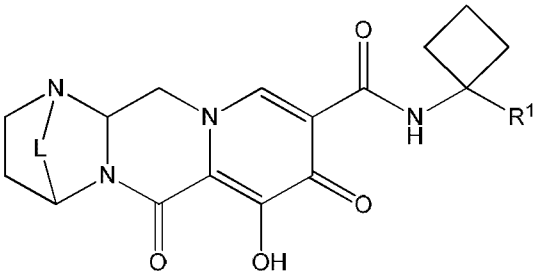


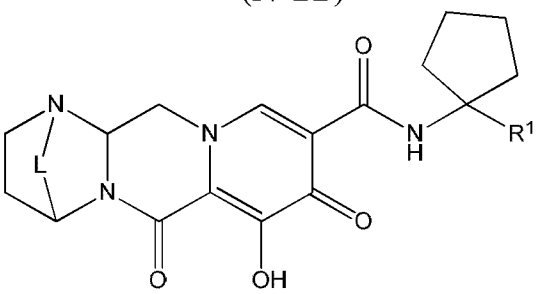
;

(IV-BA)



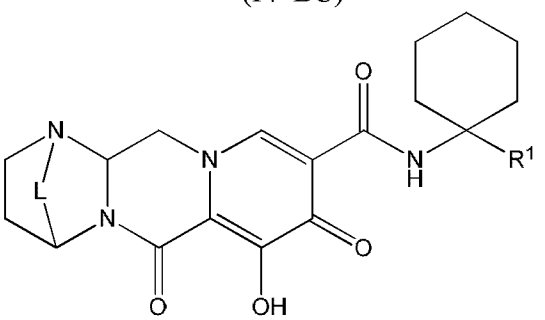
;

(IV-BB)



;

(IV-BC)



;

(IV-BD)

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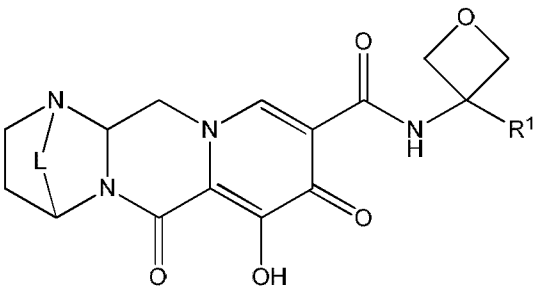
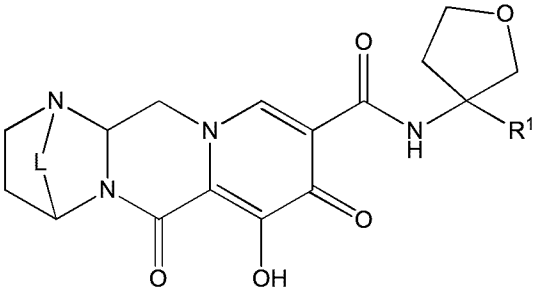


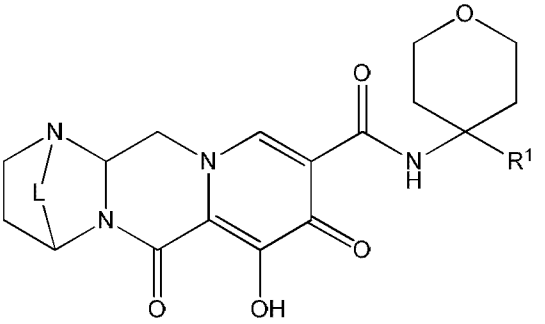
;

(IV-BE)



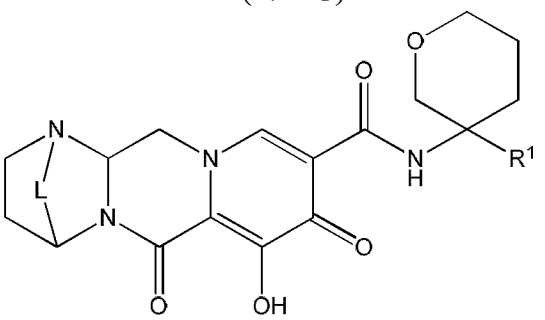
;

(IV-BF)



; or

(IV-BG)



,

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(IV-BH)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

57. A compound of any one of claims 47-50 or 54-56 wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, or $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$.

58. A compound of claim 57 wherein L is $-C(R^a)_2-$.

59. A compound of claim 57 wherein L is $-C(R^a)_2C(R^a)_2-$.

60. A compound of claim 57 wherein L is $-C(R^a)_2C(R^a)_2C(R^a)_2-$.

61. A compound of any one of claims 47-50 or 54-60 wherein each R^a is hydrogen.

62. A compound of any one of claims 47-50 or 54-60 wherein one R^a is methyl and each remaining R^a is hydrogen.

63. A compound of any one of claims 47-50 or 54-60 wherein at least one R^a is halogen and each remaining R^a is hydrogen.

