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APPLICATION NUMBER: *15/346,335*
FILING DATE: *November 08, 2016*
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ISSUE DATE: *February 04, 2020*

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PTO/AIA/15 (03-13)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	1147.P2C
First Named Inventor	Benjamin Micah Collman
Title	THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents

1. [ ] Fee Transmittal Form (PTO/SB/17 or equivalent)
2. [ ] Applicant asserts small entity status. See 37 CFR 1.27
3. [ ] Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [X] Specification [Total Pages 109] Both the claims and abstract must start on a new page. *(See MPEP § 606.01(a) for information on the preferred arrangement)*
5. [X] Drawing(s) (35 U.S.C. 113) [Total Sheets 6]
6. Inventor's Oath or Declaration [Total Pages 3] *(including substitute statements under 37 CFR 1.63 and assignments serving as an oath or declaration under 37 CFR 1.63(c))*
   a. [X] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [X] Application Data Sheet * *See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. CD-ROM or CD-R in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, items a. – c. are required)*
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ACCOMPANYING APPLICATION PAPERS

10. [ ] Assignment Papers (cover sheet & document(s))
    Name of Assignee
11. [ ] 37 CFR 3.73(c) Statement *(when there is an assignee)* [ ] Power of Attorney
12. [ ] English Translation Document *(if applicable)*
13. [ ] Information Disclosure Statement (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] Preliminary Amendment
15. [ ] Return Receipt Postcard *(MPEP § 503) (Should be specifically itemized)*
16. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
17. [ ] Nonpublication Request under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [ ] Other:

*Note: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 must be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[X] The address associated with Customer Number: 25000 OR [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature		Date	November 1, 2016
Name (Print/Type)	Mary J. Edwards	Registration No. (Attorney/Agent)	55,140

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: 11/9/2016 Signature: (Abigail Edesari)

Application Data Sheet

Inventor Information

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Postal or Zip Code of mailing address::	94404

Correspondence Information

Correspondence Customer Number::	25000

Application Information

Application Type::	Regular
Subject Matter::	Utility
CD-ROM or CD-R?::	None

Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS
Attorney Docket Number::	1147.P2C
Request for Early Publication?::	No
Request for Non-Publication?::	No
Total Drawing Sheets::	6
Small Entity?::	No
Petition included?::	No
Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2::	No

Representative Information

Representative Customer Number::	25000

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::	Prior Appl Status::
This Application	An application claiming the benefit under 35 USC 119(e)	62/399,999	09/26/16	Pending
This Application	An application claiming the benefit under 35 USC 119(e)	62/253,042	11/09/15	Pending

Foreign Priority Information

Applicant Information

Applicant Number::	1
Applicant Type::	Assignee
Organization Name::	Gilead Sciences, Inc.
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E-Mail Address::	IPDocketing@gilead.com

Assignee Information Including Non-Applicant Assignee Information

Authorization or Opt-Out of Authorization to Permit Access

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant must opt-out of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is ONLY reviewed and processed with the INITIAL filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby grants the USPTO authority to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant DOES NOT authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant DOES NOT authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet must be signed by a patent practitioner if one or more of the applicants is a juristic entity (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, all joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of all joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature		Date (YYYY-MM-DD)	2016-11-07
Name	Mary J. Edwards	Registration Number	55,140

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	PHARMACEUTICAL FORMULATIONS

As the below named inventor, I hereby declare that:

This declaration is directed to:

[x] The attached application, or

[ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Benjamin Micah Coliman Date (Optional): 19 Oct 2016

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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- [ ] United States application or PCT international application number _____ filed on _____

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LEGAL NAME OF INVENTOR

Inventor: Joanna M. Koziara Date (Optional): Oct 11, 2016

Signature: Joanna Koziara

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of invention	PHARMACEUTICAL FORMULATIONS

As the below named inventor, I hereby declare that:

This declaration is directed to: [X] The attached application, or

[ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Lei Hong Date (Optional): 12 Oct 2016

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

CROSS-REFERENCE TO THE RELATED APPLICATIONS

[0001] This patent application claims the benefit of priority of U.S. Application Serial No. 62/253,042, filed November 9, 2015 and of U.S. application serial No. 62/399,999, filed September 26, 2016. The content of each of these provisional applications is hereby incorporated herein in its entirety.

TECHNICAL FIELD

[0002] Pharmaceutical formulations suitable for treating viral infections such as HIV are provided, in particular solid oral dosage forms including the compound of Formula I, emtricitabine and tenofovir alafenamide.

BACKGROUND

[0003] Human immunodeficiency virus, type 1 (HIV-1) infection is a life-threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide (Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic, **2013**). Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and halt disease progression.

[0004] There is also a need for medications to serve populations with limited treatment options (e.g., children, women, and the elderly). In certain situations, these populations may have difficulty maintaining treatment because of pill burden (number of pills to take each day, as well as different combinations of pills) or the size of the pills themselves, once they are coformulated into a multidrug composition. For example, there is currently no fixed dose combination registered for once a day dosing (i.e., QD) for very young children (e.g., younger than age 12 years).

[0005] 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. In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions (e.g., metformin, rifampin, HCV antivirals, hormonal contraceptives, etc.). Because the standard of care requires the use of multiple different drugs to suppress HIV, as well as to treat other conditions

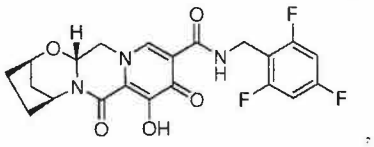
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the patient may be experiencing, the potential for drug-drug interaction is a criterion for selection of a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for drug-drug interactions (e.g., those that affect transporters (e.g., OCT-2) or activate receptors (e.g., PXR).

SUMMARY

[0006] All the compositions and oral dosage forms herein include a compound of Formula I, (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, having the following structure:

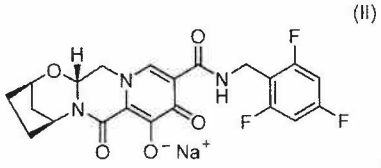
(I)



or a pharmaceutically acceptable salt thereof.

[0007] In certain embodiments, the pharmaceutically acceptable salt of the compound of Formula I is a compound of Formula II, sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure:

(II)



[0008] The inventors have successfully formulated an oral dosage form containing the compound of Formula I, tenofovir alafenamide and emtricitabine. This oral dosage form is suitable for use in medicine, and in particular in treating viral infections such as HIV.

[0009] In one aspect, a solid oral dosage form comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof is provided. In certain embodiments, the dosage form comprises 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof,

and 200 mg emtricitabine. For instance, in certain embodiments, the dosage form comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine. In certain embodiments, the dosage form comprises 52 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine.

[0010] In another aspect, a solid oral dosage form comprising 75 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine is provided. In certain embodiments, a solid oral dosage form comprising 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine is provided. In certain embodiments, a solid oral dosage form comprising 78 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

[0011] The inventors have found that it is possible to formulate solid oral dosage forms that are pharmaceutically acceptable (*i.e.* pharmacologically efficacious and physically acceptable) while reducing the total amount of excipients necessary to achieve an acceptable pharmacokinetic profile. Accordingly, in one aspect a solid oral dosage form is provided, comprising 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the dosage form has a total weight of less than 850 mg (*e.g.* less than 800 mg or less than 730 mg or less than 700 mg).

[0012] In another one aspect a solid oral dosage form is provided, comprising 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the dosage form has a total weight of less than 850 mg (*e.g.* less than 800 mg or less than 700 mg).

[0013] In another aspect, a coated tablet comprising 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided.

[0014] In another aspect, a coated tablet comprising 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided.

[0015] In another aspect, a tablet comprising 52 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

[0016] In another aspect, a tablet comprising 78 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

[0017] In another aspect, a tablet comprising (a) 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1.5 g (*e.g.*, less than about 1 g). Typically, (a) and (b) are present within separate layers in a multilayer tablet.

[0018] In another aspect, a tablet comprising (a) 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1.5 g (*e.g.*, less than about 1 g). Typically, (a) and (b) are present within separate layers in a multilayer tablet.

[0019] In another aspect, a tablet comprising from 6.5-11.0 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof is provided, where the weight percentages denote a proportion of the whole tablet. In some embodiments, (a) the compound of Formula I is present as of the compound of Formula II and/or (b) the tenofovir alafenamide is present as tenofovir alafenamide hemifumarate.

[0020] In another aspect, a tablet comprising from 9.5-11.5 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 2.5-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 26-33 % w/w emtricitabine or a pharmaceutically acceptable salt thereof is provided, where the weight percentages denote a proportion of the whole tablet. In some embodiments, (a) the compound of Formula I is present as of the compound of Formula II and/or (b) the tenofovir alafenamide is present as tenofovir alafenamide hemifumarate.

[0021] The inventors have found that the use of a fixed dose combination may assist in achieving appropriate pharmacokinetic parameters and/or adequate tablet stability. In addition, the use of a multilayer tablet as a particular type of fixed dose combination may also provide pharmacokinetic and/or stability benefits. Accordingly, in another aspect a fixed dose combination tablet comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a

pharmaceutically acceptable salt thereof is provided. Additionally, multilayer tablet comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided.

[0022] In another aspect, a kit comprising (a) a tablet comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, and (b) a desiccant (*e.g.* silica gel) is provided.

[0023] Methods of producing solid oral dosage forms such as tablets are also provided, as discussed in more detail below.

[0024] In addition, methods for treating patients are provided, which are also discussed in more detail below.

BRIEF DESCRIPTION OF DRAWINGS

[0025] Figure 1 shows the results of studies carried out on Formulations F1, F2, and F3 to assess the dissolution of 78 mg of the Compound of Formula II as a single agent compared to a bi-layer using fasted simulated intestinal fluid as a dissolution medium.

[0026] Figure 2 shows the results of studies carried out on Formulations F1 and F2 to assess the dissolution of 78 mg of the Compound of Formula II as a single agent compared to a bi-layer using fed simulated intestinal fluid as a dissolution medium.

[0027] Figure 3 shows the results of studies carried out on Formulations F1, F2, F4, F5, and F6 to assess the dissolution of 78 mg of the Compound of Formula II in tablets containing various excipients.

[0028] Figure 4 shows the results of studies carried out on Formulations F7 and F8 to assess the dissolution of 52 mg of the Compound of Formula II as a single agent compared to a bi-layer using fasted simulated intestinal fluid as a dissolution medium.

[0029] Figure 5 is a flow diagram illustrating the preparation of a tablet formulation containing the compound of Formula II.

[0030] Figure 6 is a flow diagram illustrating the preparation of a tablet formulation containing the compound of Formula II, emtricitabine, and tenofovir alafenamide hemifumarate.

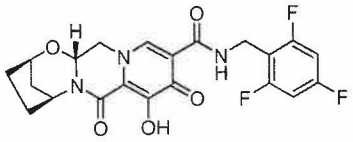
DETAILED DESCRIPTION

[0031] Typically, the oral dosage forms disclosed herein comprise three active pharmaceutical ingredients: the compound of Formula I (or a pharmaceutically acceptable salt thereof), tenofovir alafenamide (or a pharmaceutically acceptable salt thereof), and emtricitabine (or a pharmaceutically acceptable salt thereof).

(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

[0032] (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 (Formula I), is a potent HIV integrase inhibitor with *in vitro* activity against wild type HIV-1. It has the following formula (see WO2014/100323):

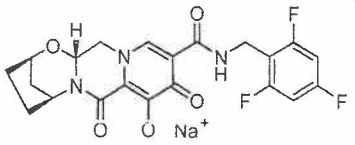
(I)



[0033] Its IUPAC name is (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. Its CAS name is 2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-, (2R,5S,13aR). The compound of Formula I is a weak acid with pKa of 8.6. The aqueous solubility of the compound of Formula I free acid is pH-dependent, with solubility increasing with increasing pH, with a maximum at pH 10.5.The chemical stability of the compound of Formula I is also pH dependent, with maximum stability at pH 4. The compound of Formula I is considered a BCS Class 2 compound, with low solubility and high permeability.

[0034] Solid oral dosage forms disclosed herein include the compound of Formula I, usually in the form of a pharmaceutically acceptable salt. The compound of Formula I can be present within an oral dosage form in solvated or unsolvated form, and references to "Formula I" include both of these forms. Typically, the compound of Formula I is in the form of the compound of Formula II, having the formula below:

(II)

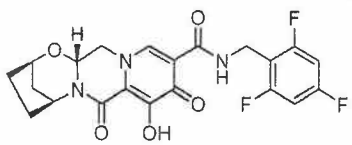


[0035] In certain specific embodiments, solid oral dosage forms containing 50 mg of the compound of Formula I, *e.g.* as about 52 mg of the compound of Formula II, are provided.

[0036] In certain specific embodiments, solid oral dosage forms containing 75 mg of the compound of Formula I, *e.g.* as about 78 mg of the compound of Formula II, are provided.

[0037] As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of the compound of Formula I (*e.g.* Formula II), any dosages, whether expressed in *e.g.* milligrams or as a % by weight, should be taken as referring to the amount of the compound of Formula I free acid, *i.e.* the amount of:

(I)

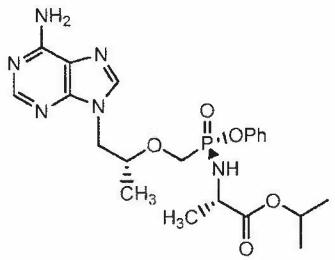


[0038] For example, therefore, a reference to "50 mg of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of the compound of Formula I as 50 mg of the compound of Formula I free acid.

[0039] For example, therefore, a reference to "75 mg of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of the compound of Formula I as 75 mg of the compound of Formula I free acid.

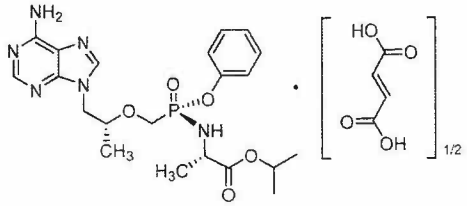
Tenofovir alafenamide

[0040] Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor having the formula below (see WO02/08241 A2):

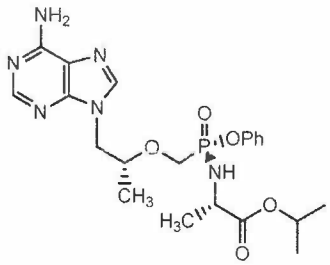


[0041] Its IUPAC name is (*S*)-isopropyl-2-(((*S*)-((((*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl)oxy)methyl)(phenoxy)phosphoryl)amino)propanoate. It is also referred to as {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl] amino]phenoxyphosphinyl]-methoxy]propyl]adenine}. Tenofovir alafenamide is a weak base, with a pKa of 3.9. Its solubility increases with decreasing pH, with a maximum solubility at about pH 3. Tenofovir alafenamide is considered a BCS Class 3 compound, with high equilibrium solubility and lower apparent permeability.

[0042] Solid oral dosage forms disclosed herein include tenofovir alafenamide, usually in the form of a pharmaceutically acceptable salt. Tenofovir alafenamide can be present within an oral dosage form in solvated or unsolvated form, and references to "tenofovir alafenamide" include both of these forms. In particular, tenofovir alafenamide may be associated with fumarate, such as monofumarate or hemifumarate. Typically, tenofovir alafenamide is in the form of tenofovir alafenamide hemifumarate having the formula below (see WO 2013/025788 A1):



[0043] As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of tenofovir alafenamide, any dosages, whether expressed in *e.g.* milligrams or as a % by weight, should be taken as referring to the amount of tenofovir alafenamide, *i.e.* the amount of:

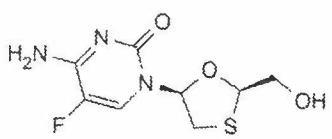


[0044] For example, therefore, a reference to "25 mg tenofovir alafenamide or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of tenofovir alafenamide or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of tenofovir alafenamide as 25 mg of tenofovir alafenamide free base.

[0045] The amount of tenofovir alafenamide in a solid oral dosage form provided herein is generally between 10 mg and 30 mg, for instance within the range of 20 mg to 30 mg, and more typically between 24 mg and 28 mg. In certain specific embodiments, solid oral dosage forms containing 25 mg of tenofovir alafenamide *e.g.* as about 28 mg of tenofovir alafenamide hemifumarate, are provided.

Emtricitabine

[0046] Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor having the formula below:

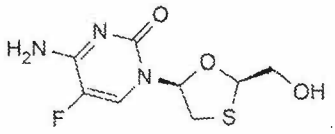


[0047] Its IUPAC name is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one. It is also referred to as 5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. It is currently authorised as part of EMTRIVA® (emtricitabine 200 mg), TRUVADA® (emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg), ATRIPLA® (emtricitabine 200 mg, efavirenz 600 mg, tenofovir disoproxil fumarate 300 mg) and STRIBILD® (emtricitabine 200 mg, cobicistat 150 mg, tenofovir disoproxil fumarate 300 mg, elvitegravir 150 mg) and COMPLERA®/EVIPLERA® (rilpivirine 25 mg, emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg).

[0048] Emtricitabine is a free base, exhibiting a pKa of 2.65. Solubility is enhanced under acidic conditions. It is considered a BCS Class 1 compound, with high solubility and high permeability.

[0049] Solid oral dosage forms disclosed herein include emtricitabine, optionally as a pharmaceutically acceptable salt. Emtricitabine can be present within an oral dosage form in solvated or unsolvated form, and references to "emtricitabine" include both of these forms. Typically, emtricitabine is present as a free base.

[0050] As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of emtricitabine, any dosages, whether expressed in *e.g.* milligrams or as a % by weight, should be taken as referring to the amount of emtricitabine, *i.e.* the amount of:



[0051] For example, therefore, a reference to "200 mg emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of emtricitabine as 200 mg of emtricitabine free base.

[0052] The amount of emtricitabine in a solid oral dosage form provided herein is generally between 180 mg and 220 mg, for instance between 190 mg and 210 mg, and more typically between 195 mg and 205 mg. In certain specific embodiments, solid oral dosage forms containing 200 mg of emtricitabine are provided.

Solid oral dosage forms

[0053] The inventors have successfully formulated the compound of Formula I, emtricitabine and tenofovir alafenamide in a single, stable dosage form that is pharmacologically efficacious and physically acceptable. The solid oral dosage forms disclosed herein are intended for pharmaceutical use in human subjects. Accordingly, they must be of an appropriate size and weight for oral human administration (*e.g.* they should have a total weight of less than about 1.5 g, e.g., less than about 1.0 g), in addition to being therapeutically efficacious.

[0054] In certain embodiments, formulations of the three active ingredients into a solid oral dosage form which has a total weight of less than about 1.0 g are provided, for instance less than about 800 mg, or even less than about 750 mg, or even less than 700 mg. This is advantageous given that TRIUMEQ® (abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine) has a total weight of more than about 1000 mg, based on the weight of the active ingredients in each tablet (due to the amount of excipients that are required to produce a pharmaceutically acceptable tablet). The provision of a relatively small dosage

form (in particular a tablet) represents a clinical advantage because it may be expected to increase patient convenience and thus compliance as compared to larger dosage forms which are more burdensome for patients to swallow. In specific embodiments, the solid oral dosage form disclosed herein has a total weight of between 700 and 750 mg. In certain embodiments, the solid oral dosage form disclosed herein has a total weight of between 700 and 725 mg, or about 700 mg. In specific embodiments, the solid oral dosage form disclosed herein has a total weight of between about 50 and about 750 mg, between about 100 and about 750 mg, between about 200 and about 750 mg, or between about 250 and about 750 mg. The presently disclosed dosage forms may comprise less than 600 mg of excipients, such as less than 500 mg of excipients, or less than 450 mg of excipients. For example, solid oral dosage forms disclosed herein may comprise between 300 and 600 mg of excipients, or between 350 mg and 500 mg of excipients, or between 400 mg and 500 mg of excipients. Most typically, solid oral dosage forms disclosed herein comprise between 425 mg and 450 mg of excipients. In such embodiments, the dosage forms comprise as active ingredients (a) 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof. In certain embodiments, the dosage forms comprise as active ingredients (a) 52 mg of the compound of Formula II, (b) 28 mg tenofovir alafenamide hemifumarate, and (c) 200 mg emtricitabine. In some embodiments, the dosage forms comprise as active ingredients (a) 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof. In certain embodiments, the dosage forms comprise as active ingredients (a) 78 mg of the compound of Formula II, (b) 28 mg tenofovir alafenamide hemifumarate, and (c) 200 mg emtricitabine.

[0055] The solid oral dosage forms disclosed herein will typically be in the form of a fixed dose combination tablet. This is because the inventors have found that the use of fixed dose combination tablets may assist in optimizing the pharmacokinetic properties of the active ingredients, particularly the total exposure of the compound of Formula I or a pharmaceutically acceptable salt thereof, as measured by area under the curve (AUC) and C_{max}. In particular embodiments, the solid oral dosage forms disclosed herein are in the form of a multilayer tablet. In certain embodiments, the use of a fixed dose combinations, e.g., multilayer tablets, may affect the dissolution profile of one or more of the active ingredients within the dosage form, and is therefore likely to have an impact on the *in vivo* pharmacokinetics of the dosage form. In particular, it has been observed that the dissolution of the compound of Formula I (e.g., as Formula II) varies depending on whether the tablet is in a fixed dose combination formulation with tenofovir alafenamide and emtricitabine and/or whether the tablet is a monolayer or multilayer tablet. It has also been observed that the presence of certain excipients in the multilayer tablet formulation (or absence of others) affects the dissolution profile of one or more of

the active ingredients within the dosage form. The provision of a tablet with particular pharmacokinetic parameters, *e.g.* pharmacokinetic parameters is a particular advantage afforded by the present disclosure.

[0056] In one embodiment, a multilayer tablet comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided. Typically, each layer contains at least one of (a), (b), and (c). For instance, in certain embodiments, the tablet comprises a first layer comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, and a second layer comprising (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and further comprises (c) emtricitabine or a pharmaceutically acceptable salt thereof. In such embodiments, typically the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.* the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof).

[0057] A particular embodiment provides a tablet, wherein the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, Formula II) and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof). In a particular embodiment, a tablet is provided, wherein the first layer comprises 52 mg of the compound of Formula II and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer

containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch. In one embodiment, the layer containing the compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone and/or sodium stearyl fumarate.

[0058] A particular embodiment provides a tablet, wherein the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, Formula II) and is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof). In a particular embodiment, a tablet is provided, wherein (a) the first layer comprises 52 mg of the compound of Formula II and is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing emtricitabine or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch. In one embodiment, the layer containing the compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone and/or sodium stearyl fumarate.

[0059] A particular embodiment provides a tablet, wherein the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, Formula II) and is substantially free of tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight each of tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof). In a particular embodiment, a tablet is provided, wherein (a) the first layer comprises 52 mg of the compound of Formula II and is substantially free of tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight tenofovir alafenamide and emtricitabine or a pharmaceutically

acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch. In one embodiment, the layer containing the compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone and/or sodium stearyl fumarate.

{0060} In a particular embodiment, a tablet is provided, wherein (a) the first layer comprises 78 mg of the compound of Formula II and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.* the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 355 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch.

{0061} Unless otherwise specified, the terms "first layer", "second layer", "third layer" and so forth do not specify a particular order or orientation of the multilayer tablet formulations disclosed herein. Rather, these terms are used to distinguish the sections of the composition from each other and to specify the characteristics or components of each section or compartment. By way of example, in an embodiment, a tablet is provided wherein a first layer comprises 52 mg of the compound of Formula II and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. The first layer may be synthesized first or may be synthesized second. The first layer may be on the bottom or may be on the top or may be on a side. The term "first layer" is not limiting as to order and orientation.

[0062] The tablets disclosed herein are typically immediate release tablets. In one embodiment, a tablet is provided which releases at least 50% of the compound of Formula I or a pharmaceutically acceptable salt thereof in about 20 minutes, measured using USP apparatus II, in 333 mL of fasted state simulated intestinal fluid, pH 6.5, at 37 °C and paddle speed of 100 rpm. In certain embodiments, the tablets disclosed herein release at least 60% of the compound of Formula I or a pharmaceutically acceptable salt thereof in 20 minutes, measured using USP apparatus II, in 333 mL of 50 mM fasted state simulated intestinal fluid, at 37 °C and paddle speed of 100 rpm. In some embodiments, a tablet that releases at least 70% of the compound of Formula I in 60 minutes is provided, measured using USP Apparatus II, in 333 mL of fasted state simulated intestinal fluid at 37 °C and paddle speed of 100 rpm.

[0063] Tablets disclosed herein will generally have a hardness within the range 14-20 kP, and, in certain specific embodiments, have a hardness of 17 kP. Hardness can conveniently be assessed by driving an anvil to compress a tablet at a constant loading rate until it fractures, operating in accordance with USP <1217> (using *e.g.* a TBH 220, ERWEKA GmbH, Heusenstamm Germany hardness tester).

[0064] Tablets disclosed herein will generally have a friability of <1% by weight. Friability can be assessed according to USP <1216>.

[0065] The core of a tablet provided herein may have a hardness of between 14-20 kP, and a friability of <1% by weight.

[0066] Tablets will typically include one or more excipients. Excipients should be compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. Examples of suitable excipients are well known to the person skilled in the art of tablet formulation and may be found *e.g.* in *Handbook of Pharmaceutical Excipients* (eds. Rowe, Sheskey & Quinn), 6th edition **2009**. As used herein the term "excipients" is intended to refer to *inter alia* basifying agents, solubilisers, glidants, fillers, binders, lubricant, diluents, preservatives, surface active agents, dispersing agents and the like. The term also includes agents such as sweetening agents, flavoring agents, coloring agents, preserving agents, and coating agents. Such components will generally be present in admixture within the tablet.

[0067] Examples of solubilisers include, but are not limited to, ionic surfactants (including both ionic and non-ionic surfactants) such as sodium lauryl sulphate, cetyltrimethylammonium bromide, polysorbates (such as polysorbate 20 or 80), poloxamers (such as poloxamer 188 or 207), and macrogols. In a particular embodiment, a tablet that comprises the compound of Formula I or a pharmaceutically acceptable salt thereof, includes a polysorbate, in particular polysorbate 20. In certain specific embodiments, the amount of polysorbate 20 in a tablet disclosed herein is less than about 5 mg, such as less than about 1 mg, or about 0.5 mg.

[0068] Examples of lubricants, glidants and flow aids include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl behenate, sodium stearyl fumarate, colloidal silicon dioxide, and talc. The amount of lubricant in a tablet is generally between about 0.5-5% by weight. In certain embodiments, the amount of lubricant in a tablet is about 1.5% by weight. In certain specific embodiments, tablets disclosed herein include magnesium stearate. In certain other embodiments, the tablets disclosed herein do not include sodium stearyl fumarate. In certain embodiments, the tablet includes less than about 10 mg magnesium stearate, or less than about 7.5 mg magnesium stearate. In certain embodiments, the tablet includes less than about 9 mg magnesium stearate, or less than about 8.75 mg magnesium stearate. In certain embodiments, the tablet includes about 5 mg to about 10 mg magnesium stearate, or about 6 mg to about 9 mg magnesium stearate, or about 7 mg to about 9 mg magnesium stearate, or about 8 mg to about 9 mg magnesium stearate, or about 8.1 mg, about 8.2 mg, about 8.3 mg, about 8.4 mg, about 8.5 mg, about 8.6 mg, about 8.7 mg, about 8.8 mg or about 8.9 mg magnesium stearate.

[0069] Examples of disintegrants include, but are not limited to, starches, celluloses, cross-linked PVP (crospovidone), sodium starch glycolate, croscarmellose sodium, *etc*. In certain embodiments, the tablets disclosed herein include croscarmellose sodium. In certain other embodiments, the tablets disclosed herein do not include crospovidone. In certain embodiments, the tablet includes less than about 50 mg croscarmellose sodium, or less than about 25 mg croscarmellose sodium. In certain embodiments, the tablet includes about 30 mg to about 60 mg croscarmellose sodium, or about 40 mg to about 60 mg croscarmellose sodium, or about 45 mg to about 55 mg croscarmellose sodium, or about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg or about 53 mg, or about 54 mg, or about 55 mg croscarmellose sodium.

[0070] Examples of fillers (also known as bulking agents or diluents) include, but are not limited to, starches, maltodextrins, polyols (such as lactose), and celluloses. In certain embodiments, tablets provided herein may microcrystalline cellulose. In certain other embodiments, tablets provided herein do not contain lactose. In certain embodiments, tablets provided herein include less than about 300 mg microcrystalline cellulose, in particular less than about 250 mg microcrystalline cellulose, and/or less than about 225 mg microcrystalline cellulose. In certain embodiments, tablets provided herein include less than about 500 mg microcrystalline cellulose, or less than about 450 mg microcrystalline cellulose, or less than about 400 mg microcrystalline cellulose, or less than about 375 mg microcrystalline cellulose. In certain embodiments, tablets provided herein include about 250 mg to about 500 mg microcrystalline cellulose, or about 300 mg to about 450 mg microcrystalline cellulose, or about 300 mg to about 400 mg microcrystalline cellulose, or about 325 mg to about 375 mg microcrystalline cellulose, or about 350 mg to about 370 mg microcrystalline cellulose. In certain embodiments, tablets provided herein include about 300 mg, or about 310 mg, or about 320 mg, or about 330 mg, or about 340 mg, or about 350 mg, or about

360 mg, or about 370 mg, or about 380 mg, or about 390 mg, or about 400 mg microcrystalline cellulose.

[0071] Examples of binders include, but are not limited to, cross-linked PVP, HPMC, sucrose, starches, *etc.*

[0072] In certain embodiments, tablets provided herein are uncoated. In certain other embodiments, tablets provided herein are coated (in which case they include a coating). Although uncoated tablets may be used, it is more usual in the clinical setting to provide a coated tablet, in which case a conventional non-enteric coating may be used. Film coatings are known in the art and can be composed of hydrophilic polymer materials, but are not limited to, polysaccharide materials, such as hydroxypropylmethyl cellulose (HPMC), methylcellulose, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), poly(vinylalcohol-co-ethylene glycol) and other water soluble polymers. Though in certain embodiments the water soluble material included in the film coating of the embodiments disclosed herein includes a single polymer material, in certain other embodiments it is formed using a mixture of more than one polymer. In certain embodiments, the coating is yellow or brown. Suitable coatings include, but are not limited to, polymeric film coatings such as those comprising polyvinyl alcohol *e.g.* 'Opadry® II' (which includes part-hydrolysed PVA, titanium dioxide, macrogol 3350 (PEG) and talc, with optional colouring such as iron oxide (e.g., iron oxide red or iron oxide black) or indigo carmine or iron oxide yellow or FD&C yellow #6). The amount of coating is generally between about 2-4% of the core's weight, and in certain specific embodiments, about 3%. Unless specifically stated otherwise, where the dosage form is coated, it is to be understood that a reference to % weight of the tablet means that of the total tablet, *i.e.* including the coating.

Pharmacokinetics

[0073] In certain embodiments, the pharmaceutical compositions disclosed herein result in increased systemic exposure (AUC_{inf}, C_{max}) for the compound of Formula I or a pharmaceutically acceptable salt thereof. In particular embodiments, the multilayer tablet formulations disclosed herein result in increased systemic exposure for the compound of Formula I or a pharmaceutically acceptable salt thereof compared to a single agent tablet formulation of the compound of Formula I or a pharmaceutically acceptable salt thereof. In certain embodiments, the multilayer tablet formulation results in an increase of at least about 20% in the systemic exposure of the compound of Formula I or a pharmaceutically acceptable salt thereof compared to a single agent tablet formulation of the compound of Formula I or a pharmaceutically acceptable salt thereof. In some embodiments, the increase in systemic exposure is at least about 25% or at least about 30%. In some embodiments, the increase in systemic exposure is about 30%.

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C_{max}

[0074] C_{max} is the maximum observed plasma/serum concentration of drug.

[0075] In particular embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the compound of Formula I in fasted patients of from about 5300 to about 8900 ng/mL, *e.g.* about 7100 ng/mL.

[0076] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine in fasted patients of from about 1700 to about 2800 ng/mL, *e.g.* about 2300 ng/mL.

[0077] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide in fasted patients of from about 190 to about 320 ng/mL, *e.g.* about 250 ng/mL.

[0078] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the Compound of Formula I of from about from about 4200 ng/mL to about 8000 ng/mL, regardless of whether the subject was fed or fasted.

[0079] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the compound of Formula I in fasted patients of from about 4200 ng/mL to about 6500 ng/mL, or from about 4700 ng/mL to about 5300 ng/mL, or from about 4700 ng/mL to about 5800 ng/mL, or from about 5000 ng/mL to about 5500 ng/mL.

[0080] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the compound of Formula I in fed

patients of from about 4500 ng/mL to about 8000 ng/mL, or from about 4800 ng/mL to about 7900 ng/mL, or from about 5300 ng/mL to about 6900 ng/mL, or from about 5600 ng/mL to about 6600 ng/mL.

[0081] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine of from about from about 1770 ng/mL to about 2800 ng/mL, regardless of whether the subject was fed or fasted.

[0082] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine in fasted patients of from about 1770 ng/mL to about 2800 ng/mL, or from about 2000 ng/mL to about 2600 ng/mL, or from about 2000 ng/mL to about 2500 ng/mL, or from about 2100 ng/mL to about 2400 ng/mL.

[0083] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine in fed patients of from about 1000 ng/mL to about 3000 ng/mL, or from about 1500 ng/mL to about 2000 ng/m from about 1700 ng/mL to about 2200 ng/mL L, or from about 1800 ng/mL to about 2100 ng/mL.

[0084] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide of from about from about 185 ng/mL to about 315 ng/mL, regardless of whether the subject was fed or fasted.

[0085] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide in fasted patients of from about 185 ng/mL to about 315 ng/mL, or from about 200 ng/mL to about 300 ng/mL, or from about 210 ng/mL to about 290 ng/mL, or from about 220 ng/mL to about 275 ng/mL, or from about 230 ng/mL to about 265 ng/mL, or from about 240 ng/mL to about 260 ng/mL.

[0086] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide in fed patients of from about 150 ng/mL to about 350 ng/mL, or from about 185 ng/mL to about 300 ng/m from about 210 ng/mL to about 280 ng/mL L, or from about 250 ng/mL to about 265 ng/mL.

AUC_{inf}

[0087] AUC_{inf} is the area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$.

[0088] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the compound of Formula I in fed patients of from about 117000 to about 196000 h•ng/mL, *e.g.* about 157000 h•ng/mL.

[0089] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine in fed patients of from about 8700 to about 14500h•ng/mL, *e.g.* about 2300h•ng/mL.

[0090] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide in fed patients of from about 150 and 260 h•ng/mL, *e.g.* about 210 h•ng/mL.

[0091] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the Compound of Formula I of from about from about 84450 h•ng/mL to about 141000 h•ng/mL, regardless of whether the subject was fed or fasted.

[0092] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the compound of Formula I

in fasted patients of from about 84450 h•ng/mL to about 141000 h•ng/mL, or from about 90000 h•ng/mL to about 135000 h•ng/mL, or from about 95000 h•ng/mL to about 130000 h•ng/mL, or from about 100000 h•ng/mL to about 125000 h•ng/mL, or from about 110000 h•ng/mL to about 120000 h•ng/mL.

[0093] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the compound of Formula I in fed patients of from about 100000 h•ng/mL to about 200000 ng/mL, or from about 112000 h•ng/mL to about 175000 ng/mL, or from about 126000 h•ng/mL to about 155000 ng/mL, or from about 133000 h•ng/mL to about 147000 ng/mL.

[0094] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine of from about from about 8100 h•ng/mL to about 13600 h•ng/mL, regardless of whether the subject was fed or fasted.

[0095] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine in fasted patients of from about 8100 h•ng/mL to about 13600 h•ng/mL, or from about 8700 h•ng/mL to about 13000 h•ng/mL, or from about 92000 h•ng/mL to about 12500 h•ng/mL, or from about 9700 h•ng/mL to about 12000 h•ng/mL, or from about 10000 h•ng/mL to about 11400 h•ng/mL.

[0096] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine in fed patients of from about 7500 h•ng/mL to about 15000 ng/mL, or from about 8300 h•ng/mL to about 14000 ng/mL, or from about 9500 h•ng/mL to about 12000 ng/mL, or from about 9900 h•ng/mL to about 11600 ng/mL.

[0097] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide of from

about from about 200 h•ng/mL to about 500 h•ng/mL, regardless of whether the subject was fed or fasted.

[0098] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide in fasted patients of from about 200 h•ng/mL to about 265 h•ng/mL, or from about 200 h•ng/mL to about 300 h•ng/mL, or from about 210 h•ng/mL to about 290 h•ng/mL, or from about 220 h•ng/mL to about 270 h•ng/mL, or from about 230 h•ng/mL to about 265 h•ng/mL.

[0099] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide in fed patients of from about 200 h•ng/mL to about 500 ng/mL, or from about 230 h•ng/mL to about 400 ng/mL, or from about 260 h•ng/mL to about 350 ng/mL, or from about 275 h•ng/mL to about 370 ng/mL.

AUC_{last}

[0100] AUC_{last} is the area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration.

[0101] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I in fed patients of from about 114000 to about 190000 h•ng/mL, *e.g.* about 152000 h•ng/mL.

[0102] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of emtricitabine in fed patients of from about 8600 to about 14000 h•ng/mL, *e.g.* about 11000 h•ng/mL.

[0103] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of tenofovir alafenamide in fed patients of from about 150 and 260 h•ng/mL, *e.g.* about 210 h•ng/mL.

[0104] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I of from about from about 81700 h•ng/mL to about 140000 h•ng/mL, regardless of whether the subject was fed or fasted.

[0105] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I in fasted patients of from about 81700 h•ng/mL to about 140000 h•ng/mL, from about 87000 h•ng/mL to about 131000 h•ng/mL, from about 92000 h•ng/mL to about 130000 h•ng/mL, from about 98100 h•ng/mL to about 120000 h•ng/mL, from about 104000 h•ng/mL to about 115000 h•ng/mL.

[0106] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I in fed patients of from about 100000 h•ng/mL to about 200000 ng/mL, or from about 108000 h•ng/mL to about 170000 ng/mL, or from about 122000 h•ng/mL to about 150000 ng/mL, or from about 128000 h•ng/mL to about 142000 ng/mL.

[0107] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of emtricitabine of from about from about 7500 h•ng/mL to about 15000 h•ng/mL, regardless of whether the subject was fed or fasted.

[0108] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the emtricitabine in fasted patients of from about 8000 h•ng/mL to about 13400 h•ng/mL, from about 8500 h•ng/mL to about 12800 h•ng/mL, from about 9000 h•ng/mL to about 12300 h•ng/mL, from about 9500 h•ng/mL to about 11000 h•ng/mL, from about 10000 h•ng/mL to about 11200 h•ng/mL.

[0109] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of emtricitabine in fed patients of from about 7500 h•ng/mL to about 15000 ng/mL, or from about 8000 h•ng/mL to about 14000 ng/mL, or from about 9000 h•ng/mL to about 12000 ng/mL, or from about 9700 h•ng/mL to about 11300 ng/mL.

[0110] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of tenofovir alafenamide of from about from about 165 h•ng/mL to about 400 h•ng/mL, regardless of whether the subject was fed or fasted.

[0111] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the tenofovir alafenamide in fasted patients of from about 165 h•ng/mL to about 390 h•ng/mL, from about 186 h•ng/mL to about 227 h•ng/mL, from about 196 h•ng/mL to about 217 h•ng/mL.

[0112] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of tenofovir alafenamide in fed patients of from about 200 h•ng/mL to about 400 ng/mL, or from about 230 h•ng/mL to about 390 ng/mL, or from about 260 h•ng/mL to about 345 ng/mL, or from about 275 h•ng/mL to about 330 ng/mL.

C_{last}

[0113] C_{last} is the last observed quantifiable plasma/serum concentration of the drug.

[0114] C_{max}, C_{last}, AUC_{inf}, and AUC_{last} are standard pharmacokinetic parameters that can be estimated manually or by using modelling software well known in the art, such as the Pharsight WinNonlin package using a non-compartmental model. The general basis for calculation of these quantities is well-known (*e.g.* see Rowland & Tozer (2010) *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications* ISBN 978-0781750097, or Jambhekar & Breen (2012) *Basic Pharmacokinetics* ISBN 978-0853699804). Typically the parameters will be assessed

as the average (*e.g.* geometric or arithmetic mean) from within a group of at least 12 (and normally between 24 and 36) healthy human adults. Parameters should be measured in accordance with standards and practices which would be acceptable to a pharmaceutical regulatory agency such as FDA, EMA, MHLW, or WHO. The values may be based on measurements taken at appropriate intervals following the time of tablet ingestion, such as every hour, or at increasingly sparse sampling intervals, such as 1, 3, 5, 7, 9, 11, 13, 15, 20, and 24 hours after ingestion. They can be assessed either following a single-dose of drug or at steady state, but will typically be assessed following a single-dose.

[0115] It is well known in the bioavailability and bioequivalence arts how to determine whether any particular tablet meets regulatory requirements for equivalent bioavailability and pharmacokinetic bioequivalence *e.g.* see: Niazi (2014) *Handbook of Bioequivalence Testing*, 2nd Edition, ISBN 978-1482226379; *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* FDA March 2003; and *Guideline On The Investigation Of Bioequivalence*, EMEA 2010 CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. To ensure statistical power a study to measure the C_{max}, AUC_{last} and AUC_{inf} values will be performed in multiple subjects *e.g.* in a group of at least 12 (and normally between 24 and 36) healthy human adults.

[0116] Because determining the C_{max}, AUC_{last} and AUC_{inf} values is necessarily destructive these parameters will not be determined directly for the dosage form (in particular the tablet) in question, but rather for a dosage form made by the same manufacturing process with the same components. Thus a batch of a dosage form (*e.g.* tablets) can be made by a particular process, and the 90% confidence interval of C_{max}, AUC_{last} and AUC_{inf} will be assessed on a sample of those tablets. If these values meet the 80-125% requirement noted above then tablets made by the manufacturing process in question are tablets of the present invention.

[0117] A fixed dose combination tablet is provided comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* Formula II), (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

[0118] In an embodiment, a multilayer tablet is provided, comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* Formula II), (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

[0119] In an embodiment, the multilayer tablet disclosed herein comprises (a) a first layer comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) a second

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layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) further comprises emtricitabine or a pharmaceutically acceptable salt thereof.

[0120] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0121] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0122] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof and tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0123] In an embodiment, the multilayer tablet disclosed herein comprises (a) a first layer comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) a second layer containing emtricitabine or a pharmaceutically acceptable salt thereof, and (c) further comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof.

[0124] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0125] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0126] In an embodiment of the multilayer tablet disclosed herein, the first layer is substantially free of emtricitabine.

[0127] In one embodiment, the multilayer tablet disclosed herein comprises 50 ± 6 mg of the compound of Formula I. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 25 ± 3 mg of tenofovir alafenamide.

[0128] In one embodiment, the multilayer tablet disclosed herein comprises 75 ± 6 mg of the compound of Formula I. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 25 ± 3 mg of tenofovir alafenamide.

[0129] In one embodiment, the multilayer tablet disclosed herein comprises 52 ± 6 mg of the compound of Formula II. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 28 ± 3 mg of tenofovir alafenamide hemifumarate.

[0130] In one embodiment, the multilayer tablet disclosed herein comprises 78 ± 6 mg of the compound of Formula II. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 28 ± 3 mg of tenofovir alafenamide hemifumarate.

[0131] In one embodiment, a first layer of the multilayer tablet disclosed herein comprises one or more excipients, for example one or more diluents, disintegrants, binders, or lubricants.

[0132] In one embodiment, a first layer of the multilayer tablet comprises croscarmellose sodium. In one embodiment, a first layer of the multilayer tablet comprises croscarmellose sodium, microcrystalline cellulose, and magnesium stearate.

[0133] In one embodiment a tablet is provided wherein less than about 25 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 20 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 16 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 5 to about 20 weight percent, or about 10 to about 18 weight percent, or about 14 to about 18 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 16 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0134] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 290 mg.

[0135] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 300 mg.

[0136] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 310 mg.

[0137] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 320 mg.

[0138] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 330 mg.

[0139] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 340 mg.

[0140] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 350 mg.

[0141] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 360 mg.

[0142] In one embodiment a tablet is provided wherein the first layer comprises 52± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 290 mg and is less than about 360 mg.

[0143] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 300 mg and is less than about 350 mg.

[0144] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 310 mg and is less than about 330 mg.

[0145] In one embodiment, the first layer of the multilayer tablet has a total weight of 323 ± 75 mg, or 323 ± 25 mg. or 323 ± 10 mg, or 323 mg.

[0146] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
The compound of Formula I or a salt thereof	40-60
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	1-10

[0147] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
the compound of Formula II	30-60
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	2-8

[0148] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
the compound of Formula II	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5± 1.5

[0149] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	52 ± 5.6
Microcrystalline cellulose	246 ± 10
Croscarmellose sodium	19 ± 2.5
Magnesium stearate	5 ± 0.75

[0150] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	52 ± 2.8
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

[0151] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	52.5
Microcrystalline cellulose	246.3
Croscarmellose sodium	19.4
Magnesium stearate	4.9

[0152] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula I or a pharmaceutically acceptable salt thereof	52.5 ± 1.6
Microcrystalline cellulose	214 ± 7.3
Croscarmellose sodium	19 ± 0.6
Magnesium stearate	2.4 ± 0.5
Extragranular	
Microcrystalline cellulose	32 ± 1
Magnesium stearate	2.4 ± 0.5
Total layer weight	*323*

[0153] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula II	52.5 ± 1.6
Microcrystalline cellulose	214 ± 7.3
Croscarmellose sodium	19 ± 0.6
Magnesium stearate	2.4 ± 0.5
Extragranular	
Microcrystalline cellulose	32 ± 1
Magnesium stearate	2.4 ± 0.5
Total layer weight	*323*

[0154] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula II	52.5 ± 1.6
Microcrystalline cellulose	214 ± 6.4
Croscarmellose sodium	19.4 ± 0.6
Magnesium stearate	2.45 ± 0.5
Extragranular	
Microcrystalline cellulose	32.3 ± 1
Magnesium stearate	2.45 ± 0.5
Total layer weight	*323*

[0155] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula I, or a pharmaceutically acceptable salt therof	52.5 ± 1.6
Microcrystalline cellulose	214 ± 6.4
Croscarmellose sodium	19.4 ± 0.6
Magnesium stearate	2.43 ± 0.5
Extragranular	
Microcrystalline cellulose	32.3 ± 1
Magnesium stearate	2.43 ± 0.5
Total layer weight	*323*

[0156] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula II	52.5 ± 1.6
Microcrystalline cellulose	214 ± 6.4
Croscarmellose sodium	19.4 ± 0.6
Magnesium stearate	2.43 ± 0.5
Extragranular	
Microcrystalline cellulose	32.3 ± 1
Magnesium stearate	2.43 ± 0.5
Total layer weight	*323*

[0157] In one embodiment a tablet is provided wherein less than about 30 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 25 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 22 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 15 to about 27 weight percent, or about 17 to about 25 weight percent, or about 19 to about 23 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 21 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0158] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 320 mg.

[0159] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 330 mg.

[0160] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 340 mg.

[0161] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 350 mg.

[0162] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 360 mg.

[0163] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 370 mg.

[0164] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 380 mg.

[0165] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 390 mg.

[0166] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 320 mg and is less than about 390 mg.

[0167] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 330 mg and is less than about 380 mg.

[0168] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 350 mg and is less than about 360 mg.

[0169] In one embodiment, the first layer of the multilayer tablet has a total weight of 353 ± 75 mg, or 353 ± 25 mg, or 353 ± 10 mg, or 353 mg.

[0170] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
The compound of Formula I or a salt thereof	40-85
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	1-10

[0171] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
The compound of Formula II	30-90
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	2-8

[0172] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
The compound of Formula II	80 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5± 1.5

[0173] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
The compound of Formula II	78 ± 5.6
Microcrystalline cellulose	250 ± 10
Croscarmellose sodium	20 ± 2.5
Magnesium stearate	5 ± 0.75

[0174] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	78 ± 2.8
Microcrystalline cellulose	247 ± 5
Croscarmellose sodium	21 ± 1.75
Magnesium stearate	5 ± 0.5

[0175] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	78.7
Microcrystalline cellulose	247.8
Croscarmellose sodium	21.2
Magnesium stearate	5.3

[0176] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula II	78.7
Microcrystalline cellulose	212.5
Croscarmellose sodium	21.2
Magnesium stearate	2.65
Extragranular	
Microcrystalline cellulose	35.3
Magnesium stearate	2.65
Total layer weight	*353*

[0177] In one embodiment, the second layer of the multilayer tablet does not comprise lactose. In one embodiment, the second layer of the multilayer tablet does not comprise starch. In one embodiment, the second layer of the multilayer tablet comprises neither lactose nor starch.

[0178] In one embodiment, the second layer of the multilayer tablet comprises one or more excipients, for example, one or more diluents, disintegrants, binders, or lubricants.

[0179] In one embodiment, the second layer of the multilayer tablet comprises microcrystalline cellulose and croscarmellose sodium.

[0180] In one embodiment, the second layer of the multilayer tablet comprises microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

[0181] In one embodiment, the second layer of the multilayer tablet comprises 20-40 mg of croscarmellose sodium. In one embodiment, the second layer of the multilayer tablet comprises 105-125 mg of microcrystalline cellulose. In one embodiment, the second layer of the multilayer tablet comprises 1-8 mg of magnesium stearate.

[0182] In one embodiment, the second layer of the multilayer tablet does not comprise lactose. In one embodiment, the second layer of the multilayer tablet does not comprise starch. In one embodiment, the second layer of the multilayer tablet comprises neither lactose nor starch.

[0183] In one embodiment, the second layer of the multilayer tablet has a total weight of less than 600 mg, or less than 500 mg, or less than 400 mg, or less than 380 mg. In one embodiment, the second layer of the multilayer tablet has a total weight of 377 mg ± 50 mg or 377 mg ± 25 mg, or 377 mg ± 5 mg, or 377 mg.

[0184] In one embodiment, over 50 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 55 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 60 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, about 55 % to about 65% by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 60 % by weight of the second layer of the multilayer tablet is emtricitabine and tenofovir alafenamide hemifumarate. In one embodiment, about 55 % to about 65% by weight of the second layer of the multilayer tablet is emtricitabine and tenofovir alafenamide hemifumarate.

[0185] In one embodiment, the second layer of the multilayer tablet contains less than 250 mg of excipients, for example less than 200 mg, or less than 150 mg.

[0186] In one embodiment, at least 50% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, at least 53% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, about 45% to about 65% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, about 50% to about 60% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, about 51% to about 53% by weight of the second layer of the multilayer tablet is emtricitabine.

[0187] In one embodiment, at least 4% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 6% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 7% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 5% to about 10% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 6% to about 9% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 7% to about 8% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 7% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate.

[0188] In one embodiment, less than 20% by weight of the second layer of the multilayer tablet is croscarmellose sodium. In one embodiment, less than 10% by weight of the second layer of the multilayer tablet is croscarmellose sodium. In one embodiment, about 5% to about 10% by weight of the second layer of the multilayer tablet is croscarmellose sodium. In certain embodiments, the use of about 5 to 7% (*e.g.* about 6%) croscarmellose sodium by weight of the second layer may provide enhanced dissolution of the compound of Formula I or a pharmaceutically acceptable salt thereof, relative to other disintegrants *e.g.* polyvinylpyrrolidone (crospovidone). In certain embodiments, the

use of about 5 to 10% croscarmellose sodium by weight of the second layer may provide enhanced dissolution of the compound of Formula I or a pharmaceutically acceptable salt thereof, relative to other disintegrants *e.g.* polyvinylpyrrolidone (crospovidone).

[0189] In one embodiment, less than 50% by weight of the second layer of the multilayer tablet is microcrystalline cellulose. In one embodiment, less than 40% by weight of the second layer of the multilayer tablet is microcrystalline cellulose. In one embodiment, less than 31% by weight of the second layer of the multilayer tablet is microcrystalline cellulose.

[0190] In one embodiment, less than 5% by weight of the second layer of the multilayer tablet is magnesium stearate. In one embodiment, less than 3% by weight of the second layer of the multilayer tablet is magnesium stearate. In one embodiment, less than 2% by weight of the second layer of the multilayer tablet is magnesium stearate. In one embodiment, about 0.5% to about 1.5% by weight of the second layer of the multilayer tablet is magnesium stearate. In certain embodiments, the use of about 1% to about 2% (*e.g.* about 1.5%) magnesium stearate by weight of the second layer may provide enhanced dissolution of the compound of Formula I or a pharmaceutically acceptable salt thereof, relative to other lubricants *e.g.* sodium stearyl fumarate.

[0191] In one embodiment, the total weight of the second layer is less than 150% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 125% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 116% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 106% of the total weight of the first layer.

[0192] In one embodiment, the second layer of the multilayer tablet comprises:

Ingredient	**Mass (mg)**
Emtricitabine or a salt thereof	150-250
Tenofovir alafenamide or a salt thereof	20-35
Microcrystalline cellulose	90-130
Croscarmellose sodium	20-35
Magnesium stearate	1-7

[0193] In one embodiment, the second layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
Emtricitabine	170-230
Tenofovir alafenamide hemifumarate	22-32
Microcrystalline cellulose	100-120
Croscarmellose sodium	20-35
Magnesium stearate	1-7

[0194] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	5.6 ±1.1

[0195] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	5.6 ±0.5

[0196] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28.1
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	5.7

[0197] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Intergranular	
Emtricitabine	200.00
Tenofovir alafenamide hemifumarate	28.1
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	2.85
Extragramular	
Magnesium stearate	2.85
Total layer weight	*377*

[0198] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide	25 ±3
Microcrystalline cellulose	115 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	3.8 ±1.1

[0199] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	115 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	3.8 ±1.1

[0200] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	115 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	3.8 ±0.5

[0201] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28.1
Microcrystalline cellulose	115
Croscarmellose sodium	30.2
Magnesium stearate	3.8

[0202] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	115
Croscarmellose sodium	30.2
Magnesium stearate	1.9
Extragranular	
Magnesium stearate	1.9
Total layer weight	*377*

[0203] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	5.7

[0204] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	115
Croscarmellose sodium	30.2
Magnesium stearate	3.8

[0205] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	2.85
Extragranular	
Magnesium stearate	2.85
Total layer weight	*377*

[0206] In one embodiment of the multilayer tablet formulations disclosed herein, the first layer is in contact with the second layer.

[0207] In one embodiment, the first layer is produced first, followed be the second layer. That is, in one embodiment, the first layer is prepared and pressed into a first layer, followed by the second layer being prepared and being pressed with the first layer into a multilayer tablet. In one embodiment, the second layer is produced first, followed be the first layer. That is, in one embodiment, the second layer is prepared and pressed into a second layer, followed by the first layer being prepared and being pressed with the second layer into a multilayer tablet.

[0208] As used herein, when describing the multilayer tablets disclosed herein, the terms "first layer" and "second layer" are not intended to indicate the method by which the tablets are produced, in particular the order in which the layers are obtained.

[0209] In certain embodiments, the multilayer tablet further comprises additional layers. In certain embodiments, the additional layer or layers are located between the first and second layers. In certain embodiments, the additional layer or layers are located on either side of the first and/or second layer, such that they are an outside layer of the table and/or are disposed between the first and/or second layer and a coating layer. In some embodiments, the additional layer or layers encapsulate the first and second layers.

[0210] In one embodiment, the multilayer tablet further comprises a third layer that is between and that separates the first layer and the second layer. In one embodiment, the third layer of the multilayer tablet comprises lactose monohydrate, or microcrystalline cellulose, or a mixture thereof.

[0211] In one embodiment, the multilayer tablet further comprises a film coating. In one embodiment, the multilayer tablet further comprises about 14 mg to about 28 mg of a film coating. In one embodiment, the multilayer tablet further comprises about 19 mg to about 23 mg of a film coating. In one embodiment, the multilayer tablet further comprises about 21 mg of a film coating.In one embodiment the film coating comprises polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and black iron oxide. In one embodiment the film coating consists of 21 ± 7 mg of Opadry II Brown 85F165072. In one embodiment the film coating consists of 21 ± 7 mg of Opadry II Yellow 85F92259.

[0212] In one embodiment, the multilayer tablet further includes a film coating. In one embodiment, the multilayer tablet further comprises about 1.9% to about 3.9% w/w of a film coating. In one embodiment, the multilayer tablet further comprises about 2.5% to about 3.5% w/w of a film coating. In one embodiment, the multilayer tablet further comprises about 3% of a film coating. In one embodiment the film coating includes polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, iron oxide red, and black iron oxide. In one embodiment the film coating includes 36%-40% polyvinyl alcohol, 18%-22% polyethylene glycol, 13%-16% talc, 20%-24% titanium dioxide, 2%-3% iron oxide red, and 0.5%-0.7% black iron oxide.

[0213] In one embodiment a tablet is provided comprising about 6.4-8.5% w/w of the compound of Formula II, about 25-32% w/w mg emtricitabine, about 3.5-4.5% w/w mg tenofovir alafenamide hemifumarate, about 46-57% w/w mg microcrystalline cellulose, about 5.9-8.5% w/w mg croscarmellose sodium, and about 1.0-2.0% w/w mg magnesium stearate.

[0214] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 20 mg emtricitabine, 28 ± 3 mg tenofovir alafenamide hemifumarate, 360 ± 30 mg Microcrystalline cellulose, 50 ± 8 mg Croscarmellose sodium, and 10.5 ± 3 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg.

[0215] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 10 mg emtricitabine, 28 ± 1.5 mg tenofovir alafenamide hemifumarate, 360 ± 15 mg Microcrystalline cellulose, 50 ± 4 mg Croscarmellose sodium, and 10.5 ± 1.5 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg and is less than about 715 mg.

[0216] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 20 mg emtricitabine, 28 ± 3 mg Tenofovir alafenamide hemifumarate, 360 ± 30 mg Microcrystalline cellulose, 50 ± 8 mg Croscarmellose sodium, and 8.6 ± 3 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg.

[0217] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 10 mg emtricitabine, 28 ± 1.5 mg Tenofovir alafenamide hemifumarate, 360 ± 15 mg Microcrystalline cellulose, 50 ± 4 mg Croscarmellose sodium, and 8.6 ± 1.5 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg and is less than about 715 mg.

[0218] In one embodiment, the tablet has a total weight of 700 ± 75 mg, or 700 ± 25 mg, or 700 ± 10 mg, or 700 mg. In one embodiment, the tablet is uncoated and has a total weight of about 700 ± 75 mg, or about 700 ± 25 mg, or about 700 ± 10 mg, or about 700 mg. In one embodiment, the tablet has a total weight of about 720 ± 75 mg, or about 720 ± 25 mg, or about 720 ± 10 mg, or about 720 mg, or about 721 mg, or about 722 mg, or about 723 mg, or about 724 mg, or about 725 mg, or about 726 mg, or about 727 mg, or about 728 mg, or about 729 mg, or about 730 mg.

[0219] In one embodiment a tablet is provided comprising 80 ± 6 mg of the compound of Formula II, 200 ± 20 mg emtricitabine, 28 ± 3 mg Tenofovir alafenamide hemifumarate, 360 ± 30 mg Microcrystalline cellulose, 50 ± 8 mg Croscarmellose sodium, and 11 ± 3 mg magnesium stearate and wherein the total weight of the tablet is at least about 715 mg.

[0220] In one embodiment a tablet is provided comprising 78 ± 2.3 mg of the compound of Formula II, 200 ± 10 mg emtricitabine, 28 ± 1.5 mg Tenofovir alafenamide hemifumarate, 361 ± 15 mg Microcrystalline cellulose, 51 ± 4 mg Croscarmellose sodium, and 11 ± 1.5 mg magnesium stearate and wherein the total weight of the tablet is at least about 715 mg and is less than about 745 mg.

[0221] In one embodiment, the tablet has a total weight of 730 ± 75 mg, or 730 ± 25 mg, or 730 ± 10 mg, or 730 mg. In one embodiment, the tablet has a total weight of about 750 ± 75 mg, or about 750 ± 25 mg, or about 750 ± 10 mg, or about 750 mg, or about 751 mg, or about 752 mg, or about 753 mg, or about 754 mg, or about 755 mg.

[0222] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 6
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	10.5 ± 3

[0223] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	52.5 ± 3
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28.1 ±1.5
Microcrystalline cellulose	360 ± 15
Croscarmellose sodium	50 ± 4
Magnesium stearate	10.5 ± 1.5

[0224] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 5
Emtricitabine	200 ±20
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ±3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	8.6 ± 3

[0225] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 2.5
Emtricitabine	200 ±10
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ±1.5
Microcrystalline cellulose	360 ± 15
Croscarmellose sodium	50 ± 4
Magnesium stearate	8.6 ± 1.5

[0226] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	52 ± 6
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	8.6 ± 3

[0227] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 6
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	8.6 ± 3

[0228] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula II	52.5 ± 3
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28.1 ± 1.5
Microcrystalline cellulose	360 ± 15
Croscarmellose sodium	50 ± 4
Magnesium stearate	8.6 ± 1.5

[0229] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Microcrystalline cellulose	113 ± 9
Croscarmellose sodium	30 ± 3
Magnesium stearate	5.6 ± 1.1

[0230] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	4 ±1.1

[0231] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	4 ±1.1

[0232] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula II	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	4 ±1.1

[0233] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 2.8
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	5.6 ±0.5

[0234] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt therof	50 ± 3
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide, or a pharmacetuically acceptable salt thereof	25 ±3
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	4 ±0.5

[0235] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 2.8
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	4 ±0.5

[0236] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	80 ± 6
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	11 ± 3

[0237] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	78.6 ± 2.3
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28.1 ±1.5
Microcrystalline cellulose	361 ± 15
Croscarmellose sodium	51 ± 4
Magnesium stearate	11 ± 1.5

[0238] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	80 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5± 1.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	5.6 ±1.1

[0239] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	78 ± 2.8
Microcrystalline cellulose	247 ± 5
Croscarmellose sodium	21 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	5.6 ±0.5

[0240] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	5-10
Microcrystalline cellulose	26-44
Croscarmellose sodium	2-4
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in tablet)
Emtricitabine	21-36
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	3-5
Microcrystalline cellulose	12-20
Croscarmellose sodium	3-6
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0241] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	5-10
Microcrystalline cellulose	26-44
Croscarmellose sodium	2-4
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in tablet)
Emtricitabine	21-36
Tenofovir alafenamide hemifumarate	3-5
Microcrystalline cellulose	12-20
Croscarmellose sodium	3-6
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0242] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	6-9
Microcrystalline cellulose	30-40
Croscarmellose sodium	2.4-3.2
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	24-33
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	3.4-4.6
Microcrystalline cellulose	14-19
Croscarmellose sodium	3.6-4.9
Magnesium stearate	0.6-0.8

and optionally a film coating.

[0243] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	6-9
Microcrystalline cellulose	30-40
Croscarmellose sodium	2.4-3.2
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	24-33
Tenofovir alafenamide hemifumarate	3.4-4.6
Microcrystalline cellulose	14-19
Croscarmellose sodium	3.6-4.9
Magnesium stearate	0.6-0.8

and optionally a film coating.

[0244] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7-8
Microcrystalline cellulose	32-37
Croscarmellose sodium	2.7-2.9
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	26-30
Tenofovir alafenamide hemifumarate	3.7-4.6
Microcrystalline cellulose	15-17
Croscarmellose sodium	4.0-4.5
Magnesium stearate	0.5-0.6

and optionally a film coating.

[0245] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7-8
Microcrystalline cellulose	33-36
Croscarmellose sodium	2.7-2.8
Magnesium stearate	0.7-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	27-29
Tenofovir alafenamide hemifumarate	3.8-4.2
Microcrystalline cellulose	16-17
Croscarmellose sodium	4.1-4.4
Magnesium stearate	0.5-0.8

and optionally a film coating.

[0246] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7.5
Microcrystalline cellulose	35.2
Croscarmellose sodium	2.8
Magnesium stearate	0.7

and a second layer including:

	% w/w (in tablet)
Emtricitabine	28.6
Tenofovir alafenamide hemifumarate	4.0
Microcrystalline cellulose	16.4
Croscarmellose sodium	4.3
Magnesium stearate	0.5

and optionally a film coating.

[0247] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7.5
Microcrystalline cellulose	35.2
Croscarmellose sodium	2.8
Magnesium stearate	0.7

and a second layer including:

	% w/w (in tablet)
Emtricitabine	28.6
Tenofovir alafenamide hemifumarate	4.0
Microcrystalline cellulose	16.2
Croscarmellose sodium	4.3
Magnesium stearate	0.8

and optionally a film coating.

[0248] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I, or a pharmaceutically accpetable salt thereof	11-19
Microcrystalline cellulose	51-86
Croscarmellose sodium	4-7
Magnesium stearate	0.5-0.9
Extragranular	
Microcrystalline cellulose	7-12
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	39-67
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	5-10
Microcrystalline cellulose	22-38
Croscarmellose sodium	6-10
Magnesium stearate	0.3-0.7
Intergranular	
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0249] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	11-19
Microcrystalline cellulose	51-86
Croscarmellose sodium	4-7
Magnesium stearate	0.5-0.9
Extragranular	
Microcrystalline cellulose	7-12
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	39-67
Tenofovir alafenamide hemifumarate	5-10
Microcrystalline cellulose	22-38
Croscarmellose sodium	6-10
Magnesium stearate	0.3-0.7
Intergranular	
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0250] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I, or a pharmaceutically acceptable salt thereof	13-17
Microcrystalline cellulose	58-79
Croscarmellose sodium	4.6-6.3
Magnesium stearate	0.6-0.8
Extragranular	
Microcrystalline cellulose	5-11
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	45-61
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	6-9
Microcrystalline cellulose	25-35
Croscarmellose sodium	6.5-9.2
Magnesium stearate	0.4-0.5
Intergranular	
Magnesium stearate	0.4-0.5

and optionally a film coating.

[0251] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	13-17
Microcrystalline cellulose	58-79
Croscarmellose sodium	4.6-6.3
Magnesium stearate	0.6-0.8
Extragranular	
Microcrystalline cellulose	5-11
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	45-61
Tenofovir alafenamide hemifumarate	6-9
Microcrystalline cellulose	25-35
Croscarmellose sodium	6.5-9.2
Magnesium stearate	0.4-0.5
Intergranular	
Magnesium stearate	0.4-0.5

and optionally a film coating.

[0252] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I, or a pharmaceutically acceptable salt thereof	14-16
Microcrystalline cellulose	66-73
Croscarmellose sodium	5.2-5.8
Magnesium stearate	0.65-0.75
Extragranular	
Microcrystalline cellulose	8-10
Magnesium stearate	0.65-0.75

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	50-56
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	7-8
Microcrystalline cellulose	28-32
Croscarmellose sodium	7.5-8.5
Magnesium stearate	0.45-0.55
Intergranular	
Magnesium stearate	0.45-0.55

and optionally a film coating.

[0253] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	14-16
Microcrystalline cellulose	66-73
Croscarmellose sodium	5.2-5.8
Magnesium stearate	0.65-0.75
Extragranular	
Microcrystalline cellulose	8-10
Magnesium stearate	0.65-0.75

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	50-56
Tenofovir alafenamide hemifumarate	7-8
Microcrystalline cellulose	28-32
Croscarmellose sodium	7.5-8.5
Magnesium stearate	0.45-0.55
Intergranular	
Magnesium stearate	0.45-0.55

and optionally a film coating.

[0254] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	15
Microcrystalline cellulose	69
Croscarmellose sodium	5.5
Magnesium stearate	0.7
Extragranular	
Microcrystalline cellulose	9
Magnesium stearate	0.7

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	53
Tenofovir alafenamide hemifumarate	7.5
Microcrystalline cellulose	30
Croscarmellose sodium	8
Magnesium stearate	0.5
Intergranular	
Magnesium stearate	0.5

and optionally a film coating.

[0255] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	15
Microcrystalline cellulose	69
Croscarmellose sodium	5.5
Magnesium stearate	0.7
Extragranular	
Microcrystalline cellulose	9
Magnesium stearate	0.7

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	53
Tenofovir alafenamide hemifumarate	7.5
Microcrystalline cellulose	30
Croscarmellose sodium	8
Magnesium stearate	0.7
Intergranular	
Magnesium stearate	0.7

and optionally a film coating.

]0256] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in layer)
Intragranular		
The compound of Formula II	52.5	16.24
Microcrystalline cellulose	149.9-246.3	46.41-76.26
Croscarmellose sodium	19.4	8.00
Magnesium stearate	1.98-2.45	0.6-1.0
Extragranular		
Microcrystalline cellulose	0-97.0	0-30
Magnesium stearate	1.98-2.45	0.6-1.0

and a second layer including:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	1.93-2.85	0.50-0.75
Extragranular		
Magnesium stearate	1.93-2.85	0.50-0.75

and optionally a film coating.

[0257] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	52.5	16.24
Microcrystalline cellulose	149.9-246.3	46.41-76.26
Croscarmellose sodium	19.4	8.00
Magnesium stearate	1.98-2.45	0.6-1.0
Extragranular		
Microcrystalline cellulose	0-97.0	0-30
Magnesium stearate	1.98-2.45	0.6-1.0

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	1.93-2.85	0.50-0.75
Extragranular		
Magnesium stearate	1.93-2.85	0.50-0.75

and optionally a film coating.

[0258] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	78.7	22.3
Microcrystalline cellulose	212.5	60.2
Croscarmellose sodium	21.2	6.00
Magnesium stearate	2.65	0.75
Extragranular		
Microcrystalline cellulose	35.30	10.0
Magnesium stearate	2.65	0.75

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.0	7.4
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	2.83	0.75
Extragranular		
Magnesium stearate	2.83	0.75

and optionally a film coating.

[0259] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	52.5	16.25
Microcrystalline cellulose	0-246.3	0-76.25
Croscarmellose sodium	19.4	8.00
Magnesium stearate	1.98-2.45	0.6-1.0
Extragranular		
Microcrystalline cellulose	0-97.0	0-30
Magnesium stearate	2.45	0.6-1.0

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	2.85	0.75
Extragranular		
Magnesium stearate	2.85	0.75

and a film coating consisting of 21 mg of Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0260] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	52.5	13-21
Microcrystalline cellulose	0-246	0-59
Croscarmellose sodium	19	5-25
Magnesium stearate	2.0-2.5	0.5-3.2
Extragranular		
Microcrystalline cellulose	0-97	0-30
Magnesium stearate	2.0-2.5	0.5-3.2

and a second layer including:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200	35
Tenofovir alafenamide hemifumarate	28	4.9
Microcrystalline cellulose	113	20
Croscarmellose sodium	30	5.2
Magnesium stearate	2.9	0.5
Extragranular		
Magnesium stearate	2.9	0.5

and a film coating consisting of 21 mg of Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0261] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in tablet)
The compound of Formula II	47-58	6.75-8.25
Microcrystalline cellulose	222-271	32-59
Croscarmellose sodium	17-21	2.5-3.1
Magnesium stearate	4.4-5.4	0.6-0.8

and a second layer including:

	Mass (mg)	% w/w (in tablet)
Emtricitabine	180-220	26-31
Tenofovir alafenamide hemifumarate	25-31	3.6-4.4
Microcrystalline cellulose	104-127	15-18
Croscarmellose sodium	27-33	2.6-4.7
Magnesium stearate	3.4-6.0	0.4-1.0

and optionally a film coating (e.g., Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0262] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in tablet)
The compound of Formula II	52.5	7.5
Microcrystalline cellulose	246	35
Croscarmellose sodium	19	2.8
Magnesium stearate	5	0.7

and a second layer including:

	Mass (mg)	% w/w (in tablet)
Emtricitabine	200	29
Tenofovir alafenamide hemifumarate	28	4
Microcrystalline cellulose	115	16
Croscarmellose sodium	30	4.3
Magnesium stearate	4	0.5

and optionally a film coating (e.g., Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0263] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	78.6	22.3
Microcrystalline cellulose	212.5	60.2
Croscarmellose sodium	21.2	6.00
Magnesium stearate	2.65	0.75
Extragranular		
Microcrystalline cellulose	35.3	10.0
Magnesium stearate	2.65	0.75

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.1	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	2.85	0.75 (0.5-0.75)
Extragranular		
Magnesium stearate	2.83	0.75 (0.5-7.5)

and a film coating consisting of 21.9 mg of Opadry II Yellow 85F92259 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide and iron yellow).

[0264] In one embodiment, a composition is provided including about 75 mg of a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), about 25 mg tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and about 200 mg emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{last} of each component following a single dose administered to a human is from about 81700 h-ng/mL to about 140000 h-ng/mL of the compound of Formula I, from about 7500 h-ng/mL to about 15000 h-ng/mL of emtricitabine, and from about 165 h-ng/mL to about 400 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In

certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer.

[0265] In one embodiment, a composition is provided including a compound of 50 mg Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), 25 mg tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{last} of each component following a single dose is from about 87,000 h-ng/mL to about 131,000 h-ng/mL of the compound of Formula I, from about 8500 h-ng/mL to about 12,800 h-ng/mL of emtricitabine, and from about 186 h-ng/mL to about 227 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0266] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{inf} of each component following a single dose administered to a human is from about 84450 h-ng/mL to about 141000 h-ng/mL of the compound of Formula I, from about 8100 h-ng/mL to about 136000 h-ng/mL of emtricitabine, and from about 200 h-ng/mL to about 500 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0267] In one embodiment, a composition is provided including a compound of Formula I (e.g., a compound of Formula II), tenofovir alafenamide, and emtricitabine, wherein the mean C_{max} of each component following a single dose is from about 90,000 h-ng/mL to about 135,000 h-ng/mL of the compound of Formula I, from about 8,700 h-ng/mL to about 13,000 h-ng/mL of emtricitabine, and from about 200 h-ng/mL to about 300 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and

tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0268] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean C_{max} of each component following a single dose administered to a human is from about 4200 ng/mL to about 8000 mg/mL of the compound of Formula I, from about 1770 ng/mL to about 2800 ng/mL of emtricitabine, and from about 185 ng/mL to about 315 ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0269] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean C_{max} of each component following a single dose is from about 4700 ng/mL to about 5300 ng/mL of the compound of Formula I, from about 2000 ng/mL to about 2600 ng/mL of emtricitabine, and from about 200 ng/mL to about 300 ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0270] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{last}, AUC_{inf}, and/or C_{max} of each component following a single dose administered to a human in the fed state is 80-125%, 80-120%, 85-115%, 90-110%, or 95-105% of the mean AUC_{last}, AUC_{inf}, and/or C_{max} of each component following a single dose administered to a human in the fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0271] In certain embodiments, the pharmacokinetic profile of the compositions described herein is within acceptable ranges, regardless of whether the subject has eaten prior to taking the medication. Accordingly, in certain embodiments, the compositions described herein can be taken without regard to food intake by the subject. In certain embodiments, food intake is a low fat, moderate fat, or high fat meal.

[0272] In one embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 160% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 145% of the mean AUC_{last} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 135% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 125% of the mean AUC_{last} of a single dose following administration to fasted patients.

[0273] In certain embodiments, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 60% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 45% of the mean AUC_{last} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 35% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiments a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 25% of the mean AUC_{last} of a single dose following administration to fasted patients.

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[0274] In one embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 160% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 150% of the mean AUC_{inf} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 135% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 125% of the mean AUC_{inf} of a single dose following administration to fasted patients.

[0275] In certain embodiments, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 60% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 50% of the mean AUC_{inf} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 35% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiments a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 25% of the mean AUC_{inf} of a single dose following administration to fasted patients.

[0276] In one embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 160% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 130% of the mean C_{max} of a single dose following administration to fasted

patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 120% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 115% of the mean C_{max} of a single dose following administration to fasted patients.

[0277] In certain embodiments, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 60% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 30% of the mean C_{max} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 20% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiments a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 15% of the mean C_{max} of a single dose following administration to fasted patients.

Manufacturing methods

[0278] Methods for producing the compositions and dosage forms (in particular tablets) disclosed herein are also provided. In some embodiments, the method comprises (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer. For example, in some embodiments, the method comprises (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, followed by (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer. In other embodiments, the method comprises (a) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof followed by (b) compressing the

compound of Formula I or a pharmaceutically acceptable salt thereof as another layer. In other embodiments, the method comprises (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as one layer followed by (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as another layer. The first layer and second layer may be compressed separately and subsequently combined. However, more typically, a first layer is formed by compression and subsequently a second layer is compressed onto the first layer. In certain embodiments, the choice of layer order in the tableting of multilayer tablets may have an impact on the properties of the tablets (*e.g.* the adhesion of the layers within the tablet).

[0279] In some embodiments, a tablet is provided wherein the first layer is obtainable by a method of (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer. In other embodiments, a tablet is provided wherein the second layer is obtainable by a method of (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a first layer.

[0280] In certain embodiments, the methods will include a step of coating the tablet cores after compression, *e.g.* with a film coating as described above.

[0281] In general, tableting methods are well known in the art of pharmacy. Techniques and formulations generally are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA), which is hereby incorporated by reference herein in its entirety.

[0282] A tablet can be made by compression or molding, optionally with one or more excipients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with excipients.

Therapeutic methods

[0283] The solid oral dosage forms (in particular tablets) disclosed herein are used for treatment of HIV infection (*e.g.* HIV-1 infection). In certain embodiments, the solid oral dosage forms (in particular tablets) disclosed herein are used for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1.

[0284] Accordingly, methods for treating a subject infected with HIV are provided, comprising administering a solid oral dosage form disclosed herein (in particular a tablet) to the subject. Similarly, a solid oral dosage form (in particular a tablet) is provided for use in such treatment methods. Also provided is the use of the compound of Formula I or a pharmaceutically acceptable

salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form disclosed herein (in particular a tablet) for treatment of HIV infection. In some embodiments, the invention provides the use of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form disclosed herein (in particular a tablet) for treatment of HIV infection.

[0285] In certain embodiments, the solid oral dosage forms (in particular tablets) disclosed herein are used for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1. Accordingly, methods for preventing infection in a subject at risk of infection with HIV are provided, comprising administering a solid oral dosage form disclosed herein (in particular a tablet) to the subject. Similarly, a solid oral dosage form disclosed herein (in particular a tablet) is provided for use in such treatment methods. The invention also provides the use of the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form disclosed herein (in particular a tablet) for prevention of HIV infection in a subject at risk for infection. In some embodiments, the invention provides the use of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form disclosed herein (in particular a tablet) for prevention of HIV infection.

[0286] In certain embodiments, a method of treating a subject with HIV with the compositions disclosed herein is provided, wherein the method does not increase the risk of a drug-drug interaction in the patient. In certain embodiments, a method of treating a subject with HIV with the compositions disclosed herein is provided, wherein the method decreases the risk of a drug-drug interaction in the patient. Exemplary drug-drug interactions include interactions between the compound of Formula I, tenofovir alafenamide, or emtricitabine with rifampin, metformin, one or more hormonal contraceptives or an HCV antiviral agent (e.g., one or more of sofosbuvir, ledipasvir, velpatasvir, voxilaprevir, grazoprevir, boceprevir, elbasvir, dasabuvir, ombitasvir, paritaprevir, ABT-530, and ABT-493). In certain embodiments, a method of treating a subject with HIV is provided, wherein the subject is administered one or the compositions disclosed herein, wherein the subject is also being treated with rifampin, metformin, or an HCV antiviral agent (e.g., one or more of sofosbuvir, ledipasvir, velpatasvir, voxilaprevir, grazoprevir, boceprevir, elbasvir, dasabuvir, ombitasvir, paritaprevir, ABT-530, and ABT-493).

[0287] The methods involve administering an oral dosage form disclosed herein (in particular a tablet) to the subject, typically a human, and will generally involve repeated administrations, typically once daily. The treatment may be prophylactic or therapeutic treatment.

General

[0288] The term "fed" in relation to administration of a solid oral dosage form to a human subject means administration of the dosage form orally under fed conditions (moderate fat meal) *e.g.* administration within about 30 minutes of the human consuming a standardized meal of about 300 to 600 calories and about 10 to about 15 grams of fat. In some embodiments, "fed" refers to administration within about 30 minutes of the human consuming a high fat meal.

[0289] The term "substantially free" in relation to the presence of a given component within *e.g.* a composition means that less than 5% by weight of the composition (*e.g.* less than 1% by weight of the composition) is that given component. The word "substantially" does not exclude "completely" *e.g.* a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

[0290] The term "segregated" as used in relation to certain components (*e.g.* A and B) within a tablet means that those components are physically discrete such that the presence of one component (*e.g.* A) does not substantially affect the stability in storage of the other component(s) (*e.g.* B) from which it is segregated. Typically, when components are segregated in a tablet then they will be present in separate layers in a multilayer tablet. By way of example, components A and B may be present in separate layers in a multilayer tablet, wherein (a) the layer containing component A is substantially free of component B and (b) the layer containing component B is substantially free of component A. The separate layers may be in contact with each other or may be separated *e.g.* by one or more additional layers.

[0291] The term "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".

[0292] The term "between" with reference to two values includes those two values *e.g.* the range "between" 10 mg and 20 mg encompasses *e.g.* 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20 mg.

[0293] The term "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity). For example, in certain nonlimiting example the term "about" in relation to a numerical value *x* refers to $x\pm10\%$, $x\pm5\%$, or $x\pm1\%$.

[0294] "% w/w" means the weight of a component as a percentage of the total weight of *e.g.* a layer or dosage form in which the component is present. For example, a composition comprising "5% w/w X" refers to a composition in which the weight of component X is 5% of the total weight of the composition.

[0295] 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 provided herein. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0296] The term "pharmaceutically acceptable" with respect to a substance refers to that substance which is generally regarded as safe and suitable for use without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio. "Pharmaceutically acceptable" with regard to excipients 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.

[0297] "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. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-napththalenesulfonic acid, oleic acid, palmitic acid, propionic acid, stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, and the like, and salts formed when an acidic proton 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.

[0298] As used herein, the term "salts" includes co-crystals. The term "co-crystal" refers to a crystalline compound comprising two or more molecular components, *e.g.* wherein proton transfer between the molecular components is partial or incomplete.

[0299] The term "solvate" means a molecular complex comprising a compound and one or more pharmaceutically acceptable solvent molecules. Examples of solvent molecules include water and C_{1-6} alcohols, *e.g.* ethanol. When the solvate is water, the term "hydrate" may be used.

[0300] "Treating" and "treatment" of a disease include the following:

(1) preventing or reducing the risk of developing the disease, *i.e.* causing the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease.

(2) inhibiting the disease, *i.e.* arresting or reducing the development of the disease or its clinical symptoms, and

(3) relieving the disease, *i.e.* causing regression of the disease or its clinical symptoms.

The term "effective amount" refers to an amount that may be effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The effective amount will vary depending on the compound, the disease and its severity and the age, weight, *etc.* of the subject to be treated. The effective amount can include a range of amounts.

EXAMPLES

[0301] The following examples are provided for purposes of illustration, not limitation.

Example 1 – Compound of Formula II single agent tablets

[0302] A formulation (tablet F1) of the compound of Formula II was prepared by dry granulation. Figure 5 is a flow diagram illustrating the preparation of this formulation. The composition of the single agent formulation is shown in the table below:

	Tablet Formulation F1	
Component	**Mass (mg/tablet)**	**% w/w/ tablet**
Compound of Formula II	78.7*	26.2
Microcrystalline cellulose	120	40
Lactose monohydrate	75.8	25.3
Crospovidone	21	7
Sodium Stearyl Fumarate**	4.5	1.5
Total Weight	**300**	

*Equivalent to 75 mg of the Compound of Formula I

** Intergranular:2.25 mg (0.75%; Extragranular: 2.25 mg (0.75%)

[0303] In the pharmacokinetic studies of Example 3, the tablets of Formulation F1 were film coated with 12 mg Opadry II Yellow 85F92259. The total weight of the film coated tablets was 312 mg.

[0304] The Compound of Formula II was blended with intergranular excipients (lactose, microcrystalline cellulose, and crospovidone), further blended with the intergranular portion of the sodium stearyl fumarate), roller compacted, milled, and final blended with the sodium stearyl fumarate to yield a final powder blend for compression. The final powder blend had a mean particle size of 347 μm with a compressibility index of 21%. The final powder blend was compressed into tablet cores, which were film-coated as described above to a target weight gain of 4%.

Example 2 – Compound of Formula II / emtricitabine / tenofovir alafenamide bilayer tablets

[0305] A bilayer formulation (tablet F2) of the compound of Formula II, emtricitabine, and tenofovir alafenamide hemifumarate was prepared using the method described in Example 8. Figure 6 is a flow diagram illustrating the preparation of bilayer tablets. The composition of the formulation is summarized in the table below:

Ingredient	**Bilayer tablet F2 (mg/tablet)**	
	Compound of Formula II Layer	Emtricitabine/ tenofovir alafenamide hemifumarate Layer
Compound of Formula II	78.7*	
Emtricitabine		200
Tenofovir alafenamide hemifumarate		28.1**
Microcrystalline cellulose	247.8***	113.1
Croscarmellose sodium	21.2	30.2
Magnesium Stearate	5.3†	5.7††
Layer Weight	353	377
Tablet Core Weight	**730**	

*Equivalent to 75 mg of the Compound of Formula I

**Equivalent to 25 mg tenofovir alafenamide

***Intergranular: 212.5 mg (29.1%); Extragranular: 2.65 mg (0.4%)

†Intergranular: 2.65 mg (0.4%); Extragranular: 2.65 mg (0.4%)

††Intergranular: 2.83 mg (0.4%); Extragranular: 2.83 mg (0.4%)

[0306] In the pharmacokinetic studies of Example 3, the tablets of Formulation F2 were film coated with 21.9 mg Opadry II Yellow 85F92259 (represented 3% weight gain). The total weight of the film coated tablets was 752 mg.

[0307] The tablets were manufactured using a dry granulation by roller compaction process. An emtricitabine / tenofovir alafenamide final powder blend was manufactured by dry granulation of emtricitabine and tenofovir alafenamide with excipients (microcrystalline cellulose, croscarmellose sodium, intergranular magnesium stearate), followed by blending with extragranular lubricant (extragranular magnesium stearate). The final powder blend of the Compound of Formula I was manufactured by dry granulation of the active component with excipients (microcrystalline cellulose, croscarmellose sodium, intergranular magnesium stearate) followed by blending with the

extragranular filler and lubricant (microcrystalline cellulose and extragranular magnesium stearate). In this study, the emtricitabine/tenofovir alafenamide final powder blend was compressed as layer 1 and the final powder blend of the Compound of Formula I was compressed as layer 2 to give a final bilayer tablet core. The core was film coated as described above.

Example 2A Emtricitabine / tenofovir alafenamide tablets

[0308] The composition of the emtricitabine / tenofovir alafenamide (F/TAF) fixed dose combination tablets used in subsequent studies is shown in the following table:

Component	Tablet Formulation F3 Emtricitabine/tenofovir alafenamide 200/25 mg (mg/tablet)
Intergranular	
Emtricitabine	200
Tenofovir Alafenamide Hemifumarate	28.0
Microcrystalline Cellulose	88.7
Croscarmellose Sodium	28.0
Magnesium Stearate	2.6
Extragranular	
Magnesium Stearate	2.6
Total Tablet Core Weight	**350**
Film-Coating	
Opadry II Blue 85F105057	10.5

[0309] Emtricitabine and tenofovir alafenamide hemifumarate were co-blended with microcrystalline cellulose and croscarmellose sodium, followed by lubrication with magnesium stearate. The roller compaction pre-blend was then roller compacted and milled using an oscillating mill. The resultant granules were lubricated with magnesium stearate and compressed into 350 mg tablet cores which that were subsequently film coated.

Example 3 – Pharmacokinetic Studies

[0310] Studies were carried out to assess the pharmacokinetic profiles of the formulations F1, F2, and F3 of Examples 1, 2, and 2A. A randomized, open-label, multiple-period, fixed-sequence,

crossover study was performed to evaluate the relative bioavailability of bilayer tablet formulation F2 compared with that of single agent tablet formulation F1 co-administered simultaneously with a fixed-dose combination tablet containing emtricitabine and tenofovir alafenamide (tablet formulation F3). The bioavailability was evaluated in healthy subjects.

Study Design and Duration of Treatment

[0311] Three single doses of the following tablet formulations were administered orally during up to 21 days total study duration:

(a) a fixed dosed combination tablet containing emtricitabine and tenofovir alafenamide (200/25 mg – Tablet F3) and a single agent tablet containing the compound of Formula I (75 mg - Tablet F1) administered simultaneously, under fasted conditions (dosed on day 1; days 2-8 washout);

(b) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (75/200/25 mg – Tablet F2) administered under fasted conditions (dosed on day 9; days 10-16 washout); and

(c) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (75/200/25 mg – Tablet F2) administered under fed conditions with a high-fat meal (dosed on day 17; day 21 discharge).

Criteria for Evaluation

[0312] The following plasma pharmacokinetic parameters were calculated: C_{max}, AUC_{last}, and AUC_{inf}.

Statistical Methods

[0313] Pharmacokinetics: Plasma concentrations and PK parameters were listed and summarized by analyte and treatment group using descriptive statistics. In addition, a parametric analysis of variance using a mixed-effects model appropriate for a crossover design was fitted to the natural logarithmic transformation of the PK parameters (AUC_{inf}, AUC_{last}, and C_{max}). Two-sided 90% confidence intervals (CIs) were constructed for the ratio of geometric least-squares means (GLSMs) of each PK parameter for the compound of Formula I, emtricitabine, and tenofovir alafenamide.

Results

[0314] Subject Disposition and Demographics

[0315] A total of 28 subjects were randomized and received at least 1 dose of study drug.

[0316] The results for the first cohort of the clinical study are summarized in the table below. This table presents the mean (%CV) values, Geometric Least Squares Mean (GLSM) ratios, and 90% CI

values of the plasma PK parameters AUC_{last}, AUC_{inf}, and C_{max} for each active ingredient, following administration of bilayer tablet formulation F2 or the single agent tablet formulation F1, co-administered with a fixed dose combination of emtricitabine and tenofovir alafenamide under fasted conditions.

PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Compound of Formula I /F/TAF (75/200/25 mg) (Test) (N = 28)	Compound of Formula I (75 mg) + F/TAF (200/25 mg) (Reference) (N = 28)	
Compound of Formula I			
AUC_{last} (h•ng/mL)	151,844.0 (26.9)	119,619.4 (26.6)	126.76 (117.82, 136.37)
AUC_{inf} (h•ng/mL)	156,637.5 (27.5)	123,174.0 (26.6)	126.82 (117.87, 136.45)
C_{max} (ng/mL)	7123.9 (21.6)	5593.9 (31.0)	130.72 (119.95, 142.45)
FTC			
AUC_{last} (h•ng/mL)	11,412.3 (13.5)	11,199.3 (13.7)	101.89 (99.50, 104.33)
AUC_{inf} (h•ng/mL)	11,642.8 (13.2)	11,436.4 (13.2)	101.78 (99.45, 104.16)
C_{max} (ng/mL)	2264.3 (22.7)	2153.6 (21.5)	104.86 (97.73, 112.50)
TAF			
AUC_{last} (h•ng/mL)	205.5 (45.5)	223.6 (45.2)	91.62 (82.13, 102.21)
AUC_{inf} (h•ng/mL)	206.8 (45.2)	225.1 (45.0)	91.56 (82.27, 101.91)
C_{max} (ng/mL)	253.3 (44.2)	276.7 (51.7)	95.47 (79.88, 114.10)

[0317] The total exposure of the compound of Formula I, under fasted conditions, was approximately 30% higher when dosed in the bilayer tablet formulation F2, containing two additional therapeutic agents (TAF and FTC), compared to single agent tablet formulation F1, co-dosed with a fixed dose combination tablet containing TAF and FTC (F3). Under fasted conditions, the AUC_{inf} and C_{max} of the compound of Formula I were 27% and 31% higher, respectively, following administration of bilayer tablet formulation F2 than following administration of single-agent tablet formulation F1 with the F/TAF fixed dose combination (F3, 200/25 mg). Emtricitabine and tenofovir alafenamide exposure was similar following administration of bilayer tablet formulation F2 or single-agent tablet formulation F1 with the F/TAF FDC (F3, 200/25 mg).

[0318] Based on the data from this study, a new fixed dose formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide was developed.

[0319] The effect of food on the pharmacokinetics of the compound of Formula I was also examined in a non-randomized, open label, crossover, 2 period, fixed sequence, and single dose cohort consisting of 8 unique subjects. In this study, a single dose of the compound of Formula I was administered in two periods with fixed sequence under fasted and fed conditions respectively. A washout of at least five half-lives was required between fasted and fed sequences.

[0320] The compound of Formula I was prepared according to percent weight of the tablet formulation of Example 1, a dose equivalent to 100 mg of the compound of Formula I and excipient amounts adjusted accordingly to arrive at the designated weight percentages (100 mg/tablet). A single tablet containing the compound of Formula I (100 mg/tablet) was administered with approximately 240 mL water after an overnight fast (no food or drink, except water, for at least 10 hours) on Day 1. Subjects continued to fast until 4 hours post dose or until collection of the 4-hour postdose blood sample. On Day 9, A single tablet containing the compound of Formula I (100 mg/tablet) was administered with approximately 240 mL water after an overnight fast (no food or drink, except water, for at least 10 hours) and within 5 minutes of the subjects finishing a standard high-fat breakfast (approximately 800 calories with 50% of calories from fat).

[0321] The evaluation of the effect of food on compound of Formula I was obtained by comparing AUC_{inf}, $AUC_{0\text{-}last}$, and C_{max} on Days 1 and 9 under fed and fasted conditions. The natural log-transformed PK parameters (i.e., AUC_{inf}, $AUC_{0\text{-}last}$, and C_{max}) were evaluated using a mixed-effects model with food as a fixed effect and subject as a random effect. The 90% CI for the geometric least square mean (GLSM) ratios for fast versus fed was constructed. The statistical comparison of the pharmacokinetic parameters of the compound of Formula I following single dose administration of this tablet formulation in fed and fasted states is presented in the table below.

	Mean (%CV)		
Compound of Formula I PK Parameter	**Test Compound of Formula I 100 mg Fed (n=8)**	**Reference Compound of Formula I 100 mg Fasted (n=8)**	**% GLSM Ratio (90% CI)**
AUC_{inf} (hr*ng/mL)	214,146.3 (15.9)	117,777.1 (23.3)	183.97 (152.05, 222.59)
AUC_{last} (hr*ng/mL)	209,259.9 (15.1)	115,681.7 (24.0)	183.58 (151.91, 221.86)
C_{max} (ng/mL)	11,268.8 (15.1)	5885.0 (34.9)	200.69 (165.93, 242.74)

[0322] The Table above presents the GLSM ratios and associated 90% confidence intervals (CIs) for the test (fed) versus reference (fasted) treatments for the primary plasma PK parameters of the compound of Formula I. Administration of a single dose of the compound of Formula I 100 mg with food (high-calorie/high-fat breakfast) increased the GLSM values of C_{max} and AUC_{inf} 101% (90% CI

of GLSM ratio 165.93% to 242.74%) and 84% (90% CI of GLSM ratio 152.05% to 222.59%), respectively. There were no apparent changes in clearance and $t_{1/2}$ following administration with food, indicating that food enhanced the bioavailability of the compound of Formula I by improving its solubility and/or absorption.

[0323] The effect of food on the PK of the compound of formula I, emtricitabine, and tenofovir alafenamide when administered as the tablet formulation F2 tablet was evaluated in the clinical study described above (The randomized, open-label, multiple-period, fixed-sequence, crossover study involving 28 subjects comparing bilayer tablet formulation F2 with that of single agent tablet formulation F1 co-administered simultaneously with a fixed-dose combination tablet containing emtricitabine and tenofovir alafenamide (tablet formulation F3).

[0324] The mean (%CV) values, GLSM ratios, and 90% CI values of the plasma for PK parameters AUC_{last}, AUC_{inf}, and C_{max} for the compound of Formula I, emtricitabine, and tenofovir alafenamide following administration of tablet formulation F1 under fasted conditions or with a high-fat meal are presented in the following table.

PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Compound of Formula I /F/TAF (75/200/25 mg) (High-Fat Meal; Test) (N = 28)	Compound of Formula I /F/TAF (75/200/25 mg) (Fasted; Reference) (N = 28)	
Compound of Formula I			
AUC_{last} (h•ng/mL)	216,733.1 (23.4)	151,844.0 (26.9)	144.45 (134.26, 155.40)
AUC_{inf} (h•ng/mL)	226,142.1 (24.9)	156,637.5 (27.5)	145.88 (135.58, 156.95)
C_{max} (ng/mL)	8941.1 (16.9)	7123.9 (21.6)	126.74 (116.30, 138.12)
FTC			
AUC_{last} (h•ng/mL)	11,483.0 (15.7)	11,412.3 (13.5)	100.34 (97.99, 102.75)
AUC_{inf} (h•ng/mL)	11,706.4 (15.6)	11,641.6 (13.2)	100.25 (97.96, 102.59)
C_{max} (ng/mL)	1872.5 (20.1)	2264.3 (22.7)	83.18 (77.53, 89.25)
TAF			
AUC_{last} (h•ng/mL)	315.3 (44.0)	205.5 (45.5)	156.81 (140.57, 174.94)
AUC_{inf} (h•ng/mL)	319.7 (43.1)	206.8 (45.2)	158.20 (142.14, 176.08)
C_{max} (ng/mL)	212.2 (49.4)	253.3 (44.2)	83.22 (69.63, 99.46)

[0325] Compared with administration under fasted conditions, administration of the tablet formulation F2 with a high-fat meal resulted in a 46% higher AUC_{inf} and a 27% higher C_{max} for the

compound of Formula I. The impact of food on emtricitabine and tenofovir alafenamide exposure was similar to that previously observed.

[0326] The data presented in the two tables above also demonstrate that the effect of food on the total exposure of the compound of Formula I is reduced in bilayer tablet formulation F2, relative to the single agent tablet formulation F1. The geometric mean ratio of AUC_{inf} for the compound of Formula I in single agent tablet formulation F1 was 1.84, while the geometric mean ratio of AUC_{inf} for the compound of Formula I in bilayer tablet formulation F2 was 1.46. In comparison the geometric mean ratio of AUC_{inf} for emtricitabine in to 0.91 and 1.00 for emtricitabine and 1.75 and 1.58 for tenofovir alafenamide in each formulation respectively (comparing the emtricitabine and tenofovir alafenamide exposures of the tablet formulation F2 with that of tablet formulation F1 codosed with the tablet formulation F3). The geometric mean ratio of C_{max} for single agent tablet formulation F1 was 2.01, while the geometric mean ratio of C_{max} for bilayer tablet formulation F2 was 1.27. In comparison, the geometric mean ratios of C_{max} for emtricitabine and tenofovir alafenamide in tablet formulations F1 and F2 were 0.85 and 0.83, respectively. These data indicate that a fixed dosed combination tablet formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide may be taken without regard to food.

Example 4 – Dissolution Studies

[0327] Studies were carried out to assess the dissolution profiles of tablets F1, F2, and F3-A. Dissolution of the compound of Formula II was measured using USP Apparatus II, in 250 mL of pH 6.5 fasted state simulated intestinal fluid (FaSSIF), at 37 °C and paddle speed of 100 rpm. FaSSIF was prepared by adding simulated intestinal fluid (SIF) powder (Biorelevant.com) to pH 6.5 phosphate buffer at approximately 4.48 g/L. Once the powder was dissolved, the volume of the resulting solution was doubled. In the case of the single agent tablet formulation F1, dissolution of the compound of Formula II was measured in the presence of the fixed dose combination tablet formulation F3 of Example 2A containing emtricitabine and tenofovir alafenamide hemifumarate. The results are shown in Figure 1. These data show that the bilayer formulation (tablet F2) exhibited enhanced dissolution of the compound of Formula II, compared to the single agent formulation (tablet F1 codosed with F3). Tablet formulation F3-A was prepared as a single agent formulation according to the process described in Example 1 according to the table below.

Ingredient	Tablet F3-A (mg/tablet)
	Compound of Formula II Layer
Compound of Formula II	78.7*
Emtricitabine	
Tenofovir alafenamide hemifumarate	
Microcrystalline cellulose	247.8***
Croscarmellose sodium	21.2
Magnesium Stearate	5.3*
Tablet Core Weight	353

*Equivalent to 75 mg of the Compound of Formula I

***Intergranular: 212.5 mg (29.1%); Extragranular: 2.65 mg (0.4%)

*Intergranular: 2.65 mg (0.4%); Extragranular: 2.65 mg (0.4%)

[0328] As shown above, Tablet F3-A used the composition (excipient selection and quantities) of the Compound of Formula II Layer of Example 2 (F2). Figure 1 further demonstrates that Tablet formulation F2 exhibited enhanced dissolution of the compound of Formula II compared to Tablet formulations F1 and F3-A. The total percentage of the compound of Formula II dissolved from formulation F1 and F3-A was comparable at approximately 60%. The total amount of the compound of Formula II dissolved from formulation F2 was approximately 10% higher.

[0329] In a second study, dissolution of the compound of Formula II was measured using fed state simulated intestinal fluid (FeSSIF) as dissolution medium. FeSSIF was prepared by adding simulated intestinal fluid (SIF) powder (Biorelevant.com) to pH 5.0 phosphate buffer at approximately 22.405 g/L. Once the power was dissolved, the volume of the resulting solution was doubled. In this study, dissolution of the compound of Formula II was measured using USP Apparatus II, in 250 mL of pH 5.5 fed simulated intestinal fluid, at 37 °C and paddle speed of 100 rpm. As in the previous study using fasted simulated intestinal fluid, the single agent tablet formulation F1 was tested in the presence of a second tablet formulation containing emtricitabine and tenofovir alafenamide hemifumarate (tablet F3). The results are shown in Figure 2. These data also show that the bilayer formulation (tablet F2) exhibited enhanced dissolution of the compound of Formula II, compared to the single agent formulation (tablet F1).

Example 5 – Excipient Studies

[0330] To further assess the effect of specific excipients on dissolution of the compound of Formula I, three additional bilayer tablet formulations were prepared, F4, F5, and F6. Tablet formulation F4 is similar to tablet formulation F2, with croscarmellose sodium being replaced with crospovidone. Likewise, tablet formulation F5 is similar to tablet formulation F2, with magnesium stearate being replaced with sodium stearyl fumarate. Finally, tablet formulation F6 is similar to tablet formulation F2, with both croscarmellose sodium and magnesium stearate being replaced with crospovidone and sodium stearyl fumarate, respectively. Tablets F4, F5, and F6 were prepared using the method described in Example 8.

Ingredient		**Bilayer tablet F4**	**Bilayer tablet F5**	**Bilayer tablet F6**
	Emtricitabine/ tenofovir alafenamide hemifumarate Layer (mg/tablet)	**Compound of Formula I Layer (mg/tablet)**		
Emtricitabine	200			
Tenofovir alafenamide hemifumarate	28.1			
Compound of Formula II		78.7	78.7	78.7
Microcrystalline cellulose	113	244	248	244
Croscarmellose sodium	30.2		21.2	
Crospovidone		24.7		24.7
Magnesium Stearate	5.7	5.3		
Sodium Stearyl Fumarate			5.3	5.3
Layer Weight	377	353	353	353
Tablet Core Weight		**730**	**730**	**730**

[0331] Figure 3 shows the results of dissolution studies performed on tablet formulations F4, F5, and F6, as well as tablet formulation F1 and F2. These data demonstrate that the substitution of each excipient enhances the dissolution of the compound of Formula I.

Example 6 – Compound of Formula I / emtricitabine / tenofovir alafenamide bilayer tablets – 50 mg dose

[0332] As a result of the higher *in vivo* exposure of the compound of Formula I that was observed in the pharmacokinetic studies, a bilayer formulation (tablet F7) of the compound of Formula II, emtricitabine, and tenofovir alafenamide hemifumarate was prepared incorporating a lower dose of the compound of Formula I. Tablet formulation F7 was prepared as described previously, *i.e.*, using the method described in Example 8. The composition of the formulation is summarized in the table below:

Ingredient	**Bilayer tablet F7 (mg/tablet)**	
	Compound of Formula II Layer	Emtricitabine/ tenofovir alafenamide hemifumarate Layer
Compound of Formula II	52.5*	
Emtricitabine		200
Tenofovir alafenamide hemifumarate		28**
Microcrystalline cellulose	246.3	113.2
Croscarmellose sodium	19.4	30.2
Magnesium Stearate	4.9	5.7
Layer Weight	323	377
Tablet Core Weight	**700**	
Opadry II Brown 85F165072	21	
Film Coated Tablet	**721**	

*Equivalent to 50 mg of the Compound of Formula I

**Equivalent to 25 mg tenofovir alafenamide

Example 7 – Compound of Formula I single agent tablets (50 mg)

[0333] Dissolution studies were performed comparing the 50 mg dose bilayer tablet F7 with a 50 mg single agent tablet.

[0334] A 50 mg formulation (tablet F8) of the compound of Formula II was prepared in a similar manner as tablet formulation F1 of Example 1. The composition of the single agent formulation is shown in the table below:

	Tablet Formulation F8	
Component	**Mass (mg/tablet)**	**% w/w/ tablet**
Compound of Formula II	52.5	26.2
Microcrystalline cellulose	80	40
Lactose	50.5	25.3
Crospovidone	14	7
Sodium Stearyl Fumarate	3	1.5
Total Weight	**200**	

[0335] Figure 4 shows the dissolution of 50 mg bilayer tablet formulation (fixed dose combination) F7 and 50 mg single agent tablet formulation F8. Dissolution of the compound of Formula II was measured using USP Apparatus II, in 333 mL of pH 6.5 FaSSIF, at 37 °C and paddle speed of 100 rpm. Two tablets of each tablet formulation, F7 and F8 were tested. As in Example 3, in the case of the single agent tablet formulation F8, dissolution of the compound of Formula II was measured in the presence of the fixed dose combination tablet formulation of Example 2A containing emtricitabine and tenofovir alafenamide hemifumarate. These data show that the 50 mg bilayer formulation (tablet F7) exhibited enhanced dissolution of the compound of Formula II, compared to the single agent formulation (tablet F8).

Example 8 – manufacturing process

[0336] The manufacturing/packaging procedure for the compound of Formula II/emtricitabine/tenofovir alafenamide hemifumarate tablets is divided into five unit processes:

1. mixing of the compound of Formula II drug substance with intergranular excipients, roller compaction or slugging, milling, and blending with extragranular excipients to yield the final powder blend for the compound of Formula II;

2. mixing of emtricitabine and tenofovir alafenamide hemifumarate drug substances with intergranular excipients, dry granulation, milling, and blending with extragranular excipients to yield emtricitabine/tenofovir alafenamide hemifumarate final powder blend;
3. tablet compression to yield bilayer tablet cores;
4. tablet film-coating to yield film-coated tablets; and
5. packaging.

[0337] The manufacturing process steps to produce the final drug product are detailed below.

Final Powder Blend for the Compound of Formula II (Dispensing, Blending, Dry Granulation, Milling, Final Blending)

1. Weigh the compound of Formula II and the excipients (microcrystalline cellulose and croscarmellose sodium). Correct the weight of the compound of Formula II based on the drug content factor (DCF), with a concomitant reduction in the weight of microcrystalline cellulose.
2. Blend in intergranular portion of magnesium stearate to the tumble blender and blend.
3. Dry granulate the resulting blend using a roller compactor or slug the resulting blend and mill.
4. Add extragranular microcrystalline cellulose and magnesium stearate and blend.

Emtricitabine/tenofovir alafenamide hemifumarate Final Powder Blend (Dispensing, Blending, Dry Granulation, Milling, Final Blending)

5. Weigh emtricitabine and tenofovir alafenamide hemifumarate drug substances and excipients (microcrystalline cellulose and croscarmellose sodium). Adjust the weight of emtricitabine and tenofovir alafenamide hemifumarate drug substances based on their corresponding DCF, with a concomitant adjustment to the weight of microcrystalline cellulose.
6. Blend in emtricitabine and tenofovir alafenamide hemifumarate drug substance, microcrystalline cellulose, and croscarmellose sodium to a tumble blender and blend.
7. Blend in intergranular portion of magnesium stearate to the tumble blender and blend.
8. Dry granulate the resulting blend using a roller compactor or slug the resulting blend and mill.
9. Blend in the extragranular portion of magnesium stearate.

Tableting

10. Compress the final powder blend of the compound of Formula II as the first layer and the emtricitabine/tenofovir alafenamide hemifumarate final powder blend as the second layer, with an appropriate main compression force to achieve a target hardness of 17 kP (range: 14 to 20 kP). For tablet formulations containing 50 mg of the compound of Formula II, the final

powder blend is compressed to a target layer weight of 323 mg using a target total tablet weight of 700 mg. For tablet formulations containing 75 mg of the compound of Formula II, the final powder blend is compressed to a target layer weight of 353 mg using a target total tablet weight of 730 mg.

Film-coating

11. Prepare a suspension of Opadry® II Brown 85F165072 (for tablets containing 50 mg compound of Formula I) or Opadry® II Yellow 85F92259 (for tablets containing 75 mg compound of Formula I). Film-coat the tablet cores to achieve the target tablet weight gain of 3% (range 2-4%). Dry film-coated tablets prior to cooling and discharge.

Example 9 – Pharmacokinetic Studies – Cohort 2

[0338] The pharmacokinetic study of Example 3 was continued with a second treatment group (cohort) to assess the pharmacokinetic profile of formulation F7 of Example 7 compared with that of formulation F2.

Study Design and Duration of Treatment

[0339] Four single doses of the following tablet formulations were administered once per day orally during 36 days total study duration:

(a) a fixed dosed combination tablet containing emtricitabine and tenofovir alafenamide (200/25 mg – Tablet F3) and a single agent tablet containing the compound of Formula I (75 mg - Tablet F1) administered simultaneously, under fasted conditions (Treatment A) (dosed on day 1; days 2-8 washout);

(b) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (50/200/25 mg – Tablet F2) administered under fasted conditions (Treatment D) (dosed on day 9; days 10-16 washout); and

(b) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (50/200/25 mg – Tablet F2) administered under fed conditions with a high-fat meal (Treatment E) (dosed on day 17; days 18-24 washout);

(c) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (50/200/25 mg – Tablet F2) administered under fed conditions with a moderate-fat meal (Treatment F) (dosed on day 25; day 29 discharge).

Criteria for Evaluation

[0340] The following plasma pharmacokinetic parameters were calculated: AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, C_{last}, T_{max}, T_{last}, CL/F, V_z/F, and $t_{1/2}$.

Statistical Methods

[0341] Pharmacokinetics: Individual subject concentration data and individual subject PK parameters for each analyte (compound of Formula 1, FTC, and TAF) were listed and summarized using descriptive statistics by treatment group (cohort) and treatment. Summary statistics were determined for both individual subject concentration data by time point, cohort, and treatment and individual subject PK parameters by cohort and treatment. Also, the geometric mean, 95% confidence interval (CI), and the mean, and standard deviation (SD) of the natural log-transformed values were presented for individual subject PK parameter data. The sample size for each time point was based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration below the level of quantitation (BLQ) was presented for each time point.

[0342] Statistical comparisons of the natural log-transformed PK parameters for each analyte and treatment comparison of interest were performed. The statistical modelling was based on the PK Analysis set for the analyte under evaluation. For each analyte, all subjects with available data for the PK parameter under evaluation were included in the modelling. The statistical comparisons using Treatment A as a reference only used data from this cohort, not from the earlier cohort of Example 3 (i.e., Treatment A was not pooled).

For each analyte and each PK parameter, a parametric (normal theory) mixed-effects ANOVA model was fitted to the natural log-transformed values of the PK parameter under evaluation. The statistical model included treatment as a fixed effect and subject as a random effect.

[0343] A total of 27 subjects completed the second treatement group of the study.

Results

[0344] Plasma pharmacokinetic parameters for each analyte are presented below. This table presents the mean (%CV) values, Geometric Least Squares Mean (GLSM) ratios, and 90% CI values of the plasma PK parameters AUC_{last}, AUC_{inf}, and C_{max} for each active ingredient, following administration of bilayer tablet formulation F7 and monolayer tablet formulation F1 coadministered with F/TAF formulation F3, under fasted conditions.

	Mean (%CV)		
	Formulation F7 Compound of Formula I/F/TAF (50/200/25 mg), fasted (Test) (N = 27)	Formulation F1 + F3 Compound of Formula (75 mg) + F/TAF (200/25 mg)), fasted (Reference) (N = 28)	%GLSM Ratio (90% CI) (Test/Reference)
Compound of Formula I PK Parameter			
AUC_{last} (hr•ng/mL)	109,061.4 (21.0)	142,396.6 (30.5)	78.46 (73.38, 83.89)
AUC_{inf} (hr•ng/mL)	112,619.6 (21.9)	146,931.6 (31.1)	78.56 (73.44, 84.04)
C_{max} (ng/mL)	5228.1 (16.9)	6791.1 (26.4)	78.07 (73.41, 83.01)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,652.9 (13.6)	11,035.5 (14.4)	96.52 (93.95, 99.15)
AUC_{inf} (hr•ng/mL)	10,873.9 (13.6)	11,234.6 (14.2)	96.76 (94.22, 99.37)
C_{max} (ng/mL)	2220.4 (30.1)	2166.4 (27.0)	102.36 (93.85, 111.64)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	207.1 (46.5)	236.7 (45.3)	85.37 (75.24, 96.85)
AUC_{inf} (hr•ng/mL)	208.8 (46.3)	238.3 (45.0)	85.48 (75.33, 97.00)
C_{max} (ng/mL)	249.2 (51.6)	291.9 (55.4)	84.17 (67.59, 104.81)

[0345] In particular, these data confirmed that the exposure of the compound of Formula I in Formulation F7 was proportionally lower than that observed in Formulation F2 and were consistent with predicted exposures for the revised dose. These data were consistent with the modelling of earlier clinical data confirming that these exposures provided anti-HIV antiviral efficacy. FTC and TAF exposure were similar between Formulation F7 and Formulation F2 coadministered with F3; TAF Cmax was slightly lower (by approximately 16%) for Formulation F7 than for the coadministration of F2 and F3.

[0346] The effect of food on the pharmacokinetics of the compound of Formula I, emtricitabine and tenofovir alafenamide when administered in formulation F7 was also examined in a further treatment group of the above described clinical study.

[0347] The mean (%CV) values, GLSM ratios, and 90% CI values of the plasma for PK parameters AUC_{last}, AUC_{inf}, and C_{max} for the compound of Formula I, emtricitabine, and tenofovir alafenamide following administration of tablet formulation F7 under fasted conditions or with a high-fat meal and with a moderate-fat meal are presented in the following table.

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Compound of Formula I/F/TAF (50/200/25 mg) high fat meal (Test) (N = 27)	Compound of Formula I/F/TAF (50/200/25 mg) fasted (Reference) (N = 27)	
Compound of Formula I PK Parameter			
AUC_{last} (hr•ng/mL)	135,117.3 (21.1)	109,061.4 (21.0)	123.96 (115.91, 132.57)
AUC_{inf} (hr•ng/mL)	140,032.4 (21.8)	112,619.6 (21.9)	124.41 (116.27, 133.11)
C_{max} (ng/mL)	5936.3 (18.3)	5228.1 (16.9)	113.23 (106.45, 120.43)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,213.0 (12.0)	10,652.9 (13.6)	96.02 (93.47, 98.65)
AUC_{inf} (hr•ng/mL)	10,467.0 (11.9)	10,873.9 (13.6)	96.41 (93.88, 99.02)
C_{max} (ng/mL)	1881.1 (24.2)	2220.4 (30.1)	85.52 (78.37, 93.31)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	310.3 (34.9)	207.1 (46.5)	162.62 (143.10, 184.80)
AUC_{inf} (hr•ng/mL)	318.4 (32.8)	208.8 (46.3)	166.55 (146.54, 189.29)
C_{max} (ng/mL)	236.6 (65.1)	249.2 (51.6)	91.71 (73.46, 114.49)

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Compound of Formula I/F/TAF (50/200/25 mg) moderate fat meal (Test) (N = 27)	Compound of Formula I/F/TAF (50/200/25 mg) fasted (Reference) (N = 27)	
Compound of Formula I PK Parameter			
AUC_{last} (hr•ng/mL)	135,217.3 (22.9)	109,061.4 (21.0)	123.56 (115.53, 132.14)
AUC_{inf} (hr•ng/mL)	140,197.7 (23.6)	112,619.6 (21.9)	124.06 (115.95, 132.74)
C_{max} (ng/mL)	6279.6 (18.3)	5228.1 (16.9)	119.90 (112.72, 127.53)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,738.3 (9.8)	10,652.9 (13.6)	101.17 (98.48, 103.94)
AUC_{inf} (hr•ng/mL)	10,973.3 (9.5)	10,873.9 (13.6)	101.33 (98.66, 104.06)
C_{max} (ng/mL)	1998.9 (18.4)	2220.4 (30.1)	91.84 (84.17, 100.21)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	290.6 (41.3)	207.1 (46.5)	148.20 (130.41, 168.41)
AUC_{inf} (hr•ng/mL)	293.1 (40.9)	208.8 (46.3)	148.23 (130.42, 168.47)
C_{max} (ng/mL)	251.1 (66.7)	249.2 (51.6)	99.04 (79.33, 123.65)

a N = 28 for the Reference group

[0348] Compared with administration under fasted conditions, administration of the tablet formulation F7 with a high-fat meal resulted in a 24% higher AUC_{inf} and a 13% higher C_{max} for the compound of Formula I. Administration of a moderate fat meal, resulted in a 24% higher AUC_{inf} and

a 20% higher C_{max} for the compound of Formula I. The impact of food on emtricitabine and tenofovir alafenamide exposure was similar to that previously observed.

[0349] These data confirm that a fixed dosed combination tablet formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide may be taken without regard to food.

Example 10 – Compression Studies

[0350] To further investigate the properties of the compositions, the following studies investigated blend compressibility and layer adhesion.

[0351] First, various final blend compositions including the Compound of Formula I (as a sodium salt, i.e., the Compound of Formula II) were prepared with varying levels of intergranular or extragranular lactose is shown in the table below.

Compound of Formula II: Final Powder Blends Containing Lactose

Components	Tablet Formulation					
	F9	F10	F11	F12	F13	F14
Intergranular % w/w						
Compound of Formula II	16.24	16.24	16.24	16.24	14.86	14.86
Microcrystalline Cellulose	46.25	56.25	56.25	56.25	69.12	60.63
Lactose	20.00	NA	NA	NA	0.00	8.50
Croscarmellose Sodium	6.00	6.00	6.00	6.00	5.49	5.49
Magnesium Stearate	0.75	0.75	0.75	0.75	0.69	0.69
Extragranular % w/w						
Microcrystalline Cellulose	10.00	10.00	5.00	15.00	9.15	9.15
Lactose	NA	10.00	15.00	5.00	NA	NA
Magnesium Stearate	0.75	0.75	0.75	0.75	0.69	0.69
Layer weight (mg)	323	323	323	323	353	353

[0352] Next, final blend compositions of the Compound of Formula II with varying amounts of magnesium stearate ranging from 0.75% to 0.5% were prepared as shown on the following table:

Compound of Formula I: Final Powder Blends with Varying Levels of Magnesium Stearate

Components	Tablet Formulation					
	F15	F16	F17	F18	F19	F20
Intergranular %w/w						
Compound of Formula II	16.24	16.24	16.24	16.24	16.24	16.24
Microcrystalline Cellulose	66.25	66.30	66.40	66.40	66.50	66.75
Croscarmellose Sodium	6.00	6.00	6.00	6.00	6.00	6.00
Magnesium Stearate	0.75	0.70	0.60	0.60	0.50	0.50
Extragranular %w/w						
Microcrystalline Cellulose	10.00	10.00	10.00	10.00	10.00	10.00
Magnesium Stearate	0.75	0.75	0.75	0.75	0.75	0.5
Layer weight (mg)	323	323	323	323	323	323

[0353] Finally, final blend compositions containing emtricitabine and tenofovir alafenamide were prepared with varying amounts of magnesium stearate ranging from 0.75% to 0.5% as shown in the table below:

Quantitative Compositions of F/TAF Final Powder Blends

Components	Tablet Formulation			
	F21	F22	F23	F24
Intergranular %w/w				
Tenofovir Alafenamide Hemifumarate	7.5	7.5	7.5	7.5
Emtricitabine	53.1	53.1	53.1	53.1
Microcrystalline Cellulose	29.9	30.4	30	30.2
Croscarmellose Sodium	8.0	8.0	8.0	8.0
Magnesium Stearate	0.75	0.50	0.70	0.60
Extragranular %w/w				
Magnesium Stearate	0.75	0.50	0.70	0.60
Layer Weight (mg)	377	377	377	377

[0354] Altering magnesium stearate content was studied to evaluate the impact on the compound of Formula 1 and emtricitabine / tenofovir alafenamide blend compressibility and layer adhesion. Formulations were also monitored for punch filming and sticking.

[0355] Fourteen combinations of the final powder blends described in the above tables were prepared as summarized in the table below. Critical tamp force was determined for all fourteen combinations.

Compression Study Critical Layer 1 Tamp Force Results

Formulation Combination	Tablet Formulation Layer 1	Tablet Formulation Layer 2	Critical Tamp Force (kN)	Observation
A*	F21	F15	1.0	Layers adhered
B*	F21	F9	<1.5	Delamination
C*	F21	F10	<1.5	Delamination
D*	F21	F11	<1.5	Delamination
E*	F21	F12	<1.5	Delamination
F*	F21	F13	<1.5	Delamination
G*	F21	F14	<1.5	Delamination
H	F15	F21	1.5	Delamination
I	F15	F22	2.0	Layers adhered
J	F16	F23	2.0	Layers adhered
K	F17	F24	1.5	Layers adhered
L	F18	F22	2.0	Layers adhered
M	F19	F22	2.5	Layers adhered, sticking
N	F20	F22	2.5	Layers adhered, sticking

* Note F/TAF as layer 1 and Compound of Formula I as layer 2

IG: Intergranular

EG: Extragranular

MgSt Magnesium Stearate

[0356] Combination A represents layer order and composition used as baseline for comparison of other compositions. The tablet formulation of each layer corresponds to the corresponding layer of tablet formulation F7.One objective was to investigate whether it was possible to improve on the critical tamp force of 1.0 kN observed for Combination A.

[0357] Combinations B – G represent studies in which lactose was included in the layer including the Compound of Formula I to investigate evaluate layer adhesion. Combination G included 20% lactose in the intergranular portion, with none in the extragranular portion. The ratio of lactose to microcrystalline cellulose ranged from 1:1, 3:1, 1:3 in Combinations C, D, and E, respectively. Combination G included 20 mg lactose in the intergranular portion. Delamination was observed at 1.5kN for Combinations B – G. As a result, lower tamp forces were not further investigated. When layer order was reversed (Combination H), delamination did not occur at 1.0 kN but was observed at 1.5 kN using the layer compositions of Combination A.

[0358] In Combinations I – N, varying the amount of magnesium stearate in each layer was investigated to determine the effect on compressibility and layer adhesion. Intergranular magnesium stearate was 0.75%, 0.70% and 0.60% in the Compound of Formula I layer of Combinations I, J, and K, respectively. Total magnesium stearate content in the F/TAF layer of each of Combinations I, J, and K was 1.0 %, 1.4% and 1.2%%, respectively. Intergranular magnesium stearate was 0.6% and 0.5% in the Compound of Formula I layer of Combinations L and M, respectively (with 0.75% extragranular magnesium stearate in each). Combination N has the lowest overall level of magnesium stearate in both layers (1.0% in each layer).

[0359] It was found that reducing magnesium stearate from 0.75% to 0.5% in each of the intergranular and extragranular portions the emtricitabine / tenofovir alafenamide layer increased critical tamp force to 2.0 kN (combination I). Critical tamp force could be further improved to 2.5 kN when magnesium stearate was reduced to 0.5% extragranular and/or intergranular in the layer containing the Compound of Formula I (combinations M and N). However, despite gaining an increase in critical tamp force, decreasing magnesium stearate to 0.5% in each component of the powder blend containing the Compound of Formula I had a negative effect on sticking. Intermediate changes in magnesium stearate (Combinations J – L) had no further improvement over combination I. As a result, magnesium stearate level was decreased in the emtricitabine/tenofovir alafenamide layer only (formulation combination I). A critical layer 1 tamp force of 1377 N was ultimately determined. The table below summarizes the composition of Formulation I.

[0360] Thus, the addition of intergranular or extragranular lactose to the layer containing the Compound of Formula I had little to ono effect on layer adhesion. Decreasing magnesium stearate from each of final powder blends improved compressibility.

Quantitative Composition of Combination Formulation I

Components	Quantity per Tablet (mg)	w/w (%)
Compound of Formula I Layer		
Compound of Formula II[a]	52.5[a, b]	7.5
Microcrystalline Cellulose	246.3	35.2
Croscarmellose Sodium	19.4	2.8
Magnesium Stearate	4.9	0.7
Subtotal	323	46.1
F/TAF Layer		
Emtricitabine[c]	200.0[c]	28.6
Tenofovir Alafenamide Fumarate[c]	28.0[c, d]	4.0
Microcrystalline Cellulose	115.0	16.4
Croscarmellose Sodium	30.2	4.3
Magnesium Stearate	3.8	0.5
Subtotal	377	53.9
Total Bilayer Tablet Core Weight	700	100
Film Coat		
Opadry II Brown 85F165072[e]	21[f]	3[f]
Purified Water[g]	---[g]	---[g]

a The quantity used is adjusted on the basis of the purity of each batch of Compound of Formula II with a concomitant adjustment of the quantity of microcrystalline cellulose.

b Equivalent to 50 mg of Compound of Formula I free acid.

c The quantity used is adjusted on the basis of the purity of each batch of emtricitabine and tenofovir alafenamide hemifumarate with a concomitant adjustment of the quantity of microcrystalline cellulose.

d Equivalent to 25 mg of tenofovir alafenamide free base.

e Opadry II Brown 85F165072 contains polyvinyl alcohol, USP (40.0% w/w); titanium dioxide, USP (22.0% w/w); polyethylene glycol, NF (20.2% w/w); talc, USP (14.8% w/w); iron oxide red, NF (2.4% w/w); iron oxide black, NF (0.6% w/w).

f Represents a theoretical weight gain of 3% w/w (range 2% to 4% w/w) onto the tablet core weight.

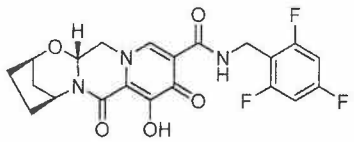
g Sufficient purified water is used for film coating and is removed during the process

[0361] All publications, patents and patent applications are incorporated by reference in their entirety, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

CLAIMS

1. A solid oral dosage form comprising the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof.

2. The solid oral dosage form of claim 1, wherein the dosage form comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

3. The solid oral dosage form of claim 1 or 2, wherein the dosage form comprises 52 mg of the sodium salt of the compound of Formula I and 28 mg tenofovir alafenamide hemifumarate.

4. The solid oral dosage form of any preceding claim, wherein the dosage form has a total weight of less than about 800 mg.

5. The solid oral dosage form of any preceding claim, wherein the dosage form has a total weight of less than about 730 mg.

6. The solid oral dosage form of any preceding claim, wherein the dosage form is a tablet.

7. A coated tablet comprising 50 mg of a compound of Formula I:

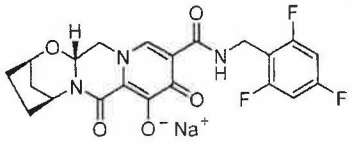
(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof and a coating.

8. A tablet comprising 52 mg of the compound of Formula II

(II)



28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

9. A tablet comprising (a) 50 mg of the compound of Formula I:

(I)

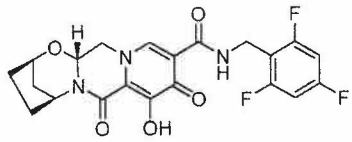


or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1 g.

10. The tablet of claim 9, wherein (a) and (b) are within separate layers in a multilayer tablet.

11. A tablet comprising from 6.5-11.0 % w/w of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet.

12. A tablet comprising from 7.0-11.0 % w/w of the compound of Formula II:

(II)



3.5-4.1 % w/w tenofovir alafenamide hemifumarate, and 25-30 % w/w emtricitabine, where the weight percentages denote a proportion of the whole tablet.

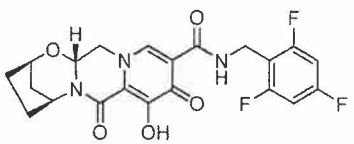
13. The tablet of any preceding claim, wherein the tablet does not contain lactose, crospovidone, and/or sodium stearyl fumarate.

14. The tablet of any preceding claim, wherein the tablet further comprises croscarmellose sodium and/or magnesium stearate.

15. The tablet of any preceding claim, wherein the tablet further comprises croscarmellose sodium, magnesium stearate, and/or microcrystalline cellulose.

16. A multilayer tablet comprising (a) a compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

17. The multilayer tablet of claim 16, wherein each layer contains at least one of (a), (b) and (c).

18. The tablet of claim 16 or 17, wherein the tablet comprises (a) a first layer comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, (b) a second layer comprising tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) further comprises emtricitabine or a pharmaceutically acceptable salt thereof.

19. The tablet of claim 18, wherein (a) the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of a compound of Formula I or a pharmaceutically acceptable salt thereof.

20. The tablet of claim 18 or 19, wherein (a) the first layer comprises a compound of Formula I or a pharmaceutically acceptable salt thereof and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of a compound of Formula I or a pharmaceutically acceptable salt thereof.

21. The tablet of any one of claims 16-20, wherein the layer containing a compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone, and/or sodium stearyl fumarate.

22. The tablet of any one of claims 16-20, wherein the layer containing a compound of Formula I or a pharmaceutically acceptable salt thereof comprises croscarmellose sodium and/or magnesium stearate.

23. The tablet of any one of claims 16-20, wherein the layer containing a compound of Formula I or a pharmaceutically acceptable salt thereof comprises croscarmellose sodium and/or magnesium stearate and/or microcrystalline cellulose.

24. The tablet of any one of claims 16-20, wherein the tablet comprises from 6.5-11.0 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet.

25. The tablet of any one of claims 16-20, wherein the tablet comprises from 7.0-11.0 % w/w of a sodium salt of the compound of Formula I, 3.5-4.1 % w/w tenofovir alafenamide hemifumarate, and 25-30 % w/w emtricitabine, where the weight percentages denote a proportion of the whole tablet.

26. The solid oral dosage form or tablet of any preceding claim, wherein the tablet contains less than about 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

27. The solid oral dosage form or tablet of any preceding claim, wherein the tablet contains less than about 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

28. The solid oral dosage form or tablet of any preceding claim, wherein the tablet releases at least about 50% of a compound of Formula I or a pharmaceutically acceptable salt thereof in about 20 minutes, measured using USP apparatus II, in 333 mL of fasted simulated intestinal fluid, pH 6.5, at 37 °C and paddle speed of 100 rpm.

29. The solid oral dosage form or tablet of claim 28, wherein the tablet releases at least about 60% of a compound of Formula I or a pharmaceutically acceptable salt thereof in about 20 minutes.

30. The solid oral dosage form or tablet of any preceding claim, wherein the tablet releases at least about 70% of a compound of Formula I or a pharmaceutically acceptable salt thereof in about 60 minutes.

31. A method of producing a tablet of any one of the preceding claims, wherein the method comprises (a) compressing the a compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer.

32. The method of claim 31, wherein the first layer and second layer are compressed separately and subsequently combined.

33. The method of claim 31, wherein the first layer is formed by compression and subsequently the second layer is compressed onto the first layer.

34. The first layer obtainable by the method of claim 31.

35. The second layer obtainable by the method of claim 31.

36. A kit comprising (a) a tablet comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, and (b) a desiccant.

37. The kit of claim 36, wherein the desiccant is silica gel.

38. A solid oral dosage form or tablet according to any one of the preceding claims for use in the therapeutic treatment of an HIV infection.

39. A method of therapeutic treatment of an HIV infection comprising administering to a subject a solid oral dosage form or tablet according to any one of the preceding claims.

40. A composition comprising about 40 mg to about 60 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, about 200 mg to about 400 mg microcrystalline cellulose, about 1 mg to about 40 mg croscarmellose sodium.

41. The composition of claim 40, wherein the composition is a first layer of a multilayer tablet.

42. The composition of claim 41, wherein the composition further comprises a second layer, wherein the second layer comprises about 150 mg to about 250 mg emtricitabine or a pharmaceutically salt thereof, about 20 mg to about 35 mg tenofovir alafenamide or a pharmaceutically salt thereof, about 90 mg to about 130 mg microcrystalline cellulose, about 20 mg to about 35 mg croscarmellose sodium, and about 1 mg to about 7 mg magnesium stearate.

43. A tablet comprising a first layer and a second layer, wherein
the first layer comprises about 5% to about 10% w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, about 26% to about 44% w/w microcrystalline cellulose, about 2% to about 4% w/w croscarmellose sodium, and about 0.5% to about 0.9% w/w magnesium stearate; and
the second layer comprises about w/w 21% to about 36% emtricitabine, about 3% to about 5% w/w tenofovir alafenamide, about 12% to about 20% w/w microcrystalline cellulose, about w/w 3% to about 6% croscarmellose sodium, and about w/w 0.3% to about 0.7% magnesium stearate.

44. A tablet composition comprising from about 6.4 w/w to about 8.5% w/w of the compound of Formula II, about 25% w/w to about 32% w/w emtricitabine, about 3.5% w/w to about 4.5% w/w tenofovir alafenamide hemifumarate, about 46% w/w to about 57% w/w microcrystalline cellulose, about 5.9% w/w to about 8.5% w/w croscarmellose sodium, and about 1.0-2.0% w/w magnesium stearate.

45. The composition of any one of claims 40 to 44, futher comprising a film coating.

46. A composition comprising 50 mg Compound of Formula I (e.g., a compound of Formula II), 25 mg tenofovir alafenamide, and 200 mg emtricitabine, wherein the mean AUC_{last} following administration of a single dose is from about 81700 h-ng/mL to about 140000 h-ng/mL of the compound of Formula I, from about 8100 h-ng/mL to about 13600 h-ng/mL of emtricitabine, and from about 165 h-ng/mL to about 400 h-ng/mL of tenofovir alafenamide.

47. The composition of claim 46, wherein the mean AUC_{inf} is from about 84,450 h-ng/mL to about 141,000 h-ng/mL of the compound of Formula I, from about 8,100 h-ng/mL to about 13,600 h-ng/mL of emtricitabine, and from about 200 h-ng/mL to about 500 h-ng/mL of tenofovir alafenamide.

48. The composition of claim 46 or 47, wherein the mean C_{max} is from about 4200 ng/mL to about 8000 ng/mL of the compound of Formula I, from about 1770 ng/mL to about 2800 ng/mL of emtricitabine, and from about 185 ng/mL to about 315 ng/mL of tenofovir alafenamide.

49. A composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 60% of the mean AUC_{last} of a single dose following administration to fasted patients.

50. A composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 60% of the mean AUC_{inf} of a single dose following administration to fasted patients.

51. A composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine, wherein the mean C_{max} of a single dose following administration to fed patients is within about 60% of the mean C_{max} of a single dose following administration to fasted patients.

ABSTRACT

A solid oral dosage form is provided, comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof.

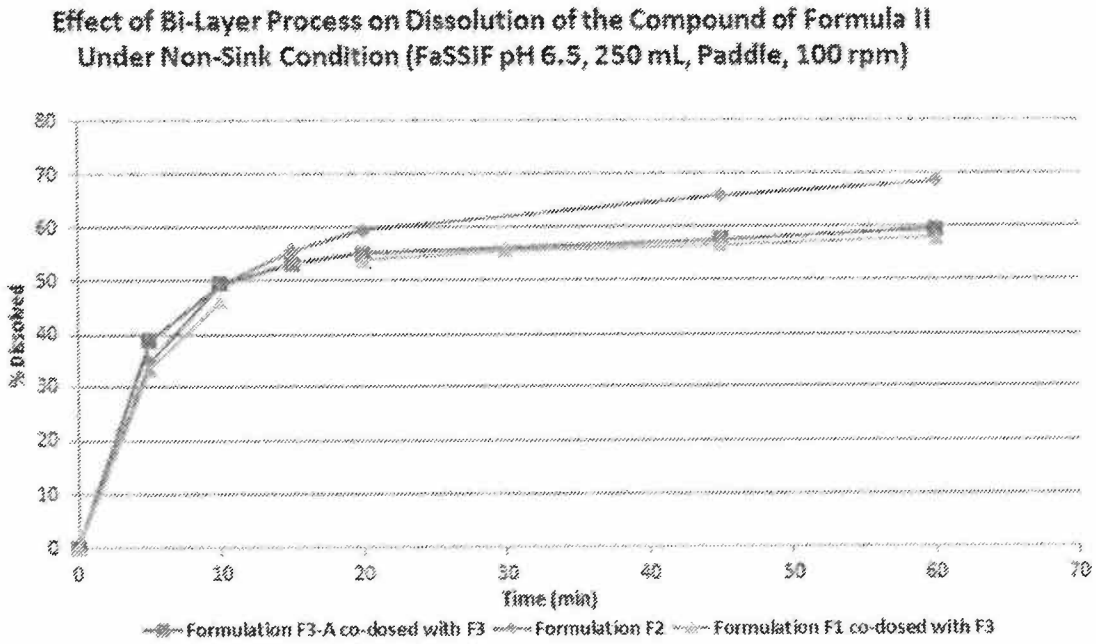


FIGURE 1

BICANDA00005022

1147.P2C

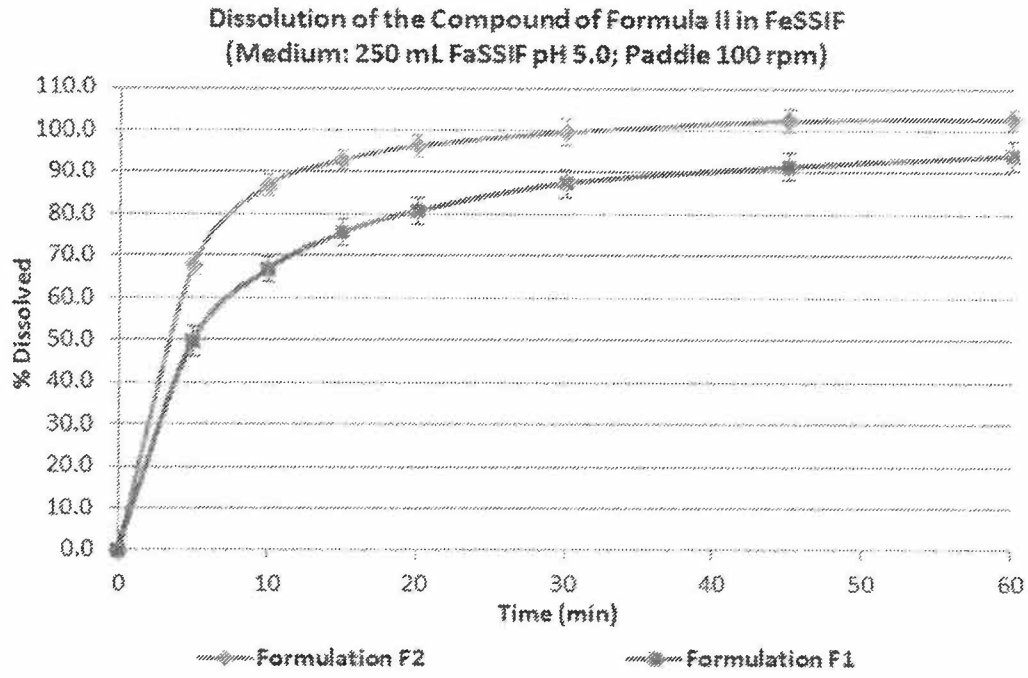


FIGURE 2

BICANDA00005023

1147.P2C

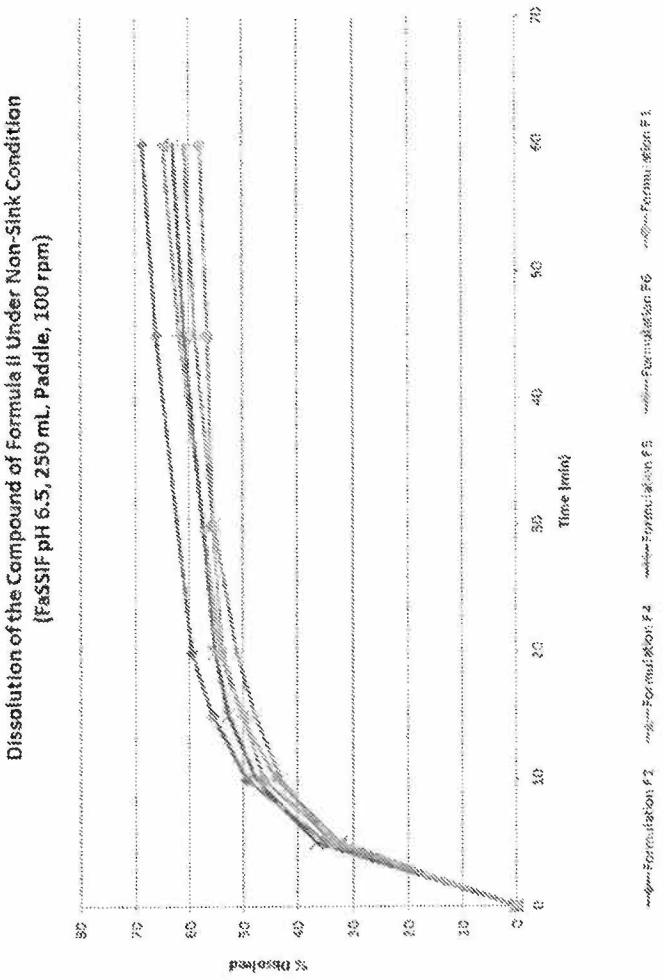

Dissolution of the Compound of Formula II Under Non-Sink Condition
(FaSSIF pH 6.5, 250 mL, Paddle, 100 rpm)
% dissolved
Time (min)

FIGURE 3

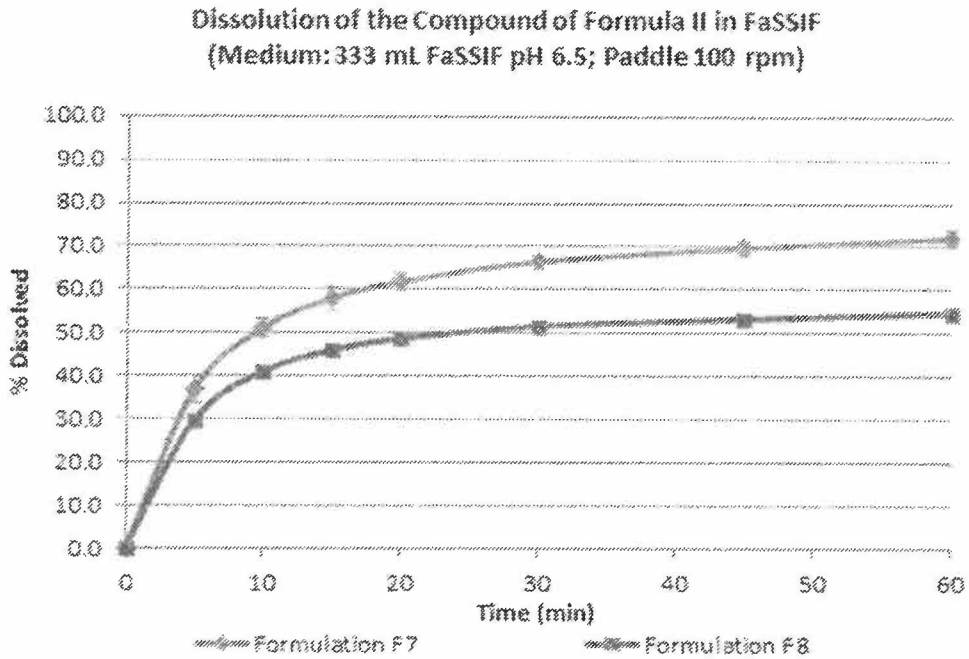


FIGURE 4

BICANDA00005025

1147.P2C

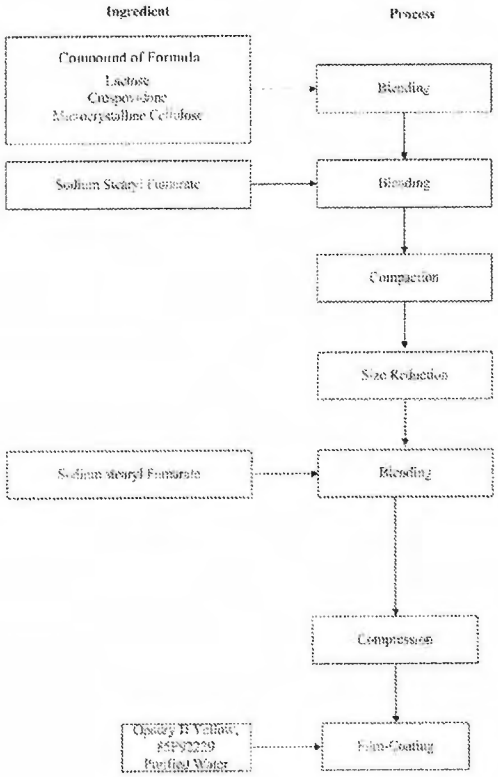

Ingredient
Process
Compound of Formula
Lactose
Crospovidone
Microcrystalline Cellulose
Blending
Sodium Stearyl Fumarate
Blending
Compaction
Size Reduction
Sodium stearyl Fumarate
Blending
Compression
Opadry II Yellow,
85F92229
Purified Water
Film-Coating

FIGURE 5

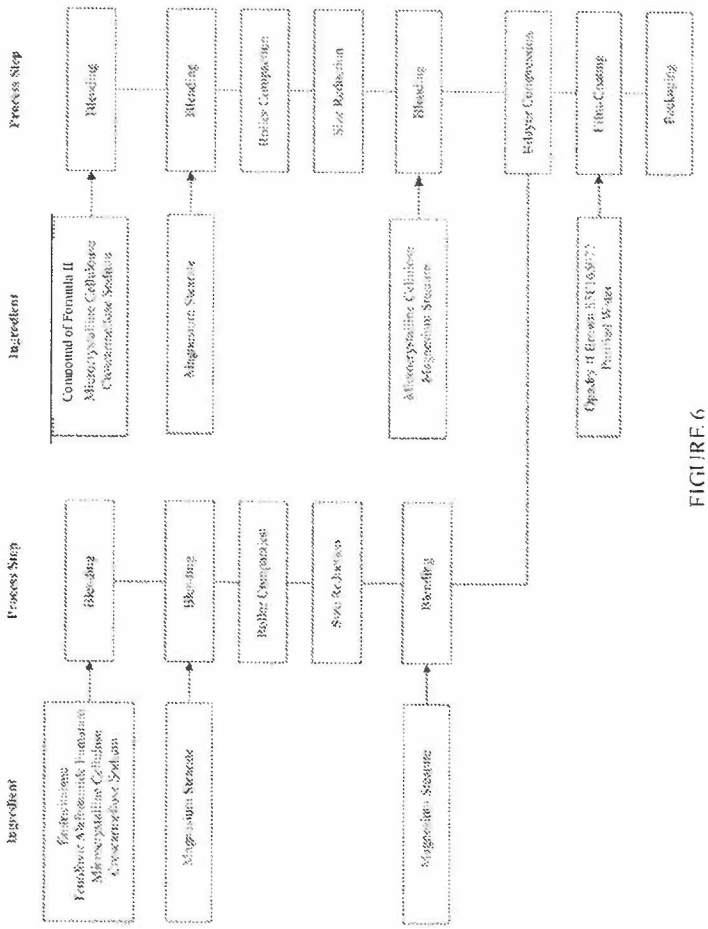

Ingredient
Process Step
Ingredient
Process Step
Compound of Formula II
Microcrystalline Cellulose
Magnesium Stearate
Blending
Roller Compaction
Slug Reduction
Polymer Coating
Packaging

FIGURE 6

Electronic Acknowledgement Receipt	
EFS ID:	27451563
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Customer Number:	25000
Filer:	Mary J. Edwards/Abigail Edesan
Filer Authorized By:	Mary J. Edwards
Attorney Docket Number:	1147.P2C
Receipt Date:	08-NOV-2016
Filing Date:	
Time Stamp:	16:31:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1147P2C_Transmittal_ADS.pdf	340206 b1467d5df7c31948aa1a2b1f4cb01661a29318f76	yes	7

	Multipart Description/PDF files in .zip description			
	Document Description	**Start**	**End**	
	Transmittal of New Application	1	1	
	Application Data Sheet	2	7	
Warnings:				
Information:				
2	Oath or Declaration filed	1147P2C_Declaration.pdf	222566 b5c86f4af7792a73669912aa56d8e3a20cc0aab7	no	3
Warnings:				
Information:				
3		1147P2C_Application_asFiled.pdf	664655 bfad290e1b2a04ac4ea6eee12ffa7835607da5d0	yes	109
	Multipart Description/PDF files in .zip description			
	Document Description	**Start**	**End**	
	Specification	1	102	
	Claims	103	108	
	Abstract	109	109	
Warnings:				
Information:				
4	Drawings-only black and white line drawings	1147P2C_US_Drawings.pdf	2332121 cea9568f5f3f27c025077f98c9ac01c16aad86f	no	6
Warnings:				
Information:				
		Total Files Size (in bytes):	3559548	

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/346,335	11/08/2016	1629	0.00	1147.P2C	51	15

CONFIRMATION NO. 1307

25000
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

FILING RECEIPT



Date Mailed: 11/18/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Benjamin Micah Collman, Foster City, CA;
Lei Hong, Cupertino, CA;
Joanna M. Koziara, Foster City, CA;

Applicant(s)

Gilead Sciences, Inc., Foster City, CA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 62/399,999 09/26/2016
and claims benefit of 62/253,042 11/09/2015

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/15/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/346,335**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/346,335

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	59 minus 20 =	* 39			OR	x 80 =	3120
INDEPENDENT CLAIMS (37 CFR 1.16(h))	15 minus 3 =	* 12				x 420 =	5040
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							780
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	10540

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE(S)	SMALL ENTITY ADDITIONAL FEE(S)	OR	OTHER THAN SMALL ENTITY RATE(S)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE(S)	ADDITIONAL FEE(S)	OR	RATE(S)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C

CONFIRMATION NO. 1307

25000
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

FORMALITIES LETTER

OC000000087240987

Date Mailed: 11/18/2016

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Additional claim fees of $ **8940** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **280** basic filing fee.
- $ **140** surcharge.
- $ **600** search fee.
- $ **720** examination fee.
- $ **5040** for **12** independent claims over 3.
- $ **3120** for **39** total claims over 20.

- $ **780** for multiple dependent claim surcharge.
- $(**0**) previous unapplied payment amount.
- $ **10680** TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/bcao/

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)	Application Number 15346335	Filing Date
	Applicant(s) Benjamin Micah Collman	
	* May be used for additional claims or amendments	

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
2		1				
3		2				
4		(1)				
5		(1)				
6		(1)				
7	1					
8	1					
9	1					
10		1				
11	1					
12	1					
13		(1)				
14		(1)				
15		(1)				
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Total Indep	15		0		0	
Total Depend	44	↵	0	↵	0	↵
Total Claims	59		0		0	

	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
51	1					
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To: IPDocketing@gilead.com,IPUS2@gilead.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 25000

Nov 18, 2016 05:10:56 AM

Dear PAIR Customer:

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 25000 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
15346335	APP.FILE.REC	11/18/2016	1147.P2C
	NTC.MISS.PRT	11/18/2016	1147.P2C

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 15346335 Document Date: 11/08/2016

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Drawings – Other than Black and White Line Drawings

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

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Form Revision Date: September 30, 2013

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: 01/17/2017 Signature: /Abigail Edesan/
(Abigail Edesan)

Docket No.: 1147.PC
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Benjamin Micah Collman et al.

Application No.: 15/346,335 Confirmation No.: 1307

Filed: November 8, 2016 Art Unit: 1629

For: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus Examiner: Not Yet Assigned

PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 9 of this paper.

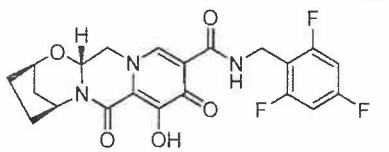
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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of the claims in the application:

1. (Original) A solid oral dosage form comprising the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof.

2. (Original) The solid oral dosage form of claim 1, wherein the dosage form comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

3. (Currently Amended) The solid oral dosage form of claim ~~1 or~~ 2, wherein the dosage form comprises 52 mg of the sodium salt of the compound of Formula I and 28 mg tenofovir alafenamide hemifumarate.

4. (Currently Amended) The solid oral dosage form of ~~any preceding~~ claim 2, wherein the dosage form has a total weight of less than about 800 mg.

5. (Currently Amended) The solid oral dosage form of ~~any preceding~~ claim 2, wherein the dosage form has a total weight of less than about 730 mg.

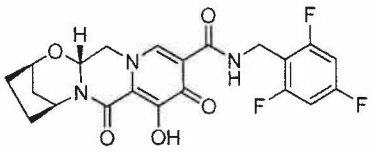
6. (Currently Amended) The solid oral dosage form of ~~any preceding~~ claim 2, wherein the dosage form is a tablet.

7. (Canceled)

8. (Canceled)

9. (Original) A tablet comprising (a) 50 mg of the compound of Formula I:

(I)

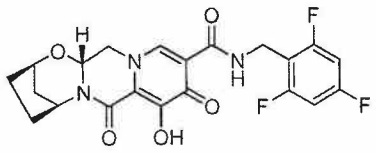


or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1 g.

10. (Original) The tablet of claim 9, wherein (a) and (b) are within separate layers in a multilayer tablet.

11. (Original) A tablet comprising from 6.5-11.0 % w/w of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet.

12. (Original) A tablet comprising from 7.0-11.0 % w/w of the compound of Formula II:

(II)



3.5-4.1 % w/w tenofovir alafenamide hemifumarate, and 25-30 % w/w emtricitabine, where the weight percentages denote a proportion of the whole tablet.

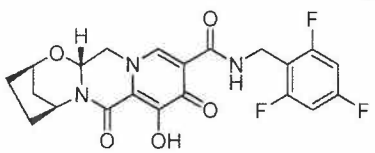
13. (Currently Amended) The tablet of ~~any preceding~~ claim 2, wherein the tablet does not contain lactose, crospovidone, and/or sodium stearyl fumarate.

14. (Currently Amended) The tablet of ~~any preceding~~ claim 2, wherein the tablet further comprises croscarmellose sodium and/or magnesium stearate.

15. (Currently Amended) The tablet of ~~any preceding~~ claim 2, wherein the tablet further comprises croscarmellose sodium, magnesium stearate, and/or microcrystalline cellulose.

16. (Original) A multilayer tablet comprising (a) a compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

17. (Original) The multilayer tablet of claim 16, wherein each layer contains at least one of (a), (b) and (c).

18. (Currently Amended) The tablet of claim 16 ~~or 17~~, wherein the tablet comprises (a) a first layer comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, (b) a second layer comprising tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) further comprises emtricitabine or a pharmaceutically acceptable salt thereof.

19. (Original) The tablet of claim 18, wherein (a) the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of a compound of Formula I or a pharmaceutically acceptable salt thereof.

20. (Currently Amended) The tablet of claim ~~18 or~~ 19, wherein (a) the first layer comprises a compound of Formula I or a pharmaceutically acceptable salt thereof and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of a compound of Formula I or a pharmaceutically acceptable salt thereof.

21. (Currently Amended) The tablet of ~~any one of claims 16~~ claim 20, wherein the layer containing a compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone, and/or sodium stearyl fumarate.

22. (Currently Amended) The tablet of ~~any one of claims 16~~ claim 20, wherein the layer containing a compound of Formula I or a pharmaceutically acceptable salt thereof comprises croscarmellose sodium and/or magnesium stearate.

23. (Currently Amended) The tablet of ~~any one of claims 16~~ claim 20, wherein the layer containing a compound of Formula I or a pharmaceutically acceptable salt thereof comprises croscarmellose sodium and/or magnesium stearate and/or microcrystalline cellulose.

24. (Currently Amended) The tablet of ~~any one of claims 16~~ claim 20, wherein the tablet comprises from 6.5-11.0 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet.

25. (Currently Amended) The tablet of ~~any one of claims 16~~ claim 20, wherein the tablet comprises from 7.0-11.0 % w/w of a sodium salt of the compound of Formula I, 3.5-4.1 % w/w tenofovir alafenamide hemifumarate, and 25-30 % w/w emtricitabine, where the weight percentages denote a proportion of the whole tablet.

26. (Currently Amended) The ~~solid oral dosage form or~~ tablet of ~~any preceding~~ claim 20, wherein the tablet contains less than about 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

27. (Currently Amended) The ~~solid oral dosage form or~~ tablet of ~~any preceding~~ claim 20, wherein the tablet contains less than about 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

28. (Currently Amended) The solid oral dosage form ~~or tablet~~ of ~~any preceding~~ claim 2, wherein the tablet releases at least about 50% of a compound of Formula I or a pharmaceutically acceptable salt thereof in about 20 minutes, measured using USP apparatus II, in 333 mL of fasted simulated intestinal fluid, pH 6.5, at 37 °C and paddle speed of 100 rpm.

29. (Original) The solid oral dosage form or tablet of claim 28, wherein the tablet releases at least about 60% of a compound of Formula I or a pharmaceutically acceptable salt thereof in about 20 minutes.

30. (Currently Amended) The solid oral dosage form ~~or tablet~~ of ~~any preceding~~ claim 2, wherein the tablet releases at least about 70% of a compound of Formula I or a pharmaceutically acceptable salt thereof in about 60 minutes.

31. (Original) A method of producing a tablet of any one of the preceding claims, wherein the method comprises (a) compressing the a compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer.

32. (Original) The method of claim 31, wherein the first layer and second layer are compressed separately and subsequently combined.

33. (Original) The method of claim 31, wherein the first layer is formed by compression and subsequently the second layer is compressed onto the first layer.

34. (Original) The first layer obtainable by the method of claim 31.

35. (Original) The second layer obtainable by the method of claim 31.

36. (Canceled)

37. (Canceled)

38. (Canceled)

39. (Currently Amended) A method of therapeutic treatment of an HIV infection comprising administering to a subject a solid oral dosage form or tablet according to ~~any one of the preceding claims~~ claim 2.

40. (Original) A composition comprising about 40 mg to about 60 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, about 200 mg to about 400 mg microcrystalline cellulose, about 1 mg to about 40 mg croscarmellose sodium.

41. (Original) The composition of claim 40, wherein the composition is a first layer of a multilayer tablet.

42. (Original) The composition of claim 41, wherein the composition further comprises a second layer, wherein the second layer comprises about 150 mg to about 250 mg emtricitabine or a pharmaceutically salt thereof, about 20 mg to about 35 mg tenofovir alafenamide or a pharmaceutically salt thereof, about 90 mg to about 130 mg microcrystalline cellulose, about 20 mg to about 35 mg croscarmellose sodium, and about 1 mg to about 7 mg magnesium stearate.

43. (Original) A tablet comprising a first layer and a second layer, wherein
the first layer comprises about 5% to about 10% w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, about 26% to about 44% w/w microcrystalline cellulose, about 2% to about 4% w/w croscarmellose sodium, and about 0.5% to about 0.9% w/w magnesium stearate; and
the second layer comprises about w/w 21% to about 36% emtricitabine, about 3% to about 5% w/w tenofovir alafenamide, about 12% to about 20% w/w microcrystalline cellulose, about w/w 3% to about 6% croscarmellose sodium, and about w/w 0.3% to about 0.7% magnesium stearate.

44. (Original) A tablet composition comprising from about 6.4 w/w to about 8.5% w/w of the compound of Formula II, about 25% w/w to about 32% w/w emtricitabine, about 3.5% w/w to about 4.5% w/w tenofovir alafenamide hemifumarate, about 46% w/w to about 57% w/w microcrystalline cellulose, about 5.9% w/w to about 8.5% w/w croscarmellose sodium, and about 1.0-2.0% w/w magnesium stearate.

45. (Currently Amended) The composition of ~~any one of claims 40 to~~ claim 44, ~~futher~~ further comprising a film coating.

46. (Currently Amended) A composition comprising 50 mg Compound of Formula I ~~(e.g., a compound of Formula II)~~ or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine, wherein the mean AUC_{last} following administration of a single dose is from about 81700 h-ng/mL to about 140000 h-ng/mL of the compound of Formula I or a pharmaceutically acceptable salt thereof, from about 8100 h-ng/mL to about 13600 h-ng/mL of emtricitabine, and from about 165 h-ng/mL to about 400 h-ng/mL of tenofovir alafenamide or a pharmaceutically acceptable salt thereof.

47. (Currently Amended) The composition of claim 46, wherein the mean AUC_{inf} is from about 84,450 h-ng/mL to about 141,000 h-ng/mL of the compound of Formula I or a pharmaceutically

acceptable salt thereof, from about 8,100 h-ng/mL to about 13,600 h-ng/mL of emtricitabine, and from about 200 h-ng/mL to about 500 h-ng/mL of tenofovir alafenamide or a pharmaceutically acceptable salt thereof.

48. (Currently Amended) The composition of claim 46, wherein the mean C_{max} is from about 4200 ng/mL to about 8000 ng/mL of the compound of Formula I or a pharmaceutically acceptable salt thereof, from about 1770 ng/mL to about 2800 ng/mL of emtricitabine, and from about 185 ng/mL to about 315 ng/mL of tenofovir alafenamide or a pharmaceutically acceptable salt thereof.

49. (Currently Amended) A composition comprising 50 mg Compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 60% of the mean AUC_{last} of a single dose following administration to fasted patients.

50. (Currently Amended) A composition comprising 50 mg Compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 60% of the mean AUC_{inf} of a single dose following administration to fasted patients.

51. (Currently Amended) A composition comprising 50 mg Compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine, wherein the mean C_{max} of a single dose following administration to fed patients is within about 60% of the mean C_{max} of a single dose following administration to fasted patients.

REMARKS

With this amendment, claims 7, 8, and 36-38 have been canceled. Claims 3-6, 13-15, 18, 20-28, 30, 39, and 45-51 have been amended to remove dependency on multiple claims and to more specifically recite the claimed subject matter. As such, no new matter is introduced in any of the above amendments. Therefore, claims 1-6, 9-35, and 39-51 are currently pending examination.

Consideration of the application in view of the pending claims is respectfully requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 07-1250, under Order No. 1147.PC from which the undersigned is authorized to draw.

Dated: January 18, 2017

Respectfully submitted,

By /Mary J. Edwards/
Mary J. Edwards
Registration No.: 55,140
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 522-1816
Attorney For Applicant

Electronic Patent Application Fee Transmittal	
Application Number:	15346335
Filing Date:	08-Nov-2016
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Filer:	Mary J. Edwards/Abigail Edesan
Attorney Docket Number:	1147.P2C
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1740

Electronic Acknowledgement Receipt	
EFS ID:	28098521
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Customer Number:	25000
Filer:	Mary J. Edwards/Abigail Edesan
Filer Authorized By:	Mary J. Edwards
Attorney Docket Number:	1147.P2C
Receipt Date:	18-JAN-2017
Filing Date:	08-NOV-2016
Time Stamp:	16:50:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1740
RAM confirmation Number	011917INTEFSW00003555071250
Deposit Account	071250
Authorized User	Abigail Edesan
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Preliminary Amendment	1147PC_PreliminaryAmendment.pdf	156402 182ce4228af4664390 7a5f5f17206b17c121 1c5f	no	9
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	37530 7421851ed29122c2ab77c820465ae4dc7af 89580	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	193932		

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt	
EFS ID:	28098521
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Customer Number:	25000
Filer:	Mary J. Edwards/Abigail Edesan
Filer Authorized By:	Mary J. Edwards
Attorney Docket Number:	1147.P2C
Receipt Date:	18-JAN-2017
Filing Date:	08-NOV-2016
Time Stamp:	16:50:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1740
RAM confirmation Number	011917INTEFSW00003555071250
Deposit Account	071250
Authorized User	Abigail Edesan
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Preliminary Amendment	1147PC_PreliminaryAmendment.pdf	156402 182ce4228af4864390745f5f17206b17c1211c5f	no	9
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	37530 7421851ed29122c2ab27e820465aefdc7a189580	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	193932		

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National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/346,335	11/08/2016	1629	7600	1147.P2C	46	12

CONFIRMATION NO. 1307

25000
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

UPDATED FILING RECEIPT

OC000000090175178

Date Mailed: 03/27/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Benjamin Micah Collman, Foster City, CA;
Lei Hong, Cupertino, CA;
Joanna M. Koziara, Foster City, CA;

Applicant(s)

Gilead Sciences, Inc., Foster City, CA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 62/399,999 09/26/2016
and claims benefit of 62/253,042 11/09/2015

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/15/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/346,335**

Projected Publication Date: 07/06/2017

Non-Publication Request: No

Early Publication Request: No
Title

Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/346,335

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	46 minus 20 =	* 26			OR	x 80 =	2080
INDEPENDENT CLAIMS (37 CFR 1.16(h))	12 minus 3 =	* 9				x 420 =	3780
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	7460

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE(S)	SMALL ENTITY ADDITIONAL FEE(S)	OR	OTHER THAN SMALL ENTITY RATE(S)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE(S)	ADDITIONAL FEE(S)	OR	RATE(S)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C

CONFIRMATION NO. 1307

PUBLICATION NOTICE

25000
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

OC00000092568774

Title: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

Publication No.US-2017-0189337-A1
Publication Date:07/06/2017

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Sheet 1 of 4

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	Jessica N. Worsham
Attorney Docket Number	1147.PC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-8,592,397	11-26-2013	Dahl et al.	
	AB	US-8,716,264	05-06-2014	Dahl et al.	
	AC	US-9,216,996	12-22-2015	Jin et al.	
	AD	US-9,457,036	10-04-2016	Dahl et al.	
	AE	US-9,663,528	05-30-2017	Desai et al.	
	AF	US-9,682,084	06-20-2017	Carra et al.	
	AG	US-9,708,342	07-18-2017	Carra et al.	
	AH	US-9,732,092	08-15-2017	Jin et al.	
	AI	US-2007/0219243-A1	09-20-2007	Kearney et al.	
	AJ	US-2010/0285122-A1	11-11-2010	Oliyai et al.	
	AK	US-2013/0243857-A1	09-19-2013	Oliyai et al.	
	AL	US-2014/0213556-A1	07-31-2014	DAHL et al.	
	AM	US-2014/0221355-A1	08-07-2014	LAZERWITH et al.	
	AN	US-2015/0111856-A1	04-23-2015	Dahl et al.	
	AO	US-2015/0150810-A1	06-04-2015	OLIYAI et al.	
	AP	US-2016/0194335-A1	07-07-2016	Jin et al.	
	AQ	US-2017/0027967-A1	02-02-2017	Koziara et al.	
	AR	US-2017/0114074-A1	04-27-2017	Jin et al.	
	AS	US-2017/0197985-A1	07-13-2017	Carra et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	WO-2004/024078-A2	03-25-2004	Merck & Co., Inc.		
	BB	WO-2006/030807-A1	03-23-2006	Shionogi & Co., Ltd		
	BC	WO-2006/116764-A1	11-02-2006	Shionogi & Co., Ltd		
	BD	WO-2015/039348-A1	03-26-2015	Merck Sharp & Dohme		
	BE	WO-2014/100323-A1	06-26-2014	Gilead Sciences, Inc		
	BF	WO-2015/196137-A1	12-23-2015	Gilead Sciences, Inc		

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Sheet 2 of 4

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	Jessica N. Worsham
Attorney Docket Number	1147.PC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AT	US-2017/0000807-A1	01-05-2017	Koziara et al.	
	AU	US-8,841,310	09-23-2014	Janssen R & D Ireland	
	AV	US-2014/0349971-A1	11-27-2014	Janssen R & D Ireland	
	AW	US-2008/0200435-A1	08-21-2008	Janssen R & D Ireland	
	AX	US-2015/0283135-A1	10-08-2015	Janssen R & D Ireland	
	AY	US-2014/0142070-A1	05-22-2014	Delaet et al.	
	AZ	US-8,598,185	12-03-2013	Dahl et al.	
	AA1	US-9,018,192	04-28-2015	Dahl et al.	
	AB1	US-9,545,414	01-17-2017	Dahl et al.	
	AC1	US-2017-0079999-A1	03-23-2017	DAHL et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BG	WO-2015/196116-A1	12-23-2015	Gilead Sciences, Inc.		
	BH	WO-2013/116720-A1	08-08-2013	Gilead Sciences, Inc		
	BI	WO-2015/022351-A1	02-19-2015	Ratiopharm Gmbh		

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Sheet 3 of 4

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	Jessica N. Worsham
Attorney Docket Number	1147.PC

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Eron, Joe et al. (2016) "Retesting of suspected low-level HIV-1 viral load blips: A new paradigm to prevent extra clinic visits and unnecessary patient anxiety" Abstract, 10/28/2016 New Orleans	
	CB	Gallant Joel et al. (2016) Abstract "Novel INSTI GS-9883 10 Day Monotherapy in HIV-1 Infected Subjects " ASM2016	
	CC	Gallant, Joel et al. (2016) "Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1-Infected Patients" ASMMicrobe2016	
	CD	Jones, Gregg et al. (2016) Poster #413 "Bictegravir (GS-9883), a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile"	
	CE	Lazerwith, Scott E. (2016) Poster #414 "Discovery of Bictegravir (GS-9883), a Novel, Unboosted, Once-Daily HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and In Vitro Resistance Profile"	
	CF	Lazerwith, Scott E. et al. Abstract "Discovery of GS-9883, an HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and In Vitro Resistance Profile "	
	CG	Moss et al. (2012) "Divalent metals and pH alter raltegravir disposition in vitro." American Society for Microbiology doi:10.1128/AAC.06407-11	
	CH	Patel, Parul et al. (2014) "Relative bioavailability of a paediatric granule formulation of the HIV intergrase inhibitor dolutegravir in healthy adult subjects." Antiviral Therapy (19):229-233	
	CI	Sax, Paul E. (2016) "Randomized Trial of Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy" CROI BIC 09/08/2016	
	CJ	Search Report - Intl Search Report - Written Opinion dated January 24, 2007 for PCT/US2016/060989	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 4

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	Jessica N. Worsham
Attorney Docket Number	1147.PC

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CK	Thomson Reuters Drug News (2011) "Gilead and Tibotec finalize agreement on single-tablet HIV regimen" http://drugnews.thomson-pharma.com/ddn/article.do?id=113441&source=Company Communication&section=AIDS#	
	CL	Tsiang, M. et al. "Antiviral Activity of GS-9883, a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor" (ASMMicrobe20161)	
	CM	Tsiang, M. et al. "GS-9883, a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile" (ASMMicrobe20162)	
	CN	Tsiang, M. et al. (2016) Poster #416 "Antiviral Activity of Bictegravir (GS-9883), a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor"	
	CO	White, Kristen et al. (2016) "Potent Activity of Bictegravir (BIC; GS-9883), a Novel Unboosted; HIV-1 Integrase Strand Transfer Inhibitor (INSTI), Against Patient Isolates; with INSTI-Resistance" EU Workshop HIV Hepatitis;	
	CP	White, Kristen et al. (2016) Poster "The Integrase Strand Transfer Inhibitor Bictegravir has; a Long Integrase/DNA Dissociation Half-life" ;	
	CQ	White, Kristen et al. (2016) The Integrase Strand Transfer Inhibitor Bictegravir has a Long Integrase/DNA Dissociation Half-life	
	CR	White, Kritsten et al. (2017) "Bictegravir Dissociation Half-life from HIV-1 G140S+Q148H Integrase/DNA Complexes " CROI BIC	
	CS	Zhang et al. (2017) "Clinical Pharmacology of the HIV Integrase Strand Transfer Inhibitor Bictegravir " CROI BIC 09/26/2016	

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Novel INSTI GS-9883 10 Day Monotherapy in HIV-1 Infected Subjects

J. Gallant[1], M. Thompson[2], T. Mills[3], E. DeJesus[4], G. Voskuhl[5], L. Wei[6], J. Zack[6], K. White[6], H. Martin[6], J. Szwarcberg[6]

[1] Southwest CARE Center, Santa Fe, NM, [2]AIDS Research Consortium of Atlanta, Atlanta, GA, [3]Southern California Men's Medical Group, Los Angeles, CA [4]Orlando Immunology Center, Orlando, FL, [5]AIDS Arms, Inc., Dallas, TX, [6]Gilead Sciences, Foster City, CA, USA.

Background:

Integrase strand transfer inhibitor (INSTI)-based regimens comprise 5 of the 6 DHHS recommended regimens for treatment of HIV-1. GS-9883 is a novel, unboosted INSTI with potent in-vitro activity against HIV-1.

Methods:

HIV-1-positive INSTI-naïve subjects were randomized to receive GS-9883 5, 25, 50, or 100 mg, or placebo once daily for 10 days. Primary endpoint was time-weighted average HIV-1 RNA change from baseline on day 11 ($DAVG_{11}$). Mean change in HIV-1 RNA, PK, and safety and laboratory data were analyzed.

Results:

20 subjects received study treatment and completed the study. Most were male; median age was 29 years; median HIV-1 RNA was 4.32 $\log_{10}$ copies/mL. GS-9883 demonstrated a dose-dependent reduction in HIV-1 RNA, with increased exposures correlating with greater reductions in plasma HIV-1 RNA, up to 2.43 $\log_{10}$ copies/mL at Day 11 (Table). Response was durable through day 17 in the higher dose groups. PK/PD analysis suggested that near maximal efficacy was associated with GS-9883 exposures achieved at doses between 50 and 100 mg. No primary resistance mutations emerged. No serious adverse events (AEs) or clinically significant lab abnormalities were reported; there were no discontinuations due to AEs.

Conclusions:

Daily dosing of GS-9883 for 10 days at 5, 25, 50 and 100 mg was well tolerated and resulted in rapid, dose-dependent decreases in HIV-1 RNA of > 2 log at the higher doses. Based on PK/PD analyses, exposures associated with 75 mg dose of single agent GS-9883 would provide near-maximal virologic response, with a predicted $_{pa}IQ_{95}$[a] for wild type HIV of ~20.

Character count: 1699 + 500 (Table) = 1999
Allowed: 2200

	GS-9883 5 mg (n=3)	GS-9883 25 mg (n=4)	GS-9883 50 mg (n=4)	GS-9883 100 mg (n=4)
Δ HIV-1 RNA Day 11 from baseline (log10 copies/mL) Mean (SD)	-1.45 (0.097)	-2.08 (0.209)	-2.06 (0.345)	-2.43 (0.386)
$DAVG_{11}$ (log10 copies/mL) Mean (SD)	-0.92 (0.104)	-1.33 (0.174)	-1.37 (0.310)	-1.61 (0.256)
AUC_{tau} (ng*h/mL) Mean (%CV)	9983.0 (26.7)	48,950.3 (40.0)	87, 537/4 (32.7)	178,901.7 (17.8)
C_{tau} (ng/mL) Mean (%CV)	225.3 (37.5)	1052.3 (54.1)	2053.0 (47.6)	4520.0 (21.9)
t ½ (h) (median, Q1, Q3)	20.79 (17.15, 23.80)	15.86 (14.07, 19.37)	17.84 (15.50, 20.51)	20.88 (17.91, 24.47)
$_{pa}IQ\ 95^a$ Median (range)	1.3 (0.9 – 2.1)	4.9 (4.4 – 11.7)	13.4 (5.3 – 18.6)	25.9 (23.0 – 36.9)

[a]The protein-adjusted IQ95 value is estimated based on steady state C_{tau} values and the in vitro $_{pa}IC95$ value for wild type HIV-1 (162 ng/mL)

Discovery of GS-9883, an HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and *In Vitro* Resistance Profile

S. E. Lazerwith, R. Cai, X. Chen, G. Chin, M. Desai, S. Eng, R. Jacques, M. Ji, G. Jones, H. Martin, C. McMahon, M. Mish, P. Morganelli, J. Mwangi, H.-J. Pyun, G. Stepan, J. Szwarcberg, J. Tang, M. Tsiang, J. Wang, K. Wang, K. White, L. Wiser, J. Zack, H. Jin.

Background: Currently approved INSTI based treatments comprise 5 of 6 DHHS recommended regimens for HIV-1 infection. Limitations of early INSTIs include twice-daily dosing (RAL) and the need for a booster (EVG). DTG exhibits an improved resistance profile compared to RAL and EVG. However, due to dose-limiting exposure above 50 mg, it requires twice-daily dosing in some patients. GS-9883 is a potent, new INSTI with a longer half-life and an improved resistance profile.

Methods: New INSTIs were synthesized and tested for a wide variety of properties including HIV potency (MT-4 and MT-2 cells), metabolic stability (microsomes), and protein binding (equilibrium dialysis).

Results: Tetracyclic pyridones containing rigid, sterically-demanding ring systems were synthesized. These tetracycles are potent INSTIs and unexpectedly showed reduced PXR activation. Further work led to the optimization of potency, protein binding, metabolic stability, solubility and an improved resistance profile. This resulted in GS-9883, a potent INSTI (MT-4 EC_{50} = 2.4 nM) with a low potential for drug-drug interactions. GS-9883 shows a remarkable combination of both improved preclinical pharmacokinetics (rat MRT = 45.7 h) and an enhanced resistance profile compared to approved agents (2-fold less susceptible to G140S/Q148R vs. WT). An unusually strong relationship between plasma protein binding and in vivo clearance in preclinical species will be detailed, and the structure of GS-9883 will be disclosed.

Conclusion: Due to its excellent preclinical PK and its in-vitro potency against many integrase-resistant strains, GS-9883 was selected for development, and is being tested in Phase III studies combined with F/TAF.

Randomized Trial of Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy

Authors:

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Background

Because of their potency and safety, integrase strand transfer inhibitors (INSTIs) are widely recommended initial HIV-1 treatments in most major treatment guidelines. Bictegravir (BIC, GS-9883) is a novel, unboosted, once-daily INSTI that demonstrated potent activity in a 10-day monotherapy study and has in vitro activity against most INSTI-resistant viruses.

Methods

Treatment naïve, HIV-infected adults were randomized 2:1 to receive blinded treatment once daily with BIC 75 mg or dolutegravir (DTG) 50 mg; both were given with open label emtricitabine 200 mg/tenofovir alafenamide 25 mg (FTC/TAF). Treatments were administered without regard for food for 48 weeks. The primary endpoint was the proportion with HIV RNA <50 copies/mL (c/mL) at Week (W) 24 using snapshot analysis. Noninferiority was assessed through 95% confidence intervals (CI) at W24 and W48. Safety (adverse events [AEs] and laboratory results through Week 48) was a secondary endpoint.

Results

Of 98 patients enrolled, 65 were randomized to BIC+FTC/TAF and 33 to DTG+FTC/TAF. Most subjects were male, had asymptomatic HIV infection, with median HIV-1 RNA 4.4-4.5 $\log_{10}$; baseline characteristics were balanced between arms. Virologic success (HIV-1 RNA <50 c/mL) at W24 was 97% for the BIC arm and 94% for the DTG arm, and at W48 was 97% and 91%, respectively (Table). One subject in the DTG arm had HIV-1 RNA >50 c/mL at W48. No viral resistance was detected in the BIC+FTC/TAF arm. Mean CD4 count increases at W48 were 258 cells/μL in the BIC arm and 192 cells/μL in the DTG arm. There were no treatment-related serious adverse events and no deaths. The most commonly reported adverse events were diarrhea (12% in

each arm) and nausea (8% BIC, 12% DTG). One subject in the BIC arm discontinued due to an adverse event of urticaria following the W24 visit. Median changes in estimated glomerular filtration by Cockcroft-Gault (GFR_{CG}) at W48 were -7.0 mL/min for BIC and -11.3 mL/min for DTG, with no discontinuations due to renal adverse events.

Conclusions

Bictegravir+FTC/TAF and DTG+FTC/TAF both demonstrated high virologic response rates at W24 that were maintained at W48. No treatment-emergent resistance was detected in the BIC+FTC/TAF arm through W48. Both treatments were well tolerated, and no significant safety signal was detected in either arm. Estimated GFR_{CG} changes were consistent with known inhibition of tubular creatinine transport by BIC and DTG. Further evaluation of BIC for the treatment of HIV infection is warranted.

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Table

	Week 24[a]		Week 48[b]	
N (%)	BIC + FTC/TAF (n=65)	DTG + FTC/TAF (n=33)	BIC + FTC/TAF (n=65)	DTG + FTC/TAF (n=33)
HIV-1 RNA < 50 copies/mL	63 (96.9)	31 (93.9)	63 (96.9)	30 (90.9)
HIV-1 RNA > 50 copies/mL	2 (3.1)	2 (6.1)	1 (1.5)	2 (6.1)
HIV-1 RNA ≥ 50 copies/mL	1 (1.5)	1 (3.0)	0	1 (3.0)
Discontinued due to lack of efficacy	0	0	0	0
Discontinued due to other reason and last HIV-1 RNA ≥ 50 copies/mL	1 (1.5)	1 (3.0)	1 (1.5)	1 (3.0)
No virologic data in window	0	0	1 (1.5)	1 (3.0)
Discontinued due to AE/death	0	0	1 (1.5)	0
Discontinued due to other reason and last HIV-1 RNA < 50 copies/mL	0	0	0	1 (3.0)
Missing data in window but on drug	0	0	0	0

a Difference in percentages (BIC+FTC/TAF vs DTG+FTC/TAF) at Week 24: 2.9% (-8.5% to 14.2%); p=0.50
b Difference in percentages (BIC+FTC/TAF vs DTG+FTC/TAF) at Week 48: 6.4% (-6.0% to 18.8%); p=0.17

Antiviral Activity of GS-9883, a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor

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Background: GS-9883 is a potent once-daily unboosted integrase strand transfer inhibitor currently in clinical development in combination with tenofovir alafenamide (TAF) and emtricitabine (FTC) for the treatment of HIV-1 infection.

Methods: The inhibitory activity of GS-9883 was tested against wild-type HIV-1 integrase enzyme. Antiviral potency and cytotoxicity were assessed in MT-2 and MT-4 T-cell lines and primary human CD4+ T-cells and macrophages. Inhibition of integration was assessed by qPCR of 2-LTR circles and integration junctions. A panel of 14 HIV-1 and one HIV-2 clinical isolates was used for antiviral profiling. Antiviral activity of GS-9883 was also tested against several non-HIV viruses. Cytotoxicity of GS-9883 was also tested in four non-target cell lines (Huh-7, HepG2, PC-3, MRC-5) and human primary hepatocytes. Antiviral activity of GS-9883 in pairwise combination with antiretrovirals was also assessed.

Results: GS-9883 inhibited HIV-1 integrase enzyme strand transfer activity (IC_{50} = 7.5 ± 0.3 nM). Treatment with GS-9883 increased abortive 2-LTR circles and decreased viral-host DNA integration junctions in infected cells. GS-9883 exhibited high potency and selectivity in HIV-1 assays using lymphoblastoid T-cell lines, primary human CD4+T cells, and macrophages with EC_{50} range of 1.5 to 6.6 nM and selectivity indices of 1500 to 8700. GS-9883 was highly potent against all tested HIV-1 subtypes and HIV-2 in human PBMCs (mean EC_{50} = 0.81 nM range of <0.05 to 1.71 nM), and showed no activity against HBV, HCV, Influenza, HRV or RSV. GS-9883 had low cytotoxicity in multiple human cell lines (CC_{50} range from 35 to >44 μM) and in primary human hepatocytes (CC_{50} >100 μM). Highly synergistic *in vitro* antiviral effect was observed for combinations of GS-9883 with TAF, FTC or darunavir.

Conclusions: GS-9883 is a novel, potent and selective HIV integrase strand transfer inhibitor. GS-9883 was highly synergistic in combinations with TAF, FTC or darunavir. These data support the clinical investigation of GS-9883 for the treatment of HIV-1 infection.

GS-9883, a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized *In Vitro* Resistance Profile

G. Jones[1], J. Goldsmith[1], A. Mulato[1], K. White[1], D. Hansen[1], K. Stray[1], S. Yant[1], S. Lazerwith[1], H. Jin[1], T. Cihlar[1] and M. Tsiang[1]. [1]*Gilead Sciences Inc., Foster City, CA, US*

Background: GS-9883 is a potent once-daily unboosted INSTI in clinical development combined with tenofovir alafenamide (TAF) and emtricitabine (FTC) for the treatment of HIV-infection.

Methods: HIV-1 site-directed mutants with either NRTI, NNRTI, PI, or INSTI resistance mutations as well as a panel of 18 clonal and 47 patient-derived HIV-1 isolates with high-level INSTI resistance were profiled for susceptibility to GS-9883. *In vitro* resistant variants were selected with escalating doses of GS-9883, dolutegravir (DTG), and elvitegravir (EVG), and emergent HIV-1 variants were genotyped and phenotyped. *In vitro* resistance breakthrough studies using clinically relevant fixed doses of GS-9883, EVG and DTG were conducted in MT-2 cells and primary human $CD4^+$ T-cells.

Results: GS-9883 showed potent antiviral activity (EC_{50} = 1.7 to 3.2 nM) against wild-type virus and mutants resistant to NRTIs, NNRTIs, and PIs. A panel of HIV-1 site-directed mutants with up to 1520-fold change (FC) in susceptibilities to raltegravir (RAL) and EVG remained largely susceptible to GS-9883 (FC = 1 to 9). In addition, GS-9883 had an improved resistance profile (FC = 0.5 to 19; mean and median FC = 2.8 and 2.0, resp.) compared to DTG (FC = 0.64 to 63; mean and median FC = 5.8 and 3.4, resp.) against INSTI-resistant patient-derived isolates, particularly those with high-level INSTI-resistance. Both GS-9883 and DTG displayed a higher barrier to *in vitro* resistance emergence relative to EVG. HIV-1 variants selected *in vitro* by GS-9883 contained the known R263K and M50I integrase mutations and exhibited low level cross-resistance to RAL and DTG (FC = 3 to 8), and intermediate cross-resistance to EVG (FC = 15 to 26) but remained susceptible to other antiretroviral classes. In the viral breakthrough selection studies at clinically relevant concentrations, GS-9883 and DTG, but not EVG or RAL completely suppressed resistance breakthrough in both MT-2 and primary CD4+ T cells.

Conclusions: GS-9883 is a novel potent INSTI with an *in vitro* resistance profile that is improved compared to RAL and EVG. In addition, GS-9883 was more potent than DTG against a number of patient-derived isolates with high-level INSTI resistance. Overall, these data support further development of GS-9883 as a novel antiretroviral agent.

Bictegravir Dissociation Half-life from HIV-1 G140S+Q148H Integrase/DNA Complexes

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Background: Long dissociation half-life ($t_{1/2}$) of HIV integrase strand transfer inhibitors (INSTI) correlates with high antiretroviral activity and barrier to resistance. The dissociation $t_{1/2}$ of bictegravir (BIC) from wild-type (WT) integrase (IN)/DNA complexes is longer than that of elvitegravir (EVG), raltegravir (RAL), and dolutegravir (DTG). BIC has improved activity against HIV isolates with INSTI resistance mutations, particularly the 140/148 combination. Here, we evaluate phenotypic resistance and dissociation kinetics using G140S+Q148H mutant IN.

Methods: INSTIs were phenotyped with 17 G140S+Q148H clinically-derived isolates with or without other IN mutations. The apparent association and dissociation $t_{1/2}$ of ^{3}H-labelled RAL, EVG, DTG, and BIC were measured using WT and G140S/Q148H mutant HIV IN/DNA complexes with a scintillation proximity assay. The association and dissociation kinetics were analyzed using both a single exponential decay function and an equilibrium binding model that generates half-lives that may be more representative of the $t_{1/2}$ in cells.

Results: HIV isolates with G140S+Q148H in IN had mean phenotypic fold-change values of 3.6±1.9 for BIC, 8.1±4.7 for DTG ($p<0.01$ for DTG vs BIC), and >100 for RAL and EVG. The apparent association $t_{1/2}$ of BIC and DTG to G140S+Q148H mutant HIV IN/DNA complexes were 37±4 min and 34±5 min, respectively, and similar to that for WT. For BIC and DTG, the dissociation $t_{1/2}$ from G140S+Q148H IN/DNA complexes were both shorter compared to WT ($p\leq0.01$). The BIC apparent $t_{1/2}$ from the mutant IN/DNA complexes using single exponential fit was longer than DTG (5.5±0.1 h vs 2.0±0.01 h, respectively, $p<0.01$). Similarly, dissociation $t_{1/2}$ determined from equilibrium binding models were longer for BIC than DTG (2.5±0.07 h vs 0.65±0.2 h, respectively, $p<0.01$). In contrast, EVG and RAL had no measurable association or dissociation with the mutant IN/DNA, consistent with high-level resistance.

Conclusions: BIC has improved activity compared to DTG, EVG, and RAL against HIV isolates with the 140+148 INSTI resistance mutations. BIC dissociates more slowly than DTG from the G140S+Q148H mutant IN/DNA complex and may explain the improved in vitro activity of BIC compared to other INSTIs against this mutant.

Potent Activity of Bictegravir (BIC; GS-9883), a Novel Unboosted HIV-1 Integrase Strand Transfer Inhibitor (INSTI), Against Patient Isolates with INSTI-Resistance

Kirsten White, Tomas Cihlar and Michael D. Miller

Gilead Sciences, Foster City, CA

Poster O-01

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Introduction

- Integrase strand transfer inhibitors (INSTI) are a class of antiretroviral drugs for the treatment of HIV-1 infection that inhibit HIV-1 replication by blocking the strand transfer step of viral DNA integration into the host genome
- Two first-line INSTIs, dolutegravir (DTG) and elvitegravir (EVG), dosed once-daily with boosting agent are approved for clinical use in combination antiretroviral therapy. However, their anti-EVG cross-resistance profiles suggest that viruses resistant to one drug are often cross-resistant to the other drug, which potentially limits the sequencing options of these two INSTIs
- Once-daily EVG/c is often an INSTI-only 3-drug or 4-drug regimen that has a higher barrier to resistance development. However, EVG is not as potent (with activity often demonstrated with cytochrome P450 (CYP) inhibitor-pharmacokinetic (PK) boosting by cobicistat (COBI) initiation). Twice-daily dosing is also required in patients with past INSTI use and INSTI resistance as a result of INSTI resistance
- Bictegravir (BIC; GS-9883) is a novel, unboosted once-daily antiretroviral (ARV) currently in clinical development in combination with tenofovir alafenamide (TAF) and emtricitabine (FTC), in a single tablet regimen for the treatment of HIV-1 infection
- We aimed to phenotypically profile the activity of BIC, DTG, EVG, and RAL against patient isolates with INSTI resistance associated mutations

Methods

- A panel of 47 patient-derived HIV-1 isolates with high-level INSTI resistance were profiled for susceptibility to BIC, DTG, EVG, and RAL using the PhenoSense® assay conducted by Monogram Biosciences (South San Francisco, CA)
  - The panel was chosen from the available Monogram HIV-1 library and includes all available isolates with ≥ 5 INSTI-resistant substitutions (at R263, E92, T97, G140, Y143, S147, Q148, N155, or R263) and/or ≥ 2 substitutions at 2 of these positions (n=27). G140S/Q148H and G140A/Q148R are representative isolates with EVG and/or RAL resistance (n=2)
- Statistical significance was determined using the Student's t-test

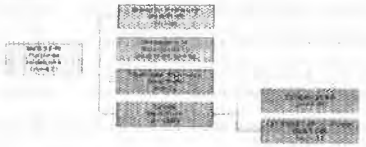
BIC has Potent Activity Against Wild-type HIV-1

INSTI	Mean EC50 (nM)
BIC	1.9
DTG	3.0
EVG	2.7
RAL	2.0

BIC has Potent Activity Against INSTI-Resistant HIV-1 (cont'd)

INSTI	Fold-Change vs. WT
	4-to-<9	9-to-<23	≥23
BIC	1	1	2
DTG	1	1	2
EVG	8	6	60
RAL	2	3	58

Patterns of INSTI-Resistant HIV-1



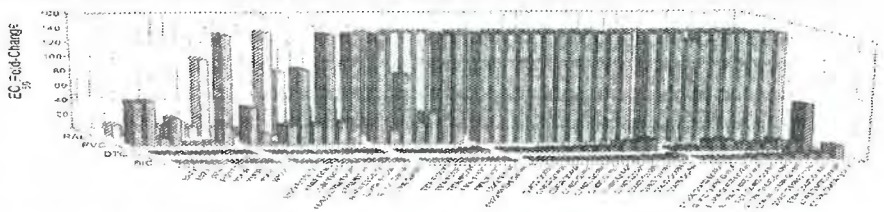
Results

BIC has an Improved Resistance Profile Relative to DTG, EVG, and RAL

Integrase Genotype*	Susceptibility (Fold-Change vs WT)**			
	BIC	DTC	EVC	RAL
Single INSTI-R				
E92Q	1	1	10	1
T66A	1	1	10	1
T97A	1	1	1	1
E138K	1	1	1	1
Y143R	1	1	1	1
Y143H	1	1	1	1
Y143C	1	1	1	1
N155H	1	1	1	1
Primary + Secondary INSTI-R				
R263K + E92Q	1	1	1	1
L74M, T97A	1	1	1	1
L68V, Y143C	1	1	1	1
L68V, L74M, Y143C	1	1	1	1
L74M, N155H	1	1	1	1
N155H, E192Q	1	1	1	1
Q148R, L391A	1	1	1	1
N155H, Q148R	1	1	1	1
E138K, Q148R	1	1	1	1
High-level INSTI-R				
T66A, E92Q	1	1	1	1
T97A, Y143R	1	1	1	1
T97A, Y143H	1	1	1	1
T97A, Y143C	1	1	1	1
T97A, Y143R	1	1	1	1
R263K, N155H	1	1	1	1
E92Q, N155H, G193R	1	1	1	1
G140S, Q148H	1	1	1	1
G140S, Q148R	1	1	1	1
G140A, Q148R	1	1	1	1
G140S, Q148H	1	1	1	1
G140C, Q148R	1	1	1	1
G140C, Q148H	1	1	1	1
G140S, Q148R	1	1	1	1
G140S, Q148H	1	1	1	1
G140C, Q148R	1	1	1	1
G140C, Q148H	1	1	1	1
G140S, Q148R	1	1	1	1
G140S, Q148H, N155H	1	1	1	1
E138K, G140S, Q148H	1	1	1	1
G140S, Q148H, G193R	1	1	1	1
R263K, G140S, Q148H	1	1	1	1
R263K, G140C, Q148H	1	1	1	1
T97A, G140S, Q148H	1	1	1	1
L74M, G140S, Q148H	1	1	1	1
E138K, G140A, Q148R	1	1	1	1
Wild-type	1	1	1	1
Mean	1	1	1	1
p-value vs. BIC		0.042	<0.001	<0.001

- ≤ 2.5-fold
- > 2.5 to ≤ 5-fold
- > 5 to ≤ 10-fold
- > 10-fold

BIC Has an Improved Resistance Profile Relative to DTG, EVG, and RAL Against 47 HIV-1 Patient-derived Isolates with INSTI-R Mutations



Conclusions

- Bictegravir (BIC; GS-9883) is a novel integrase strand transfer inhibitor (INSTI) with low nM potency against wild-type HIV-1
- BIC displays an improved resistance profile relative to EVG, RAL, and DTG in patient isolates
- BIC is more potent than DTG, RAL, and EVG against a number of patient-derived isolates with high-level INSTI resistance
  - particularly for E92Q+N155H or Q148R/H/K+G140A/C/S in IN
- BIC in combination with FTC and TAF as a single tablet regimen is in Phase 3 clinical trials for the once-daily treatment of HIV-infected patients

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BICANDA00005075

The Integrase Strand Transfer Inhibitor Bictegravir has a Long Integrase/DNA Dissociation Half-life

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Background: The HIV integrase strand transfer inhibitor (INSTI) bictegravir (formerly GS-9883) has a high barrier to resistance selection in vitro[1]. Bictegravir has an improved in vitro resistance profile for most HIV isolates with resistance to the other INSTIs raltegravir, elvitegravir, and dolutegravir[1,2]. The apparent dissociation rate constant of dolutegravir from integrase/DNA complexes was previously shown to be longer than raltegravir and elvitegravir and was predicted to correlate with potent antiretroviral activity and a higher genetic barrier to resistance[3]. Here, the dissociation kinetics of bictegravir were evaluated.