64. A compound of any one of claims 47-50 or 54-60 wherein two R^a are halogen and each remaining R^a is hydrogen.

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65. A compound of any one of claims 47-50 or 54-60 wherein one R^a is halogen and each remaining R^a is hydrogen.

66. A compound of any one of claims 47-50 or 54-56 wherein L is $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, or $-C(R^a)_2SO_2C(R^a)_2-$.

67. A compound of any one of claims 47-50 or 54-56 wherein L is $-C(R^a)_2OC(R^a)_2-$.

68. A compound of claim 66 or 67 wherein each R^a is hydrogen.

69. A compound of claim 66 or 67 wherein one R^a is methyl and each remaining R^a is hydrogen.

70. A compound of claim 66 or 67 wherein at least one R^a is halogen and each remaining R^a is hydrogen.

71. A compound of claim 66 or 67 wherein two R^a are halogen and each remaining R^a is hydrogen.

72. A compound of claim 66 or 67 wherein one R^a is halogen and each remaining R^a is hydrogen.

73. A compound of any one of claims 47–55 or 57–72 wherein X is -O-.

74. A compound of claim 73 wherein Z^2 is hydrogen.

75. A compound of any one of claims 47–72 wherein X is $-NZ^3-$.

76. A compound of any one of claims 47-72 wherein X is -NH-.

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77. A compound of any one of claims 47-55 or 57-72 wherein X is -CHZ^3-

78. A compound of any one of claims 47–55 or 57–72 wherein X is -CH_2-.

79. A compound of any one of claims 47-49, 51, 54 or 57-78 wherein Z^4 is a bond or -CH_2-.

80. A compound of any one of claims 47-49, 51, 54 or 57-78 wherein Z^4 is -CH_2-.

81. A compound of any one of claims 47-49, 51, 54 or 57-78 wherein Z^4 is a bond.

82. A compound of any one of claims 47-49 or 57-81 wherein Y^1 and Y^2 are each independently hydrogen, methyl or trifluoromethyl.

83. A compound of any one of claims 47-82 wherein R^1 is phenyl.

84. A compound of any one of claims 47-82 wherein R^1 is pyridinyl.

85. A compound of any one of claims 47-84 wherein R^1 is substituted with at least one halogen.

86. A compound of any one of claims 47-84 wherein R^1 is substituted with one halogen.

87. A compound of claim 86 wherein R^1 is 4-fluorophenyl or 2-fluorophenyl.

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88. A compound of any one of claims 47-84 wherein R^1 is substituted with two halogens.

89. A compound of claim 88 wherein R^1 is 2,4-difluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-chlorophenyl, 3,4-difluorophenyl, 2-fluoro-4-chlorophenyl, or 3,5-difluorophenyl.

90. A compound of claim 89 wherein R^1 is 2,4-difluorophenyl.

91. A compound of any one of claims 47–84 wherein R^1 is substituted with three halogens.

92. A compound of claim 91 wherein R^1 is 2,4,6-trifluorophenyl or 2,3,4-trifluorophenyl.

93. A compound of claim 92 wherein R^1 is 2,4,6-trifluorophenyl.

94. A compound of claim 85 wherein R^1 is 3-trifluoromethyl-4-fluorophenyl or 2-cyclopropoxy-4-fluorophenyl.

95. A pharmaceutical composition comprising a compound of any one of claims 47-94, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

96. A pharmaceutical composition of claim 95 further comprising one or more additional therapeutic agents.

97. A pharmaceutical composition of claim 96 wherein the one or more one additional therapeutic agents is an anti-HIV agent.

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98. A pharmaceutical composition of claim 97 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and combinations thereof.

99. A method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of claims 47-94 or a pharmaceutical composition of claim 95.

100. A method of claim 99 further comprising administering to the human a therapeutically effective amount of one or more additional therapeutic agents.

101. A method of claim 100 wherein the one or more additional therapeutic agents is an anti-HIV agent.

102. A method of claim 101 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and other drugs for treating HIV, and combinations thereof.

103. Use of a compound of any one of claims 47-94 or a pharmaceutical composition of claim 95 for the treatment of an HIV infection in a human having or at risk of having the infection.

104. A use of claim 103 further comprising administering to the human a therapeutically effective amount of one or more additional therapeutic agents.

105. A use of claim 104 wherein the one or more additional therapeutic agents is an anti-HIV agent.

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106. A use of claim 105 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and other drugs for treating HIV, and combinations thereof.

107. A compound as described in any one of claims 47-94, or a pharmaceutically acceptable salt thereof for use in medical therapy.

108. A compound as described in any one of claims 47-94, or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment of an HIV infection.

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