Methods: The apparent association and dissociation kinetics of ^{3}H-labelled INSTIs raltegravir, elvitegravir, dolutegravir, and bictegravir were measured using wild-type HIV integrase/DNA complexes and a scintillation proximity assay as previously described[3]. Single exponential decay functions were used to analyze both the binding and competition binding phases yielding apparent association doubling times (t_d) and dissociation half-lives ($t_{1/2}$). However, the competition binding phases deviated significantly from the single exponential decay function due to the gradual sedimentation of the SPA beads, necessitating modeling of the equilibrium binding with on- and off-rate constants as decreasing functions of time with k_{on} and k_{off} as initial values of each function, respectively.

Results: The INSTIs bictegravir, dolutegravir, elvitegravir, and raltegravir showed rapid association with integrase/DNA complexes with apparent association doubling times (t_d) ranging from 14 to 34 min: elvitegravir (14±4 min), raltegravir (22±11 min), bictegravir (31±4 min), and dolutegravir (34±1 min). The apparent dissociation half-lives ($t_{1/2}$) of INSTIs from integrase/DNA complexes ranged from 3.6 to 122 h: elvitegravir (3.6±0.9 h), raltegravir (15±2 h), dolutegravir (71±13 h), and bictegravir (122±14 h); p=0.0018 for bictegravir vs. dolutegravir. The initial values of the dissociation rate constants (k_{off}) were determined using the model and converted to a $t_{1/2}$ which may be more representative of the actual $t_{1/2}$: elvitegravir (1.6±0.2 h), raltegravir (5.4±0.4 h), dolutegravir (11±2), and bictegravir (35±19 h); p=0.046 for bictegravir vs. dolutegravir.

Conclusions: The dissociation half-life of bictegravir is the longest reported for any INSTI that is approved or in development. Long residence times of INSTIs on the integrase/DNA complex have been correlated with potent antiretroviral activity against wild-type HIV-1 integrase and a high barrier to resistance in vitro[3]. The barrier to clinical resistance for bictegravir is being assessed in ongoing Phase 3 studies with the once-daily, unboosted bictegravir/emtricitabine/tenofovir alafenamide single tablet regimen.

1. Jones, et al., ASM Microbe, Boston, MA. USA (2016), Poster #413
2. White, et al., 14th European Workshop on HIV & Hepatitis, Rome, Italy, (2016), Poster O-01
3. Hightower, et al., Antimicrobial Agents and Chemotherapy (2011), 55 (10) 4552-4559.

The Integrase Strand Transfer Inhibitor Bictegravir has a Long Integrase/DNA Dissociation Half-life

Poster Number P025

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Introduction

- Bictegravir (BIC; GS-9883) is a novel, potent once-daily unboosted INSTI currently in clinical development in combination with tenofovir alafenamide (TAF) and emtricitabine (FTC) as a single-tablet regimen for the treatment of HIV-1 infection[1,2]
- Bictegravir has an improved resistance profile compared to elvitegravir (EVG), raltegravir (RAL), and dolutegravir (DTG) in patient isolates, particularly for isolates with high-level INSTI resistance containing combinations of mutations such as E92Q+N155H or G140C/S+Q148R/H/K[3]
- In biochemical studies, the apparent dissociation rate constant of DTG from integrase/DNA complexes was shown to be longer than RAL or EVG and was predicted to correlate with potent antiretroviral activity and a higher genetic barrier to resistance[4]
- In this study, we report the dissociation kinetics of bictegravir and other INSTIs from wild-type HIV-1 integrase/DNA complexes *in vitro*

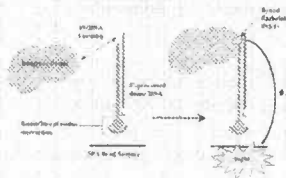
Methods

- **SPA Assay**: The apparent association and dissociation kinetics of ^{3}H-labeled bictegravir, dolutegravir, elvitegravir, and raltegravir were measured using wild-type HIV-1 integrase/DNA complexes and a scintillation proximity assay as previously described (Figure 1)[4]

Figure 1. SPA-Based INSTI Binding Assay

k_{on} determined from direct binding of ^{3}H-INSTI

k_{off} determined from competition binding of ^{3}H-INSTI with cold/non-radioactive compound



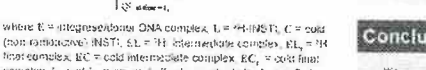
- **Exponential Decay Analysis**: The apparent association $t_{1/2}$ was determined by curve fitting the binding phase using equation (1)

$y = \Delta(1 - e^{-kt})$ (1) where Δ is the plateau and $t_{1/2} = (\ln 2)/k$

- The apparent dissociation $t_{1/2}$ was determined by curve fitting the competition binding phase using equation (2)

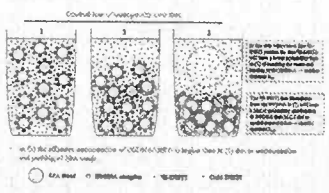
$y = \Delta e^{-kt}$ (2) where Δ is the starting value and $t_{1/2} = (\ln 2)/k$

- The k_{on} and k_{off} values of the compounds were determined by curve fitting an equilibrium binding model (scheme A) simultaneously to both the binding and competition binding phases. The actual dissociation $t_{1/2}$ was calculated as $(\ln 2)/k_{off}$



where E = integrase/donor DNA complex, L = ^{3}H-INSTI, C = cold (non-radioactive) INSTI, EL = ^{3}H intermediate complex, EL_1 = ^{3}H final complex, EC = cold intermediate complex, EC_1 = cold final complex, k_{on} and k_{off} = on- and off-rate constants for L and C, k_1 & k_{-1} = k_{on} and k_{off} for EL and EC, r = rate of addition of C and ○ = dosing fraction for C (0 or 1)

Figure 2. Gradual Sedimentation of the SPA Beads Leads to Rate Constants of Association and Dissociation that Appear Decreased Over Time



Methods (cont'd)

- **Equilibrium Binding Model Analysis**: We observed that the competition binding phase deviates significantly from the single exponential decay because the SPA beads gradually sediment over time (Figure 2). For this reason, the on- and off-rate constants appear to change over time. The equilibrium binding model incorporates a correction for the gradual sedimentation by replacing k_{on} and k_{off} with decreasing hyperbolic functions of time (r_{on} and r_{off}) where t is the time of cold competitor addition and r and c are correction factors

$r_{on} = k_{on} \quad (\text{for } t < t_c) \qquad r_{on} = \frac{k_{on}(r-1)}{r(t-t_c)+r} + \frac{k_{on}}{r} \quad (\text{for } t \geq t_c)$

$r_{off} = k_{off} \quad (\text{for } t < t_c) \qquad r_{off} = \frac{k_{off}(r-1)}{r(t-t_c)+r} + \frac{k_{off}}{r} \quad (\text{for } t \geq t_c)$

- This correction enabled the determination of an initial half-life (i.e. actual dissociation $t_{1/2} = (\ln 2)/k_{off}$) and a terminal half-life (i.e. a prolonged $t_{1/2} = (\ln 2)/r_{off}$) due to the gradual sedimentation of the SPA beads)

Results

Figure 3. Structure of Bictegravir (BIC) and other INSTIs

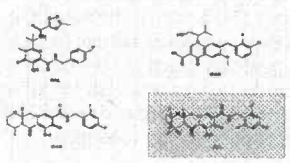


Table 1. Apparent Association/Binding Half-life of INSTIs from WT HIV-1 Integrase/DNA Complexes

INSTI	Apparent Association of INSTI from DNA Complexes: Experimental $t_{1/2}$ (min)[a]	Equilibrium k_{on} (/nM/min)
BIC	33 ± 2	0.648
DTG	30 ± 1	0.620
RAL	24 ± 0	0.420
EVG	11 ± 0	0.0930

Table 2. Apparent Dissociation Half-life of INSTIs from WT HIV-1 Integrase/DNA Complexes

INSTI	Apparent Dissociation of INSTI from DNA Complexes[a]			
	Experimental Decay: $t_{1/2}$ (hr) [T/2]	Fraction in IEC	Equilibrium: $t_{1/2}$ (hr)	Fraction in EC
BIC	133 ± 20 [5.5]		38 ± 18	
DTG	79 ± 13 [3.3]	~ 0.0001	18 ± 8	0.017
RAL	4 ± 3 [0.16]	< 0.0001	0.2 ± 0.05	0.005
EVG	2.5 ± 0.7 [0.1]	< 0.0001	1.5 ± 0.2	0.0001

[a] Values are mean ± SD. Experimental decay: $t_{1/2}$ = half-life of dissociation; T/2 = number of half-lives. Equilibrium: $t_{1/2}$ = half-life of dissociation; EC = extended complex

Results (cont'd)

Figure 4. Time Course of the Binding and Competition Binding (Association and Dissociation) of INSTIs from WT HIV-1 Integrase/DNA Complexes and Exponential Decay Fit

Single Exponential Decay Fit (red lines) of the Competition Binding Phase Deviates from the Experimental Data (black plot)

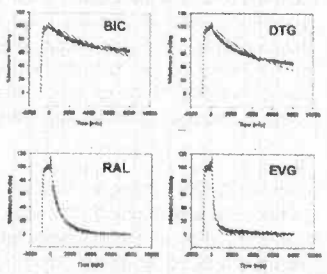
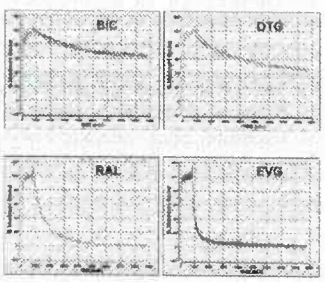


Figure 5. Time Course of the Binding and Competition Binding (Association and Dissociation) of INSTIs from WT HIV-1 Integrase/DNA Complexes and Equilibrium Binding Model Fit

Equilibrium Binding Model Fit of the Competition Binding Phase (smooth lines starting at 30 min) are Consistent with the Experimental Data



Conclusions

- Bictegravir is a potent INSTI with a high barrier to resistance and improved potency against HIV-1 with INSTI resistance mutations
- Bictegravir has the longest reported dissociation half-life from wild-type HIV-1 IN/DNA complexes compared to DTG, RAL, and EVG
- Long residence times of INSTIs on the integrase/DNA complex have been correlated with potent antiretroviral activity against wild-type HIV-1 integrase and a high barrier to resistance *in vitro*[5]
- Phase 3 clinical studies of the single tablet regimen of BIC/FTC/TAF are ongoing and will examine the relationship of high resistance barrier associated with long dissociation half-life *in vitro* with clinical outcomes

References

1. [illegible]
2. [illegible]
3. [illegible]
4. [illegible]
5. [illegible]

HIV Glasgow, 23-26 October 2016, Glasgow, UK

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Clinical Pharmacology of the HIV Integrase Strand Transfer Inhibitor Bictegravir

Heather Zhang, Joseph M. Custodio, Xuelian Wei, Hui Wang, Amanda Vu, John Ling, Hal Martin, Erin Quirk, and Brian P. Kearney; Gilead Sci. Inc., Foster City, CA

Background
Bictegravir (BIC) is an investigational, once-daily, unboosted HIV integrase strand transfer inhibitor (INSTI) with potent in vitro activity against most INSTI-resistant variants. BIC is currently in development as a single tablet regimen (STR) coformulated with FTC/TAF for treatment of HIV-1 infection in adults and adolescents. Clinical pharmacology assessments of the PK, ADME and DDI potential were performed.

Methods
A single- (SD) and multiple-dose (MD) randomized, double-blind, placebo-controlled (6 active; 2 placebo/cohort) of staggered dose-escalation evaluated SD BIC 5, 25, 50, 100, 300 or 600 mg; or once-daily MD 5, 25, 50, 100 or 300 mg for 14 days (fasted) in healthy volunteers. An ADME/ mass balance study included 8 healthy male subjects dosed with a SD 100 mg plus 100 μCi [^{14}C]-labeled BIC. Blood, urine and feces samples were analyzed for total radioactivity and pooled plasma and excreta samples were radio-profiled. An open-label, six-cohort (n=15/cohort), fixed sequence and cross-over study assessed the DDI liability of BIC as a victim through utilization of CYP3A4, UGT1A1, and/or P-gp inhibitors and inducers. Safety was assessed throughout each study.

Results
BIC exposure was dose proportional following SD of 25-100mg. Accumulation at steady-state was approximately 1.6x, consistent with the observed half-life of approximately 18 hours. Following a SD of [^{14}C]-labeled BIC, the total recovery of radioactivity was 95% ± 1.5%, with 60% ± 5.5% from feces and 35% ± 5.0% from urine. Balanced glucuronidation and oxidation contributed to the major clearance pathways of BIC. The DDI study (Table 1) showed increased BIC AUC (61-74%) by CYP3A4 inhibitors voriconazole and DRV/COBI, but showed a greater increase (~4x) by potent dual inhibitors of UGT1A1 and CYP3A4, ATV and ATV+COBI. Coadministration of BIC with a potent CYP3A4/UGT1A1/P-gp inducer, rifampin resulted in a 75% decrease of BIC AUC_τ in contrast, a lesser reduction (38%) was associated with the moderate CYP3A4/P-gp inducer, rifabutin. Overall, BIC was well tolerated at all doses studied. No deaths, SAEs, or Grade 3 or 4 AEs were reported. The safety profile for BIC did not differ with increasing doses of SD or MD.

Conclusions
The favorable BIC PK profile supports once daily dosing. The DDI results of BIC are consistent with its ADME profile, in which both CYP3A4 and UGT1A1contributed to BIC elimination. BIC was safe and well tolerated in healthy volunteers.

Table 1. Effects of Concomitant Medications on BIC PK in Healthy Volunteers

BIC Coadministered Drug(s) and Dose(s)	Dose (s) of BIC	Geometric Mean Ratio % (90% CI) of BIC PK with/without Coadministered Drugs n=15 for each cohort		
		C_{max}	AUC	C_{tau}
ATV (400 mg) QD	BIC (75mg) SD fed	128 (123, 134)	415 (381, 451)	NA
ATV (300 mg)+ COBI (150 mg) QD	BIC (75mg) SD fed	131 (123, 140)	406 (376, 438)	NA
Voriconazole (300 mg) BID	BIC (75mg) SD fasted	109 (96.1,123)	161 (141,184)	NA
DRV/COBI (800 150 mg) QD [c]	BIC (75mg) MD fed	152 (140, 164)	174 (162, 187)	211 (195, 229)
Rifabutin (300 mg) QD [c]	BIC (75mg) MD fasted	80.4 (66.9, 96.5)	62.0 (53.1, 72.5)	44.0 (37.1, 52.1)
Rifampin (600 mg) QD	BIC (75mg) SD fed	72.2 (67.1, 77.8)	24.5 (22.0, 27.3)	NA

ATV = atazanavir; COBI = cobicistat; DRV = darunavir; SD = single-dose, MD = multiple-dose; NA = not applicable [c] Test arm n = 13

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First Named Inventor/Applicant Name:	Benjamin Micah Collman
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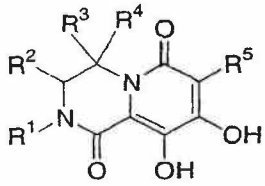
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(54) Title: DIHYDROXYPYRIDOPYRAZINE-1,6-DIONE COMPOUNDS USEFUL AS HIV INTEGRASE INHIBITORS



(I)

(57) Abstract: 8,9-Dihydroxydihydropyridopyrazine-1,6-diones and 8,9-dihydroxypyridopyrazine-1,6-diones are inhibitors of HIV integrase and inhibitors of HIV replication. In one embodiment, the pyridopyrazinediones are of Formula (I): (I),wherein R^1, R^2, R^3, R^4 and R^5 are defined herein. The compounds are useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS. The compounds are employed against HIV infection and AIDS as compounds per se or in the form of pharmaceutically acceptable salts. The compounds and their salts can be employed as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of preventing, treating or delaying the onset of AIDS and methods of preventing or treating infection by HIV are described.

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TITLE OF THE INVENTION

DIHYDROXYPYRIDOPYRAZINE-1,6-DIONE COMPOUNDS USEFUL AS HIV INTEGRASE INHIBITORS

This application claims the benefit of U.S. Provisional Application No. 60/409,741, filed September 11, 2002, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention is directed to dihydroxypyridopyrazine-1,6-diones and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds of the present invention and their pharmaceutically acceptable salts are useful for preventing or treating infection by HIV and for treating, delaying the onset of, or preventing AIDS.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the insertion by virally-encoded integrase of proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner et al., *Nature* 1985, 313: 277]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh et al., *EMBO J.* 1985, 4: 1267; Power et al., *Science* 1986, 231: 1567; Pearl et al., *Nature* 1987, 329: 351]. All three enzymes have been shown to be essential for the replication of HIV.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar

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diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhbitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The inhibition of integrase in vitro and of HIV replication in cells is a direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase in vitro in HIV infected cells. A particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication.

The following references are of interest as background:

Chemical Abstracts No. 33-2525 discloses the preparation of 5-chloro-8-hydroxy-1,6-naphthyridine-7-carboxylic acid amide from the corresponding methyl ester.

US 5,294,620 discloses certain 1,6-naphthyridin-2-one derivatives having angiotensin II antagonist activity.

US 2003/0055071 (Publication of U.S. Application Serial No. 09/973,853, filed October 10, 2001) and WO 02/30930 (Publication of International Application No. PCT/US 01/31456, filed October 9, 2001) each disclose certain 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors, wherein the carboxamido nitrogen is directly or indirectly attached to phenyl or phenyl fused to a carbocycle. The carboxamides are disclosed to be useful, *inter alia*, for treating HIV infection and AIDS. WO 02/30426 discloses another group of 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors, wherein the carboxamido nitrogen is directly or indirectly attached to a heterocycle. WO 02/055079 discloses still another group of 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors, wherein the carboxamido nitrogen is part of a heterocyclic ring system.

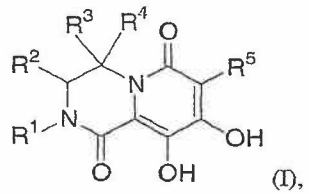
WO 02/036734 discloses certain aza- and polyaza-naphthalenyl ketones to be HIV integrase inhbitors. The ketones include certain 1-aryl-1-(poly)azanaphthylenyl methanones and 1-heterocyclyl-1-(poly)azanaphthylenyl methanones. Quinolinyl, naphthyridinyl, and quinoxalinyl are disclosed as suitable (poly)azanaphthalenyl groups in the ketones.

WO 03/35076 discloses certain 5,6-dihydroxypyrimidine-4-carboxamides as HIV integrase inhibitors, and WO 03/35077 discloses certain N-substituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamides as HIV integrase inhibitors.

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SUMMARY OF THE INVENTION

The present invention is directed to novel dihydroxypyridopyrazine-1,6-diones. These compounds and their pharmaceutically acceptable salts are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS, either as compounds or their pharmaceutically acceptable salts, or as pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

wherein

R^1 is C_{1-6} alkyl which is substituted with 1 or 2 substituents each of which is independently:

(1) C_{3-8} cycloalkyl,

(2) aryl,

(3) a 5- or 6-membered saturated or mono-unsaturated heterocyclic ring containing from 1 to 4 heteroatoms independently selected from N, O and S,

(4) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, or

(5) a 9- or 10-membered fused bicyclic heterocycle containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein at least one of the rings is aromatic;

wherein

(A) each cycloalkyl is optionally substituted with from 1 to 3 substituents, each of which is independently halo, $-C_{1-6}$ alkyl, or $-O-C_{1-6}$ alkyl;

(B) each aryl is optionally substituted with from 1 to 5 substituents each of which is independently

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(1) -C_{1-6} alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$,

(2) -O-C_{1-6} alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -$S(O)_nR^c$, -$C(=O)N(R^aR^b)$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$,

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} haloalkyl,

(5) -OH,

(6) halo,

(7) -CN,

(8) -NO_2,

(9) -$N(R^aR^b)$,

(10) -$C(=O)N(R^aR^b)$,

(11) -$C(=O)R^a$,

(12) -CO_2R^c,

(13) -SR^c,

(14) -$S(=O)R^c$,

(15) -SO_2R^c,

(16) -$N(R^a)SO_2R^c$,

(17) -$SO_2N(R^aR^b)$,

(18) -$N(R^a)C(=O)R^b$,

(19) -$N(R^a)CO_2R^c$, or

(20) phenyl;

(C) each saturated or mono-unsaturated heterocyclic ring is

(i) optionally substituted with from 1 to 5 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

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(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; and

(D) each heteroaromatic ring or each fused bicyclic heterocycle is

(i) optionally substituted with from 1 to 7 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C_{1-6} alkyl-aryl;

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

R^3 is -H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{1-6} alkyl substituted with one of -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$;

R^4 is:

(1) -H,

(2) -C_{1-6} alkyl optionally substituted with one of -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -$N(R^a)$-$C(R^b)$=O, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, -$N(R^a)C(=O)N(R^aR^b)$, -O-C_{1-6} alkyl-$C(=O)N(R^aR^b)$, -S-C_{1-6} alkyl-$C(=O)N(R^aR^b)$, -$N(R^a)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$, or -$N(SO_2R^c)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(3) -C_{1-6} haloalkyl,

(4) -$C(=O)R^a$,

(5) -CO_2R^c,

(6) -$C(=O)N(R^aR^b)$,

(7) -$SO_2N(R^aR^b)$,

(8) -C_{2-6} alkenyl,

(9) -C_{2-6} alkenyl-C(=O)-$N(R^a)_2$,

(10) -C_{2-5} alkynyl,

(11) -C_{2-5} alkynyl-$CH_2N(R^a)_2$,

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(12) -C_{2-5} alkynyl-CH_2OR^a,
(13) -C_{2-5} alkynyl-$CH_2S(O)_nR^c$, or
(14) -R^k,
(15) -C_{1-6} alkyl substituted with R^k,
(16) -C_{1-6} haloalkyl substituted with R^k,
(17) -C_{1-6} alkyl-O-R^k,
(18) -C_{1-6} alkyl-O-C_{1-6} alkyl-R^k,
(19) -C_{1-6} alkyl-$S(O)_n$-R^k,
(20) -C_{1-6} alkyl-$S(O)_n$-C_{1-6} alkyl-R^k,
(21) -C_{1-6} alkyl-$N(R^a)$-R^k,
(22) -C_{1-6} alkyl-$N(R^a)$-C_{1-6} alkyl-R^k,
(23) -C_{1-6} alkyl-$N(R^a)$-C_{1-6} alkyl-OR^k, with the proviso that the -$N(R^a)$- moiety and the -OR^k moiety are not both attached to the same carbon of the -C_{1-6} alkyl- moiety,
(24) -C_{1-6} alkyl-C(=O)-R^k,
(25) -C_{1-6} alkyl-C(=O)$N(R^a)$-R^k,
(26) -C_{1-6} alkyl-$N(R^a)$C(=O)-R^k,
(27) -C_{1-6} alkyl-C(=O)$N(R^a)$-C_{1-6} alkyl-R^k, or
(28) -C_{1-6} alkyl-$N(R^a)$-C_{0-6} alkyl-$S(O)_nR^k$;

wherein R^k is

(i) aryl, which is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} haloalkyl, -C_{1-6} alkyl-$N(R^aR^b)$, -C_{1-6} alkyl-C(=O)$N(R^aR^b)$, -C_{1-6} alkyl-C(=O)R^a, -C_{1-6} alkyl-CO_2R^c, -C_{1-6} alkyl-$S(O)_nR^c$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halo, -$N(R^aR^b)$, -C(=O)$N(R^aR^b)$, -C(=O)R^a, -CO_2R^c, -$S(O)_nR^c$, or -$SO_2N(R^aR^b)$;

(ii) a 4- to 7-membered saturated or mono-unsaturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is:

(a) optionally substituted with from 1 to 5 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

(b) optionally mono-substituted with aryl or HetA;

wherein HetA is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring, and HetA is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; or

(iii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo;

or alternatively R^3 and R^4 are joined together to form C_{5-8} cycloalkyl or a 5- to 7-membered saturated heterocyclic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein

the cycloalkyl is optionally substituted with from 1 to 3 substituents each of which is independently halo, -C_{1-6} alkyl, or -O-C_{1-6} alkyl; and

the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo;

or alternatively:

(i) R^2 and R^3 together form a direct bond to give a ring double bond, and R^4 is an independent group as defined above;

(ii) R^2 and R^3 together with the ring carbon atoms to which they are attached form a fused cyclopropyl ring which is optionally substituted at the non-fused cyclopropyl ring carbon with -OR^d, and R^4 is -H; or

(iii) R^2 and R^3 together with the ring carbon atoms to which they are attached form a fused phenyl ring or a fused pyridyl ring, and R^4 is absent;

R^5 is:

(1) -H,

(2) -C_{1-6} alkyl,

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(3) $-C_{1-6}$ alkyl-$N(R^aR^b)$,
(4) $-C_{1-6}$ alkyl-$C(=O)N(R^aR^b)$,
(5) $-C_{1-6}$ alkyl-$C(=O)R^a$,
(6) $-C_{1-6}$ alkyl-CO_2R^c,
(7) $-C_{1-6}$ alkyl-SR^c,
(8) $-C_{1-6}$ alkyl-$S(=O)R^c$,
(9) $-C_{1-6}$ alkyl-SO_2R^c,
(10) $-C_{1-6}$ alkyl-$SO_2N(R^aR^b)$
(11) $-C_{1-6}$ haloalkyl,
(12) $-O-C_{1-6}$ alkyl,
(13) $-O-C_{1-6}$ haloalkyl,
(14) halo,
(15) -CN,
(16) $-C(=O)R^a$,
(17) $-CO_2R^c$,
(18) $-SR^c$,
(19) $-S(=O)R^c$,
(20) $-SO_2R^c$,
(21) $-N(R^aR^b)$,
(22) $-C(=O)N(R^aR^b)$, or
(23) $-SO_2N(R^aR^b)$;
(24) aryl
(25) $-C_{1-6}$ alkyl-aryl
(26) HetB,
(27) $-C_{1-6}$ alkyl-HetB,
(28) HetC, or
(29) $-C_{1-6}$ alkyl-HetC,

wherein

HetB is a 5- or 6-membered saturated or mono-unsaturated ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the ring is optionally substituted with from 1 to 5 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, oxo, $-C(=O)-C_{1-6}$ alkyl, $-C(=O)-C_{1-6}$ haloalkyl, or $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl; and

HetC is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S,

wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo;

each R^a and R^b is independently -H or -$C_{1\ 6}$ alkyl;

each R^c is independently a -C_{1-6} alkyl;

R^d is a -C_{1-6} alkyl, allyl, or benzyl; and

each n is independently an integer equal to 0, 1 or 2.

An aspect of the present invention is a compound of Formula (I) as defined above, except that: in the definition of R^1, the optional substitution on each aryl is restricted to 1 to 5 substituents each of which is independently one of groups (1) to (19) (i.e., the choice of optional substituents on aryl does not include phenyl); in the alternative definitions of R^2 and R^3, R^2 and R^3 are restricted to definition (i) (i.e., the formation of a ring double bond; the joining of R^2 and R^3 to form a fused cyclopropyl ring, a fused phenyl ring, or a fused pyridyl ring is excluded); and in the definition of HetB in R^5, the optional substitution on the saturated or mono-unsaturated ring is restricted to 1 to 5 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo.

The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of preventing AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention includes the dihydroxypyridopyrazine-1,6-diones of Formula (I) above. These compounds and pharmaceutically acceptable salts thereof are HIV integrase inhibitors.

A first embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is -C_{1-4} alkyl mono-substituted with aryl; wherein the aryl is optionally substituted with from 1 to 4 substituents each of which is independently

(1) -C_{1-4} alkyl, optionally mono-substituted with -OH, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, -CN, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$,

(2) -O-C_{1-4} alkyl, optionally mono-substituted with -OH, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, -$S(O)_nR^c$, -$N(R^a)$-CO_2R^c, -$C(=O)N(R^aR^b)$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$,

(3) -C_{1-4} haloalkyl,

(4) -O-C_{1-4} haloalkyl,

(5) -OH,

(6) halo,

(7) -CN,

(8) -NO_2,

(9) -$N(R^aR^b)$,

(10) -SR^c,

(11) -$S(=O)R^c$,

(12) -SO_2R^c,

(13) -$N(R^a)SO_2R^c$,

(14) -$SO_2N(R^aR^b)$,

(15) -$N(R^a)C(=O)R^b$,

(16) -$N(R^a)CO_2R^c$, or

(17) phenyl;

and all other variables are as originally defined above.

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In an aspect of the first embodiment, each of the optional substituents on the aryl is independently one of the groups (1) to (16) set forth above (i.e., phenyl is excluded as a possible optional substituent).

A second embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is $-(CH_2)_{1-4}$-phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently

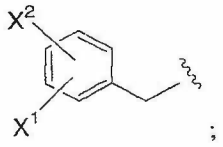
(1) $-C_{1-4}$ alkyl, optionally mono-substituted with -OH, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, -CN, $-N(R^aR^b)$, $-C(=O)N(R^aR^b)$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, or $-SO_2N(R^aR^b)$,
(2) $-O-C_{1-4}$ alkyl,
(3) $-C_{1-4}$ haloalkyl,
(4) $-O-C_{1-4}$ haloalkyl,
(5) -OH,
(6) halo,
(7) -CN,
(8) $-NO_2$,
(9) $-N(R^aR^b)$,
(10) $-SR^c$,
(11) $-S(=O)R^c$,
(12) $-SO_2R^c$,
(13) $-N(R^a)SO_2R^c$,
(14) $-SO_2N(R^aR^b)$,
(15) $-N(R^a)C(=O)R^b$,
(16) $-N(R^a)CO_2R^c$, or
(17) phenyl;

and all other variables are as originally defined above.

In an aspect of the second embodiment, each of the optional substituents on the phenyl is independently one of the groups (1) to (16) set forth above (i.e., phenyl is excluded as a possible optional substituent).

A third embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is

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wherein X^1 and X^2 are each independently

(1) -H,
(2) methyl,
(3) ethyl,
(4) methoxy,
(5) ethoxy,
(6) $-CF_3$,
(7) fluoro,
(8) bromo, or
(9) chloro,
(10) -CN,
(11) $-S-CH_3$, or
(12) phenyl;

and all other variables are as originally defined above.

In an aspect of the third embodiment, X^1 and X^2 are each independently selected from one of groups (1) to (9) set forth above (i.e., -CN, $-S-CH_3$, and phenyl are each excluded as possible substituents).

In another aspect of the third embodiment, R^1 is 4-fluorobenzyl.

A fourth embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^2 is is -H or $-C_{1-4}$ alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments or aspects. In an aspect of this embodiment, R^2 is -H.

A fifth embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is -H or $-C_{1-4}$ alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments or aspects thereof. In an aspect of this embodiment, R^3 is -H.

A sixth embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) -H,

(2) -C_{1-4} alkyl optionally substituted with one of -OH, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, -CN, -N(R^aR^b), -C(=O)N(R^aR^b), -C(=O)R^a, -CO_2R^c, -S(O)$_n$$R^c$, -$SO_2$N($R^aR^b$), -N($R^a$)-C($R^b$)=O, -N($R^a$)$SO_2R^b$, or -N($R^a$)$SO_2$N($R^aR^b$),

(3) -C(=O)N(R^aR^b),

(4) -R^k,

(5) -C_{1-4} alkyl substituted with R^k,

(6) -C_{1-4} alkyl-O-R^k, or

(7) -C_{1-4} alkyl-O-C_{1-4} alkyl-R^k;

and all other variables are as originally defined or as defined in any of the preceding embodiments or aspects thereof.

A seventh embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) -H,

(2) -C_{1-4} alkyl optionally substituted with one of -OH, -N(R^aR^b), or -C(=O)N(R^aR^b),

(3) -C(=O)N(R^aR^b),

(4) -$(CH_2)_{1-3}$-R^k,

(5) -$(CH_2)_{1-3}$-O-R^k, or

(6) -$(CH_2)_{1-3}$-O-$(CH_2)_{1-3}$-R^k;

and all other variables are as originally defined or as defined in any of the first five embodiments or aspects thereof.

An eighth embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^k is:

(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} alkyl-OH, -C_{1-4} alkyl-O-C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} haloalkyl, -C_{1-4} alkyl-N(R^aR^b), -C_{1-4} alkyl-C(=O)N(R^aR^b), -C_{1-4} alkyl-C(=O)R^a, -C_{1-4} alkyl-CO_2R^c, -C_{1-4}

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alkyl-$S(O)_nR^c$, -O-C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} haloalkyl, -OH, halo, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$, or -$SO_2N(R^aR^b)$;

(ii) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is:

(a) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo; and

(b) optionally mono-substituted with phenyl or HetA;

wherein HetA is a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein HetA is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo; or

(iii) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo;

and all other variables are as originally defined or as defined in any of the preceding embodiments or aspects thereof.

In an aspect of the eighth embodiment, HetA is a 5- or 6-membered heteroaromatic ring containing 1 or 2 N atoms, wherein HetA is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo. In another aspect of the eighth

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embodiment, HetA is pyrrolyl, pyrazolyl, imidazolyl, pyridyl, or pyrazinyl; which is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl (e.g., methyl), -C_{1-4} haloalkyl (e.g., trifluoromethyl) , -O-C_{1-4} alkyl (e.g., methoxy), -O-C_{1-4} haloalkyl (e.g., -OCF_3), or oxo.

A ninth embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^k is:

(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} alkyl-OH, -C_{1-4} alkyl-O-C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} haloalkyl, -C_{1-4} alkyl-N(R^aR^b), -C_{1-4} alkyl-C(=O)N(R^aR^b), -C_{1-4} alkyl-C(=O)R^a, -C_{1-4} alkyl-CO_2R^c, -C_{1-4} alkyl-S(O)$_n R^c$, -O-C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} haloalkyl, -OH, halo, -N(R^aR^b), -C(=O)N(R^aR^b), -C(=O)R^a, -CO_2R^c, -S(O)$_n R^c$, or -SO_2N(R^aR^b); or

(ii) a saturated heterocyclic ring selected from the group consisting of piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, thiadiazepanyl, dithiazepanyl, azepanyl, diazepanyl, thiadiazinanyl, and dioxanyl; wherein the saturated heterocyclic ring is:

(a) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo; and

(b) optionally mono-substituted with phenyl or HetA; wherein HetA is a heteroaromatic ring selected from the group consisting of pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, oxatriazolyl, thiazolyl, isothiazolyl, and thiadiazolyl; wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4}

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alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo;

and all other variables are as originally defined or as defined in any of the first seven embodiments or aspects thereof.

A tenth embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^5 is:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} alkyl-N(R^aR^b),
(4) -C_{1-4} alkyl-C(=O)N(R^aR^b),
(5) -C_{1-4} alkyl-SO_2N(R^aR^b)
(6) -C_{1-4} haloalkyl,
(7) halo,
(8) -CN,
(9) aryl
(10) -C_{1-4} alkyl-aryl
(11) HetB,
(12) -C_{1-4} alkyl-HetB,
(13) HetC, or
(14) -C_{1-4} alkyl-HetC,

wherein

HetB is a 5- or 6-membered saturated ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, oxo, -C(=O)-C_{1-4} alkyl, -C(=O)-C_{1-4} haloalkyl, or -C_{1-4} alkyl-C_{3-6} cycloalkyl; and

HetC is a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo;

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and all other variables are as originally defined or as defined in any of the preceding embodiments or aspects thereof.

In an aspect of the tenth embodiment, in the definition of HetB, the optional substitution on the saturated ring is restricted to 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo.

An eleventh embodiment of the present invention is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^5 is:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} alkyl-N(R^aR^b),
(4) halo,
(5) -CN, or
(6) -C_{1-4} alkyl-HetB;

wherein

HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms and carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, oxo, -C(=O)-C_{1-4} alkyl, -C(=O)-C_{1-4} haloalkyl, or -C_{1-4} alkyl-C_{3-6} cycloalkyl;

and all other variables are as originally defined or as defined in any of the first nine embodiments or aspects thereof.

In an aspect of the eleventh, in the definition of HetB, the optional substitution on the saturated ring is restricted to 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo.

In another aspect of the eleventh embodiment, HetB is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, or piperazinyl, which is optionally substituted with from 1 to 4 substituents each of which is independently halogen (e.g., fluoro, chloro, or bromo), -C_{1-4} alkyl (e.g., methyl), -C_{1-4} haloalkyl (e.g.,

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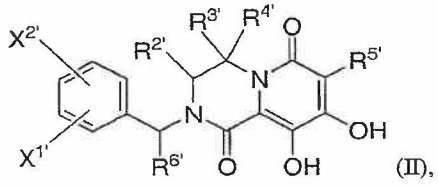
trifluoromethyl) , -O-C_{1-4} alkyl (e.g., methoxy), -O-C_{1-4} haloalkyl (e.g., -OCF_3), or oxo.

Other embodiments of the present invention include compounds of Formula (I), wherein each R^a and R^b is independently -H or -C_{1-4} alkyl; each R^c is independently a -C_{1-4} alkyl; and all other variables are as originally defined or as defined in any of the foregoing embodiments or aspects thereof.

Still other embodiments of the present invention include compounds of Formula (I), wherein each R^a and R^b is independently -H, methyl, or ethyl; each R^c is independently methyl or ethyl; and all other variables are as originally defined or as defined in any of the foregoing embodiments or aspects thereof.

Still other embodiments of the present invention include compounds of Formula (I), wherein R^d is a -C_{1-4} alkyl (e.g., methyl, ethyl or n-propyl), allyl, or benzyl; and all other variables are as originally defined or as defined in any of the foregoing embodiments or aspects thereof.

A class of the present invention includes compounds of Formula (II), or a pharmaceutically acceptable salt thereof:



(II),

wherein:

$X^{1'}$ and $X^{2'}$ are each independently:

(1) -H,
(2) C_{1-4} alkyl,
(2) -O-C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} haloalkyl,
(5) halo,
(6) -CN,

(7) -S-C_{1-4} alkyl, or

(8) phenyl;

$R^{2'}$ is -H or -C_{1-4} alkyl;

$R^{3'}$ is -H or -C_{1-4} alkyl;

$R^{4'}$ is:

(1) -H,

(2) -C_{1-4} alkyl optionally substituted with one of -OH, -N($R^{a'}R^{b'}$), or -C(=O)N($R^{a'}R^{b'}$),

(3) -C(=O)N($R^{a'}R^{b'}$),

(4) -$(CH_2)_{1-3}$-$R^{k'}$,

(5) -$(CH_2)_{1-3}$-O-$R^{k'}$, or

(6) -$(CH_2)_{1-3}$-O-$(CH_2)_{1-3}$-$R^{k'}$;

wherein $R^{k'}$ is:

(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl, -O-C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} haloalkyl, or halo; or

(ii) HetD, wherein HetD is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, 0 or 1 S atoms, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halo, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo;

or alternatively:

(i) $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond, and $R^{4'}$ is an independent group as defined above;

(ii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused cyclopropyl ring which is optionally substituted at the non-fused cyclopropyl ring carbon with -$OR^{d'}$, and $R^{4'}$ is -H; or

(iii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused phenyl ring or a fused pyridyl ring, and $R^{4'}$ is absent;

$R^{5'}$ is:

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(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} alkyl-N($R^{a'}R^{b'}$),
(4) halo,
(5) -CN, or
(6) -$(CH_2)_{1-3}$-HetB;

wherein

HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, zero or 1 O atom, zero or 1 S atom, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, oxo, -C(=O)-C_{1-4} alkyl, -C(=O)-C_{1-4} haloalkyl, or -C_{1-4} alkyl-C_{3-6} cycloalkyl;

$R^{6'}$ is -H or methyl;

each $R^{a'}$ and $R^{b'}$ is independently -H or -C_{1-4} alkyl; and

$R^{d'}$ is -C_{1-4} alkyl, allyl, or benzyl.

A sub-class of the present invention includes compounds of Formula (II), or a pharmaceutically acceptable salt thereof, wherein:

wherein $X^{1'}$ and $X^{2'}$ are each independently:
(1) -H,
(2) methyl,
(2) -OCH_3,
(3) -CF_3,
(4) -O-CF_3,
(5) chloro,
(6) fluoro,
(7) bromo;
(6) -CN,
(7) -S-CH_3, or
(8) phenyl;

$R^{2'}$ is -H or methyl;

$R^{3'}$ is -H or methyl;

$R^{4'}$ is:

(1) -H,
(2) methyl,
(3) $-CH_2OH$,
(3) $-C(=O)N(CH_3)_2$,
(4) $-CH_2-R^{k'}$, or
(5) $-CH_2-O-CH_2-R^{k'}$;

wherein $R^{k'}$ is:

(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, chloro, bromo or fluoro; or

(ii) HetD, wherein HetD is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, 0 or 1 S atoms, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently chloro, bromo, fluoro, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, or oxo;

or alternatively:

(i) $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond, and $R^{4'}$ is an independent group as defined above;

(ii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused cyclopropyl ring which is optionally substituted at the non-fused cyclopropyl ring carbon with -OMe, -OEt, -O-allyl, or -O-benzyl, and $R^{4'}$ is -H; or

(iii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused phenyl ring or a fused pyridyl ring, and $R^{4'}$ is absent;

$R^{5'}$ is:

(1) -H,
(2) methyl,
(3) $-(CH_2)_{1-2}-N(CH_3)_2$,
(4) fluoro,
(5) bromo,

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(6) iodo,
(7) -CN, or
(8) $-CH_2$-HetB;
wherein

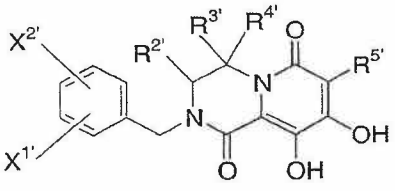
HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, zero or 1 O atom, zero or 1 S atom, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently chloro, bromo, fluoro, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, oxo, $-C(=O)-CH_3$, $-C(=O)-CF_3$, or $-CH_2$-cyclopropyl; and

$R^{6'}$ is -H or methyl.

In an aspect of the preceding sub-class, $R^{2'}$ and $R^{3'}$ are each -H or methyl, with the proviso that $R^{2'}$ and $R^{3'}$ are not both methyl; or alternatively $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond, with the proviso that when $R^{2'}$ and $R^{3'}$ together form a direct bond, $R^{4'}$ is -H.

In another aspect of the preceding sub-class, HetB is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, which is optionally substituted with from 1 to 4 substituents each of which is independently chloro, bromo, fluoro, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, oxo, $-C(=O)-CH_3$, $-C(=O)-CF_3$, or $-CH_2$-cyclopropyl.

Another sub-class of the present invention includes compounds of Formula (IIa), or a pharmaceutically acceptable salt thereof, wherein:



(IIa),

wherein:

$X^{1'}$ and $X^{2'}$ are each independently:
(1) -H,

(2) C_{1-4} alkyl,
(2) -O-C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} haloalkyl, or
(5) halo;

$R^{2'}$ is -H or -C_{1-4} alkyl;

$R^{3'}$ is -H or -C_{1-4} alkyl;

or alternatively $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond;

$R^{4'}$ is:
(1) -H,
(2) -C_{1-4} alkyl optionally substituted with one of -OH, -N($R^{a'}R^{b'}$), or -C(=O)N($R^{a'}R^{b'}$),
(3) -C(=O)N($R^{a'}R^{b'}$),
(4) -$(CH_2)_{1-3}$-$R^{k'}$,
(5) -$(CH_2)_{1-3}$-O-$R^{k'}$, or
(6) -$(CH_2)_{1-3}$-O-$(CH_2)_{1-3}$-$R^{k'}$;
wherein $R^{k'}$ is:
(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl, -O-C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} haloalkyl, or halo; or
(ii) HetD, wherein HetD is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, 0 or 1 S atoms, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halo, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo;

$R^{5'}$ is:
(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} alkyl-N($R^{a'}R^{b'}$),
(4) halo,

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(5) -CN, or
(6) -$(CH_2)_{1-3}$-HetB;

wherein

HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms and carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo; and

each $R^{a'}$ and $R^{b'}$ is independently -H or -C_{1-4} alkyl.

In an aspect of the preceding sub-class, $R^{2'}$ and $R^{3'}$ are each -H or methyl, with the proviso that $R^{2'}$ and $R^{3'}$ are not both methyl; or alternatively $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond, with the proviso that when $R^{2'}$ and $R^{3'}$ together form a direct bond, $R^{4'}$ is -H.

In another aspect of the preceding sub-class, HetB is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, or piperazinyl, which is optionally substituted with from 1 to 4 substituents each of which is independently halogen (e.g., fluoro, chloro, or bromo), -C_{1-4} alkyl (e.g., methyl), -C_{1-4} haloalkyl (e.g., trifluoromethyl) , -O-C_{1-4} alkyl (e.g., methoxy), -O-C_{1-4} haloalkyl (e.g., -OCF_3), or oxo.

Still another sub-class of the present invention includes compounds of Formula (IIa), or a pharmaceutically acceptable salt thereof, wherein:

$X^{1'}$ and $X^{2'}$ are each independently:
(1) -H,
(2) methyl,
(2) -OCH_3,
(3) -CF_3,
(4) -O-CF_3,
(5) chloro,
(6) fluoro, or
(7) bromo;

$R^{2'}$ is -H or methyl;

$R^{3'}$ is -H or methyl;

or alternatively $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond;

$R^{4'}$ is:

(1) -H,
(2) methyl,
(3) $-CH_2OH$,
(3) $-C(=O)N(CH_3)_2$,
(4) $-CH_2-R^{k'}$, or
(5) $-CH_2-O-CH_2-R^{k'}$;

wherein $R^{k'}$ is:

(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, chloro, bromo or fluoro; or

(ii) HetD, wherein HetD is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, 0 or 1 S atoms, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently chloro, bromo, fluoro, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, or oxo; and

$R^{5'}$ is:

(1) -H,
(2) methyl,
(3) $-(CH_2)_{1-2}-N(CH_3)_2$,
(4) fluoro,
(5) bromo,
(6) iodo,
(7) -CN, or
(8) $-CH_2$-HetB;

wherein

HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms and carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is

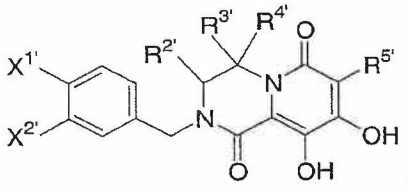
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independently chloro, bromo, fluoro, -CH_3, -CF_3, -OCH_3, -OCF_3, or oxo.

In an aspect of the preceding sub-class, $R^{2'}$ and $R^{3'}$ are each -H or methyl, with the proviso that $R^{2'}$ and $R^{3'}$ are not both methyl; or alternatively $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond, with the proviso that when $R^{2'}$ and $R^{3'}$ together form a direct bond, $R^{4'}$ is -H.

In another aspect of the preceding sub-class, HetB is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, or piperazinyl, which is optionally substituted with from 1 to 4 substituents each of which is independently chloro, bromo, fluoro, -CH_3, -CF_3, -OCH_3, -OCF_3, or oxo.

Another class of the present invention includes compounds of Formula (III), or a pharmaceutically acceptable salt thereof:



(III),

wherein:

$X^{1'}$ and $X^{2'}$ are each independently -H or halo;

and all other variables are as set forth in Formula (II) for the preceding class. A sub-class of this class includes compounds of Formula (III), or a pharmaceutically acceptable salt thereof, wherein $X^{1'}$ and $X^{2'}$ are each independently -H or halo; and all other variables are as defined above in any one of the sub-classes of the preceding class defined by Formula (II) (including sub-classes defined by Formula (IIa)). Aspects of this sub-class are analogous to the aspects set forth above for the preceding Formula (II) sub-class (including aspects defined by Formula (IIa)).

Another sub-class of this class includes compounds of Formula (III), or a pharmaceutically acceptable salt thereof, wherein $X^{1'}$ and $X^{2'}$ are each independently -H, fluoro, chloro, or bromo; and all other variables are as defined for

the class or as defined in a sub-class thereof. In still another sub-class, $X^{1'}$ is fluoro and $X^{2'}$ is -H; and all other variables are as defined for the class or as defined in a sub-class thereof.

Other embodiments of the present invention include compounds of Formula (II), (IIa), or (III) respectively, wherein each $R^{a'}$ and $R^{b'}$ is independently -H or -C_{1-4} alkyl; and all other variables are as originally defined or as defined in any of the foregoing embodiments or aspects thereof.

Still other embodiments of the present invention include compounds of Formula (II), (IIa), or (III) respectively, wherein each $R^{a'}$ and $R^{b'}$ is independently -H, methyl, or ethyl; and all other variables are as originally defined or as defined in any of the foregoing embodiments or aspects thereof.

Still other embodiments of the present invention include compounds of Formula (II), wherein $R^{d'}$ is a -C_{1-4} alkyl (e.g., methyl, ethyl or n-propyl), allyl, or benzyl; and all other variables are as originally defined or as defined in any of the foregoing embodiments or aspects thereof.

Another embodiment of the present invention is a compound selected from the group consisting of

2-benzyl-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-bromo-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-iodo-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(3-chlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

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2-(4-chlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

2-(3,4-dichlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(3,4-difluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

2-(3-chloro-4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

2-(4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-1-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(3-chloro-4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-1-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(dimethylamino)methyl]-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-benzyl-8,9-dihydroxy-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-4-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

2-(4-fluorobenzyl)-8,9-dihydroxy-4,4-dimethyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-3-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-1,6-dioxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-a]-pyrazine-7-carbonitrile;

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2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(4-methyl-3-oxopiperazin-1-yl)methyl]-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(3-oxopiperazin-1-yl)methyl]-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

4-[(benzyloxy)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

4-(hydroxymethyl)-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

4-[(1,1-dioxido-1,2-thiazinan-2-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-1-ylmethyl)-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(3-oxopiperazin-1-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(4-methyl-3-oxopiperazin-1-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(morpholin-4-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(thiomorpholin-4-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-[4-fluoro-2-(methylthio)benzyl)-8,9-dihydroxy-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-[(1-acetylpiperidin-4-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-{[1-(trifluoroacetyl)piperidin-4-yl]methyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

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7-{[1-(cyclopropylmethyl)piperidin-3-yl]methyl}-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-[(1-acetylpiperidin-3-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-[(1-acetylpiperidin-2-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-{[1-(cyclopropylmethyl)piperidin-2-yl]methyl}-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(3-cyanobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-(biphenyl-3-ylmethyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

(±)-1-[(benzyloxy)methyl]-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

(±)-1-(methoxymethyl)-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

(±)-1-[(allyloxy)methyl]-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

(±)-1-(ethoxymethyl)-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

(±)-1-(n-propoxymethyl)-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

2-[1-(4-fluorophenyl)ethyl]-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

5-(4-fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*]quinoxaline-6,10-dione;

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5-(4-fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*:3',2'-*e*]pyrazine-6,10-dione;

5-(4-fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*:2',3'-*e*]pyrazine-6,10-dione;

and pharmaceutically acceptable salts thereof.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention (e.g., a compound of Formula (I) or Formula (II) or Formula (III) or any of the specific compounds set forth above) and a pharmaceutically acceptable carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(e) A combination useful for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS, which is a therapeutically effective amount of a compound of the invention and a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(f) The combination of (e), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

(g) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of the invention.

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(h) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of the invention.

(i) The method of (h), wherein the compound of the invention is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(j) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of the invention.

(k) The method of (j), wherein the compound is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors

(l) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(m) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(n) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

The present invention also includes a compound of the present invention (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HIV protease, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS. In these uses, the compounds of the present invention can optionally be employed in combination with one or more HIV/AIDS treatment agents selected from HIV/AIDS antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(n) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, or an aspect or feature or sub-feature thereof, described above.

In all of the foregoing embodiments describing compositions, combinations and methods, the compound may optionally be used in the form of a pharmaceutically acceptable salt.

As used herein, the term "C_{1-6} alkyl" (or "C_1-C_6 alkyl") means a linear or branched chain alkyl group having from 1 to 6 carbon atoms and includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. "C_{1-4} alkyl" means n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "C_0" as employed in expressions such as "-C_{0-6} alkyl-" means a direct covalent bond. For example, in the group -C_{1-6} alkyl-$N(R^a)$-C_{0-6} alkyl-$S(O)_nR^k$, when the second alkylene group is "C_0", then the group is -C_{1-6} alkyl-$N(R^a)$-$S(O)_nR^k$.

The term "-C_{1-6} alkyl-" refers to a C_1 to C_6 linear or branched alkyl group as just defined which is bivalent. It can alternatively be referred to as "C_{1-6} alkylene" or "C_{1-6} alkanediyl". A class of alkylenes of particular interest with respect to the invention is -$(CH_2)_{1-6}$-, and sub-classes of particular interest include -$(CH_2)_{1-4}$-, -$(CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-, and -CH_2-.

The term "C_{2-6} alkenyl" (or "C_2-C_6 alkenyl") means a linear or branched chain alkenyl group having from 2 to 6 carbon atoms and includes all of the hexenyl and pentenyl isomers as well as 1-butenyl, 2-butenyl, 3-butenyl, isobutenyl, 1-propenyl, 2-propenyl, and ethenyl (or vinyl). Similar terms such as "C_{2-4} alkenyl" have an analogous meaning. A class of alkenyls of particular interest with respect to the invention is -CH_2=CH-$(CH_2)_{0-4}$H, and sub-classes of particular interest include -CH=CH-$(CH_2)_{1-2}$H, -CH=CH-CH_3, and-CH=CH_2. Another class of alkenyls of particular interest with respect to the invention is alkenyls selected from -$(CH_2)_2$-CH=CH-$(CH_2)_{0-2}$H and -CH_2-CH=CH-$(CH_2)_{0-3}$H.

The term "C_{2-5} alkynyl" (or "C_2-C_5 alkynyl") means a linear or branched chain alkynyl group having from 2 to 5 carbon atoms and includes all of the pentynyl isomers as well as 1-butynyl, 2-butynyl, 3-butynyl, 1-propynyl, 2-propynyl, and ethynyl (or acetylenyl). Similar terms such as "C_{2-4} alkynyl" have an analogous meaning. A class of alkynyls of particular interest with respect to the invention is $-C\equiv C-(CH_2)_{1-4}H$ (e.g., $-C\equiv C-CH_3$). Another class of alkynyls of particular interest with respect to the invention is alkynyls selected from $-CH_2-\equiv-(CH_2)_{1-3}H$ and $-(CH_2)_2-\equiv-(CH_2)_{1-2}H$.

The term "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") means a cyclic ring of an alkane having three to eight total carbon atoms (i.e., cyclopropyl,

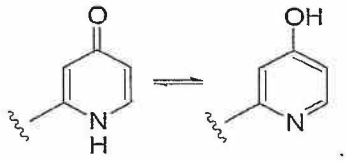
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cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl). Similar terms such as "C_{3-6} cycloalkyl" have an analogous meaning.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "C_{1-6} haloalkyl" (which may alternatively be referred to as "C_1-C_6 haloalkyl" or "halogenated C_1-C_6 alkyl") means a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "C_{1-4} haloalkyl" has an analogous meaning. The term "C_{1-6} fluoroalkyl" has an analogous meaning except that the halogen substituents are restricted to fluoro. A class of fluoroalkyls of particular interest with respect to the invention is the series $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

The term "oxo" means a divalent oxygen substituent; i.e., =O. An oxo substituent on a carbon atom in a heteroaromatic ring refers to the keto form of the keto-enol tautomer, as exemplified here for an oxopyridinyl substituent:



Compounds of the present invention having an oxo substituent on a carbon atom of a heteroaromatic ring are understood to include compounds in which only the keto form is present, compounds in which only the enol form is present, and compounds in which the keto and enol forms are both present.

The term "aryl" as used herein refers to an aromatic carbocyclic ring or an aromatic carbocyclic fused ring system. The fused ring system contains two or more carbocyclic rings in which each ring shares two adjacent carbon atoms with at least one other ring. The aryl group may be attached to the rest of the molecule at any carbon atom which results in a stable compound. A subset of aryl groups particularly suitable for use in the present invention (e.g., in the definition of R^k) includes those selected from phenyl, naphthyl, anthryl, and phenanthryl. Another particularly suitable subset of aryl groups is phenyl and naphthyl. Still another particularly suitable subset of aryl groups is phenyl per se.

The term "heterocyclic ring" refers to a 4- to 8-membered, saturated or unsaturated monocyclic ring that contains one or more heteroatoms (e.g., from 1 to 6 heteroatoms, from 1 to 5 heteroatoms, from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, 1 or 2 heteroatoms, or 1 heteroatom) independently selected from N, O

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and S and a balance of carbon atoms (the ring typically contains at least one carbon atom); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. The heterocyclic ring may be attached to the rest of the molecule via any heteroatom or carbon atom in the ring, provided that attachment results in the creation of a stable structure. When the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

A subset of the heterocyclic rings useful in the present invention (e.g., in the definition of R^k) includes any 4- to 7-membered saturated or mono-unsaturated heterocyclic ring, wherein the ring contains at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S. A subgroup of this subset includes any 4- to 7-membered saturated or mono-unsaturated heterocyclic ring in which the ring contains at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms. Representative examples of saturated heterocyclic rings include piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl (e.g., 1,2-thiazinanyl ), thiazepanyl, thiadiazepanyl, dithiazepanyl, azepanyl (i.e., ), diazepanyl, thiadiazinanyl (e.g., 1,2,6-thiadiazinanyl ), and dioxanyl. Representative examples of mono-unsaturated rings are the same as the saturated rings listed in the preceding sentence except that each ring contains a double bond.

Another subset of the heterocyclic rings useful in the present invention (e.g., in the definition of HetB) includes any 5- or 6-membered saturated or mono-unsaturated ring containing from 1 to 4 heteroatoms independently selected from N, O and S. A useful subgroup of this subset includes any 5- or 6-membered saturated or mono-unsaturated heterocyclic ring in which the ring contains at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms. Another useful subgroup is identical to the preceding subgroup, except that it is limited to saturated heterocyclic rings. Still another subgroup of this subset of heterocyclic rings suitable for use in the present invention includes any 5- or 6-membered saturated ring containing 1 or 2 N atoms and carbon atoms. Representative examples of this subgroup include

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piperidinyl, pyrazolidinyl, imidazolidinyl, piperazinyl, piperidinyl, and hexahydropyrimidinyl.

Another subset of the heterocyclic rings useful in the present invention (e.g., in the definition of HetD) includes any 5- or 6-membered saturated ring containing 1 or 2 N atoms, 0 or 1 S atoms, and a balance of carbon atoms.

Still another subset of the heterocyclic rings useful in the present invention are the heteroaromatic rings. The term "heteroaromatic ring" (alternatively "heteroaryl ring") generally refers to a heterocyclic ring as defined above in which the ring is an aromatic ring. A useful subgroup of this subset (e.g., in the definition of R^k, HetA, or HetC) includes any 5- or 6-membered monocyclic aromatic ring which consist of carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S. Representative examples of this subgroup include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, oxatriazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. Another useful subgroup of this subset includes any 5- or 6-membered heteroaromatic ring in which the ring contains a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms. Another useful subgroup includes any 5- or 6-membered heteroaromatic ring containing 1 or 2 N atoms and carbon atoms.

The term "fused bicyclic heterocycle" refers to any 8- to 12-membered bicyclic ring system containing one or more heteroatoms (e.g., from 1 to 6 heteroatoms, from 1 to 5 heteroatoms, from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, 1 or 2 heteroatoms, or 1 heteroatom) independently selected from N, O and S, in which one ring contains all of the heteroatoms or each ring contains at least one of the heteroatoms, and wherein each ring is saturated or unsaturated, and two adjacent ring atoms are shared by each of the rings in the ring system and each of the two shared atoms is independently a carbon atom or a heteroatom. Any one or more of the nitrogen and sulfur heteroatoms in the ring system is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. The fused bicyclic heterocycle may be attached to the rest of the molecule via any heteroatom or carbon atom in the ring, provided that attachment results in the creation of a stable structure. When the bicyclic heterocycle has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

A subset of the fused bicyclic heterocycles useful in the present invention (e.g., in the definition of R^1) includes any 9- or 10-membered fused bicyclic heterocycle containing from 1 to 4 heteroatoms independently selected from N, O and

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S, wherein at least one of the rings is aromatic. Representative examples of bicyclic heterocycles in this subset include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl (i.e., ), and benzo-1,3-dioxolyl (i.e., ).

Unless expressly stated to the contrary, an "unsaturated" ring is a partially or fully unsaturated ring.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" means the ring can contain 1, 2, 3 or 4 heteroatoms.

When any variable (e.g., R^a, R^b, or R^c) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

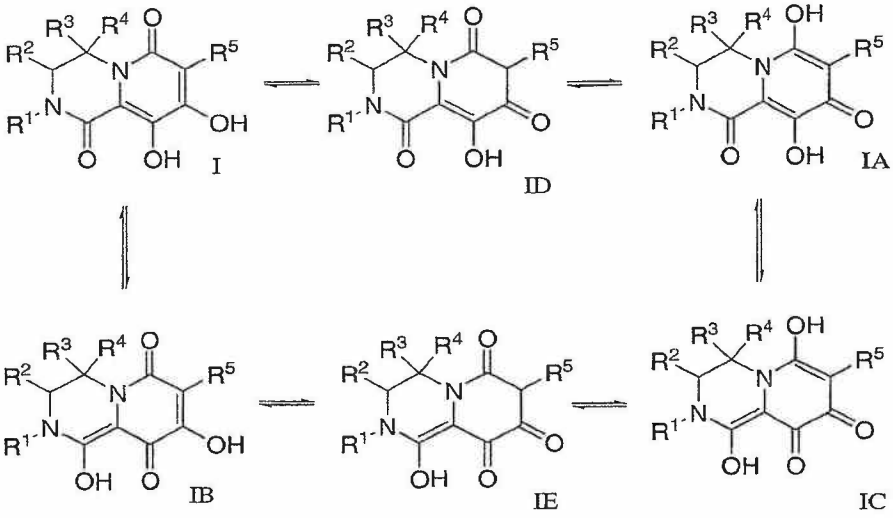
The term "substituted" (e.g., as in "each aryl is optionally substituted with from 1 to 5 substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed.

The symbol " ~~~ " in front of an open bond in the structural formula of a group marks the point of attachment of the group to the rest of the molecule.

The compounds of the present invention may have asymmetric centers and may occur, except when specifically noted, as mixtures of stereoisomers or as individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

As would be recognized by one of ordinary skill in the art, all of the compounds of the present invention can exist as tautomers such as the following:

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It is to be understood for the purposes of the present invention that a reference herein to a compound of Formula I is a reference to compound I per se, or to any one of its tautomers per se (e.g., IA, IB, IC, ID or IE), or to mixtures of two or more tautomers (e.g., two or more of I, IA, IB, IC, ID and IE).

The compounds of the present invention are useful in the inhibition of HIV integrase, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the prevention, treatment or the delay in the onset of consequent pathological conditions such as AIDS. Preventing AIDS, treating AIDS, delaying the onset of AIDS, or preventing or treating infection by HIV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other

antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

The compounds of the present invention can be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. When the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

For the purpose of preventing or treating HIV infection or preventing, treating or delaying the onset of AIDS, the compounds of the present invention can be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing a therapeutically effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the compound to the individual in need of treatment. When a compound of the invention is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HIV infection or AIDS), "administration" and its variants are each understood to include concurrent and sequential provision of the compound and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combining the specified ingredients in the specified amounts.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

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The term "subject" (which may be alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated. When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

The pharmaceutical compositions can be in the form of orally-administrable suspensions or tablets or capsules, nasal sprays, sterile injectible preparations, for example, as sterile injectible aqueous or oleagenous suspensions or suppositories. These compositions can be prepared by methods and contain excipients which are well known in the art. Suitable methods and ingredients are described in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990, which is herein incorporated by reference in its entirety.

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention is also directed to use of the HIV integrase inhibitor compounds of the present invention with one or more agents useful in the treatment of HIV infection or AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more of the

HIV/AIDS antivirals, imunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS. Suitable antiviral agents include those listed in the following Table:

Drug Name	Manufacturer (Tradename and/or Location)	Indication (Activity)
abacavir GW 1592 1592U89	Glaxo Welcome (ZIAGEN®)	HIV infection, AIDS, ARC (nRTI)
abacavir + lamivudine + zidovudine	GlaxoSmithKline (TRIZIVIR®)	HIV infection, AIDS, ARC (nRTIs)
acemannan	Carrington Labs (Irving, TX)	ARC
ACH 126443	Achillion Pharm.	HIV infections, AIDS, ARC (nRTI)
acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
adefovir dipivoxil GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL, HIV positive, AIDS
alpha interferon	GlaxoSmithKline	Kaposi's sarcoma, HIV, in combination w/Retrovir
AMD3100	AnorMed	HIV infection, AIDS, ARC (CXCR4 antagonist)
amprenavir 141 W94 GW 141 VX478 (Vertex)	GlaxoSmithKline (AGENERASE®)	HIV infection, AIDS, ARC (PI)
ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
antibody which neutralizes pH labile alpha aberrant interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC

AR177	Aronex Pharm	HIV infection, AIDS, ARC
atazanavir (BMS 232632)	Bristol-Myers Squibb (REYATAZ™)	HIV infection, AIDS, ARC (PI)
beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (PI)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (PI)
capravirine (AG-1549, S-1153)	Pfizer	HIV infection, AIDS, ARC (nnRTI)
CI-1012	Warner-Lambert	HIV-1 infection
cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
curdlan sulfate	AJI Pharma USA	HIV infection
cytomegalovirus immune globin	MedImmune	CMV retinitis
cytovene ganciclovir	Syntex	sight threatening CMV peripheral CMV retinitis
delavirdine	Pharmacia-Upjohn (RESCRIPTOR®)	HIV infection, AIDS, ARC (nnRTI)
dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC (zalcitabine, dideoxycytidine)	Hoffman-La Roche (HIVID®)	HIV infection, AIDS, ARC (nuclesodie reverse transcriptase inhibitor)
ddI (didanosine, dideoxyinosine)	Bristol-Myers Squibb (VIDEX®)	HIV infection, AIDS, ARC; combination with AZT/d4T (nRTI)
DPC 681 & DPC 684	DuPont	HIV infection, AIDS, ARC (PIs)
DPC 961 & DPC 083	Bristol-Myers Squibb (from DuPont Pharma)	HIV infection AIDS, ARC (nnRTIs)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
efavirenz (DMP 266)	Bristol-Myers Squibb (SUSTIVA®) Merck (STOCRIN®)	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)

famciclovir	Novartis (FAMVIR®)	herpes zoster, herpes simplex
emtricitabine FTC	Gilead (from Triangle Pharmaceuticals) (COVIRACIL®) Emory University	HIV infection, AIDS, ARC (nRTI)
emvirine	Gilead (from Triangle Pharmaceuticals) (COACTINON®)	HIV infection, AIDS, ARC (nnRTI)
enfuvirtide T-20	Trimeris & Roche (FUZEON®)	HIV infection, AIDS, ARC (fusion inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (nnRTI)
fosamprenavir	Glaxo Smith Kline	HIV infection, AIDS, ARC (prodrug of amprenavir)
hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
recombinant human interferon beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
interferon alfa-n3	Interferon Sciences	ARC, AIDS
indinavir	Merck (CRIXIVAN®)	HIV infection, AIDS, ARC, asymptomatic HIV positive, (PI)
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
JE2147/AG1776	Agouron	HIV infection, AIDS, ARC (PI)
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
lamivudine, 3TC	GlaxoSmithKline (EPIVIR®)	HIV infection, AIDS, ARC (nRTI)
lamivudine + zidovudine	GlaxoSmithKline (COMBIVIR®)	HIV infection, AIDS, ARC (nRTI)
lobucavir	Bristol-Myers Squibb	CMV infection
lopinavir (ABT-378)	Abbott	HIV infection, AIDS, ARC (PI)
lopinavir + ritonavir (ABT-378/r)	Abbott (KALETRA®)	HIV infection, AIDS, ARC (PI)
mozenavir (DMP-450)	AVID (Camden, NJ)	HIV infection, AIDS, ARC (PI)
nelfinavir	Agouron (VIRACEPT®)	HIV infection, AIDS, ARC (PI)

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nevirapine	Boeheringer Ingleheim (VIRAMUNE®)	HIV infection, AIDS, ARC (nnRTI)
novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
peptide T octapeptide sequence	Peninsula Labs (Belmont, CA)	AIDS
PRO 140	Progenics	HIV infection, AIDS, ARC (CCR5 co-receptor inhibitor)
PRO 542	Progenics	HIV infection, AIDS, ARC (attachment inhibitor)
trisodium phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (PI)
probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
ritonavir (ABT-538)	Abbott (NORVIR®)	HIV infection, AIDS, ARC (PI)
saquinavir	Hoffmann-LaRoche (FORTOVASE®)	HIV infection, AIDS, ARC (PI)
stavudine; d4T didehydrodeoxy-thymidine	Bristol-Myers Squibb (ZERIT®)	HIV infection, AIDS, ARC (nRTI)
T-1249	Trimeris	HIV infection, AIDS, ARC (fusion inhibitor)
TAK-779	Takeda	HIV infection, AIDS, ARC (injectable CCR5 receptor antagonist)
tenofovir	Gilead (VIREAD®)	HIV infection, AIDS, ARC (nucleotide reverse transcriptase inhibitor)
tipranavir (PNU-140690)	Boehringer Ingelheim	HIV infection, AIDS, ARC (PI)
TMC-120 & TMC-125	Tibotec	HIV infections, AIDS, ARC (nnRTIs)
TMC-126	Tibotec	HIV infection, AIDS, ARC (PI)

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valaciclovir	GlaxoSmithKline	genital HSV & CMV infections
virazole ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
zidovudine; AZT	GlaxoSmithKline (RETROVIR®)	HIV infection, AIDS, ARC, Kaposi's sarcoma in combination with other therapies (nRTI)

PI = protease inhibitor

nnRTI = non-nucleoside reverse transcriptase inhibitor

nRTI = nucleoside reverse transcriptase inhibitor

A compound of the present invention can also be administered in combination with an HIV integrase inhibitor such as a compound described in WO 99/62513,WO 99/62520, or WO 99/62897. A compound of the present invention can also be administered in combination with a CCR5 receptor antagonist, such as a compound described in WO 99/04794, WO 99/09984, WO 99/38514, WO 00/59497, WO 00/59498, WO 00/59502, WO 00/59503, WO 00/76511, WO 00/76512, WO 00/76513, WO 00/76514 , WO 00/76792, or WO 00/76793. The compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more HIV/AIDS antivirals, immunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS disclosed in the Table in WO 02/30930, which is herein incorporated by reference in its entirety.

It will be understood that the scope of combinations of the compounds of this invention with HIV/AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to those described or referenced above, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS. The HIV/AIDS antivirals and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including the dosages described in the Physicians' Desk Reference, 54th edition, Medical Economics Company, 2000. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

Abbreviations used in the instant specification, particularly the Schemes and Examples, include the following:

AIDS = acquired immunodeficiency syndrome

ARC = AIDS related complex

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Bn = benzyl
BOP = benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate
CBZ = carbobenzoxy (alternatively, benzyloxycarbonyl)
DMAP = dimethylaminopyridine
DMF = dimethylformamide
DMSO = dimethyl sulfoxide
EDC or EDAC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ES-MS = eletron spray mass spectroscopy
Et = ethyl
FT ICR = fourier transform ion cyclotron resonance
Hal = halide
HIV = human immunodeficiency virus
HOBt = 1-hydroxy benzotriazole hydrate
HPLC = high performance liquid chromatography
LC = liquid chromatography
Me = methyl
MS = mass spectroscopy
NBS = N-bromosuccinimide
NMR = nuclear magnetic resonance
TFA = trifluoroacetic acid
THF = tetrahydrofuran

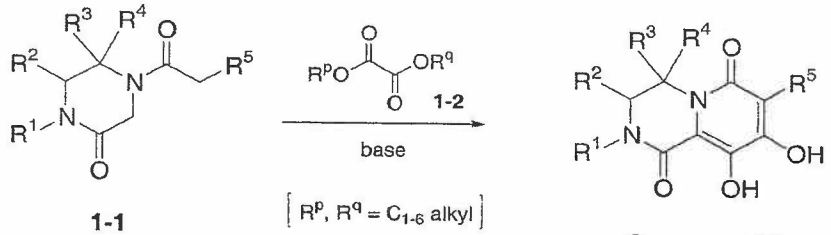
The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

The compounds of the present invention, 8,9-dihydroxydihydropyridopyrazine-1,6-diones and 8,9-dihydroxypyridopyrazine-1,6-diones, can be prepared by subjecting 1-alkyl-4-acyl piperazin-2-ones and 1-alkyl-4-acyl-3,4-dihydropyrazine-2(1H)-ones, respectively, to an oxalation-cyclization sequence. Scheme 1 depicts the general approach to the preparation of compounds of

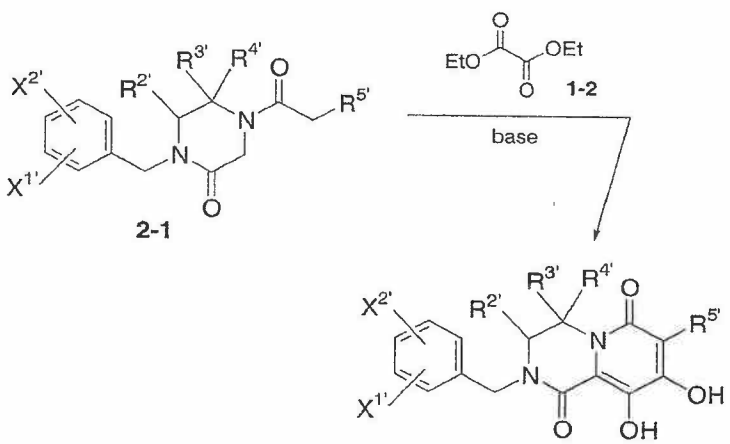
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Formula (I). In Scheme 1, piperazin-2-one **1-1** is treated with oxalate **1-2** in the presence of base (e.g., lithium or sodium bis(trimethylsilyl)amide, or lithium diisopropylamide) at low temperature (e.g., from about 0 to about 25°C) in an anhydrous non-protic solvent (e.g., DMF) to give a dihydroxypyridopyrazinedione of Formula (I). Scheme 2 exemplifies the same approach for the preparation of compounds of Formula (II). An analogous procedure can be used to prepare compounds of Formula (III) as earlier defined and described.

SCHEME 1



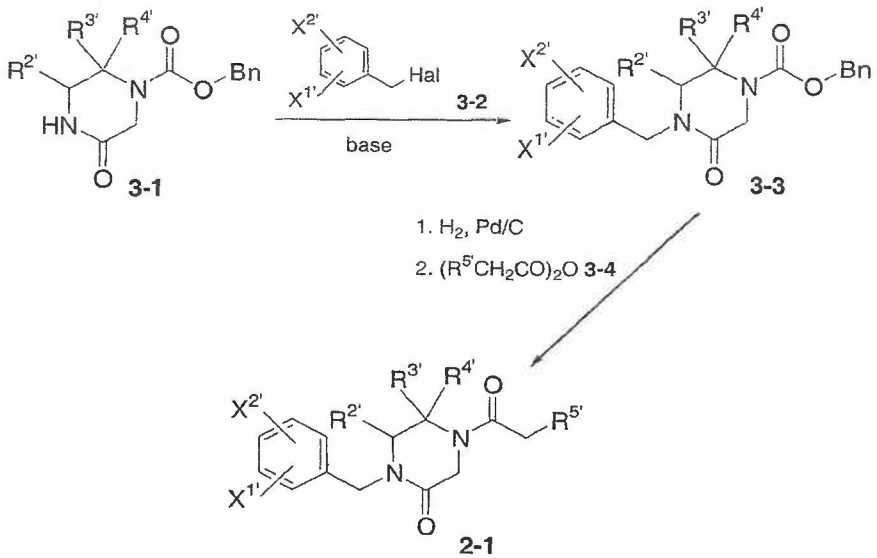
SCHEME 2



1-Alkyl-4-acyl piperazin-2-ones of formula **1-1** can be prepared by alkylating a piperazin-2-one having a protective group on the 4-piperazinyl nitrogen, deprotecting the alkylated product, and then acylating with a suitable acylating agent to introduce R^5. The protection and deprotection of the amine in the piperazin-2-one can be accomplished using conventional amine protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973 and in T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. Further description of the preparation of piperazin-2-ones **1-1** via this chemistry is provided in Bernotas et al., *Tetrahedron Lett.* 1996, 7339; Saari et al., *J. Med. Chem.* 1990, 2590; Sugihara et al., *J. Med. Chem.* 1998, 489. This method is exemplified in Scheme 3 for the preparation of compound **2-1**, wherein CBZ-protected piperazin-2-one **3-1** is alkylated with benzyl halide (e.g., benyl bromide) **3-2** in the presence of a base (e.g., in the presence of Li or Na bis(trimethylsilyl)amide or Li diisopropylamide at 0-25°C in an anhydrous non-protic solvent such as DMF), and the alkylated product **3-3** is then treated with a reducing agent (e.g., H_2 over Pd/C) to remove the CBZ protective group. The deprotected product is then acylated with anhydride **3-4** to afford **2-1**. Further description of this chemistry can be found in Wei et al., *Bioorg. Med. Chem.* 2000, 1737. Compound **3-1** can be prepared using methods described in Choi et al., *J. Med. Chem.* 1999, 3647; Najman-Bronzewska et al., *Pharmazie* 1997, 198; Fryer et al., *J. Org. Chem.* 1991, 3715, or routine variations thereof.

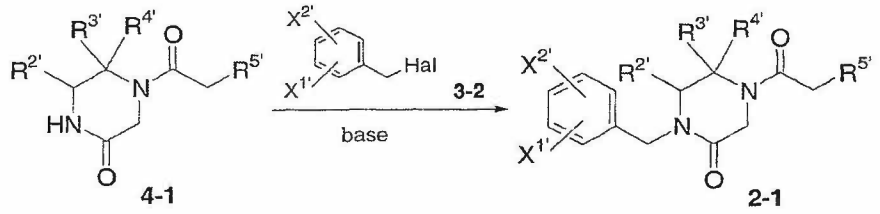
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SCHEME 3

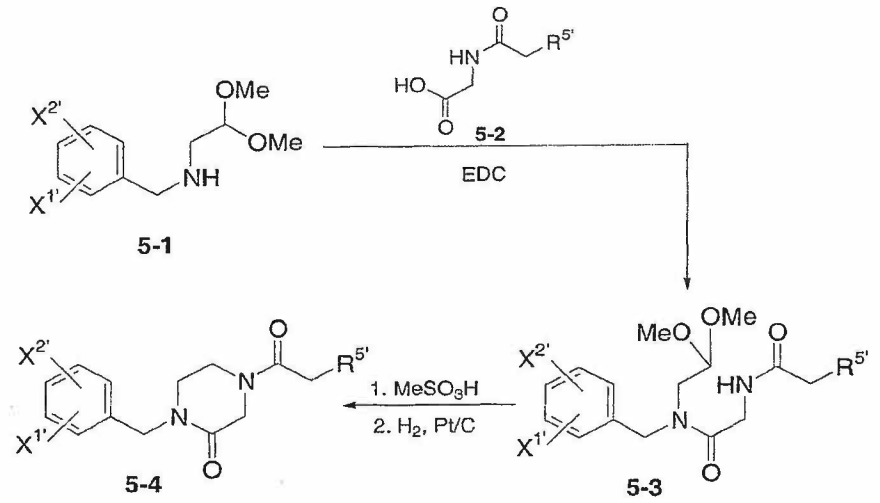


Other methods for preparing piperazin-2-ones **1-1** are exemplified in Schemes 4 and 5 showing the preparation of piperazin-2-ones **2-1** and **5-4** respectively. (Note: Piperazin-2-one **5-4** is equivalent to **2-1** having $R^{2'} = R^{3'} = R^{4'} = H$.) In Scheme 4, 4-acylpiperazin-2-one **4-1** is alkylated with benzyl halide (e.g., benzyl bromide) **3-2** in the presence of a base such as Li or Na bis(trimethylsilyl)amide or Li diisopropylamide at low temperature (e.g., 0 to 25°C) in an anhydrous non-protic solvent such as DMF. Further description of this chemistry can be found in Hori et al., *Chem. Pharm. Bull.* 1981, 1594. In Scheme 5, N-(2,2-dimethoxyethyl)-N-benzylamine is obtained by reductive alkylation of the corresponding benzaldehyde and dimethoxyethylamine. The alkylation product is acylated with N-acyl-glycine with standard coupling reagents (eg. EDC, BOP, etc). Treatment of the acylation product with acid (e.g., $MeSO_3H$ in CH_2Cl_2, Kim et al., *Heterocycles* 1998, 2279; aqueous TFA, Horwell et al., *Tetrahedron* 1998, 4591; p-TsOH in toluene, Uchida et al., *Chem. Pharm. Bull.* 1997, 1228; HCl-acetonitrile, Kurihara et al., *Heterocycles* 1982, 191) provided the cyclization product, which was catalytically hydrogenated to produce 4-acyl-1-(benzyl)piperazin-2-one **5-4**.

SCHEME 4



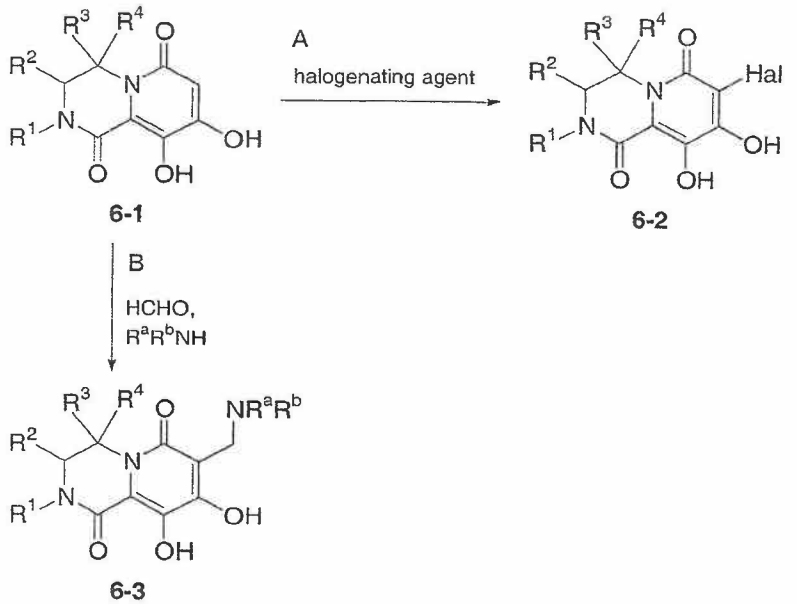
SCHEME 5



Scheme 6 illustrates a method for introducing functional groups at the 7-position of pyridopyrazine ring subsequent to the preparation of the dihydroxypyridopyrazinedione. As shown in Part A of Scheme 6, halogen can be introduced by treating the dihydroxypyridopyrazinedione **6-1** with a suitable halogenating agent (e.g., Br_2, NBS, ICl, etc). Further description of this chemistry can be found in March, Advanced Organic Chemistry, 531-534, 4th edition. Part B of Scheme 6 shows the introduction of an alkylamino group via the Mannich reaction, which is described in March, Advanced Organic Chemistry, 900-902, 4th edition. In Part B, dihydroxypyridopyrazinedione **6-1** is treated with a mixture of an aldehyde and

a nucleophilic secondary amine in an alcoholic solution to provide the 7-aminoalkylated dihydroxypyridopyrazinedione **6-3**.

SCHEME 6

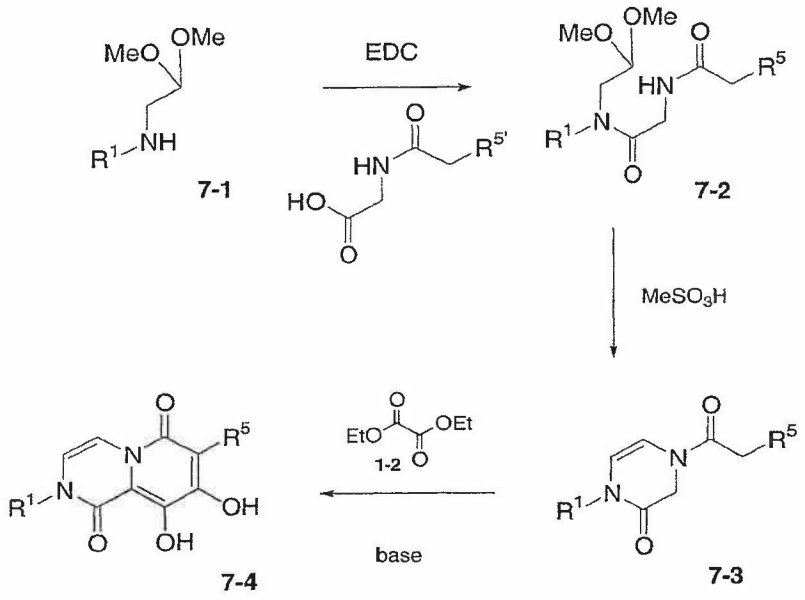


6-1 **6-2** **6-3**

Scheme 7 depicts a method for preparing dihydroxypyridopyrazine-1,6-diones embraced by Formula (I) of the present invention. In Scheme 7, N-(2,2-dimethoxyethyl)-N-alkylamine is acylated with N-acyl-glycine with standard coupling reagents (eg. EDC, BOP, etc). Treatment of the acylation product **7-1** with acid (suitable acids include those disclosed above in the discussion of Scheme 5) will afford 4-acylpyrazin-2-one **7-2**, which can be cyclized to provide dihydroxypyridopyrazinedione **7-3** via the oxalation-cyclization procedure depicted in Schemes 1 and 2.

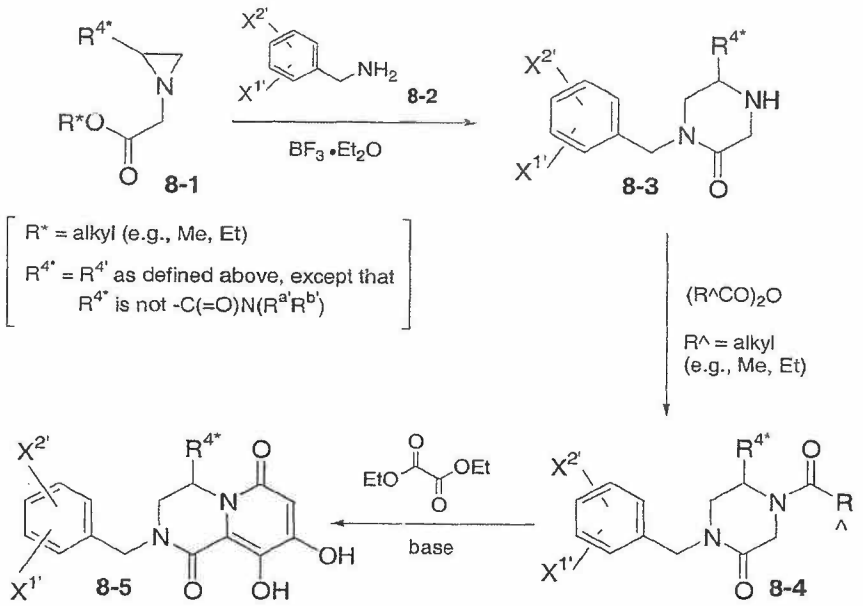
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SCHEME 7



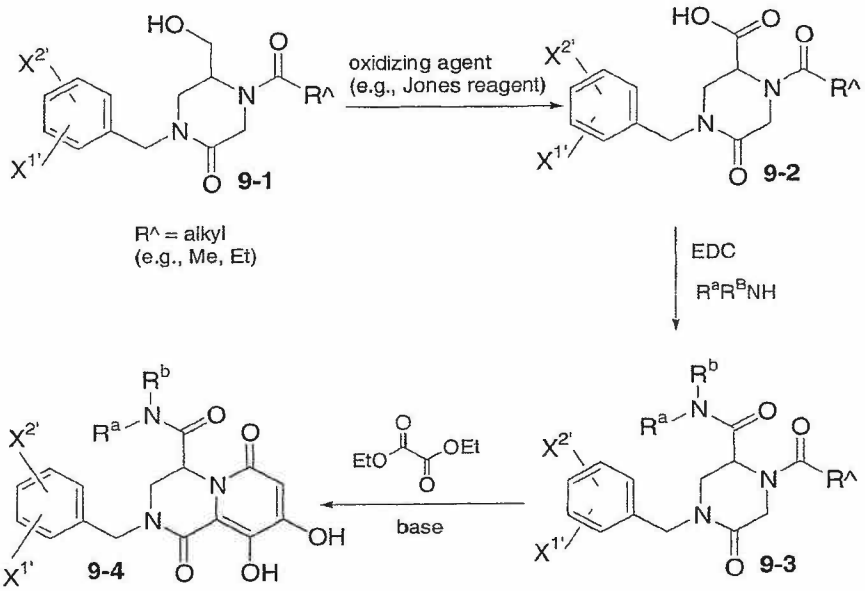
Scheme 8 shows a method for preparing dihydroxydihydropyrido-pyrazine-1,6-diones having an alkyl or substituted alkyl at the 4-position of the ring. In Scheme 8, treatment of alkyl (2-susbstituted aziridin-1-yl)acetate **8-1** with benzylamine **8-2** in the presence of borontrifluoride etherate provided the 5-substituted 1-benzylpiperazin-2-one **8-3**. Acylation of the piperazinone, followed by the oxalation-cyclization procedure depicted in Scheme 1 provided the 4-substituted dihydroxydihydropyrido-pyrazine-1,6-diones **8-5**. Note that in the case where $R^{4'}$ = benzyloxymethyl, compound **8-5** can be hydrogenated (e.g., H_2 over Pd) to afford $R^{4'}$ = hydroxymethyl.

SCHEME 8



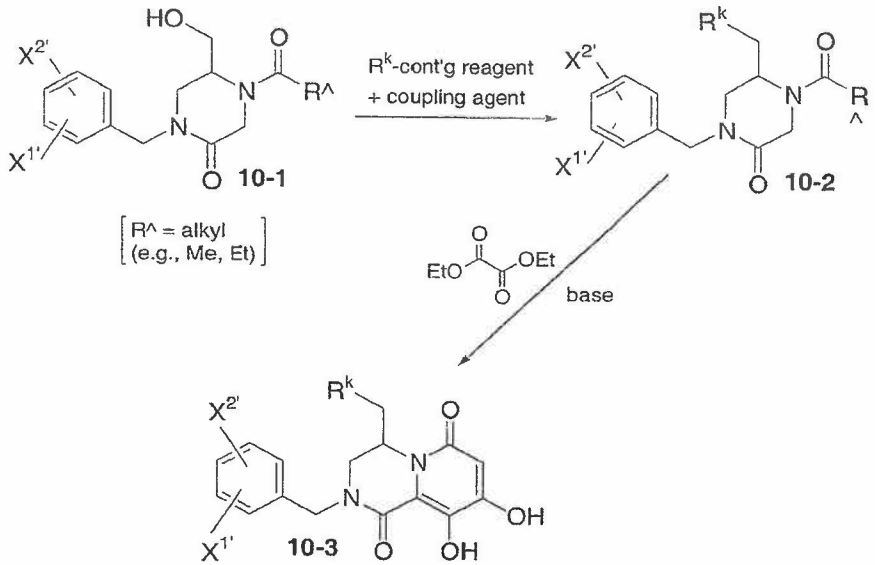
Scheme 9 shows a method for preparing dihydroxydihydropyrido-pyrazine-1,6-diones having an aminocarbonyl substituent at the 4-position of the ring. In Scheme 9, the hydroxymethylpiperazinone **9-1** was oxidized with an oxidizing reagent such as Jones reagent. The resulting acid **9-2** was converted to the corresponding amide **9-3** with coupling reagent such as EDC in the presence of an amine. Treatment of **9-3** with the oxalation-cyclization procedure depicted in Scheme 1 can provide the amide substituted dihydroxydihydropyrido-pyrazine-1,6-diones **9-4.**

SCHEME 9



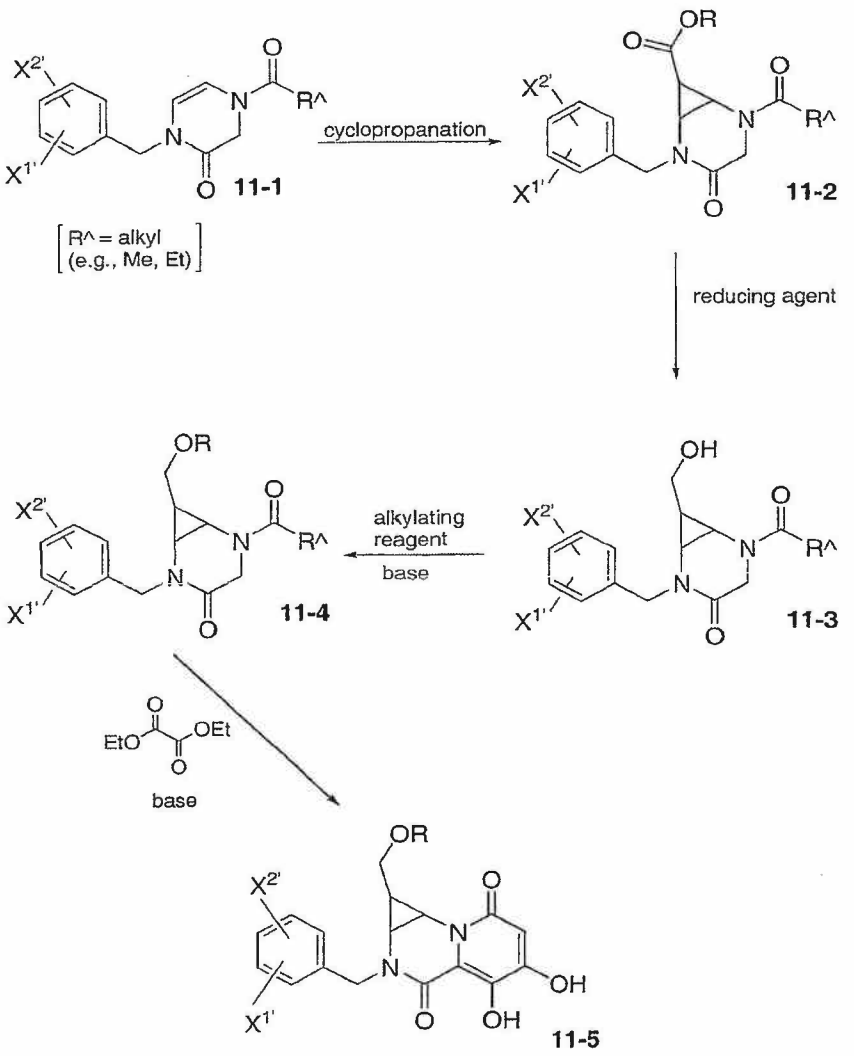
Scheme 10 depicts a method for preparing dihydroxydihydropyrido-pyrazine-1,6-diones having a heterocyclylmethyl substituent at the 4-position of the ring. According to Scheme 10, the hydroxymethylpiperazinone **10-1** can be treated with heterocyclic sulfonamides or amide in the presence of coupling reagent such as cyanomethylene tri-n-butylphosphorane or diethylazodicarboxylate-triphenylphosphine to provide the 4-heterocyclic-methyl susbtituted piperazin-2-one **10-2**. Treatment of **10-2** with the oxalation-cyclization procedure depicted in Scheme 1 can provide the heterocyclic-methyl susbtituted dihydroxydihydropyrido-pyrazine-1,6-diones **10-3.**

SCHEME 10



Scheme 11 depicts a method for preparing 4,5-dihydroxy-tetrahydrocyclopropapyrido-pyrazine-3,7-diones, wherein 3,4-dihydropyrazine **11-1** is cyclopropanated with a cyclopropanation reagent such as ethyl diazoacetate and copper bronze. The resulting ester **11-2** can be treated with a reducing agent (e.g., sodium borohydride) to proivee the corresponding alcohol **11-3**, which can be treated with an alkylating reagent (e.g., benzyl bromide or an alkyl halide such as methyl iodide) and a base (e.g., NaH) to afford alkylation product **11-4**. Subjecting **11-4** to the oxalation-cyclization procedure depicted in Scheme 1 can then proivde the desired 4,5-dihydroxy-tetrahydrocyclopropapyrido-pyrazine-3,7-dione **11-5**.

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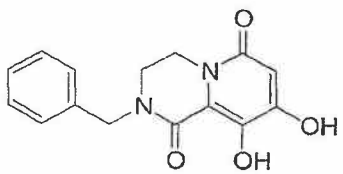
In the processes for preparing compounds of the present invention set forth in the foregoing schemes, functional groups in various moieties and substituents may be sensitive or reactive under the reaction conditions employed and/or in the presence of the reagents employed. Such sensitivity/reactivity can interfere with the progress of the desired reaction to reduce the yield of the desired product, or possibly even preclude its formation. Accordingly, it may be necessary or desirable to protect

sensitive or reactive groups on any of the molecules concerned. Protection can be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973 and in T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protective groups may be removed at a convenient subsequent stage using methods known in the art.

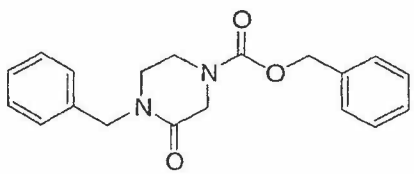
The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLE 1

2-Benzyl-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



Step 1: Benzyl 4-benzyl-3-oxopiperazine-1-carboxylate



To a cold (0 °C) solution of benzyl 3-oxopiperazine-1-carboxylate (4.7 g, 20 mmol) in DMF (75 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (24 mL, 24 mmol) was added and stirred at the temperature for 30 min. The resultant solution was treated with benzyl bromide (2.9 mL, 24 mmol), and stirred at room temperature overnight. The product mixture was concentrated under vacuum, and the residue partitioned between aqueous HCl and ethyl acetate. The organic extracted was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 50-50 mixture of

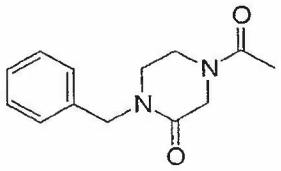
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ethyl acetate and hexane. Collection and concentration of appropriate fractions provided the benzylated product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4-7.2 (m, 10H), 5.15 (s, 2H), 4.63 (s, 2H), 4.25 (s, 2H), 3.66 (br t, J = 5.3 Hz, 2H), 3.27 (br s, 2H).

ES MS M+1 = 325

Step 2: 4-Acetyl-1-benzylpiperazin-2-one



A mixture of benzyl 4-benzyl-3-oxopiperazine-1-carboxylate (4.7 g, 14.5 mmol) and 10% Pd/C (0.47 g) in ethanol (150 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature overnight. The product mixture was filtered through a pad of Celite, and concentrated under vacuum to provide 1-benzylpiperazin-2-one. A portion of the resultant oil (1.06 g, 5.5 mmol) was treated with a mixture of N,N-diisopropylethylamine (1.46 mL, 8.3 mmol), DMAP (68 mg, 0.55 mmol), and acetic anhydride (0.73 mL, 7.8 mmol) in methylene chloride (30 mL) at 0 °C. After stirring at room temperature overnight, the resultant mixture was concentrated and the residue was subjected to column chromatography on silica gel eluting with a 10-90 mixture of methanol and ethyl acetate. Collection and concentration of appropriate fractions provided the title piperazinone.

^{1}H NMR (400 MHz, $CDCl_3$) ~2:1 mixture of rotomers δ 7.4-7.2 (m, 5H), 4.64 (s, 2/3H), 4.63 (s, 1 1/3H), 4.32 (s, 2/3H), 4.21 (s, 1 1/3H), 3.76 (br t, J = 5.3 Hz, 1 1/3H), 3.63 (br t, J = 5.3 Hz, 2/3H), 3.30 (br t, J = 5.3 Hz, 2/3H), 3.27 (br t, J = 5.3 Hz, 1 1/3H), 2.11 (s, 2H), 2.10 (s, 1H).

ES MS M+1 = 233

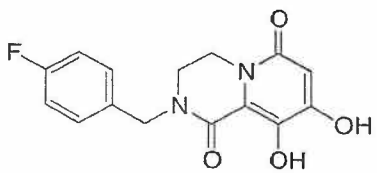
Step 3: 2-Benzyl-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

To a cold (0 °C) solution of 4-acetyl-1-benzylpiperazin-2-one (0.49 g, 2.1 mmol) in DMF (10 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (2.5 mL, 2.5 mmol) was added and stirred at the

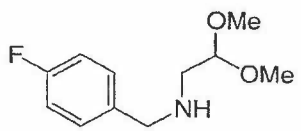
temperature for 30 min. The resultant solution was treated with diethyl oxalate (0.43 mL, 3.1 mmol), and stirred at room temperature overnight. The resultant mixture was then treated with additional lithium bis(trimethylsilyl)amide in THF (10 mL, 10 mmol) and stirred at room temperature for 6 h. The product mixture was concentrated under vacuum, and the residue partitioned between aqueous HCl and ethyl acetate. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 11.07 (br s, 1H), 7.39-7.25 (m, 5H), 5.93 (s, 1H), 4.70 (s, 2H), 3.97 (t, J = 5.5 Hz, 2H), 3.56 (t, J = 5.5 Hz, 2H).
ES MS M+1 = 287

EXAMPLE 2

2-(4-Fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



Step 1: N-(2,2-Dimethoxyethyl)-N-(4-fluorobenzyl)amine

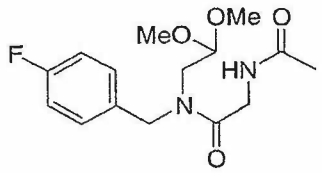


A mixture of 4-fluorobenzaldehyde (227.6 g, 1.83 mol) and dimethoxyethylamine (192.6 g, 1.83 mol) in methanol (2.5 L) was heated at 65 °C for 1.5 h. The solution was allowed to cool to room temperature overnight and treated with sodium borohydride (47.6 g 1.26 mol) in portions over a period of 2 h. The resultant mixture was stirred at room temperature for 3 h and quenched with water (1 L). The product mixture was concentrated to about 1 L and extracted with diethyl ether (3X). The ethereal extracts were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the title compound as yellow oil.

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^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 5.5, 8.6 Hz, 2H), 7.00 (t, J = 6.8 Hz, 2H), 4.48 (t, J = 5.5 Hz, 1H), 3.77 (s, 2H), 3.37 (s, 6H), 2.73 (d, J = 5.5 Hz, 2H).
ES MS M+1 = 214

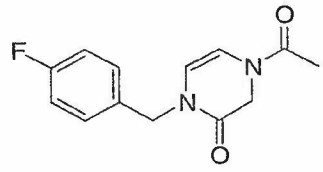
Step 2: N^2-acetyl-N^1-(2,2-dimethoxyethyl)-N^1-(4-fluorobenzyl)glycinamide



To a solution of N-(2,2-dimethoxyethyl)-N-(4-fluorobenzyl)amine (366.5 g, 1.72 mol), N-acetylglycine (213.7 g, 1.83 mol), EDC (350.0 g, 1.83 mol), and HOBt (29.1 g, 0.19 mol) in anhydrous DMF (2.5 L), N,N-diisopropylethylamine (~250 mL) was added until the solution is about pH 8. The reaction mixture was stirred at room temperature overnight and concentrated under vacuum. The residue was partitioned between dichloromethane (4 L) and water (1 L). The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) ~1:1 mixture of rotomers δ 7.27-6.99 (m, 4H), 6.57 (br s, 1H), 4.67 (s, 1H), 4.58 (s, 1H), 4.52 (t, J = 5.3 Hz, 0.5H), 4.32 (t, J = 5.3 Hz, 0.5H), 4.20 (d, J = 4.0 Hz, 1H), 4.11 (d, J = 4.0 Hz, 1H), 3,46 (d, J = 5.3 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 3.31 (d, J = 5.3 Hz, 1H), 2.06 (s, 1.5H), 2.04 (s, 1.5H).
ES MS M-OCH_3 = 281

Step 3: 4-Acetyl-1-(4-fluorobenzyl)-3,4-dihydropyrazin-2(1*H*)-one



To a solution of methanesulfonic acid (314 g) in dichloromethane (10 L) at room temperature, a solution of N^2-acetyl-N^1-(2,2-dimethoxyethyl)-N^1-(4-fluorobenzyl)glycinamide (438 g, 1.07 mol) in dichloromethane (2 L) was added slowly over a period of 2 h. The reaction mixture was stirred at room temperature overnight

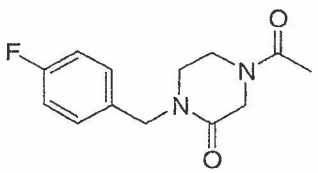
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and treated with saturated aqueous sodium carbonate (3 L). The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. To the residual oil, ethyl acetate (1 L) was added and stirred at room temperature. The solid precipitated was filtered to provide the title compound.

^{1}II NMR (400 MHz, $CDCl_3$) ~5:1 mixture of rotomers δ 7.3-7.2 (m, 2H), 7.1-7.0 (m, 2H), 6.70(d, *J* = 6.4 Hz, 1/5H), 6.11(d, *J* = 6.4 Hz, 4/5H), 5.61(d, *J* = 6.4 Hz, 1/5H), 5.53(d, *J* = 6.4 Hz, 4/5H), 4.68 (s, 1 3/5H), 4.66 (s, 2/5H), 4.42 (s, 1 3/5H), 4.36 (s, 2/5H), 2.16 (s, 3H).

ES MS M+1 = 249

Step 4: 4-Acetyl-1-(4-fluorobenzyl)piperazin-2-one



A mixture of 4-acetyl-1-(4-fluorobenzyl)-3,4-dihydropyrazin-2(1*H*)-one (141 g, 0.57 mol) and 5% Pd/C (10.4 g) in ethanol (500 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature overnight. The product mixture was filtered through a pad of Celite, and concentrated under vacuum to provide the title compound. Residual ethanol was removed by co-evaporation with toluene (3X) under vacuum. The resultant oil solidify on standing and was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) ~2:1 mixture of rotomers δ 7.3 (m, 2H), 7.0 (m, 2H), 4.58 (s, 2H), 4.32 (s, 2/3H), 4.20 (s, 1 1/3H), 3.77 (br t, *J* = 5.4 Hz, 1 1/3 H), 3.63 (br t, *J* = 5.4 Hz, 2/3 H), 3.30 (br t, *J* = 5.4 Hz, 2/3 H), 3.26 (br t, *J* = 5.4 Hz, 1 1/3 H), 2.12 (s, 2H), 2.11 (s, 1H).

ES MS M+1 = 251

Step 5: 2-(4-Fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

To a cold (0 °C) solution of 4-acetyl-1-(4-fluorobenzyl)piperazin-2-one (30.6 g, 122 mmol) in DMF (700 mL) under an atmosphere of nitrogen, a solution of sodium bis(trimethylsilyl)amide in THF (2 M, 73 mL, 146 mmol) was added and

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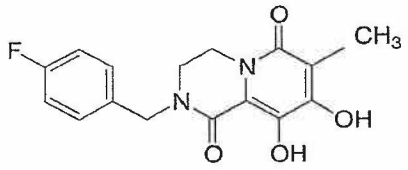
stirred at the temperature for 30 min. The resultant solution was treated with diethyl oxalate (16.7 mL, 123 mmol), and stirred at room temperature overnight. The resultant mixture was then treated with additional sodium bis(trimethylsilyl)amide in THF (2 M, 73 mL, 146 mmol) and stirred at room temperature for 4 h. The product mixture was concentrated under vacuum, and the residue treated with a mixture of aqueous HCl and ethyl acetate. The resultant precipitate was obtained by filtration to provide the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 11.07 (br s, 1H), 7.40 (dd, J = 8.3, 5.8 Hz, 2H), 7.20 (t, J = 8.3 Hz, 2H), 5.98 (s, 1H), 4.68 (s, 2H), 3.97 (t, J = 5.3 Hz, 2H), 3.56 (t, J = 5.3 Hz, 2H).

ES MS M+1 = 305

EXAMPLE 3

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



The title compound was prepared using a procedure similar to that described in Example 1, except that benzyl bromide (Step 1) was substituted with 4-fluorobenzyl bromide, and acetic anhydride (Step 2) was substituted with propionic anhydride.

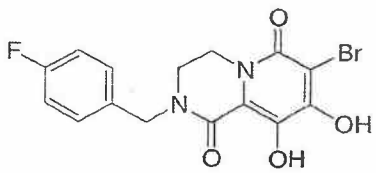
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.50 (s, 1H), 7.4-7.0 (m, 4H), 6.40 (br s, 1H), 4.74 (s, 2H), 4.22 (t, J = 5.5 Hz, 2H), 3.55 (t, J = 5.5 Hz, 2H), 2.17 (s, 3H).

ES MS M+1 = 319

EXAMPLE 4

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-bromo-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

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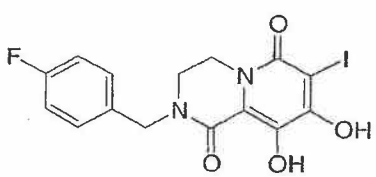
To a suspension of 2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione (0.1 g, 0.33 mmol) in chloroform (5 mL), N-bromo-succinimide (64 mg, 0.36 mmol) was added and stirred at room temperature overnight. The product mixture was concentrated and the residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (s, 1H), 11.62 (br s, 1H), 7.41 (dd, J = 5.8, 8.4 Hz, 2H), 7.20 (t, J = 8.8 Hz, 2H), 4.69 (s, 2H), 4.07 (t, J = 5.3 Hz, 2H), 3.59 (t, J = 5.3 Hz, 2H).

ES MS M+1 = 383/385

EXAMPLE 5

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-iodo-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

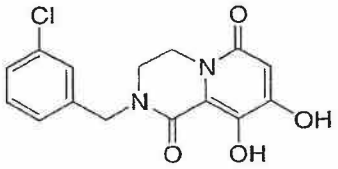


To a suspension of 2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione (5 g, 16.4 mmol) in methylene chloride (300 mL) at room temperature, a solution of iodine monochloride (2.8 g, 17.2 mmol) in methylene chloride (50 mL) was added. The suspension was stirred at room temperature overnight and concentrated under vacuum. The residue was dissolved in ethyl acetate and washed subsequently with an aqueous solution of sodium metabisulfite and brine. The organic extract was dried over anhydrous magnesium sulfate, filtered, concentrated. The residual solid was stirred in diethyl ether overnight, and collected by filtration.

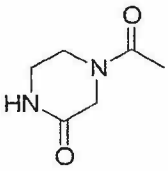
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 11.82 (s, 1H), 7.41 (dd, J = 6.0, 8.4 Hz, 2H), 7.20 (t, J = 8.8 Hz, 2H), 4.69 (s, 2H), 4.07 (t, J = 5.3 Hz, 2H), 3.59 (t, J = 5.3 Hz, 2H).
ES MS M+1 = 431

EXAMPLE 6

2-(3-Chlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



Step 1: 4-Acetylpiperazin-2-one



To a cold (0 °C) solution of piperazin-2-one (2.50 g, 24.9 mmol) and N,N-diisopropylethylamine (4.78 mL, 27.5 mmol) in methylene chloride (50 mL) under an atmosphere of nitrogen, acetic anhydride (2.47 mL, 26.2 mmol) was added and stirred at the temperature for overnight. The resultant solution was concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 90:10:1 mixture of chloroform, methanol, and ammonium hydroxide. Collection and concentration of appropriate fractions provided the title product.
^{1}H NMR (400 MHz, $CDCl_3$) ~2:3 mixture of rotomers δ 6.81 (br s, 2/5H), 6.59 (br s, 3/5 H), 4.25 (s, 4/5H), 4.13 (s, 1 1/5 H), 3.82 (t, J = 5.4 Hz, 1 1/5 H), 3.67 (t, J = 5.4 Hz, 4/5 H), 3.46 (m, 4/5 H), 3.40 (m, 1 1/5 H), 2.15 (s, 1H), 2.12 (s, 2H).
ES MS M+1 = 143

Step 2: 2-(3-chlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

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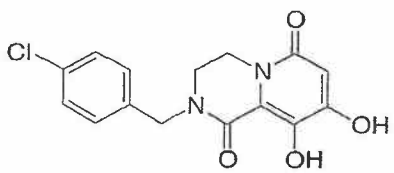
To a cold (0 °C) solution of 4-acetylpiperazin-2-one (1.0 g, 7.0 mmol) in DMF (75 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)-amide in THF (7.7 mL, 7.7 mmol) was added and stirred at the temperature for 30 min. The resultant solution was treated with 3-chlorobenzyl bromide (0.92 mL, 7.0 mmol), and stirred at room temperature overnight. The resultant mixture was cooled to 0 °C, treated with a solution of lithium bis(trimethylsilyl)amide in THF (8.4 mL, 8.4 mmol) and stirred for 30 min, and then treated with diethyl oxalate (0.96 mL, 7.0 mmol). The resultant mixture was stirred at room temperature overnight. Additional solution of lithium bis(trimethylsilyl)amide in THF (16.8 mL, 16.8 mmol) was added and stirred for 4 hrs. The product mixture was concentrated under vacuum, and the residue was treated with a mixture of aqueous HCl and ethyl acetate. The white solid precipitated was collected by filtration and was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 11.07 (br s, 1H), 7.44-7.31 (m, 4H), 5.93 (s, 1H), 4.69 (s, 2H), 3.98 (t, J = 5.5 Hz, 2H), 3.59 (t, J = 5.5 Hz, 2H).

ES MS M+1 = 322

EXAMPLE 7

2-(4-Chlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



The title compound was prepared using a procedure similar to that described in Example 6, except that 3-chlorobenzyl bromide (Step 2) was substituted with 4-chlorobenzyl bromide.

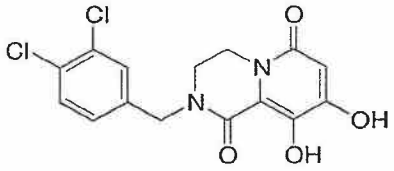
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 1H), 11.10 (br s, 1H), 7.42 (t, J = 8.6 Hz, 2H), 7.37 (t, J = 8.6 Hz, 2H), 5.94 (s, 1H), 4.68 (s, 2H), 3.97 (t, J = 6.1 Hz, 2H), 3.57 (t, J = 6.1 Hz, 2H).

ES MS M+1 = 322

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EXAMPLE 8

2-(3,4-Dichlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



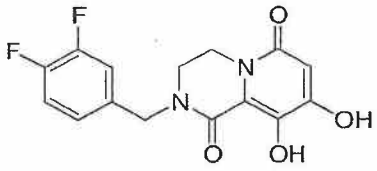
The title compound was prepared using a procedure similar to that described in Example 6, except that 3-chlorobenzyl bromide (Step 2) was substituted with 3,4-dichlorobenzyl bromide.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 11.09 (br s, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.35 (dd, J = 1.8, 8.8 Hz, 1H), 5.94 (s, 1H), 4.69 (s, 2H), 3.96 (t, J = 5.3 Hz, 2H), 3.59 (t, J = 5.3 Hz, 2H).

ES MS M+1 = 356

EXAMPLE 9

2-(3,4-Difluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



The title compound was prepared using a procedure similar to that described in Example 6, except that 3-chlorobenzyl bromide (Step 2) was substituted with 3,4-difluorobenzyl bromide.

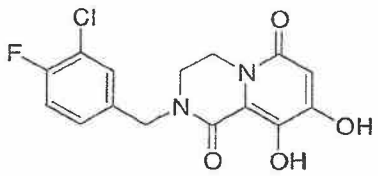
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 11.19 (br s, 1H), 7.48-7.39 (m, 2H), 7.23-7.20 (m, 1H), 6.00 (s, 1H), 4.68 (s, 2H), 3.99 (t, J = 5.9 Hz, 2H), 3.59 (t, J = 5.9 Hz, 2H).

ES MS M+1 = 323

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EXAMPLE 10

2-(3-Chloro-4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



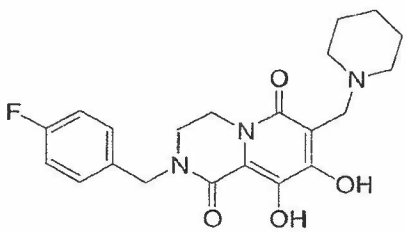
The title compound was prepared using a procedure similar to that described in Example 6, except that 3-chlorobenzyl bromide (Step 2) was substituted with 3-chloro-4-fluorobenzyl bromide.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 11.05 (br s, 1H), 7.60 (d, J = 7.0 Hz, 2H), 7.43-7.36 (m, 2H), 5.93 (s, 1H), 4.67 (s, 2H), 3.98 (t, J = 5.6 Hz, 2H), 3.59 (t, J = 5.6 Hz, 2H).

ES MS M+1 = 339

EXAMPLE 11

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-(piperidin-1-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

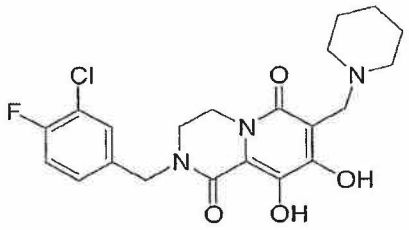


A mixture of 2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione (0.2 g, 0.66 mmol), piperidine (0.13 mL, 1.3 mmol), and formaldehyde (0.08 mL, 37% solution in water) in absolute ethanol (5 mL) was stirred at room temperature for 6 h. The product mixture was concentrated under vacuum, and the residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 11.91 (s, 1H), 7.41 (dd, J = 5.8, 8.4 Hz, 2H), 7.22 (t, J = 8.8 Hz, 2H), 4.72 (s, 2H), 4.08 (br s, 4H), 3.62 (t, J = 5.5 Hz, 2H), 3.3 (br s, 2H), 2.9 (br s, 2H), 1.7 (br m, 6H).
ES MS M+1 = 402

EXAMPLE 12

2-(3-Chloro-4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-1-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

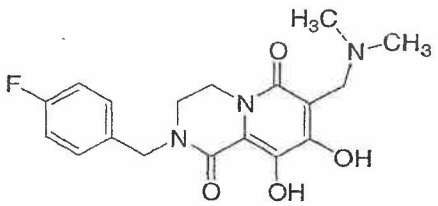


The title compound was prepared using a procedure similar to that described in Example 11, except that 2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione was substituted with 2-(3-chloro-4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 11.95 (br s, 1H), 7.62 (br d, J = 6.9 Hz, 1H), 7.45-7.40 (m, 2H), 4.71 (s, 2H), 4.08 (br signal, 4H), 3.65 (t, J = 5.5 Hz, 2H), 2.96 (br signal, 2H), 2.68 (br s, 2H), 2.33 (br s, 2H), 1.7 (br m, 6H).
ES MS M+1 = 436

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EXAMPLE 13

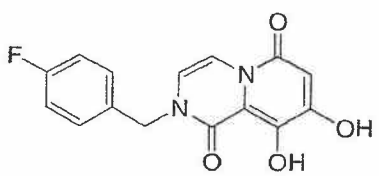
2-(4-Fluorobenzyl)-8,9-dihydroxy-7-[(dimethylamino)methyl]-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



The title compound was prepared using a procedure similar to that described in Example 11, except that piperidine was substituted with dimethylamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.63 (s, 1H), 11.90 (br s, 1H), 7.41 (dd, J = 6.0, 8.4 Hz, 2H), 7.21 (t, J = 8.8 Hz, 2H), 4.72 (s, 2H), 4.22 (s, 2H), 4.08 (t, J = 5.5 Hz, 2H), 3.63 (t, J = 5.5 Hz, 2H), 2.74 (s, 6H).
ES MS M+1 = 362

EXAMPLE 14

2-(4-Fluorobenzyl)-8,9-dihydroxy-2H-pyrido[1,2-a]pyrazine-1,6-dione



A mixture of anhydrous DMSO and sodium hydride (0.24 g, 60% oil dispersion, washed 3x with hexane) under an atmosphere of nitrogen was heated with stirring at 50 °C for 3 h. After cooling to room temperature, a solution of 4-acetyl-1-(4-fluorobenzyl)-3,4-dihydropyrazin-2(1*H*)-one (0.5 g, 2.0 mmol; Example 2, Step 3) in anhydrous DMSO (5 mL) was added over a period of 10 min and the resultant mixture stirred at room temperature for 30 min. The mixture was then treated with diethyl oxalate (0.29 mL, 2.1 mmol) and stirred at room temperature overnight. The product mixture was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

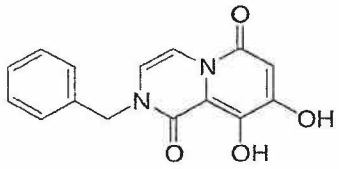
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H), 11.40 (s, 1H), 7.44 (dd, J = 5.6, 8.1 Hz, 2H), 7.39 (d, J = 6.4 Hz, 1H), 7.21 (t, J = 8.1 Hz, 2H), 6.76 (d, J = 6.4 Hz, 1H), 6.09 (s, 1H), 4.92 (s, 2H).
ES MS M+1 = 303

The title compound was also prepared as follows:

To a cold (0 C) solution of 4-acetyl-1-(4-fluorobenzyl)-3,4-dihydro-pyrazin-2(1*H*)-one (0.41 g, 1.65 mmol; Example 2, Step 3) in anhydrous DMF (16 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (3.3 mL, 3.3 mmol) was added and stirred at that temperature for 15 min. The resultant solution was treated with N,N'-dimethyloxy-N,N'-dimethyloxalamide (0.29 g, 1.65 mmol; *J. Org. Chem.* 1995, p. 5016) in one portion, allowed to warm to, and stirred at room temperature overnight. After 16 hrs. the resultant mixture was treated with additional lithium bis(trimethylsilyl)amide in THF (1.6 mL, 1.6 mmol) and stirred at room temperature for 1 h. The product mixture was concentrated under vacuum, and the dark brown residue was stirred in a mixture of 1M aqueous hydrochloric acid (75 mL) in ice for 15 min. The dark brown solid formed was isolated by filtration and air dried. The dried solid was washed with diethyl ether 2 times, air dried, then dried under vacuum to afford the crude product which was used without further purification in the preparation of the compound of Example 25.

EXAMPLE 15

2-Benzyl-8,9-dihydroxy-2H-pyrido[1,2-a]pyrazine-1,6-dione

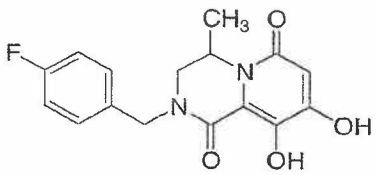


The title compound was prepared using procedures similar to that described in Examples 2 and 14, except that N-(2,2-dimethoxyethyl)-N-(4-fluoro-benzyl)amine (Example 2, Step 2) was substituted with N-benzylaminoacetaldehyde diethyl acetal.

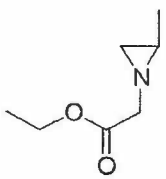
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.95 (s, 1H), 10.56 (br s, 1H), 7.52 (d, J = 6.6 Hz, 1H), 7.4 - 7.3 (m, 5H), 6.33 (s, 1H), 6.22 (d, J = 6.6 Hz, 1H), 4.92 (s, 2H).
ES MS M+1 = 285

EXAMPLE 16

2-(4-Fluorobenzyl)-8,9-dihydroxy-4-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



Step 1: Ethyl (2-methylaziridin-1-yl)acetate

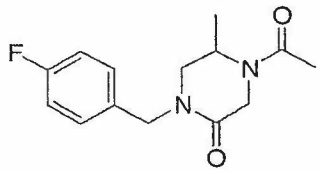


To a cold (-78 °C) solution of 2-methylaziridine (5.6 g, 99 mmol) and N,N-diisopropylethylamine (18.8 mL, 108 mmol) in dichloromethane (250 mL) under an atmosphere of nitrogen, ethyl bromoacetate (10 mL, 90 mmol) was added over a period of 1 h. The resultant mixture was allowed to slowly warm up and stirred at room temperature overnight. The resultant mixture was concentrated under vacuum, and the residue was suspended in chloroform. A stream of anhydrous ammonia gas was bubbled into the mixture with stirring for a period of 15 min. The resultant suspension was filtered, and the filtrate concentrated under vacuum. The residue was further treated with anhydrous diethyl ether and the milky solution filtered through a pad of Celite. The filtrate was concentrated under vacuum, and the residue subjected to distillation under reduced pressure (bp ~60 °C, 18 torr) to provide the title compound as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, J = 7.1 Hz, 2H), 3.13 (d, J = 16.1 Hz, 1H), 3.00 (d, J = 16.1 Hz, 1H), 1.64 (d, J = 3.7 Hz, 1H), 1.47 (m, 1H), 1.33 (d, J = 6.2 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.23 (d, J = 5.5 Hz, 3 H).

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Step 2: 4-Acetyl-1-(4-fluorobenzyl)-5-methylpiperazin-2-one



A mixture of ethyl (2-methylaziridin-1-yl)acetate (4.0 g, 28 mmol), 4-fluorobenzylamine (5.3 g, 42 mmol), and boron trifluoride etherate (0.5 mL) was heated in a sealed stainless steel vessel inside a Teflon liner at 95 °C for 60 h (*Bull. Chem. Soc. Jpn.* 1986, 59: 321). The resulting mixture was dissolved in dichloromethane (50 mL), cooled to 0 °C , and treated with a mixture of triethylamine (13 mL, 95 mmol) and acetic anhydride (6.7 mL, 71 mmol). The reaction mixture was stirred at room temperature overnight, and extracted successively with saturated aqueous solution of sodium bicarbonate, dilute aqueous HCl, and brine. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a mixture of 7 - 10 % methanol in ethyl acetate. Collection and concentration of appropriate fractions provided the title piperazinone.
ES MS M+1 = 265

Step 3: 2-(4-Fluorobenzyl)-8,9-dihydroxy-4-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

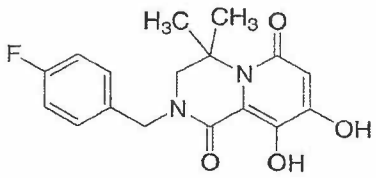
The title compound was prepared using a procedure similar to that described in Example 1 (Step 3), except that 4-acetyl-1-benzylpiperazin-2-one was substituted with 4-acetyl-1-(4-fluorobenzyl)-5-methylpiperazin-2-one. After the product solution was concentrated, the residue was treated with a mixture of dichloromethane and aqueous HCl. The chalky organic extract was isolated and concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.41 (s, 1H), 11.04 (br s, 1H), 7.43 (dd, J = 8.6, 5.7 Hz, 2H), 7.21 (t, J = 8.6 Hz, 2H), 5.92 (s, 1H), 4.83 (d, J = 14.5 Hz, 2H), 4.50 (d, J = 14.5 Hz, 1H), 3.74 (dd, J = 13.2, 4.0 Hz, 1H), 3.35 (d, J = 14.5 Hz, 1H), 0.98 (d, J = 6.0 Hz, 3H).

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ES MS M+1 = 319

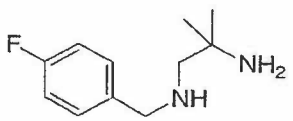
EXAMPLE 17

2-(4-Fluorobenzyl)-8,9-dihydroxy-4,4-dimethyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



Step 1: N^1-(4-Fluorobenzyl)-2-methylpropane-1,2-diamine

A mixture of 4-fluorobenzaldehyde (3.1 g, 25 mmol), 1,2-diamino-2-

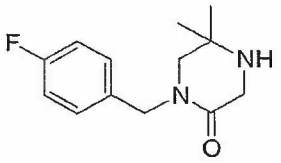


methylpropane (2.2 g, 25 mmol), and a few drop of acetic acid in absolute ethanol (150 mL) was stirred at room temperature overnight. The resultant mixture was cooled to 0 °C, and treated with sodium borohydride to provide predominately a major mono alkylation product. The reaction mixture was quenched with trifluoroacetic acid, and concentrated under vacuum. The residue was dissolved in methanol and subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the TFA salt of the title compound. This was converted to the corresponding HCl salt by addition of HCl in diethyl ether and concentration under vacuum. The reaction is regioselective and the regiochemistry of the product was confirmed with NOE experiments on the bis HCl salt.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (br s, 2H), 8.67 (br s, 3H), 7.72 (dd, J = 8.4, 5.9 Hz, 2H), 7.29 (t, J = 8.8 Hz, 2H), 4.20 (s, 2H), 3.17 (s, 2H), 1.39(s, 6H).

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Step 2: 1-(4-Fluorobenzyl)-5,5-dimethylpiperazin-2-one



A mixture of N^1-(4-fluorobenzyl)-2-methylpropane-1,2-diamine bis hydrochloride salt (0.6 g, 2.23 mmol), N,N-diisopropylethylamine (2 mL, 11.5 mmol), and methyl bromoacetate (0.5 mL, 5.3 mmol) in dichloromethane (20 mL) was stirred at room temperature overnight to provide selectively a major alkylation/cyclization product (LC-MS). The resultant mixture was concentrated under vacuum, treated with a saturated solution of ammonia in chloroform, and filtered through a pad of Celite. The filtrate was concentrated and the residue was dissolved in methanol and subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the TFA salt of the title compound. This was converted to the corresponding HCl salt by addition of HCl in diethyl ether and concentration under vacuum. The reaction is regioselective and the regiochemistry assigned is substantiated with subsequent successful acetylation.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (br s, 2H), 7.34 (dd, J = 8.4, 5.9 Hz, 2H), 7.19 (t, J = 8.8 Hz, 2H), 4.55 (s, 2H), 3.85 (s, 2H), 3.34 (s, 2H), 1.31(s, 6H).
ES MS M+1 = 237

Step 3: 2-(4-Fluorobenzyl)-8,9-dihydroxy-4-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

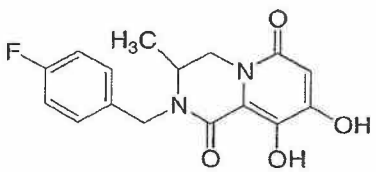
The title compound was prepared using a procedure similar to that described in Example 1 (Step 2-3), except that 1-benzylpiperazin-2-one (Step 2) was substituted with 1-(4-fluorobenzyl)-5,5-dimethylpiperazin-2-one dihydrochloride salt. After the product solution was concentrated, the residue was treated with a mixture of dichloromethane and aqueous HCl. The chalky organic extract was isolated and concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

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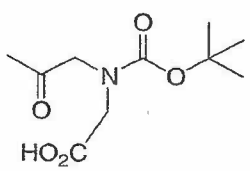
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 10.95 (br s, 1H), 7.43 (dd, J = 8.6, 5.7 Hz, 2H), 7.20 (t, J = 8.6 Hz, 2H), 5.82 (s, 1H), 4.64 (s, 2H), 3.23 (s, 2H), 1.45 (s, 2H).
ES MS M+1 = 333

EXAMPLE 18

2-(4-Fluorobenzyl)-8,9-dihydroxy-3-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



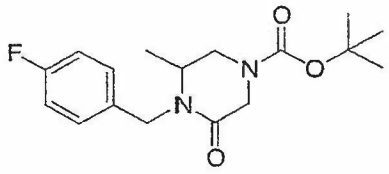
Step 1: N-[(tert-Butoxy)carbonyl]-N-(2-oxopropyl)glycine



To a cold (0 °C) solution of N-[(tert-butoxy)carbonyl]-N-[(methoxy)-(methyl)carbamoylmethyl]glycine (1.0 g, 3.6 mmol; *Helvetica Chimica Acta* 2000, 83: 1825), in anhydrous THF (30 mL) under an atmosphere of nitrogen, a solution of methyl magnesium bromide in ether (2.6 mL, 3M, 7.8 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, cooled back to 0 °C, quenched with aqueous HCl, and diluted with ether. The organic extract was washed with brine (pH adjusted to ~4-5 with addition of aqueous sodium hydroxide), dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide the title compound.
^{1}H NMR (400 MHz, DMSO-d_6) ~1:1 mixture of rotomers δ 4.06 (s, 1H), 4.03 (s, 1H), 3.88 (s, 1H), 3.84 (s, 1H), 2.05 (s, 3H), 1.36 (s, 9/2H), 1.33 (s, 9/2H).

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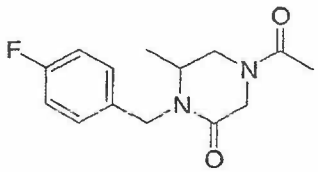
Step 2: 4-[(tert-Butoxy)carbonyl]-1-(4-fluorobenzyl)-6-methylpiperazin-2-one



A mixture of N-[(tert-butoxy)carbonyl]-N-(2-oxopropyl)glycine (0.66 g, 2.87 mmol), 4-fluorobenzylamine (0.23 g, 1.87 mmol) in dichloroethane (14 mL) was stirred at room temperature for one hour. Sodium triacetoxyborohydride (0.79 g, 3.73 mmol) was added and the reaction mixture stirred at room temperature overnight. The resultant mixture was concentrated under vacuum. The residue was dissolved in DMF (12 mL), treated with EDC (0.55 g), and stirred at room temperature overnight. The resultant mixture was concentrated under vacuum. The residue was partitioned between ethyl acetate and dilute aqueous HCl. The organic extract was washed with brine (to pH 7), dried over anhydrous magnesium sulfate, filtered, and concentrated to provide the title compound.

ES MS M+1 = 323

Step 3: 4-Acetyl-1-(4-fluorobenzyl)-6-methylpiperazin-2-one



A steady stream of anhydrous HCl gas was bubbled through a cold (0 °C) solution of 4-[(tert-butoxy)carbonyl]-1-(4-fluorobenzyl)-6-methylpiperazin-2-one (0.62 g, 1.9 mmol) in ethyl acetate (20 mL) for 5 minutes. The resultant mixture was capped and stirred at the same temperature for 1 h. The product mixture was concentrated under vacuum. The residue was treated with a mixture of N,N-diisopropylethylamine (1.00 mL, 5.8 mmol), DMAP (5 mg), and acetic anhydride (0.22 mL, 2.3 mmol) in methylene chloride (10 mL). The resultant mixture was concentrated and the residue was subjected to column chromatography on silica gel eluting with a mixture of 10% methanol in ethyl acetate. Collection and concentration of appropriate fractions provided the title piperazinone.

^{1}H NMR (400 MHz, $CDCl_3$) ~2:1 mixture of rotomers δ 7.72 (dd, J = 8.4, 5.9 Hz, 2H), 7.29 (t, J = 8.8 Hz, 2H), ... 2.14 (s, 2H), 2.11 (s, 1H), .1.24 (d, J = 6.8 Hz, 1H), 1.19 (d, J = 6.8 Hz, 2H).

ES MS M+1 = 265

Step 3: 2-(4-Fluorobenzyl)-8,9-dihydroxy-4-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

The title compound was prepared using a procedure similar to that described in Example 2 (Step 5), except that 4-acctyl-1-(4-fluorobenzyl)piperazin-2-one was substituted with 4-acetyl-1-(4-fluorobenzyl)-6-methylpiperazin-2-one. After the product solution was concentrated, the residue was treated with a mixture of dichloromethane and aqueous HCl. The chalky organic extract was isolated and concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

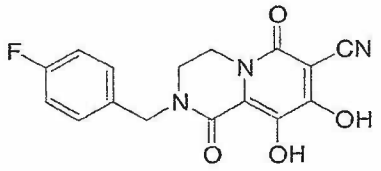
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 10.10 (br s, 1H), 7.43 (dd, J = 8.6, 5.7 Hz, 2H), 7.20 (t, J = 8.6 Hz, 2H), 5.94 (s, 1H), 4.98 (d, J = 15.0 Hz, 1H), 4.40 (d, J = 15.0 Hz, 2H), 3.85 (m, 1H), 3.49 (dd, J = 14, 3.8 Hz, 1H), 1.08 (d, J = 6.6 Hz, 3H).

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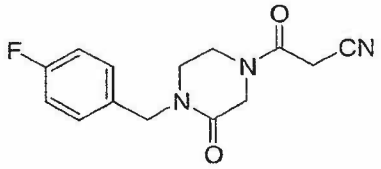
ES MS M+1 = 319

EXAMPLE 19

2-(4-Fluorobenzyl)-8,9-dihydroxy-1,6-dioxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-a]-pyrazine-7-carbonitrile



Step 1: 3-[4-(4-Fluorobenzyl)-3-oxopiperazin-1-yl]-3-oxopropanenitrile



To a solution of 1-(4-fluorobenzyl)piperazin-2-one (1.99 g, 9.6 mmol), cyanoacetic acid (0.82 g, 9.6 mmol), EDC (2.02 g, 10.5 mmol), and HOBt (0.15 g, 0.96 mmol) in anhydrous DMF (40 mL), N,N-diisopropylethylamine was added until the solution is about pH 6. The reaction mixture was stirred at room temperature overnight and concentrated under vacuum. The residue was partitioned between chloroform and water. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide the title compound. The residue was subjected to column chromatography on silica gel eluting with a mixture of 9:1:0.1 mixture of chloroform, methanol, and aq ammonium hydroxide. Collection and concentration of appropriate fractions provided the title product. Residual protic solvent was removed by co-evaporation with benzene (3X).
ES MS M-OCH_3 = 276

Step 2: 2-(4-Fluorobenzyl)-8,9-dihydroxy-1,6-dioxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-a]-pyrazine-7-carbonitrile

The title compound was prepared using a procedure similar to that described in Example 2 (Step 5), except that 4-acetyl-1-(4-fluorobenzyl)piperazin-2-

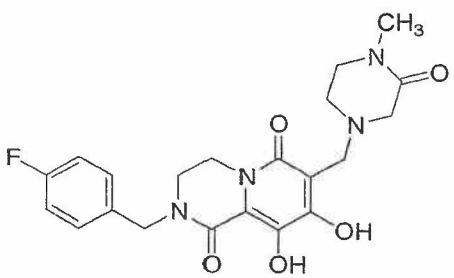
one was substituted with 3-[4-(4-fluorobenzyl)-3-oxopiperazin-1-yl]-3-oxopropanenitrile. After the product solution was concentrated, the residue was treated with a mixture of dichloromethane and aqueous HCl. The chalky organic extract was isolated and concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 10.10 (br s, 1H), 7.43 (dd, J = 8.6, 5.7 Hz, 2H), 7.20 (t, J = 8.6 Hz, 2H), 4.68 (s, 2H),. 3.97 (t, J = 5.3 Hz, 2H), 3.56 (t, J = 5.3 Hz, 2H).

ES MS M+1 = 330

EXAMPLE 20

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-[(4-methyl-3-oxopiperazin-1-yl)methyl]-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



The title compound was prepared using a procedure similar to that described in Example 11, except that piperidine was substituted with 4-methyl-3-oxopiperazine.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.63 (s, 1H), 11.90 (br s, 1H), 7.41 (dd, J = 6.0, 8.4 Hz, 2H), 7.21 (t, J = 8.8 Hz, 2H), 4.72 (s, 2H), 4.19 (br s, 2H), 4.07 (t, J = 5.1 Hz, 2H), 3.78 (br s, 2H), 3.63 (t, J = 5.1 Hz, 2H), 2.84 (s, 3H).

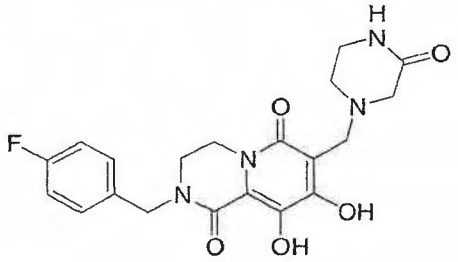
ES MS M+1 = 545

EXAMPLE 21

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-[(3-oxopiperazin-1-yl)methyl]-3,4-dihydro-2H-pyrido[1,2-

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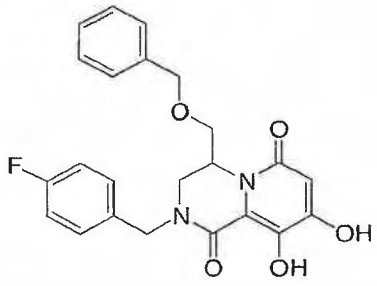
a]pyrazine-1,6-dione



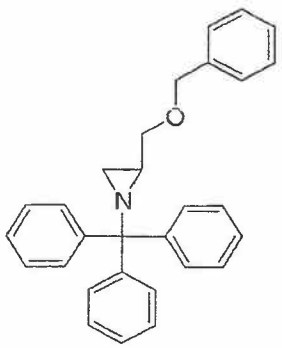
The title compound was prepared using a procedure similar to that described in Example 11, except that piperidine was substituted with 2-oxopiperazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 11.92 (br s, 1H), 8.32 (s, 1H), 7.41 (dd, J = 6.0, 8.4 Hz, 2H), 7.21 (t, J = 8.8 Hz, 2H), 4.71 (s, 2H), 4.21 (br s, 2H), 4.07 (t, J = 5.1 Hz, 2H), 3.74(br s, 2H), 3.62 (t, J = 5.1 Hz, 2H), 3.37 (br s, 2H).
ES MS M+1 = 530

EXAMPLE 22

4-[(Benzyloxy)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



Step 1: 2-[(Benzyloxy)methyl]-1-tritylaziridine

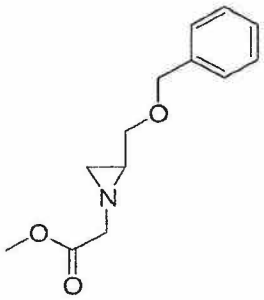


To a cold (0 °C) solution of lithium aluminum hydride in diethyl ether (1 M, 15 mL, 15 mmol) under an atmosphere of nitrogen, a solution of methyl 1-trityl-2-aziridinecarboxylate (5.04 g, 14.7 mmol) in anhydrous ether (60 mL) was added over a period of 0.5 h. The resultant mixture was allowed to slowly warm up and stirred at room temperature for 1 hour. The resultant mixture was cooled back to 0 °C and treated successively with water (0.57 mL) over a period of 10 minutes, followed by addition of 15% aq NaOH (0.57 mL), and water (1.7 mL). The resultant suspension was filtered through a pad of Celite. The filtrate was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was treated with a mixture of ether (40 mL) and hexane (200 mL) with cooling. The precipitate was collected by filtration to provide (1-tritylaziridin-2-yl)methanol as white solid. Without further purification, the alcohol (1.0 g, 3.17 mmol) was added portionwise to a suspension of sodium hydride (60% dispersion in mineral oil, 0.24 g, 6.0 mmol). To the resultant mixture, terta-n-butylammonium iodide (50 mg, 0.14 mmol) and benzyl bromide (0.65 g, 3.8 mmol) were added. The reaction mixture was stirred at room temperature overnight and treated with water (20 mL). The organic extract was diluted with ether, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a mixture of 5 % ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.18 (m, 20 H), 4.52 (s, 2H), 3.86 (dd, J = 10.1, 5.1 Hz, 1H), 3.52 (dd, J = 10.1, 5.9 Hz, 1H), 1.72 (d, J = 3 Hz, 1H), 1.54 (m, overlap with H_2O signal), 1.18 (d, J = 5.9 Hz, 1H).

ES MS M+1 = 406

Step 2: Methyl {2-[(benzyloxy)methyl]aziridin-1-yl}acetate



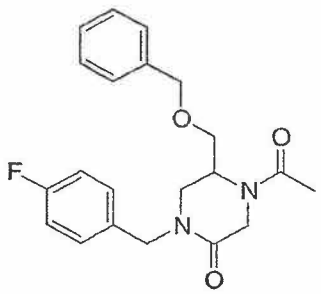
To a cold (0 °C) solution of 2-[(benzyloxy)methyl]-1-tritylaziridine (1.28 g, 3.16 mmol) in dichloromethane (13 mL), trifluoroacetic acid (1 mL) and triethylsilane (2.0 mL) was added and stirred at the temperature for 1 h. The resultant mixture was concentrated under vacuum, and the residue was partitioned between ether and brine. The organic extract was dried with anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a mixture of 50-100 % THF in hexane. Collection and concentration of appropriate fractions provided 2-[(benzyloxy)methyl]aziridine.

To a cold (-78 °C) solution of 2-[(benzyloxy)methyl]aziridine (0.42 g, 2.57 mmol) and N,N-diisopropylethylamine (0.5 mL, 2.90 mmol) in dichloromethane (15 mL) under an atmosphere of nitrogen, ethyl bromoacetate (0.39, 2.5 mmol) was added over a period of 1 h. The resultant mixture was allowed to slowly warm up to room temperature and stirred overnight. The resultant mixture was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a mixture of 70 % ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.26 (m, 5 H), 4.59 (d, J = 11.9 Hz, 1H), 4.53 (d, J = 11.9 Hz, 1H), 3.74 (s, 3H), 3.52 (m, 2H), 3.25 (d, J = 16.1 Hz, 1H), 2.98 (d, J = 16.1 Hz, 1H), 1.83(d, J = 3.6 Hz, 1H), 1.79 (m, 1H), 1.43 (d, J = 6.4 Hz, 1H).

ES MS M+1 = 236

Step 3: 4-Acetyl-5-[(benzyloxy)methyl]-1-(4-fluorobenzyl)piperazin-2-one



A mixture of methyl {2-[(benzyloxy)methyl]aziridin-1-yl}acetate (0.4 g, 1.7 mmol), 4-fluorobenzylamine (0.38 g, 3.3 mmol), and boron trifluoride etherate (50 μL) was heated in a sealed glass tube at 95 °C for 68 h (Bull. Chem. Soc. Jpn., **1986**, *59*, 321). The resulting mixture was dissolved in dichloromethane (50 mL), cooled to 0 °C, and treated with a mixture of triethylamine (0.95 mL, 6.8 mmol), DMAP (21 mg, 0.17 mmol), and acetic anhydride (0.48 mL, 5.1 mmol). The mixture was stirred at room temperature overnight, and extracted successively with saturated aqueous solution of sodium bicarbonate, dilute aqueous HCl, and brine. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a mixture of 2% methanol in ethyl acetate. Collection and concentration of appropriate fractions provided the title piperazinone.
ES MS M+1 = 371

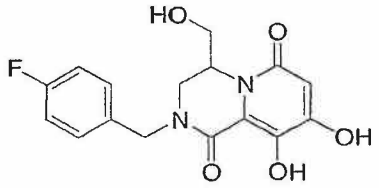
Step 4: 4-[(Benzyloxy)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

The title compound was prepared using a procedure similar to that described in Example 1 (Step 3), except that 4-acetyl-1-benzylpiperazin-2-one was substituted with 4-acetyl-5-[(benzyloxy)methyl]-1-(4-fluorobenzyl)piperazin-2-one.
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.50 (s, 1H), 8.20 (br s, 1H), 7.33-6.99 (m, 9H), 6.14 (s, 1H), 5.09 (m, 1H), 4.75 (d, J = 14.6 Hz, 2H), 4.47 (d, J = 14.6 Hz, 1H), 4.37 (d, J = 11.7, Hz, 1H), 4.25 (d, J = 11.7 Hz, 1H), 3.73 (d, J = 13.2 Hz, 1H), 3.66 (m, 1H), 3.49 (m, 2H), 3.35 (d, J = 9.3 Hz, 1H).
ES MS M+1 = 425

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EXAMPLE 23

4-(Hydroxymethyl)-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



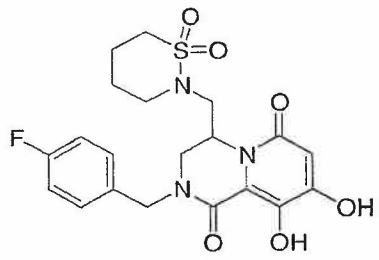
A mixture of 4-[(benzyloxy)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione (151 mg) and 5% Pd/C (57 mg) in ethanol (20 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature overnight. The product mixture was filtered through a pad of Celite, and concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 1H), 11.10 (s, 1H), 7.41 (dd, J = 5.6, 8.6 Hz, 2H), 7.21 (t, J = 9.0 Hz, 2H), 5.93 (s, 1H), 5.11 (t, J = 5.7 Hz, 1H), 4.72-4.60 (m, 2H), 3.69 (br s, 2H).

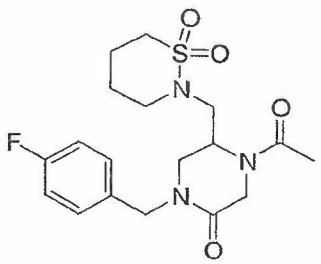
ES MS M+1 = 335

EXAMPLE 24

4-[(1,1-Dioxido-1,2-thiazinan-2-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



Step 1: 4-Acetyl-5-[(1,1-Dioxido-1,2-thiazinan-2-yl)methyl]-1-(4-fluorobenzyl)-piperazin-2-one



A mixture of 4-acetyl-5-[(benzyloxy)methyl]-1-(4-fluorobenzyl)piperazin-2-one (6.5 g) and 20% Pd/C (1.4 g) in ethanol (175 mL) was shaken under an atmosphere of hydrogen (60 psi) at room temperature overnight. The product mixture was filtered through a pad of Celite, and concentrated under vacuum. Residual ethanol was removed by co-evaporation with toluene under vacuum (3X). The resultant alcohol was used without further purification. A mixture of the alcohol (1.0 g, 3.57 mmol), 1,2-thiazinane 1,1-dioxide (0.73, 5.4 mmol), and cyanomethylenetri-n-butylphosphorane (1.3 g, 5.4 mmol; [157141-27-0]) in benzene (20 mL) was purged with nitrogen and heated in a sealed tube at 100 °C overnight. The reaction mixture was concentrated under vacuum, and the residue was subjected to column chromatography on silica gel eluting with a mixture of 5% methanol in ethyl acetate. Collection and concentration of appropriate fractions provided the title compound.

High Resolution FT-ICR M+H = 398.1556; $C_{18}H_{24}FN_3O_4S$ + H calculated 398.1545.

Step 2: 4-[(1,1-dioxido-1,2-thiazinan-2-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

To a cold (0 °C) solution of 4-acetyl-5-[(1,1-dioxido-1,2-thiazinan-2-yl)methyl]-1-(4-fluorobenzyl)-piperazin-2-one (75 mg, 0.19 mmol) and diethyl oxalate (29 µL, 0.21 mmol) in DMF (3 mL) under an atmosphere of nitrogen, a solution of sodium bis(trimethylsilyl)amide in THF (1M, 0.21 mL, 0.21 mmol) was added over a period of 0.5 h and stirred at the temperature for 30 min. Then additional sodium bis(trimethylsilyl)amide in THF (1M, 0.21 mL, 0.21 mmol) was added over a period of 0.5 h and stirred at the temperature for 1 h. The product mixture was concentrated under vacuum, and the residue partitioned between aqueous

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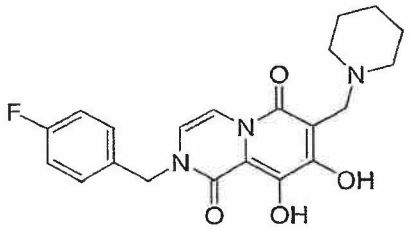
HCl and ethyl acetate. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.39 (s, 1H), 11.16 (s, 1H), 7.40 (dd, J = 8.3, 5.8 Hz, 2H), 7.20 (t, J = 8.3 Hz, 2H), 5.93 (s, 1H), 5.07 (d, J = 14.6 Hz, 1H), 4.82 (m, 1H), 4.25 (d, J = 14.6 Hz, 1H), 3.68 (dd, J = 13.4, 4.4 Hz, 1H), 3.56 (d, J = 13.5, Hz, 1H), 3.4-2.9 (m), 1.98 (m, 2H), 1.49 (m, 2H).

High Resolution FT-ICR M+H = 452.1284; $C_{20}H_{23}FN_3O_6S$ + H calculated 452.1286.

EXAMPLE 25

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-(piperidin-1-ylmethyl)-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



The title compound was prepared using a procedure similar to that described in Example 11, except that 2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione was substituted with 2-(4-fluorobenzyl)-8,9-dihydroxy-2H-pyrido[1,2-*a*]pyrazine-1,6-dione (Example 14).

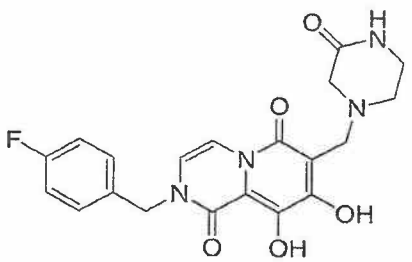
^{1}H NMR (500 MHz, DMSO-d_6) δ 12.00 (br s, 1H), 9.08 (br s, 1H), 7.50 (d, J = 6.3 Hz, 1H), 7.45 (dd, J = 8.4, 5.7 Hz, 2H), 7.22 (t, J = 8.7 Hz, 2H), 6.89 (d, J = 6.3 Hz, 1H), 4.97 (s, 2H), 4.15 (s, 2H), 3.6 – 2.9 (br m), 1.8 – 1.4 (br m).

HRMS FT-ICR m/z obsd 400.1655, $C_{21}H_{22}FN_3O_4$ + H required 400.1667

EXAMPLE 26

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-[(3-oxopiperazin-1-yl)methyl]-2H-pyrido[1,2-a]pyrazine-

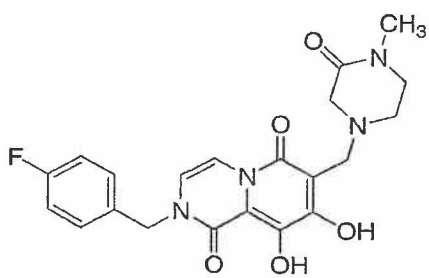
1,6-dione



The title compound was prepared using a procedure similar to that described in Example 25, except that piperidine was substituted with 3-oxopiperazine.
^{1}H NMR (500 MHz, DMSO-d_6) δ 12.00 (br s, 1H), 8.28 (s, 1H), 7.49 (d, J = 6.6 Hz, 1H), 7.45 (dd, J = 8.8, 5.4 Hz, 2H), 7.22 (t, J = 8.9 Hz, 2H), 6.89 (d, J = 6.6 Hz, 1H), 4.97 (s, 2H), 4.24 (s, 2H), 3.72 (s, 2H), 3.35 (br s, 4H).
HRMS FT-ICR m/z obsd 415.1406, $C_{20}H_{19}FN_4O_5$ + H required 415.1412.

EXAMPLE 27

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-[(4-methyl-3-oxopiperazin-1-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione

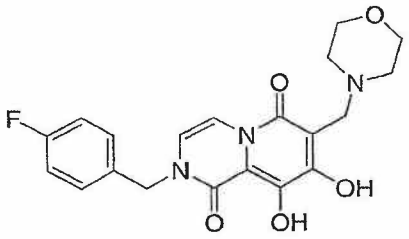


The title compound was prepared using a procedure similar to that described in Example 25, except that piperidine was substituted with 4-methyl-3-oxopiperazine.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (br s, 1H), 7.49 (d, J = 6.5 Hz, 1H), 7.45 (dd, J = 8.7, 5.6 Hz, 2H), 7.20 (t, J = 8.9 Hz, 2H), 6.88 (d, J = 6.6 Hz, 1H), 4.97 (s, 2H), 4.22 (s, 2H), 3.76 (s, 2H), 3.43(m, 4H), 2.83 (s, 3H).
HRMS FT-ICR m/z obsd 429.1562, $C_{21}H_{21}FN_4O_5$ + H required 429.1569.

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EXAMPLE 28

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-[(morpholin-4-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione

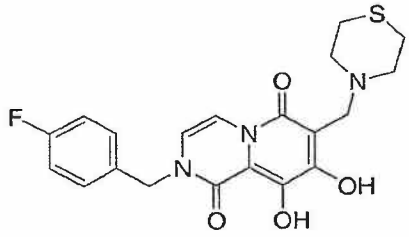


The title compound was prepared using a procedure similar to that described in Example 25, except that piperidine was substituted with morpholine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (br s, 1H), 7.47 (d, J = 6.5 Hz, 1H), 7.45 (dd, J = 8.4, 5.6 Hz, 2H), 7.22 (t, J = 8.8 Hz, 2H), 6.83 (d, J = 6.5 Hz, 1H), 4.96 (s, 2H), 4.19 (s, 2H), 3.79 (br s, 4H), 3.18(br s, 4H).

HRMS FT-ICR m/z obsd 402.1452, $C_{20}H_{20}FN_3O_5$ + H required 402.1460.

EXAMPLE 29

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-[(thiomorpholin-4-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione



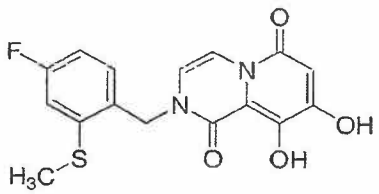
The title compound was prepared using a procedure similar to that described in Example 25, except that piperidine was substituted with thiomorpholine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (m, 3H), 7.22 (t, J = 8.8 Hz, 2H), 6.79 (d, J = 6.4 Hz, 1H), 4.94 (s, 2H), 4.16 (s, 2H), 3.35 (br s, 4H), 2.90(br s, 4H).

HRMS FT-ICR m/z obsd 418.1215, $C_{20}H_{20}FN_3O_4S$ + H required 418.1232.

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EXAMPLE 30

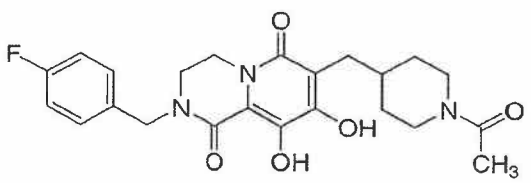
2-[4-Fluoro-2-(methylthio)benzyl)-8,9-dihydroxy-2H-pyrido[1,2-a]pyrazine-1,6-dione



The title compound was prepared using procedures similar to that described in Examples 2 and 14, except that 4-fluorobenzaldehyde was substituted with 4-fluoro-2-(methylthio)benzaldehyde in Step 1, Example 2.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 -12.3 (br signal, 2H), 7.39 (d, J = 6.5 Hz, 1H), 7.25 (dd, J = 8.4, 6.4 Hz, 1H), 7.18 (dd, J = 10.4, 2.4 Hz, 1H), 6.98 (br t, 1H), 6.53 (d, J =6.5 Hz, 1H), 6.10 (s, 1H), 4.89 (s, 2H), 2.54 (s, 3H).
HRMS FT-ICR m/z obsd 349.0656, $C_{16}H_{13}FN_2O_4S$ + H required 349.0653

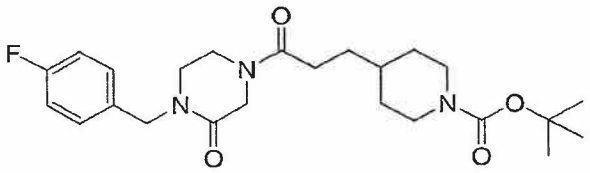
EXAMPLE 31

7-[(1-Acetylpiperidin-4-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione



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Step 1: *tert*-Butyl 4-{3-[4-(4-fluorobenzyl)-3-oxopiperazin-1-yl]-3-oxopropyl}piperidine-1-carboxylate

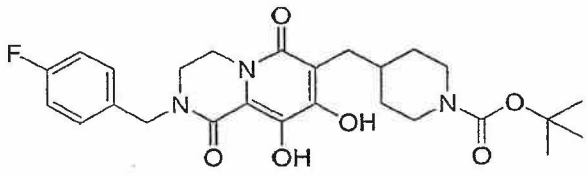


To a solution of 1-boc-piperidin-4-ylpropionic acid (1.20 g, 4.7 mmol, *Astatech*) in DMF (10 mL), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.16 g, 6.1 mmol) and 1-hydroxy-7-azabenzotriazole (0.83 g, 6.1 mmol) were added and the solution was stirred at room temperature for 30 min. To the resultant solution, a solution of 1-(4-fluorobenzyl)piperazin-2-one (1.07 g, 5.1 mmol, see Example 31, Steps 5 -8) in DMF (2 mL) was added and the mixture was stirred for two hours. The product mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (ISCO column, 120 g silica gel) eluting with a 0-6% MeOH/$CHCl_3$ gradient over 40 min. Collection and concentration of appropriate fractions provided the coupled product as a white solid.

^{1}H NMR (400 MHz, d_6 DMSO) δ 7.31 (m, 2H), 7.18 (m, 2H), 4.53 (s, 2H), 4.19 (s, 1H), 4.07 (s, 1H), 3.91 (m, 2H), 3.67 (m, 2H), 3.31 (m, 2H), 3.21 (m, 1H), 2.64 (m, 2H), 2.34 (m, 2H), 1.62 (m, 2H), 1.41 (m, 2H), 1.39 (s, 9H), and 0.95 (m, 2H).

ES MS M+1 = 448

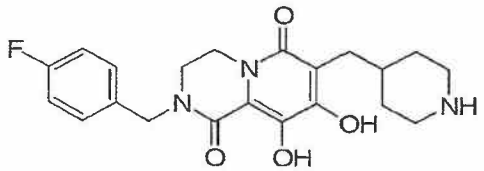
Step 2: *tert*-Butyl 4-{[2-(4-fluorobenzyl)-8,9-dihydroxy-1,6-dioxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-a]pyrazin-7-yl]methyl}piperidine-1-carboxylate



The title compound was prepared using a procedure similar to that described in Example 2 (Step 5) using *tert*-butyl 4-{3-[4-(4-fluorobenzyl)-3-oxo-piperazin-1-yl]-3-oxopropyl}piperidine-1-carboxylate (1.0 g, 2.23 mmol). The crude product was taken on as is to the next step.

ES MS M+1 = 402

Step 3: 2-(4-Fluorobenzyl)-8,9-dihydroxy-7-(piperidin-4-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione mono TFA salt



To a cold (0 °C) solution of *tert*-butyl 4-{[2-(4-fluorobenzyl)-8,9-dihydroxy-1,6-dioxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-a]pyrazin-7-yl]methyl}piperidine-1-carboxylate (1.12 g, 2.23 mmol) in methylene chloride (10 mL), trifluoroacetic acid (3.4 mL, 45 mmol) was added and the mixture was stirred for 2 hours. The mixture was concentrated *in vacuo* and the residue was purified by prep HPLC (Waters prep LC 4000 System using a Waters Nova Pak column [3*10x40 mm I.D. cartridges, C18, 6 μM pore size) eluting with 95-5% water (0.10% TFA) / acetonitrile (0.10% TFA) gradient at 60 mL/min]. Combined and concentrated the product fractions to give a yellow solid. The solids were triturated with acetonitrile and collected by vacuum filtration.

^{1}H NMR (400 MHz, d_6 DMSO) δ 12.61 (s, 1H), 10.42 (s, 1H), 8.41 (m, 1H), 8.10 (m, 1H), 7.40 (m, 2H), 7.20 (m, 2H), 4.68 (s, 2H), 4.02 (m, 2H), 3.57 (m, 2H), 3.22 (m, 2H), 2.80 (m, 2H), 2.43 (m, 2H), 1.84 (m, 1H), 1.67 (m, 2H), and 1.37 (m, 2H).

High Resolution FT-ICR $C_{21}H_{24}FN_3O_4$+H = 402.1833; calculated 402.1824.

Step 4: 7-[(1-Acetylpiperidin-4-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

To a suspension of 2-(4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-4-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione mono TFA salt (50 mg, 0.125 mmol) in anhydrous methylene chloride (2 mL), pyridine (12 μL, 0.149 mmol) and acetic anhydride (14 μL, 0.149 mmol) were added. The reaction mixture was

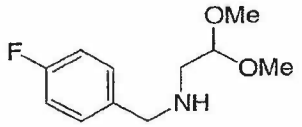
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stirred at room temperature overnight. The reaction mixture was concentrated under vacuum, and the residue was purified by prep HPLC (Gilson semi preparative HPLC system using a Waters Nova Pak column [10x40 mm I.D. cartridge, C18, 6 μM pore size) eluting with 95-5% water (0.10% TFA) / acetonitrile (0.10% TFA) gradient at 35 mL/min]. Collection and lyophilization of appropriate fractions provided he title compound as white solid.

^{1}H NMR (400 MHz, d_6 DMSO) δ 12.60 (s, 1H), 10.25 (br s, 1H), 7.40 (m, 2H), 7.20 (m, 2H), 4.68 (s, 2H), 4.28 (d, 1H, J = 12.9 Hz), 4.03 (m, 2H), 3.74 (d, 1H, J = 13.2 Hz), 3.58 (m, 2H), 2.91 (m, 1H), 2.42 (m, 3H), 1.96 (s, 3H), 1.79 (m, 1H), 1.53 (m, 2H), and 0.96-1.17 (m, 2H).

High Resolution FT-ICR $C_{23}H_{26}FN_3O_5$+H = 444.1929; calculated 444.1929.

Step 5: N-(2,2-Dimethoxyethyl)-N-(4-fluorobenzyl)amine



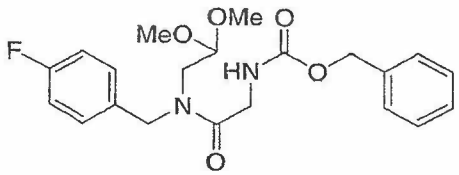
A mixture of 4-fluorobenzaldehyde (227.6 g, 1.83 mol) and dimethoxyethylamine (192.6 g, 1.83 mol) in methanol (2.5 L) was heated at 65 °C for 1.5 h. The solution was allowed to cool to room temperature overnight and treated with sodium borohydride (47.6 g 1.26 mol) in portions over a period of 2 h. The resultant mixture was stirred at room temperature for 3 h and quenched with water (1 L). The product mixture was concentrated to about 1 L and extracted with diethyl ether (3X). The ethereal extracts were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the title compound as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 5.5, 8.6 Hz, 2H), 7.00 (t, J = 6.8 Hz, 2H), 4.48 (t, J = 5.5 Hz, 1H), 3.77 (s, 2H), 3.37 (s, 6H), 2.73 (d, J = 5.5 Hz, 2H).

ES MS M+1 = 214

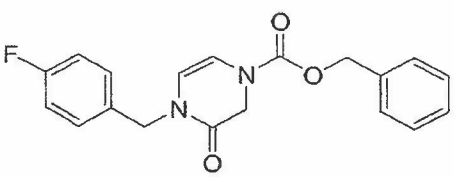
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Step 6: N^2-Benzyloxycarbonyl-N^1-(2,2-dimethoxyethyl)-N^1-(4-fluorobenzyl)-glycinamide



To a solution of N-(2,2-dimethoxyethyl)-N-(4-fluorobenzyl)amine (50.6 g, 237.3 mmol), N-CBZ-glycine (54.6 g, 260.8 mmol), EDC (50.0 g, 260.8 mmol), and HOBt (4.2 g, 27 mmol) in anhydrous DMF (500 mL), N,N-diisopropylethylamine (~10 mL) was added until the solution is about pH 7. The reaction mixture was stirred at room temperature overnight and concentrated under vacuum. The residue was partitioned between dichloromethane (1 L) and water (250 mL). The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the title compound. ES MS M-OCH_3 = 374

Step 7: 4-Benzyloxycarbonyl-1-(4-fluorobenzyl)-3,4-dihydropyrazin-2(1*H*)-one



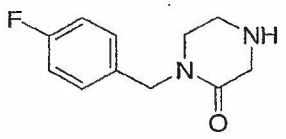
To a solution of N^2-benzyloxycarbonyl-N^1-(2,2-dimethoxyethyl)-N^1-(4-fluorobenzyl)glycinamide (61.5 g, 152 mmol) and p-toluenesulfonic acid monohydrate (3 g) in toluene (450 mL) was stirred at 75 °C for 5 days. Each day an additional 3 g of toluenesulfonic acids was added. The resultant reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated under vacuum, and the residue dissolved in dichloromethane. The organic solution was washed successively with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. To the residual solid was subjected to column chromatography on silica gel eluting with dichloromethane and then 5% ethyl acetate in dichloromethane. Appropriate fractions were collected and concentrated under vacuum. Residual ethyl acetate and

dichloromethane was removed by co-evaporation with toluene for 3 time for subsequent hydrogenation. The residue was triturated with hexane, and filtered to provide the cyclization product as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (br s, 5H), 7.23 (m, 2H), 7.02 (t, J = 8.6 Hz, 2H), 6.44 (d, J = 6.0 Hz, ½H), 6.32 (d, J = 6.0 Hz, ½H), 5.53 (d, J = 6.0 Hz, ½H), 5.42 (d, J = 6.0 Hz, ½H), 5.21 (s, 2H), 4.65 (s, 2H), 4.38 (s, 2H).

ES MS M+1 = 341

Step 8: 1-(4-Fluorobenzyl)piperazin-2-one



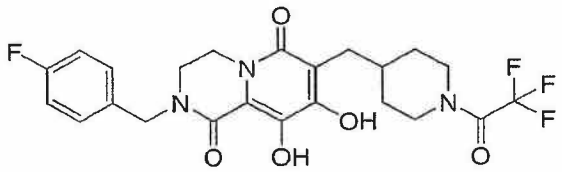
A mixture of 4-benzyloxycarbonyl-1-(4-fluorobenzyl)-3,4-dihydro-pyrazin-2(1*H*)-one (0.5 g, 14.5 mmol) and Pearlman's catalyst (26 mg; 20% palladium hydroxide on carbon) in methanol (25 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature overnight. The product mixture was filtered through a pad of Celite, and concentrated under vacuum to provide 1-(4-fluorobenzyl)piperazin-2-one.

^{1}H NMR (400 MHz, d_6 DMSO) δ 7.29 (dd, J = 8.4, 5.7 Hz, 2H), 7.16 (t, J = 9.0 Hz, 2H), 4.48 (s, 2H), 3.28 (s, 2H), 3.14 (t, J = 5.3 Hz, 2H) 2.84 (t, J = 5.3 Hz, 2H).

ES MS M+1 = 209

EXAMPLE 32

2-(4-Fluorobenzyl)-8,9-dihydroxy-7-{[1-(trifluoroacetyl)piperidin-4-yl]methyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione



To a solution of 2-(4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-4-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione mono TFA salt [50 mg, 0.125 mmol; Example 31 (Step 3)] in methylene chloride (2 mL), pyridine (12 μL, 0.149 mmol), trifluoroacetic anhydride (26 mg, 0.149 mmol) and a couple drops of

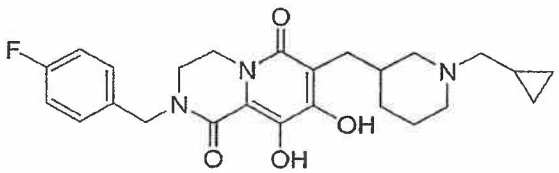
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DMF were added. After one hour, the reaction mixture was concentrated under vacuum, and the residue was purified by prep HPLC [Gilson semi preparative HPLC system using a Waters Nova Pak column (10x40 mm I.D. cartridge, C18, 6 μM pore size) eluting with 95-5% water (0.10% TFA) / acetonitrile (0.10% TFA) gradient at 35 mL/min]. The product fractions were collected and lyophilized to provide the title compound as a white solid.

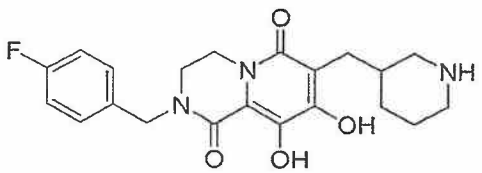
^{1}H NMR (400 MHz, d_6 DMSO) δ 12.59 (s, 1H), 10.33 (s, 1H), 7.42 (m, 2H), 7.20 (m, 2H), 4.69 (s, 2H), 4.23 (m, 1H), 4.03 (m, 2H), 3.82 (m, 1H), 3.57 (m, 2H), 3.17 (m, 1H), 2.83 (t, 1H, J = 12.3 Hz), 2.44 (m, 2H), 1.91 (m, 1H), 1.67 (m, 2H), and 1.17 (m, 2H). High Resolution FT-ICR $C_{23}H_{23}F_4N_3O_5$+H = 498.1655; calculated 498.1647.

EXAMPLE 33

7-{[1-(Cyclopropylmethyl)piperidin-3-yl]methyl}-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione mono TFA salt



Step 1: 2-(4-Fluorobenzyl)-8,9-dihydroxy-7-(piperidin-3-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione mono TFA salt



In a manner similar to that described in Example 31 (Step 1 to 3), the title compound was prepared as a white solid using 1-boc-piperidin-3-ylpropionic acid from *Astatech* in Step 1.

^{1}H NMR (400 MHz, d_6 DMSO) δ 12.61 (s, 1H), 10.54 (s, 1H), 8.49 (m, 1H), 8.18 (m, 1H), 7.40 (m, 2H), 7.20 (m, 2H), 4.69 (s, 2H), 4.02 (m, 2H), 3.57 (m, 2H), 3.17 (d, 1H, J = 12.0 Hz), 3.06 (d, 1H, J = 12.0 Hz), 2.79 (m, 1H), 2.61 (m, 1H), 2.43 (m, 2H), 1.98 (m, 1H), 1.67-1.78 (m, 2H), 1.52 (m, 1H), and 1.24 (m, 1H).

High Resolution FT-ICR $C_{21}H_{24}FN_3O_4$+H = 402.1834; calculated 402.1824.

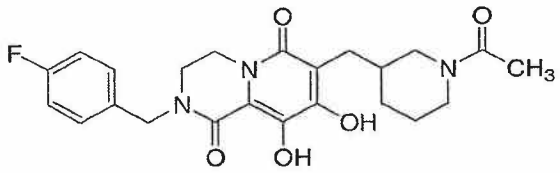
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Step 2: 7-{[1-(Cyclopropylmethyl)piperidin-3-yl]methyl}-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione mono TFA salt

To a solution of 2-(4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-3-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione mono TFA salt (50 mg, 0.097 mmol) in anhydrous methanol (2 mL) under nitrogen, cyclopropanecarboxaldehyde (9 μL, 0.116mmol) was added and the solution was stirred at room temperature for one hour. Sodium cyanoborohydride (8 mg, 0.129 mmol) was added and the solution was stirred for another hour. The reaction mixture was concentrated under vacuum and the residue was purified by prep HPLC [Gilson semi preparative HPLC system using a Waters Nova Pak column (10x40 mm I.D. cartridge, C18, 6 μM pore size) eluting with 95-5% water (0.10% TFA) / acetonitrile (0.10% TFA) gradient at 35 mL/min]. The product fractions were collected and lyophilized to provide the title compound as white solid.
^{1}H NMR (400 MHz, d_6 DMSO) δ 12.61 (s, 1H), 10.57 (s, 1H), 9.01 (br s, 1H), 7.41 (m, 2H), 7.20 (m, 2H), 4.69 (s, 2H), 4.02 (m, 2H), 3.58 (m, 2H), 3.49 (m, 1H), 3.32 (m, 1H), 2.80-2.99 (m, 3H), 2.68 (m, 1H), 2.38-2.47 (m, 2H), 2.09 (m, 1H), 1.83 (m, 1H), 1.57-1.70 (m, 2H), 1.17 (m,1H), 1.01 (m, 1H), 0.61 (m, 2H), and 0.33 (m, 2H).
High Resolution FT-ICR $C_{25}H_{30}FN_3O_4$+H = 456.2296; calculated 456.2293.

EXAMPLE 34

7-[(1-Acetylpiperidin-3-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

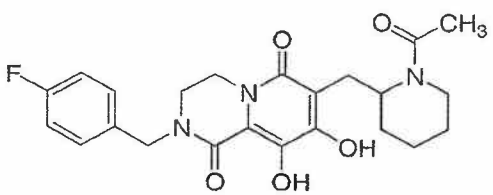


In a manner similar to that described in Example 31 (Step 4), the title compound was prepared as a white solid from 2-(4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-3-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione mono TFA salt from Example 33 (Step 1).
^{1}H NMR (400 MHz, d_6 DMSO) δ 12.61 (s, 1H), 10.33 (br s, 1H), 7.40 (m, 2H), 7.19 (m, 2H), 4.68 (s, 2H), 4.28 (m, 1H), 4.02 (m, 2H), 3.69 (m, 1H), 3.59 (m, 2H), 2.92

(m, 1H), 2.32-2.43 (m, 2H), 2.26 (m, 1H), 1.94 (s, 3H), 1.62-1.76 (m, 3H), and 1.13-1.32 (m, 2H). High Resolution FT-ICR $C_{23}H_{26}FN_3O_5$+H = 444.1911; calculated 444.1929.

EXAMPLE 35

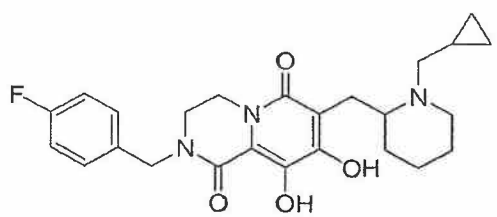
7-[(1-Acetylpiperidin-2-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione



In a manner similar to that described in Example 31 (Step 1 to 4), the title compound was prepared as white solid using 1-boc-piperidin-2-ylpropionic acid from *Astatech* instead of 1-boc-piperidin-3-ylpropionic acid in Step 1.
^{1}H NMR (400 MHz, d_6 DMSO) δ 12.59 (s, 1H), 10.59 (s, 1H), 7.41 (m, 2H), 7.19 (m, 2H), 4.68 (s, 2H), 4.23-4.31 (m, 2H), 4.02 (m, 2H), 3.56 (m, 2H), 2.91 (m, 1H), 2.67-2.78 (m, 2H), 1.95 (s, 3H), and 1.12-1.87 (m, 6H).
High Resolution FT-ICR $C_{23}H_{26}FN_3O_5$+H = 444.1912; calculated 444.1929.

EXAMPLE 36

7-{[1-(Cyclopropylmethyl)piperidin-2-yl]methyl}-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione mono TFA salt



In a manner similar to that described in Example 33, the title compound was prepared as white solid using 1-boc-piperidin-2-ylpropionic acid from *Astatech* in Step 1.

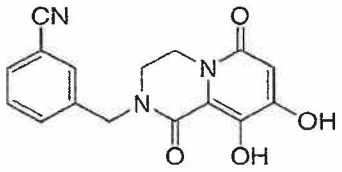
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^{1}H NMR (400 MHz, d_6 DMSO) δ 12.62 (s, 1H), 10.95 (d, 1H, J = 7.7 Hz), 9.22 (br s, 1H), 7.41 (m, 2H), 7.20 (m, 2H), 4.69 (s, 2H), 4.03 (m, 2H), 3.57 (m, 2H), 3.03-3.42 (m, 5H), 3.00 (m, 1H), 2.78 (m, 1H), 1.20-1.79 (m, 7H), 0.65 (m, 2H), and 0.42 (m, 2H).

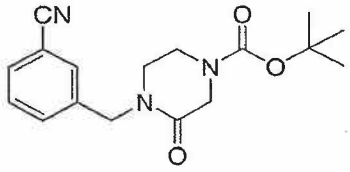
High Resolution FT-ICR $C_{25}H_{30}FN_3O_4$+H = 456.2291; calculated 456.2293.

EXAMPLE 37

2-(3-Cyanobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione



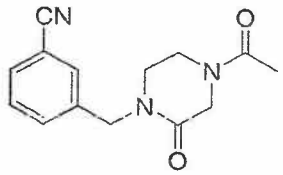
Step 1: *tert*-Butyl 4-(3-cyanobenzyl)-3-oxopiperazine-1-carboxylate



To a stirred solution of 4-Boc-2-piperazinone (2.0 g, 10 mmol), 3-cyanobenzyl bromide (1.8 g, 10 mmol) in DMF (35 mL) at 0 °C was added sodium hydride (480 mg of a 60% suspension in mineral oil, 12 mmol) in several portions over a period of 15 min. The mixture was stirred a 0 °C for1 h and then at ambient temperature for 1 h. Acetic acid (1 mL) was added and the solvent was removed in vacuo. The residue was partitioned between EtOAc and saturated aqueous sodium bicarbonate solution. The EtOAc layer was separated, dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. The residue was triturated in ether and the white solid was collected by filtration to give 1-(3-cyanobenzyl)-4-Boc-2-piperazinone (2.6 g).

LC-MS m/z = 316

Step 2: 3-[(4-Acetyl-2-oxopiperazin-1-yl)methyl]benzonitrile



To a stirred solution of 1-(3-cyanobenzyl)-4-Boc-2-piperazinone (2.5 g, 7.9 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added TFA (10 mL). The mixture was stirred at 0 °C for 2 h, then the solvents were removed *in vacuo*. The crude 1-(3-cyanobenzyl)-2-piperazinone TFA salt was partitioned between EtOAc (30 mL) and saturated aqueous sodium bicarbonate solution (30 mL). To the stirred two-phase mixture was added acetic anhydride (1.5 mL, 15 mmol) dropwise over a period of 5 min. The mixture was stirred at ambient temperature for 16 h. The EtOAc layer was separated, dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. The residue was purified on a silica gel column using a gradient mobile phase of 2%, 3%, 4% MeOH in CH_2Cl_2. 1-(3-cyanobenzyl)-4-acetyl-2-piperazinone was obtained as a solid.

^{1}H NMR ($CDCl_3$), 7.4-7.6 ppm (m, 3H), 4.65 (minor) and 4.63 (major) ppm (s, 2H), 4.34 (minor) and 4.23 (major) ppm (s, 2H), 3.81 (major) and 3.68 (minor) ppm (t, J = 7 Hz, 2H), 3.34 (minor) and 3.30 (major) ppm (t, J = 7 Hz, 2H), 2.13 ppm (s, 3H). LC-MS m/z = 258.

Step 3: 2-(3-Cyanobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

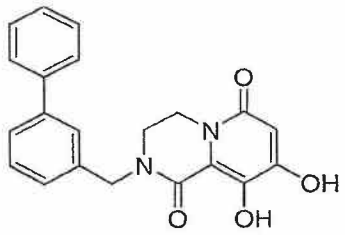
In a manner similar to that described in Example 1, Step 3, and 4-acetyl-1-benzylpiperazin-2-one was substituted with 3-[(4-acetyl-2-oxopiperazin-1-yl)methyl]benzonitrile, the title compound was prepared.

^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1H), 7.72-7.66 (m, 2H), 7.6-7.54 (t, 1H), 6.08 (s, 1H), 4.8 (s, 2H), 4.16-4.10 (m, 2H), 3.68-3.62 (m, 2H

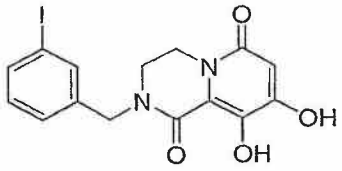
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EXAMPLE 38

2-(Biphenyl-3-ylmethyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione



Step 1: 8,9-Dihydroxy-2-(3-iodobenzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione



To a cold (0 °C) solution of 4-acetyl-1-(3-iodobenzyl)piperazin-2-one (0.22 g, 0.614 mmol) in DMF (5 mL) under an atmosphere of nitrogen, a solution of sodium bis(trimethylsilyl)amide in THF (1 M, 0.74mL, 0.74 mmol) was added and stirred at the temperature for 30 min. The resultant solution was treated with diethyl oxalate (16.7 mL, 123 mmol), and stirred at room temperature for 30 min. The resultant mixture was then treated with additional sodium bis(trimethylsilyl)amide in THF (1 M, 2.2 mL, 2.2 mmol) and stirred at room temperature overnight. The product mixture was concentrated under vacuum, and the residue treated with a mixture of aqueous HCl and ethyl acetate. The resultant precipitate was obtained by filtration to provide the title compound as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (m, 2H), 7.30 (d, J = 7.3 Hz, 1H), 7.15 (m, 1H), 4.99 (s, 1H), 4.59 (s, 2H), 3.83 (s, 2H), 3.34 (br s, 4H).

ES MS M+1 = 413

Step 2: 2-(1,1'-Biphenyl-3-ylmethyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

A solution of 8,9-dihydroxy-2-(3-iodobenzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (0.05 g, 0.121 mmol) in DMF (5 mL) was degassed for 5 minutes with nitrogen and placed under an atmosphere of nitrogen. To this was added phenyl boronic acid (0.015 g, 0.123 mmol), triethylamine (0.051mL, 0.364mmol), and bis(tri-*t*-butylphosphine)palladium(0) (0.003 g, 0,006 mmol) and heated with stirring at 110 °C overnight. The product mixture was concentrated under vacuum, and the residue was triturated with methylene chloride. The resultant precipitate was filtered off and the filtrate concentrated under vacuum. The filtrate residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Desired fractions were concentrated under vacuum to afford the title compound as off white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.6 (m, 4H), 7.42 (m, 3H), 7.32 (m, 2H), 6.07 (s, 1H), 4.84 (s, 2H), 4.09 (t, *J* = 5.8 Hz, 2H), 3.63 (t, *J* = 5.8 Hz, 2H).

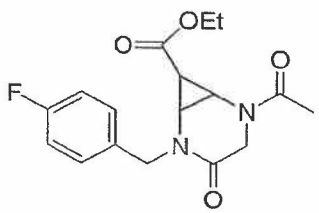
ES MS M+1 = 363

EXAMPLE 39

(±)-1-[(Benzyloxy)methyl]-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione

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Step 1: (±)-Ethyl 5-acetyl-2-(4-fluorobenzyl)-3-oxo-2,5-diazabicyclo[4.1.0]-heptane-7-carboxylate



To a suspension of 4-acetyl-1-(4-fluorobenzyl)-3,4-dihydropyrazin-2(1*H*)-one (5.0 g, 20.0 mmol; Example 2, Step 3) and copper bronze (320 mg, 5.0 mmol) in anhydrous toluene (50 mL) under nitrogen at 120 °C (oil bath) was added ethyl diazoacetate (6.4 mL, 60.0 mmol) via a syringe pump at a speed of 2.5 mL/h. After 3 h, TLC (eluted with ethyl acetate) showed no starting material left. The reaction mixture was cooled to room temperature, filtered and concentrated. The

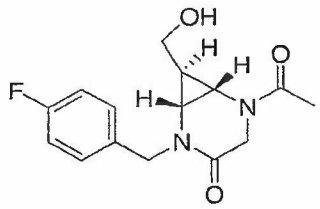
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residue was purified by column chromatography on silica gel using ethyl acetate and methanol as eluents to give both exo and endo diastereomers.

Exo diastereomer (Rf higher isomer):
^{1}H NMR (400 MHz, $CDCl_3$) ~6:1 mixture of rotomers δ 7.26-7.32 (m, 2H), 7.02-7.08 (m, 2H), 4.60-4.83 (m, 3H), 4.10-4.20 (m, 2H), 3.50-3.59 (m, 2H), 3.22-3.32 (m, 1H), 2.16 (s, .2.6H), 2.13 (s, 0.4H), 1.63-1.72 (m, 1H), 1.27 (q, J = 7.2 Hz, 3H).
ES MS M+1 = 335.3

Endo diastereomer (Rf lower isomer):
^{1}H NMR (400 MHz, $CDCl_3$) ~1:1 mixture of rotomers δ 7.30-7.35 (m, 2H), 7.04 (t, J = 8.6 Hz, 2H), 4.80-4.98 (m, 1.5H), 4.18-4.36 (m, 1.5H), 3.80-4.10 (m, 2.5H), 3.56-3.64 (m, 1.5H), 3.28-3.38 (m, 1H), 2.16 (s, .0.5H), 2.13 (s, 0.5H), 2.02-2.06 (m, 1H), 1.14-1.20 (m, 3H).
ES MS M+1 = 335.3

Step 2: (±)-5-Acetyl-2-(4-fluorobenzyl)-7-(hydroxymethyl)-2,5-diazabicyclo-[4.1.0]heptane-3-one

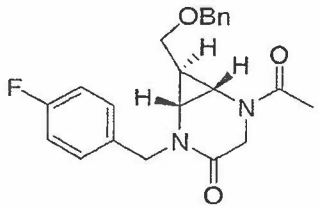


To a solution of the exo isomer of ethyl 5-acetyl-2-(4-fluorobenzyl)-3-oxo-2,5-diazabicyclo[4.1.0]heptane-7-carboxylate (3.3 g, 9.87 mmol) in 32 ml EtOH at room temperature was added sodium borohydride (398 mg, 10.5 mmol). After stirring overnight, the reaction mixture was treated with 200 mL MeOH, stirred for 1 h and then concentrated. The residue was dissolved in dichloromethane (100 mL), treated with 1N HCl (10 mL) and water (20 mL). The aqueous phase was back extracted with chloroform (2 x 50 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate and methanol as eluents to give title product.

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^{1}H NMR (400 MHz, $CDCl_3$) ~3:2 mixture of rotomers δ 7.26-7.35 (m, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 4.42-4.88 (m, 3H), 4.00-4.18 (m, 1H), 3.46-3.76 (m, 2.6H), 3.19 (dd, *J* = 10.0, 9.2 Hz, 0.4H), 3.07 (dd, *J* = 7.9, 3.7 Hz, 0.6H), 2.92 (dd, *J* = 7.9, 4.0 Hz, 0.4H), 2.72-2.80 (m, 1H), 2.21 (s, 1.8H), 2.12 (s, 1.2H), 1.16-1.22 (m, 1H).
ES MS M+1 = 293.3

Step 3: (±)-5-Acetyl-2-(4-fluorobenzyl)-7-[(benzyloxy)methyl]-2,5-diazabicyclo[4.1.0]heptane-3-one



To a solution of 5-acetyl-2-(4-fluorobenzyl)-7-(hydroxymethyl)-2,5-diazabicyclo[4.1.0]heptane-3-one (1.3 g, 4.45 mmol) in 40 mL anhydrous THF under nitrogen, sodium hydride (60% in mineral oil, 231 mg, 5.78 mmol) was added. After stirring for 1 h, benzyl bromide (0.58 ml, 4.89 mmol) in THF (1 mL) was added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted with chloroform three times. The combined organic phases were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel using hexanes and ethyl acetate as eluents to give the title product.

^{1}H NMR (400 MHz, $CDCl_3$) ~9:1 mixture of rotomers δ 7.22-7.40 (m, 7H), 6.99 (t, *J* = 8.6 Hz, 2H),), 4.94 (d, *J* = 14.1 Hz, 0.1H), 4.83 (d, *J* = 17.1 Hz, 0.9H), 4.74 (d, *J* = 14.3 Hz, 0.9H), 4.44-4.50 (m, 2.9H), 4.26 (d, *J* = 14.1 Hz, 0.1H), 4.08 (d, *J* = 16.5 Hz, 0.1H), 3.95 (d, *J* = 16.3 Hz, 0.1H), 3.78 (dd, *J* = 10.2, 4.7 Hz, 0.1H), 3.46 (d, *J* = 17.1 Hz, 0.9H), 3.37 (dd, *J* = 10.0, 5.8 Hz, 0.9H), 3.26 (dd, *J* = 10.0, 6.7 Hz, 0.9H), 3.13 (dd, *J* = 10.2, 7.8 Hz, 0.1H), 3.03 (dd, *J* = 7.9, 3.5 Hz, 1H), 2.71 (dd, *J* = 7.9, 3.6 Hz, 1H), 2.20 (s, .2.7H), 2.10 (s, 0.3H), 1.16-1.24 (m, 1H).
ES MS M+1 = 383.3

Step 4: (±)-1-[(Benzyloxy)methyl]-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclopropa[e]pyrido[1,2-a]pyrazine-3,7-dione

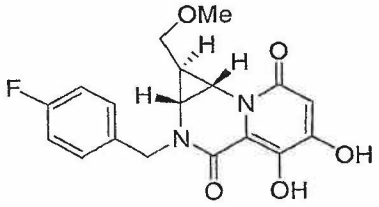
To a cold (0 °C) solution of 5-acetyl-2-(4-fluorobenzyl)-7-[(benzyloxy)-methyl]-2,5-diazabicyclo[4.1.0]heptane-3-one (700 mg, 1.83 mmol) in DMF (10 mL) under nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (1.0 M, 2.0 mL, 2.0 mmol) was added. After 30 min, diethyl oxalate (401 mg, 2.74 mmol) in DMF (2 mL) was added. After stirring for 1 h at room temperature, the resultant mixture was treated with additional lithium bis(trimethylsilyl)amide (1.0 M, 7.1 mL, 7.1 mmol), and stirred at room temperature overnight. The reaction mixture was treated with 1 N HCl, concentrated under vacuum. The residue was partitioned between brine and chloroform. The aqueous layer was extracted with chloroform twice. The combined organic phases were dried over sodium sulfate, filtered and concentrated. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (dd, J = 8.6, 5.5 Hz, 2H),), 7.26-7.36 (m, 5H), 7.02 (t, J = 8.7 Hz, 2H), 6.09 (s, 1H), 4.96 (d, J = 14.4 Hz, 1H), 4.69 (d, J = 14.5 Hz, 1H), 4.48 (s, 2H), 3.81 (dd, J = 8.8, 4.6 Hz, 1H), 3.57 (dd, J = 10.6, 5.3 Hz, 1H), 3.31-3.34 (m, 1H), 3.14 (dd, J = 8.8, 4.2 Hz, 1H), 1.20-1.25 (m, 1H).

ES MS M+1 = 437.2

EXAMPLE 40

(±)-1-(Methoxymethyl)-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclopropa[e]pyrido[1,2-a]pyrazine-3,7-dione

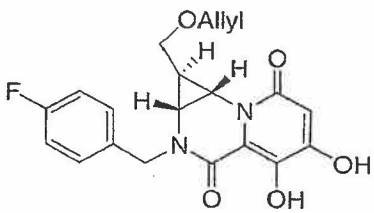


The title compound was prepared using a procedure similar to that described in Example 39, except that benzyl bromide was substituted with methyl iodide in Step 3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.6, 5.3 Hz, 2H),), 7.07 (t, J = 8.4 Hz, 2H), 6.25 (s, 1H), 4.81 (d, J = 14.3 Hz, 1H), 4.75 (d, J = 14.5 Hz, 1H), 3.87 (dd, J = 8.8, 4.4 Hz, 1H), 3.59 (dd, J = 10.6, 5.0 Hz, 1H), 3.31 (s, 3H), 3.18 (dd, J = 10.6, 7.1 Hz, 1H), 2.98 (dd, J = 8.7, 4.2 Hz, 1H), 1.12-1.18 (m, 1H).
ES MS M+1 = 361.2

EXAMPLE 41

(±)-1-[(Allyloxy)methyl]-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclopropa[e]pyrido[1,2-a]pyrazine-3,7-dione



The title compound was prepared using a procedure similar to that described in Example 39, except that benzyl bromide was substituted with allyl bromide in Step 3.

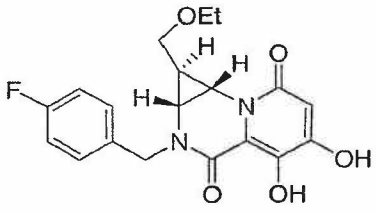
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.6, 5.1 Hz, 2H),), 7.06 (t, J = 8.6 Hz, 2H), 6.28 (s, 1H), 5.82-5.90 (m, 1H), 5.19-5.28 (m, 2H), 4.81 (d, J = 14.1 Hz, 1H), 4.75 (d, J = 14.1 Hz, 1H), 3.92-3.98 (m, 2H), 3.87 (dd, J = 8.6, 4.4 Hz, 1H), 3.70 (dd, J = 10.6, 4.7 Hz, 1H), 3.19 (dd, J = 10.6, 7.1 Hz, 1H), 2.99 (dd, J = 8.6, 4.0 Hz, 1H), 1.12-1.18 (m, 1H).
ES MS M+1 = 387.2

EXAMPLE 42

(±)-1-(Ethoxymethyl)-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-

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propa[e]pyrido[1,2-a]pyrazine-3,7-dione

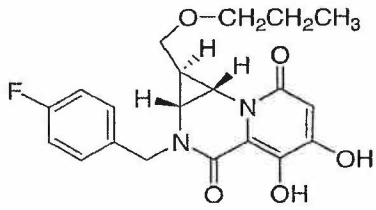


The title compound was prepared using a procedure similar to that described in Example 39, except that benzyl bromide was substituted with iodoethane in Step 3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.0 (s, 1H), 7.41 (dd, J = 8.0, 5.6 Hz, 2H),), 7.07 (t, J = 8.4 Hz, 2H), 6.26 (s, 1H), 4.81 (d, J = 14.3 Hz, 1H), 4.77 (d, J = 14.5 Hz, 1H), 3.86 (dd, J = 8.6, 4.4 Hz, 1H), 3.65 (dd, J = 10.6, 4.8 Hz, 1H), 3.40-3.50 (m, 2H), 3.19 (dd, J = 10.6, 7.3 Hz, 1H), 2.99 (dd, J = 8.7, 4.1 Hz, 1H), 1.12-1.20 (m, 4H).
ES MS M+1 = 375.3

EXAMPLE 43

(±)-1-(n-Propoxymethyl)-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclopropa[e]pyrido[1,2-a]pyrazine-3,7-dione



The title compound was prepared using a procedure similar to that described in Example 39, except that benzyl bromide was substituted with 1-iodopropane in Step 3.

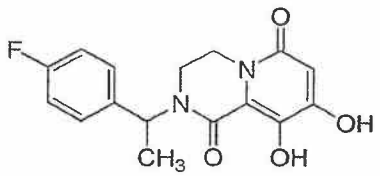
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.0 (s, 1H), 7.41 (dd, J = 8.5, 5.3 Hz, 2H),), 7.07 (t, J = 8.4 Hz, 2H), 6.24 (s, 1H), 4.81 (d, J = 14.3 Hz, 1H), 4.75 (d, J = 14.3 Hz, 1H), 3.85 (dd, J = 8.4, 4.2 Hz, 1H), 3.68 (dd, J = 10.6, 4.5 Hz, 1H), 3.30-3.40 (m, 2H), 3.18

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(dd, J = 10.6, 7.3 Hz, 1H), 2.99 (dd, J = 8.6, 4.0 Hz, 1H), 1.52-1.60 (m, 2H), 1.15-1.20 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H).
ES MS M+1 = 389.3

EXAMPLE 44

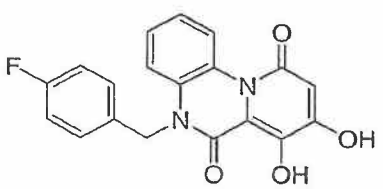
2-[1-(4-Fluorophenyl)ethyl]-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione



The title compound was prepared using a procedure similar to that described in Example 1, Steps 1 to 3, except that benzyl bromide (Step 1) was substituted with 1-[4-fluorophenyl)-1-bromoethane.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 11.05 (br s, 1H), 7.43 (dd, J = 8.5, 5.6 Hz, 2H), 7.21 (t, J = 8.5 Hz, 2H), 5.92 (s, 1H), 5.80 (q, J = 7.1 Hz, 1H), 4.05 (m, 1H), 3.74 (m, 1H), 3.54 (m, 1H), 3.15 (m, 1H), 1.55 (d, J = 7.0 Hz, 3H).
ES MS M+1 = 319

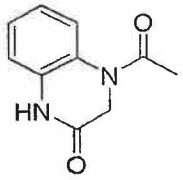
EXAMPLE 45

5-(4-Fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*]quinoxaline-6,10-dione



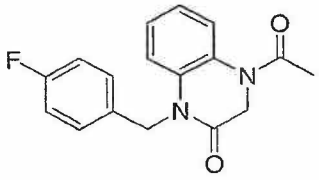
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Step 1: 4-Acetyl-3,4-dihydroquinoxalin-2(1*H*)-one



To a cold (0 °C) solution of 3,4-dihydroquinoxalin-2(1*H*)-one (1.0 g, 6.7 mmol; J. Med. Chem. 758, 1994) and N,N-diisopropyl-N-ethylamine (1.7 mL, 10.1 mmol) in dichloromethane (30 mL) under an atmosphere of nitrogen, acetic anhydride (0.76 mL, 8.1 mmol) was added and stirred at room temperature overnight. The resultant solution was concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 1% methanol in chloroform. Collection and concentration of appropriate fractions provided the acetylation product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1 (br s, 1H), 7.23-7.04 (m, 4H), 4.53 (br s, 2H), 2.28 (br s, 3H).
ES MS M+1 = 191

Step 2: 4-Acetyl-1-(4-fluorobenzyl)-3,4-dihydroquinoxalin-2(1*H*)-one



To a cold (0 °C) solution of 4-acetyl-3,4-dihydroquinoxalin-2(1*H*)-one (0.13 g, 0.68 mmol) in DMF (3.5 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (0.75 mL, 0.75 mmol) was added and stirred at the temperature for 30 min. The resultant solution was treated with 4-fluorobenzyl bromide (0.089 mL, 0.72 mmol), and stirred at room temperature for 3 hours. The product mixture was concentrated under vacuum, and the residue partitioned between aqueous HCl and ethyl acetate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 50% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title compound.

ES MS M+1 = 299

Step 3: 5-(4-Fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*]quinoxaline-6,10-dione

To a cold (0 °C) solution of 4-acetyl-1-(4-fluorobenzyl)-3,4-dihydro-quinoxalin-2(1*H*)-one (0.15 g, 0.52 mmol) in DMF (5 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (0.57 mL, 0.57 mmol) was added and stirred at the temperature for 30 min. The resultant solution was treated with diethyl oxalate (0.078 mL, 0.57 mmol), and stirred at room temperature overnight. The resultant mixture was then treated with additional lithium bis(trimethylsilyl)amide in THF (1.6 mL, 1.6 mmol) and stirred at room temperature for 6 h. The product mixture was concentrated under vacuum, and the residue partitioned between aqueous HCl and dichloromethane. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 11.53 (br s, 1H), 9.24 (d, J = 8.1 Hz, 1H), 7.42 (dd, J = 8.2, 5.7 Hz, 2H), 7.20-7.13 (m, 5H), 6.18 (s, 1H), 5.36 (s, 2H).

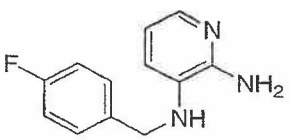
ES MS M+1 = 353

EXAMPLE 46

5-(4-Fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*:3',2'-*e*]pyrazine-6,10-dione



Step 1: N^3-(4-Fluorobenzyl)pyridine-2,3-diamine



To a suspension of 2,3-diaminopyridine (3.0 g, 27.5 mmol) and dried molecular sieves (4 Å) in THF (230 mL), 4-fluorobenzaldehyde (4.56 mL, 42.3 mmol) was added. The resultant mixture was stirred at room temperature overnight, filtered through a pad of Celite, and the filtrate concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 25 – 100% ethyl acetate in hexane gradient. Collection and concentration of appropriate fractions provided the imine intermediate. To a cold (0 °C) solution of resultant imine (3.0 g, 13.9 mmol) in anhydrous ethanol (50 mL), sodium borohydride (1.04 g, 28 mmol) was added portionwise. The resultant solution was stirred at room temperature overnight, and quenched with methanol. The product mixture was concentrated under vacuum, and the residue partitioned between ethyl acetate and water. The organic extract was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to provide the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 4.7 Hz, 1H), 7.33 (dd, J = 8.2, 5.8 Hz, 2H), 7.04 (br t, J = 8.2 Hz, 2H), 6.78 (d, J = 7.7 Hz, 1H), 6.67 (dd, J = 7.7, 4.7 Hz, 1H), 4.26 (d, J = 4.2 Hz, 2H), 3.56 (br s, 2H).

ES MS M+1 = 218

Step 2: 4-Acetyl-1-(4-fluorobenzyl)-3,4-dihydropyrido[2,3-*b*]pyrazin-2(1*H*)-one



To a cold (0 °C) solution of N^3-(4-fluorobenzyl)pyridine-2,3-diamine (4.4 g, 20.28 mmol) and pyridine (2.5 mL, 31 mmol) in dichloromethane (100 mL) under an atmosphere of nitrogen, chloroacetyl chloride (1.8 mL, 22 mol) was added. The resultant solution was stirred at room temperature overnight. The product mixture was concentrated under vacuum, and the residue was partitioned between aqueous HCl and ethyl acetate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 50 - 100% ethyl acetate in hexane gradient. Collection and concentration of appropriate fractions provided the bis chloroacetylated intermediate. ES MS M+1 = 370.

To a cold (0 °C) solution of the bis chloroacetylation product (120 mg, 0.32 mmol) in anhydrous THF (3 mL), a solution of lithium bis(trimethylsilyl)amide in THF (0.32 mL, 0.32 mmol) was added. The reaction mixture was stirred at room temperature for a half hour and concentrated under vacuum. The residue was partitioned between aqueous ammonium chloride and ethyl acetate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with an ethyl acetate in hexane gradient. Collection and concentration of appropriate fractions provided the cyclization intermediate 4-chloro-acetyl-1-(4-fluorobenzyl)-3,4-dihydropyrido[2,3-*b*]pyrazin-2(1*H*)-one as white solid.

A mixture of 4-chloro-acetyl-1-(4-fluorobenzyl)-3,4-dihydropyrido[2,3-*b*]pyrazin-2(1*H*)-one (2.2 g, 5.96 mmol) and 10% Pd/C (0.5 g) in methanol (50 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature for 5 hours. The product mixture was filtered through a pad of Celite, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with ethyl acetate and hexane. Collection and concentration of appropriate fractions provided the title compound.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 4.8 Hz, 1H), 7.24-7.01 (m, 6H), 5.11 (s, 2H), 4.72 (s, 2H), 2.48 (s, 3H).
ES MS M+1 = 300

Step 3: 5-(4-Fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*:3',2'-*e*]pyrazine-6,10-dione

To a cold (0 °C) solution of 4-acetyl-1-(4-fluorobenzyl)-3,4-dihydro-pyrido[2,3-*b*]pyrazin-2(1*H*)-one (0.275 g, 0.903 mmol) in DMF (10 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (1.44 mL, 1.44 mmol) was added and stirred at the temperature for 30 min. The resultant solution was treated with dimethyl oxalate (0.21 g, 1.8 mmol), and stirred at room temperature overnight. The resultant mixture was then treated with additional lithium bis(trimethylsilyl)amide in THF (3.6 mL, 3.6 mmol) and stirred at room temperature for 6 h. The product mixture was concentrated under vacuum, and the residue partitioned between aqueous HCl and dichloromethane. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound as white solid.

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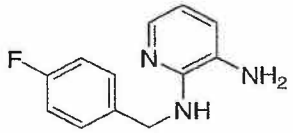
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 3.7 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.45 (dd, J = 8.2, 5.7 Hz, 2H), 7.33 (dd, J = 8.2, 4.7 Hz, 1H), 7.18 (t, J = 8.8 Hz, 2H), 6.10 (s, 1H), 5.32 (s, 2H).
ES MS M+1 = 354

EXAMPLE 47

5-(4-Fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*:2',3'-*e*]pyrazine-6,10-dione



Step 1: N^2-(4-Fluorobenzyl)pyridine-2,3-diamine

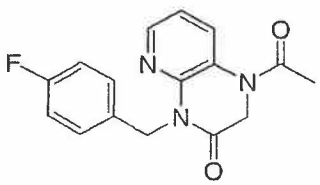


A mixture of 2-fluoro-3-nitropyridine (2.5 g, 17.6 mmol), 4-fluorobenzyl-amine (4.40 g, 35.2 mmol), and N,N-diisopropyl-N-ethylamine (4.55 g, 35.2 mmol) in anhydrous acetonitrile (30 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 15% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the 2-(4-fluorobenzylamino)-3-nitropyridine intermediate as yellow solid.

A mixture of 2-(4-fluorobenzylamino)-3-nitropyridine (1.0 g, 4.05 mmol) and 10% Pd/C (0.3 g) in methanol (50 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature for 5 hours. The product mixture was filtered through a pad of Celite, and concentrated under vacuum. The residual methanol was removed by co-evaporation with benzene. The resultant N^2-(4-Fluorobenzyl)pyridine-2,3-diamine was used in the following step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 4.7 Hz, 1H), 7.38 (dd, J = 8.2, 5.8 Hz, 2H), 7.05 (br t, J = 8.2 Hz, 2H), 6.88 (d, J = 7.7 Hz, 1H), 6.58 (dd, J = 7.7, 4.7 Hz, 1H), 4.60 (d, J = 4.2 Hz, 2H), 3.49 (br s, 2H).
ES MS M+1 = 218

Step 2: 1-Acetyl-4-(4-fluorobenzyl)-1,4-dihydropyrido[2,3-*b*]pyrazin-3(2*H*)-one



The title compound was prepared using a procedure similar to that described in Example 46, Step 2, except that N^3-(4-luorobenzyl)pyridine-2,3-diamine was substituted with N^2-(4-fluorobenzyl)pyridine-2,3-diamine.

Step 3: 5-(4-Fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*:2',3'-*e*]pyrazine-6,10-dione

The title compound was prepared using a procedure similar to that described in Example 46, Step 3, except that 4-acetyl-1-(4-fluorobenzyl)-3,4-dihydro-pyrido[2,3-*b*]pyrazin-2(1*H*)-one was substituted with 1-acetyl-4-(4-fluorobenzyl)-1,4-dihydropyrido[2,3-*b*]pyrazin-3(2*H*)-one.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 11.65 (br s, 1H), 9.72 (d, J = 8.6 Hz, 1H), 8.22 (d, J = 4.0 Hz, 1H), 7.44 (dd, J = 8.2, 5.7 Hz, 2H), 7.25 (m, 1H), 7.11 (t, J = 8.8 Hz, 2H), 6.17 (s, 1H), 5.44 (s, 2H).
ES MS M+1 = 354

EXAMPLE 48

Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 50 mg of compound of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule. Encapsulated oral compositions containing any one of the compounds of Examples 2-47 can be similarly prepared.

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EXAMPLE 49

HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase

Assays for the strand transfer activity of integrase were conducted in accordance with WO 02/30930 for recombinant integrase. Representative compounds of the present invention exhibit inhibition of strand transfer activity in this assay. For example, the compounds prepared in Examples 1-47 were tested in the integrase assay and all were found to have IC_{50}'s less than 5 micromolar, and all but the compounds prepared in Examples 37, 38 and 44 were found to have $ICIC_{50}$'s less than 0.5 micromolar.

Further description on conducting the assay using preassembled complexes is found in Wolfe, A.L. et al., *J. Virol.* 1996, 70: 1424-1432, Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al., *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

EXAMPLE 50

Assay for inhibition of HIV replication

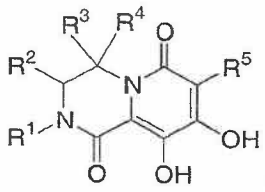
Assays for the inhibition of acute HIV infection of T-lymphoid cells were conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. Representative compounds of the present invention exhibit inhibition of HIV replication in this assay. For example, the compounds prepared in Examples 1-47 were tested in the present assay and all were found to have IC_{95}'s less than 10 micromolar. In particular, the compounds of Examples 1-18 were found to have IC_{95}'s less than 5 micromolar, and the compounds of Examples 2, 6, 8-12, 14, 15, 25, 27-30, 34, 35, 42 and 43 were found to have IC_{95}'s less than 1 micromolar.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

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WHAT IS CLAIMED IS:

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



(I),

wherein

R^1 is C_{1-6} alkyl which is substituted with 1 or 2 substituents each of which is independently:

(1) C_{3-8} cycloalkyl,

(2) aryl,

(3) a 5- or 6-membered saturated or mono-unsaturated heterocyclic ring containing from 1 to 4 heteroatoms independently selected from N, O and S,

(4) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, or

(5) a 9- or 10-membered fused bicyclic heterocycle containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein at least one of the rings is aromatic;

wherein

(A) each cycloalkyl is optionally substituted with from 1 to 3 substituents, each of which is independently halo, $-C_{1-6}$ alkyl, or $-O-C_{1-6}$ alkyl;

(B) each aryl is optionally substituted with from 1 to 5 substituents each of which is independently

(1) $-C_{1-6}$ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, -CN, $-NO_2$, $-N(R^aR^b)$, $-C(=O)N(R^aR^b)$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, $-SO_2N(R^aR^b)$, $-N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^c$, $-N(R^a)SO_2R^c$, $-N(R^a)SO_2N(R^aR^b)$, $-OC(=O)N(R^aR^b)$, or $-N(R^a)C(=O)N(R^aR^b)$,

(2) -O-C_{1-6} alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -$S(O)_nR^c$, -$C(=O)N(R^aR^b)$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$,

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} haloalkyl,

(5) -OH,

(6) halo,

(7) -CN,

(8) -NO_2,

(9) -$N(R^aR^b)$,

(10) -$C(=O)N(R^aR^b)$,

(11) -$C(=O)R^a$,

(12) -CO_2R^c,

(13) -SR^c,

(14) -$S(=O)R^c$,

(15) -SO_2R^c,

(16) -$N(R^a)SO_2R^c$,

(17) -$SO_2N(R^aR^b)$,

(18) -$N(R^a)C(=O)R^b$,

(19) -$N(R^a)CO_2R^c$, or

(20) phenyl;

(C) each saturated or mono-unsaturated heterocyclic ring is

(i) optionally substituted with from 1 to 5 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; and

(D) each heteroaromatic ring or each fused bicyclic heterocycle is

(i) optionally substituted with from 1 to 7 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6}

haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C_{1-6} alkyl-aryl;

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

R^3 is -H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, or -C_{1-6} alkyl substituted with one of -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^c$, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, or -$N(R^a)C(=O)N(R^aR^b)$;

R^4 is:

(1) -H,

(2) -C_{1-6} alkyl optionally substituted with one of -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$, -$SO_2N(R^aR^b)$, -$N(R^a)$-$C(R^b)$=O, -$N(R^a)SO_2R^c$, -$N(R^a)SO_2N(R^aR^b)$, -$OC(=O)N(R^aR^b)$, -$N(R^a)C(=O)N(R^aR^b)$, -O-C_{1-6} alkyl-$C(=O)N(R^aR^b)$, -S-C_{1-6} alkyl-$C(=O)N(R^aR^b)$, -$N(R^a)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$, or -$N(SO_2R^c)$-C_{1-6} alkyl-$C(=O)N(R^aR^b)$,

(3) -C_{1-6} haloalkyl,

(4) -$C(=O)R^a$,

(5) -CO_2R^c,

(6) -$C(=O)N(R^aR^b)$,

(7) -$SO_2N(R^aR^b)$,

(8) -C_{2-6} alkenyl,

(9) -C_{2-6} alkenyl-$C(=O)$-$N(R^a)_2$,

(10) -C_{2-5} alkynyl,

(11) -C_{2-5} alkynyl-$CH_2N(R^a)_2$,

(12) -C_{2-5} alkynyl-CH_2OR^a,

(13) -C_{2-5} alkynyl-$CH_2S(O)_nR^c$, or

(14) -R^k,

(15) -C_{1-6} alkyl substituted with R^k,

(16) -C_{1-6} haloalkyl substituted with R^k,

(17) -C_{1-6} alkyl-O-R^k,

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(18) -C_{1-6} alkyl-O-C_{1-6} alkyl-R^k,
(19) -C_{1-6} alkyl-$S(O)_n$-R^k,
(20) -C_{1-6} alkyl-$S(O)_n$-C_{1-6} alkyl-R^k,
(21) -C_{1-6} alkyl-$N(R^a)$-R^k,
(22) -C_{1-6} alkyl-$N(R^a)$-C_{1-6} alkyl-R^k,
(23) -C_{1-6} alkyl-$N(R^a)$-C_{1-6} alkyl-OR^k, with the proviso that the -$N(R^a)$- moiety and the -OR^k moiety are not both attached to the same carbon of the -C_{1-6} alkyl- moiety,
(24) -C_{1-6} alkyl-C(=O)-R^k,
(25) -C_{1-6} alkyl-C(=O)$N(R^a)$-R^k,
(26) -C_{1-6} alkyl-$N(R^a)$C(=O)-R^k,
(27) -C_{1-6} alkyl-C(=O)$N(R^a)$-C_{1-6} alkyl-R^k, or
(28) -C_{1-6} alkyl-$N(R^a)$-C_{0-6} alkyl-$S(O)_nR^k$;

wherein R^k is

(i) aryl, which is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkyl-O-C_{1-6} haloalkyl, -C_{1-6} alkyl-$N(R^aR^b)$, -C_{1-6} alkyl-C(=O)$N(R^aR^b)$, -C_{1-6} alkyl-C(=O)R^a, -C_{1-6} alkyl-CO_2R^c, -C_{1-6} alkyl-$S(O)_nR^c$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halo, -$N(R^aR^b)$, -C(=O)$N(R^aR^b)$, -C(=O)R^a, -CO_2R^c, -$S(O)_nR^c$, or -$SO_2N(R^aR^b)$;

(ii) a 4- to 7-membered saturated or mono-unsaturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is:

(a) optionally substituted with from 1 to 5 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

(b) optionally mono-substituted with aryl or HetA;

wherein HetA is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring, and HetA is optionally substituted with from 1 to 4

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substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; or

(iii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo;

or alternatively R^3 and R^4 are joined together to form C_{5-8} cycloalkyl or a 5- to 7-membered saturated heterocyclic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein

the cycloalkyl is optionally substituted with from 1 to 3 substituents each of which is independently halo, -C_{1-6} alkyl, or -O-C_{1-6} alkyl; and

the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo;

or alternatively:

(i) R^2 and R^3 together form a direct bond to give a ring double bond, and R^4 is an independent group as defined above;

(ii) R^2 and R^3 together with the ring carbon atoms to which they are attached form a fused cyclopropyl ring which is optionally substituted at the non-fused cyclopropyl ring carbon with -OR^d, and R^4 is -H; or

(iii) R^2 and R^3 together with the ring carbon atoms to which they are attached form a fused phenyl ring or a fused pyridyl ring, and R^4 is absent;

R^5 is:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -C_{1-6} alkyl-N(R^aR^b),
(4) -C_{1-6} alkyl-C(=O)N(R^aR^b),
(5) -C_{1-6} alkyl-C(=O)R^a,
(6) -C_{1-6} alkyl-CO_2R^c,
(7) -C_{1-6} alkyl-SR^c,

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(8) $-C_{1-6}$ alkyl-S(=O)R^c,
(9) $-C_{1-6}$ alkyl-SO_2R^c,
(10) $-C_{1-6}$ alkyl-$SO_2N(R^aR^b)$
(11) $-C_{1-6}$ haloalkyl,
(12) $-O-C_{1-6}$ alkyl,
(13) $-O-C_{1-6}$ haloalkyl,
(14) halo,
(15) -CN,
(16) $-C(=O)R^a$,
(17) $-CO_2R^c$,
(18) $-SR^c$,
(19) $-S(=O)R^c$,
(20) $-SO_2R^c$,
(21) $-N(R^aR^b)$,
(22) $-C(=O)N(R^aR^b)$, or
(23) $-SO_2N(R^aR^b)$;
(24) aryl
(25) $-C_{1-6}$ alkyl-aryl
(26) HetB,
(27) $-C_{1-6}$ alkyl-HetB,
(28) HetC, or
(29) $-C_{1-6}$ alkyl-HetC,

wherein

HetB is a 5- or 6-membered saturated or mono-unsaturated ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the ring is optionally substituted with from 1 to 5 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, oxo, $-C(=O)-C_{1-6}$ alkyl, $-C(=O)-C_{1-6}$ haloalkyl, or $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl; and

HetC is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or oxo;

each R^a and R^b is independently -H or $-C_{1-6}$ alkyl;

each R^c is independently a -C_{1-6} alkyl;

R^d is a -C_{1-6} alkyl, allyl, or benzyl; and

each n is independently an integer equal to 0, 1 or 2.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is -C_{1-4} alkyl mono-substituted with aryl; wherein the aryl is optionally substituted with from 1 to 4 substituents each of which is independently

(1) -C_{1-4} alkyl, optionally mono-substituted with -OH, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, -CN, -N(R^aR^b), -C(=O)N(R^aR^b), -C(=O)R^a, -CO_2R^c, -S(O)$_n$$R^c$, -$SO_2$N($R^aR^b$), -N($R^a$)C(=O)$R^b$, -N($R^a$)$CO_2R^c$, -N($R^a$)$SO_2R^c$, -N($R^a$)$SO_2$N($R^aR^b$), -OC(=O)N($R^aR^b$), or -N($R^a$)C(=O)N($R^aR^b$),

(2) -O-C_{1-4} alkyl, optionally mono-substituted with -OH, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, -S(O)$_n$$R^c$, -N($R^a$)-$CO_2R^c$, -C(=O)N($R^aR^b$), -$SO_2$N($R^aR^b$), -N($R^a$)C(=O)$R^b$, -N($R^a$)$CO_2R^c$, -N($R^a$)$SO_2R^c$, -N($R^a$)$SO_2$N($R^aR^b$), -OC(=O)N($R^aR^b$), or -N($R^a$)C(=O)N($R^aR^b$),

(3) -C_{1-4} haloalkyl,

(4) -O-C_{1-4} haloalkyl,

(5) -OH,

(6) halo,

(7) -CN,

(8) -NO_2,

(9) -N(R^aR^b),

(10) -SR^c,

(11) -S(=O)R^c,

(12) -SO_2R^c,

(13) -N(R^a)SO_2R^c,

(14) -SO_2N(R^aR^b),

(15) -N(R^a)C(=O)R^b,

(16) -N(R^a)CO_2R^c, or

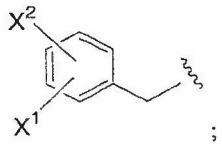
(17) phenyl.

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3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is -$(CH_2)_{1-4}$-phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently

(1) -C_{1-4} alkyl, optionally mono-substituted with -OH, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, -CN, -$N(R^aR^b)$, -$C(=O)N(R^aR^b)$, -$C(=O)R^a$, -CO_2R^c, -$S(O)_nR^c$, or -$SO_2N(R^aR^b)$,
(2) -O-C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} haloalkyl,
(5) -OH,
(6) halo,
(7) -CN,
(8) -NO_2,
(9) -$N(R^aR^b)$,
(10) -SR^c,
(11) -$S(=O)R^c$,
(12) -SO_2R^c,
(13) -$N(R^a)SO_2R^c$,
(14) -$SO_2N(R^aR^b)$,
(15) -$N(R^a)C(=O)R^b$,
(16) -$N(R^a)CO_2R^c$, or
(17) phenyl.

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



;

wherein X^1 and X^2 are each independently

(1) -H,
(2) methyl,
(3) ethyl,
(4) methoxy,

(5) ethoxy,
(6) $-CF_3$,
(7) fluoro,
(8) bromo,
(9) chloro,
(10) -CN,
(11) $-S-CH_3$, or
(12) phenyl.

5. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is 4-fluorobenzyl.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^2 is -H or $-C_{1-4}$ alkyl;

R^3 is -H or $-C_{1-4}$ alkyl; and

R^4 is:

(1) -H,
(2) $-C_{1-4}$ alkyl optionally substituted with one of -OH, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, -CN, $-N(R^aR^b)$, $-C(=O)N(R^aR^b)$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, $-SO_2N(R^aR^b)$, $-N(R^a)-C(R^b)=O$, $-N(R^a)SO_2R^b$, or $-N(R^a)SO_2N(R^aR^b)$,
(3) $-C(=O)N(R^aR^b)$,
(4) $-R^k$,
(5) $-C_{1-4}$ alkyl substituted with R^k,
(6) $-C_{1-4}$ alkyl-O-R^k, or
(7) $-C_{1-4}$ alkyl-O-C_{1-4} alkyl-R^k.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^5 is:

(1) -H,
(2) $-C_{1-4}$ alkyl,
(3) $-C_{1-4}$ alkyl-$N(R^aR^b)$,
(4) $-C_{1-4}$ alkyl-$C(=O)N(R^aR^b)$,

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(5) -C_{1-4} alkyl-$SO_2N(R^aR^b)$
(6) -C_{1-4} haloalkyl,
(7) halo,
(8) -CN,
(9) aryl
(10) -C_{1-4} alkyl-aryl
(11) HetB,
(12) -C_{1-4} alkyl-HetB,
(13) HetC, or
(14) -C_{1-4} alkyl-HetC,

wherein

HetB is a 5- or 6-membered saturated ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, oxo, -C(=O)-C_{1-4} alkyl, -C(=O)-C_{1-4} haloalkyl, or -C_{1-4} alkyl-C_{3-6} cycloalkyl; and

HetC is a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo.

8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein R^5 is:

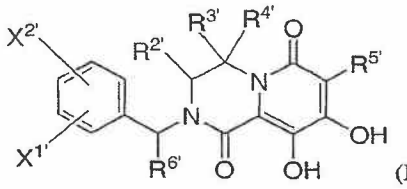
(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} alkyl-$N(R^aR^b)$,
(4) halo,
(5) -CN, or
(6) -C_{1-4} alkyl-HetB;

wherein

HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms and carbon atoms, wherein the saturated ring is optionally

substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, oxo, -C(=O)-C_{1-4} alkyl, -C(=O)-C_{1-4} haloalkyl, or -C_{1-4} alkyl-C_{3-6} cycloalkyl.

9. A compound of Formula (II), or a pharmaceutically acceptable salt thereof:



(II),

wherein:

$X^{1'}$ and $X^{2'}$ are each independently:

(1) -H,
(2) C_{1-4} alkyl,
(2) -O-C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} haloalkyl,
(5) halo,
(6) -CN,
(7) -S-C_{1-4} alkyl, or
(8) phenyl;

$R^{2'}$ is -H or -C_{1-4} alkyl;

$R^{3'}$ is -H or -C_{1-4} alkyl;

$R^{4'}$ is:

(1) -H,
(2) -C_{1-4} alkyl optionally substituted with one of -OH, -N($R^{a'}R^{b'}$), or -C(=O)N($R^{a'}R^{b'}$),
(3) -C(=O)N($R^{a'}R^{b'}$),
(4) -$(CH_2)_{1-3}$-$R^{k'}$,

(5) $-(CH_2)_{1-3}-O-R^{k'}$, or

(6) $-(CH_2)_{1-3}-O-(CH_2)_{1-3}-R^{k'}$;

wherein $R^{k'}$ is:

(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-O-C_{1-4}$ haloalkyl, or halo; or

(ii) HetD, wherein HetD is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, 0 or 1 S atoms, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halo, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, or oxo;

or alternatively:

(i) $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond, and $R^{4'}$ is an independent group as defined above;

(ii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused cyclopropyl ring which is optionally substituted at the non-fused cyclopropyl ring carbon with $-OR^{d'}$, and $R^{4'}$ is -H; or

(iii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused phenyl ring or a fused pyridyl ring, and $R^{4'}$ is absent;

$R^{5'}$ is:

(1) -H,

(2) $-C_{1-4}$ alkyl,

(3) $-C_{1-4}$ alkyl-$N(R^{a'}R^{b'})$,

(4) halo,

(5) -CN, or

(6) $-(CH_2)_{1-3}$-HetB;

wherein

HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, zero or 1 O atom, zero or 1 S atom, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, oxo, $-C(=O)-C_{1-4}$ alkyl, $-C(=O)-C_{1-4}$ haloalkyl, or $-C_{1-4}$ alkyl-C_{3-6} cycloalkyl;

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$R^{6'}$ is -H or methyl;

each $R^{a'}$ and $R^{b'}$ is independently -H or -C_{1-4} alkyl; and

$R^{d'}$ is -C_{1-4} alkyl, allyl, or benzyl.

10. A compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein:

wherein $X^{1'}$ and $X^{2'}$ are each independently:

(1) -H,
(2) methyl,
(2) -OCH_3,
(3) -CF_3,
(4) -O-CF_3,
(5) chloro,
(6) fluoro,
(7) bromo;
(6) -CN,
(7) -S-CH_3, or
(8) phenyl;

$R^{2'}$ is -H or methyl;

$R^{3'}$ is -H or methyl;

$R^{4'}$ is:

(1) -H,
(2) methyl,
(3) -CH_2OH,
(3) -$C(=O)N(CH_3)_2$,
(4) -CH_2-$R^{k'}$, or
(5) -CH_2-O-CH_2-$R^{k'}$;

wherein $R^{k'}$ is:

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(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently -CH_3, -OCH_3, -CF_3, -OCF_3, chloro, bromo or fluoro; or

(ii) HetD, wherein HetD is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, 0 or 1 S atoms, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently chloro, bromo, fluoro, -CH_3, -CF_3, -OCH_3, -OCF_3, or oxo;

or alternatively:

(i) $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond, and $R^{4'}$ is an independent group as defined above;

(ii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused cyclopropyl ring which is optionally substituted at the non-fused cyclopropyl ring carbon with -OMe, -OEt, -O-allyl, or -O-benzyl, and $R^{4'}$ is -H; or

(iii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused phenyl ring or a fused pyridyl ring, and $R^{4'}$ is absent;

$R^{5'}$ is:

(1) -H,
(2) methyl,
(3) -$(CH_2)_{1-2}$-$N(CH_3)_2$,
(4) fluoro,
(5) bromo,
(6) iodo,
(7) -CN, or
(8) -CH_2-HetB;

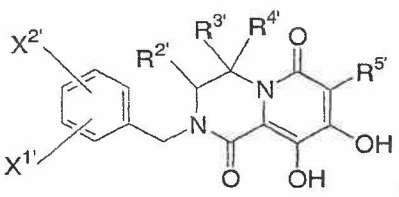
wherein

HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, zero or 1 O atom, zero or 1 S atom, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently chloro, bromo, fluoro, -CH_3, -CF_3, -OCH_3, -OCF_3, oxo, -C(=O)-CH_3, -C(=O)-CF_3, or -CH_2-cyclopropyl; and

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$R^{6'}$ is -H or methyl.

11. The compound according to claim 9, which is a compound of Formula (IIa), or a pharmaceutically acceptable salt thereof:



(IIa),

wherein:

$X^{1'}$ and $X^{2'}$ are each independently:

(1) -H,
(2) C_{1-4} alkyl,
(2) -O-C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} haloalkyl, or
(5) halo;

$R^{2'}$ is -H or -C_{1-4} alkyl;

$R^{3'}$ is -H or -C_{1-4} alkyl;

or alternatively $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond;

$R^{4'}$ is:

(1) -H,
(2) -C_{1-4} alkyl optionally substituted with one of -OH, -N($R^{a'}R^{b'}$), or -C(=O)N($R^{a'}R^{b'}$),
(3) -C(=O)N($R^{a'}R^{b'}$),
(4) -$(CH_2)_{1-3}$-$R^{k'}$,
(5) -$(CH_2)_{1-3}$-O-$R^{k'}$, or
(6) -$(CH_2)_{1-3}$-O-$(CH_2)_{1-3}$-$R^{k'}$;

wherein $R^{k'}$ is:

(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently -C_{1-4} alkyl, -O-C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} haloalkyl, or halo; or

(ii) HetD, wherein HetD is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, 0 or 1 S atoms, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halo, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo;

$R^{5'}$ is:

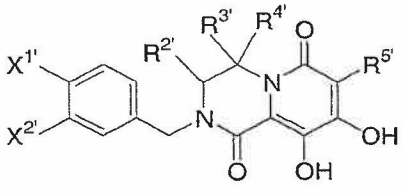
(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} alkyl-N($R^{a'}R^{b'}$),
(4) halo,
(5) -CN, or
(6) -$(CH_2)_{1-3}$-HetB;

wherein

HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms and carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or oxo; and

each $R^{a'}$ and $R^{b'}$ is independently -H or -C_{1-4} alkyl.

12. The compound according to claim 9, which is a compound of Formula (III), or a pharmaceutically acceptable salt thereof:



(III),

wherein:

$X^{1'}$ and $X^{2'}$ are each independently -H or halo.

13. The compound according to claim 12, or a pharmaceutically acceptable salt thereof,

wherein $X^{1'}$ and $X^{2'}$ are each independently -H, fluoro, chloro, or bromo;

$R^{2'}$ is -H or methyl;

$R^{3'}$ is -H or methyl;

$R^{4'}$ is:

(1) -H,
(2) methyl,
(3) $-CH_2OH$,
(3) $-C(=O)N(CH_3)_2$,
(4) $-CH_2-R^{k'}$, or
(5) $-CH_2-O-CH_2-R^{k'}$;

wherein $R^{k'}$ is:

(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, chloro, bromo or fluoro; or

(ii) HetD, wherein HetD is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, 0 or 1 S atoms, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently chloro, bromo, fluoro, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, or oxo; and

or alternatively:

(i) $R^{2'}$ and $R^{3'}$ together form a direct bond to give a ring double bond, and $R^{4'}$ is an independent group as defined above;

(ii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused cyclopropyl ring which is optionally substituted at the non-fused cyclopropyl ring carbon with $-OR^{d'}$, and $R^{4'}$ is -H; or

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(iii) $R^{2'}$ and $R^{3'}$ together with the ring carbon atoms to which they are attached form a fused phenyl ring or a fused pyridyl ring, and $R^{4'}$ is absent;

$R^{5'}$ is:

(1) -H,
(2) methyl,
(3) $-(CH_2)_{1-2}-N(CH_3)_2$,
(4) fluoro,
(5) bromo,
(6) iodo,
(7) -CN, or
(8) $-CH_2$-HetB;

wherein

HetB is a 5- or 6-membered saturated ring containing 1 or 2 N atoms, zero or 1 O atom, zero or 1 S atom, and a balance of carbon atoms, wherein the saturated ring is optionally substituted with from 1 to 4 substituents each of which is independently chloro, bromo, fluoro, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, oxo, $-C(=O)-CH_3$, $-C(=O)-CF_3$, or $-CH_2$-cyclopropyl.

14. The compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein $X^{1'}$ is fluoro and $X^{2'}$ is -H.

15. A compound selected from the group consisting of:

2-benzyl-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-bromo-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

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2-(4-fluorobenzyl)-8,9-dihydroxy-7-iodo-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(3-chlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-chlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

2-(3,4-dichlorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(3,4-difluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

2-(3-chloro-4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

2-(4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-1-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(3-chloro-4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-1-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(dimethylamino)methyl]-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-benzyl-8,9-dihydroxy-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-4-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione

2-(4-fluorobenzyl)-8,9-dihydroxy-4,4-dimethyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-3-methyl-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

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2-(4-fluorobenzyl)-8,9-dihydroxy-1,6-dioxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-a]-pyrazine-7-carbonitrile;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(4-methyl-3-oxopiperazin-1-yl)methyl]-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(3-oxopiperazin-1-yl)methyl]-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

4-[(benzyloxy)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

4-(hydroxymethyl)-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

4-[(1,1-dioxido-1,2-thiazinan-2-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-(piperidin-1-ylmethyl)-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(3-oxopiperazin-1-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(4-methyl-3-oxopiperazin-1-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(morpholin-4-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-[(thiomorpholin-4-yl)methyl]-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-[4-fluoro-2-(methylthio)benzyl)-8,9-dihydroxy-2H-pyrido[1,2-a]pyrazine-1,6-dione;

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7-[(1-acetylpiperidin-4-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(4-fluorobenzyl)-8,9-dihydroxy-7-{[1-(trifluoroacetyl)piperidin-4-yl]methyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-{[1-(cyclopropylmethyl)piperidin-3-yl]methyl}-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-[(1-acetylpiperidin-3-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-[(1-acetylpiperidin-2-yl)methyl]-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

7-{[1-(cyclopropylmethyl)piperidin-2-yl]methyl}-2-(4-fluorobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione;

2-(3-cyanobenzyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

2-(biphenyl-3-ylmethyl)-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione

(±)-1-[(benzyloxy)methyl]-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

(±)-1-(methoxymethyl)-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

(±)-1-[(allyloxy)methyl]-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

(±)-1-(ethoxymethyl)-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

(±)-1-(n-propoxymethyl)-2-(4-fluorobenzyl)-4,5-dihydroxy-1,1a,2,8a-tetrahydrocyclo-propa[e]pyrido[1,2-a]pyrazine-3,7-dione;

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2-[1-(4-fluorophenyl)ethyl]-8,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione;

5-(4-fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*]quinoxaline-6,10-dione;

5-(4-fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*:3',2'-*e*]pyrazine-6,10-dione;

5-(4-fluorobenzyl)-7,8-dihydroxy-5H-pyrido[1,2-*a*:2',3'-*e*]pyrazine-6,10-dione;

and pharmaceutically acceptable salts thereof.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1, or a pharmaceutically acceptable salt thereof.

18. A method for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1, or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition which comprises the product prepared by combining an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

20. A combination useful for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS, which is a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of an HIV infection/AIDS antiviral agent selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

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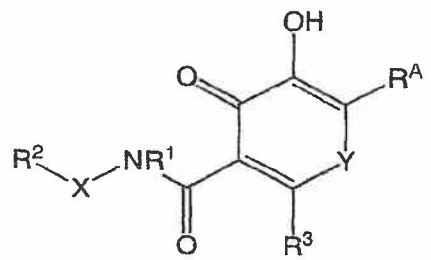
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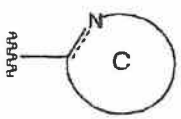
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(54) **Title:** CARBAMOYLPYRIDONE DERIVATIVE HAVING HIV INTEGRASE INHIBITORY ACTIVITY

(54) 発明の名称: ＨＩＶインテグラーゼ阻害活性を有するカルバモイルピリドン誘導体



(I)



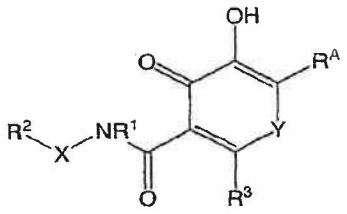
(57) Abstract: A compound represented by the formula (I), which has antiviral activity, especially HIV integrase inhibitory activity, a pharmaceutically acceptable salt of the compound, or a solvate of either; and a medicine, especially an anti-HIV drug, which contains the compound, salt, or solvate. (In the formula, Y is NR^4 (R^4 is hydrogen, etc.), O, S, SO_3 or SO_2; R^A is (1) a group represented by the formula $-COR^5$ (R^5 is a group selected among substituents (A)) or (2) a group represented by the formula (wherein ring C is an optionally substituted, nitrogenous aromatic heterocycle in which at least one of the atoms adjacent to the atom having a bond for external linkage is an unsubstituted nitrogen atom; and the broken line indicates the presence or absence of a bond); R^1 is hydrogen, etc.; X is a single bond, etc.; R^2 is a group selected among substituents (A); and R^3 is hydrogen, etc.; provided that the substituents (A) are hydrogen, hydroxy, optionally substituted lower alkyls, etc.)

[続葉有]

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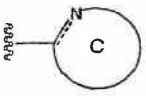
(57) 要約:

本発明は、抗ウイルス作用、特にHIVインテグラーゼ阻害活性を有する、式(I)で表される化合物、その製薬上許容される塩、又はそれらの溶媒和物、並びに、それを含有する医薬、特に抗HIV薬を提供する。



(I)

(式中、
Yは、NR^4(R^4は水素等)、O、S、SO、又はSO_2;
R^Aは、1)式:$-COR^5$(R^5は置換基群Aから選択される基)で示される基、
又は2)式:



(式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である。破線は結合の存在又は非存在を表わす。)で示される基;
R^1は、水素等;
Xは、単結合等;
R^2は、置換基群Aから選択される基;
R^3は、水素等;
置換基群Aは、水素、ヒドロキシ、置換されていてもよい低級アルキル等である。)

明 細 書

HIVインテグラーゼ阻害活性を有するカルバモイルピリドン誘導体

技術分野

[0001] 本発明は、抗ウイルス作用を有する新規化合物、更に詳しくは、HIVインテグラーゼ阻害活性を有するカルバモイルピリドン誘導体及びそれを含有する医薬、特に抗HIV薬に関する。

背景技術

[0002] ウイルスのなかでも、レトロウイルスの一種であるヒト免疫不全ウイルス(Human Immunodeficiency Virus、以下HIVと略す)は、後天性免疫不全症候群(Acquired immnodeficiency syndrome、以下エイズ(AIDS)と略す)の原因となることが知られている。そのエイズの治療薬としては、これまでのところ逆転写酵素阻害剤(AZT、3TC等)とプロテアーゼ阻害剤(インディナビル等)が主流であるが、腎臓障害等の副作用や耐性ウイルスの出現等の問題が判明しており、それらとは異なる作用メカニズムを有する抗HIV薬の開発が期待されている。

また、エイズの治療においては、耐性ウイルスが容易に出現するという理由から、現在、多剤併用療法が効果的であると報告されている。抗HIV薬としては、逆転写酵素阻害剤、プロテアーゼ阻害剤の2種が臨床で使用されているが、同じ作用メカニズムを有する薬剤はしばしば交叉耐性を示し、又は付加的な効果を示すに過ぎず、異なった作用メカニズムの抗HIV薬の開発が要望されている。

このような状況下、新規メカニズムの抗HIV薬として、インテグラーゼ阻害剤が注目されている(参照:特許文献1、2)。また同作用を有する抗HIV薬として、カルバモイル置換ヒドロキシピリミジノン誘導体(参照:特許文献3、4)、カルバモイル置換ヒドロキシピロリジオン誘導体(参照:特許文献5)が公知である。またカルバモイル置換ヒドロキシピリドン誘導体(参照:特許文献6、実施例8)が出願されている。

またその他のカルバモイルピリドン誘導体として、5－アルコキシピリジン－3－カルボキサミド誘導体やγ－ピロン－3－カルボキサミド誘導体が公知であるが、植物成長抑制剤や除草剤である(参照:特許文献7～9)。

特許文献1:WO03／0166275

特許文献2:WO2004／024693

特許文献3:WO03／035076

特許文献4:WO03／035076

特許文献5:WO2004／004657

特許文献6:特願2003－32772

特許文献7:特開平2－108668

特許文献8:特開平2－108683

特許文献9:特開平2－96506

発明の開示

発明が解決しようとする課題

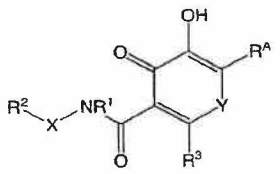
[0003] 上記の状況下、新規なインテグラーゼ阻害剤の開発が要望されていた。

課題を解決するための手段

[0004] 本発明者らは鋭意、研究した結果、新規なカルバモイルピリドン誘導体が強いHIVインテグラーゼ阻害作用を有することを見出した。さらに、本発明化合物及びそれらを含有する医薬が、抗ウイルス薬(例:抗レトロウイルス薬、抗HIV薬、抗HTLV－1(Human T cell leukemia virus type 1:ヒトT細胞白血病ウイルス1型)薬、抗FIV(Feline immunodeficiency virus:ネコエイズウイルス)薬、抗SIV(Simian immunodeficiency virus:サルエイズウイルス)薬)、特に抗HIV薬、抗AIDS薬、またはその関連疾患の治療薬等として有用であることを見出し、以下に示す本発明を完成した。

(1)式:

[化1]



(1)

(式中、

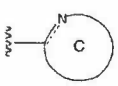
Yは、NR^4（R^4は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、または置換されていてもよいアラルキル）、O、S、SO、またはSO_2；

R^Aは、1）式：$-COR^5$（R^5は置換基群Aから選択される基）で示される基

（置換基群A：水素、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキルオキシ、置換されていてもよいアミノ、置換されていてもよいアミノオキシ、置換されていてもよい複素環式基、置換されていてもよい複素環オキシ、置換されていてもよいアリール、置換されていてもよいアリールオキシ、置換されていてもよいアラルキル、置換されていてもよいアラルキルオキシ、ホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル、置換されていてもよいシクロアルキルカルボニル、置換されていてもよいアリールカルボニル）

または2）式：

[化2]



（式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である。破線は結合の存在又は非存在を表わす。）で示される基；

R^1は、水素または低級アルキル；

Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレン；

R^2は、上記置換基群Aから選択される基；

R^3は水素、ハロゲン、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルケニル、置換されていてもよい低級アルコキシ、置換されていてもよいアミノ、置換されていてもよい低級アルキルアミノ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキル低級アルキル、置換されていてもよい

アリール、置換されていてもよいアラルキル、置換されていてもよい複素環式基、または置換されていてもよい複素環低級アルキル）

で示される化合物、その製薬上許容される塩、またはそれらの溶媒和物。

上記（1）の一態様は、R^2が置換されていてもよいアリール、かつR^3は水素、ハロゲン、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルケニル、置換されていてもよい低級アルコキシ、置換されていてもよいアミノ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキル低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよい複素環式基、または置換されていてもよい複素環低級アルキルである場合を包含する。

（2）YはNR^4（R^4は前記と同意義）またはOである、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

（3）YはNR^4（R^4は水素、低級アルキル、フェニルまたはベンジル）である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

（4）YはOである、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

（5）YはS、SOまたはSO_2である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

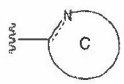
（6）R^Aは、－COR^5（R^5は前記と同意義）である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

（7）R^Aは、－COR^5（R^5は、水素、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいフェニル、置換されていてもよいベンジル、置換されていてもよい複素環基または置換されていてもよいアミノ）である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

（8）R^Aは、－COR^5（R^5は、水素、ヒドロキシ、低級アルキル、低級アルコキシ、または置換されていてもよいアミノ）である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

(9)R^Aは、式:

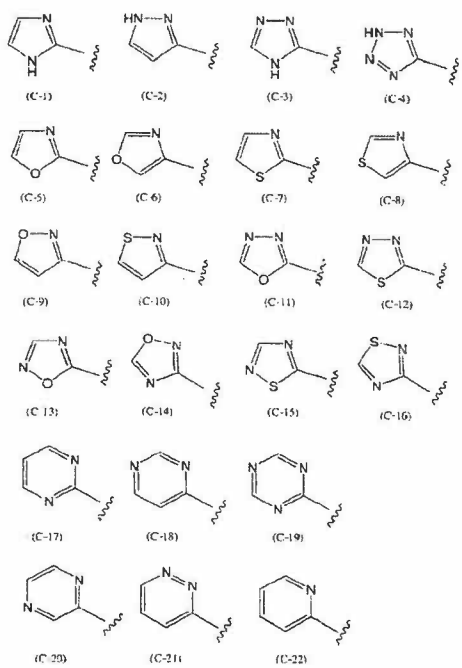
[化3]



(式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である。破線は結合の存在又は非存在を表わす。)で示される基である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

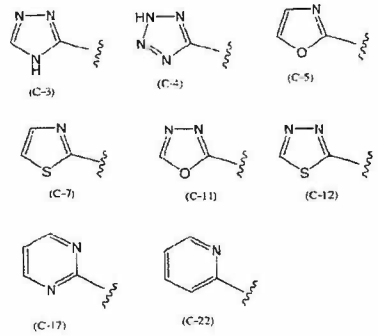
(10)R^Aは、置換されていてもよい、以下に示されるいずれかの含窒素芳香族複素環式基である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[化4]



(11)R^Aは、置換されていてもよい、以下に示されるいずれかの含窒素芳香族複素環式基である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[化5]



(12)R^1は、水素またはメチルである、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

(13)Xは、低級アルキレンまたはO;R^2は、置換されていてもよいフェニルである、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

(14)R^3は、水素、ヒドロキシ、置換されていてもよい低級アルコキシ、または置換されていてもよいアミノである、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

(15)R^3は水素である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

(16)YはNR^4(R^4は前記と同意義)またはO;R^1は、水素またはメチル;Xは、低級アルキレンまたはO;R^2は、置換されていてもよいフェニル;R^3は水素である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

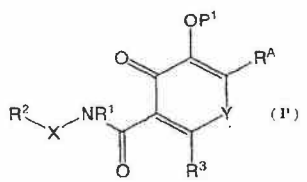
(17)YはNR^4(R^4は水素、低級アルキル、フェニルまたはベンジル)またはO;R^1は、水素またはメチル;Xは、メチレンまたはO;R^2は、ハロゲンで置換されていてもよいフェニル;R^3は水素である、上記1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

(18)上記1～17のいずれかに記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物を含有する医薬組成物。

(19)上記1～17のいずれかに記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物を含有する、抗HIV剤。

(20)式:

[化45]



(I')

(式中、

P^1はヒドロキシ保護基;

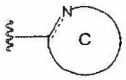
Yは、NR^4(R^4は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、または置換されていてもよいアラルキル)、O、S、SO、またはSO_2;

R^Aは、1)式:$-COR^5$(R^5は置換基群Aから選択される基)で示される基

(置換基群A:水素、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキルオキシ、置換されていてもよいアミノ、置換されていてもよいアミノオキシ、置換されていてもよい複素環式基、置換されていてもよい複素環オキシ、置換されていてもよいアリール、置換されていてもよいアリールオキシ、置換されていてもよいアラルキル、置換されていてもよいアラルキルオキシ、ホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル、置換されていてもよいシクロアルキルカルボニル、置換されていてもよいアリールカルボニル)

または2)式:

[化46]



(式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である。破線は結合の存在又は非存在を表わす。)で示される基;

R^1は、水素または低級アルキル;

Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレン;

R^2は、上記置換基群Aから選択される基;

R^3は水素、ハロゲン、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルケニル、置換されていてもよい低級アルコキシ、置換されていてもよいアミノ、置換されていてもよい低級アルキルアミノ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキル低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよい複素環式基、または置換されていてもよい複素環低級アルキル)

で示される化合物、またはその製薬上許容される塩、またはそれらの溶媒和物。

(21)式:

[化47]



(式中、

P^3は水素またはヒドロキシ保護基;

P^4はヒドロキシ保護基;

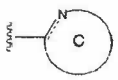
Yは、NR^4(R^4は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、または置換されていてもよいアラルキル)、O、S、SO、またはSO_2;

R^Aは、1)式:$-COR^5$(R^5は置換基群Aから選択される基)で示される基

(置換基群A:水素、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキルオキシ、置換されていてもよいアミノ、置換されていてもよいアミノオキシ、置換されていてもよい複素環式基、置換されていてもよい複素環オキシ、置換されていてもよいアリール、置換されていてもよいアリールオキシ、置換されていてもよいアラルキル、置換されていてもよいアラルキルオキシ、ホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル、置換されていてもよいシクロアルキルカルボニル、置換されていてもよいアリールカルボニル)

または2)式:

[化48]



(式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である。破線は結合の存在又は非存在を表わす。)で示される基;

R^1は、水素または低級アルキル;

Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレン;

R^2は、上記置換基群Aから選択される基;

R^3は水素、ハロゲン、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルケニル、置換されていてもよい低級アルコキシ、置換されていてもよいアミノ、置換されていてもよい低級アルキルアミノ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキル低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよい複素環式基、または置換されていてもよい複素環低級アルキル)

で示される化合物、またはその製薬上許容される塩、またはそれらの溶媒和物。

発明の効果

[0005] 本発明化合物は、ウイルス、特にHIVに対してインテグラーゼ阻害活性および／または細胞増殖阻害活性を有する。よって、インテグラーゼが関与する各種疾患やウイルス感染症（例：エイズ）等の予防または治療に有用である。また本発明は、インテグラーゼ阻害の合成中間体も提供する。

発明を実施するための最良の形態

[0006] 本明細書中で用いる用語を以下に説明する。各用語は単独で又は他の用語と一緒になって以下の意味を有する。

「低級アルキレン」は、炭素数1～6個の直鎖状又は分枝状の低級アルキレンを意味し、例えば、メチレン、エチレン、トリメチレン、プロピレン、テトラメチレン、エチルエチレン、ペンタメチレン又はヘキサメチレン等が挙げられる。好ましくは、炭素数1～4個の直鎖状の低級アルキレンであり、例えば、メチレン、エチレン、トリメチレン又はテトラメチレンが挙げられる。より好ましくはメチレンまたはエチレンである。

「低級アルケニレン」は、上記「低級アルキレン」に1個又はそれ以上の二重結合を有する炭素数2～6個の直鎖状又は分枝状の低級アルケニレン基を意味し、例えば、ビニレン、プロペニレン又はブテニレンが挙げられる。好ましくは、炭素数2～3個の直鎖状の低級アルケニレンであり、例えば、ビニレン又はプロペニレンが挙げられる。

「アルキル」は、炭素数1～10個の直鎖状又は分枝状のアルキル基を意味し、例えば、メチル、エチル、n-プロピル、イソプロピル、n-ブチル、イソブチル、sec-ブチル、tert-ブチル、n-ペンチル、イソペンチル、ネオペンチル、tert-ペンチル、n-ヘキシル、イソヘキシル、n-ヘプチル、n-オクチル、n-ノニル、n-デシル等が挙げられる。好ましくは、炭素数1～6個の低級アルキル、より好ましくは炭素数1～4個の低級アルキルであり、例えば、メチル、エチル、n-プロピル、イソプロピル、n-ブチル、イソブチル、sec-ブチル、tert-ブチル、n-ペンチル、イソペンチル、ネオペンチル、tert-ペンチル、n-ヘキシル、イソヘキシルが挙げられる。

「アルケニル」は、上記「アルキル」に1個又はそれ以上の二重結合を有する炭素数2～8個の直鎖状又は分枝状のアルケニルを意味し、例えば、ビニル、1-プロペニル

、2-プロペニル、1-ブテニル、2-ブテニル、3-ブテニル、1,3-ブタジエニル、3-メチル-2-ブテニル等が挙げられる。好ましくは、炭素数2～6個の低級アルキル、より好ましくは炭素数2～4個の低級アルキルである。

「シクロアルキル」は、炭素数3～10個の環状飽和炭化水素基を意味し、例えば、シクロプロピル、シクロブチル、シクロペンチル、シクロヘキシル、シクロヘプチル、シクロオクチル等が挙げられる。好ましくは、炭素数3～6個のシクロアルキルである。

「シクロアルケニル」は、炭素数3～10個の環状の非芳香族炭化水素基を意味し、例えば、シクロプロペニル（例えば、1-シクロプロペニル）、シクロブテニル（例えば、1-シクロブテニル）、シクロペンテニル（例えば、1-シクロペンテン-1-イル、2-シクロペンテン-1-イル、3-シクロペンテン-1-イル）、シクロヘキセニル（例えば、1-シクロヘキセン-1-イル、2-シクロヘキセン-1-イル、3-シクロヘキセン-1-イル）、シクロヘプテニル（例えば、1-シクロヘプテニル）、シクロオクテニル（例えば、1-シクロオクテニル）等が挙げられる。

「アリール」は、単環芳香族炭化水素基（フェニル）及び多環芳香族炭化水素基（例えば、1-ナフチル、2-ナフチル、1-アントリル、2-アントリル、9-アントリル、1-フェナントリル、2-フェナントリル、3-フェナントリル、4-フェナントリル、9-フェナントリル等）を意味する。好ましくは、フェニル又はナフチル（1-ナフチル、2-ナフチル）が挙げられる。

「アラルキル」は、1～3個の上記「アリール」が置換した上記「アルキル」を意味し、例えば、ベンジル、ジフェニルメチル、トリフェニルメチル、フェネチル、1-ナフチルメチル、2-ナフチルメチル等）等が挙げられる。好ましくは、ベンジルである。

「複素環式基」は、「ヘテロサイクル」または「ヘテロアリール」を意味する。

「ヘテロサイクル」は、窒素原子、酸素原子、及び／又は硫黄原子を少なくとも1個以上環内に有する、置換可能な任意の位置に結合手を有する非芳香族複素環式基（好ましくは5～7員環）を意味し、例えば、1-ピロリニル、2-ピロリニル、3-ピロリニル、1-ピロリジニル、2-ピロリジニル、3-ピロリジニル、1-イミダゾリニル、2-イミダゾリニル、4-イミダゾリニル、1-イミダゾリジニル、2-イミダゾリジニル、4-イミダゾリジニル、1-ピラゾリニル、3-ピラゾリニル、4-ピラゾリニル、1-ピラゾリジニル、3-ピラゾリジニル、4-ピラゾリジニル、ピペリジノ、2-ピペリジル、3-ピペリジル、4-ピペリジル、1-ピペラジニル、

2-ピペラジニル、2-モルホリニル、3 -モルホリニル、モルホリノ、テトラヒドロピラニル等が挙げられる。なお、「非芳香族複素環式基」は、非芳香族であれば、飽和であってもよく、不飽和であってもよい。

「ヘテロアリール」は、単環芳香族複素環式基及び縮合芳香族複素環式基を意味する。

単環芳香族複素環式基は、酸素原子、硫黄原子、および／又は窒素原子を環内に1～4個含んでいてもよい5～8員の芳香環から誘導される、置換可能な任意の位置に結合手を有していてもよい基を意味する。

縮合芳香族複素環式基は、酸素原子、硫黄原子、および／又は窒素原子を環内に1～4個含んでいてもよい5～8員の芳香環が、1～4個の5～8員の芳香族炭素環もしくは他の5～8員の芳香族ヘテロ環と縮合している、置換可能な任意の位置に結合手を有していてもよい基を意味する。

「ヘテロアリール」としては、例えば、フリル（例えば、2-フリル、3-フリル）、チエニル（例えば、2-チエニル、3-チエニル）、ピロリル（例えば、1-ピロリル、2-ピロリル、3-ピロリル）、イミダゾリル（例えば、1-イミダゾリル、2-イミダゾリル、4-イミダゾリル）、ピラゾリル（例えば、1-ピラゾリル、3-ピラゾリル、4-ピラゾリル）、トリアゾリル（例えば、1, 2, 4-トリアゾール-1-イル、1, 2, 4-トリアゾール-3-イル、1, 2, 4-トリアゾール-4-イル）、テトラゾリル（例えば、1-テトラゾリル、2-テトラゾリル、5-テトラゾリル）、オキサゾリル（例えば、2-オキサゾリル、4-オキサゾリル、5-オキサゾリル）、イソキサゾリル（例えば、3-イソキサゾリル、4-イソキサゾリル、5-イソキサゾリル）、チアゾリル（例えば、2-チアゾリル、4-チアゾリル、5-チアゾリル）、チアジアゾリル、イソチアゾリル（例えば、3-イソチアゾリル、4-イソチアゾリル、5-イソチアゾリル）、ピリジル（例えば、2-ピリジル、3-ピリジル、4-ピリジル）、ピリダジニル（例えば、3-ピリダジニル、4-ピリダジニル）、ピリミジニル（例えば、2-ピリミジニル、4-ピリミジニル、5-ピリミジニル）、フラザニル（例えば、3-フラザニル）、ピラジニル（例えば、2-ピラジニル）、オキサジアゾリル（例えば、1, 3, 4-オキサジアゾール-2-イル）、ベンゾフリル（例えば、2-ベンゾ[b]フリル、3-ベンゾ[b]フリル、4-ベンゾ[b]フリル、5-ベンゾ[b]フリル、6-ベンゾ[b]フリル、7-ベンゾ[b]フリル）、ベンゾチエニル（例えば、2-ベンゾ[b]チエニル、3-ベンゾ[b]チエニル、4-ベン

ゾ[b]チエニル、5-ベンゾ[b]チエニル、6-ベンゾ[b]チエニル、7-ベンゾ[b]チエニル)、ベンズイミダゾリル(例えば、1-ベンゾイミダゾリル、2-ベンゾイミダゾリル、4-ベンゾイミダゾリル、5-ベンゾイミダゾリル)、ジベンゾフリル、ベンゾオキサゾリル、キノキサリル(例えば、2-キノキサリニル、5-キノキサリニル、6-キノキサリニル)、シンノリニル(例えば、3-シンノリニル、4-シンノリニル、5-シンノリニル、6-シンノリニル、7-シンノリニル、8-シンノリニル)、キナゾリル(例えば、2-キナゾリニル、4-キナゾリニル、5-キナゾリニル、6-キナゾリニル、7-キナゾリニル、8-キナゾリニル)、キノリル(例えば、2-キノリル、3-キノリル、4-キノリル、5-キノリル、6-キノリル、7-キノリル、8-キノリル)、フタラジニル(例えば、1-フタラジニル、5-フタラジニル、6-フタラジニル)、イソキノリル(例えば、1-イソキノリル、3-イソキノリル、4-イソキノリル、5-イソキノリル、6-イソキノリル、7-イソキノリル、8-イソキノリル)、プリル、プテリジニル(例えば、2-プテリジニル、4-プテリジニル、6-プテリジニル、7-プテリジニル)、カルバゾリル、フェナントリジニル、アクリジニル(例えば、1-アクリジニル、2-アクリジニル、3-アクリジニル、4-アクリジニル、9-アクリジニル)、インドリル(例えば、1-インドリル、2-インドリル、3-インドリル、4-インドリル、5-インドリル、6-インドリル、7-インドリル)、イソインドリル、ファナジニル(例えば、1-フェナジニル、2-フェナジニル)又はフェノチアジニル(例えば、1-フェノチアジニル、2-フェノチアジニル、3-フェノチアジニル、4-フェノチアジニル)等が挙げられる。

「アルコキシ」のアルキル部分は、上記「アルキル」と同意義であり、「アルコキシ」としては、例えば、メトキシ、エトキシ、n-プロポキシ、イソプロポキシ、n-ブトキシ、イソブトキシ、tert-ブトキシなどが挙げられる。

「アルコキシカルボニル」は、上記「アルコキシ」が置換したカルボニルを意味し、例えば、メトキシカルボニル、エトキシカルボニル、n-プロポキシカルボニル、イソプロポキシカルボニル、n-ブトキシカルボニル、イソブトキシカルボニル、tert-ブトキシカルボニル等が挙げられる。

「アルコキシアルキル」は、上記「アルコキシ」が置換した上記「アルキル」を意味し、例えば、メトキシメチル、エトキシメチル、n-プロポキシメチル、イソプロポキシメチル、n-ブトキシメチル、イソブトキシメチル、tert-ブトキシメチル、メトキシエチル、エトキシエチル、n-プロポキシエチル、イソプロポキシエチル、n-ブトキシエチル、イソブトキシ

エチル、tert-ブトキシエチルなどが挙げられる。

「アルカノイル」は、上記「アルキル」が置換したカルボニルを意味し、例えばアセチル、プロピオニル、ブチリル、イソブチリル、バレリル、イソバレリル、ピバロイル、ヘキサノイル、オクタノイル、ラウロイルなどが挙げられる。

「アルキニル」は、上記「アルキル」に1個又はそれ以上の三重結合を有する炭素数2～8個のアルキニルを意味し、例えば、エチニル、1-プロピニル、2-プロピニル、1-ブチニル、2-ブチニル、3-ブチニル等が挙げられる。

「アルキルチオ」は、上記「アルキル」が硫黄原子に置換した基を意味し、例えば、メチルチオ、エチルチオ、n-プロピルチオ、イソプロピルチオ、n-ブチルチオ、イソブチルチオ、sec-ブチルチオ、tert-ブチルチオ、n-ペンチルチオ、イソペンチルチオ、ネオペンチルチオ、tert-ペンチルチオ、n-ヘキシルチオ、イソヘキシルチオ、n-ヘプチルチオ、n-オクチルチオ、n-ノニルチオ、n-デシルチオ等が挙げられる。好ましくは、炭素数1～6個のアルキルが硫黄原子に置換した基である。

「ハロアルキル」は、1個以上のハロゲンで置換された上記「アルキル」を意味する。特に、炭素数1～3個のハロゲン化アルキルが好ましく、例えば、トリフルオロメチル、クロロメチル、ジクロロメチル、1,1-ジクロロエチル、2,2,2-トリクロロエチルなどが挙げられる。

「ハロアルコキシ」は、上記「ハロアルキル」が酸素原子に置換した基を意味し、例えば、トリフルオロメトキシ、クロロメトキシ、ジクロロメトキシ、1,1-ジクロロエトキシ、2,2,2-トリクロロエトキシなどが挙げられる。

「アシル」は、上記「アルキル」が置換したカルボニルおよび上記「アリール」が置換したカルボニルを意味し、例えば、アセチル、プロピオニル、ブチリル、イソブチリル、バレリル、イソバレリル、ピバロイル、ヘキサノイル、オクタノイル、ラウロイル、ベンゾイル等が挙げられる。

「置換されていてもよい低級アルキル」、「置換されていてもよい低級アルケニル」、「置換されていてもよい低級アルコキシ」、「置換されていてもよいシクロアルキル」、「置換されていてもよいシクロアルキル低級アルキル」、「置換されていてもよい低級アルキルアミノ」、「置換されていてもよい複素環式基」、「置換されていてもよいアリール」

、「置換されていてもよいアラルキル」、「置換されていてもよい低級アルカノイル」、「置換されていてもよい低級アルコキシカルボニル」、「置換されていてもよい複素環カルボニル」、「置換されていてもよいシクロアルキルカルボニル」、「置換されていてもよいアリールカルボニル」、「置換されていてもよい含窒素芳香族複素環」、「置換されていてもよい複素環低級アルキル」、「置換されていてもよいシクロアルキルオキシ」、「置換されていてもよい複素環オキシ」、「置換されていてもよいアリールオキシ」、「置換されていてもよいアラルキルオキシ」等が置換基を有する場合、それぞれ同一又は異なる1～4個の、置換基群Bから選択される基で任意の位置が置換されていてもよい。

置換基群Bの例としては、例えば、ヒドロキシ、カルボキシ、ハロゲン(F、Cl、Br、I)、ハロアルキル(例えば、CF_3、CH_2CF_3、CH_2CCl_3等)、アルキル(例えば、メチル、エチル、イソプロピル、tert-ブチル等)、アルケニル(例えば、ビニル)、アルキニル(例えば、エチニル)、シクロアルキル(例えば、シクロプロピル)、シクロアルケニル(例えば、シクロプロペニル)、アルコキシ(例えば、メトキシ、エトキシ、プロポキシ、ブトキシ等)、アルケニルオキシ(例えば、ビニルオキシ、アリルオキシ等)、アルコキシカルボニル(例えば、メトキシカルボニル、エトキシカルボニル、tert-ブトキシカルボニル等)、ニトロ、ニトロソ、置換されていてもよいアミノ(例えば、アルキルアミノ(例えば、メチルアミノ、エチルアミノ、ジメチルアミノ等)、アシルアミノ(例えば、アセチルアミノ、ベンゾイルアミノ等)、アラルキルアミノ(例えば、ベンジルアミノ、トリチルアミノ)、ヒドロキシアミノ等)、アジド、アリール(例えば、フェニル等)、アラルキル(例えば、ベンジル等)、シアノ、イソシアノ、イソシアナト、チオシアナト、イソチオシアナト、メルカプト、アルキルチオ(例えば、メチルチオ等)、アルキルスルホニル(例えば、メタンスルホニル、エタンスルホニル)、置換されていてもよいカルバモイル(例えば、アルキルカルバモイル(例えば、メチルカルバモイル、エチルカルバモイル、ジメチルカルバモイル等)等)、スルファモイル、アシル(例えば、ホルミル、アセチル等)、ホルミルオキシ、ハロホルミル、オキザロ、チオホルミル、チオカルボキシ、ジチオカルボキシ、チオカルバモイル、スルフィノ、スルフォ、スルホアミノ、ヒドラジノ、アジド、ウレイド、アミジノ、グアニジノ、フタルイミド、オキソ等が挙げられる。

「置換されていてもよいアミノ」または「置換されていてもよいカルバモイル」の置換基としては、置換されていてもよいアルキル（例えば、メチル、エチル、イソプロピル、ベンジル、カルバモイルアルキル（例：カルバモイルメチル）、モノまたはジアルキルカルバモイルアルキル（例：ジメチルカルバモイルエチル）、ヒドロキシアルキル、ヘテロサイクルアルキル（例：モルホリノエチル、テトラヒドロピラニルエチル）、アルコキシカルボニルアルキル（例：エトキシカルボニルメチル、エトキシカルボニルエチル）、モノまたはジアルキルアミノアルキル（例：ジメチルアミノエチル）等）、アルコキシアルキル（例えば、メトキシエチル、エトキシメチル、エトキシエチル、イソプロポキシエチル等）、アシル（例えば、ホルミル、置換されていてもよいアルキルカルボニル（例えば、アセチル、プロピオニル、ブチリル、イソブチリル、バレリル、イソバレリル、ピバロイル、ヘキサノイル、オクタノイル、メトキシエチルカルボニル、2,2,2-トリフルオロエチルカルボニル、エトキシカルボニルメチルカルボニル、アルコキシアルキルカルボニル（例：メトキシエチルカルボニル）、アルキルカルバモイルアルキルカルボニル（例：メチルカルバモイルエチルカルボニル）、アルコキシカルボニルアセチル等）、置換されていてもよいアリールカルボニル（例えば、ベンゾイル、トルオイル等）、置換されていてもよいアラルキル（例えば、ベンジル、4-フルオロベンジル等）、ヒドロキシ、置換されていてもよいアルキルスルホニル（例えば、メタンスルホニル、エタンスルホニル、イソプロピルスルホニル、2,2,2-トリフルオロエタンスルホニル、ベンジルスルホニル、メトキシエチルスルホニル等）、アルキルまたはハロゲンで置換されていてもよいアリールスルホニル（例えば、ベンゼンスルホニル、トルエンスルホニル、4-フルオロベンゼンスルホニル）、シクロアルキル（例えば、シクロプロピル等）、アルキルで置換されていてもよいアリール（例えば、フェニル、トリチル等）、アルキルアミノスルホニル（例えば、メチルアミノスルホニル、ジメチルアミニスルホニル等）、アルキルアミノカルボニル（例えば、ジメチルアミノカルボニル等）、アルコキシカルボニル（例えば、エトキシカルボニル等）、シクロアルキルカルボニル（例えば、シクロプロピルカルボニル、シクロヘキシルカルボニル等）、置換されていてもよいスルファモイル（例えば、スルファモイル、メチルスルファモイル、ジメチルスルファモイル等）、アルキルカルボニルアミノ（例：メチルカルボニルアミノ）、ヘテロサイクル（例：モルホリノ、テトラヒドロピラニル）、置換され

ていてもよいアミノ(例:モノまたはジアルキルアミノ(例:ジメチルアミノ)、ホルミルアミノ)等が挙げられる。好ましくはメチルである。上記置換基は、モノまたはジ置換のいずれでもよい。

「置換されていてもよいアミノ」または「置換されていてもよいカルバモイル」、「置換されていてもよいカルバモイルカルボニル」のアミノ基は、アミノ基の2つの置換基が隣接する窒素原子と共に硫黄原子および/または酸素原子を環内に含有していてもよい含窒素ヘテロサイクル(好ましくは5～7員環であり、また好ましくは飽和である)を形成してもよく、該環はオキソまたはヒドロキシで置換されていてもよい。環を形成する硫黄原子はオキソで置換されていてもよい。例えば、ピペラジニル、ピペリジノ、モルホリノ、ピロリジノ、チアジナン-2-イル、2-オキソピペリジノ、2-オキソピロリジノ、1,1-ジオキシド-1,2-チアジナン-2-イル、4-ヒドロキシモルホリノ等の5員または6員の環等が好ましい。

(より好ましい態様)

Yは、2価の基であればよく、置換されていてもよいイミノやO、S、SO、またはSO_2が例示される。好ましくは置換されていてもよいイミノ、具体的には－N(R^4)－(R^4は水素、置換されていてもよい低級アルキル、置換されていてもよいアリールまたは置換されていてもよいアラルキル)で示される基であるか、または－O－である。R^1の置換されていてもよい低級アルキルまたは置換されていてもよいアリールの置換基として好ましくは、ハロゲン、低級アルコキシ、アミノ、ヒドロキシが例示される。R^4は好ましくは、水素、低級アルキル、フェニルまたはベンジルである。

R^Aにおいては、前記1)で示されるアシル基中のカルボニル基、または前記2)で示されるC環中のN原子が薬理活性上、特に重要であり、その他の部分構造は主薬理活性に悪影響を及ぼさない限り種々の構造を取り得る。

R^Aは、1)式:－COR^5(R^5は置換基群Aから選択される基)で示される基である。

置換基群Aは、水素、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキルオキシ、置換されていてもよいアミノ、置換されていてもよいアミノオキシ、置換されていてもよい複素環式基、置換されていてもよい複素環オキシ、置

換されていてもよいアリール、置換されていてもよいアリールオキシ、置換されていてもよいアラルキル、置換されていてもよいアラルキルオキシ、ホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル、置換されていてもよいシクロアルキルカルボニル、および置換されていてもよいアリールカルボニルである。

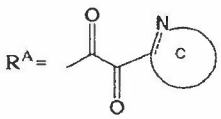
置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいシクロアルキルの置換基として好ましくは、ヒドロキシ、ハロゲン、アミノ、低級アルコキシ(例:メトキシ、エトキシ)が例示される。置換されていてもよいアミノの置換基として好ましくは、低級アルキル(例:メチル、エチル、ジメチル)、低級アルコキシ(例:メトキシ、エトキシ)、置換されていてもよいアリール、置換されていてもよいアラルキル(例:ベンジル、4－F－ベンジル)が例示される。置換されていてもよい複素環式基、置換されていてもよいアリールの置換基として好ましくは、低級アルキル、低級アルコキシ、アミノ、低級アルキルアミノ、ジ低級アルキルアミノ、ヒドロキシ、ハロゲンが例示される。

R^5は好ましくは、水素、ヒドロキシ、置換されていてもよい低級アルキル(置換基の例:ヒドロキシ、低級アルコキシ)、置換されていてもよい低級アルコキシ(置換基の例:ヒドロキシ、低級アルコキシ)、または置換されていてもよいアミノ(置換基の例:低級アルキル、ヒドロキシ低級アルキル、低級アルコキシ、低級アルコキシ低級アルキル、フェニル、ベンジル、4-フルオロベンジル)、フェニル、置換されていてもよいフェノキシ(例:フェノキシ、4-フルオロフェニルオキシ)、置換されていてもよいベンジル(例:ベンジル、4-フルオロベンジル)、置換されていてもよいベンジルオキシ(例:ベンジルオキシ、4-フルオロベンジルオキシ)、モルホリノ、モルホリノオキシ、2,2－ジメチルヒドラジノ、メトキシアミノ等である。 別の態様においてR^5は好ましくは、ホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル、置換されていてもよいシクロアルキルカルボニル、および置換されていてもよいアリールカルボニルである。これらの「置換されていてもよい」の置換基とし

て好ましくは、低級アルキル、低級アルコキシ、アミノ、低級アルキルアミノ、ヒドロキシ、ハロゲン、フェニルが例示される。

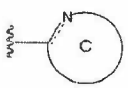
R^5が複素環カルボニルの場合、該複素環としては前記C環が例示され、R^Aは例えば以下に示す構造を取り得る。但し、この場合、C環中の窒素原子の位置は、結合手の隣接部位以外の位置であってもよく、以下の構造に限定されない。

[化6]



本発明の別の態様においてR^Aは、2)式:

[化7]



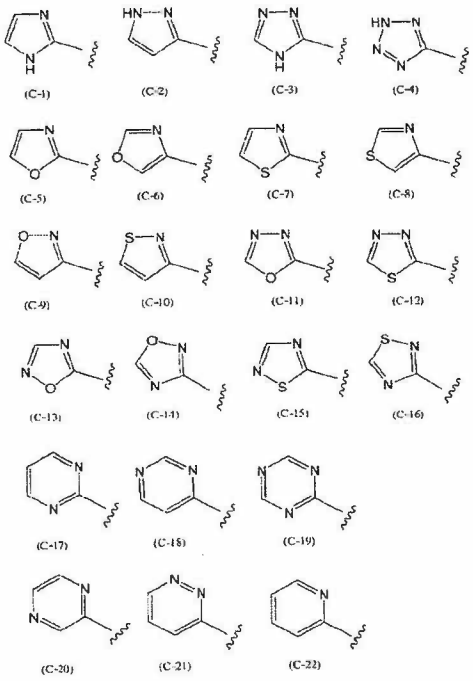
(式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である。破線は結合の存在又は非存在を表わす。)で示される基である。

C環は、結合部位に隣接する原子のうち、少なくとも1つの原子が非置換の窒素原子である含窒素芳香族複素環を意味する。破線は結合の存在または不存在を示す。曲線部分は、C環を構成する原子及び結合を意味し、C環が芳香性を表わすように選択すればよい。C環は好ましくは、結合部位の原子が炭素原子であり、該炭素原子は、隣接する一方の原子と二重結合で結ばれ、隣接する他方の原子と単結合で結ばれている。

C環は好ましくは、5～8員環であり、より好ましくは5または6員環であるが、他の環(例:炭素環、複素環)との縮合環であってもよい。C環は、1個のN原子以外にさらに、O、SおよびN原子からなる群から選択される1～4個、好ましくは1～3個の同一また

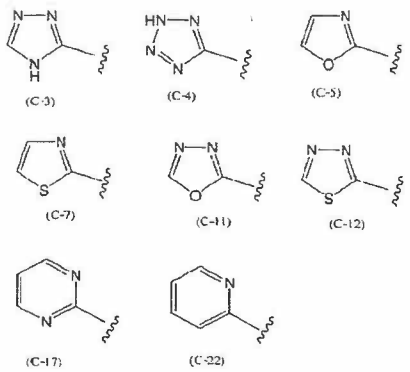
は異なるヘテロ原子を含有し得る。C環は好ましくは、N原子を1～3個含有するか、またはN原子を1または2個含有し、かつOまたはS原子を1個含有する。具体例を以下に示す。

[化8]



C環はより好ましくは、以下に示す環である。

[化9]



C環が縮合環である例としては、上記単環に1～4個の5～8員の芳香族炭素環(5～8員の芳香族炭素環)及び／又は他の5～8員の芳香族ヘテロ環(O原子、S原子、および／又はN原子を環内に1～4個含んでいてもよい5～8員の芳香族複素環)が縮合したヘテロアリールを意味する。例えば、ベンズイミダゾール-2-イル、ベンゾオキサゾール-2-イル、キノキサリン-2-イル、シンノリン-3-イル、キナゾリン-2-イル、キナゾリン-4-イル、キノリン-2-イル、フタラジン-1-イル、イソキノリン-1-イル、イソキノリン-3-イル、プリン-2-イル、プリン-6-イル、プリン-8-イル、プテリジン-2-イル、プテリジン-4-イル、プテリジン-6-イル、プテリジン-7-イル、カルバゾール-1-イル、フェナントリジン-6-イル、インドール-2-イル、イソインドール-1-イル等が挙げられる。

上記C環が置換されている場合、置換基としてより好ましくは、水素、置換されていてもよい低級アルキル(置換基の例:ヒドロキシ、低級アルコキシ、アミノ、ハロゲン)、置換されていてもよいアリール(例:フェニル、4-フルオロフェニル)、置換されていてもよいアラルキル(例:ベンジル、4-フルオロベンジル)、置換されていてもよいアリールオキシ(例:フェニルオキシ、4-フルオロフェニルオキシ)、置換されていてもよいアラルキルオキシ(例:ベンジルオキシ、4-フルオロベンジルオキシ)、複素環基(例:モルホリノ)、置換されていてもよいアミノ(置換基の例:低級アルキル(例:メチル、エチル)、アミノ、モノまたはジ低級アルキルアミノ、低級アルコキシ(例:メトキシ、エトキシ))、ハロゲン、ヒドロキシ、低級アルキルカルボニル(例:アセチル)、低級アルコキシカ

ルボニル(例:メトキシカルボニル)、置換されていてもよいカルバモイル(置換基の例:低級アルキル)が例示される。さらに好ましくは、後記のR^{7a}およびR^{7b}即ち、(1)水素(2)メチル(3)エチル(4)n-プロピル(5)イソプロピル(6)2-ヒドロキシエチル(7)2-メトキシエチル(8)フェニル(9)ベンジル(10)モルホリン(11)1,1-ジメチルヒドラジン(12)O-メチルヒドロキシルアミン(13)ハロゲン(F, Cl, Br, I)(14)ヒドロキシ(15)アセチル(16)メトキシカルボニル(17)カルバモイル(18)4-フルオロベンジル(19)4-フルオロフェニルオキシ(20)4-フルオロベンジルオキシ等が例示される。これらの置換基は、同一または異なって、C環上に1～3個、好ましくは1～2個、置換し得る。

C環はより好ましくは、後記実施例に記載のR^A-4～R^A-11で示される基である。

[0007] R^1は、水素または低級アルキルであり、好ましくは水素または炭素数1～3個の低級アルキル(例:メチル)であり、特に好ましくは水素である。

Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基(以下、Mで表わすこともある)、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレンである。ここで「介在」とは、該ヘテロ原子基が、1)アルキレンもしくはアルケニレンを構成する炭素原子間に存在する場合、2)Xに隣接するカルバモイル基のN原子と結合する場合、および/または3)Xに隣接するR^2と結合する場合を意味する。また該ヘテロ原子基(M)は、同一または異なる、1個またはそれ以上の基であってよい。例えば、低級アルキレンにヘテロ原子基が介在する場合として、$-M-CH_2-$、$-CH_2-M-CH_2-$、$-CH_2-M-$、$-CH_2-M-M-CH_2-$などが例示される。Xは好ましくは、1～3個の原子が連結してなるスペーサーである。Xはより好ましくはヘテロ原子基が介在してもよい、低級アルキレンもしくは低級アルケニレン、またはOであり、さらに好ましくは炭素数1～3個の低級アルキレンまたは炭素数2～3個の低級アルケニレン、またはOであり、特に好ましくはメチレンまたはOである。

R^2は、上記置換基群Aから選択される基であり、好ましくは置換されていてもよいアリールである。アリールは好ましくはフェニルである。アリール上の置換基として好ましくは、ハロゲン、ヒドロキシ、アミノ、低級アルキルアミノ、シアノ、カルボキシ、ホルミル、オキソ、低級アルキル、低級アルコキシ、低級アルキルチオ、カルバモイル、および

低級アルキルカルバモイルからなる群から選択される、同一または異なる1～3個、好ましくは1～2個の置換基が例示され、より好ましくは、ハロゲン、ヒドロキシ、アミノ、シアノ、低級アルキル、および低級アルコキシから選択され、特に好ましくはハロゲン(例:F)である。アリール上の置換基の位置は好ましくは4位である。R^2はより好ましくは、ハロゲンで置換されていてもよいフェニル、さらに好ましくはフェニルまたは少なくともハロゲンで置換されたフェニルである。特に好ましくは4－ハロゲノフェニル(例:4－F－フェニル)である。

R^3としては、化合物(I)の薬理活性に悪影響を及ぼさないものであれば種々の置換基であり得、例えば、水素、ハロゲン、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルケニル、置換されていてもよい低級アルコキシ、置換されていてもよいアミノ、置換されていてもよい低級アルキルアミノ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキル低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよい複素環式基、または置換されていてもよい複素環低級アルキルである。「置換されていてもよい」の置換基としては、ハロゲン、ヒドロキシ、アミノ、低級アルキルアミノ、シアノ、カルボキシ、ホルミル、オキソ、低級アルキル、低級アルコキシ、低級アルキルチオ、カルバモイル、低級アルキルカルバモイル、アリール、複素環基、低級アルキルカルボニル、低級アルキルカルボニルオキシ、低級アルコキシカルボニル、ハロゲン化低級アルキル、ハロゲン化低級アルコキシなどが例示される。R^3は好ましくは、水素または低級アルキル(例:メチル)であり、より好ましくは水素である。

[0008] 化合物(I)はより好ましくは、以下の態様を含む。

(1)Yは、NR^4(R^4は水素、置換されていてもよい低級アルキル(例:メチル)、置換されていてもよいアリール(例:フェニル)、置換されていてもよいアラルキル(例:ベンジル))またはO、好ましくはNR^4(R^4は水素、低級アルキル(例:メチル)、フェニルまたはベンジル)またはO、より好ましくはNHであり; R^Aは、式:－COR^5(R^5は置換基群Aから選択される基)で示される基であり;R^1は、水素または低級アルキル(例:メチル)、好ましくは水素であり、Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは

低級アルケニレン、好ましくは該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレンまたはO、より好ましくは該ヘテロ原子基が介在していてもよいC1～C3アルキレンまたはC2～C3アルケニレンまたはO、特に好ましくはメチレンであり;R^2は置換されていてもよいアリール、好ましくは置換されていてもよいフェニル、より好ましくはハロゲンで置換されていてもよいフェニルである場合。

この場合、R^5は好ましくは、低級アルコキシ(例:メトキシ、エトキシ)、アミノ、モノまたはジ低級アルキルアミノ(例:メチルアミノ、ジメチルアミノ)、ヒドロキシであり、より好ましくは低級アルコキシである。また別の態様において、R^5は好ましくはホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル(例:前記C環)、置換されていてもよいシクロアルキルカルボニル、および置換されていてもよいアリールカルボニルである。

R^3は好ましくは水素、ハロゲン、ヒドロキシ、低級アルキルであり、より好ましくは水素である。

(2)Yは、NR^4(R^4は水素、置換されていてもよい低級アルキル(例:メチル)、置換されていてもよいアリール(例:フェニル))、置換されていてもよいアラルキル(例:ベンジル))またはO、好ましくはNR^4(R^4は水素、低級アルキル(例:メチル)、フェニルまたはベンジル)またはO、より好ましくはNHであり; R^Aは、前記2)で示される含窒素芳香族複素環基(C環)であり;R^1は、水素または低級アルキル(例:メチル)、好ましくは水素であり、Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレン、好ましくは該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレンまたはO、より好ましくは該ヘテロ原子基が介在していてもよいC1～C3アルキレンまたはC2～C3アルケニレンまたはO、特に好ましくはメチレンであり;R^2は置換されていてもよいアリール、好ましくは置換されていてもよいフェニル、より好ましくはハロゲンで置換されていてもよいフェニルである場合。

この場合、R^3は好ましくは水素、ハロゲン、ヒドロキシ、低級アルキルであり、より好ましくは水素である。

(3)Yは、O、S、SOまたはSO_2、好ましくはOであり; R^Aは、式:$-COR^5$(R^5は置換基群Aから選択される基)で示される基であり;R^1は、水素または低級アルキル(例:メチル)、好ましくは水素であり、Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレン、好ましくは該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレンまたはO、より好ましくは該ヘテロ原子基が介在していてもよいC1～C3アルキレンまたはC2～C3アルケニレンまたはO、特に好ましくはメチレンであり;R^2は置換されていてもよいアリール、好ましくは置換されていてもよいフェニル、より好ましくはハロゲンで置換されていてもよいフェニルである場合。

この場合、R^5は好ましくは、低級アルコキシ(例:メトキシ、エトキシ)、アミノ、モノまたはジ低級アルキルアミノ(例:メチルアミノ、ジメチルアミノ)、ヒドロキシであり、より好ましくは低級アルコキシである。R^3は好ましくは水素、ハロゲン、ヒドロキシ、低級アルキルであり、より好ましくは水素である。また別の態様において、R^6は好ましくはホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル(例:前記C環)、置換されていてもよいシクロアルキルカルボニル、および置換されていてもよいアリールカルボニルである。

(4)Yは、O、S、SOまたはSO_2、好ましくはOであり; R^Aは、前記2)で示される含窒素芳香族複素環基(C環)であり;R^1は、水素または低級アルキル、好ましくは水素であり、Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレン、好ましくは該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレンまたはO、より好ましくは該ヘテロ原子基が介在していてもよいC1～C3アルキレンまたはC2～C3アルケニレンまたはO、特に好ましくはメチレンであり;R^2は置換されていてもよいアリール、好ましくは置換されていてもよいフェニル、より好ましくはハロゲンで置換されていてもよいフェニルである場合。

この場合、R^3は好ましくは水素、ハロゲン、ヒドロキシ、低級アルキルであり、より好ましくは水素である。

(5)Yは、NR^4(R^4は水素、置換されていてもよい低級アルキル(例:メチル)、置換されていてもよいアリール(例:フェニル))、置換されていてもよいアラルキル(例:ベンジル))OまたはS; R^Aは、前記2)で示される含窒素芳香族複素環基(C環、好ましくは、各置換されていてもよい、C-3, C-5, C-7, C-11, C-12, C-17, C-22であり、より好ましくはR^A-4, R^A-5, R^A-6, R^A-7, R^A-8, R^A-10, R^A-11);R^1は、水素または低級アルキル、好ましくは水素であり、R^2-Xが水素、低級アルキル、置換された低級アルキル(置換基の例:ヒドロキシ、低級アルコキシ)、フェニル、アラルキル(例:ベンジル)、複素環式基(好ましくは、5～7員環)、1,1-ジメチルヒドラジン 、またはO-メチルヒドロキシルアミンである場合。

この場合、R^3は好ましくは水素、ハロゲン、ヒドロキシ、低級アルキルであり、より好ましくは水素である。

(6)Yは、NR^4(R^4は水素、置換されていてもよい低級アルキル(例:メチル)、置換されていてもよいアリール(例:フェニル))、置換されていてもよいアラルキル(例:ベンジル))、OまたはS; R^Aは、$-COR^5$(R^5は、置換されていてもよいアミノ(置換基の例:アラルキル(例:ベンジル)、置換アラルキル(例:4－F－ベンジル))、置換されていてもよいアラルキルオキシ(例:ベンジルオキシ、4－F－ベンジルオキシ));R^1は、水素または低級アルキル、好ましくは水素であり、R^2-Xが水素、低級アルキル、置換された低級アルキル(置換基の例:ヒドロキシ、低級アルコキシ)、フェニル、アラルキル(例:ベンジル)、複素環式基(好ましくは、5～7員環)、1,1-ジメチルヒドラジン 、またはO-メチルヒドロキシルアミンである場合。

この場合、R^3は好ましくは水素、ハロゲン、ヒドロキシ、低級アルキルであり、より好ましくは水素である。

[0009] 化合物(I)は、その化学構造として少なくとも以下の特徴を有する。

(1)主骨格であるヘテロ環上に、オキソ(=O)、ヒドロキシ(OH)およびR^Aが隣接して結合し、かつR^Aは該ヘテロ環に結合する炭素原子の隣接部位にヘテロ原子(OまたはN)を有する。

(2)主骨格であるヘテロ環上のオキソの隣接部位に、置換されたカルバモイル基($-CONR^1XR^2$)を有する。R^2は上記置換基群Aから選択される基、好ましくは、置換さ

れていてもよいアリールである。

このような構造を有することにより、HIVを含むウイルスに対して、非常に強いインテグラーゼ阻害作用および／または細胞増殖阻害活性を示す。

本発明は、化合物(I)の製薬上許容される塩及びそれらの溶媒和物も提供する。本発明化合物の理論上可能なすべての互変異性体、幾何異性体等も、本発明の範囲内である。

本発明化合物の製薬上許容される塩としては、塩基性塩として、例えば、ナトリウム塩、カリウム塩等のアルカリ金属塩;カルシウム塩、マグネシウム塩等のアルカリ土類金属塩;アンモニウム塩;トリメチルアミン塩、トリエチルアミン塩、ジシクロヘキシルアミン塩、エタノールアミン塩、ジエタノールアミン塩、トリエタノールアミン塩、ブロカイン塩、メグルミン塩、ジエタノールアミン塩またはエチレンジアミン塩等の脂肪族アミン塩;N,N-ジベンジルエチレンジアミン、ベネタミン塩等のアラルキルアミン塩;ピリジン塩、ピコリン塩、キノリン塩、イソキノリン塩等のヘテロ環芳香族アミン塩;テトラメチルアンモニウム塩、テトラエチルアモニウム塩、ベンジルトリメチルアンモニウム塩、ベンジルトリエチルアンモニウム塩、ベンジルトリブチルアンモニウム塩、メチルトリオクチルアンモニウム塩、テトラブチルアンモニウム塩等の第4級アンモニウム塩;アルギニン塩、リジン塩等の塩基性アミノ酸塩等が挙げられる。酸性塩としては、例えば、塩酸塩、硫酸塩、硝酸塩、リン酸塩、炭酸塩、炭酸水素塩、過塩素酸塩等の無機酸塩;酢酸塩、プロピオン酸塩、乳酸塩、マレイン酸塩、フマール酸塩、酒石酸塩、リンゴ酸塩、クエン酸塩、アスコルビン酸塩等の有機酸塩;メタンスルホン酸塩、イセチオン酸塩、ベンゼンスルホン酸塩、p-トルエンスルホン酸塩等のスルホン酸塩;アスパラギン酸塩、グルタミン酸塩等の酸性アミノ酸等が挙げられる。

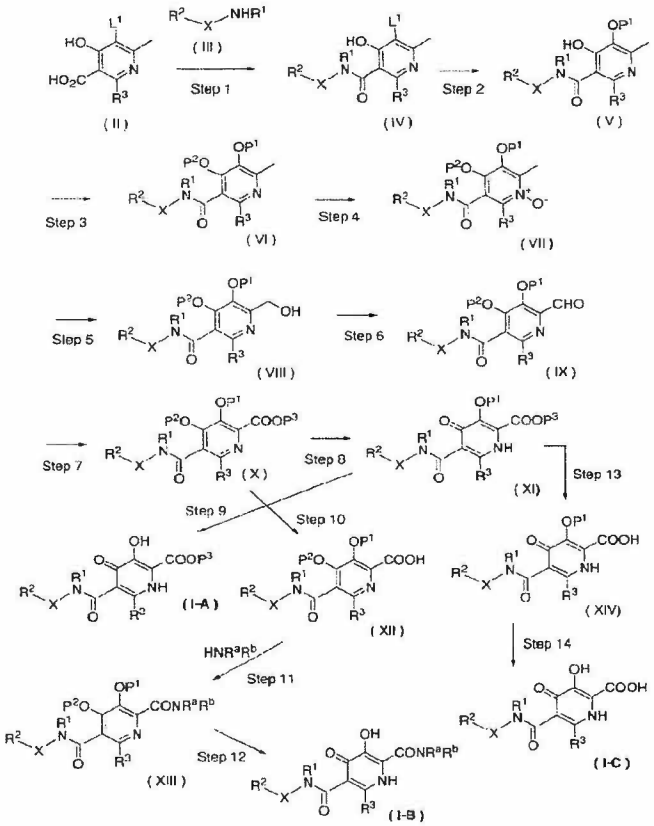
本発明化合物の溶媒和物としては、アルコール和物や水和物等が挙げられる。

[0010] 本発明化合物の一般的製法を以下に例示する。

(製法1)

Y=NH、$R^{\wedge}$=－COR^{5}である場合(化合物I-A, I-B, I-C)

[化10]



(式中、L^1は脱離基(例;ハロゲン);P^1、P^2はヒドロキシ保護基;P^3はカルボキシ保護基(例:低級アルキル);R^a、R^bは水素またはアミノ基上の置換基)

ヒドロキシ保護基(P^1、P^2)としては、例えば、アシル(例:アセチル、ピバロイル、ベンゾイル)、アラルキル(例:ベンジル)、低級アルキル(例:メチル)、アルコキシアルキル(例:メトキシメチル、メトキシエチル)、低級アルキルスルホニル(例:メタンスルホニル)、アリールスルホニル(例:ベンゼンスルホニル、トルエンスルホニル)、アルコキシカルボニル(例:メトキシカルボニル)等が挙げられる。

カルボキシ保護基(P^3)としては、低級アルキル(例;メチル、エチル)、アラルキル(例:ベンジル)が例示される。

[0011] (第1工程)

本工程は、化合物(II)と化合物(III)を縮合させて化合物(IV)を製造する反応である。反応は、一般に行われるカルボン酸のアミド化反応の条件に準じて行えばよい。化合物(II)はそのまま反応させてもよいが、対応する酸クロリドや活性エステルに変換してから反応させてもよい。好ましくは縮合剤の存在下、適当な溶媒中で行う。

縮合剤としては、ジシクロヘキシルカルボジイミド、1-エチル-3-(3-ジメチルアミノプロピル)カルボジイミド塩酸塩等を使用することができる。必要ならば、1-ヒドロキシベンゾトリアゾールやN-ヒドロキシスクシンイミド等の試薬、トリエチルアミン、N-メチルモルホリン、ピリジンなどの塩基を添加することもできる。

反応温度としては、0～150℃、好ましくは室温から70℃である。

反応溶媒としては、広く非プロトン性溶媒が使用でき、テトラヒドロフラン(THF)、1,4-ジオキサン、ジメチルホルムアミド(DMF)、塩化メチレン、クロロホルム等が好ましい。

反応時間は、数分～数十時間、好ましくは9～17時間である。

(第2工程)

本工程は、化合物(IV)に保護ヒドロキシ基(OP^1)を導入して化合物(V)を製造する反応である。反応は、一般に行われるアルコキシ化反応等の条件に準じて行えばよい。

例えば、化合物(IV)に金属アルコキサイド(例:Me ONa)を反応させることにより、P^1＝メチルである化合物(V)を合成できる。

反応温度としては、0～200℃、好ましくは80から120℃である。

反応溶媒としては、アルコール、ジメチルホルムアミド(DMF)、ジメチルスルホキシド(DMSO)が例示される。

反応時間は、数分～数十時間、好ましくは2～4時間である。

(第3工程)

本工程は、化合物(V)のヒドロキシを保護して化合物(VI)を製造する反応である。反応は、一般に行われるヒドロキシの保護反応の条件に準じて行えばよい。例えばアルコールおよび各種ホスフィンと共に、アゾジカルボン酸ジイソプロピルやアゾジカルボン酸ジエチルを用いることによってP^2＝アルキルである化合物(VI)を合成できる.

反応温度としては、0～100℃、好ましくは0℃～室温である。

反応溶媒としては、THF、トルエン、ジクロロメタン等が例示される。

反応時間は、数分～数十時間、好ましくは1～3時間である。

(第4工程)

本工程は、化合物(VI)のN原子を酸化して化合物(VII)を製造する反応である。反応は、一般に行われる酸化剤を用いる酸化反応の条件に準じて行えばよい。

反応温度としては、0～100℃、好ましくは氷冷下から室温である。

反応溶媒としては、クロロホルム、塩化メチレン, 酢酸等が例示される。

酸化剤としては、メタクロロ過安息香酸、過酸化水素等が例示される。

反応時間は、数分～数十時間、好ましくは1～5である。

(第5工程)

本工程は、化合物(VII)のメチル基をヒドロキシ化する反応である。好ましくは、無水酢酸と反応させてアセトキシ化(反応温度:0～150℃、好ましくは室温から100℃)した後、加水分解(例:塩基(例:水酸化アルカリ金属)で処理)すればよい。

反応時間は、数分～数十時間、好ましくはアセトキシ化に0.5～2時間、加水分解に0.5～1時間である。

(第6工程)

本工程は、化合物(VIII)のヒドロキシを酸化して化合物(IX)を合成する反応である。

反応温度としては、0～150℃、好ましくは室温から70℃である。

反応溶媒としては、クロロホルム等が例示される。

酸化剤としては、ジメチルスルホキサイド等が例示される。

反応時間は、数分～数十時間、好ましくは0.1～1時間である。

(第7工程)

本工程は、化合物(IX)のホルミルを酸化して化合物(X)を合成する反応である。

反応温度としては、0～150℃、好ましくは氷冷下～室温である。

反応溶媒としては、アルコール等が例示される。

酸化剤としては、水酸化カリウムとヨウ素が例示される。

反応時間は、数分～数十時間、好ましくは0.5～3時間である。

(第8工程)

本工程は、化合物(X)のOP^2部分を脱保護して化合物(XI)を合成する反応である。反応は、一般に行われるヒドロキシ保護基の脱保護反応の条件に準じて行えばよい。

反応温度としては、0～150℃、好ましくは氷冷下～室温である。

反応溶媒としては、アセトニトリル、塩化メチレン、テトラヒドロフラン(THF)等が例示される。

反応時間は、数分～数十時間、好ましくは1～3時間である。

(第9工程)

本工程は、化合物(XI)のOP^1部分を脱保護して本発明化合物(I-A)を合成する反応である。反応は、好ましくはルイス酸(例:塩化アルミニウム)で処理すればよい。

反応温度としては、0～150℃、好ましくは10～50℃である。

反応溶媒としては、塩化メチレン、THF等が例示される。

反応時間は、数分～数十時間、好ましくは1～3時間である。

(第10工程)

本工程は、化合物(X)のエステル部分($COOP^3$)を脱保護してカルボン酸(XII)を合成する反応である。好ましくはアルカリ(例:NaOH)で加水分解すればよい。

反応温度としては、0～150℃、好ましくは10～50℃である。

反応溶媒としては、メタノール、水等が例示される。

反応時間は、数分～数十時間、好ましくは数分～2時間である。

カルボン酸(XII)は、種々の誘導体(例;アミド)に変換可能である。

(第11工程)

本工程は、化合物(XII)に各種アミンを反応させて化合物(XIII)を合成する反応である。反応は、一般に行われるカルボン酸のアミド化反応の条件に準じて行えばよく、例えば第1工程と同様に反応させればよい。

反応温度としては、0～150℃、好ましくは室温から70℃である。

反応溶媒としては、広く非プロトン性溶媒が使用でき、テトラヒドロフラン(THF)、1,4-ジオキサン、ジメチルホルムアミド(DMF)、塩化メチレン、クロロホルム等が好ましい。

反応時間は、数分～数十時間、好ましくは数分～3時間である。

得られた化合物(XIII)のアミド部分をさらに化学修飾(例:N－アルキル化)してもよい。

(第12工程)

本工程は、化合物(XIII)のOP^1およびOP^2部分を脱保護して、本発明化合物(I－B)を合成する反応である。反応は、一般に行われるヒドロキシ保護基の脱保護反応の条件に準じて行えばよい。

例えばピリジン塩酸塩を用いる場合、反応温度としては、0～200℃、好ましくは150～180度である。

反応時間は、数分～数十時間、好ましくは1～5分である。

(第13工程)

本工程は、化合物(XI)のエステル部分($COOP^3$)を脱保護してカルボン酸(XIV)を合成する反応である。好ましくはアルカリ(例:LiOH)で加水分解すればよい。

反応温度としては、0～150℃、好ましくは10～50℃である。

反応溶媒としては、メタノール、水等が例示される。

反応時間は、数分～数十時間、好ましくは数分～3時間である。

(第14工程)

本工程は、化合物(XIV)のOP^1部分を脱保護して本発明化合物(I-C)を合成する反応である。反応は、好ましくはルイス酸(例:三臭化ホウ素)で処理すればよい。

反応温度としては、0～150℃、好ましくは氷冷下～室温である。

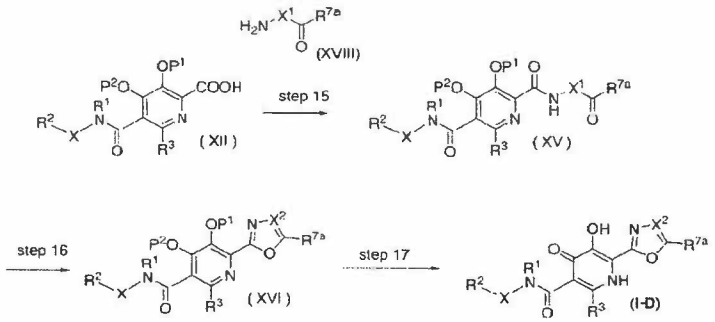
反応溶媒としては、ジクロロメタン等が例示される。

反応時間は、数分～数十時間、好ましくは数分～5時間である。

[0012] (製法2)

Y＝NH、R^A＝C環で示される複素環基である場合(化合物I-D)

[化11]



(式中X^1はNHまたはCHR7^b;X^2はNまたはCR7^b;7^{a}および7^{b}は、複素環上の置換基;その他の記号は前記と同意義)

(第15工程)

本工程は、化合物(XII)と化合物(XVIII)を縮合させて化合物(XV)を製造する反応である。反応は、一般に行われるカルボン酸のアミド化反応の条件に準じて行えばよい。化合物(XII)はそのまま反応させてもよいが、対応する酸クロリドや活性エステルに変換してから反応させてもよい。好ましくは縮合剤の存在下、適当な溶媒中で行う。

縮合剤としては、ジシクロヘキシルカルボジイミド、1-エチル-3-(3-ジメチルアミノプロピル)カルボジイミド塩酸塩等を使用することができる。必要ならば、1-ヒドロキシベンゾトリアゾールやN-ヒドロキシスクシンイミド等の試薬、トリエチルアミン、N-メチルモルホリン、ピリジンなどの塩基を添加することもできる。

反応温度としては、0～150℃、好ましくは室温から70℃である。

反応溶媒としては、広く非プロトン性溶媒が使用でき、テトラヒドロフラン(THF)、1,4-ジオキサン、ジメチルホルムアミド(DMF)、塩化メチレン、クロロホルム等が好ましい。

反応時間は、数分～数十時間、好ましくは9～17時間である。

(第16工程)

本工程は、化合物(XV)から脱水環化反応を行なって化合物(XVI)を製造する反応である。反応は一般に行なわれる脱水反応の条件に準じて行なえばよい。たとえ

ば化合物(XV)にオキシ塩化りん等を反応させることにより、化合物(XVI)を合成できる。

反応温度としては、0～150℃、好ましくは室温から100℃である。

反応溶媒としては、トルエン、塩化メチレン、クロロホルム等が好ましい。

反応時間は、数分～数十時間、好ましくは1～3時間である。

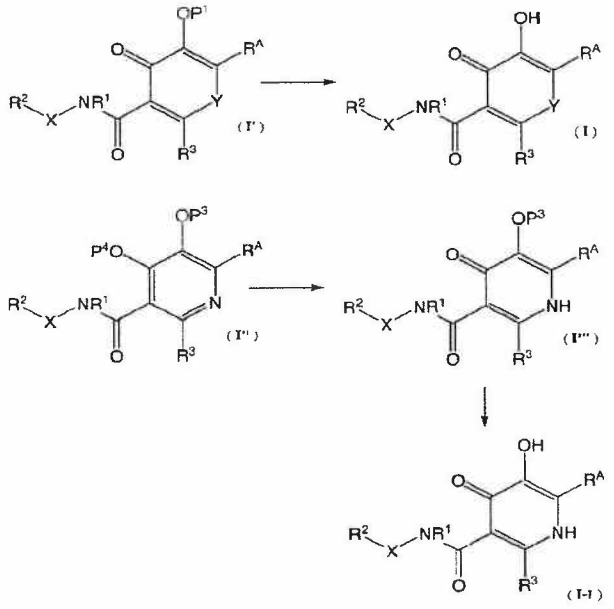
(第17工程)

本工程は、化合物(XVI)のOP^1およびOP^2部分を脱保護して、本発明化合物(I－D)を合成する反応である。第12工程に準じて行なえばよい.

[0013] なお上記で得られた本発明化合物をさらに化学修飾して、別の化合物を合成してもよい。また上記反応中で、側鎖部分などに反応性官能基(例:OH、COOH、NH_2)が存在する場合には、所望により、反応前に保護し、反応後に脱保護してもよい。

本発明はさらに、化合物(I)の合成中間体として化合物(I')、(I'')または(I''')を提供する。これらの化合物を、前記製法1や2における脱保護反応の条件に準じて脱保護することにより化合物(I)が得られる。

[化36]



(式中、P^1はヒドロキシ保護基;P^3は水素またはヒドロキシ保護基;P^4はヒドロキシ保護基;その他の記号は前記と同意義)

化合物(I')、(I'')または(I''')の好ましい態様について以下に説明する。

上記の各ヒドロキシ保護基は好ましくは、低級アルキル(例:メチル、エチル)やアラルキル(例:ベンジル)である。

R^1は好ましくは、水素または低級アルキル、特に好ましくは水素である。

Xは好ましくは低級アルキレン、より好ましくはC1～C3低級アルキレン、特に好ましくはメチレンである。

R^2は好ましくは、置換されていてもよいフェニル、より好ましくはフェニルまたは少なくともハロゲンで置換されたフェニル(例:4－F－フェニル)である。

R^3は好ましくは、水素である。

R^Aは好ましくは、式:－COR^5(R^5は、前記置換基群Aから選択される基)で示される基である。より好ましくは、R^5は水素、ヒドロキシ、または低級アルキルである。

Yは好ましくはNR^4(R^4は好ましくは、水素または置換されていてもよい低級アルキルである)。R^4の置換されていてもよい低級アルキルにおける置換基は、好ましくは、－CH＝CH_2、－CHO等である。R^4はより好ましくは、水素、－CH_2CH＝CH_2、－CH_2CHO等である。

化合物(I')および(I''')の態様は、前記化合物(XI)、(XIV)を含む。

化合物(I'')の態様は、前記化合物(X)、(XII)、(XIII)、(XV)、(XVI)を含む。

本発明化合物は、例えば抗ウイルス薬等の医薬として有用である。本発明化合物は、ウイルスのインテグラーゼに対して顕著な阻害作用を有する。よって本発明化合物は、動物細胞内で感染時に少なくともインテグラーゼを産出して増殖するウイルスに起因する各種疾患に対して、予防又は治療効果が期待でき、例えば、レトロウイルス(例、HIV-1、HIV-2、HTLV-1、SIV、FIV等)に対するインテグラーゼ阻害剤として有用であり、抗HIV薬等として有用である。

また、本発明化合物は、逆転写酵素阻害剤および／又はプロテアーゼ阻害剤等の異なる作用メカニズムを有する抗HIV薬と組み合わせて併用療法に用いることもできる。特に現在、インテグラーゼ阻害剤は上市されておらず、本発明化合物と逆転写酵

素阻害剤および／又はプロテアーゼ阻害剤とを組み合わせて併用療法に用いることは有用である。

さらに、上記の使用としては、抗HIV用合剤としてのみならず、カクテル療法等のように、他の抗HIV薬の抗HIV活性を上昇させるような併用剤としての使用も含まれる。

また、本発明化合物は、遺伝子治療の分野において、HIVやMLVをもとにしたレトロウイルスベクターを用いる際に、目的の組織以外にレトロウイルスベクターの感染が広がるのを防止するために使用することができる。特に、試験管内で細胞等にベクターを感染しておいてから体内にもどすような場合に、本発明化合物を事前に投与しておくと、体内での余計な感染を防ぐことができる。

本発明化合物は、経口的又は非経口的に投与することができる。経口投与による場合、本発明化合物は通常の製剤、例えば、錠剤、散剤、顆粒剤、カプセル剤等の固形剤；水剤；油性懸濁剤；又はシロップ剤もしくはエリキシル剤等の液剤のいずれかの剤形としても用いることができる。非経口投与による場合、本発明化合物は、水性又は油性懸濁注射剤、点鼻液として用いることができる。その調製に際しては、慣用の賦形剤、結合剤、滑沢剤、水性溶剤、油性溶剤、乳化剤、懸濁化剤、保存剤、安定剤等を任意に用いることができる。なお、抗HIV薬としては、特に経口剤が好ましい。本発明の製剤は、治療有効量の本発明化合物を製薬上許容される担体又は希釈剤とともに組み合わせる（例えば混合する）ことによって製造される。

本発明化合物の投与量は、投与方法、患者の年齢、体重、状態および疾患の種類によっても異なるが、通常、経口投与の場合、成人1日あたり約0．05mg～3000mg、好ましくは、約0．1mg～1000mgを、要すれば分割して投与すればよい。また、非経口投与の場合、成人1日あたり約0．01mg～1000mg、好ましくは、約0．05mg～500mgを投与する。

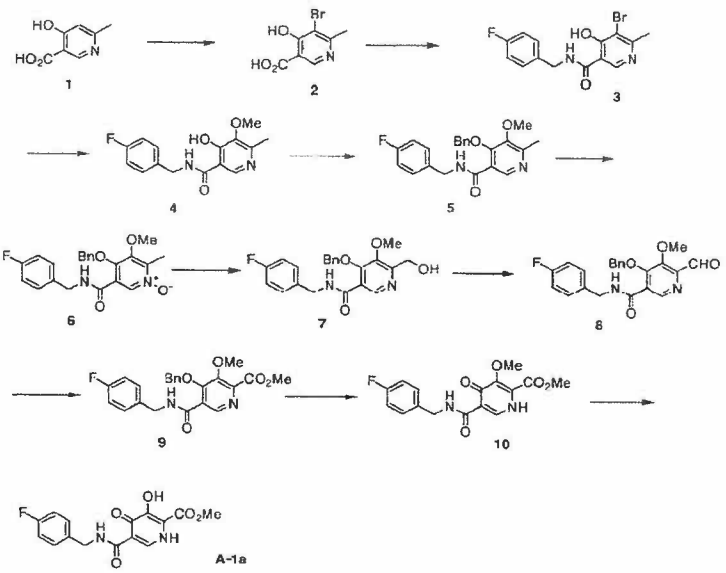
実施例

[0014] （略号）

Me＝メチル；Bn＝ベンジル

実施例A-1

[化12]



A-1a. 5-(4-フルオロベンジルカルバモイル)-3-ヒドロキシ-4-オキソ-1,4-ジヒドロピリジン-2-カルボン酸メチル

1)4-ヒドロキシ-6-メチルニコチン酸1(95.6g、0.625 mol)を酢酸(950ml)と水(190ml)に溶かし、臭素(39ml、0.750mol)を15分間かけて加えた. 溶液を60℃で5時間撹拌した後、溶媒を減圧下留去し、メタノール(200ml)を加え結晶を濾取した. 溶液を減圧下留去し、残渣に再度メタノールを加え結晶を濾取した. 合わせて142.2g(98%)の5-ブロモ-4-ヒドロキシ-6-メチルニコチン酸2を無色結晶として得た.

NMR(DMSO-d_6) δ : 2.53(3H, s), 8.56(1H, s), 13.45(1H, br s), 14.80(1H, br s).

2) 上記化合物2(138g、0.596mol)、1-エチル-3-(3-ジメチルアミノプロピル)カルボジイミドハイドロクロライド(148g、0.775mol)、および1-ヒドロキシベンゾトリアゾール(100g、0.656mol)をジメチルホルムアミド(970ml)に溶解し、4-フルオロベンジルアミン(79ml、0.715mol)を加えた. 反応液を室温で9時間撹拌した後、水(2l)を加え結晶を濾取し、エーテルで洗浄した. 5-ブロモ-N-(4-フルオロベンジル)-4-ヒドロキシ-6-メチルニコチンアミド3(156g、77%)を無色結晶として得た.

NMR(DMSO-d_6) δ : 2.47(3H, s), 4.50(2H, d, J=5.9Hz), 7.12-7.20(m, 2H), 7.32-7.39

(m, 2H), 8.38(1H, s), 10.50(1H, t, J=5.9Hz), 12.72(1H, br s).

3) 上記化合物3(75.2g、222mmol)およびヨウ化銅(I)(21.1g、111mmol)をジメチルホルムアミド(750ml)に溶解し、28%ナトリウムメトキサイド-メタノール溶液(216ml、888mmol)を加え、105℃で100分間撹拌した. 冷却後、氷水(800ml)を加え、不要物を濾去した. 溶液に2M塩酸(443ml)を加え、結晶を濾取した. N-(4-フルオロベンジル)-4-ヒドロキシ-5-メトキシ-6-メチルニコチンアミド1(56.0g、87%)を無色結晶として得た.

NMR(DMSO-d_6) δ : 2.26(3H, s), 3.74(3H, s), 4.49(2H, d, J=6.0Hz), 7.10-7.19(2H, m), 7.30-7.38(2H, m), 8.24(1H, s), 10.68(1H, t, J=6.0Hz), 12.21(1H, br s).

4) 上記化合物4(100g、344mmol)、ベンジルアルコール(46ml、447mmol)、およびトリブチルホスフィン(128ml、516mmol)のテトラヒドロフラン(1.0l)溶液に、氷冷下、40%アゾジカルボン酸ジイソプロピル-トルエン溶液(280ml、516mmol)を30分間かけて加えた. 氷冷下30分撹拌した後に室温に昇温しさらに2時間撹拌した. 減圧下溶媒を留去し、残渣にトルエン(100ml)およびヘキサン(2l)を加え、析出した結晶を濾去した. 溶媒を減圧下留去し、残渣にジエチルエーテル(200ml)およびヘキサン(2l)を加え、析出した結晶を濾去した. 減圧下溶媒を濾去し、残渣をシリカゲルカラムクロマトグラフィ(ヘキサン / 酢酸エチル)にて精製した. 4-ベンジロキシ-N-(4-フルオロベンジル)-5-メトキシ-6-メチルニコチンアミド5(68.5g、52%)を無色結晶として得た.

NMR($CDCl_3$) δ : 2.58(3H, s), 3.86(3H, s), 4.40(2H, d, J=5.7Hz), 5.21(2H, s), 6.91-7.00(2H, m), 7.08-7.14(2H, m), 7.19-7.27(2H, m), 7.32-7.40(3H, m), 7.87(1H, br s), 8.97(1H, s).

5) 上記化合物5(67.5g、177mmol)のクロロホルム(350ml)溶液に、氷冷下、メタクロロ過安息香酸(65%)(49.5g、186mmol)のクロロホルム(350ml)溶液を30分かけて加えた. 氷冷下45分撹拌した後に、室温に昇温し75分間撹拌した. 反応液に飽和重曹水を加え、クロロホルムで抽出した. 有機層を飽和重曹水で洗浄し、無水硫酸ナトリウムで乾燥した. 溶媒を減圧下留去し、残渣にジエチルエーテル(200ml)を加え、析出した結晶(47.8g)を濾取した. 溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィ(トルエン / アセトン)にて精製し、2.65gの結晶を得た. 合わせて50.5g(72%)の4-ベンジロキシ-N-(4-フルオロベンジル)-5-メトキシ-6-メチル-1-オキシニコチンアミ

ド6を無色結晶として得た.

NMR($CDCl_3$) δ : 2.55(3H, s), 3.90(3H, s), 4.40(2H, d, J=5.7Hz), 5.16(2H, s), 6.93-6.70(2H, s), 6.90-7.19(5H, m), 7.30-7.38(2H, m), 7.94(1H, br s), 8.81(1H, s).

6) 上記化合物6(49.4g、125mmol)を無水酢酸(350ml)に溶解し、80℃で30分撹拌した. 溶媒を減圧下留去した後、メタノール(500ml)に溶解し、氷冷下28%ナトリウムメトキサイド-メタノール溶液(7.5ml、31.3mmol)を加え、室温で1時間撹拌した. 反応液にアンバーライト(登録商標)IR-120Bを、溶液が中性になるまで加えた後、固形物を濾去した. 溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィ(ヘキサン / 酢酸エチル)にて精製した. 4-ベンジロキシ-N-(4-フルオロベンジル)-6-ヒドロキシメチル-5-メトキシニコチンアミド7(25.4g、51%)を無色結晶として得た.

NMR($CDCl_3$) δ : 3.42(1H, br s), 3.89(3H, s), 4.41(2H, d, J=5.7Hz), 4.83(2H, s), 5.23(2H, s), 6.92-6.99(2H, m), 7.09-7.14(2H, m), 7.19-7.23(2H, m), 7.28-7.37(3H, m), 7.85(1H, br s), 9.03(1H, s).

7) 上記化合物7(25.0g、63.1mmol)、ジメチルスルホキサイド(44.8ml、631mmol)、およびトリエチルアミン(44.3ml、378mmol)のクロロホルム(250ml)溶液に、氷冷下、三酸化硫黄ピリジン錯体(50.2g、315mmol)を加え、室温で20分間撹拌した. 反応液に水を加え、減圧下クロロホルムを留去し、残渣を酢酸エチルで抽出した. 抽出液を水洗し、無水硫酸ナトリウムで乾燥した. 溶媒を減圧下留去し、残渣にジエチルエーテルを加え、結晶(17.7g)を濾取した. 溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィにて精製し、3.16gの結晶を得た. 合わせて20.9g(84%)の、4-ベンジロキシ-N-(4-フルオロベンジル)-6-ホルミル-5-メトキシニコチンアミド8を無色結晶として得た.

NMR($CDCl_3$) δ : 4.02(3H, s), 4.41(2H, d, J=5.7Hz), 5.30(2H, s), 6.93-6.70(2H, m), 7.09-7.15(2H, m), 7.20-7.27(2H, m), 7.31-7.40(3H, m), 7.83(1H, br s), 9.20(1H, s), 10.26(1H, s).

8) 上記化合物8(300mg、0.761mmol)のメタノール(1ml)溶液に、氷冷下、水酸化カリウム(111mg、1.99mmol)のメタノール(1ml)溶液を加えた後、さらにヨウ素(251mg、1.00mmol)のメタノール(4ml)溶液を加え、同温度で1時間撹拌した. 反応液に5%亜

硫酸水素ナトリウム水溶液および水を加え、析出した結晶を濾取した．4-ベンジロキシ-5-(4-フルオロベンジルカルバモイル)-3-メトキシピリジン-2-カルボン酸メチル9(275 mg、85%)を無色結晶としてえた．

NMR($CDCl_3$) δ：3.99(3H, s), 4.02(3H, s), 7.40(2H, d, J=5.7Hz), 5.26(2H, s), 6.92-6.99(2H, m), 7.10-7.15(2H, m), 7.19-7.23(2H, m), 7.25-7.39(3H, m), 7.81(1H, br s), 9.09(1H, s).

9)ヨウ化ナトリウム(5.51g、36.8mmol)のアセトニトリル(50ml)懸濁液に、クロロトリメチルシラン(4.66ml、36.8mmol)を加え室温で10分間撹拌した．この溶液に、氷冷下、の上記化合物9(2.60g、6.13mmol)を加えた後、同温度で20分間撹拌した．反応液に5%亜硫酸水素ナトリウム溶液を加え、酢酸エチルで抽出した．抽出液を、飽和重曹水および飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥した．減圧下溶媒を留去し、得られた固形物を再結晶し(アセトン-ジイソプロピルエーテル)、5-(4-フルオロベンジルカルバモイル)-3-メトキシ-4-オキソ-1,4-ジヒドロピリジン-2-カルボン酸メチル10(1.73g、84%)を無色結晶として得た．

NMR($CDCl_3$) δ：4.04(6H, s), 4.60(2H, d, J=6.0Hz), 6.96-7.03(2H, m), 7.29-7.35(2H, m), 8.63(1H, s), 9.68(1H, br s), 10.34(1H, br s).

10)上記化合物10(1.73g、5.17mmol)のジクロロメタン(150ml)溶液に塩化アルミニウム(6.97g、51.7mmol)を加え室温で2時間撹拌した．反応液を氷を入れた2M塩酸中に注ぎ、酢酸エチルで抽出した．抽出液を2M塩酸および水で洗浄し、無水硫酸ナトリウムで乾燥した．減圧下溶媒を留去し、得られた固形物を再結晶(テトラヒドロフラン-メタノール)し、化合物A-1a(919mg、56%)を無色結晶として得た．

融点：242-244℃

元素分析：$C_{15}H_{13}FN_2O_5$として

計算値(%): C, 56.25; H, 4.09; F, 5.93; N, 8.75.

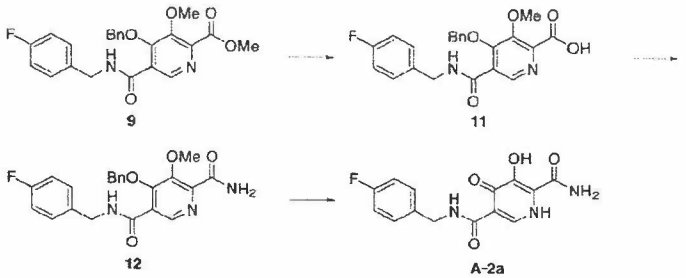
分析値(%): C, 56.00; H, 4.03; F, 5.58; N, 8.69.

NMR(DMSO-d_6) δ：3.91(3H, s), 4.52(2H, d, J=5.8Hz), 7.12-7.19(2H, m), 7.34-7.40(2H, m), 8.19-8.22(1H, m), 10.12(1H, br s), 10.20(1H, d, J=5.8Hz), 12.43(1H, br s)

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[0015] 実施例A-2

[化13]



1)9(900mg、2.12 mmol)をメタノール(8ml)に溶かし、2N水酸化ナトリウム水溶液(4ml)を加えた. 溶液を室温で2時間撹拌した後、2M塩酸(3ml)を加え結晶を濾取した. 4-ベンジルオキシ-5-(4-フルオロ-ベンジルカルバモイル)-3-メトキシ-ピリジン-2-カルボン酸11(474mg、54%)を無色結晶として得た.

NMR($CDCl_3$)δ: 4.05(3H, s), 4.40(2H, d, J=5.6Hz), 5.36(2H, s), 6.94-7.01(2H, m), 7.08-7.12(2H, m), 7.21-7.24(2H, m), 7.29-7.41(3H, m), 7.87(1H, brs), 9.03(1H, s).

2)上記化合物11(155mg、0.378mmol)、1-エチル-3-(3-ジメチルアミノプロピル)カルボジイミドハイドロクロライド(87mg、0.453mmol)、および1-ヒドロキシベンゾトリアゾール(61mg、0.453mmol)をジメチルホルムアミド(2ml)に溶解し、室温で30分撹拌した. その後、塩化アンモニウム(40mg、0.756mmol)、およびジイソプロピルエチルアミン(198ul、1.13mmol)を加えた. 反応液を室温で1時間撹拌した後、水を加え結晶を濾取し、エーテルで洗浄した. 4-ベンジルオキシ-3-メトキシ-ピリジン-2,5-ジカルボン酸 2-アミド 5-(4-フルオロ-ベンジルアミド) 12(127mg、82%)を無色結晶として得た.

3)上記化合物12(127mg、0.310mmol)に塩化ピリジニウム(1.27g)を加え、180℃で5分間加熱した. 冷却後、水を加え結晶を濾取し、エーテルで洗浄した. 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 2-アミド 5-(4-フルオロ-ベンジルアミド) A-2a(88mg、93%)を肌色結晶として得た.

融点:300℃以上

元素分析:$C_{14}H_{12}FN_3O_4$として

計算値 (%): C, 55.08; H, 3.96; F, 6.22; N, 13.77.

分析値 (%): C, 54.82; H, 3.96; F, 5.75; N, 13.53; Cl, 0.79.

NMR(DMSO-d_6) δ : 4.53(2H, d, J=5.6Hz), 7.14-7.20(2H, m), 7.35-7.40(2H, m), 7.79(1H, s), 8.24(1H, d, J=7.0Hz), 8.33(1H, s), 10.33(1H, t, J=5.6Hz), 12.23(1H, d, J=7.0Hz).

同様の方法で、以下の化合物を合成した。

A-2b 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 5-(4-フルオロ-ベンジルアミド) 2-メチルアミド

融点:300℃以上

元素分析:$C_{15}H_{14}FN_3O_4$として

計算値 (%): C, 56.43; H, 4.42; F, 5.95; N, 13.16.

分析値 (%): C, 56.18; H, 4.36; F, 5.63; N, 12.96.

NMR(DMSO-d_6) δ : 2.91(3H, d, J=4.7Hz), 4.53(2H, d, J=5.8Hz), 7.14-7.20(2H, m), 7.35-7.40(2H, m), 8.23-8.25(1H, m), 8.35(1H, d, J=5.0Hz), 10.35(1H, t, J=5.8Hz), 12.23(1H, d, J=6.3Hz).

A-2c 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 2-ジメチルアミド 5-(4-フルオロ-ベンジルアミド)

融点:269-270℃

元素分析:$C_{16}H_{16}FN_3O_4$として

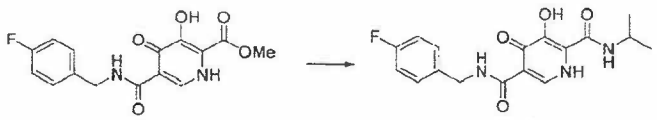
計算値 (%): C, 57.65; H, 4.84; F, 5.70; N, 12.61.

分析値 (%): C, 57.44; H, 4.79; F, 5.40; N, 12.41; Cl, 0.59.

NMR(DMSO-d_6) δ : 2.92(3H, s), 3.00(3H, s), 4.53(2H, d, J=5.8Hz), 7.13-7.19(2H, m), 7.34-7.39(2H, m), 8.19-8.21(1H, m), 9.63(1H, brs), 10.44(1H, t, J=5.8Hz), 12.60(1H, brs).

実施例A-2d

[化37]



A-1a A-2d

1)A-1a(100mg、0.3 mmol)をメタノール(1ml)に溶かし、マイクロウェーブ反応装置にて140℃で15分間反応した. 室温まで冷却後、2N塩酸(3ml)を加えて撹拌し析出した結晶を濾取した. 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 5-(4-フルオロ-ベンジルアミド) 2-イソプロピルアミドA-2d(93mg、86%)を無色結晶として得た.

融点:295-299℃

NMR(DMSO-d_6) δ : 1.21(6H, d, J=6.6Hz), 4.06-4.15(1H, m), 4.53(2H, d, J=5.8Hz), 7.13-7.21(2H, m), 7.35-7.40(2H, m), 8.16(1H, d, J=7.6Hz), 8.24(1H, d, J=7.0Hz), 10.33(1H, t, J=5.7Hz), 12.24(1H, d, J=5.5Hz).

同様の方法で、以下の化合物の合成を行った.

A-2e 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 5-(4-フルオロ-ベンジルアミド) 2-[(2-メトキシ-エチル)-アミド]

融点:295-299℃

NMR(DMSO-d_6) δ : 3.28(3H, s), 3.39-3.62(4H, m), 4.52(2H, d, J=5.9Hz), 7.14-7.20(2H, m), 7.35-7.39(2H, m), 8.24(1H, d, J=7.2Hz), 8.46(1H, t, J=5.2Hz), 10.32(1H, t, J=5.8Hz), 12.23(1H, d, J=5.8Hz).

A-2f 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 5-(4-フルオロ-ベンジルアミド) 2-[(2-ヒドロキシ-エチル)-アミド]

融点:285-287℃

NMR(DMSO-d_6) δ : 3.44-3.61(4H, m), 4.53(2H, d, J=6.0Hz), 4.91(1H, s), 7.13-7.21(2H, m), 7.35-7.40(2H, m), 8.24(1H, s), 8.53(1H, s), 10.34(1H, t, J=5.7Hz), 12.23(1H, brs).

A-2g 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 5-(4-フルオロ-ベンジルアミド) 2-[(チオフェン-2-イルメチル)-アミド]

融点:297-300℃

NMR(DMSO-d_6) δ : 4.53(2H, d, J=5.6Hz), 4.75(2H, d, J=5.8Hz), 6.96-6.99(1H, m), 7.06-7.07(1H, m), 7.14-7.21(2H, m), 7.35-7.44(3H, m), 8.24(1H, d, J=7.0Hz), 8.88 (1H, t, J=6.0Hz), 10.33(1H, t, J=5.7Hz), 12.32(1H, d, J=6.3Hz).

A-2h 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 ビス-(4-フルオロ-ベンジルアミド)

融点:279-280℃

NMR(DMSO-d_6) δ : 4.53(2H, d, J=5.6Hz), 4.57(2H, d, J=6.0Hz), 7.14-7.20(4H, m), 7.36-7.42(4H, m), 8.24(1H, d, J=7.1Hz), 8.85(1H, t, J=6.4Hz), 10.34(1H, t, J=5.9Hz), 12.28(1H, d, J=7.0Hz).

A-2i 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 5-(4-フルオロ-ベンジルアミド) 2-[(3-イミダゾール-1-イル-プロピル)-アミド]

NMR(DMSO-d_6) δ : 2.07-2.16(2H, m), 3.40(2H, q, J=6.6Hz), 4.26(2H, t, J=7.1Hz), 4.53(2H, d, J=5.6Hz), 7.14-7.22(2H, m), 7.34-7.40(2H, m), 7.70-7.71(1H, m), 7.83 -7.84(1H, m), 9.18(1H, s), 10.34(1H, t, J=5.8Hz), 12.29(1H, brs), 14.74(1H, brs).

A-2j 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 2-シクロヘキシルアミド 5-(4-フルオロ-ベンジルアミド)

融点:290-293℃

NM R(DMSO-d_6) δ : 1.24-1.89(10H, m), 3.85-3.87(1H, m), 4.53(2H, d, J=5.6Hz), 7 .13-7.20(2H, m), 7.34-7.40(2H, m), 8.23-8.26(2H, m), 10.33(1H, t, J=5.6Hz), 12.2 4(1H, d, J=7.3Hz).

A-2k 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 5-(4-フルオロ-ベンジルアミド) 2-{[3-(2-オキソ-ピロリジン-1 -イル)-プロピル]-アミド}

融点:248-252℃

NMR(DMSO-d_6) δ : 1.72(2H, t, J=6.9Hz), 1.93(2H, q, J=7.5Hz), 2.22(2H, t, J=8.0Hz), 3.22(2H, t, J=6.9Hz), 3.30-3.37(4H, m), 4.53(2H, d, J=5.6Hz), 7.14-7.20(2H, m), 7.35-7.40(2H, m), 8.23-8.25(1H, m), 8.49(1H, t, J=6.0Hz), 10.35(1H, t, J=5.8Hz) , 12.23(1H, d, J=7.3Hz).

A-2l 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 5-(4-フルオロ-ベンジルアミド) 2-[(2-フェノキシ-エチル)-アミド]

融点:279-282℃

NMR(DMSO-d_6) δ : 3.74-3.80(2H, m), 4.12-4.16(2H, d, J=5.5Hz), 4.50-4.53(2H, m), 6.92-7.00(3H, m), 7.13-7.20(3H, m), 7.27-7.40(4H, m), 8.24(1H, s), 8.70(1H, s), 10.34(1H, t, J=5.6Hz), 12.24(1H, brs).

A-2m 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 2-{[2-(4-クロロ-フェニル)-エチル]-アミド} 5-(4-フルオロ-ベンジルアミド)

融点:241-245℃

NMR(DMSO-d_6) δ : 2.86(2H, t, J=7.1Hz), 3.61(2H, q, J=6.4Hz), 4.53(2H, d, J=5.6Hz), 7.14-7.20(2H, m), 7.27-7.40(6H, m), 8.23(1H, d, J=7.2Hz), 8.45(1H, t, J=5.9Hz), 10.34(1H, t, J=5.8Hz), 12.23(1H, d, J=7.0Hz).

A-2n 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 2-[((S)-1-シクロヘキシル-エチル)-アミド] 5-(4-フルオロ-ベンジルアミド)

融点:262-264℃

NMR(DMSO-d_6) δ : 0.92-1.77(10H, m), 3.90-3.97(1H, m), 4.53(2H, d, J=5.6Hz), 7.13-7.21(2H, m), 7.35-7.40(2H, m), 8.17-8.25(2H, m), 10.33(1H, t, J=6.1Hz), 12.23(1H, d, J=5.8Hz).

A-2o 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 5-(4-フルオロ-ベンジルアミド) 2-インダン-1-イルアミド

融点:237-240℃

NMR(DMSO-d_6) δ : 1.89-1.96(1H, m), 2.55-2.60(1H, m), 2.86-3.00(2H, m), 4.53(2H, d, J=5.6Hz), 5.55-5.58(1H, m), 7.14-7.40(8H, m), 8.27(1H, d, J=6.6Hz), 8.55(1H, d, J=8.1Hz), 10.32(1H, t, J=5.8Hz), 12.35(1H, d, J=5.8Hz).

A-2p 3-ヒドロキシ-4-オキソ-1,4-ジヒドロ-ピリジン-2,5-ジカルボン酸 2-[(2-シクロヘキシ-1-エニル-エチル)-アミド] 5-(4-フルオロ-ベンジルアミド)

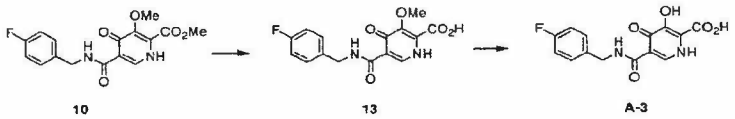
融点:251-253℃

NMR(DMSO-d_6) δ : 1.48-1.59(4H, m), 1.94-1.95(4H, m), 2.14-2.19(2H, m), 3.42-3

.49(2H, m), 2.91(3H, d, J=4.7Hz), 4.53(2H, d, J=5.6Hz), 5.46(1H, s), 7.14-7.20(2H, m), 7.35-7.40(2H, m), 8.24(1H, d, J=7.0Hz), 8.36(1H, d, J=5.6Hz), 10.35(1H, t, J=5.6Hz), 12.23(1H, d, J=7.3Hz).

[0016] 実施例A-3

[化14]



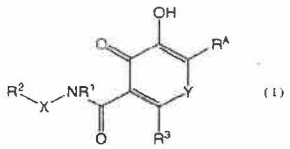
1)化合物10(4.8g, 14mmol)のメタノール(60ml)溶液に, 氷冷下2規定水酸化リチウム水溶液(30ml)を加えた. 室温下1.5時間撹拌した後, 2規定塩酸を酸性になるまでゆっくり加えた. 析出結晶を水洗, 乾燥して化合物13(3.75g)を得た.

2)化合物13(200mg、0.624mmol)のジクロロメタン(4ml)溶液に、1.0M三臭化ほう素ジクロロメタン溶液(3.1ml、3.10mmol)を加え室温で3時間30分撹拌した.反応液を、氷水中に注ぎ、2M塩酸を加えた後に、酢酸エチルで抽出した. 抽出液を水洗し、無水硫酸ナトリウムで乾燥した.減圧下溶媒を留去し、残渣を酢酸エチル-メタノールの混液で洗浄し、化合物A-3を無色結晶(35mg)として得た.

NMR(DMSO-d_6) δ : 4.51(2H, d, J=5.7Hz), 7.12-7.19(2H, m), 7.33-7.39(2H, m), 8.17(1H, s).

[0017] 本発明は以下の化合物も包含する。

[化15]



(I)

R^1：水素またはメチル

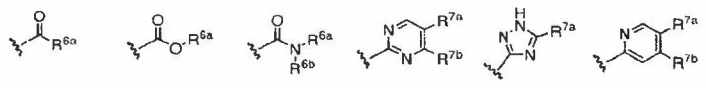
R^2—X：



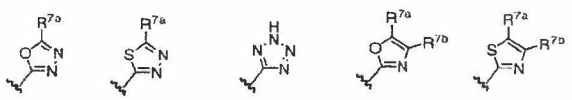
R^3：水素

Y：>NH, >NMe, >NPh, >NBn, >O

R^A：



R^A-1 R^A-2 R^A-3 R^A-4 R^A-5 R^A-6



R^A-7 R^A-8 R^A-9 R^A-10 R^A-11

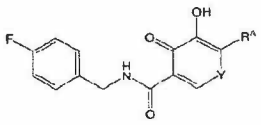
R^{6a}, R^{6b}：(1)水素 (2)メチル (3)エチル (4)n-プロピル (5)イソプロピル (6)2-ヒドロキシエチル (7)2-メトキシエチル (8)フェニル (9)ベンジル (10)モルホリン (11)1,1-ジメチルヒドラジン (12)O-メチルヒドロキシルアミン (13) 4-フルオロベンジル (14) 4-フルオロフェニルオキシ (15)4-フルオロベンジルオキシ

R^{7a}, R^{7b}：(1)水素 (2)メチル (3)エチル (4)n-プロピル (5)イソプロピル (6)2-ヒドロキシエチル (7)2-メトキシエチル (8)フェニル (9)ベンジル (10)モルホリン (11)1,1-ジメチルヒドラジン (12)O-メチルヒドロキシルアミン (13)ハロゲン(F, Cl, Br, I) (14)ヒドロキシ (15)アセチル (16)メトキシカルボニル (17)カルバモイル (18) 4-フルオロベンジル (19) 4-フルオロフェニルオキシ (20)4-フルオロベンジルオキシ

[0018] より具体的には以下の化合物を包含する。

(表中、各記号は前記の置換基を示す。例えば、"R^{6a}, R^{6b}= (1, 2)" は、R^{6a}が (1) 水素であり、R^{6b} が (2)メチルであることを意味する。)

[化16]



(14)

1) Y= NH

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化17]

2) Y= NMe

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化18]

3) Y= NPh

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化19]

4) Y=Bn

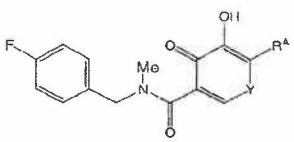
No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化20]

5) Y=O

No	R^	R^6^, R^7^
1-1 1-2	R^-1 または R^-2	R^6a^= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^-3	R^6a^, R^6b^= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^-4 R^-6 R^-10 または R^-11	R^7a^, R^7b^= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^-5 R^ 7 または R^-8	R^3a^= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^-9	

[化21]



(I-2)

1) Y＝NH

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A 8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化22]

2) Y=NMe

No	R^A	R^5, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A 11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化23]

3) Y= NPh

No	R^A	R^6, R^7
1-1 1-2	R^A−1 または R^A−2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A−3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A−4 R^A−6 R^A−10 または R^A−11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A−5 R^A−7 または R^A−8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A−9	

[化24]

4) Y=Bn

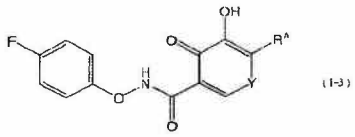
No	R^	R^6, R^7
1-1 1-2	R^-1 または R^-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^-4 R^-6 R^-10 または R^-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^-5 R^-7 または R^-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^-9	

[化25]

5) Y= O

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化26]



(I-3)

1) Y=NH

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20)、 (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化27]

2) Y=NMe

No	R^	R^6, R^7
1-1 1-2	R^-1 または R^-2	R^{6n}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^-3	R^{6n}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^-4 R^-6 R^-10 または R^-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^-5 R^-7 または R^-8	R^{7n}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^-9	

[化28]

3) Y= NPh

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化29]

4) Y=Bn

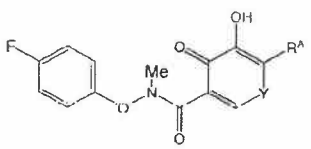
No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20).. (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1). (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20). (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化30]

5) Y= O

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6b}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8)、または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),. (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化31]



(14)

1) Y=NH

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A 6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),. (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化32]

2) Y= NMe

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8). または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A 5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化33]

3) Y=NPh

No	R^	R^6, R^7
1-1 1-2	R^-1 または R^-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^-4 R^-6 R^-10 または R^-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^-5 R^-7 または R^-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^-9	

[化34]

4) Y= Bn

No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1), (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

[化35]

5) Y=O

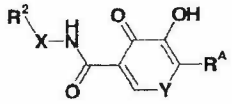
No	R^A	R^6, R^7
1-1 1-2	R^A-1 または R^A-2	R^{6a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14)または (15)
1-3	R^A-3	R^{6a}, R^{6b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12) , (1, 13), (1, 14), (1, 15) (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12) , (3, 13), (3, 14), (3, 15) (4, 4), (4, 5), (4, 6), (4, 7), (4, 8), (4, 9), (4, 10), (4, 11), (4, 12), (4, 13), (4, 14), (4, 15) (5, 5), (6, 6), (7, 7), (8, 8), または(9, 9)
1-4 1-6 1-10 1-11	R^A 4 R^A-6 R^A-10 または R^A-11	R^{7a}, R^{7b}= (1, 1), (1, 2), (1, 3), (1, 4), (1, 5), (1, 6), (1, 7), (1, 8), (1, 9), (1, 10), (1, 11), (1, 12), (1, 13), (1, 14), (1, 15), (1, 16), (1, 17), (1, 18), (1, 19) (1, 20),, (2, 1), (3, 1), (4, 1), (5, 1), (6, 1), (7, 1), (8, 1), (9, 1), (10, 1), (11, 1), (12, 1), (13, 1), (14, 1), (15, 1), (16, 1), (17, 1), (18, 1), (19, 1), (20, 1). (2, 2), (2, 3), (2, 4), (2, 5), (2, 6), (2, 7), (2, 8), (2, 9), (2, 10), (2, 11), (2, 12), (2, 13), (2, 14), (2, 15), (2, 16), (2, 17), (2, 18), (2, 19), (2, 20), (3, 2), (4, 2), (5, 2), (6, 2), (7, 2), (8, 2), (9, 2), (10, 2), (11, 2), (12, 2), (13,21), (14, 2), (15, 2), (16, 2), (17, 2), (18, 2), (19, 2), (20, 2) (3, 3), (3, 4), (3, 5), (3, 6), (3, 7), (3, 8), (3, 9), (3, 10), (3, 11), (3, 12), (3, 13), (3, 14), (3, 15), (3, 16), (3, 17), (3, 18), (3, 19), (3, 20) (4, 3), (5, 3), (6, 3), (7, 3), (8, 3), (9, 3), (10, 3), (11, 3), (12, 3), (13, 3), (14, 3), (15, 3), (16, 3), (17, 3), (18, 3), (19, 3), (20, 3)
1-5 1-7 1-8	R^A-5 R^A-7 または R^A-8	R^{7a}= (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) ,(17),(18),(19)または (20)
1-9	R^A-9	

本発明はさらに以下の化合物を提供する。R^A、R^{7a}, R^{7b}は、前記の群から選択される。

R^2-Xは、以下の群から選択される。

(1)水素 (2)メチル (3)エチル (4)n-プロピル (5)イソプロピル (6)2-ヒドロキシエチル (7)2-メトキシエチル (8)フェニル (9)ベンジル (10)モルホリン (11)1,1-ジメチルヒドラジン (12)O-メチルヒドロキシルアミン

[化38]



(I-5)

1) Y= NH, R^2—X = (1) ~(12)

No	R^A	R^7
1-5 1-7 1-8	R^A—5 R^A—7 R^A—8	R^{7a}=(18), (19),(20)
1-4 1-6 1-10 1-11	R^A—4 R^A—6 R^A—10 R^A—11	R^{7a}, R^{7b} = (9, 1), (18, 1),(19,1), (1,9), (1,18), (1, 19), (1, 20)

[化39]

2) Y= NMe, R^2—X = (1) ~(12)

No	R^A	R^7
1-5 1-7 1-8	R^A—5 R^A—7 R^A—8	R^{7a}=(18), (19),(20)
1-4 1-6 1-10 1-11	R^A—4 R^A—6 R^A—10 R^A—11	R^{7a}, R^{7b} = (9, 1), (18, 1),(19,1), (1,9), (1,18), (1, 19), (1, 20)

[化40]

3) Y= NPh, R^2—X = (1) ~(12)

No	R^A	R^7
1-5 1-7 1-8	R^A—5 R^A—7 R^A—8	R^{7a}=(18), (19),(20)
1-4 1-6 1-10 1-11	R^A—4 R^A—6 R^A—10 R^A—11	R^{7a}, R^{7b} = (9, 1), (18, 1),(19,1), (1,9), (1,18), (1, 19), (1, 20)

[化41]

4) Y= NBn, R^2-X = (1) ～(12)

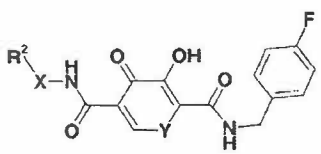
No	R^A	R^7
1-5 1-7 1-8	R^A-5 R^A-7 R^A-8	R^{7a}=(18), (19),(20)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 R^A-11	R^{7a}, R^{7b} = (9, 1), (18, 1),(19,1), (1.9), (1,18), (1, 19), (1, 20)

[化42]

5) Y=O, R^2-X = (1) ～(12)

No	R^A	R^7
1-5 1-7 1-8	R^A-5 R^A-7 R^A-8	R^{7a}=(18), (19),(20)
1-4 1-6 1-10 1-11	R^A-4 R^A-6 R^A-10 R^A-11	R^{7a}, R^{7b} = (9, 1), (18, 1),(19,1), (1.9), (1.18), (1, 19), (1, 20)

[化43]

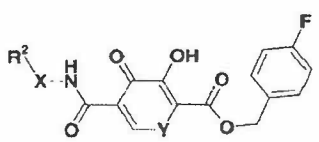


(I-6)

Y = NH, NMe, NPh, NBn, O, S

R^2-X = (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), または (12)

[化44]



(I-7)

Y= NH, NMe, NPh, NBn, O, S

R^2-X = (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), または (12)

[0019] 試験例1

HIVインテグラーゼ阻害作用を以下に示すアッセイ法に基づき調べた。

(1)DNA溶液の調製

WO2004／024693号の試験例1に記載の方法と同一の方法で、基質DNA溶液(2 pmol/μl)およびターゲットDNA溶液(5 pmol/μl)を調製した。ターゲットDNA各溶液は、一旦煮沸後、ゆるやかに温度を下げて相補鎖同上をアニーリングさせてから用いた。基質DNAとターゲットDNAの各配列は、同試験例に記載の通りである。

(2)阻害率(IC_{50}値)の測定

Streptavidin(Vector Laboratories社製)を0.1M炭酸バッファー液(組成: 90 mM Na_2CO_3, 10 mM $NaHCO_3$)に溶かし、濃度を 40 μg/mlにした。この溶液、各50 μlをイムノプレート(NUNC社製)のウエルに加え、4℃で一夜静置、吸着させる。次に各ウエルをリン酸バッファー(組成: 13.7 mM NaCl, 0.27 mM KCl, 0.43 mM Na_2HPO_4, 0.14 mM KH_2PO_4)で2回洗浄後、1% スキムミルクを含むリン酸バッファー 300 μlを加え、30 分間ブロッキングした。さらに各ウエルをリン酸バッファーで2回洗浄後、基質DNA溶液(2 pmol/μl) 50 μlを加え、振盪下、室温で30 分間吸着させた後、リン酸バッファーで2回、次いで蒸留水で1回洗浄した。

次に上記方法で調製した各ウエルに、バッファー(組成:150 mM MOPS (pH7.2), 75 mM $MnCl_2$, 50 mM 2-mercaptoethanol, 25% glycerol, 500 μg/ml bovine serum albumin -fraction V) 12 μl、蒸留水39 μlから調製した反応溶液51 μlを加えた。次にインテグラーゼ溶液(30 pmol) 9 μlを加え、良く混合した。ネガティブコントロール(NC)としてのウエルには、希釈液(組成: 20 mM MOPS (pH7.2), 400 mM potassium glutamete, 1 mM EDTA, 0.1% NP-40, 20% glycerol, 1 mM DTT, 4 M urea) 9 μlを加えプレートミキサーを用いて良く混合した。

プレートを30 ℃で60分インキュベート後、反応液を捨て、250 μlの洗浄バッファー(組成:150 mM MOPS (pH7.2), 50 mM 2-mercaptoethanol, 25% glycerol, 500 μg/ml bovine serum albumin -fraction V)で3回洗浄した。

次に各ウエルにバッファー(組成:150 mM MOPS (pH7.2), 75 mM $MgCl_2$, 50 mM 2-mercaptoethanol, 25% glycerol, 500 μg/ml bovine serum albumin -fraction V) 12 μl、蒸留水41 μlから調製した反応溶液53 μlを加える。さらに各ウエルに被検化合物のDMSO溶液6 μlを加え、ポジティブコントロール(PC)としてのウエルには、DMS

O 6 μlを加え、プレートミキサーを用いてよく混合する。プレートを30 ℃で30分インキュベート後、ターゲットDNA (5 pmol/ μl)1 μlを加え、プレートミキサーを用いてよく混合した。

各プレートを30 ℃で10分間インキュベート後、反応液を捨て、リン酸バッファーで2回洗浄した。次にアルカリフォスファターゼ標識した抗ジゴキシゲニン抗体(ヒツジFabフラグメント:ベーリンガー社製)を抗体希釈液で2000倍に希釈して10 0 μl加え、30 ℃で1時間結合させた後、0.05 % Tween20を含むリン酸バッファーで2回、リン酸バッファーで1回、順次洗浄した。次に、アルカリフォスファターゼ呈色バッファー(組成:10 mMパラニトロフェニルホスフェート(Vector Laboratories社製), 5 mM $MgCl_2$, 100 mM NaCl, 100 mM Tris−塩酸(pH 9.5))を150 μl加えて30 ℃で2時間反応させ、1N NaOH溶液50 μlを加え反応を止めた後、各ウエルの吸光度(OD405nm)を測定し、以下の計算式に従い阻害率(IC_{50})を求めた。

阻害率(%) =100[1−{(C abs.− NC abs.) / (PC abs.− NC abs.)}]

C abs.;化合物のウエルの吸光度

NC abs.:NCの吸光度

PC abs.:PCの吸光度

上記試験結果を以下に示す。

[表1]

実施例(化合物番号)	インテグラーゼ阻害作用 (IC_{50}, ng / ml)
A−1 (A−1a)	6.4
A−3 (A−3)	3.1

本発明化合物は、HIVに対して強いインテグラーゼ阻害作用を示した。

製剤例

「活性成分」なる用語は、本発明化合物、その互変異性体、それらのプロドラッグ、それらの製薬的に許容される塩又はそれらの溶媒和物を意味する。

(製剤例1)

硬質ゼラチンカプセルは次の成分を用いて製造する:

用量

	用量 (mg／カプセル)
活性成分	250
デンプン(乾燥)	200
ステアリン酸マグネシウム	10
合計	460mg

(製剤例2)

錠剤は下記の成分を用いて製造する:

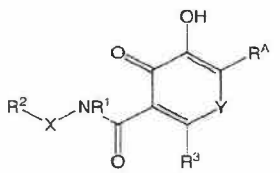
	用量 (mg／錠剤)
活性成分	250
セルロース(微結晶)	400
二酸化ケイ素(ヒューム)	10
ステアリン酸	5
合計	665mg

成分を混合し、圧縮して各重量665mgの錠剤にする。

請求の範囲

[1] 式:

[化1]



(I)

(式中、

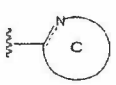
Yは、NR^4(R^4は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、または置換されていてもよいアラルキル)、O、S、SO、またはSO_2;

R^Aは、1)式:$-COR^5$(R^5は置換基群Aから選択される基)で示される基

(置換基群A:水素、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキルオキシ、置換されていてもよいアミノ、置換されていてもよいアミノオキシ、置換されていてもよい複素環式基、置換されていてもよい複素環オキシ、置換されていてもよいアリール、置換されていてもよいアリールオキシ、置換されていてもよいアラルキル、置換されていてもよいアラルキルオキシ、ホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル、置換されていてもよいシクロアルキルカルボニル、置換されていてもよいアリールカルボニル)

または2)式:

[化2]



(式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である

。破線は結合の存在又は非存在を表わす。)で示される基;

R^1は、水素または低級アルキル;

Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレン;

R^2は、上記置換基群Aから選択される基;

R^3は水素、ハロゲン、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルケニル、置換されていてもよい低級アルコキシ、置換されていてもよいアミノ、置換されていてもよい低級アルキルアミノ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキル低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよい複素環式基、または置換されていてもよい複素環低級アルキル)

で示される化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[2] YはNR^4(R^4は前記と同意義)である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[3] YはNR^4(R^4は水素、低級アルキル、フェニルまたはベンジル)である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[4] YはOである、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[5] YはS、SOまたはSO_2である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[6] R^Aは、−COR^5(R^5は前記と同意義)である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

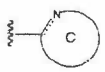
[7] R^Aは、−COR^5(R^5は、水素、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいフェニル、置換されていてもよいベンジル、置換されていてもよい複素環基または置換されていてもよいアミノ)である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[8] R^Aは、−COR^5(R^5は、水素、ヒドロキシ、低級アルキル、低級アルコキシ、または置換されていてもよいアミノ)である、請求項1記載の化合物、その製薬上許容される塩

、またはそれらの溶媒和物。

[9] $R^{\wedge}$は、式:

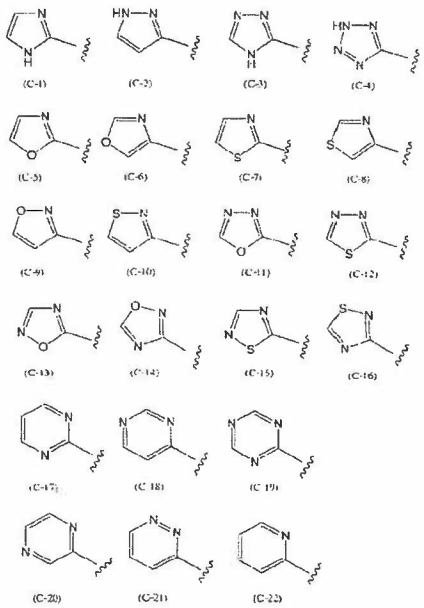
[化3]



(式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である。破線は結合の存在又は非存在を表わす。)で示される基である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[10] $R^{\wedge}$は、置換されていてもよい、以下に示されるいずれかの含窒素芳香族複素環式基である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[化4]

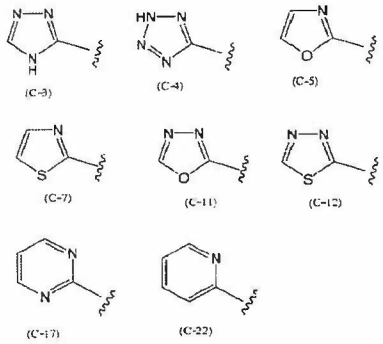


[11] $R^{\wedge}$は、置換されていてもよい、以下に示されるいずれかの含窒素芳香族複素環式基

である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物

。

[化5]



[12] R^1は、水素またはメチルである、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[13] Xは、低級アルキレンまたはO;R^2は、置換されていてもよいフェニルである、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[14] R^3は、水素、ヒドロキシ、置換されていてもよい低級アルコキシ、または置換されていてもよいアミノである、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[15] R^3は水素である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[16] YはNR^4(R^4は請求項1の場合と同意義)またはO;R^1は、水素またはメチル;Xは、低級アルキレンまたはO;R^2は、置換されていてもよいフェニル;R^3は水素である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

[17] YはNR^4(R^4は水素、低級アルキル、フェニルまたはベンジル)またはO;R^1は、水素またはメチル;Xは、メチレンまたはO;R^2は、ハロゲンで置換されていてもよいフェニル;R^3は水素である、請求項1記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物。

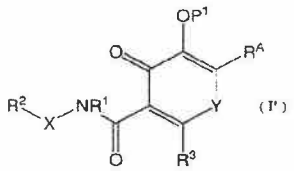
[18] 請求項1～17のいずれかに記載の化合物、その製薬上許容される塩、またはそれら

の溶媒和物を含有する医薬組成物。

[19] 請求項1～17のいずれかに記載の化合物、その製薬上許容される塩、またはそれらの溶媒和物を含有する抗HIV剤。

[20] 式:

[化6]



(I')

(式中、

P^1はヒドロキシ保護基;

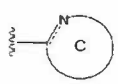
Yは、NR^4(R^4は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、または置換されていてもよいアラルキル)、O、S、SO、またはSO_2;

R^Aは、1)式:$-COR^5$(R^5は置換基群Aから選択される基)で示される基

(置換基群A:水素、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキルオキシ、置換されていてもよいアミノ、置換されていてもよいアミノオキシ、置換されていてもよい複素環式基、置換されていてもよい複素環オキシ、置換されていてもよいアリール、置換されていてもよいアリールオキシ、置換されていてもよいアラルキル、置換されていてもよいアラルキルオキシ、ホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル、置換されていてもよいシクロアルキルカルボニル、置換されていてもよいアリールカルボニル)

または2)式:

[化7]



(式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である。破線は結合の存在又は非存在を表わす。)で示される基;

R^1は、水素または低級アルキル;

Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレン;

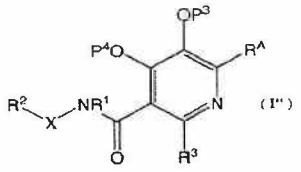
R^2は、上記置換基群Aから選択される基;

R^3は水素、ハロゲン、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルケニル、置換されていてもよい低級アルコキシ、置換されていてもよいアミノ、置換されていてもよい低級アルキルアミノ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキル低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよい複素環式基、または置換されていてもよい複素環低級アルキル)

で示される化合物、またはその製薬上許容される塩、またはそれらの溶媒和物。

[21] 式:

[化8]



(式中、

P^3は水素またはヒドロキシ保護基;

P^4はヒドロキシ保護基;

Yは、NR^4(R^4は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、または置換されていてもよいアラルキル)、O、S、SO、またはSO_2;

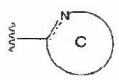
$R^\wedge$は、1)式:$-COR^5$(R^5は置換基群Aから選択される基)で示される基

(置換基群A:水素、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルコキシ、置換されていてもよいシクロアルキル、置換されていてもよい

シクロアルキルオキシ、置換されていてもよいアミノ、置換されていてもよいアミノオキシ、置換されていてもよい複素環式基、置換されていてもよい複素環オキシ、置換されていてもよいアリール、置換されていてもよいアリールオキシ、置換されていてもよいアラルキル、置換されていてもよいアラルキルオキシ、ホルミル、カルボキシ、置換されていてもよい低級アルカノイル、置換されていてもよい低級アルコキシカルボニル、置換されていてもよいカルバモイル、置換されていてもよい複素環カルボニル、置換されていてもよいシクロアルキルカルボニル、置換されていてもよいアリールカルボニル)

または2)式:

[化9]



(式中、C環は、結合手を有する原子に隣接する原子のうち、少なくとも一つの原子が非置換の窒素原子であり、かつ置換されていてもよい含窒素芳香族複素環である。破線は結合の存在又は非存在を表わす。)で示される基;

R^1は、水素または低級アルキル;

Xは、単結合、O、S、SO、SO_2およびNHから選択されるヘテロ原子基、または該ヘテロ原子基が介在していてもよい低級アルキレンもしくは低級アルケニレン;

R^2は、上記置換基群Aから選択される基;

R^3は水素、ハロゲン、ヒドロキシ、置換されていてもよい低級アルキル、置換されていてもよい低級アルケニル、置換されていてもよい低級アルコキシ、置換されていてもよいアミノ、置換されていてもよい低級アルキルアミノ、置換されていてもよいシクロアルキル、置換されていてもよいシクロアルキル低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよい複素環式基、または置換されていてもよい複素環低級アルキル)

で示される化合物、またはその製薬上許容される塩、またはそれらの溶媒和物。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/016904

A. CLASSIFICATION OF SUBJECT MATTER
C07D213/82 (2006.01), ***A61K31/366*** (2006.01), ***A61K31/455*** (2006.01), ***A61K31/506*** (2006.01), ***A61K31/5377*** (2006.01), ***A61P31/18*** (2006.01), ***C07D309/38*** (2006.01), ***C07D405/04*** (2006.01), ***C07D413/04*** (2006.01), ***C07D417/04*** (2006.01),
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D213/82 (2006.01), ***A61K31/366*** (2006.01), ***A61K31/455*** (2006.01), ***A61K31/506*** (2006.01), ***A61K31/5377*** (2006.01), ***C07D309/38*** (2006.01), ***C07D405/04*** (2006.01), ***C07D413/04*** (2006.01), ***C07D417/04*** (2006.01), ***C07D409/12*** (2006.01),

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAOLD(STN), CAplus(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	JP 2004-244320 A (Shionogi & Co., Ltd.), 02 September, 2004 (02.09.04), Full text; particularly, Claim 1; example 8; page 27, lines 40 to 50; pages 35 to 36 (Family: none)	1-3,6-8, 12-19,21 4,5,9-11,20
X	WO 2003/016275 A1 (Shionogi & Co., Ltd.), 27 February, 2003 (27.02.03), Full text; particularly, 'compound E-52', 'compound L-4'; Claims 1, 14, 18, 20, 93; page 61, line 23 to page 62, line 4; page 69, line 6 to page 71, line 5; page 97, lines 15 to 21; 'compound E-50'; pages 141 to 142 & CA 2452769 A1 & EP 1422218 A1 & BR 2002011750 A & CN 1558898 A & US 2004/229909 A1	1-21

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October, 2005 (11.10.05)	25 October, 2005 (25.10.05)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/016904

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/004657 A2 (BRISTOL-MYERS SQUIBB CO.), 15 January, 2004 (15.01.04) & US 2004/110804 A1	1-21
A	WO 2003/035076 A1 (INSTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA), 01 May, 2003 (01.05.03) & CA 2463975 A1 & EP 1441734 A1 & JP 2005-510500 A & US 2005/075356 A1	1-21
A	WO 2000/39086 A1 (Shionogi & Co., Ltd.), 06 July, 2000 (06.07.00) & AU 200017979 A & NO 200103179 A & BR 9916583 A & EP 1142872 A1 & CZ 200102160 A3 & KR 2001089708 A & CN 1335834 A & ZA 200104622 A & AU 763040 B & US 6620841 B1 & NZ 512184 A & HU 200201472 A2 & US 6645956 B1 & US 2004/002485 A1 & RU 2225860 C2	1-21
A	TEWTRAKUL, S. et al., Flavanone and flavonol glycosides from the leaves of Thevetia peruviana and their HIV-1 reverse transcriptase and HIV-1 integrase inhibitory activities, Chem.Pharm.Bull., 2002, Vol.50, No.5, p.630-5	1-21
A	WO 2004/024693 A1 (Shionogi & Co., Ltd.), 25 March, 2004 (25.03.04) & EP 1541558 A1	1-21
A	JP 02-108668 A (Daicel Chemical Industries, Ltd.), 20 April, 1990 (20.04.90) (Family: none)	1-21
A	JP 02-108683 A (Daicel Chemical Industries, Ltd.), 20 April, 1990 (20.04.90) (Family: none)	1-21
P,A	WO 2005/042524 A1 (VIROCHEM PHARMA INC.), 12 May, 2005 (12.05.05) & US 2005/176767 A1	1-21
P,A	EP 1544199 A1 (JAPAN TOBACCO INC.), 22 June, 2005 (22.06.05) & WO 2005/016927 A1 & US 2005/054645 A1	1-21

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/016904

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

A61P31/14 (2006.01), ***C07D409/12*** (2006.01), ***A61K31/4436*** (2006.01), ***C07D401/12*** (2006.01), ***A61K31/4439*** (2006.01)

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

Continuation of B. FIELDS SEARCHED
Minimum documentation searched (International Patent Classification (IPC))

A61K31/4436 (2006.01), ***C07D401/12*** (2006.01), ***A61K31/4439*** (2006.01)

Minimum documentation searched (classification system followed by classification symbols)

国際調査報告	国際出願番 PCT／JP2005／016904

A. 発明の属する分野の分類（国際特許分類（IPC））

Int.Cl.' ***C07D213/82***(2006.01), ***A61K31/366***(2006.01), ***A61K31/455***(2006.01), ***A61K31/506***(2006.01), ***A61K31/5377***(2006.01), ***A61P31/18***(2006.01), ***C07D309/38***(2006.01), ***C07D405/04***(2006.01), ***C07D413/04***(2006.01), ***C07D417/04***(2006.01), ***A61P31/14***(2006.01), ***C07D409/12***(2006.01), （特別ページへ続く）

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int.Cl.' ***C07D213/82***(2006.01), ***A61K31/366***(2006.01), ***A61K31/455***(2006.01), ***A61K31/506***(2006.01), ***A61K31/5377***(2006.01), ***C07D309/38***(2006.01), ***C07D405/04***(2006.01), ***C07D413/04***(2006.01), ***C07D417/04***(2006.01), ***C07D409/12***(2006.01), ***A61K31/4436***(2006.01), ***C07D401/12***(2006.01), ***A61K31/4439***(2006.01)

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAOLD(STN), CAplus(STN), REGISTRY(STN)

C. 関連すると認められる文献

引用文献のカテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X A	JP 2004-244320 A (塩野義製薬株式会社) 2004.09.02, 文献全体、特に、請求項1、実施例8、第27頁第40－50行及び第35－36頁参照 (ファミリーなし)	1－3, 6－8, 12－19, 21 4, 5, 9-11, 20
X	WO 2003/016275 A1 (塩野義製薬株式会社) 2003.02.27, 文献全体、特に、「化合物E－52」及び「化合物L－4」等、請求項1、14、18、20及び93、第61頁第23行－第62頁第4行、第69頁第6行－第71頁第5行、第97頁第15－21行、「化合物E－50」、並びに、第141－142頁参照 & CA 2452769 A1 & EP 1422218 A1 & BR 2002011750 A & CN 1558898	1－21

☑ C欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊ 引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
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「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
11.10.2005	25.10.2005

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）	4P	9550
日本国特許庁（ISA／JP） 郵便番号100－8915 東京都千代田区霞が関三丁目4番3号	谷尾 忍		
	電話番号 03－3581－1101 内線	3492	

様式PCT／ISA／210（第2ページ）（2005年4月）

C（続き）．関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
	A & US 2004/229909 A1	
A	WO 2004/004657 A2 (BRISTOL-MYERS SQUIBB COMPANY) 2004.01.15 & US 2004/110804 A1	1－21
A	WO 2003/035076 A1 (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA) 2003.05.01 & CA 2463975 A1 & EP 1441734 A1 & JP 2005-510500 A & US 2005/075356 A1	1－21
A	WO 2000/39086 A1 (塩野義製薬株式会社) 2000.07.06 & AU 200017979 A & NO 200103179 A & BR 9916583 A & EP 1142872 A1 & CZ 200102160 A3 & KR 2001089708 A & CN 1335834 A & ZA 200104622 A & AU 763040 B & US 6620841 B1 & NZ 512184 A & HU 200201472 A2 & US 6645956 B1 & US 2004/002485 A1 & RU 2225860 C2	1－21
A	TEWTRAKUL, S., et al., Flavanone and flavonol glycosides from the leaves of Thevetia peruviana and their HIV-1 reverse transcriptase and HIV-1 integrase inhibitory activities, Chem. Pharm. Bull., 2002, Vol.50, No.5, p.630-5	1－21
A	WO 2004/024693 A1 (塩野義製薬株式会社) 2004.03.25 & EP 1541558 A1	1－21
A	JP 02-108668 A (ダイセル化学工業株式会社) 1990.04.20 (ファミリーなし)	1－21
A	JP 02-108683 A (ダイセル化学工業株式会社) 1990.04.20 (ファミリーなし)	1－21
PA	WO 2005/042524 A1 (VIROCHEM PHARMA INC.) 2005.05.12 & US 2005/176767 A1	1－21
PA	EP 1544199 A1 (JAPAN TOBACCO INC.) 2005.06.22 & WO 2005/016927 A1 & US 2005/054645 A1	1－21

A. 発明の属する分野の分類（国際特許分類（IPC））の続き

A61K31/4436 (2006.01), *C07D401/12* (2006.01), *A61K31/4439* (2006.01)

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A61K 31/50 (2006.01) *C07D 487/00* (2006.01)
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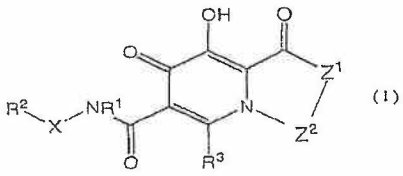
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,

[Continued on next page]

(54) Title: POLYCYCLIC CARBAMOYLPYRIDONE DERIVATIVE HAVING HIV INTEGRASE INHIBITORY ACTIVITY



(1)

(57) Abstract: The present invention is to provide a novel compound (I), having the anti-virus activity, particularly the HIV integrase inhibitory activity, and a drug containing the same, particularly an anti-HIV drug, as well as a process and an intermediate thereof. Compound (I) wherein Z^1 is NR^4; R^1 is hydrogen or lower alkyl; X is a single bond, a hetero atom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene in which the hetero atom group may intervene; R^2 is optionally substituted aryl; R^3 is hydrogen, a halogen, hydroxy, optionally substituted lower alkyl etc; and R^4 and Z^2 part taken together forms a ring, to form a polycyclic compound, including e.g., a tricyclic or tetracyclic compound.

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RO, SE, SI, SK, TR). OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SPECIFICATION

Polycyclic Carbamoylpyridone Derivative Having HIV Integrase Inhibitory Activity

[Technical Field]

[0001]

The present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.

[Background Art]

[0002]

Among viruses, human immunodeficiency virus (HIV), a kind of retrovirus, is known to cause acquired immunodeficiency syndrome (AIDS). The therapeutic agent for AIDS is mainly selected from a group of reverse transcriptase inhibitors (e.g., AZT, 3TC) and protease inhibitors (e.g., Indinavir), but they are proved to be accompanied by side effects such as nephropathy and the emergence of resistant viruses. Thus, the development of anti-HIV agents having the other mechanism of action has been desired.

On the other hand, a combination therapy is reported to be efficient in treatment for AIDS because of the frequent emergence of the resistant mutant. Reverse transcriptase inhibitors and protease inhibitors are clinically used as an anti-HIV agent, however agents having the same mechanism of action often exhibit cross-resistance or only an additional activity. Therefore, anti-HIV agents having the other mechanism of action are desired.

Under the circumstances above, an HIV integrase inhibitor has been focused on as an anti-HIV agent having a novel mechanism of action (Ref: Patent Documents 1 and 2) . As an anti-HIV agent having such a mechanism of action, known are carbamoyl-substituted hydroxypyrimidinone derivative (Ref: Patent Documents 3 and 4) and carbamoyl-substituted hydroxypyrrolidione derivative (Ref: Patent Document 5). Further, a patent application concerning carbamoyl-substituted hydroxypyridone derivative has been filed (Ref: Patent Document 6, Example 8) .

Other known carbamoylpyridone derivatives include 5-alkoxypyridine-3-carboxamide derivatives and γ-pyrone-3-carboxamide derivatives, which are a plant growth inhibitor or herbicide (Ref: Patent Documents 7-9).

Other HIV integrase inhibitors include N-containing condensed cyclic compounds

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(Ref: Patent Document 10).

[Patent Document 1]WO03/0166275

[Patent Document 2]WO2004/024693

[Patent Document 3]WO03/035076

[Patent Document 4]WO03/035076

[Patent Document 5]WO2004/004657

[Patent Document 6]JP Patent Application 2003-32772

[Patent Document 7]JP Patent Publication 1990-108668

[Patent Document 8]JP Patent Publication 1990-108683

[Patent Document 9]JP Patent Publication 1990-96506

[Patent Document 10]WO2005/016927

[Disclosure of Invention]

[Problem to be Solved by the Invention]

[0003]

The development of a novel integrase inhibitor has been desired.

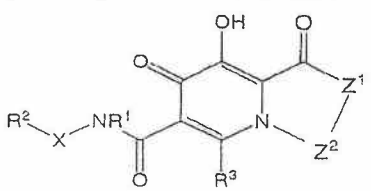
[Means to Solve the Problem]

[0004]

The present inventors have intensively studied to find that a novel polycyclic carbamoylpyridone derivative possesses a potent HIV integrase inhibitory activity.

Moreover, the present inventors have discovered that a compound of the present invention and a pharmaceutical composition containing the same are useful as an antiviral agent, an antiretroviral agent, an anti-HIV agent, an anti-HTLV-1 (Human T cell leukemia virus type 1) agent, an anti-FIV (Feline immunodeficiency virus) agent or an anti-SIV (Simian immunodeficiency virus) agent, especially an anti-HIV agent or anti-AIDS agent, to accomplish the present invention shown below.

(1)A compound of the formula:



(I)

(wherein,

Z^1 is NR^4;

R^4 is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SO_2, NR^a (R^a is hydrogen or lower alkyl), -N= and =N-)), O or CH_2;

Z^2 is optionally substituted lower alkylene or optionally substituted lower alkenylene, each may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^5 (R^5 is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy or optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SO_2, NR^6 (R^6 is selected independently from the same substituent group as R^4), -N= and =N-)), -N= or =N-

R^1 is hydrogen or lower alkyl;

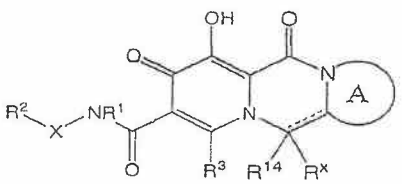
X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted

lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino;

R^4 and Z^2 part taken together forms a ring, where the compound (I) is represented by the following formula (I-1), or (I-11):



(I-1)

(wherein,

A ring is optionally substituted heterocycle;

R^{14} and R^X are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^6 (R^6 is selected independently from the same substituent group as R^4), -N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

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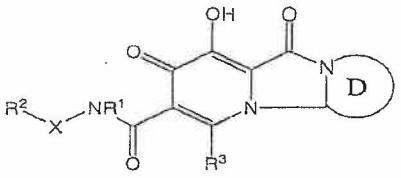
a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, R^X is not present;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino)



(I-11)

(wherein,

D ring is optionally substituted heterocycle;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino)), its pharmaceutically acceptable salt, or solvate thereof.

(2) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R^1 is hydrogen.

(3) A compound according to the above (1), pharmaceutically acceptable salt, or

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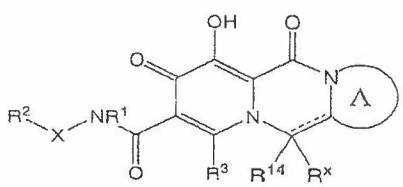
solvate thereof, wherein X is lower alkylene; R^2 is phenyl or phenyl substituted with at least halogen.

(4) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R^3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.

(5) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R^3 is hydrogen.

(6) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R^1 is hydrogen or lower alkyl; X is lower alkylene; R^2 is phenyl or phenyl substituted with at least halogen; R^3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.

(7) A compound of the formula:



(I-1)

(wherein,

A ring is optionally substituted heterocycle;

R^{1a} and R^X are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or

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lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^5 (R^5 is selected independently from the same substituent group as R^4), -N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, R^X is not present;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), its pharmaceutically acceptable salt, or solvate thereof

(8) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein R^1 is hydrogen or lower alkyl; X is lower alkylene; R^2 is phenyl or phenyl substituted with at least halogen; R^3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.

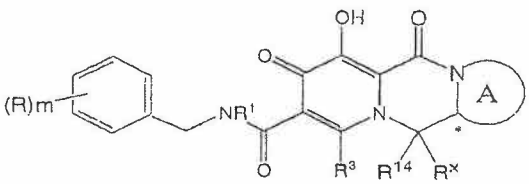
(9) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein a broken line represents the absence of a bond.

(10) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein R^X is hydrogen; R^{14} is hydrogen or optionally substituted lower alkyl.

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(11) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is an optionally substituted and optionally condensed 5- to 7- membered heterocycle containing 1 to 2 hetero atom(s).

(12) A compound of the formula:



(I-1-1)

(wherein,

A ring is an optionally substituted and optionally condensed 5- to 7- membered heterocycle containing 1 to 2 hetero atom(s);

the stereochemistry of an asymmetric carbon represented by * shows R- or S- configuration, or a mixture thereof;

R^{14} and R^X are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^5 (R^5 is selected independently from the same substituent group as R^4), -N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted

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aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

R^9 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), its pharmaceutically acceptable salt, or

R^1 is hydrogen or lower alkyl;

R is independently selected from halogen and Substituent group S1;

Substituent group S1: optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (wherein the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, O, S, SO, SO_2, NR^a (R^a is hydrogen or lower alkyl), -N= and =N-), lower alkoxy lower alkyl, amino lower alkyl optionally substituted with mono- or di- lower alkyl, halogenated lower alkyl, lower alkoxy, carbamoyl optionally substituted with mono- or di- lower alkyl, optionally substituted lower alkyl sulfonyl amino, halogenated lower alkoxy, hydroxy lower alkyl)

m is an integer of 0 to 3, its pharmaceutically acceptable salt, or solvate thereof.

(13) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^X and R^{14} are independently hydrogen or optionally substituted lower.

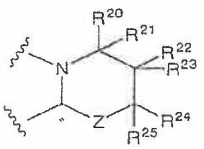
(14) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^X and R^{14} are hydrogens.

(15) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^3 is hydrogen.

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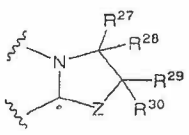
(16) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein m is 0, or 1 to 3 and at least one of R is halogen.

(17) A compound according to the above (7) or (12), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is any one of the following:



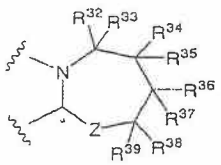
Z = O or NR^{26}

(A-1)



Z = O or NR^{31}

(A-2)



Z = O or NR^{40}

(A-3)

(wherein, R^{20} to R^{40} are each independently a group selected from Substituent group S2, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted carbocyle or optionally substituted heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring atom, may form an optionally substituted carbocyle or optionally substituted heterocycle.

Substituent group S2: hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocycle, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl, optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryl oxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl,

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optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, S, SO, SO_2, NR^5 (R^5 is independently selected from the same Substituent group as R^4), -N= and =N-)

the stereochemistry of an asymmetric carbon represented by * shows R- or S-configuration, or a mixture thereof)

(18) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein R^{20} to R^{40} are each independently hydrogen or substituted lower alkyl, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7-membered carbocyle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

(19) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); one of R^{20} to R^{26} is optionally substituted lower alkyl and the others are hydrogens.

(20) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); one of (R^{20} and R^{22}), (R^{23} and R^{24}), and (R^{25} and R^{26}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7-membered heterocycle.

(21) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); Z=NR^{26}, and R^{25} and R^{26} taken together with the neighboring atom may form an optionally substituted 5- to 7-

membered heterocycle.

(22) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); one of R^{27} to R^{30} is optionally substituted lower alkyl and the others are hydrogens.

(23) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); one of ($R^{27}$and R^{29}) and (R^{30} and R^{31}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

(24) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); Z=NR^{31}, and R^{30} and R^{31} taken together with the neighboring atom may form an optionally substituted 5- to 7- membered heterocycle.

(25) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); one of R^{32} to R^{39} is optionally substituted lower alkyl and the others are hydrogens.

(26) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); one of (R^{32}andR^{34}),(R^{35}andR^{36}),(R^{37}andR^{38}),and(R^{39}andR^{40}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

(27) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); Z=NR^{40}, and R^{39} and R^{40} taken together with the neighboring atom may form an optionally substituted 5- to 7- membered heterocycle.

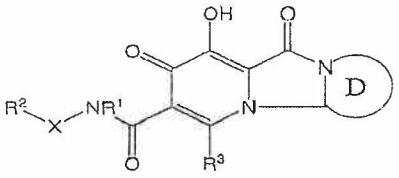
(28) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^X is hydrogen; R^{14} is hydrogen or optionally substituted lower; R^8 is hydrogen; m is 1 to 3 and at least one of Rs is halogen; A ring is a ring

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described in Claim 17.

(29) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^X is hydrogen; R^{14} is hydrogen; R^3 is hydrogen; m is 0, or 1 to 3 and at least one of Rs is halogen; A ring is a ring described in Claim 17; R^{20} to R^{40} are each independently hydrogen or substituted lower alkyl, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7- membered carbocyle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring carbon atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

(30) A compound of the formula:



(I-11)

(wherein,

D ring is optionally substituted heterocycle;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), pharmaceutically acceptable salt, or solvate thereof

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(31) A compound selected from the group consisting of:

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide;

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(4a*S*,13a*R*)-*N*-[(4-Fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3a*S*,13a*S*)-*N*-[(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-3-(1,1-Dimethylethyl)-*N*-[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(2*S*,3*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

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(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(5a*R*,14a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide;

(2*S*,3*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-3-(Cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(5a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide;

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(2*S*,3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(2*S*,3*R*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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(4*R*,12a*R*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-1-(Cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-1-(2-furanylmethyl)-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

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(4a*R*,6a*R*,14a*S*)-*N*-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide

(3*S*,4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-3-phenyl-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(6aR,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide;

(6aS,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide;

(5aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-a]pyrido[1',2':3,4]imidazo[1,2-d]pyrazine-9-carboxamide;

(4aR,14aR)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,

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14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide;

(4*R*,12a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(3-pyridinylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-1-Cyclopropyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-

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6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(3aS,5aS,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-5-(2-methylpropyl)-10,12-dioxo-2,3,3a,4,5,5a,6,10,12,13a-decahydro-1H-cyclopenta[e]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(4-morpholinyl)ethyl]-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(3aR,5aR,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[d]pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-methyl-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methyloxy)ethyl]-11,

13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-6-[2-(Acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-3-Butyl-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(4-hydroxyphenyl)methyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4S,12aS)-1-Cyclobutyl-N-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-hydroxyethyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-6-Cyclopropyl-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-6-[2-(1-pyrrolidinyl)ethyl]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide;

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

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(4S,12aS)-1-Cyclobutyl-N-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.

(32) A compound selected from the group consisting of:

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(4a*S*,13a*R*)-*N*-[(4-Fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxa

mide;

(4*S*,12a*S*)-1-(Cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4,-difluoro-benylamide;

4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4,-difluoro-benylamide;

2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benylamide;

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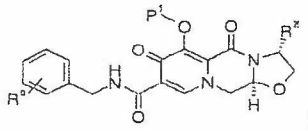
enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.

(33) A compound according to the above (31) or (32) wherein the pharmaceutically acceptable salt is a sodium salt.

(34) A pharmaceutical composition comprising a compound according to any one of the above (1) to (33), or a pharmaceutically acceptable salt, or solvate thereof.

(35) A pharmaceutical composition according to the above (34), which is an anti-HIV agent.

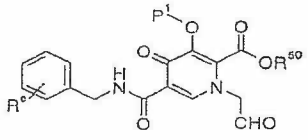
(36) A process for the preparation of a compound of formula (I-20a)



(I-20a)

wherein R^e is one or two halogen; R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy; and P^1 is C_{6-14}arylC_{1-8}alkyl;

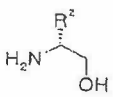
comprising condensing a compound of the formula



wherein R^e is one or two halogen; R^{60} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;

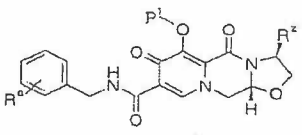
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with a compound of the formula



wherein R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy;
to form a compound of formula (I-20a).

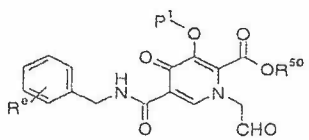
(37) A process for the preparation of a compound of formula (I-20b)



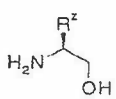
(I-20b)

wherein R^e is one or two halogen; R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula



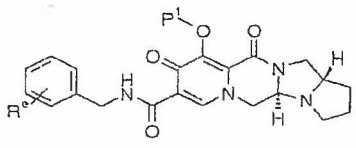
wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;
with a compound of the formula



wherein R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy;
to form a compound of formula (I-20b).

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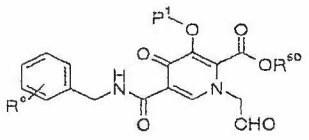
(38) A process for the preparation of a compound of formula (I-21a)



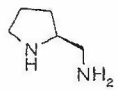
(I-21a)

wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula

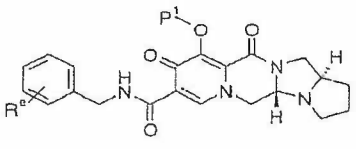


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



to form a compound of formula (I-21a).

(39) A process for the preparation of a compound of formula (I-21b)

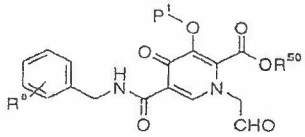


(I-21b)

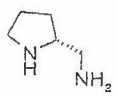
wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl;

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comprising condensing a compound of the formula

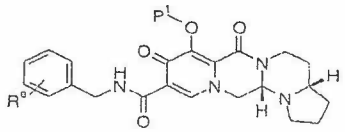


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



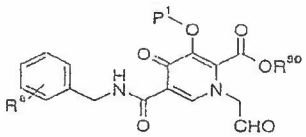
to form a compound of formula (I-21b).

(40) A process for the preparation of a compound of formula (I-22a)



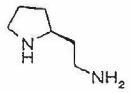
(I-22a)

wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl; comprising condensing a compound of the formula



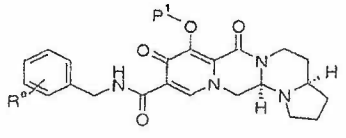
wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula

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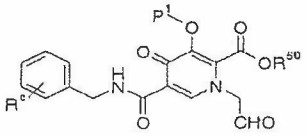
to form a compound of formula (I-22a).

(41) A process for the preparation of a compound of formula (I-22b)

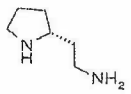


(I-22b)

wherein R^e is one or two halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$;
comprising condensing a compound of the formula

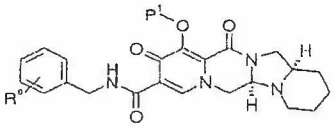


wherein R^e is one or two halogen; R^{50} is $C_{1-8}alkyl$; and P^1 is $C_{6-14}arylC_{1-8}alkyl$;
with a compound of the formula



to form a compound of formula (I-22b).

(42) A process for the preparation of a compound of formula (I-23a)

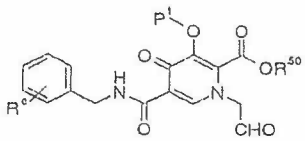


(I-23a)

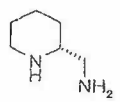
wherein R^e is one or two halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$;

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comprising condensing a compound of the formula

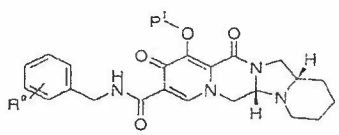


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



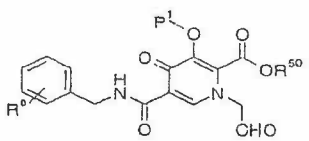
to form a compound of formula (I-23a).

(43) A process for the preparation of a compound of formula (I-23b)



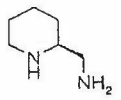
(I-23b)

wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl; comprising condensing a compound of the formula



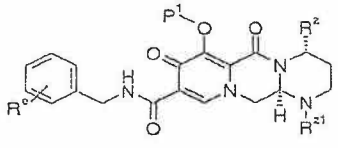
wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; with a compound of the formula

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to form a compound of formula (I-23b).

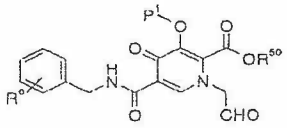
(44) A process for the preparation of a compound of formula (I-24a)



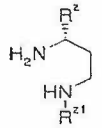
(I-24a)

wherein R^e is one or two halogen; R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula



wherein R^e is one or two halogen; and R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula

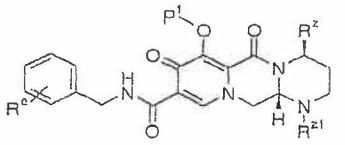


wherein R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;

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to form a compound of the formula (I-24a).

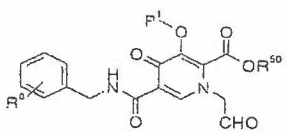
(45) A process for the preparation of a compound of formula (I-24b)



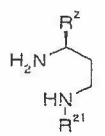
(I-24b)

wherein R^e is one or two halogen; R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula



wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;
with a compound of the formula

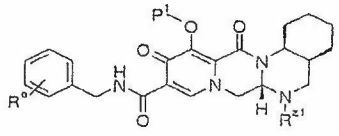


wherein R^z is C_{1-8}alkyl; and R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;

to form a compound of the formula (I-24b).

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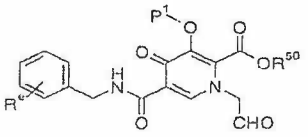
(46) A process for the preparation of a racemic compound of formula (I-25)



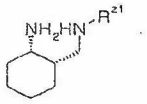
(I-25)

wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl; and P^1 is is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula



wherein R^e is one or two halogen; and R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a racemic compound of the formula

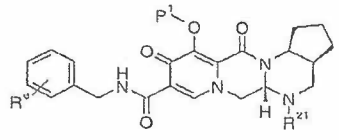


wherein R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;

to form a racemic compound of the formula (I-25).

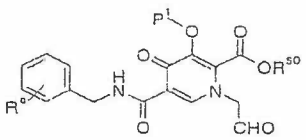
(47) A process for the preparation of a racemic compound of formula (I-26)

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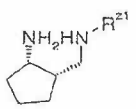


(I-26)

wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;
comprising condensing a compound of the formula



wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;
with a racemic compound of the formula

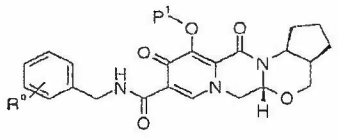


wherein R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;

to form a racemic compound of formula (I-26).

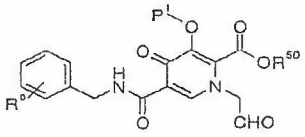
(48) A process for the preparation of a racemic compound of formula (I-27)

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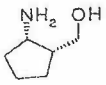


(I-27)

wherein R^e is halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$; comprising condensing a compound of the formula



wherein R^e is one or two halogen; R^{50} is $C_{1-8}alkyl$; and P^1 is $C_{6-14}arylC_{1-8}alkyl$; with a racemic compound of the formula



to form a racemic compound of formula (I-27).

(49). A compound of formula (I-20a) described in above (36), formula (I-20b) described in above (37), formula (I-21a) described in above (38), formula (I-21b) described in above (39), formula (I-22a) described in above (40), formula (I-22b) described in above (41), formula (I-23a) described in above (42), formula (I-23b) described in above (43), formula (I-24a) described in above (44), formula (I-24b) described in above (45), formula (I-25) described in above (46), formula (I-26) described in above (47), or formula (I-27) described in above (48), or a pharmaceutically acceptable salt thereof.

(50) A compound of formula (I-20a) described in above (36), formula (I-20b) described in above (37), formula (I-21a) described in above (38), formula (I-21b) described in above (39), formula (I-22a) described in above (40), formula (I-22b) described in above (41), formula (I-23a) described in above (42), formula (I-23b)

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described in above (43), formula (I-24a) described in above (44), formula (I-24b) described in above (45), formula (I-25) described in above (46), formula (I-26) described in above (47), or formula (I-27) described in above (48), or a pharmaceutically acceptable salt thereof, wherein each P^1 is hydrogen.

The present invention further provides a pharmaceutical composition containing any of the compounds shown above, a pharmaceutically acceptable salt or a solvate thereof, especially an anti-HIV agent.

[Effect of the Invention]

[0005]

The present invention compounds possess an integrase inhibitory activity and/or a cell-growth inhibitory activity against virus, especially HIV. Accordingly, they are useful for the prevention or treatment of various diseases mediated by integrase or virus infection diseases (e.g., AIDS). The present invention further provides a process for preparing a diastereomer, a mixture thereof, or racemate.

[Preferred Embodiment of the Invention]

[0006]

The terms used herein are explained below. Each term, alone or in combination with another tem, means as follows.

"Lower alkylene" means a straight or branched C1 to C6 alkylene such as methylene, ethylene, trimethylene, n-propylene, tetramethylene, ethylethylene, pentamethylene, or hexamethylene, preferably C1 to C4 straight alkylene such as methylene, ethylene, trimethylene, and tetramethylene, more preferably methylene or ethylene.

"Lower alkenylene" means a straight or branched C2 to C6 alkenylene, which consists of the above "Lower alkylene" having one or more double bonds, such as vinylene, propylene, or butenylene, preferably a straight C2 to C3 alkenylene such as vinylene or propylene.

"Lower alkyl" means a straight or branched C1 to C10 alkyl such as methyl, ethyl, n-propyl, i-propyl, t-butyl, isobutyl, sec-butyl, n-pentyl, and n-hexyl, and preferred is C1 to C3 alkyl, more preferred is methyl, ethyl or n-propyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, isohexyl, n-heptyl, n-octyl, n-nonyl, and n-desyl, preferably C1 to C6 lower alkyl, more preferably C1 to C4 lower alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, and isohexyl.

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When lower alkyl is intervened with "-N=" or "=N-", the lower alkyl may have a double bond to form $-CH_2-N=CH_2$, $-CH=N-CH_3$ etc.

"Alkenyl" means a straight or branched C2 to C8 alkenyl, which consists of the above "alkyl" having one or more double bonds, such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl, and 3-methyl-2-butenyl, preferably C2 to C6 alkenyl, and more preferably C2 to C4 alkenyl.

"Lower alkenyloxy" means oxy attached to the above lower alkenyl, such as vinyloxy, 1-propenyloxy, 2-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 1,3-butadienyloxy, and 3-methyl-2-butenyloxy.

"Cycloalkyl" means C3 to C8 cyclic saturated hydrocarbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl, and cyclooctyl, preferably C3 to C6 cycloalkyl.

"Cycloalkyl lower alkyl" means lower alkyl substituted with the above cycloalkyl, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, and cyclohexylethyl, and preferably C3 to C6 cycloalkyl lower alkyl.

"Aryl" means monocyclic aromatic hydrocarbon (e.g., phenyl) and polycyclic hydrocarbon (e.g., 1-naphthyl,2- naphthyl, 1-anthryl, 2-anthryl, 9-anthryl, 1-phenanthryl, 2-phenanthryl, 3-phenanthryl, 4-phenanthryl, 9-phenanthryl), preferably phenyl or naphthyl (e.g., 1-napthyl, 2-naphthyl).

"Aralkyl" or "aryl lower alkyl" means the above lower alkyl substituted with 1 to 3 of the above aryl, such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, 1-napthylmethyl, 2- napthylmethyl, preferably benzyl.

"Aryloxy" means oxy attached to the above aryl, such as 1-naphthyloxy, 2-naphthyloxy, 1-anthryloxy, 2-anthryloxy, 9-anthryloxy, 1-phenanthryloxy, 2-phenanthryloxy, 3-phenanthryloxy, 4-phenanthryloxy, and 9-phenanthryloxy, preferably phenyloxy or naphthyloxy (e.g., 1- napthyloxy, 2-naphthyloxy).

"Heterocyclic group" means "heteroring" or "heteroaryl".

"Heteroring" means a non-aromatic ring which has at least one of N, O and/or S in the ring and may be bonded at any substitutable position, preferably 5- to 7-membered ring, such as 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 1-pyrazolidinyl, 3-pyrazolidinyl, 4-pyrazolidinyl, piperidino, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperadinyl, 2-piperadinyl, 2-morpholinyl, 3-morpholinyl, morpholino, and tetrahydropyranyl. The non-aromatic ring is a

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saturated or unsaturated ring.

"Heteroaryl" means monocyclic aromatic hetero-type ring or condensed aromatic hetero-type ring.

"Monocyclic aromatic hetero-type ring" means a 5- to 8- membered aromatic ring, which contains 1 to 4 of O, S, P and/ or N and may be bonded at any substitutable position.

"Condensed aromatic hetero-type ring" means a group wherein an aromatic ring containing 1 to 4 of O, S, P and/ or N is condensed with 1 to 4 of 5- to 8-membered aromatic ring(s) or the other 5- to 8-membered aromatic heteroring(s).

Examples of "heteroaryl" include furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), triazolyl (e.g., 1,2,4-triazole-1-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-4-yl), tetrazolyl (e.g., 1-tetrazolyl, 2-tetrazolyl, 5-tetrazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), thiadiazolyl, isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), pyridil(e.g., 2-pyridil, 3-pyridil, 4-pyridil), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), furazanyl (e.g., 3-furazanyl), pyrazinyl (e.g., 2-pyrazinyl), oxadiazolyl (e.g., 1,3,4-oxadiazole-2-yl), benzofuryl (e.g., 2-benzo[b]furyl, 3-benzo[b]furyl, 4-benzo[b]furyl, 5-benzo[b]furyl, 6-benzo[b]furyl, 7-benzo[b]furyl), benzothienyl(e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl, 4-benzo[b]thienyl, 5-benzo[b]thienyl, 6-benzo[b]thienyl, 7-benzo[b]thienyl), benzoimidazolyl (e.g., 1-benzoimidazolyl, 2-benzoimidazolyl, 4-benzoimidazolyl, 5-benzoimidazolyl), dibenzofuryl, benzooxazolyl, quinoxalinyl (e.g., 2-quinoxalinyl, 5-quinoxalinyl, 6-quinoxalinyl), cinnolinyl (e.g., 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, 8-cinnolinyl), quinazolinyl (e.g., 2-quinazolinyl, 4-quinazolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 8-quinazolinyl), quinolyl(e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), phthalazinyl (e.g., 1-phthalazinyl, 5-phthalazinyl, 6-phthalazinyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), purinyl, pteridinyl (e.g., 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, 7-pteridinyl), carbazolyl, phenanthridinyl, acridinyl (e.g., 1-acridinyl, 2-acridinyl, 3-acridinyl, 4-acridinyl, 9- acridinyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), isoindolyl, phenandinyl (e.g., 1- phenandinyl,

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2- phenandinyl) or phenothiadinyl (e.g., 1- phenothiadinyl, 2-phenothiadinyl, 3-phenothiadinyl, 4-phenothiadinyl).

"Heterocycle" means a cycle which can be lead to the above heterocyclic group.

"Heterocyclic group lower alkyl" or "Heterocycle lower alkyl" means lower alkyl substituted with the above heterocyclic group.

"Heterocyclic group oxy" or "Heterocycle oxy" means an oxy attached to the above heterocyclic group.

"Heterocyclic group carbonyl" or "Heterocyclecarbonyl" means a carbonyl attached to the above heterocyclic group

"Lower alkoxy" or "alkoxy" means an oxy attached to the above lower alkyl, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy.

"Lower alkylcarbonyl", "cycloalkylcarbonyl", "cycloalkyl lower alkylcarbonyl", "lower alkoxycarbonyl", "arylcarbonyl", "aryl lower alkylcarbonyl", "aryloxycarbonyl", "heterocyclecarbonyl", "heterocycle lower alkylcarbonyl", and "heterocycle oxycarbonyl", each means a carbonyl attached to the above "lower alkyl", "cycloalkyl", "cycloalkyl lower alkyl", "lower alkoxy", "aryl", "aryl lower alkyl", "aryloxy", "heterocycle", "heterocycle lower alkyl", and "heterocycleoxy", respectively.

[0007]

When a substituent(s) is/are present on "optionally substituted lower alkyl", "optionally substituted cycloalkyl", "optionally substituted cycloalkyl lower alkyl", "optionally substituted lower alkenyl", "optionally substituted lower alkoxy", "optionally substituted aryl", "optionally substituted aryl lower alkyl", "optionally substituted aryloxy", "optionally substituted aryloxy lower alkyl", "optionally substituted heterocycle, "optionally substituted heterocyclic group", "optionally substituted heterocycle lower alkyl", "optionally substituted heterocycleoxy", "optionally substituted lower alkenyloxy", "optionally substituted lower alkylcarbonyl", "optionally substituted cycloalkylcarbonyl", "optionally substituted cycloalkyl lower alkylcarbonyl", "optionally substituted lower alkoxycarbonyl", "optionally substituted arylcarbonyl", "optionally substituted aryl lower alkylcarbonyl", "optionally substituted aryloxycarbonyl", "optionally substituted heterocyclecarbonyl", "optionally substituted heterocycle lower alkylcarbonyl", "optionally substituted heterocycleoxycarbonyl", "optionally substituted lower alkylene", "optionally substituted lower alkenylene", "optionally substituted phosphoric acid residue", "optionally substituted carbocycle" or "optionally

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substituted heterocycle", each may be substituted with the same or different, 1 to 4 group(s) selected from Substituent group B at any position.

Examples of Substituent group B include hydroxy, carboxy, halogen (F,Cl,Br,I), halo lower alkyl (e.g., CF_3,CH_2CF_3, CH_2CCl_3), halo lower alkoxy (e.g., OCF_3, OCH_2CF_3, OCH_2CCl_3), lower alkyl (e.g., methyl, ehtyl, isopropyl, tert-butyl), lower alkenyl (e.g., vinyl), lower alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl), cycloalkenyl (e.g., cyclopropenyl), lower alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy), lower alkenyloxy (e.g., vinyloxy, allyloxy), lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl), nitro, nitroso, optionally substituted amino (e.g., alkylamino (e.g., methylamino, ethylamino, dimethylamino), acylamino (e.g., acetylamino, benzoylamino), aralkylamino (e.g., benzylamino, trithylamino), hydroxyamino), azido, aryl (e.g., phenyl), aralkyl (e.g., benzyl), cyano, isocyano, isocyanate, thiocyanate, isothiocyanate, mercapt, alkylthio (e.g., methylthio), alkylsulfonyl (e.g., methansulfonyl, ethansulfonyl), optionally substituted alkylsulfonylamino (e.g., methanesulfonylamino, ethansulfonylamino, N-methylsulfonyl-N'-methylamino), optionally substituted carbamoyl (e.g., alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl)), sulfamoyl, acyl (e.g., formyl, acetyl), formyloxy, haloformyl, oxal, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfino, sulfo, sulfoamino, hydrazino, azido, ureido, amizino, quanidino, phthalimide, oxo, phosphoric acid residue, lower alkyl which is substituted with a phosphoric acid residue and may be intervened with a heteroatom group(s), aryl substituted with a phosphoric acid residue, aralkyl substituted with a phosphoric acid residue, hydroxyl lower alkyl, preferably hydroxy, carboxy, halogen(F,Cl,Br,I), halo lower alkyl (e.g., CF_3,CH_2CF_3, CH_2CCl_3), halo lower alkoxy (e.g., OCF_3, OCH_2CF_3, OCH_2CCl_3), lower alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl), lower alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy), optionally substituted amino (e.g., alkylamino (e.g., methylamino, ethylamino, dimethylamino), oxo, or phosphoric acid residue.

Examples of a substituent of "optionally substituted amino" or "optionally substituted carbamoyl" include mono- or di- lower alkyl, lower alkylcarbonyl, lower alkylsulfonyl, optionally substituted lower alkyl (e.g., methyl, ethyl, isopropyl, benzyl, carbamoylalkyl (e.g., carbamoylmethyl), mono- or di- lower alkylcarbamoyl lower alkyl (e.g., dimethylcarbamoylethyl), hydroxyl lower alkyl, heterocycle lower alkyl (e.g., morpholinoethyl, tetrahydropyranylethyl), alkoxycarbonyl lower alkyl (e.g., ethoxycarbonylmethyl, ethoxycarbonylethyl), mono- or di- lower alkylamino lower alkyl (e.g., dimethylaminoethyl)), lower alkoxy lower alkyl (e.g., methoxyethyl,

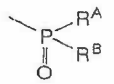
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ethoxymethyl, ethoxyethyl, isopropoxyethyl), acyl (e.g., formyl, optionally substituted lower alkylcarbonyl (e.g., acetyl, propionyl, butylyl, isobutylyl, valeryl, isovaleryl, pivaroyl, hexanoyl, octanoyl, methoxyethylcarbonyl, 2,2,2-trifluoroethylcarbonyl, ethoxycarbonylmethylcarbonyl), lower alkoxy lower alkylcarbonyl (e.g., methoxyethylcarbonyl), lower alkylcarbamoyl lower alkylcarbonyl (e.g., methylcarbamoylehtylcarbonyl), alkoxycarbonylacetyl), optionally substituted arylcarbonyl (e.g., benzoyl, toloyl), optionally substituted aralkyl (e.g., benzyl, 4-fluorobenzyl), hydroxy, optionally substituted lower alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, isopropylsulfonyl, 2,2,2-trifluoroethanesulfonyl, benzylsulfonyl, methoxyethylsulfonyl), lower alkyl, or arylsulfonyl optionally substituted with halogen (e.g., benzenesulfonyl, toluenesulfonyl, 4-fluorobenzenesulfonyl, fluorobenzenesulfonyl), cycloalkyl (e.g., cyclopropyl), aryl optionally substituted with lower alkyl (e.g., phenyl, trithyl), lower alkylaminosulfonyl (e.g., methylaminosulfonyl, dimethylaminosulfonyl), lower alkylaminocarbonyl (e.g., dimethylaminocarbonyl), lower alkoxycarbonyl (e.g., ethoxycarbonyl), cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclohexylcarbonyl), optionally substituted sulfamoyl (e.g., sulfamoyl, methylsulfamoyl, dimethylsulfamoyl), lower alkylcarbonylamino (e.g., methylcarbonylamino), heterocycle (e.g., morpholino, tetrahydropyranyl), optionally substituted amino (e.g., mono- or di-alkylamino (e.g., dimethylamino), formylamino).

As to amino of "optionally substituted amino", "optionally substituted carbamoyl", or "optionally substituted carbamoylcarbonyl", two substituents on the amino together with the neighboring N atom may form an N-containing heterocycle which optionally contains S and/or O in the ring (preferably 5- to 7- membered ring or saturated ring) and is optionally substituted with oxo or hydroxy. The optional S atom in the ring may be substituted with oxo. The N-containing heterocycle is preferably a 5- or 6-membered ring such as piperadinyl, piperidino, morpholino, pyrrolidino, 2-oxopiperidino, 2-oxopyrrolidino, 4-hydroxymorpholino.

"Phosphoric acid residue" means a group shown of the formula: $-PO(OH)_2$. "Optionally substituted phosphoric acid residue" means a phosphoric acid residue wherein the OH part and/or a hydrogen of the OH is optionally substituted with a phosphoric acid residue, preferably shown by the formula:

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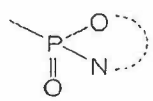
(P-1)

(wherein, R^A and R^B each is independently OR^C or NR^DR^E (wherein R^C, R^D and R^E are each independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclic group, or R^D and R^E taken together with the neighboring N atom may form an optionally substituted heterocycle (preferably 5- to 6- membered ring)) or R^A and R^B taken together with the neighboring P atom may form an optionally substituted heterocycle (preferably 5- to 6- membered ring)).

Preferably, R^A and R^B are bothOR^C, or one of them is OR^C and the other is NR^DR^E.

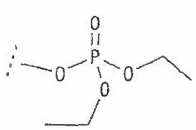
R^C, R^D and R^E each is preferably, independently, lower alkyl (e.g., methyl, ethyl).

The optionally substituted heterocycle formed by R^A and R^B taken together with the neighboring P atom may be the following structure:



(wherein, the broken line means a part of the ring)

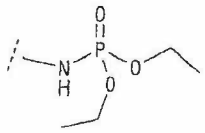
Hydroxy substituted with optionally substituted phosphoric acid residue is preferably hydroxy substituted with a phosphoric acid residue substituted with di lower alkyls, and more preferably a group of the formula:



Amino substituted with optionally substituted phosphoric acid residue is preferably amino substituted with a phosphoric acid residue substituted with di lower

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alkyls, and more preferably a group of the formula:



[0008]

(More preferable embodiments)

R^1 is hydrogen or lower alkyl, preferably hydrogen.

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH (hereafter also referred to as "M"), or lower alkylene or lower alkenylene each may be intervened by the heteroatom. The term of "intervened by" means the following cases:

1) The heteroatom group is present between carbon atoms which constitutes the alkylene or alkenylene.

2) The heteroatom group is attached to the N atom of the carbamoyl group neighboring to X.

3) The heteroatom group is attached to R^2 neighboring to X.

The heteroatom group (M) may be the same or different, and one or more atoms. Examples of that lower alkylene is intervened by a heteroatom group include -M-CH_2-, -CH_2-M-CH_2-, -CH_2-M-, and -CH_2-M-M-CH_2-.

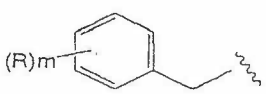
X is preferably a spacer consisting 1 to 3 joined atoms. X is more preferably lower alkylene or lower alkenylene each may be intervened by a heteroatom group, or O. X is most preferably C1 to C3 alkylene, C2 to C3 alkenylene, or O. Especially preferred is methylene or O.

R^2 is optionally substituted aryl, preferably phenyl. A substituent on the aryl is the same or different, 1 to 3, preferably 1 to 2 substituent(s), including preferably halogen, hydroxy, amino, lower alkylamino, cyano, carboxy, formyl, oxo, lower alkyl, lower alkoxy, lower alkylthio, carbamoyl, and lower alkylcarbamoyl, and Substituent group S1(: optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substitutedphosphoric acid residue, hydroxyl substituted with optionally substitutedphosphoric acid residue, amino substituted with optionally

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substitutedphosphoric acid residue, lower alkyl substituted with optionally substitutedphosphoric acid residue (said lower alkyl may be intervened with a hetero atom group(s) selected from O, S, SO, SO_2, NR^5 (R^5 is independently selected from the same substituent group for R^4), -N= and =N-), lower alkoxy lower alkyl, amino lower alkyl optionally substituted with mono- or di-lower alkyl, halogenated lower alkyl, lower alkoxy, carbamoyl optionally substituted with mono- or di-lower alkyl, optionally substituted lower alkylsulfonylamino, halogenated lower alkoxy, hydroxyl lower alkyl), more preferably halogen,hydroxy,amino,cyano,lower alkyl, lower alkoxy or Substituent group S1, and most preferred is halogen (e.g., F) and/or a group selected from Substituent group S1. A substituent on the aryl is preferably at the 4-position. R^2 is more preferably phenyl or phenyl substituted with at least halogen, and most preferably 4-halogenophenyl (e.g., 4-F-phenyl). In another embodiment, R^2 is preferably phenyl optionally substituted with 1 to 3 R(s) mentioned below.

In all compounds of the present invention, the structure of "-X-R^2" is preferably shown by the formula below:



R each is independently a group selected from halogen and Substituent group S1.

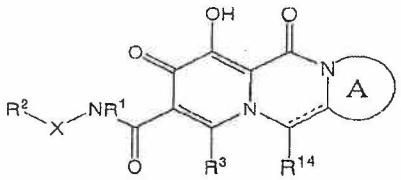
Substituent group S1: optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxyl substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, lower alkyl substituted with optionally substituted phosphoric acid residue (said lower alkyl may be intervened by a heteroatom group(s) selected from CO, O, S, SO, SO_2, NR^a (R^a is hydrogen or lower alkyl), -N= and =N-), lower alkoxy lower alkyl, optionally substituted amino lower alkyl (the substituent: mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), halogenated lower alkyl, lower alkoxy, optionally substituted carbamoyl (the substituent: mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), optionally substituted lower alkylsulfonylamino, halogenated lower alkoxy, and hydroxyl lower alkyl.

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m is an integer of 0 to 3, preferably 0 or 1 to 2. when m is 1, R is preferably halogen. When m is 2, R is more preferably the same or different group selected from halogen, lower alkyl, lower alkoxy, lower alkoxylower alkyl, halogenated lower alkyl, halogenated lower alkoxy, lower alkylsulfonylamino, carbamoyl, and lower alkylcarbamoyl. More preferably, R is two halogens, or halogen and another group. R preferably locates at the 4-position and optional another position of the benzene ring.

R^3 can be a various substituent which does not bring a negative effect to the pharmacological activity, including hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy, and optionally substituted amino. Examples of substituent of "optionally substituted" include halogen, hydroxy, amino, lower alkylamino, cyano, carboxy, formyl, oxo, lower alkyl, lower alkoxy, lower alkylthio, carbamoyl, lower alkylcarbamoyl, aryl, heterocyclic group, lower alkylcarbonyl, lower alkylcarbonyloxy, lower alkoxycarbonyl, halogenated lower alkyl, halogenated lower alkoxy, and preferably halogen, hydroxy, amino, lower alkylamino, lower alkyl, and lower alkoxy. R^3 is more preferably hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino, and most preferably hydrogen or lower alkyl (e.g., methyl), esp. hydrogen.

Z^2 shows C, CH, optionally substituted lower alkylene, lower alkenylene etc., and Z^2 and R^4 of Z^1 taken together form a ring, whereby compound (I) shows a tricyclic compound (I-1) or (I-11) shown below, or its derivative, tetracyclic compound.

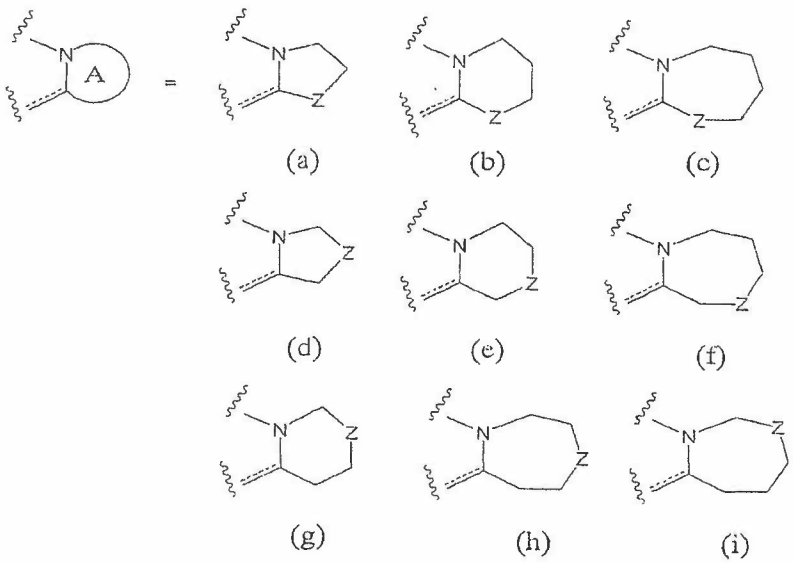


(I-1)

A ring is optionally substituted heterocycle containing at least an N atom. The

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heterocycle is a 5- to 7-membered ring which contains preferably 1 to 3, more preferably 2 to 3 atoms of O, S and/or N. The heterocycle is preferably selected from the above heterocycle. The arc optionally contains 1 to 2 heteroatom(s) at any possible position. One of preferable embodiments of A ring is an optionally substituted ring shown below.



(Z is CH_2, O, S, SO, SO_2 or NR^{19})

A ring is preferably a ring of (a), (b), or (c).

Z is preferably O or NR^{19}.

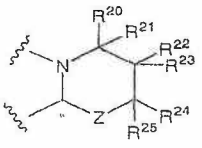
When Z is NR^{19}, examples of R^{19} include 1)hydrogen, 2)optionally substituted lower alkyl (the substituent is e.g., amino optionally substituted with mono- or di-lower alkyl; cycloalkyl; hydroxy; optionally substituted heterocyclic group (preferably 5- to 7-membered ring, e.g., furyl, thienyl, thiazolyl, pyridil, morpholino, imidazole; examples of the substituent include lower alkyl, halogen); optionally substituted heterocyclecarbonyl (the heterocycle is preferably 5- to 7-membered ring, e.g., morpholinocarbonyl); optionally substituted phenyl (the substituent is e.g., lower alkyl, amino, lower alkylamino, hydroxy, halogen, halogenated lower alkyl, lower alkoxy, halogenated lower alkoxy, lower alkylthio, lower alkylsulfonyl), acetylamino, carbamoyl, carbamoyl substituted with mono- or di- lower alkyl, lower

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alkylsulfonylamino, lower alkoxy, carbonyl, halogen, thiol, lower alkylthio), 3) lower alkenyl, 4) acyl (e.g., lower alkylcarbonyl), 5) lower alkylsulfonyl. R^{19} may be selected from Substituent group S2 shown below.

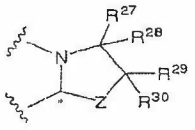
The other substituent on A ring may be selected from R^{15} to R^{18} or Substituent group S2, preferably lower alkyl. Substituents on A ring may form a condensed ring or a spiro ring as mentioned below, whereby compound (I) includes a tetracyclic compound.

A ring is more preferably any of the following rings:



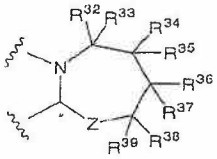
Z = O or NR^{26}

(A-1)



Z = O or NR^{31}

(A-2)



Z = O or NR^{40}

(A-3)

(wherein, R^{20} to R^{40} are each independently a group selected from Substituent group S2, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form a spiro ring, i.e., an optionally substituted carbocyle or optionally substituted heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring atom, may form an optionally substituted carbocyle or optionally substituted heterocycle.

Substitution group S2: hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocycle, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl,

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optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryl oxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl, optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, S, SO, SO_2, NR^5 (R^5 is independently selected from the same substitution group as R^4), -N= and =N-)

The stereochemistry of an asymmetric carbon represented by * shows the R- or S-configuration, or a mixture thereof)

In one embodiment, R^{20} to R^{40} each is preferably hydrogen, optionally substituted lower alkyl (examples of the substituent: OH, lower alkoxy, cycloalkyl, lower alkylthio, lower alkylsulfonyl, heterocyclic group, aryl, optionally substituited amino (examples of the substituent: lower alkyl, acyl)), cycloalkyl, optionally substituited aryl (examples of the substituent: OH, lower alkyl), and optionally substituited heterocyclic group.

In one embodiment, R^{20} to R^{25}, R^{27} to R^{30}, and R^{32} to R^{39}, each is preferably hydrogen, C1-C8 alkyl, C6-C14 aryl C1-C8 alkyl, C6-C14 aryl, or alkoxy.

In one embodiment, R^{26}, R^{31}, and R^{40}, each is preferably hydrogen, C3-6 cycloalkyl, heterocycle, or C1-8 alkyl optionally substituted with hydroxy, C3-6 cycloalkyl, alkoxy, heterocycle, heteroaryl, C6-14 aryl, or amino, wherein said amino may be optionally substituted with –C(O)C1-8 alkyl or C1-8 alkyl.

More Preferred embodiments are shown below for example

I) When A ring is A-1, preferred is that 1) Z is NR^{26} and R^{26} and R^{24} taken together form heterocycle, and the others are hydrogens; 2) Z is O or NR^{26}, (R^{20} and R^{22}) or

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(R^{23} and R^{24}) taken together form cycloalkyl which is substituted with phenyl, the others are hydrogens or optionally substituted lower alkyl.

II) When A ring is A-2, preferred is that 1) Z is O, R^{27} or R^{28} is lower alkyl, and the others are hydrogens; 2) Z is NR^{31} and R^{30} and R^{31} taken together form heterocycle and the others are hydrogens, or R^{27} and R^{29} taken together form cycloalkyl and the others are hydrogens ; 3) Z is O, R^{27} and R^{29} taken together form cycloalkyl which may be condensed with phenyl, and the others are hydrogens

R^{14} and R^x are each independently hydrogen, optionally substitutedlower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino,optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl, optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl, optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy optionally substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heterotom group(s) selected from O, S, SO, SO_2, NR^a (R^a is hydrogen or lower alkyl), -N= and =N-).

R^{14} and R^x are each independently, preferably, hydrogen, hydroxyl, optionally substituted lower alkyl (the substituent is preferably, e.g., amino, lower alkyl amino, hydroxy, lower alkoxy). R^{14} and R^x are preferably hydrogens.

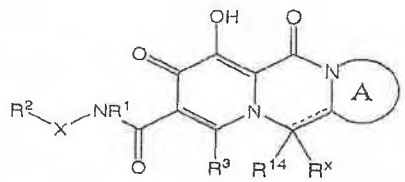
A broken line in the compound (I-1) represents the presence or absence of a bond,

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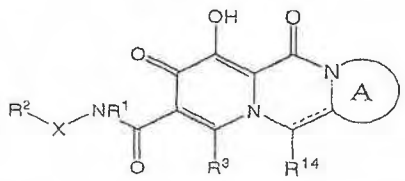
provided that when the broken line represents the presence of a bond, R^x is not present.

[0009]

The compound (I) includes the following compounds.

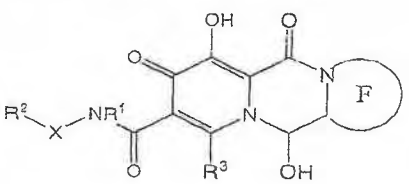


(I-1)



(I-1-1)

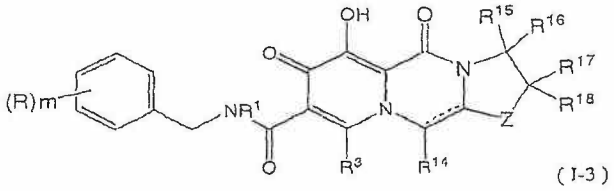
(wherein each symbol is as defined above)



(I-8)

F ring means the same heterocycle as A ring, preferably 5- to 7-membered ring, and the substituents on F ring are the same as those for A ring. The other symbols are as defined above.

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(I-3)

(wherein each symbol is as defined above; Z is O or NR^{19}; R^{15} to R^{19} are each independently hydrogen or a group selected from the above Substituent group S2, or each combination of (R^{15} and R^{16}), (R^{17} and R^{18}), (R^{16} and R^{18}), and (R^{18} and R^{19}) taken together with the neighboring atom(s), may form an optionally substituted carbocycle (preferably 5- to 6-membered ring) or an optionally substituted heterocyle (preferably 5- to 6-membered ring); or each combination of (R^{15} and R^{16}) and (R^{17} and R^{18}) taken together may fom oxo)

Compound (I-3) is preferably as follows.

(1) R^1 is hydrogen; R^3 is hydrogen; m is 1 or 2; R^{14} is hydrogen.

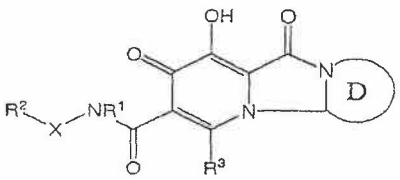
(2) m is 1 or 2, R is each independently halogen, halogenated lower alkyl, lower alkoxy, halogenated lower alkoxy, lower alkoxy lower alkyl, hydroxy lower alkyl, optionally substituted amino lower alkyl (the substituent is mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), optionally substituted carbamoyl (the substituent is mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue or sulfonylamino optionally substituted with lower alkyl; R^1 is hydrogen; R^3 is hydrogen; R^{14} is hydrogen, hydroxyl or lower alkyl optionally substituted with mono- or di- lower alkylamino; Z is O or NR^{19} (R^{19} is hydrogen or lower alkyl, lower alkoxy lower alkyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue).

(3)R is each independently, -F, $-CF_3$, -OMe, $-OCF_3$, $-CH_2OMe$, $-CH_2OH$, $-CH_2N(Me)_2$, -CONHMe, $-CON(Me)_2$, $-CH_2PO(OEt)_2$, $-PO(OEt)_2$, $-NHSO_2Me$, or $-NMeSO_2Me$;R^1 is hydrogen; R^3 is hydrogen; m is 1 or 2; R^{14} is hydrogen, hydroxyl or $-CH_2N(Me)_2$; Z is O or NR^{19} (R^{19} is hydrogen or $-CH(Me)_2$, $-(CH_2)_2OMe$,

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-$(CH_2)_2PO(OEt)_2$).

(4)R^{16} and R^{16} are hydrogens; R^{17} and R^{18} are hydrogens or taken together with the neighboring atom form a 3- to 7-membered carbocyle; and/or Z is O or NH. This case preferably also satisfys the above (2) or (3).



(I-11)

D ring means the same heterocycle as A ring, preferably 5- to 7-membered ring, and the substituents on D ring are the same as those for A ring. The other symbols are as defined above.

The structure of compound (I) has at least the following characteristics.

(1) The main structure, condensed heterocycle, is substituted with oxo (=O), hydroxyl (OH) and oxo.

(2) A substituted carbamoyl group (-$CONR^1XR^2$) is attached to the position neighboring to the oxo group on the condensed hereocycle.

The above structure contributes to a remarkably potent integrase inhibitory activity and/or cell-growth inhibitory activity against virus including HIV. In contrast, the structures of the other parts such as Z^1, Z^2, and R^3 each may be of variety, being optionally substituted or optionally condensed, and its condensed ring is also optionally substituted.

The present invention provides a pharmaceutically acceptable salt or a solvate of compound (I). All theoretically possible tautomer, geometrical isomer, optically active compound, and racemate thereof are within the scope of the invention.

Pharmaceutically acceptable salts of a compound of the present invention include, as basic salts, for example, alkali metal salts such as sodium or potassium salts; alkaline-earth metal salts such as calcium or magnesium salts; ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine or procaine salts; aralkyl amine salts

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such as N, N-dibenzylethylenediamine salts; heterocyclic aromatic amine salts such as pyridin salts, picoline salts, quinoline salts or isoquinoline salts; quaternary ammonium salts such as tetramethylammonium salts, tetraethylammonium salts, benzyltrimethylammonium salts, benzyltriethylammonium salts, benzyltributylammonium salts, methyltrioctylammonium salts or tetrabutylammonium salts; and basic amino acid salts such as arginine salts or lysine salts. Acid salts include, for example, mineral acid salts such as hydrochloride, sulfates salts, nitrate salts, phosphates salts, carbonates salts, hydrogencarbonates or perchlorate; organic acid salts such as acetates, propionates, lactates, maleates, fumarates, tararic acid salts, malates, citrates salts, ascorbates, formic acid; sulfonates such as methanesulfonates, isethionates, benzenesulfonates, or p-toluenesulfonates; and acidic amino acid salts such as aspartates or glutamates.

Solvates of a compound of the present invention include alcholates and hydrates.

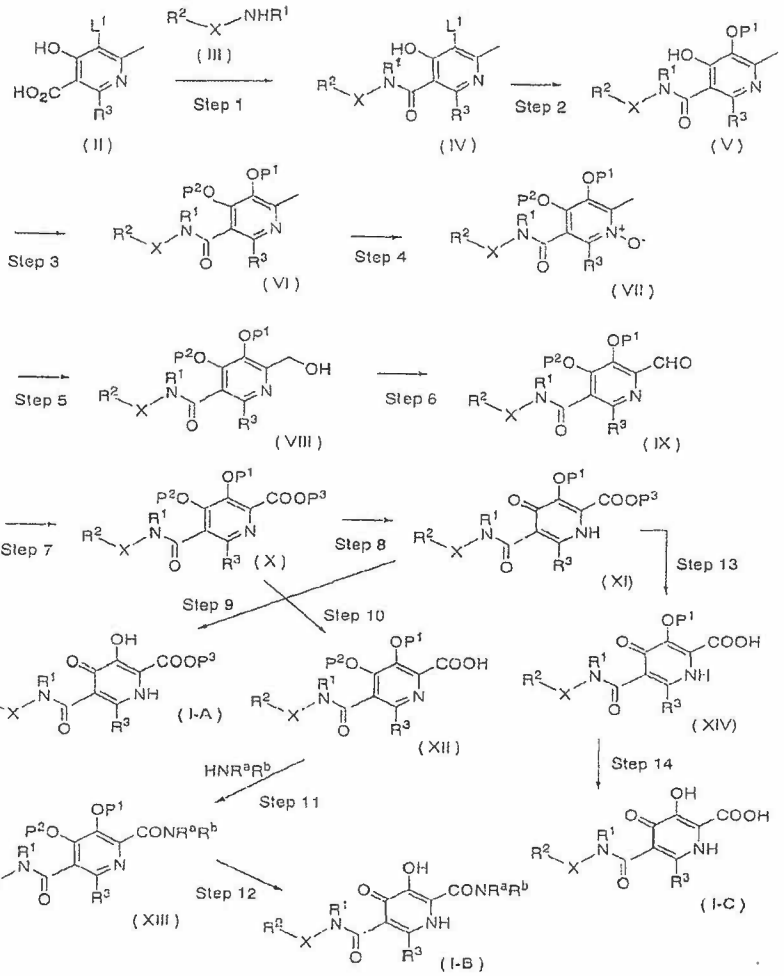
[0012]

A general process for producing the present compound will be exemplified below.

(Method of preparing raw material)

[Chemical formula 41]

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(wherein L^1 is a leaving group (e.g.; halogen); P^1 and P^2 are a hydroxy protecting group; P^3 is a carboxy protecting group (e.g.: lower alkyl); R^a and R^b are hydrogen or a substituent on an amino group)

Examples of a hydroxy protecting group (P^1, P^2) include acyl (e.g.: acetyl, pivaloyl, benzoyl), aralkyl (e.g.: benzyl), lower alkyl (e.g.: methyl), alkoxyalkyl (e.g.: methoxymethyl, methoxyethyl), lower alkylsulfonyl (e.g.: methanesulfonyl), arylsulfonyl (e.g.: benzenesulfonyl, toluenesulfonyl), alkoxycarbonyl (e.g.:

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methoxycarbonyl) and the like.

As a carboxy protecting group (P^3), lower alkyl (e.g.: methyl, ethyl), and aralkyl (e.g.: benzyl) are exemplified.

[0013]

(First step)

The present step is a reaction for condensing a compound (II) and a compound (III) to synthesize a compound (IV). The reaction may be performed according to the condition for a reaction of amidating carboxylic acid which is generally performed. A compound (II) may be reacted as it is, or may be reacted after converted into corresponding acid chloride or active ester. Preferably, the reaction is performed in a suitable solvent in the presence of a condensing agent.

As a condensing agent, dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and the like may be used. If necessary, a reagent such as 1-hydroxybenzotriazole and N-hydroxysuccinimide, or a base such as triethylamine, N-methylmorpholine, and pyridine may be added.

A reaction temperature is 0 to 150°C, preferably room temperature to 70°C.

As a reaction solvent, a non-protonic solvent can be broadly used, and tetrahydrofuran (THF), 1,4-dioxane, dimethylformamide (DMF), methylene chloride, chloroform and the like are preferable.

A reaction time is a few minutes to a few tens hours, preferably 9 to 17 hours.

(Second step)

The present step is a reaction for introducing a protected hydroxy group (OP^1) into a compound (IV) to produce a compound (V). The reaction may be performed according to the condition for an alkoxylating reaction which is generally performed.

For example, a compound (V) in which P^1 is methyl can be synthesized by reacting a compound (IV) with metal alkoxide (e.g.: sodium methoxide).

A reaction temperature is 0 to 200°C, preferably 80 to 120°C.

As a reaction solvent, alcohol, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 5 to 10 hours.

(Third step)

The present step is a reaction for protecting a hydroxy group of a compound

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(V) to produce a compound (VI). The reaction may be performed according to the condition for a reaction of protecting a hydroxy group which is generally performed. For example, by using diisopropyl azodicarboxylate or diethyl azodicarboxylate together with an alcohol and various phosphines, a compound (VI) in which P^2 is alkyl can be synthesized.

A reaction temperature is 0 to 100°C, preferably 0°C to room temperature.

As a reaction solvent, THF, toluene, dichloromethane and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 3 hours.

(Fourth step)

The present step is a reaction of oxidizing a nitrogen atom of a compoung (VI) to produce a compound (VII). The reaction may be performed according to the condition for an oxidation reaction using an oxidizing agent which is generally performed.

A reaction temperature is 0 to 100°C, preferably under ice-cooling to room temperature.

As a reaction solvent, chloroform, methylene chloride, acetic acid and the like are exemplified.

Examples of an oxidizing agent include metachloroperbenzoic acid, hydrogen peroxide and the like.

A reaction time is a few minutes to a few tens hours, preferably 1 to 5 hours.

(Fifth step)

The present step is a reaction for hydroxylating a methyl group of a compound (VII). Preferably, after acetoxylation by a reaction with acetic anhydride (reaction temperature: 0 to 150°C, preferably 120 to 140°C), this may be hydrolyzed (e.g.: treatment with a base (e.g.: alkali metal hydroxide)).

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 2 hours for acetoxylation, and 0.5 to 1 hour for hydrolysis.

(Sixth step)

The present step is a reaction for oxidizing a hydroxy group of a compound (VIII) to synthesize a compound (IX).

A reaction temperature is 0 to 150°C, preferably room temperature to 70°C.

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As a reaction solvent, chloroform and the like are exemplified.

As an oxidizing agent, dimethyl sulfoxide and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 0.1 to 1 hour.

(Seventh step)

The present step is a reaction for oxidizing a formyl group of a compound (IX) to synthesize a compound (X).

A reaction temperature is 0 to 150°C, preferably under ice-cooling to room temperature.

As a reaction solvent, an alcohol and the like are exemplified.

As an oxidizing agent, potassium hydroxide and iodine are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 3 hours.

(Eighth step)

The present step is a reaction for deprotecting an OP^2 part of a compound (X) to synthesize a compound (XI). The reaction may be performed according to the condition for a reaction of deprotecting a hydroxy protecting group which is generally performed.

A reaction temperature is 0 to 150°C, preferably under ice-cooling to room temperature.

As a reaction solvent, acetonitrile, methylene chloride, THF and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 3 hours.

(Ninth step)

The present step is a reaction for deprotecting an OP^1 part of a compound (XI) to synthesize a compound (I-A). The reaction may be treated preferably with a Lewis acid (e.g.: aluminum chloride).

A reaction temperature is 0 to 150°C, preferably 10 to 50°C.

As a reaction solvent, methylene chloride, THF and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 3 hours.

(Tenth step)

The present step is a reaction for deprotecting an ester part ($COOP^3$) of a

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compound (X) to synthesize carboxylic acid (XII). Preferably, hydrolysis with an alkali (e.g.: NaOH) may be performed.

A reaction temperature is 0 to 150°C, preferably 10 to 50°C.

As a reaction solvent, methanol, water and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably a few minutes to 2 hours.

Carboxylic acid (XII) can be converted into various derivatives (e.g.; amide).

(Eleventh step)

The present step is a reaction for reacting a compound (XII) with various amines to synthesize a compound (XIII). The reaction may be performed according to the condition for a reaction of amidating carboxylic acid which is generally performed and, for example, the reaction may be performed as in the first step.

A reaction temperature is 0 to 150°C, preferably room temperature to 70°C.

As a reaction solvent, a non-protonic solvent can be broadly used, and tetrahydrofuran (THF), 1,4-dioxane, dimethylformamide (DMF), methylene chloride, chloroform and the like are preferable.

A reaction time is a few minutes to a few tens hours, preferably a few minutes to 3 hours.

An amide part of the resulting compound (XIII) may be further chemically modified (e.g.: N-alkylation).

(Twelfth step)

The present step is a reaction for deprotecting OP^1 and OP^2 parts of a compound (XIII) to synthesize a compound (I-B). The reaction may be performed according to the condition for a reaction of deprotecting a hydroxy protecting group which is generally performed.

For example, when pyridine hydrochloride is used, a reaction temperature is 0 to 200°C, preferably 150 to 180 degree.

A reaction time is a few minutes to a few tens hours, preferably 1 to 5 minutes.

(Thirteenth step)

The present step is a reaction for deprotecting an ester part ($COOP^3$) of a compound (XI) to synthesize carboxylic acid (XIV). Preferably, hydrolysis with an

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alkali (e.g.: lithium hydroxide) may be performed.

A reaction temperature is 0 to 150°C, preferably 10 to 50°C.

As a reaction solvent, methanol, water and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably a few minutes to 3 hours.

(Fourteenth step)

The present step is a reaction for deprotecting an OP^1 part of a compound (XIV) to synthesize a compound (I-C). The reaction may be treated preferably with a Lewis acid (e.g.: boron tribromide).

A reaction temperature is 0 to 150°C, preferably under ice-cooling to room temperature.

As a reaction solvent, dichloromethane and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably a few minutes to 5 hours.

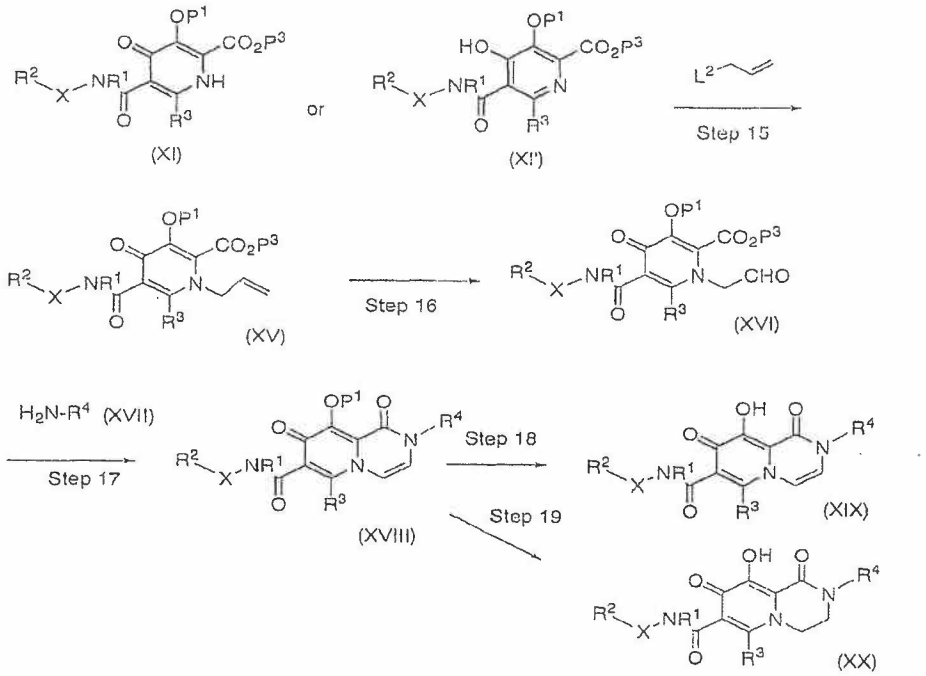
[0014]

The monocyclic carbamoylpyridone derivative obtained above is derived into a bicyclic compound by the following method.

(Process 1)

[Chemical formula 42]

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(wherein R^1, X, R^2, P^1, P^3 and R^4 are as define above, and L^2 is a leaving group such as halogen etc.)

(Fifteenth step)

The present step is a reaction for reacting the compound (XI) or a compound (XI') which is a tautomer thereof with an allyl compound to synthesize a compound (XV). A compound (XI') can be synthesized, for example, according to the method of Example A-1.

The reaction is performed preferably in the presence of a base (e.g.: cesium carbonate).

A reaction temperature is 0 to 100°C, preferably 10 to 40°C.

As a reaction solvent, dimethylformamide and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.

(Sixteenth step)

The present step is a reaction for oxidizing a compound (XV) to synthesize a compound (XVI). As an oxidizing agent, osmium tetraoxide and alkali metal osmium tetraoxide (e.g.: K_2OsO_4) are exemplified.

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A reaction temperaturwe is 0 to 100°C, preferably 10 to 40°C.

As a reaction solvent, 1,4-dioxane, tetrahydrofuran and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 5 hours.

(Seventeenth step)

The present step is a reaction for reacting a compound (XVI) with amine (XVII) to perform dehydration condensation to synthesize a compound (XVIII).

A reaction temperature is 0 to 200°C, preferably 140 to 180°C.

As a reaction solvent, methylene chloride, acetonitrile and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1.5 hours.

(Eighteenth step)

The present step is a reaction for deprotecting a compound (XVIII) preferably with an acid to synthesize a compound (XIX), and may be performed according to the condition for a conventional reaction of deprotecting a protected hydroxy group.

A reaction temperature is 0 to 200°C.

As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.

As a reaction solvent, the acid and trimethylsilyl iodide are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 hour.

(Nineteenth step)

The present step is a reaction for reducing a compound (XVIII) to synthesize a compound (XX).

As a reducing agent, H_2/Pd · C and the like are exemplified.

A reaction temperatuer is 0 to 100°C, preferably 10 to 30°C.

As a reaction sovelnt, dimethylformamide, methanol, tetrahydrofuran and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 5 to 20 hours.

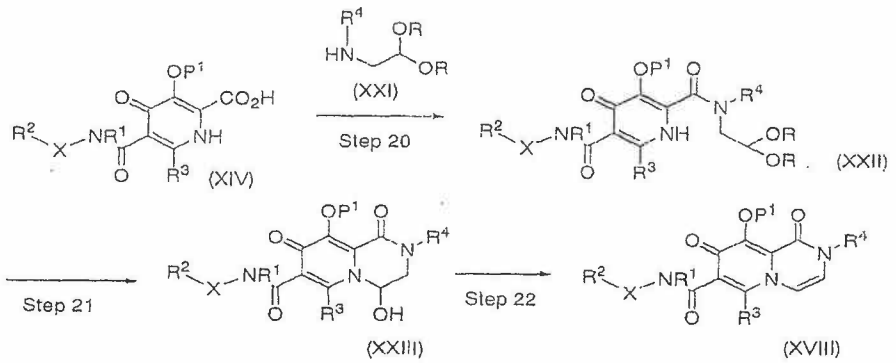
[0015]

(Process 2)

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The intermediate (XVIII) may be also synthesized by a method shown below.

[Chemical formula 43]



(Twentieth step)

The present step is a reaction for reacting a compound (XIV) with a compound (XXI) to synthesize a compound (XXII). The present reaction may be performed according to the condition for a conventional amidation reaction.

A reaction temperature is 0 to 100°C, preferably 0 to 50°C.

As a reaction solvent, dimethylformamide, methylene chloride, tetrahydrofuran and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.

(Twenty-first step)

The present step is a reaction for reacting a compound (XXII) with an acid to perform deprotection and intramolecular ring closure, to synthesize a compound (XXIII). The present reaction may be performed according to the condition for a conventional reaction of deprotecting acetal.

A reaction temperature is 0 to 100°C, preferably room temperature to 80°C.

As a reaction solvent, dioxane, tetrahydrofuran and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1 hour.

As an acid, hydrochloric acid, and paratoluenesulfonic acid are exemplified.

(Twenty-second step)

The present step is a reaction for dehydrating a compound (XXIII) to

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synthesize a compound (XXIV). The present reaction may be peformed according to the condition for a conventional dehydration reaction.

A reaction temperature is 0 to 100°C, preferably room temperature to 80°C.

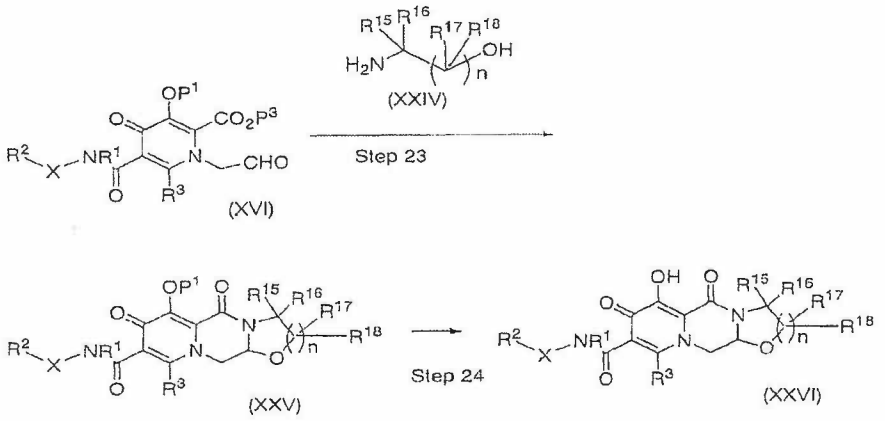
As a reaction solvent, acetonitrile, methylene chloride and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 5 hours.

[0016]

(Process 3)

[Chemical formula 44]



(Twenty-third step)

The present step is a reaction for reacting a compound (XVI) with amine (XXIV) to perform dehydration condensation to synthesize a compound (XXV) according to the seventeenth step or a method of synthesizing a compound 17-1. Preferably, as a reaction catalyst, an acid (e.g.: acetic acid) is added, and a microwave reaction apparatus is used.

A reaction temperature is 0 to 200°C, preferably 140 to 180°C.

As a reaction solvent, methylene chloride, acetonitrile and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1.5 hours.

(Twenty-fourth step)

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The present step is a reaction for deprotecting a compound (XXV) preferably with an acid to synthesize a compound (XXVI) according to the eighteenth step, and may be performed according to the condition for a conventional reaction of deprotecting a protected hydroxy group.

A reaction temprature is 0 to 200°C.

As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.

As a reaction solvent, the aforementioned acid and trimethylsilyl iodide are exemplified.

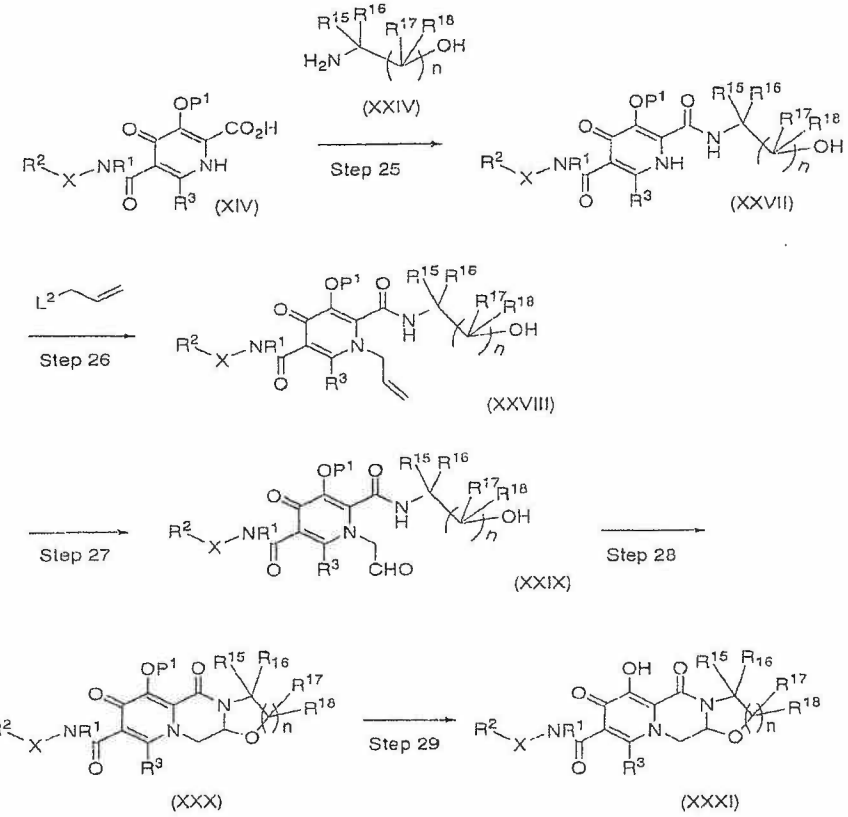
A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 hour.

[0017]

(Process 4)

[Chemical formula 45]

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(Twenty-fifth step)

The present step is a reaction for reacting a compound (XIV) with a compound (XXIV) to synthesize a compound (XXVII) according to the twentieth step. The present reaction may be performed according to the condition for a conventional amidation reaction.

A reaction temperature is 0 to 100°C, preferably 0 to 50°C.

As a reaction solvent, dimethylformamide, methylene chloride, tetrahydrofuran and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.

(Twenty-sixth step)

The present step is a reaction for reacting a compound (XXVII) or a tautomer

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thereof with an allyl compound to synthesize a compound (XXVIII) according to the fifteenth step.

A reaction is performed preferably in the presence of a base (e.g.: cesium carbonate).

A reaction temperature is 0 to 100°C, preferably 10 to 40°C.

As a reaction solvent, dimethylformamide and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.

(Twenty-seventh step)

The present step is a reaction for oxidizing a compound (XXVIII) to synthesize a compound (XXIX) according to the sixteenth step.

As an oxidizing agent, osmium tetraoxide and alkali metal osmium tetraoxide (e.g.: K_2OsO_4) are exemplified.

A reaction temperature is 0 to 100°C, preferably 10 to 40°C.

As a reaction solvent 1,4-dioxane, tetrahydrofuran and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferablky 1 to 5 hours.

(Twenty-eighth step)

The present step is a reaction for dehydration-condensing a compound (XXIX) to synthesize a compound (XXX) according to the seventeenth step or a method of synthesizing a compound 17-1. Preferably, as a reaction catalyst, an acid (e.g.: acetic acid) is added, and a microwave reaction apparatus is used.

A reaction temperature is 0 to 200°C, preferably 140 to 180°C.

As a reaction solvent, methylene chloride, acetonitrile and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1.5 hours.

(Twenty-ninth step)

The present step is a reaction for deprotecting a compound (XXX) preferably with an acid to synthesize a compound (XXXI) according to the eighteenth step, and may be peformed according to the condition for a conventional reaction of deprotecting a protected hydroxy group.

A reaction temperature is 0 to 200°C.

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As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.

As a reaction solvent, the aforementioned acid and trimethylsilyl iodide are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 hour.

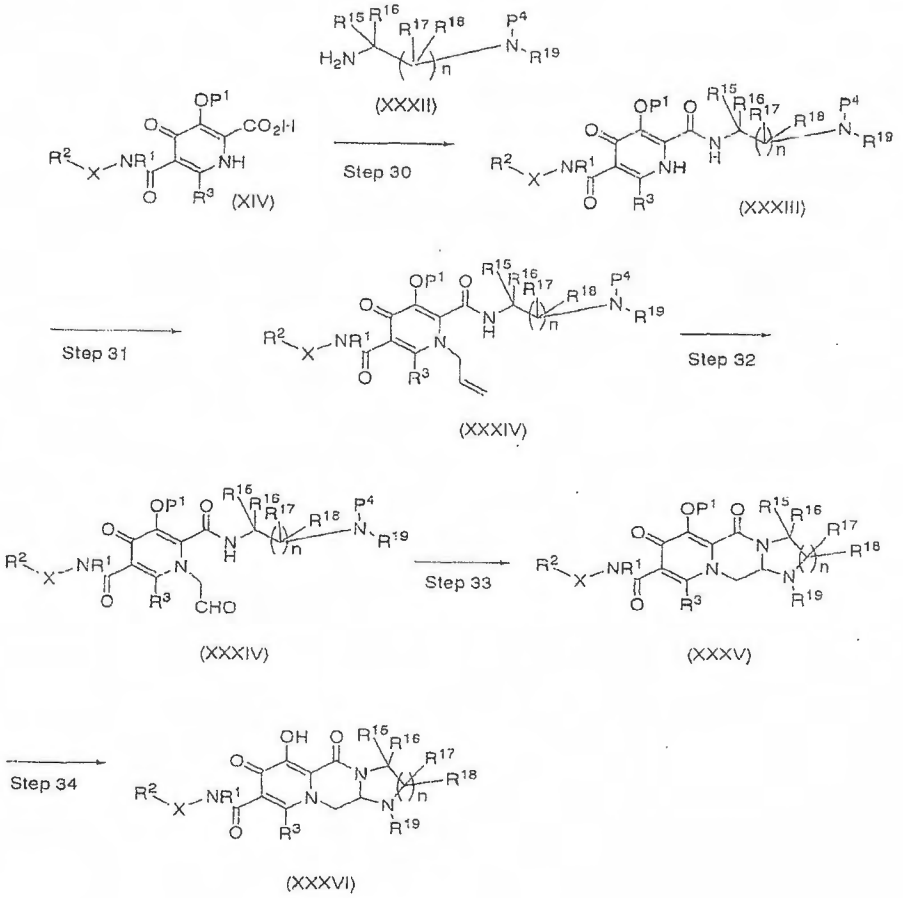
[0018]

(Process 5)

A compound (I-3) in which Z is NR^{10} can be synthesized according to the following reaction scheme, according to Process 4.

[Chemical formula 46]

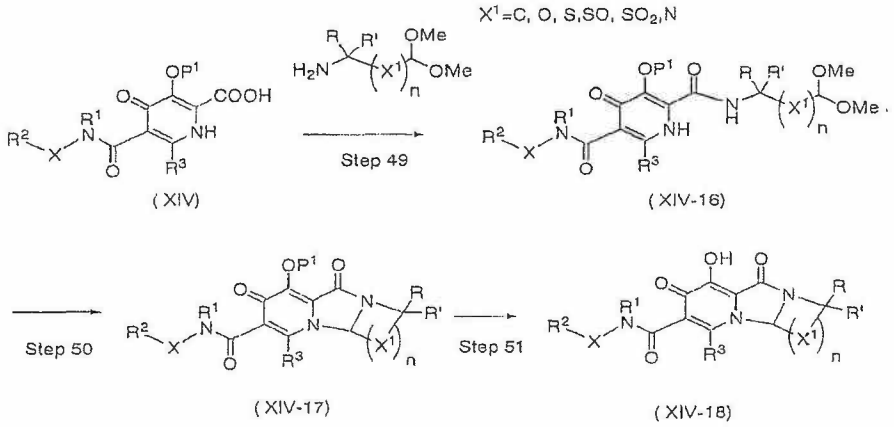
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[0019]

(Process 10)

[Chemical formula 51]



(wherein respective symbols are as defined above)

(Forty-ninth step)

A compound (XIV-16) is obtained by reacting a compound (XIV) with an amine reagent, according to the thirty-fifth step.

(Fiftieth step)

A compound (XIV-17) is obtained by subjecting a compound (XIV-16) to a general acetal deprotecting reaction according to the forty-fourth step.

(Fifty-first step)

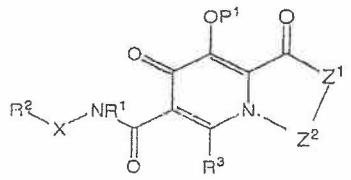
A compound (XIV-18) is obtained (D ring formation) by deprotecting a P^1 part of a compound (XIV-14) according to the thirty-eighth step.

[0020]

The present invention further provides various intermediates (I-P) shown below and a process for preparing the same, as well as a process for preparing the above mentioned compound (I) comprising the deprotection of the intermediate.

(Intermediates)

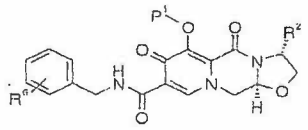
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(I-P)

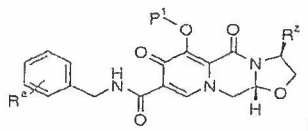
(P^1 is a hydroxyl-protecting group; the other symbols are as defined above)

Preferred compounds are shown below. Each P^1 is a hydroxyl-protecting group, such as C_{6-14}arylC_{1-8}alkyl (e.g., benzyl (=Bn)).



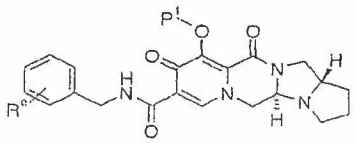
(I-20a)

Preferably, wherein R^a is one or two halogen; R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy; and P^1 is C_{6-14}arylC_{1-8}alkyl;



(I-20b)

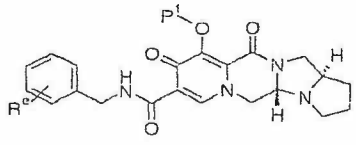
Preferably, wherein R^a is one or two halogen; R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy; and P^1 is C_{6-14}arylC_{1-8}alkyl;



(I-21a)

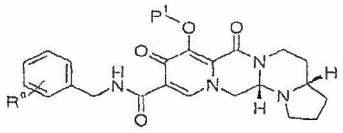
Preferably, wherein R^a is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl;

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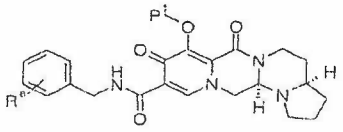
(I-21b)

Preferably, wherein R^e is one or two halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$;



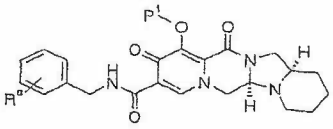
(I-22a)

Preferably, wherein R^e is one or two halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$;



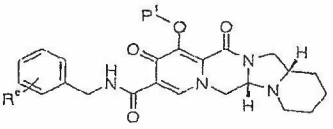
(I-22b)

Preferably, wherein R^e is one or two halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$;



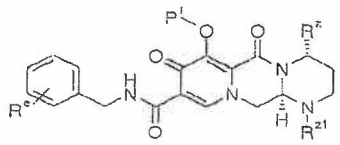
(I-23a)

Preferably, wherein R^e is one or two halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$;



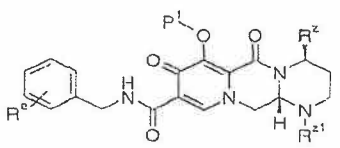
(I-23b)

Preferably, wherein R^e is one or two halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$;



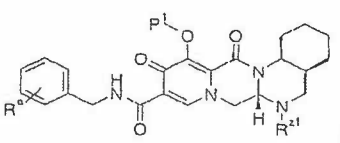
(I-24a)

Preferably, wherein R^e is one or two halogen; R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;



(I-24b)

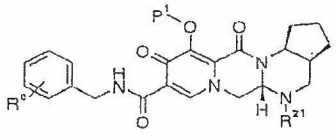
Preferably, wherein R^e is one or two halogen; R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;



(I-25)

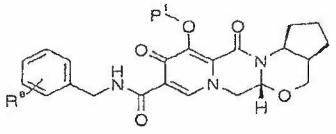
Preferably, wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;and P^1 is C_{6-14}arylC_{1-8}alkyl;

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(I-26)

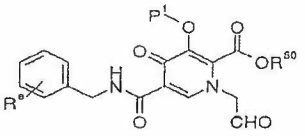
Preferably, wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;



(I-27)

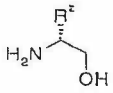
Preferably, wherein R^e is halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl;

The above intermediates, compound (I-20a), (I-20b), (I-21a), (I-21b), (I-22a), (I-22b), (I-23a), (I-23b), (I-24a), (I-24b), (I-25), (I-26), or (I-27), can be prepared by condensing a compound of the formula:

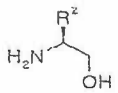


wherein R^e is one or two halogen; and R^{50} is C_{1-8}alkyl;

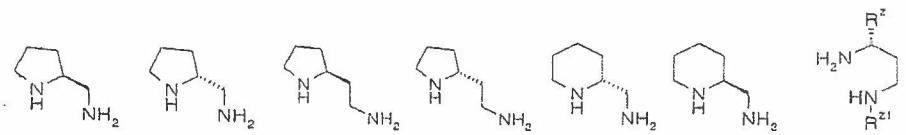
with each amine shown below, respectively:



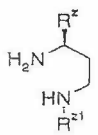
wherein R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy;



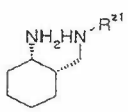
wherein R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy;



wherein R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;

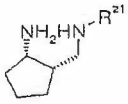


wherein R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;

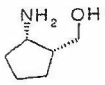


wherein R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;

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wherein R^{z1} is hydrogen, C_{3-8}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-8}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;



The condition for the above condensation is illustrated below for example.

Examples of the solvent include halocarbons such as dichloromethane, dichloroethane, and acetic acid.

The reaction temperature is preferably, 0 to 200 ℃, more preferably, 50 to 170℃.

The reaction time is usually several minutes to several hours.

The above intermediates, compound (I-20a), (I-20b), (I-21a), (I-21b), (I-22a), (I-22b), (I-23a), (I-23b), (I-24a), (I-24b), (I-25), (I-26), or (I-27), can be deprotected to give each corresponding deprotected compound wherein P^1 is hydrogen, or its pharmaceutically acceptable salt, which are encompassed within the scope of compound (I) of the present invention.

In addition, the present compound obtained above may be further chemically modified to synthesize another compound. In addition, when there is a reactive functional group (e.g.: OH, COOH, NH_2) on a side chain part etc. in the above reaction, the group may be protected before the reaction and may be deprotected after the reaction, if desired.

The present compound is useful, for example, as a drug such as an anti-virus drug. The present compound has the remarkable inhibitory action on integrase of a virus. Therefore, the present compound can be expected to have the preventive or

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therapeutic effect for various diseases derived from a virus which produces at least integrase, and is grown at infection in an animal cell, and is useful as an integrase inhibiting agent for retrovirus (e.g. HIV-1, HIV-2, HTLV-1, SIV, FIV etc.), and is useful as an anti-HIV drug etc.

In addition, the present compound may be used in joint use therapy by combining an anti-HIV drug having the different action methanism such as a reverse trascriptase inhibiter and/or a protease inhibiting agent. Particularly, currently, an integrase inhibiter is not marketed, and it is useful to use in joint use therapy by combining the present compound with a reverse transcriptase inhibiter and/or a protease inhibiter.

Further, the above use includes not only use as a medical mixture for anti-HIV, but also use as a joint use agent for increasing the anti-HIV activity of other anti-HIV drug such as cocktail therapy.

In addition, the present compound can be used in order to prevent infection with a retrovirus vector from spreading into a tissue other than an objective tissue, upon use of a retrovirus vector based on HIV or MLV in the field of gene therapy. Particularly, when a cell is infected with a vector in vitro, and the cell is returned into a body, if the present compound is administered in advance, extra infection can be prevented in a body.

The present compound can be adminitetered orally or parenterally. In the case of oral administration, the present compound can be also used as a conventional preparation, for example, as any dosage form of a solid agent such as tablets, powders, granules, capsules and the like; an aqueous agent; an oily suspension; or a liquid agent such as syrup and elixir. In the case of parenteral administration, the present compound can be used as an aqueous or oily suspension injectable, or a nasal drop. Upon preparation of it, conventional excipients, binders, lubricants, aqueous solvents, oily solvents, emulsifiers, suspending agents, preservatives, stabilizers and the like may be arbitrarily used. As an anti-HIV-drug, particularly, an oral agent is preferable. A preparation of the present invention is prepared by combining (e.g. mixing) a therapeutically effective amount of the present compound with a pharmaceutically acceptable carrier or diluent.

A dose of the present invention is different depeniding on an administration method, an age, a weight and conditionn of a patient, and a kind of a disease and, usually, in the case of oral administraton, about 0.05mg to 3000mg, preferably about 0.1mg to 1000mg may be administered per adult a day, if necessary, by dividing the

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dose. In addition, in the case of parenteral administration, about 0.01mg to 1000mg, preferably about 0.05mg to 500mg is administered per adult a day.

Examples are shown below.

[0025]

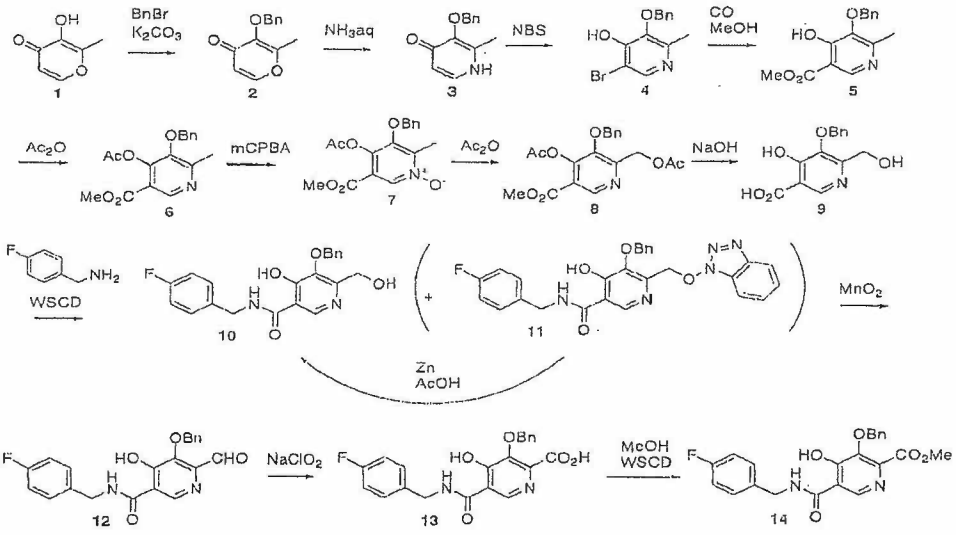
Example A-1)

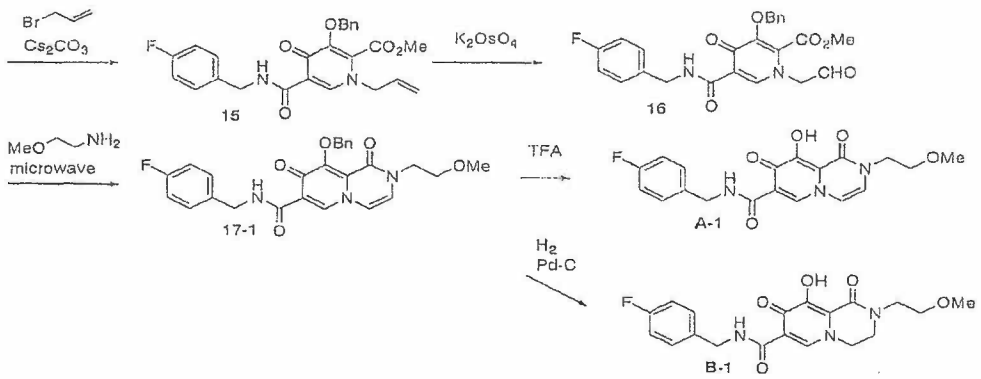
9-Hydroxy-2-(2-methoxy-ethyl)-1,8-dioxo-1,8-dihydro-2H-pyrid[1,2-a]pyrazine -7-carboxylic acid 4-fluoro-benzylamide

Example B-1)

9-Hydroxy-2-(2-methoxy-ethyl)-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrid[1,2-a]py razine-7-carboxylic acid 4-fluoro-benzylamide

[Chemical formula 52]





1) Mantol 1 (189g, 1.5mol) was dissolved in dimethylformamide (1890ml), and benzyl bromide (184ml, 1.5mol) was added. After the solution was stirred at 80°C for 15 minutes, potassium carbonate (228g, 1.65mol) was added, and the mixture was stirred for 1 hour. After the reaction solution was cooled to room temperature, an inorganic salt was filtered, and the filtrate was distilled off under reduced pressure. To the again precipitated inorganic salt was added tetrahydrofuran (1000ml), this was filtered, and the filtrate was distilled off under reduced pressure to obtain the crude product (329g, >100%) of 3-benzyloxy-2-methyl-pyran-4-one 2 as a brown oil.
NMR ($CDCl_3$)δ: 2.09(3H, s), 5.15(2H, s), 6.36(1H, d, J=5.6Hz), 7.29-7.41(5H, m), 7.60(1H, d, J=5.6Hz).

2) The compound 2 (162.2g, 750mmol) was dissolved in ethanol (487ml), and aqueous ammonia (28%, 974ml) and a 6N aqueous sodium hydroxide solution (150ml, 900mmol) were added. After the reaction solution was stirred at 90 °C for 1 hour, this was cooled to under ice-cooling, and ammonium chloride (58g, 1080mmol) was added. To the reaction solution was added chloroform, this was extracted, and the organic layer was washed with an aqueous saturated sodium bicarbonate solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, isopropyl alcohol and diethyl ether were added to the residue, and precipitated crystals were filtered to obtain 3-benzyloxy-2-methyl-1H-pyridine-4-one 3 (69.1g, 43%) as a pale yellow crystal.
NMR (DMSO-d_6)δ: 2.05(3H, s), 5.04(2H, s), 6.14(1H, d, J=7.0Hz), 7.31-7.42(5H, m), 7.46(1H, d, J=7.2Hz), 11.29(1H, brs).

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3) The above compound 3 (129g, 599mmol) was suspended in acetonitrile (1300ml), and N-bromosuccinic acid imide (117g, 659mmol) was added, followed by stirring at room temperature for 90 minutes. Precipitated crystals were filtered, and washed with acetonitrile and diethyl ether to obtain
3-benzyloxy-5-bromo-2-methyl-pyridine-4-ol 4(154g, 88%) as a colorless crystal.
NMR (DMSO-d_6)δ: 2.06(3H, s), 5.04(2H, s), 7.32-7.42(5H, m), 8.03(1H, d, J=5.5Hz), 11.82(1H, brs).

4) To a solution of the compound 4 (88g, 300mmol), palladium acetate (13.4g, 60mmol) and 1,3-bis(diphenylphosphino)propane (30.8g, 516mmol) in dimethylformamide (660ml) were added methanol (264ml) and triethylamine (210ml, 1.5mol) at room temperature. The interior of a reaction vessel was replaced with carbon monoxide, and the material was stirred at room temperature for 30 minutes, and stirred at 80 degree for 18 hours. A vessel to which ethyl acetate (1500ml), an aqueous saturated ammonium chloride solution (1500ml) and water (1500ml) had been added was stirred under ice-cooling, and the reaction solution was added thereto. Precipitates were filtered, and washed with water (300ml), ethyl acetate (300ml) and diethyl ether (300ml) to obtain 5-benzyloxy-4-hydroxy-6-methyl-nicotinic acid methyl ester 5 (44.9g, 55%) as a colorless crystal.
NMR (DMSO-d_6)δ: 2.06(3H, s), 3.72(3H, s), 5.02(2H, s), 7.33-7.42(5H, m), 8.07(1H, s).

5) After a solution of the compound 5 (19.1g, 70mmol) in acetic anhydride (134ml) was stirred at 130 °C for 40 minutes, the solvent was distilled off under reduced pressure to obtain 4-acetoxy-5-benzyloxy-6-methyl-nicotinic acid methyl ester 6 (19.9g, 90%) as a flesh colored crystal.
NMR ($CDCl_3$)δ: 2.29(3H, s), 2.52(3H, s), 3.89(3H, s), 4.98(2H, s), 7.36-7.41(5H, m), 8.85(1H, s).

6) To a solution of the compound 6 (46.2g, 147mmol) in chloroform (370ml) was added metachloroperbenzoic acid (65%) (42.8g, 161mmol) in portions under ice-cooling, and this was stirred at room temperature for 90 minutes. To the reaction solution was added a 10% aqueous potassium carbonate solution, and this was stirred for 10 minutes, followed by extraction with chloroform. The organic layer was washed with successively with a 10% aqueous potassium carbonate solution, an aqueous saturated ammonium chloride solution, and an aqueous saturated sodium chloride solution, and

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dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was washed with diisopropyl ether to obtain 4-acetoxy-5-benzyloxy-6-methyl-1-oxy-nicotinic acid methyl ester 7 (42.6g, 87%) as a colorless crystal.
NMR ($CDCl_3$)δ: 2.30(3H, s), 2.41(3H, s), 3.90(3H, s), 5.02(2H, s), 7.37-7.39(5H, m), 8.70(1H, s).

7) To acetic anhydride (500ml) which had been heated to stir at 130 °C was added the compound 7 (42.6g, 129mmol) over 2 mintues, and this was stirred for 20 minutes. The sovent was distilled off under reduced pressure to obtain 4-acetoxy-6-acetoxymethyl-5-benzyloxy-nicotinic acid methyl ester 8 (49.6g, >100%) as a black oil.
NMR ($CDCl_3$)δ: 2.10(3H, s), 2.28(3H, s), 3.91(3H, s), 5.07(2H, s), 5.20(2H, s), 7.35-7.41(5H, m), 8.94(1H, s).

8) To a solution of the compound 8 (46.8g, 125mmol) in methanol (140ml) was added a 2N aqueous sodium hydroxide solution (376ml) under ice-cooling, and this was stirred at 50 °C for 40 minutes. To the reaction solution were added diethyl ether and 2N hydrochloric acid under ice-cooling, and precipitated crystals were filtered. Resulting crystals were washed with water and diethyl ether to obtain 5-benzyloxy-4-hydroxy-6-hydroxymethyl-nicotinic acid 9 (23.3g, 68%) as a colorless crystal.
NMR (DMSO-d_6)δ: 4.49(2H, s), 5.19(2H, s), 5.85(1H, brs), 7.14-7.20(2H, m), 7.33-7.43(7H, m), 8.30(1H, s), 10.73(1H, t, J=5.8Hz), 11.96(1H, brs).

9) To a solution of the compound 9 (131g, 475mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (219g, 1140mmol) and 1-hydroxybenzotriazole (128g, 950mmol) in dimethylformamide (1300ml) was added 4-fluorobenzylamine (109ml, 950mmol), and this was stirred at 80°C for 1.5 hours. After the reaction solution was cooled to room temperature, hydrochloric acid was added, followed by extraction with ethyl acetate. The extract was washed with a 5% aqueous potassium carbonate solution, an aqueous saturated ammonium chloride solution, and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain a mixture (175g) of 10 and 11. the resulting mixture was dissolved in acetic

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acid (1050ml) and water (1050ml), and zinc (31.1g, 475mmol) was added, followed by heating to reflux for 1 hour. After the reaction solution was cooled to room tempreture, a 10% aqueous potassium carbonate solution was added, followed by extraction with ethyl acetate. The extract was washed with an aqueous saturated ammonium chloride solution, and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, this was washed with diethyl ether to obtain 5-benzyloxy-N-(4-fluoro-benzyl)-4-hydroxy-6-hydroxymethyl-nicotinic acid amide 10 (107g, 59%) as a colorless crystal.
NMR (DMSO-d_6)δ: 4.45(2H, d, J=4.3Hz), 4.52(2H, d, J=5.8Hz), 5.09(2H, s), 6.01(1H, brs), 7.36-7.43(5H, m), 8.31(1H, s), 12.63(1H, brs).

10) After manganese dioxide (49g) was added to a suspension of the compound 10 (9.8g, 25.6mmol) in chloroform (490ml), the mixture was stirred at room temperature for 1 hour. After the reaction solution was stirred at 60 °C for 20 minutes, Celite filtration was performed, and this was washed with chloroform heated at 50 °C. The filtrate was distilled off under reduced pressure to obtain 5-benzyloxy-N-(4-fluoro-benzyl)-6-formyl-4-hydroxy-nicotinic acid amide 12 (8.2g, 84%) as a pale yellow crystal.
NMR (DMSO-d_6)δ: 4.53(2H, d, J=5.8Hz), 5.38 (2H, s), 7.15-7.21(2H, m), 7.35-7.46(7H, m), 8.33(1H, s), 9.90(1H, s), 10.35(1H, t, J=5.8Hz), 12.49(1H, brs).

11) To an aqueous solution (105ml) of sodium chlorite (7.13g, 78.8mmol), and sulfamic acid (7.65g, 78.8mmol) was added a solution of the compound 12 (15.0g, 39.4mmol) in tetrahydrofuran (630ml) under ice-coling, and the mixture was stirred at room temperature for 1 hour. After water (2500ml) was added to the reaction solution, precipitated crystals were filtered. Washing with diethyl ether afforded 3-benzyloxy-5-(4-fluoro-benzylcarbamoyl)-4-hydroxy-pyridine-2-carboxylic acid 13 (14.0g, 90%) as a colorless crystal.
NMR (DMSO-d_6)δ: 4.52(2H, d, J=5.8Hz), 5.13 (2H, s), 7.14-7.19(2H, m), 7.31-7.40(5H, m), 7.47-7.49(2H, m), 8.31(1H, d, J=4.5Hz), 10.44(1H, t, J=5.9Hz), 12.47(1H, brs).

12) A solution of the compound 13 (198mg, 0.500mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115mg, 0.600mmol) and 1-hydroxybenzotriazole (81mg, 0.600mmol) in dimethylformamide (3ml) was

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stirred at room temperature for 1.5 hours. Then, methanol (3ml) and triethylamine (153ul, 1.10mmol) were added, and the mixture was heated to reflux for 1.5 hours. The reaction solution was diluted with ethyl acetate, washed with an aqueous saturated sodium bicarbonate solution, a 10% aqueous citric acid solution, and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain
3-benzyloxy-5-(4-fluoro-benzylcarbamoyl)-4-hydroxy-pyridine-2-carboxylic acid methyl ester 14 (141mg, 69%) as a colorless crystal.
NMR (DMSO-d_6)δ: 3.85(3H, s), 4.52(2H, d, J=6.0Hz), 5.15(2H, s), 7.13-7.21(2H, m), 7.31-7.47(7H, m), 8.33(1H, s), 10.41(1H, t, J=6.0Hz), 12.59(1H, brs).

13) After 3-bromopropene (2.15ml, 24.8mmol) was added to a solution of the compound 14 (6.79g, 16.5mmol), and cesium carbonate (8.09g, 24.8mmol) in dimethylformamide (54ml), the mixture was stirred at room temperature for 4.5 hours. To the reaction solution was added an aqueous ammonium chloride solution, and this was extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain
1-allyl-3-benzyloxy-5-(4-fluoro-benzylcarbamoyl)-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methyl ester 15 (6.15g, 83%) as a colorless crystal.
NMR ($CDCl_3$) δ: 3.76(3H, s), 4.54(2H, d, J=6.0Hz), 4.60(2H, d, J=6.0Hz), 5.20-5.37(2H, m), 5.25(2H, s), 5.80-5.93(1H, m), 6.98-7.04(2H, m), 7.31-7.35(7H, m), 8.45(1H, s), 10.41(1H, m).

14) To a solution of the compound 15 (7.6g, 16.9mmol) in 1,4-dioxane (228ml) was added an aqueous solution (38ml) of potassium osmate dihydrate (372mg, 1.01mmol), and sodium metaperiodate (14.5g, 67.6mmol) was further added, followed by stirring at room temperature for 2 hours. The reaction solution was added to a vessel to which ethyl acetate (300ml) and water (300ml) had been added, while stirring. The organic layer was washed with water, a 5% aqueous sodium hydrogen sulfite solution and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain

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3-benzyloxy-5-(4-fluoro-benzylcarbamoyl)-4-oxo-1-(2-oxo-ethyl)-1,4-dihydro-pyridine-2-carboxylic acid methyl ester 16 (5.39g, 71%) as a colorless crystal.
NMR ($CDCl_3$)δ: 3.74(3H, s), 4.60(2H, d, J=5.9Hz), 4.87(2H, s), 5.27(2H, s), 6.98-7.04(2H, m), 7.30-7.40(7H, m), 8.39(1H, s), 9.58(1H, s), 10.38(1H, s).

15) To a solution of the compound 16 (400mg, 0.884mmol) in methylene chloride (12ml) were added 2-methoxyethylamine (77ul, 0.884mmol) and acetic acid (18ul), and the mixture was stirred at room temperature for 5 minutes. Thereafter, the reaction was performed at 140 °C for 30 minutes in a microwave reaction apparatus. The solvent was distilled off under reduced pressure, the residue was subjected to silica gel column chromatography, and fractions eluting with toluene-acetone were concentrated under reduced pressure to obtain 9-benzyloxy-2-(2-methy-ethyl)-1,8-dioxo-1,8-dihydro-2H-pyrid[1,2-a]pyrazine-7-carboxylic acid 4-fluoro-benzylamide 17-1 (226mg, 54%) as a yellow solid.
NMR ($CDCl_3$)δ: 3.35(3H, s), 3.65(2H, t, J=5.1Hz), 3.97(2H, t, J=4.5Hz), 4.63(2H, d, J=5.7Hz), 5.28(2H, s), 6.56(2H, m), 7.01(2H, t, J=8.7Hz), 7.38-7.30(5H, m), 7.65(2H, d, J=6.6Hz), 10.63(1H, s).

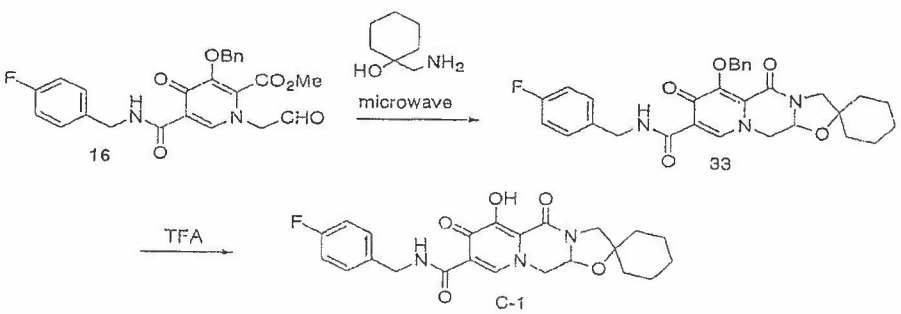
16) To the compound 17-1 (140mg, 0.293mmol) was added trifluoroacetic acid (1.4ml) under ice-cooling, and the mixture was stirred at 0 °C for 5 minutes and, then, at room temperature for 1.5 hours. The solvent was distilled off under reduced pressure, and this was diluted with chloroform, and added to ice water. This was washed with an aqueous saturated sodium bicarbonate solution, a 10% aqueous citric acid solution and water, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was recrystallized with methylene chloride-ethanol to obtain Example A-1 (89mg, 79%) as a yellow crystal.
melting point: 223-224 °C
NMR (DMSO-d_6)δ: 3.25(3H, s), 3.58(2H, t, J=5.4Hz), 3.92(2H, t, J=5.1Hz), 4.53(2H, d, J=5.7Hz), 6.87(1H, d, 6.3Hz), 7.14(2H, t, J=9.0Hz), 7.33-7.38(2H, m), 7.47(1H, d, J=6.0Hz), 8.77(1H, s), 10.56(1H, t, J=6.0Hz), 12.00(1H, brs).

17) The compound 17-1 (157mg, 0.329mmol) was dissolved in dimethylformamide (18ml) and methanol (1ml), 10% palladium-carbon powder (31mg) was added, and the mixture was stirred at room temperature for 20 hours under the hydrogen atmosphere. The reaction solution was filtered with Celite, and the filtrate was

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concentrated under reduced pressure. The residue was dissolved in chloroform, this was filtered with Celite again, and the filtrate was concentrated under reduced pressure. The residue was recrystallized with methylene chloride-methanol to obtain Example B-1 (66mg, 52%) as a brown crystal.
melting point: 197-199 °C
NMR (DMSO-d_6)δ:3.27(3H, s), 3.55(2H, t, J=5.1Hz), 3.68(2H, t, J=5.1Hz), 3.79(2H, s), 4.36(2H, s), 4.51(2H, d, J=5.7Hz), 7.15(2H, t, J=8.7Hz), 7.32-7.37(2H, m), 8.38(1H, s), 10.46(1H, t, J=5.4Hz), 12.41(1H, s).

Example C-1
[Chemical formula 55]



1) A compound 33 was synthesized using 1-aminomethylcyclopentanol hydroxyethylamine according to the method of synthesizing a compound 17-1.
1H-NMR ($CDCl_3$)δ: 1.30-1.80(10H, m), 3.47(1H, d, J=11.4Hz), 3.61(1H, d, J=11.4Hz), 3.80-3.95(1H, m), 4.30(1H, dd, J=14.7, 3.0Hz), 4.60(2H, d, J=5.7Hz), 5.17-5.23(2H, m), 5.39(1H, d, J=9.9Hz), 6.95-7.10(2H, m), 7.20-7.40(5H, m), 7.58(2H, d, J=7.2Hz), 8.41(1H, s), 10.40(1H, s).

2) A compound 33-2 was synthesized using hydroxyethylamine according to the similar method.
Compound 33-2)
5-Benzyloxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1-oxa-3a,8a-diaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluorobenzylamide
1H-NMR (DMSO-d_6)δ: 3.48-3.58(1H, m), 3.73-3.86(1H, m), 3.97-4.10(2H, m), 4.20-4.30(1H, m), 4.46-4.60(2H, m), 4.85(1H, dd, J=12.3, 3.5Hz), 5.40(1H, d, J=10.2Hz),

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5.18(1H, d, J=10.2Hz), 5.28(1H, dd, J=10.2, 3.2Hz), 7.10-7.20(2H, m), 7.23-7.40(5H, m), 7.50-7.73(2H, m), 8.60(1H, s), 10.22(1H, m).

3) Example C-1 was synthesized using a compound 33, according to the method of synthesizing Example A-1.
Melting point: >300°C
1H-NMR (DMSO-d_6)δ: 1.10-1.60(10H, m), 3.25(1H, d, J=11.4Hz), 3.37(1H, d, J=11.4Hz), 3.76(1H, t, J=10.5Hz), 4.30(2H, d, J=5.8Hz), 4.66(1H, dd, J=12.2, 3.8Hz), 5.22(1H, dd, J=3.8, 10.4Hz), 6.90-6.96(2H, m), 7.10-7.15(2H, m), 8.25(1H, s), 10.10(1H, brs), 11.32(1H, brs).

The following compounds were synthesized using the similar method.
Example C-2)
5-Hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1-oxa-3a,8a-diaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluorobenzylamide
Melting point: 272-274 °C
1H-NMR (DMSO-d_6)δ: 3.59-3.67(1H, m), 3.72-3.81(1H, m), 3.98-4.10(2H, m), 4.27-4.35(1H, m), 4.52(2H, d, J=7.2Hz), 4.92(1H, dd, J=12.3, 12.3Hz), 5.27(1H, dd, J=3.6, 9.9Hz), 7.11-7.20(2H, m), 7.30-7.40(2H, m), 8.49(1H, s), 10.32(1H, t, J=5.6Hz), 11.53(1H, s).

Example C-3)
5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diazaanthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 259 °C
1H-NMR (DMSO-d_6)δ: 1.60-1.67(1H, m), 1.72-1.85(1H, m), 3.25(1H, td, J=12.8, 3.5Hz), 3.86-3.93(1H, m), 4.06(1H, dd, J=11.4, 4.2Hz), 4.44-4.57(5H, m), 5.28(1H, t, J=3.8Hz), 7.13-7.18(2H, m), 7.33-7.37(2H, m), 8.51(1H, s), 10.36(1H, t, J=6.0Hz), 12.47(1H, s).

Example C-4)
5-Hydroxy-1-isopropyl-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 232-234°C
NMR (DMSO-d_6)δ: 1.03(3H, d, 6.6Hz), 1.14(3H, d, 6.6Hz), 2.79-3.66(5H, m), 3.82(1H, t, 10.8Hz), 4.51(3H, m), 4.90(1H, m), 7.15(2H, t, 9.0Hz), 7.34(2H, m), 8.45(1H, s),

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10.39(1H, t, 5.4Hz), 11.60(1H, s).

Example C-5)
5-Hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 256-258 °C
NMR (DMSO-d_6)δ: 3.00-3.55(5H, m), 3.96(1H, t, 11.4Hz), 4.52(2H, d, 11.7Hz), 4.76(2H, m), 7.16(2H, t, 8.7Hz), 7.35(2H, m), 8.48(1H, s), 10.42(1H, t, 5.4Hz), 11.91(1H, s).

Example C-6)
5-Hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 255°C
NMR (DMSO-d_6)δ: 1.60(1H, s), 2.75-3.16(4H, m), 4.52(2H, d, 6.0Hz), 4.13-4.68(4H, m), 7.16(2H, 9.0Hz, t), 7.34(2H, m), 10.42(1H, s), 10.44(1H, 6.0Hz, t), 12.81(1H, s).

Example C-7)
1-(2-Diethylamino-ethyl)-5-hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 186-187 °C
NMR (DMSO-d_6)δ: 0.97(6H, t, 7.2Hz), 2.42-2.91(10H, m), 3.44-3.87(5H, m), 4.23(1H, m), 4.51(2H, d, 5.7Hz), 5.00(1H, m), 7.16(2H, t, 9.0Hz), 7.33-7.37(2H, m), 8.43(1H, s), 10.39(1H, t, 5.7Hz), 11.81(1H, s).

Example C-8)
1-Hydroxy-2,11-dioxo-2,5,5a,7,8,9,10,11-octahydro-6-oxa-4a,10a-diaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluoro-benzylamide
melting point: 242-244 °C
NMR (DMSO-d_6)δ: 1.40-2.00(4H, m), 3.20-3.30(1H, m), 3.66-3.77(2H, m), 4.14-4.23(1H, m), 4.38-4.41(1H, m), 4.52(2H, d, 6.3Hz), 4.58-4.63(1H, m), 5.34(1H, brs), 7.15(2H, t, 9.0Hz), 7.33-7.37(2H, m), 8.50(1H, s), 10.39(1H, brs), 12.14(1H, s).

Example C-9)
5-Hydroxy-1-(2-hydroxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

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NMR (DMSO-d_6)δ: 1.58-1.80(1H, m), 2.70-3.60(7H, m), 4.40-4.54(6H, m), 4.77-4.82(1H, m), 7.15(2H, t, 9.0Hz), 7.33-7.38(2H, m), 8.52(1H, s), 10.43(1H, brs), 12.57(1H, s).

Example C-10)
1-Hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluoro-benzylamide
melting point: 256°C
NMR (DMSO-d_6)δ: 1.47-1.77(4H, m), 2.69-2.81(2H, m), 3.34-3.41(1H, m), 4.08-4.12(1H, m), 4.26-4.40(2H, m), 4.52(2H, d, J=6.0Hz), 7.15(2H, t, 8.8Hz), 7.33-7.36(2H, m), 8.43(1H, s), 10.46(1H, t, J=6.0Hz), 12.68(1H, s).

Example C-11)
5-Hydroxy-1-(2-methoxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 147°C
NMR (DMSO-d_6)δ: 1.56-1.74(2H, m), 2.53-2.58(1H, m), 2.66-3.10(4H, m), 3.18(3H, s), 3.41-3.39(2H, m), 4.37-4.52(5H, m), 4.73-4.80(1H, m), 7.15(2H, t, 8.8Hz), 7.33-7.37(2H, m), 8.56(1H, s), 10.40(1H, t, J=6.0Hz), 12.62(1H, s).

Example C-12)
5-Hydroxy-1-(2-isopropoxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 151 °C
NMR (DMSO-d_6)δ: 1.02(6H, dd, J=4.0, 6.0Hz), 1.56-1.67(2H, m), 2.53-2.58(1H, m), 2.74-3.04(4H, m), 3.18(3H, s), 3.41-3.52(3H, m), 4.41-4.59(5H, m), 4.79-4.83(1H, m), 7.15(2H, t, 8.8Hz), 7.34-7.36(2H, m), 8.58(1H, s), 10.40(1H, t, J=6.0Hz), 12.56(1H, s).

Example C-13)
5-Hydroxy-3,3-dimethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 275-277 °C
NMR (DMSO-d_6)δ: 2.97(3H, s), 3.01(3H, s), 3.00-3.18(3H, m), 4.45-4.56(5H, m), 5.16(1H, s), 7.15(2H, t, J=9Hz), 7.35(2H, dd, J=5.4Hz, 8.7Hz), 8.51(1H, s), 10.36(1H, t, J=5.7Hz), 12.4(1H, s).

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Example C-14)
1-Cyclohexyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid-4-fluoro-benzylamide
melting point: 275-277 °C
NMR (DMSO-d_6)δ: 1.22-1.70(2H, m), 2.50-3.02(3H, m), 4.45(4H, m), 4.52(2H, s), 4.78(1H, d, J=13.2Hz), 7.16(2H, t, J=8.7Hz), 7.35(2H, dd, J=5.7Hz, 8.4Hz), 8.62(1H, s), 10.52(1H, s), 12.55(1H, s).

Example C-15)
5-Hydroxy-1-isopropyl-6,10-dioxo-1,2,3,4,6,9,9a,10-oxtahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid-4-fluoro-benzylamide
melting point: 220 °C
NMR (DMSO-d_6)δ: 0.94(6H, d, J=9.6Hz), 1.53-1.67(2H, m), 2.92-3.30(3H, m), 4.32-4.40(4H, m), 4.52(2H, d, J=5.7Hz), 4.89(1H, d, J=14.1Hz), 7.16(2H, t, J=9.0Hz), 7.35(2H, dd, J=6.3Hz, 9.0Hz), 8.61(1H, s), 10.46(1H, s), 12.55(1H, s).

Example C-16)
5-Hydroxy-3,3-dimethyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 280 °C
NMR (DMSO-d_6)δ: 0.87(3H, s), 0.93(3H, s), 2.59-3.15(6H, m), 4.09-4.57(6H, m), 7.14(2H, d, J=9.0Hz), 7.34(2H, dd, J=5.4Hz, 8.4Hz), 8.42(1H, s), 10.46(1H, s), 12.77(1H, s).

Example C-17)
5-Hydroxy-1-(2-morpholin-4-yl-2-oxo-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 140 °C
NMR (DMSO-d_6)δ: 1.60(2H, m), 2.91-3.62(13H, m), 4.41(2H, m), 4.51(2H, d, J=4.8Hz), 4.80(2H, m), 7.15(2H, t, J=8.7Hz), 7.34(2H, m), 8.44(1H, s), 10.43(1H, s), 12.54(1H, s).

Example C-18
1-(3-Acetylamino-propyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 177-178 °C

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NMR (DMSO-d_6)δ: 1.74(3H, s), 1.49-2.98(9H, m), 3.60(1H, s), 4.25-4.65(7H, m), 7.14(2H, t, J=8.4Hz), 7.34(2H, m), 7.71(1H, s), 8.26(1H, s), 10.60(1H, s).

Example C-19)
1-Dimethycarbamoylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 190 °C
NMR (DMSO-d_6)δ: 1.60(2H, m), 2.76(3H, s), 2.83(3H, s), 2.90-3.59(5H, s), 4.40(2H, m), 4.51(2H, d, 5.7Hz), 4.80(1H, d, d=14.4Hz), 4.98(1H, s), 7.16(2H, t, J=8.4Hz), 7.34(2H, m), 8.54(1H, s), 10.42(1H, s).

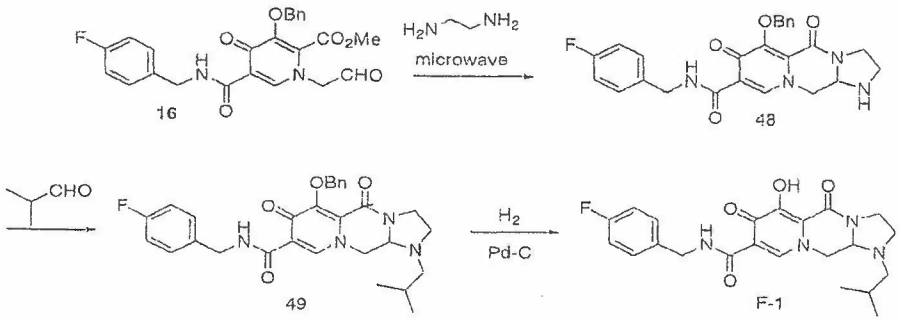
Example C-20)
5-Hydroxy-1-(3-methanesulfonylamino-propyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 176 °C
NMR (DMSO-d_6)δ: 1.54-1.75(4H, m), 2.80(3H, s), 2.30-3.04(8H, m), 4.45(2H, m), 4.52(2H, d, J=5.6Hz), 4.75(1H, d, J=13.2Hz), 6.91(1H, t, J=5.6Hz), 7.16(2H, t, J=8.8Hz), 7.36(2H, m), 8.61(1H, s), 10.41(1H, t, J=5.6Hz), 12.58(1H, s).

Example C-21)
5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-dizazaanthracene-7-carboxylic acid 4-fluorobenzylamide
NMR (CDCl3)δ: 1.27(3H, d, J=6.0Hz), 1.55-1.78(2H, m), 3.11(1H, td, J=12.9, 3.7Hz), 3.89-4.00(1H, m), 4.16(1H, dd, J=13.8, 3.9Hz), 4.34(1H, dd, J=13.8, 3.9Hz), 4.60(2H, d, J=6.0Hz), 4.71(1H, ddd, J=13.5, 4.8, 1.8Hz), 5.08(1H, t, J=3.9Hz), 6.96-7.04(2H, m), 7.26-7.35(2H, m), 8.32(1H, s), 10.41(1H, br s), 12.41(1H, br s).

Example F-1)
5-Hydroxy-1-isobutyl-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triazacyclopenta[b]naphthalene-7-carboxylic acid-4-fluorobenzylamide

[Chemical formula 59]

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1) According to the method of synthesizing a compound 17-1, the crude purified product (503mg) of a compound 48 was obtained at a yield of 82% from a compound 16 (600mg).

2) To a solution of a compound 48 (100mg, 0.22mmol), isobutylaldehyde (39μl, 0.432mmol) and acetic acid (25μl, 0.432mmol) in dichloromethane (4ml) was added sodium triacetoxyborohydride (92mg, 0.432mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. Further, isobutylaldehyde (20μl) and sodium triacetoxyborohydride (46mg) were added, and the mixture was stirred for 30 minutes. To the reaction solution was added water, this was extracted with chloroform, and the organic layer was washed with an aqueous saturated sodium bicarbonate solution. After dring, the solvent was distilled off under reduced pressure, and this was purified by silica gel column chromatography. A compound 49 (87mg) was obtained as a colorless crystal at a yield of 78%.
1H-NMR ($CDCl_3$)δ: 0.96(3H, d, J=6.6Hz), 0.97(3H, d, J=6.3Hz), 1.72-1.86(1H, m), 2.25-2.41(2H, m), 2.47-2.58(1H, m), 3.39-3.46(1H, m), 3.69-3.76(2H, m), 3.85-3.93(1H, m), 4.06(1H, dd, J=9.9, 2.7Hz), 4.16-4.22(1H, m), 4.57(1H, dd, J=15.3, 5.1Hz), 4.64(1H, dd, J=14.7, 5.1Hz), 5.20(1H, d, J=9.9Hz), 5.38(1H, d, J=9.9Hz), 6.96-7.05(2H, m), 7.28-7.36(5H, m), 7.58-7.62(2H, m), 8.40(1H, s), 10.44(1H, br s).

3) According to the method of a step 17) of Example B-1, a compound F-1 (43mg) was obtained at a yield of 64% from a compound 49 (81mg).
1H-NMR (DMSO-d_6)δ: 0.90(3H, d, J=6.4Hz), 0.91(3H, d, J=6.0Hz), 1.75-1.84(1H, m), 2.24-2.39(1H, m), 2.39-2.54(2H, m), 3.36-3.43(1H, m), 3.52-3.60(1H, m), 3.67-3.73(1H, m), 3.81-3.88(1H, m), 4.19-4.23(1H, m), 4.52(2H, d, J=6.0Hz), 4.94-4.99(1H, m),

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7.12-7.20(2H, m), 7.32-7.38(2H, m), 8.45(1H, s), 10.37(1H, t, J=2.0Hz), 11.74(1H, s).

According to the same manner as that of Example F-1, the following Example compounds F-2 to F-63 were synthesized.

Example F-2)

5-Hydroxy-1-isobutyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 146-148 °C

1H-NMR (DMSO-d_6)δ: 0.63(3H, d, J=6.6Hz), 0.79(3H, d, J=6.6Hz), 1.56-1.66(2H, m), 1.67-1.75(1H, m), 1.94-1.99(1H, m), 2.41-2.54(2H, m), 2.96-3.06(2H, m), 4.41-4.59(5H, m), 4.76-4.81(1H, m), 7.14-7.21(2H, m), 7.33-7.38(2H, m), 8.61(1H, s), 10.40(1H, d, J=5.8Hz), 12.56(1H, s).

Example F-3)

1-Cyclopropylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 182-184 °C

NMR (DMSO-d_6)δ: 0.06(2H, m), 0.43(2H, d, 8.4Hz), 0.80(1H, m), 1.66(2H, m), 2.28-3.30(4H, m), 4.40-4.50(4H, m), 4.52(2H, d, 6.0Hz), 4.78(2H, m), 7.15(2H, t, 8.7Hz), 7.34(2H, m), 8.55(1H, s), 10.47(1H, s), 12.55(1H, s).

Example F-4)

1-Cyclopentylmethyl-5-hydroxy-6,1-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 184-185 °C°C

NMR (DMSO-d_6)δ: 0.88-2.10(1H, m), 2.60(2H, m), 2.95-3.28(2H, m), 4.38-4.53(6H, m), 4.82(1H, m), 7.15(2H, t, 9.0Hz), 7.34(2H, m), 8.57(1H, s), 10.42(1H, s), 12.45(1H, s).

Example F-5)

5-Hydroxy-1-(4-methylsulfanylbenzyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.51-1.56(1H, m), 1.69-1.74(1H, m), 2.42(3H, s), 2.55-2.62(1H, m), 2.80-2.84(1H, m), 3.00-3.08(1H, m), 3.32-3.36(1H, m), 3.93(1H, d, J=13.6Hz), 4.45-4.53(4H, m), 4.58(1H, s), 4.88(1H, d, J=15.2Hz), 7.11-7.19(6H, m), 7.33-7.40(2H, m), 8.34(1H, s), 10.38(1H, t, J=6.0Hz), 12.58(1H, s).

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Example F-6)

1-(5-Chloro-1,3-dimethyl-1H-pyrazol-4-ylmethyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.56-1.59(2H, m), 1.88(3H, s), 2.37-2.45(1H, m), 2.76-2.80(1H, m), 3.00-3.06(2H, m), 3.64(3H, s), 3.87(1H, d, J=13.2Hz), 4.40-4.55(5H, m), 4.97(1H, d, J=14.4Hz), 7.13-7.19(2H, m), 7.33-7.38(2H, m), 8.56(1H, s), 10.39(1H, t, J=6.0Hz), 12.46(1H, s).

Example F-7)

5-Hydroxy-1-(3-methoxybenzyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.52-1.57(1H, m), 1.70-1.80(1H, m), 2.60-2.68(1H, m), 2.84-2.90(1H, m), 3.01-3.09(1H, m), 3.36(1H, d, J=14.0Hz), 3.61(3H, s), 3.91(1H, d, J=14.0Hz), 4.45-4.52(4H, m), 4.58(1H, s), 4.76(1H, d, J=14.8Hz), 6.68-6.73(2H, m), 6.77(1H, d, J=7.6Hz), 7.13-7.19(3H, m), 7.33-7.38(2H, m), 8.17(1H, s), 10.38(1H, t, J=6.0Hz), 12.57(1H, s).

Example F-8)

5-Hydroxy-1-(4-methanesulfonylbenzyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.54-1.58(1H, m), 1.74-1.80(1H, m), 2.67-1.74(1H, m), 2.83-2.87(1H, m), 3.05-3.12(1H, m), 3.18(3H, s), 3.52(1H, d, J=14.8Hz), 4.09(1H, d, J=14.8Hz), 4.46-4.52(4H, m), 4.67(1H, s), 4.73(1H, d, J=14.8Hz), 7.12-7.18(2H, m), 7.32-7.36(2H, m), 7.46(2H, m), 7.80(2H, d, J=8.0Hz), 8.17(1H, s), 10.37(1H, t, J=5.8Hz), 12.59(1H, s).

Example F-9)

5-Hydroxy-1-(6-methoxypyridin-3-ylmethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.51-1.56(1H, m), 1.71-1.77(1H, m), 2.58-2.66(1H, m), 2.80-2.86(1H, m), 3.01-3.09(1H, m), 3.38(1H, d, J=13.6Hz), 3.78(3H, s), 3.87(1H, d, J=13.6Hz), 4.45-4.52(4H, m), 4.60(1H, s), 4.82(1H, d, J=13.6Hz), 6.71(1H, d, J=8.6Hz), 7.12-7.19(2H, m), 7.33-7.38(2H, m), 7.49(1H, d, J=8.6Hz), 7.98(1H, s), 8.30(1H, s), 10.37(1H, t, J=6.0Hz), 12.58(1H, s).

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Example F-10)
5-Hydroxy-1-isobutyl-3,3-dimethyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
(DMSO-d_6)δ: 0.64(3H, d, J=6.4Hz), 0.82(3H, d, J=6.8Hz), 0.90(3H, s), 0.91(3H, s), 1.59-1.67(1H, m), 1.92-1.97(1H, m), 2.11-2.15(1H, m), 2.51-2.57(1H, m), 2.67(1H, d, J=12.0Hz), 2.77(1H, d, J=12.8Hz), 4.13(1H, s), 4.21(1H, d, J=12.8Hz), 4.47-4.59(3H, s), 4.80(1H, dd, J=14.4, 2.8Hz), 7.14-7.19(2H, m), 7.34-7.38(2H, m), 8.66(1H, s), 10.41(1H, t, J=6.0Hz), 12.44(1H, s).

Example F-11)
5-Hydroxy-1,3,3-trimethyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
(DMSO-d_6)δ: 0.89(6H, s), 2.14-2.18(1H, m), 2.24(3H, s), 2.54-2.58(1H, m), 2.74-2.78(1H, s), 3.88(1H, s), 4.21(1H, d, J=13.2Hz), 4.45-4.53(3H, m), 4.72-4.76(1H, m), 7.13-7.19(2H, m), 7.33-7.38(2H, m), 8.64(1H, s), 10.40(1H, t, J=6.0Hz), 12.46(1H, s).

Example F-12)
4-[7-(4-Fluorobenzylcarbamoyl)-5-hydroxy-6,10-dioxy-3,4,6,9,9a,10-hexahydro-2H-1,4a,8a-triazaanthracene-1-yl]butanoic acid ethyl ester
($CDCl_3$)δ: 1.23(3H, t, J=7.1Hz), 1.70-1.79(1H, m), 1.86-2.00(1H, m), 2.17-2.34(2H, m), 2.46-2.57(1H, m), 2.61-2.77(2H, m), 2.85-2.92(1H, m), 3.13-3.18(1H, m), 4.13(2H, q, J=7.1Hz), 4.27-4.34(2H, m), 4.57-4.63(3H, m), 4.66-4.73(1H, m), 6.95-7.03(2H, m), 7.29-7.36(2H, m), 8.36(1H, s), 10.48(1H, t, J=4.8Hz), 12.50(1H, s).

Example F-13)
1-(3-Dimethylcarbamoylpropyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
($CDCl_3$)δ:1.62-1.82(3H, m), 1.83-2.00(1H, m), 2.10-2.35(2H, m), 2.57-2.65(2H, m), 2.75-2.95(2H, m), 2.92(3H, s), 2.96(3H, s), 3.07-3.14(1H, m), 4.23-4.30(2H, m), 4.60(2H, d, J=6.0Hz), 4.68(1H, dd, J=13.2, 4.5Hz), 5.12(1H, d, J=12.6Hz), 6.95-7.02(2H, m), 7.28-7.35(2H, m), 8.42(1H, s), 1054(1H, t, J=5.4Hz), 12.51(1H, s).

Example F-14)
5-Hydroxy-1-(4-morpholin-4-yl-4-oxobutyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

($CDCl_3$)δ: 1.61-1.83(3H, m), 1.84-2.00(1H, m), 2.12-2.23(1H, m), 2.25-2.36(1H, m), 2.56-2.64(2H, m), 2.75-2.95(2H, m), 3.09-3.15(1H, m), 3.37(2H, t, J=4.8Hz), 3.61-3.66(6H, m), 4.26-4.32(2H, m), 4.59(2H, d, J=5.7Hz), 4.68(1H, dd, J=13.2, 4.5Hz), 4.95-5.01(1H, m), 6.95-7.03(2H, m), 7.28-7.35(2H, m), 8.40(1H, s), 10.52(1H, t, J=5.7Hz), 12.51(1H, s).

Example F-15)

5-Hydroxy-1-methyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 252-253°C

(DMSO-d_6)δ: 1.56-1.75(2H, m), 2.22(3H, s), 2.50-2.55(1H, m), 2.90-3.10(2H, m), 4.17(1H, brs), 4.39-4.42(2H, m), 4.52(2H, d, J=6.0Hz), 4.74-4.78(1H, m), 7.13-7.17(2H, m), 7.33-7.37(2H, m), 8.61(1H, s), 10.40(1H, t, J=6.0Hz), 12.54(1H, s).

Example F-16)

5-Hydroxy-6,10-dioxo-1-thiophen-3-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 242-243°C

(DMSO-d_6)δ: 1.52-1.73(2H, m), 2.59-2.62(1H, m), 2.87-3.03(2H, m), 3.52(1H, d, J=13.6Hz), 3.90(1H, d, J=14.4Hz), 4.40-4.56(5H, m), 4.83-4.90(1H, m), 6.92(1H, d, J=5.2Hz), 7.13-7.17(2H, m), 7.28-7.37(3H, m), 7.42-7.44(1H, m), 8.46(1H, s), 10.39(1H, t, J=6.0Hz), 12.58(1H, s).

Example F-17)

5-Hydroxy-6,10-dioxo-1-thiazol-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point 214-215°C

(DMSO-d_6)δ: 1.54-1.72(2H, m), 2.75-2.81(1H, m), 2.95-3.07(2H, m), 3.80(1H, d, J=16.0Hz), 4.37(1H, d, J=16.4Hz), 4.44-4.51(4H, m), 4.69(1H, brs), 4.89-4.93(1H, m), 7.13-7.17(2H, m), 7.32-7.35(2H, m), 7.55(1H, d, J=3.2Hz), 7.69(1H, d, J=3.2Hz), 8.37(1H, s), 10.36(1H, t, J=6.0Hz), 12.50(1H, s).

Example F-18)

5-Hydroxy-(3-methylsulfanyl-propyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

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melting point: 162-164°C
(DMSO-d_6)δ: 1.50-1.82(4H, m), 2.27(3H, s), 2.32-2.44(3H, m), 2.60-2.82(2H, m), 3.00-3.14(2H, m), 4.37-4.59(5H, m), 4.75-4.79(1H, m), 7.13-7.17(2H, m), 7.33-7.35(2H, m), 8.60(1H, s), 10.40(1H, t, J=6.0Hz), 12.57(1H, s).

Example F-19)
5-Hydroxy-6,10-dioxo-1-pyridin-4-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 180-183°C
(DMSO-d_6)δ: 1.52-1.76(2H, m), 2.62-2.80(2H, m), 3.01-3.07(1H, m), 3.42(1H, d, J=15.2Hz), 4.05(1H, d, J=15.2Hz), 4.49-4.50(4H, m), 4.64(1H, brs), 4.78-4.81(1H, m), 7.12-7.21(4H, m), 7.32-7.36(2H, m), 8.33(1H, s), 8.42(2H, d, J=4.4Hz), 10.39(1H, t, J=6.0Hz), 12.55(1H, s).

Example F-20)
1-Cyclohexylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 201-202°C
(DMSO-d_6)δ: 0.56-0.59(1H, m), 0.87-0.84(1H, m), 1.02-1.13(3H, m), 1.23-1.29(1H, m), 1.49-1.70(6H, m), 1.92-1.97(1H, m), 2.52-2.55(1H, m), 2.96-3.03(2H, m), 4.40-4.48(3H, m), 4.52(2H, d, J=6.0Hz), 4.73-4.77(1H, m), 7.12-7.16(2H, m), 7.32-7.36(2H, m), 8.59(1H, s), 10.40(1H, t, J=5.2Hz), 12.58(1H, s).

Example F-21)
5-Hydroxy-6,10-dioxo-1-pyridin-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 216-219°C
(DMSO-d_6)δ: 1.52-1.76(2H, m), 2.66-2.80(1H, m), 2.90-3.07(2H, m), 3.67(1H, d, J=15.2Hz), 4.01(1H, d, J=13.2Hz), 4.37-4.97(4H, m), 4.62(1H, brs), 4.85-4.88(1H, m), 7.07-7.25(4H, m), 7.33-7.36(2H, m), 7.64-7.68(1H, m), 8.26(1H, s), 8.45(1H, s), 10.36(1H, t, J=6.0Hz), 12.57(1H, s).

Example F-22)
1-(2-Ethyl-butyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

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melting point: 137-140°C
(DMSO-d_6)δ: 0.62(3H, t, J=7.2Hz), 0.77(3H, t, J=7.2Hz), 0.99-1.30(5H, m), 1.57-1.71(2H, m), 1.97-2.02(1H, m), 2.44-2.58(2H, m), 3.02-3.32(2H, m), 4.34-4.57(5H, m), 4.78-4.82(1H, m), 7.13-7.17(2H, m), 7.32-7.36(2H, m), 8.60(1H, s), 10.39(1H, t, J=5.2Hz), 12.54(1H, s).

Example F-23)
5-Hydroxy-1-(2-morpholin-4-ylethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 254-256°C
(DMSO-d_6)δ: 1.55-1.68(2H, m), 2.28-2.39(8H, m), 2.59-2.65(1H, m), 2.82-3.09(3H, m), 3.33-3.58(5H, m), 4.34-4.50(3H, m), 4.52(2H, d, J=5.2Hz), 4.79-4.84(1H, m), 7.12-7.17(2H, m), 7.32-7.36(2H, m), 8.52(1H, s), 10.45(1H, t, J=5.2Hz), 12.55(1H, s).

Example F-24)
1-Hydroxy-6-methyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide
melting point: 255°C
(DMSO-d_6)δ: 1.48-1.55(1H, m), 1.67-1.80(3H, m), 2.29(3H, s), 2.75-2.80(2H, m), 3.23-3.31(1H, m), 4.07-4.09(1H, m), 4.36-4.40(1H, m), 4.45-4.59(3H, m), 4.68-4.69(1H, m), 7.13-7.17(2H, m), 7.30-7.37(2H, m), 8.50(1H, s), 10.42(1H, t, J=6.0Hz), 12.42(1H, s).

Example F-25)
1-Hydroxy-6-isobutyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide
melting point: 221-223°C
DMSO-d_6)δ: 0.81(3H, d, J=6.8Hz), 0.84(3H, d, J=6.4Hz), 1.45-1.78(5H, m), 2.36-2.54(2H, m), 2.27-2.93(2H, m), 3.17-3.23(1H, m), 4.03-4.06(1H, m), 4.32-4.56(4H, m), 4.82-4.85(1H, m), 7.13-7.17(2H, m), 7.30-7.37(2H, m), 8.48(1H, s), 10.42(1H, t, J=6.0Hz), 12.53(1H, s).

Example F-26)
6-Cyclopropylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide

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melting point: 213°C
DMSO-d6)δ: 0.15-0.26(2H, m), 0.46-0.48(2H, m), 0.86-1.06(1H, m), 1.45-1.75(4H, m), 2.45-2.65(1H, m), 2.68-2.83(1H, m), 2.91-2.98(2H, m), 3.17-3.26(1H, m), 4.08-4.14(1H, m), 4.43-4.45(2H, m), 4.54(2H, d, J=5.6Hz), 4.89-4.91(1H, m), 7.15-7.19(2H, m), 7.35-7.39(2H, m), 8.50(1H, s), 10.47(1H, t, J=6.0Hz), 12.52(1H, s).

Example F-27)
1-Furan-2-ylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 193-197°C
DMSO-d6)δ: 1.67(2H, m), 2.61(1H, s), 2.93(2H, m), 3.75(1H, d, J=14.8Hz), 3.84(1H, d, J=14.8Hz), 4.34-4.47(3H, m), 4.52(2H, d, J=6.0Hz), 4.96(1H, d, J=14.8Hz), 6.36(2H, s), 7.16(2H, t, J=8.8Hz), 7.35(2H, m), 7.59(1H, s), 8.97(1H, s), 10.43(1H, s), 12.51(1H, s).

Example F-28)
1-(4-Dimethylamino-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 221-223°C
DMSO-d6)δ: 1.55-1.99(2H, m), 2.87(6H, s), 2.87-3.06(4H, m), 3.80(1H, d, J=14.0Hz), 4.50(5H, m), 4.83(1H, d, J=14.0Hz), 6.58(2H, d, J=9.6Hz), 6.98(2H, d, J=8.8Hz), 7.15(2H, t, J=8.8Hz), 7.35(2H, m), 8.31(1H, s), 10.39(1H, s), 12.58(1H, s).

Example F-29)
5-Hydroxy-6,10-dioxo-1-(4-trifluoromethyl-benzyl)-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 273-277°C
DMSO-d6)δ: 1.52-1.70(2H, m), 2.63-3.04(3H, m), 3.50(1H, d, J=14.8Hz), 4.10(1H, d, J=14.8Hz), 4.54(5H, m), 4.79(1H, d, J=14.8Hz), 7.14(2H, t, J=8.8Hz), 7.33(2H, m), 7.55(2H, d, J=6.8Hz), 7.61(2H, d, J=8.0Hz), 8.22(1H, s), 10.40(1H, s), 12.56(1H, s).

Example F-30)
5-Hydroxy-6,10-dioxo-1-pyridin-3-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 210-212°C
DMSO-d6)δ: 1.51-1.76(2H, m), 2.63(1H, t, J=12.8Hz), 2.80(1H, d, J=12.0Hz), 3.07(1H, t,

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J=12.8Hz), 3.44(1H, d, J=13.2Hz), 4.00(1H, d, 14.0Hz), 4.47(4H, m), 4.62(1H, s), 4.84(1H, d, J=14.0Hz), 7.16(2H, t, J=8.8Hz), 7.33(2H, m), 7.58(1H, d, J=7.6Hz), 8.30(1H, s), 8.45(2H, s), 10.41(1H, s), 12.57(1H, s).

Example F-31)
1-(2-Chloro-6-fluoro-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 213-215°C
DMSO-d_6)δ:1.58(2H, 2H), 2.55-3.09(3H, m), 3.45(1H, d, J=12.4Hz), 4.16(1H, d, J=12.4Hz), 4.40-4.58(4H, m), 5.12(1H, d, J=14.4Hz), 7.15-7.38(7H, m), 8.66(1H, s), 10.41(1H, t, J=6.4Hz), 12.46(1H, s).

Example F-32)
5-Hydroxy-1-(4-methoxy-benzyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 191-193°C
NMR (DMSO-d_6)δ:1.50-1.77(2H, m), 2.58-3.06(3H, m), 3.68(3H, s), 3.88(1H, d, J=13.6Hz), 4.41-4.55(4H, m), 4.80(2H, d, J=14.4Hz), 6.80(2H, d, J=8.8Hz), 7.09(2H, d, J=8.4Hz), 7.15(2H, t, J=8.8Hz), 7.35(2H, m), 8.28(1H, s), 10.48(1H, s), 12.58(1H, s).

Example F-33)
1-(3,5-Bis-trifluoromethyl-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 275-277°C
NMR (DMSO-d_6)δ:1.58-1.88(2H, m), 2.51-3.14(3H, m), 3.33-4.10(3H, m), 4.51(2H, m), 4.73(1H, m), 7.16(2H, m), 7.34(2H, m), 7.82-7.93(4H, m), 10.31(1H, s), 12.57(1H, s).

Example F-34)
1-(4-Diethylamino-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide
melting point: 182°C
NMR (DMSO-d_6)δ: 1.04(6H, t, J=6.8Hz), 1.50-1.69(2H, m), 2.55-3.05(3H, m), 3.26(4H, q, J=7.2Hz), 3.80(1H, d, J=13.6Hz), 4.44-4.57(4H, m), 4.91(1H, d, J=12.4Hz), 6.52(2H, d, J=8.8Hz), 6.94(2H, d, J=8.4Hz), 7.15(2H, t, J=8.4Hz), 7.35(2H, m), 8.46(1H, s), 10.41(1H, s), 12.60(1H, s).

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Example F-35)
5-Hydroxy-1-((E)-2-methyl-but-2-enyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 175-177°C
NMR (DMSO-d_6)δ: 1.35(3H, s), 1.51(3H, d, J=6.0Hz), 1.52-1.69(3H, m), 2.60-3.15(3H, m), 4.31-4.52(5H, m), 4.67-4.76(1H, m), 5.30-5.40(1H, m), 7.15(2H, t, J=8.4Hz), 7.28-43(2H, m), 8.46(1H, s), 10.39(1H, brs), 12.60(1H, s).

Example F-36)
1-(3-Dimethylamino-2-methyl-propyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
NMR (DMSO-d_6)δ: 0.63-0.68(2H, m), 1.57-1.82(3H, m), 2.11-2.49(10H, m), 2.98-3.11(2H, m), 4.41-4.54(5H, m), 4.78-4.80(1H, m), 7.14-7.18(2H, m), 7.31-7.38(2H, m), 8.58(1H, s), 10.40(1H, s), 12.57(1H, s).

Example F-37)
1-(3,3-Dimethyl-butyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 175-177°C
NMR (DMSO-d_6)δ: 1.19-1.36(2H, m), 1.57-1.70(2H, m), 2.23-2.30(1H, m), 2.51-2.69(2H, m), 2.97-3.04(2H, m), 4.42-4.54(5H, m), 4.78(1H, d, J=14.0Hz), 7.13-7.17(2H, m), 7.33-7.36(2H, m), 8.63(1H, s), 10.39(1H, t, J=6.0Hz), 12.56(1H, s).

Example F-38)
1-Ethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 221°C
NMR (DMSO-d_6)δ: 0.94(3H, t, J=6.8Hz), 1.56-1.71(2H, m), 2.45-2.50(1H, m), 2.59-2.76(2H, m), 2.96-3.03(2H, m), 4.40-4.44(3H, m), 4.52(2H, d, J=6.0Hz), 4.77-4.82(1H, m), 7.14-7.18(2H, m), 7.34-7.38(2H, m), 8.62(1H, s), 10.41(1H, t, J=6.0Hz), 12.59(1H, s).

Example F-39)
5-Hydroxy-6,10-dioxo-1-(2-oxo-propyl)-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anth

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racene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 244-246°C
NMR (DMSO-d_6)δ: 1.54-1.61(1H, m), 1.67-1.76(1H, m), 2.22(3H, s), 2.50-2.56(1H, m), 2.91-3.02(2H, m), 4.18(1H, s), 4.38-4.45(2H, m), 4.52(2H, d, J=6.0Hz), 4.76(1H, d, J=14.4Hz), 7.13-7.18(2H, m), 7.34-7.37(2H, m), 8.61(1H, s), 10.40(1H, t, J=6.0Hz), 12.54(1H, s).

Example F-40)
5-Hydroxy-6,10-dioxo-1-(4,4,4-trifluoro-butyl)-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 220°C
NMR (DMSO-d_6)δ: 1.53-1.62(2H, m), 1.67-1.75(1H, m), 2.07-2.18(2H, m), 2.40-2.47(1H, m), 2.64-2.78(2H, m), 2.96-3.04(2H, m), 4.42-4.49(2H, m), 4.53(2H, d, J=5.2Hz), 4.74(1H, d, J=12.8Hz), 7.13-7.17(2H, m), 7.33-7.37(2H, m), 8.61(1H, s), 10.40(1H, t, J=6.0Hz), 12.57(1H, s).

Example F-41)
5-Hydroxy-1-(3-methyl-butyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 151°C
NMR (DMSO-d_6)δ: 0.78(6H, dd, J=7.6, 16.2Hz), 1.21-1.28(2H, m), 1.41-1.48(1H, m), 1.56-1.71(2H, m), 2.22-2.31(1H, m), 2.51-2.59(1H, m), 2.66-2.73(1H, m), 2.96-3.05(2H, m), 4.41-4.55(5H, m), 4.80(1H, d, J=13.2Hz), 7.13-7.18(2H, m), 7.33-7.37(2H, m), 8.64(1H, s), 10.40(1H, t, J=6.0Hz), 12.57(1H, s).

Example F-42)
5-Hydroxy-1-isobutyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 180-182°C
NMR (DMSO-d_6)δ: 0.62(3H, d, J=6.0Hz), 0.78(3H, d, J=6.4Hz), 1.55-1.69(3H, m), 1.93-1.99(1H, m), 2.97-3.08(2H, m), 4.39-4.46(3H, m), 4.59-4.64(2H, m), 4.75-4.81(1H, m), 7.16-7.23(1H, m), 7.27-7.34(1H, m), 7.47-7.53(1H, m), 8.59(1H, s), 10.44(1H, s), 12.57(1H, s).

Example F-43)

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1-Cyclopropylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 189-192°C
NMR (DMSO-d_6)δ: 0.00-0.10(2H, m), 0.35-0.41(2H, m), 0.70-0.77(1H, m), 1.57-1.69(2H, m), 2.52-2.65(1H, m), 2.67-2.85(1H, m), 2.91-2.99(1H, m), 4.30-4.41(2H, m), 4.48-4.52(2H, m), 4.71-4.80(1H, m), 7.06-7.10(1H, m), 7.18-7.22(1H, m), 7.36-7.40(1H, m), 8.52(1H, s), 10.30(1H, s), 12.26(1H, s).

Example F-44)
1-Furan-2-ylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 190-192°C
NMR (DMSO-d_6)δ: 1.56-1.68(2H, m), 2.54-2.63(1H, m), 2.89-2.99(2H, m), 3.80(2H, dd, J=18.4, 33.2Hz), 4.37-4.51(3H, m), 4.62(2H, d, J=6.0Hz), 4.97(1H, d, J=15.2Hz), 6.39(2H, s), 7.18-7.22(1H, m), 7.31-7.34(1H, m), 7.48-7.51(1H, m), 7.58(1H, s), 8.64(1H, s), 10.45(1H, t, J=6.0Hz), 12.55(1H, s).

Example F-45)
5-Hydroxy-6,10-dioxo-1-thiazol-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 217-219°C
NMR (DMSO-d_6)δ: 1.59-1.74(2H, m), 2.76-2.83(1H, m), 2.97-3.08(2H, m), 3.90(1H, d, J=16.0Hz), 4.36(1H, d, J=16.0Hz), 4.45-4.69(5H, m), 4.89(1H, d, J=14.8Hz), 7.18-7.22(1H, m), 7.28-7.31(1H, m), 7.47-7.53(1H, m), 7.54(1H, d, J=3.2Hz), 7.68(1H, d, J=3.2Hz), 8.34(1H, s), 10.40(1H, d, J=6.0Hz), 12.52(1H, s).

Example F-46)
5-Hydroxy-6,10-dioxo-1-pyridin-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 190-193°C
NMR (DMSO-d_6)δ: 1.54-1.61(1H, m), 1.69-1.75(1H, m), 2.66-2.74(1H, m), 2.91-3.08(2H, m), 3.68(1H, d, J=14.4Hz), 4.02(1H, d, J=14.8Hz), 4.40-4.67(5H, m), 4.85(1H, d, J=12.4Hz), 7.16-7.35(3H, m), 7.46-7.52(1H, m), 7.61-7.69(1H, m), 8.20(1H, s), 8.43-8.47(1H, m), 10.41(1H, d, J=6.0Hz), 12.58(1H, s).

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Example F-47)
5-Hydroxy-1-isobutyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
melting point: 194°C
NMR (DMSO-d_6)δ: 0.62(3H, d, J=6.4Hz), 0.78(3H, d, J=6.4Hz), 1.55-1.69(3H, m), 1.93-1.99(1H, m), 2.97-3.08(2H, m), 4.39-4.46(3H, m), 4.50-4.59(2H, m), 4.77(1H, d, J=14.4Hz), 7.03-7.09(1H, m), 7.20-7.28(1H, m), 7.36-7.43(1H, m), 8.59(1H, s), 10.39(1H, s), 12.56(1H, s).

Example F-48)
1-Cyclopropylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
melting point: 169-171°C
NMR (DMSO-d_6)δ: 0.00-0.10(2H, m), 0.42-0.44(2H, m), 0.77-0.81(1H, m), 1.59-1.74(2H, m), 2.27-2.32(1H, m), 2.62-2.72(1H, m), 3.05-3.12(1H, m), 4.30-4.58(5H, m), 4.69(1H, d, J=14.8Hz), 7.03-7.11(1H, m), 7.22-7.26(1H, m), 7.37-7.40(1H, m), 8.62(1H, s), 10.40(1H, t, J=6.0Hz), 12.57(1H, s).

Example F-49)
1-Furan-2-ylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
melting point: 186-188°C
NMR (DMSO-d_6)δ: 1.55-1.68(2H, m), 2.55-2.64(1H, m), 2.88-2.99(2H, m), 3.80(2H, dd, J=15.6, 34.8Hz), 4.36-4.56(5H, m), 4.97(1H, d, J=16.0Hz), 6.39(2H, s), 7.05-7.08(1H, m), 7.21-7.26(1H, m), 7.37-7.44(1H, m), 7.58(1H, s), 8.64(1H, s), 10.38(1H, t, J=5.6Hz), 12.53(1H, s).

Example F-50)
5-Hydroxy-6,10-dioxo-1-thiazol-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
melting point: 168-170°C
NMR (DMSO-d_6)δ: 1.59-1.74(2H, m), 2.76-2.83(1H, m), 2.97-3.08(2H, m), 3.89(1H, d, J=16.4Hz), 4.36(1H, d, J=16.0Hz), 4.44-4.55(4H, m), 4.69(1H, s), 4.89(1H, d, J=14.8Hz), 7.03-7.09(1H, m), 7.20-7.27(1H, m), 7.34-7.41(1H, m), 7.54(1H, d, J=3.2Hz), 7.68(1H, d, J=3.2Hz), 8.34(1H, s), 10.35(1H, d, J=6.0Hz), 12.50(1H, s).

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Example F-51)
5-Hydroxy-6,10-dioxo-1-pyridin-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
melting point: 200-203°C
NMR (DMSO-d_6)δ: 1.54-1.61(1H, m), 1.69-1.78(1H, m), 2.71-2.79(1H, m), 2.91-3.09 (2H, m), 3.72(1H, d, J=14.4Hz), 4.07(1H, d, J=14.4Hz), 4.44-4.54(4H, m), 4.70(1H, s), 4.82(1H, d, J=14.4Hz), 7.04-7.10(1H, m), 7.21-7.42(4H, m), 7.74-7.80(1H, m), 8.17(1H, s), 8.47-8.49(1H, m), 10.35(1H, d, J=6.0Hz), 12.57(1H, s).

Example F-52)
1-Hydroxy-6-methyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 230-231°C
NMR (DMSO-d_6)δ: 1.47-1.53(1H, m), 1.62-1.78(3H, m), 2.29(3H, s), 2.77-2.81 (2H, m), 4.05-4.10(1H, m), 4.35-4.40(1H, m), 4.54-4.64(3H, m), 4.70(1H, s), 7.18-7.22(1H, m), 7.30-7.34(1H, m), 7.47-7.52(1H, m), 8.49(1H, s), 10.47(1H, d, J=6.0Hz), 12.44(1H, s).

Example F-53)
1-Hydroxy-6-isobutyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 215-216°C
NMR (DMSO-d_6)δ: 0.83(6H, dd, J=6.8, 13.6Hz), 1.45-1.80(5H, m), 2.36-2.41(1H, m), 2.77-2.93(2H, m), 3.17-3.24(1H, m), 4.02-4.09(1H, m), 4.32-4.40(2H, m), 4.61(2H, d, J=5.6Hz), 4.82-4.84(1H, m), 7.18-7.22(1H, m), 7.30-7.33(1H, m), 7.48-7.51(1H, m), 8.47(1H, s), 10.48(1H, t, J=6.0Hz), 12.55(1H, s).

Example F-54)
6-Cyclopropylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 212°C
NMR (DMSO-d_6)δ: 0.00-0.10(2H, m), 0.40-45(2H, m), 0.80-0.87(1H, m), 1.45-1.77(3H, m), 2.64-2.69(1H, m), 2.85-2.95(2H, m), 3.13-3.20(1H, m), 4.03-4.09(1H, m), 4.36-4.40(2H, m), 4.59(2H, d, J=5.6Hz), 4.84-4.86(1H, m), 7.16-7.20(1H, m), 7.28-7.32(1H, m), 7.46-7.50(1H, m), 8.45(1H, s), 10.46(1H, t, J=6.0Hz), 12.50(1H, s).

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Example F-55)
6-Furan-2-ylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide
Melting point: 189-190°C
NMR (DMSO-d_6)δ: 1.48-1.63(3H, m), 1.70-1.77(1H, m), 2.79-2.83(2H, m), 3.90(2H, dd, J=14.8, 39.6Hz), 4.05-4.11(1H, m), 4.40-4.51(2H, m), 4.61(2H, d, J=5.6Hz), 4.89-4.91(1H, m), 6.30-6.33(1H, m), 6.38-6.40(1H, m), 7.18-7.22(1H, m), 7.30-7.34(1H, m), 7.48-7.53(1H, m), 7.57(1H, s), 8.45(1H, s), 10.45(1H, t, J=6.0Hz), 12.44(1H, s).

Example F-56)
1-Hydroxy-6-methyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide
melting point: 241°C
NMR (DMSO-d_6)δ: 1.47-1.53(1H, m), 1.62-1.78(3H, m), 2.29(3H, s), 2.77-2.81 (2H, m), 4.05-4.10(1H, m), 4.35-4.40(1H, m), 4.53-4.61(3H, m), 4.69(1H, s), 7.03-7.08(1H, m), 7.20-7.27(1H, m), 7.37-7.43(1H, m), 8.49(1H, s), 10.42(1H, d, J=6.0Hz), 12.43(1H, s).

Example F-57)
1-Hydroxy-6-isobutyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide
melting point: 203°C
NMR (DMSO-d_6)δ: 0.82(6H, dd, J=6.4, 13.2Hz), 1.45-1.80(5H, m), 2.36-2.42(1H, m), 2.77-2.93(2H, m), 3.15-3.23(1H, m), 4.02-4.08(1H, m), 4.32-4.41(2H, m), 4.54(2H, d, J=5.6Hz), 4.82-4.84(1H, m), 7.02-7.09(1H, m), 7.20-7.27(1H, m), 7.36-7.43(1H, m), 8.47(1H, s), 10.41(1H, t, J=6.0Hz), 12.54(1H, s).

Example F-58)
6-Cyclopropylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide
melting point: 182-183°C
NMR (DMSO-d_6)δ: 0.00-0.10(2H, m), 0.40-45(2H, m), 0.80-0.87(1H, m), 1.43-1.77(3H, m), 2.60-2.69(1H, m), 2.85-2.95(2H, m), 3.11-3.19(1H, m), 4.00-4.06(1H, m), 4.36-4.40(2H, m), 4.51(2H, d, J=5.6Hz), 4.83-4.87(1H, m), 7.00-7.07(1H, m), 7.16-7.23(1H, m), 7.34-7.38(1H, m), 8.44(1H, s), 10.39(1H, t, J=6.0Hz), 12.47(1H, s).

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Example F-59)
6-Furan-2-ylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide
melting point: 171-173°C
NMR (DMSO-d_6)δ: 1.47-1.64(3H, m), 1.70-1.77(1H, m), 2.79-2.83(2H, m), 3.90(2H, dd, J=15.6, 39.6Hz), 4.05-4.11(1H, m), 4.41-4.57(4H, m), 4.90-4.92(1H, m), 6.30-6.33(1H, m), 6.38-6.40(1H, m), 7.03-7.09(1H, m), 7.20-7.27(1H, m), 7.37-7.45(1H, m), 7.57(1H, s), 8.44(1H, s), 10.41(1H, t, J=6.0Hz), 12.43(1H, s).

Example F-60)
5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 276°C
NMR (DMSO-d_6)δ: 1.60-1.68(1H, m), 1.77-1.84(1H, m), 3.85-3.93 (1H, m), 4.03-4.07(1H, m), 4.43-4.62(5H, m), 5.28(1H, s), 7.17-7.22(1H, m), 7.29-7.34(1H, m), 7.47-7.52(1H, m), 8.49(1H, s), 10.41(1H, d, J=6.0Hz), 12.48(1H, s).

Example F-61)
5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
melting point: 258°C
NMR (DMSO-d_6)δ: 1.60-1.69(1H, m), 1.77-1.85(1H, m), 3.86-3.92 (1H, m), 4.04-4.08(1H, m), 4.43-4.55(5H, m), 5.28(1H, s), 7.03-7.09(1H, m), 7.21-7.27(1H, m), 7.36-7.43(1H, m), 8.50(1H, s), 10.35(1H, d, J=6.0Hz), 12.47(1H, s).

Example F-62)
5-Hydroxy-1-(2-methoxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide
melting point: 193°C
NMR (DMSO-d_6)δ: 1.53-1.73(2H, m), 2.51-2.58(1H, m), 2.71-2.78(1H, m), 2.81-2.87 (1H, m), 2.95-3.08(2H, m), 3.17(3H, s), 4.40-4.52(3H, m), 4.62(1H, d, J=5.6Hz), 4.78(1H, d, J=14.4Hz), 7.18-7.22(1H, m), 7.30-7.34(1H, m), 7.47-7.52(1H, m), 8.55(1H, s), 10.45(1H, d, J=6.0Hz), 12.59(1H, s).

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Example F-63)

5-Hydroxy-1-(2-methoxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 166-168°C

NMR (DMSO-d_6)δ: 1.55-1.72(2H, m), 2.51-2.58(1H, m), 2.70-2.77(1H, m), 2.80-2.87 (1H, m), 2.97-3.07(2H, m), 3.18(3H, s), 4.39-4.52(3H, m), 4.54(1H, d, J=5.2Hz), 4.78(1H, d, J=13.6Hz), 7.03-7.09(1H, m), 7.20-7.27(1H, m), 7.37-7.43(1H, m), 8.55(1H, s), 10.40(1H, d, J=6.0Hz), 12.58(1H, s).

Example F-64)

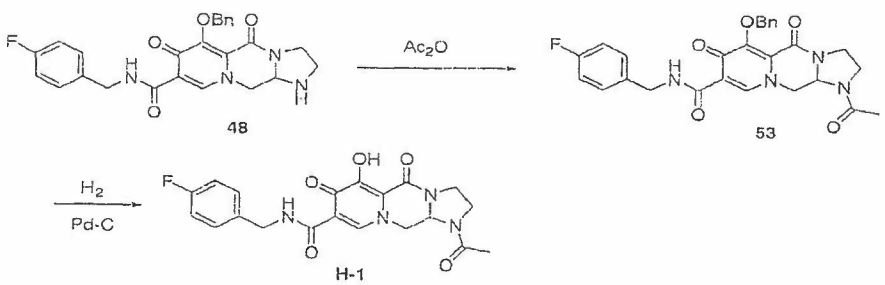
5-Hydroxy-1-(1H-imidazol-4-ylmethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.55-1.59(1H, m), 1.64-1.70(1H, m), 2.58-2.66(1H, m), 2.87-2.95(2H, m), 3.67(1H, d, J=15.2Hz), 3.73(1H, d, J=15.2Hz), 4.34(1H, s), 4.38-4.43(1H, m), 4.47-4.54(3H, m), 5.05(1H, d, J=14.0Hz), 7.00(1H, s), 7.13-7.19(2H, m), 7.33-7.38(1H, m), 7.59(1H, s), 8.55(1H, s), 10.41(1H, t, J=5.6Hz), 11.95(1H, br s), 12.59(1H, s).

Example H-1)

1-Acetyl-5-hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide

[Chemical formula 61]



1) To a solution of a compound 48 (120mg, 0.26 mmol) in methylene chloride (1.2 ml) were added triethylamine (43 µl, 0.31 mmol), acetic anhydride (29 µl, 0.31 mmol), and 4-dimethylaminopyridine (cat.) at room temperature, and the mixture was stirred for 30 minutes. Further, triethylamine (18 µl, 0.13 mmol) and acetic anhydride (12 µl, 0.13 mmol) were added, and the mixture was stirred for 4 hours. 2N hydrochloric

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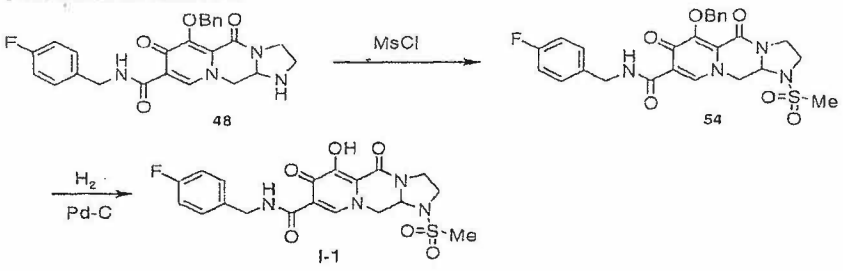
acid was added, this was extracted with chloroform, and the organic layer was washed with water, dried with sodium sulfate, and concentrated under reduced pressure. Diisopropyl ether was added to crystallize the material, which was filtered to obtain 53 (112 mg) as a pale orange crystal at a yield of 86 %.

2) An Example compound H-1 (71 mg) was obtained at a yield of 82 % from a compound 53 (106 mg), according to the method of Example B-1 17).
melting point 290°C
NMR (DMSO-d_6)δ: 2.08(3H, s), 3.44-4.21(5H, m), 4.51(2H, d, 5.7Hz), 4.93(1H, m), 5.46-5.62(1H, m), 7.15(2H, t, 9.0Hz), 7.34(2H, m), 8.49(1H, s), 10.40(1H, t, 5.7Hz), 11.48(1H, s).

An Example compound H-2 was synthesized according to the same manner as that of Example H-1.

Example H-2)
1-Acetyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 290°C
NMR (DMSO-d_6)δ: 1.95(2H, m), 2.14(3H, s), 2.85(2H, m), 4.45(4H, m), 4.51(2H, d, 5.7Hz), 5.99(1H, s), 7.15(2H, t, 9.0Hz), 7.34(2H, m), 8.37(1H, s), 10.46(1H, s), 12.28(1H, s).

Example I-1)
5-Hydroxy-1-methanesulfonyl-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 62]



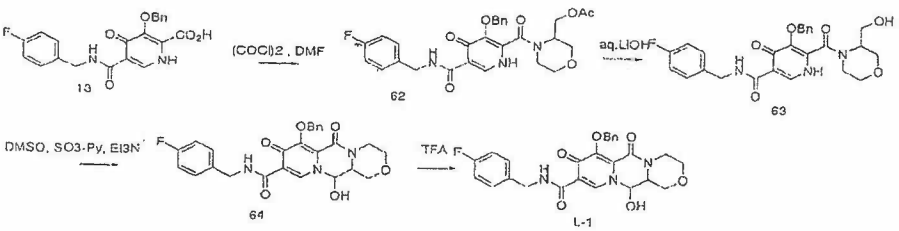
1) To a solution of a compound 48 (140 mg, 0.30 mmol) in pyridine (1.4 ml) were added methanesulfonyl chloride (28 µl, 0.36 mmol), and 4-dimethylaminopyridine (cat.) at room temperature, and the mixture was stirred for 3 hours. After 2N hydrochloric acid was added, this was extracted with ethyl acetate, and the organic layer was washed with water, dried with sodium sulfate, and concentrated under reduced pressure. Diisopropylether was added to crystallize the material, which was filtered to obtain 54 (127 mg) as a pale orange crystal at a yield of 78 %.

2) According to the method of Example B-1 17), an Example compound I-1 (21 mg) was obtained at a yield of 21 % from a compound 54 (123 mg).
melting point: 260°C
NMR (DMSO-d_6)δ: 3.16(3H, s), 3.30-4.15(5H, m), 4.45(2H, d, 5.7Hz), 4.27(2H, m), 5.36(1H, m), 7.14(2H, t, 8.7Hz), 7.33(2H, m), 8.22(1H, s), 10.53(1H, s).

According to the same manner as that of Example I-1, an Example compound I-2 was synthesized.

Example I-2)
5-Hydroxy-1-methanesulfonyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
melting point: 257-259°C
NMR (DMSO-d_6)δ: 1.80-1.96(2H, m), 3.02-3.58(2H, m), 3.16(3H, s), 4.76(2H, m), 5.56(1H, s), 7.16(2H, t, 9.0Hz), 7.35(2H, m), 8.36(1H, s), 10.39(1H, s).

Example L-1)
5,9-Dihydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-1H-2-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 65]



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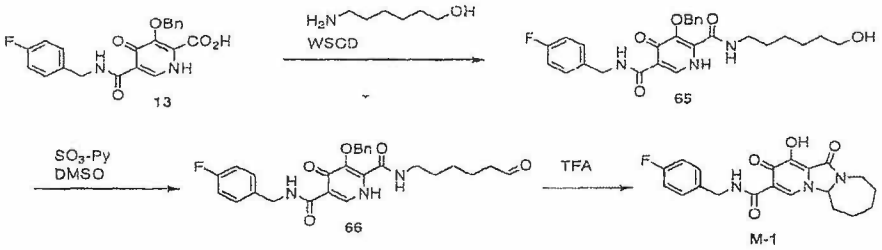
1) According to the method of synthesizing a compound 66, a compound 62 (278 mg, 57%) was obtained from a compound 13 (357 mg).

2) According to the method of synthesizing a compound 57, a compound 63 (202 mg, 79 %) was obtained from a compound 62 (278 mg).

3) To a solution of a compound 63 (200 mg, 0.403 mmol) in chloroform (2 ml) were added dimethyl sulfoxide (286 µl, 4.03 mmol), and triethylamine (337 µl, 2.42 mmol), the mixture was stirred for 10 minutes under ice-cooling, a sulfur trioxide-pyridine complex (321 mg, 2.02 mmol) was added, and the mixture was stirred at room temperature for 2 hours. To the reaction solution was added water (3 ml), and chloroform was distilled off under reduced pressure, followed by extraction with ethyl acetate. The organic layer was washed with water, dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The crystalline residue was washed with ethyl acetate to obtain a compound 64 (60 mg) at a yield of 30 %.

4) Using a compound 64, and according to the method of synthesizing Example A-1, an Example compound L-1 was synthesized.
NMR (DMSO-d_6)δ: 2.98-3.10(1H, m), 3.38-3.60(2H, m), 3.80-4.20(5H, m), 4.40-4.55(2H, m), 5.48(1H, brs), 5.85(1H, s), 7.15(2H, t, J=8.4Hz), 7.33-7.37(2H, m), 8.45(1H, s), 8.60(1H, s), 10.27-10.42(1H, m), 12.61(1H, brs).

Example M-1)
1-Hydroxy-2,10-dioxo-2,4b,5,6,7,8,9,10-octahydro-4a,9a-diaza-benzo[a]azulene-3-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 66]



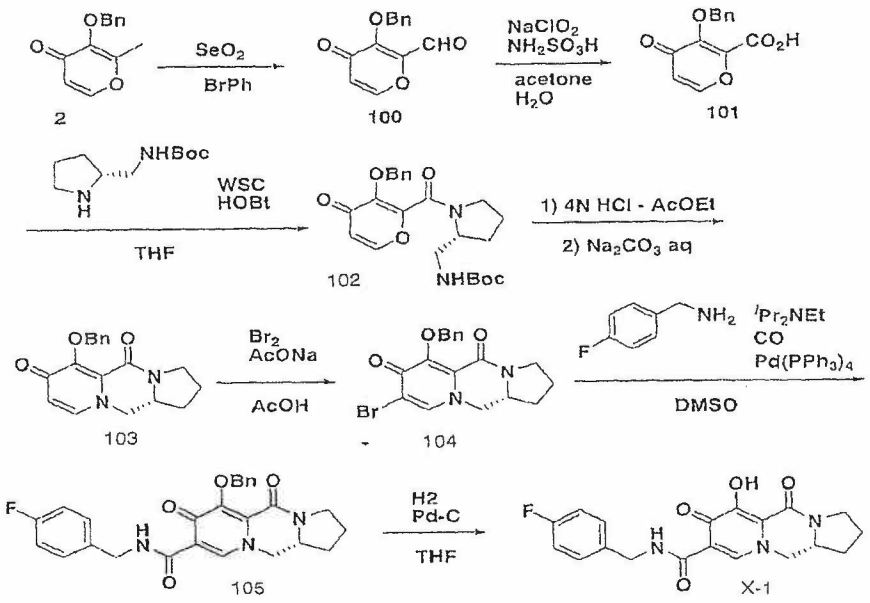
1) According to the method of synthesizing a compound 21, a compound 65 (207 mg) was obtained at a yield of 24 % from a compound 13 (250 mg).

2) According to the method of synthesizing a compound 64, a compound 66 (313 mg, 67 %) was obtained from a compound 65 (470 mg).

3) After trifluoroacetic acid (10 ml) was added to a compound 66 (100 mg, 0.020 mmol), the mixture was stirred at 75°C for 4 hours. The solvent was distilled off under reduced pressure, and this was diluted with chloroform, and added to ice water. This was washed with an aqueous saturated sodium bicarbonate solution, a 10 % aqueous citric acid solution, and water, and dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography, and fractions eluted with chloroform-methanol were concentrated under reduced pressure, and recrystallized with ethyl acetate-diisopropyl ether to obtain an Example compound M-1 (23 mg, 16 %).
melting point 281-283°C
NMR (DMSO-d_6)δ: 1.43-1.52(2H, m), 1.62-1.83(3H, m), 2.04-2.18(1H, m), 2.23-2.35(1H, m), 4.08-4.16(1H, m), 4.48-4.53(2H, m), 5.58-5.61(1H, m), 7.11-7.20(2H, m), 7.30-7.38(2H, m), 8.29(1H, s), 10.30-10.36(1H, m), 12.78(1H, brs).

Example X-1)
(R)-6-Hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro-1H-pyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 67]

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1) Selenium dioxide (666mg, 6.0mmol) was added to the solution of compound 2 (216mg, 1.0mmol) in bromobenzene (2ml). Then the mixture was heated up to 160°C, and stirred for 16h. After celite filtration the solvent was evaporate. The precipitate was purified by silicagel column chromatography, and fractions eluting with n-hexan/EtOAc were concentrated under reduced pressure to obtain compound 100 (164mg, 71%) as a yellow oil.
1H-NMR ($CDCl_3$)δ: 5.52(1H, s), 6.50(1H, d, J=6.0Hz), 7.36(5H, m), 7.74(1H, d, J=6.3Hz), 9.88(1H, s).

2) Sulfamic acid (1.50g, 15.4mmol) and $NaClO_2$ (1.05g, 11.6mmol) was added to the solution of compound 100 (2.54g, 11.0mmol) in acetone (20ml) and water (30ml). Then the mixture was stirred for 3h. The solvent was evaporated under reduced pressure to obtain compound 101 (2.18mg, 80%) as a white solid.
1H-NMR (DMSO-d_6)δ: 5.11(2H, s), 6.55(1H, d, J=5.4Hz), 7.32-7.46(5H, m), 8.21(1H, d, J=5.7Hz).

3) (R)-2-N-BOC-aminomethyl pyrrolidine (391mg, 1.95mmol) was added to the solution of compound 101 (400mg, 1.62mmol),

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (373mg, 1.95mmol), and 1-hydroxybenzotriazole (219mg, 1.62mmol) in THF (6ml). After sttiring for 16h $NaHCO_3$ aqueous solution was added to the mixture. The mixture was extracted with EtOAc, which was washed with NH_4Cl aqueous solution and brine. The organic phase was dried over $MgSO_4$. After a filtration the solvent was removed under reduced pressure to obtain compound 102 (694mg, 100%) as a white solid.
1H-NMR ($CDCl_3$)δ: 1.46(9H, s), 1.56-2.14(4H, m), 3.29(4H, m), 4.18(1H, m), 5.24(1H, s), 5.27(1H, s), 6.46(1H, d, J=5.7Hz), 7.35(5H, m), 7.69(1H, d, J=5.7Hz).

4) The solution of compound 102 (694mg, 1.95mmol) in HCl/EtOAc (4mol/l, 8ml) was stirred for 30 min. The soluvant was removed under reduced pressur, diluted with EtOH (16ml) then. A saturated $NaHCO_3$ aqueous solution was added to the solution to control pH at 9. The mixture was strred at 50 °C for 2h, then diluted with water. The mixture was extracted with $CHCl_3$, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain compound 103 (413mg, 68%) as a yellow solid.
1H-NMR ($CDCl_3$)δ: 1.54-2.22(4H, m), 3.60(2H, m), 3.80(1H, t, J=12.0Hz), 4.18(1H, d, J=12.0Hz), 5.15(1H, d, J=9.9Hz), 5.35(1H, d, J=9.9Hz), 6.71(1H, d, J=5.4Hz), 7.33(3H, m), 7.50(1H, d, J=5.1Hz), 7.63(2H, d, J=7.2Hz).

5) NaOAc (118mg, 1.44mmol) and bromine (0.234ml, 2.62mmol) were added to the solution of compound 103 (408mg, 1.31mmol) in acetic acid (8ml), stirred for 30 min then. An aqueous solution of NaOH (2M) was added to the mixture, and extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give compound 104 (390mg, 77%) as a white solid.
1H-NMR ($CDCl_3$)δ: 1.55-2.19(4H, m), 3.55-4.02(5H, m), 5.12(1H, d, J=9.6Hz), 5.35(1H, d, J=9.9Hz), 7.29-7.38(3H, m), 7.61(1H, s), 7.67(2H, d, J=6.6Hz).

6) Tetrakis triphenylphosphine paradium (0) (77mg, 0.067mmol) and N,N-diisopropylethylamine (0.29ml, 1.67mmol) were added to the solution of compound 104 (130mg, 0,334mmol) in DMSO (2.6ml). the mixture was stirred under CO atmosphere for 2h at 80°C . The reaction mixture was diluted with a saturated NH_4Cl aqueous solution, extracted with EtOAc then. And the organic phase was washed with brine, and dried over Na_2SO_4. The precipitate was purified by silicagel column chromatography, and fractions eluting with MeOH/EtOAc were concentrated

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under reduced pressure to obtain compound 105 (115mg, 75%) as a white oil.
1H-NMR ($CDCl_3$)δ: 1.56-2.33(4H, m), 3.66(2H, m), 3.90(2H, m), 4.19(1H, s), 4.66(2H, m), 5.20(1H, d, J=9.9Hz), 5.37(1H, d, J=9.9Hz), 7.00(2H, t, J=8.7Hz), 7.33(5H, m), 7.61(2H, m), 8.39(1H, m), 10.50(1H, s).

7) A mixture of compound 105 (111mg, 0.241mmol) and paradium-carbon (10%, 22mg) in THF (8ml) and MeOH (2ml) was stirred under hydrogen atmosphere for 3h. After celite filteration the solvent was removed under reduced pressure to give the example X-1 (57mg, 64%) as a white solid.
Melting point: 274°C
1H-NMR (DMSO-d_6)δ:1.56-2.25(4H, m), 3.48-3.65(2H, m), 4.01(2H, m), 4.51(2H, d, J=5.7Hz), 4.71(1H, d, J=9.9Hz), 7.14(2H, t, J=9.0Hz), 7.33(2H, dd, J=5.7, 8.7Hz), 8.41(1H, s), 10.44(1H, t, J=6.0Hz), 12.18(1H, s).

The following compounds were synthesized using the similar method.

Example X-2)
(R)-6-Hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro-1H-pyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxylic acid 2,4-difluoro-benzylamide
Melting point: 300°C
1H-NMR (DMSO-d_6)δ: 1.03-2.20(4H, m), 3.39-3.66(2H, m), 4.02(2H, m), 4.54(2H, d, J=6.0Hz), 4.71(1H, d, J=9.9Hz), 7.06(1H, m), 7.23(1H, m), 7.38(1H, m), 8.41(1H, s), 10.43(1H, t, J=6.0Hz), 12.19(1H, s).

Example X-3)
(R)-6-Hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro-1H-pyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxylic acid 3-chloro-2-fluoro-benzylamide
Melting point: 304°C
1H-NMR (DMSO-d_6)δ: 3.44-3.66(2H, m), 4.01(2H, m), 4.61(2H, d, J=5.4Hz), 4.70(1H, d, J=9.0Hz), 7.20(1H, m), 7.31(1H, m), 7.49(1H, m), 8.41(1H, s), 10.49(1H, t, J=5.7Hz), 12.20(1H, s).

Example X-4)
1-Hydroxy-2,9-dioxo-2,5,6,7,8,9,10,10a-octahydro-4a,8a-diaza-anthracene-3-carboxylic acid 4-fluoro-benzylamide

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Melting point: 259°C
1H-NMR (DMSO-d_6)δ:1.33-1.79(6H, m), 2.51(1H, m), 3.38(1H, m), 4.12(1H, dd, J=9.3, 14.1Hz), 4.38(1H, d, J=12.9Hz), 4.53(3H, m), 7.16(2H, t, J=9.0Hz), 7.34(2H, dd, J=5.7, 8.7Hz), 8.39(1H, s), 10.44(1H, t, J=6.3Hz), 12.84(1H, s).

According to the same manner as that of Example C-21, the following Example compounds Y-1 to Y-18 were synthesized.

Example Y-1)
(3S,9aS)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y-9)
(3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR ($CDCl_3$)δ: 0.90(3H, d, J=6.9Hz), 2.00-2.10(1H, m), 2.70(1H, dd, J=11.6, 13.4Hz), 3.41(1H, dd, J=11.2, 12.9Hz), 4.05-4.45(2H, m), 4.30-4.38(1H, dd, J=4.0, 14.1Hz), 4.63(2H, d, J=5.9Hz), 4.65-4.75(1H, m), 4.98(1H, t, J=3.7Hz), 6.80-6.84(2H, m), 7.32-7.40(1H, m), 8.31(1H, s), 10.38(1H, brs), 12.37(1H, s).

Example Y-2)
(4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y-3)
(4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR ($CDCl_3$)δ: 1.42(3H, d, J=7.0Hz), 1.56(1H, dd, J=2.0, 14.0Hz), 2.19-2.30(1H, m), 4.02(1H, d, J=2.2Hz), 4.05(1H, t, J=2.3Hz), 4.12(1H, dd, J=6.0, 13.6Hz), 4.27(1H, dd, J=4.2, 13.4Hz), 4.64(2H, d, J=5.9Hz), 4.95-5.05(1H, m), 5.26(2H, d, J=4.1, 5.8Hz), 6.75-6.85(2H, m), 7.30-7.40(1H, m), 8.30(1H, s), 10.38(1H, brs), 12.45(1H, s).

Example Y-4)
(2R,9aR)-5-Hydroxy-2-methoxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y-8)
(2S,9aS)-5-Hydroxy-2-methoxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a

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,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR ($CDCl_3$)δ: 1.60-1.80(2H, m), 3.09-3.21(1H, m), 3.37(3H, s), 3.35-3.50(2H, m), 4.00-4.11(1H, m), 4.24(1H, d, J=13.1Hz), 4.36(1H, d, J=10.1Hz), 4.64(1H, d, J=5.9Hz), 4.70-4.80(1H, m), 5.12(1H, s), 6.75-6.85(2H, m), 7.30-7.40(1H, m), 8.30(1H, s), 10.38(1H, brs), 12.33(1H, brs).

Example Y-5)
(5aR,6aS,10aR)-1-Hydroxy-2,12-dioxo-2,5,5a,7,8,9,10,10a,11,12-decahydro-6aH-6-oxa-4a,11a-diaza-naphthacene-3-carboxylic acid 2,4-difluoro-benzylamide [racemate]
1H-NMR (DMSO-d6)δ: 1.00-1.85(9H, m), 2.90(1H, t, J=4.2Hz), 4.36(1H, dd, J=4.2, 12.9Hz), 4.44-4.57(4H, m), 5.32(1H, t, J=3.9Hz), 7.03-7.09(1H, m), 7.20-7.27(1H, m), 7.35-7.43(1H, m), 8.49(1H, s), 10.34(1H, brs).

Example Y-6)
(2S,9aR)-2-Ethyl-5-hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y-7)
(2R,9aS)-2-Ethyl-5-hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR (DMSO-d6)δ: 0.87(3H, d, J=5.4Hz), 1.40-1.51(3H, m), 1.75(1H, d, J=10.8Hz), 3.22(1H, t, J=10.2Hz), 3.73-3.78(1H, m), 4.41-4.57(4H, m), 5.29(1H, s), 7.03-7.07(1H, m), 7.21-7.26(1H, m), 7.37-7.42(1H, m), 8.50(1H, s), 10.34(1H, brs), 12.48(1H, s).

Example Y-10)
(2S,9aS)-5-Hydroxy-6,10-dioxo-2-phenyl-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR ($CDCl_3$)δ: 1.70-1.82(1H, m), 1.98(1H, d, J=9.6Hz), 3.49(1H, t, J=9.6Hz), 4.54-4.68(5H, m), 4.98(1H, d, J=8.7Hz), 5.51(1H, s), 7.04-7.08(1H, m), 7.21-7.42(7H, m), 8.50(1H, s), 10.38(1H, s), 12.45(1H, s).

Example Y-11)
(2S,9aS)-5-Hydroxy-2-isopropyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y-12)
(2R,9aR)-5-Hydroxy-2-isopropyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-di

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aza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR (DMSO-d6)δ: 0.86(6H, dd, J=4.8, 13.5Hz), 1.41-1.49(1H, m), 1.57-1.69(1H, m), 1.72-1.78(1H, m), 3.20(1H, t, J=8.4Hz), 3.52-3.59(1H, m), 4.41-4.46(5H, m), 5.29(1H, s), 7.01-7.08(1H, m), 7.21-7.26(1H, m), 7.37-7.43(1H, m), 8.50(1H, s), 10.35(1H, brs), 12.48(1H, s).

Example Y-13)
(3S,9aS)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 4-fluoro-benzylamide
Example Y-14)
(3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 4-fluoro-benzylamide
1H-NMR (DMSO-d6)δ: 0.81(3H,d, J=6.6Hz), 1.84-1.93(1H, m), 2.86(1H, t, J=12.5Hz), 3.48(1H, t, J=11.1Hz), 3.97-4.03(1H, m), 4.41-4.60(3H, m), 4.52(2H, d, J=5.9Hz), 5.20(1H, t, J=3.8Hz), 7.12-7.20(2H, m), 7.32-7.38(2H, m), 8.52(1H, s). 10.36(1H, t, J=5.9Hz), 12.45(1H, s).

Example Y-15)
(2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y-16)
(2S,9aR)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR (DMSO-d6)δ: 1.14(3H, d, J=6.0Hz), 1.38(1H, m), 1.75(1H, d, J=13.8Hz), 3.18-3.29(1H, m), 3.95-4.06(1H, m), 4.42-4.58(3H, m), 4.54(2H, d, J=5.7Hz), 5.30(1H, t, J=3.9Hz), 7.03-7.10(1H, m), 7.20-7.29(1H, m), 7.35-7.44(1H, m), 8.50(1H, s), 10.35(1H, t, J=5.7Hz), 12.48(1H, s).

Example Y-17)
(2S,9aR)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 4-fluoro-benzylamide
Example Y-18)
(2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 4-fluoro-benzylamide
1H-NMR (DMSO-d6)δ: 1.15(3H, d, J=6.0Hz), 1.35-1.50(1H, m), 1.75(1H, d, J=12.9Hz),

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3.23(1H, td, J=13.0, 2.8Hz), 3.95-4.03(1H, m),4.41-4.59(3H, m), 4.52(2H, d, J=6.0Hz), 5.30(1H, t, J=3.9Hz), 7.12-7.19(2H, m), 7.32-7.38(2H, m), 8.52(1H, s), 10.36(1H, t, J=6.0Hz), 12.48(1H, s).

Corresponding amino-alcohol derivatives used in syntheses of Y-1 to Y-18 were prepared as optically pure version using methods similar to those described in the following reports.

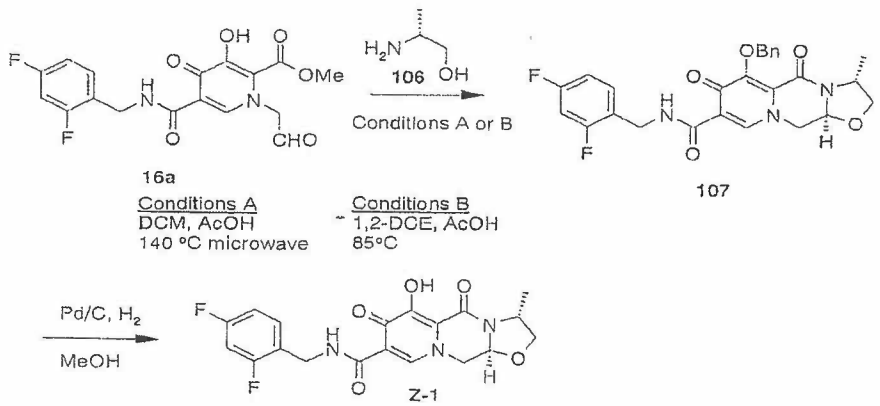
3-Amino-2-methyl-propan-1-ol, and 4-Amino-butan-2-ol were prepared according to the method of Russell A. Barrow (J. Am. Chem. Soc. 1995, 117, 2479-2490).
3-Amino-butan-1-ol were prepared according to the method of P. Besse (Tetrahedron Asymmetry 10(1999) 2213-2224).
1-Amino-pentan-3-ol, 1-Amino-4-methyl-pentan-3-ol, 4-Amino-1-methoxy-butan-2-ol, and 3-Amino-1-phenyl-propan-1-ol were prepared according to the method described in the following literatures, U.S. Pat. Appl. Publ., 2004133029, 08 Jul 2004, PCT Int. Appl., 2002012173, 14 Feb 2002.

All examples below consist of >95% ee and >6:1 diastereomeric purity unless indicated otherwise. The compounds shown in table ZZ consist of mixtures of diastereomers at the depicted stereocenter in ratios of 1:1 to >10:1. Stereocenters that were formed during the process' below have been assigned using NMR techniques well know in the art (1D and 2D method) and/or using vibrational circular dichroism techniques. Stereochemical assignment determinatons were performed on representative examples and closely related compounds were assigned by analogy in some cases. The schemes below are meant to be general guidance to how examples were synthesized. It will be possible that one skilled in the art may rearrange the order of steps or change substituents to apply the method described below and in the examples to construct compounds of the general formula. Additional methods known to those skilled in the art or commonly present in the literature may also be applied

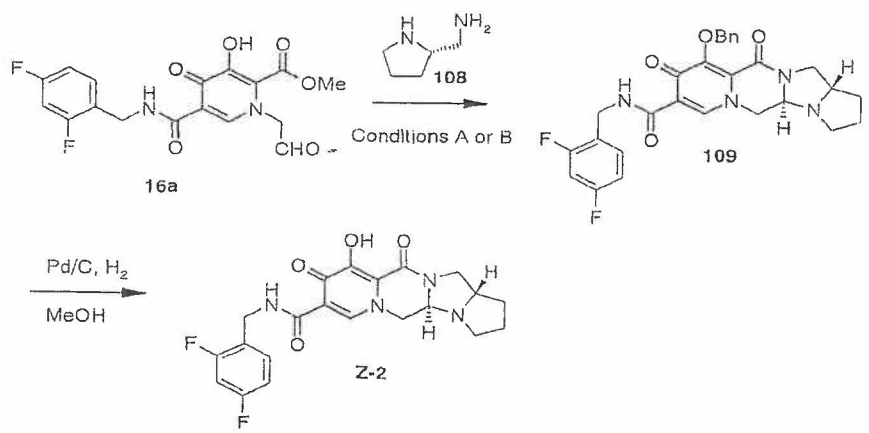
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to perform similar transformations and arriving at the same compounds of the general formula or amino alcohol and diamine precursors.

[Chemical formula 68]

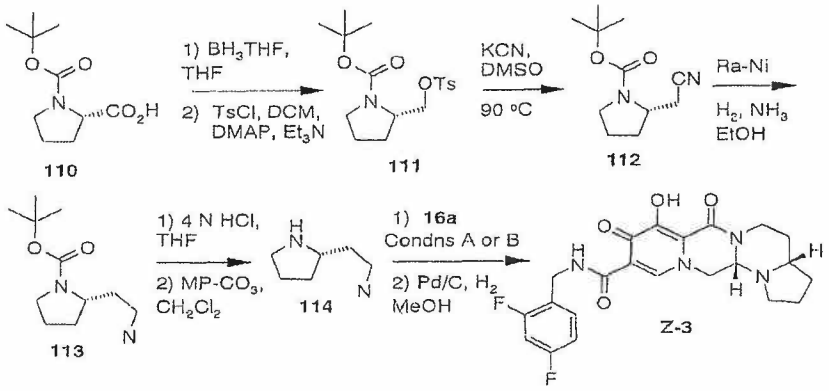


[Chemical formula 69]

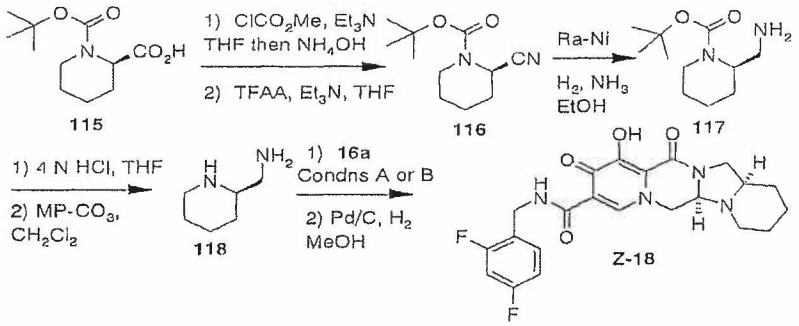


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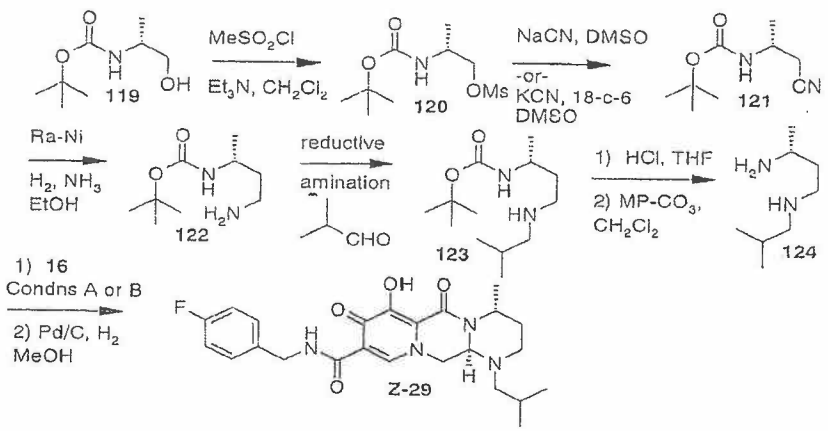
[Chemical formula 70]



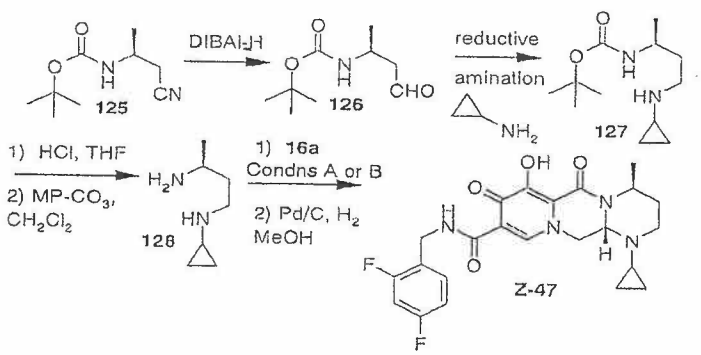
[Chemical formula 71]



[Chemical formula 72]

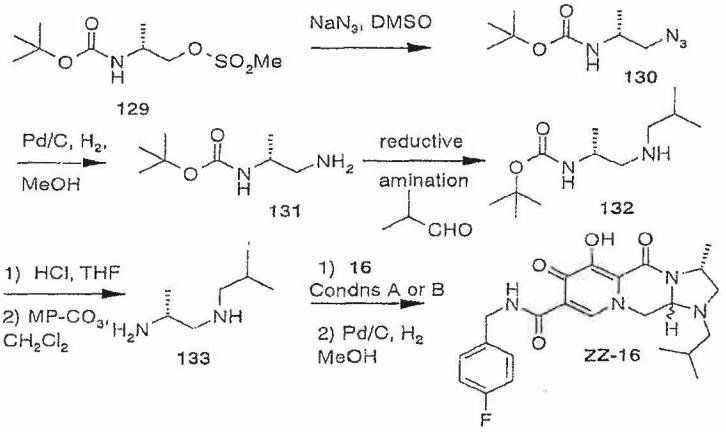


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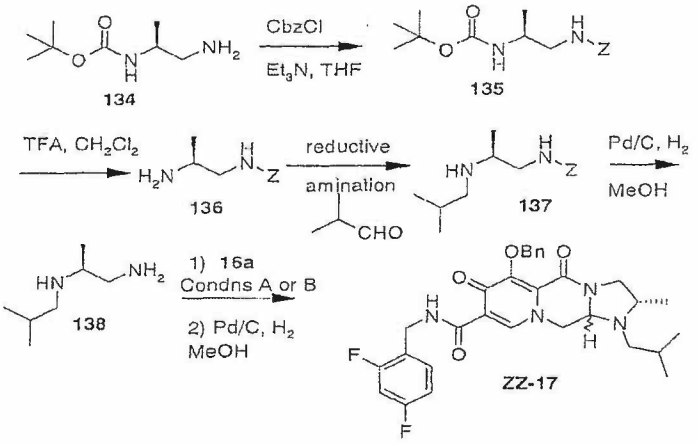


[Chemical formula 74]

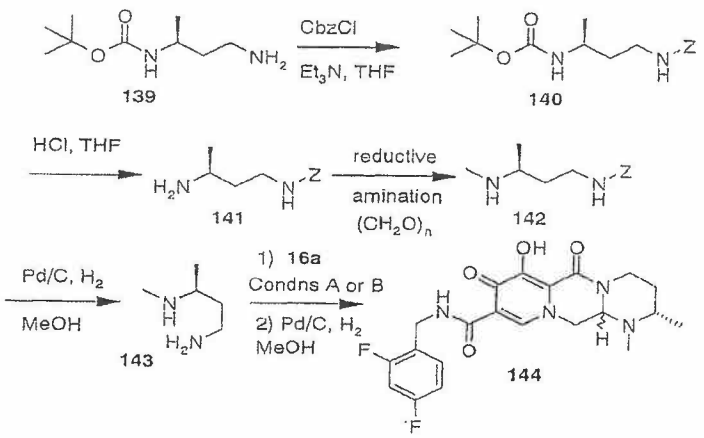
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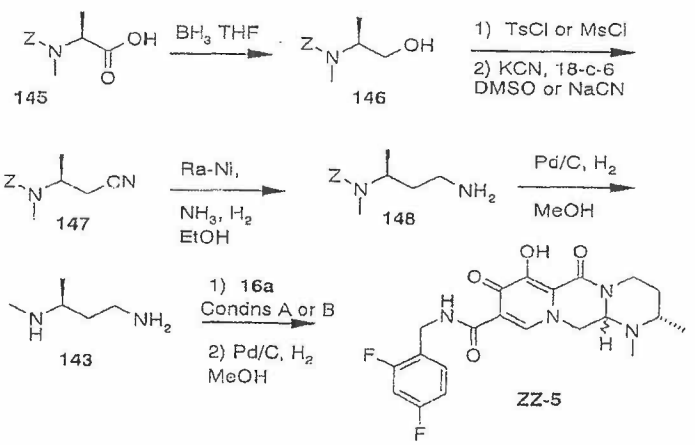
[Chemical formula 74]



[Chemical formula 75]

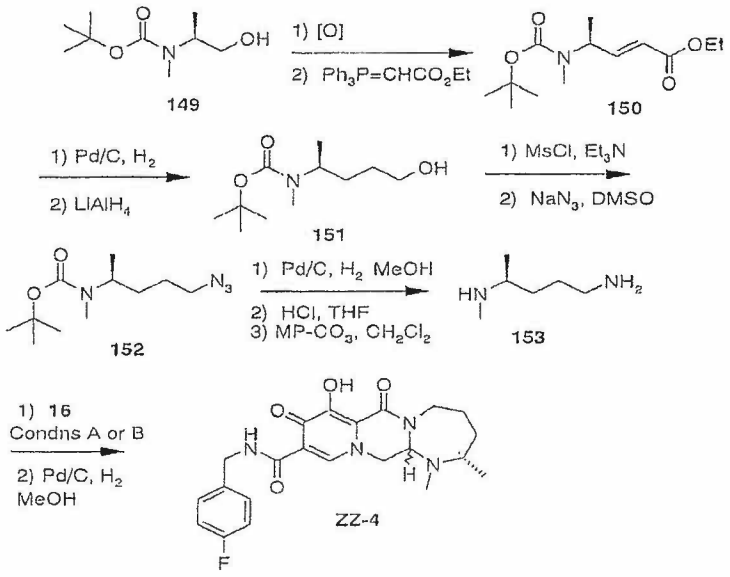


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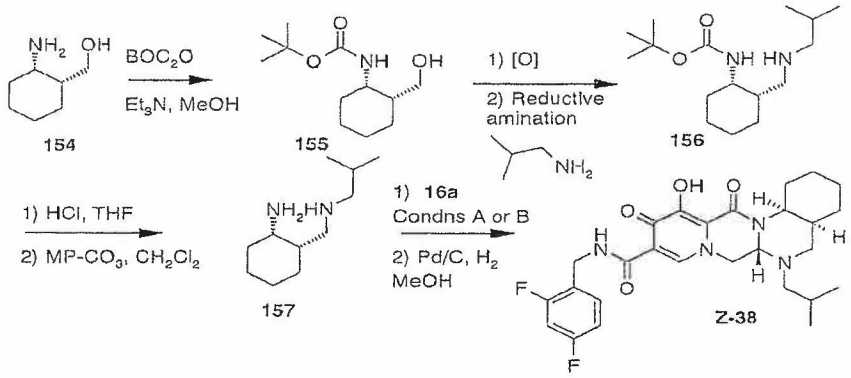


[Chemical formula 77]

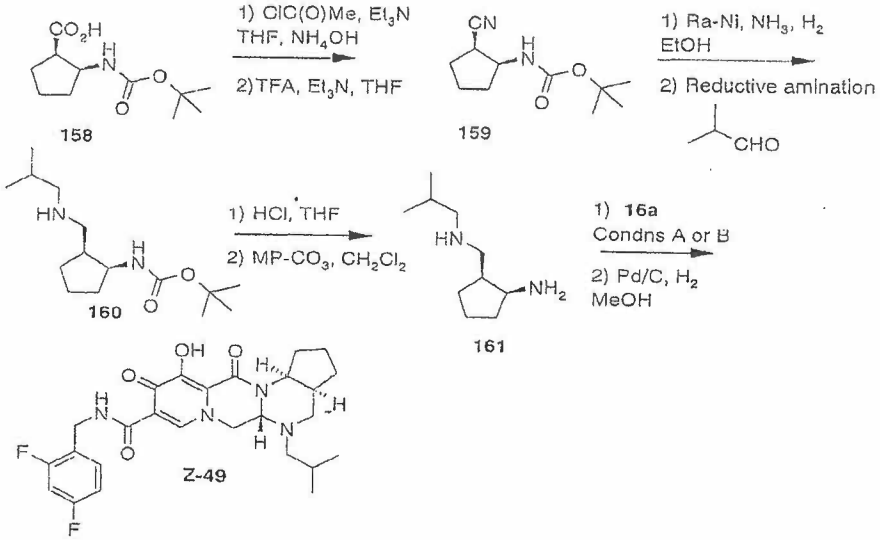
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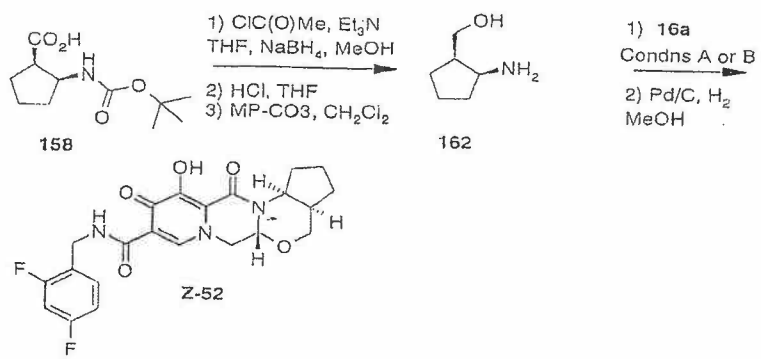
[Chemical formula 78]



[Chemical formula 79]

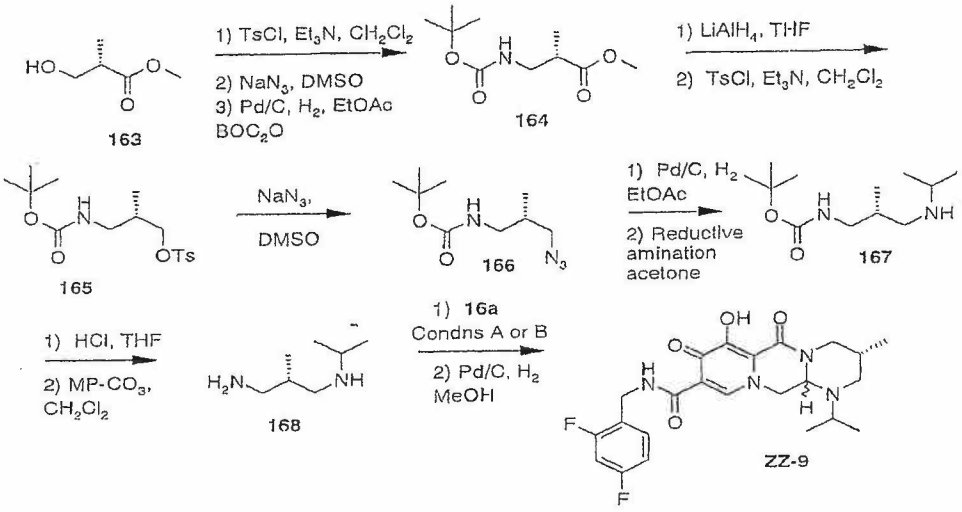


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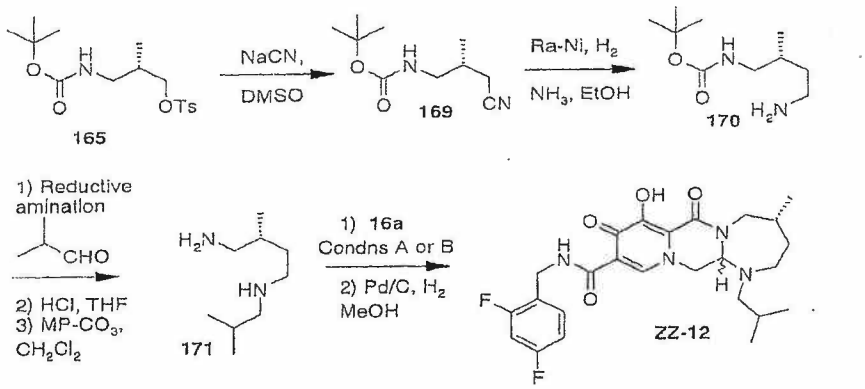


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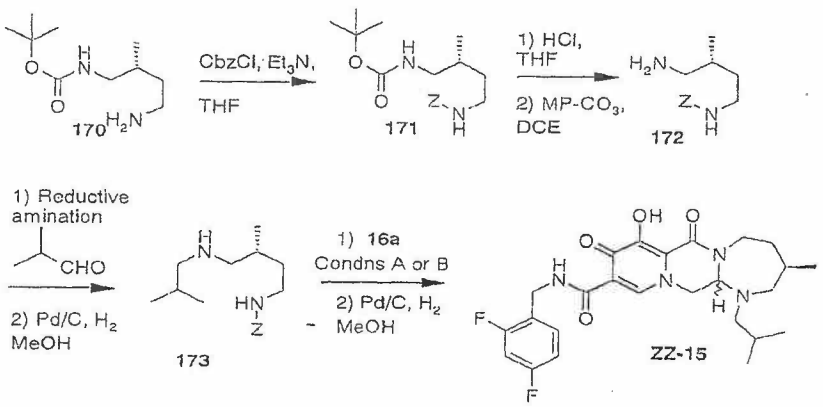
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[Chemical formula 82]

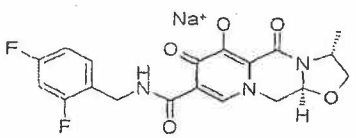


[Chemical formula 83]



Example Z-1:

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt.



a)

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide. To a solution of 16a (409 mg, 0.87 mmol) in dichloroethane (20 mL) was added

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(2*R*)-2-amino-1-propanol (0.14 mL, 1.74 mmol) and 10 drops of glacial acetic acid. The resultant solution was heated at reflux for 2 h. Upon cooling, Celite was added to the mixture and the solvents removed *in vacuo* and the material was purified via silica gel chromatography (2% CH_3OH/CH_2Cl_2 gradient elution) to give (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (396 mg, 92%) as a glass. ^1H NMR ($CDCl_3$) δ 10.38 (m, 1 H), 8.42 (s, 1 H), 7.54-7.53 (m, 2 H), 7.37-7.24 (m, 4 H), 6.83-6.76 (m, 2 H), 5.40 (d, *J* = 10.0 Hz, 1 H), 5.22 (d, *J* = 10.0 Hz, 1 H), 5.16 (dd, *J* = 9.6, 6.0 Hz, 1 H), 4.62 (m, 2 H), 4.41 (m, 1 H), 4.33-4.30 (m, 2 H), 3.84 (dd, *J* = 12.0, 10.0 Hz, 1 H), 3.63 (dd, *J* = 8.4, 7.2 Hz, 1 H), 1.37 (d, *J* = 6.0 Hz, 3 H); ES+ MS: 496 (M+1).

b)

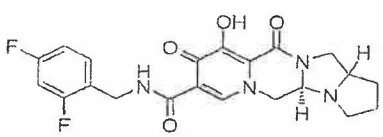
(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt. To a solution of (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (396 mg, 0.80 mmol) in methanol (30 mL) was added 10% Pd/C (25 mg). Hydrogen was bubbled through the reaction mixture via a balloon for 2 h. The resultant mixture was filtered through Celite with methanol and dichloromethane. The filtrate was concentrated *in vacuo* to give (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-

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hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide as a pink tinted white solid (278 mg, 86%). ^{1}H NMR ($CDCl_3$) δ 11.47 (m, 1 H), 10.29 (m, 1 H), 8.32 (s, 1 H), 7.36 (m, 1 H), 6.82 (m, 2 H), 5.31 (dd, J = 9.6, 3.6 Hz, 1 H), 4.65 (m, 2 H), 4.47-4.38 (m, 3 H), 3.93 (dd, J = 12.0, 10.0 Hz, 1 H), 3.75 (m, 1 H), 1.49 (d, J = 5.6 Hz, 3 H); ES$^+$ MS: 406 (M+1). The above material (278 mg, 0.66 mmol) was taken up in ethanol (10 mL) and treated with 1 *N* sodium hydroxide (aq) (0.66 mL, 0.66 mmol). The resulting suspension was stirred at room temperature for 30 min. Ether was added and the liquids were collected to provide the sodium salt of the title compound as a white powder (291 mg, 99%). ^{1}H NMR (DMSO-d_6) δ 10.68 (m, 1 H), 7.90 (s, 1 H), 7.35 (m, 1 H), 7.20 (m, 1 H), 7.01 (m, 1 H), 5.20 (m, 1 H), 4.58 (m, 1 H), 4.49 (m, 2 H), 4.22 (m, 2 H), 3.74 (dd, J = 11.2, 10.4 Hz, 1 H), 3.58 (m, 1 H), 1.25 (d, J = 4.4 Hz, 3 H).

Example Z-2:

(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide.



a)

(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide. A solution of 16a (24 mg, 0.05 mmol), [(2*S*)-2-pyrrolidinylmethyl]amine (0.1 mL) and 2 drops of glacial acetic acid were heated under microwave conditions at 140

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°C for 10 min. Upon cooling, Celite was added to the mixture and the solvents removed *in vacuo* and the material was purified via silica gel chromatography (2% CH_3OH/CH_2Cl_2 gradient elution) to give (4a*R*,13a*S*)-*N*-[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (19 mg, 71%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.41 (m, 1 H), 8.38 (s, 1 H), 7.56 (m, 2 H), 7.38-7.24 (m, 4 H), 6.80 (m, 2 H), 5.38 (d, J = 9.6 Hz, 1 H), 5.10 (d, J = 10.0 Hz, 1 H), 4.62 (m, 2 H), 4.40 (m, 1 H), 4.25 (dd, J = 12.0, 6.8 Hz, 1 H), 4.10 (d, J = 12.8 Hz, 1 H), 3.83 (m, 1 H), 3.71 (m, 1 H), 3.14-3.04 (m, 2 H), 2.78 (m, 1 H), 2.11-1.58 (m, 4 H); ES$^+$ MS: 521 (M+1).

b)

(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide.

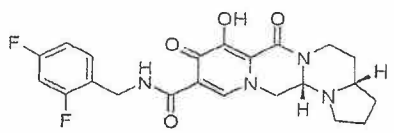
To a solution of (4a*R*,13a*S*)-*N*-[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (19 mg, 0.04 mmol) in methanol (8 mL) was added 10% Pd/C (10 mg). Hydrogen was bubbled through the reaction mixture via a balloon for 2 h. The resultant mixture was filtered through Celite with methanol and dichloromethane. The filtrate was concentrated *in vacuo* to give the title compound (6 mg, 38%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.73 (m, 1 H), 10.36 (m, 1 H), 8.31 (s, 1 H), 7.33 (m, 1 H), 6.78 (m, 2 H), 4.62 (m, 2 H), 4.50 (m, 1 H), 4.27-4.19 (m, 2 H), 3.87-3.77 (m, 2 H),

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3.16-3.08 (m, 2 H), 2.83 (m, 1 H), 2.11-1.66 (m, 4 H); ES+ MS: 431 (M+1).

Example Z-3:

(3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide.



a) *N*-BOC-(2*S*)-2-(Hydroxymethyl)-1-pyrrolidine. To a solution of *N*-BOC-L-proline (4.17 g, 19.4 mmol) in THF (40 mL) at 0 °C was added BH_3-THF (21.4 mL, 1 M in THF, 21.4 mmol) dropwise. The bath was removed and the resultant solution stirred at room temperature for 2 h. Methanol was added to quench the mixture and the solvents were removed *in vacuo*. The residue was taken up in ethyl acetate and washed with sodium bicarbonate and brine. The aqueous layers were extracted twice with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and concentrated to give *N*-BOC-(2*S*)-2-(hydroxymethyl)-1-pyrrolidine (3.82 g, 98%) as a clear oil. This material was used without further purification. ^{1}H NMR ($CDCl_3$) δ 3.94 (m, 1 H), 3.62 (dd, *J* = 11.2, 3.2 Hz, 1 H), 3.56 (dd, *J* = 10.8, 7.2 Hz, 1 H), 3.44 (m, 1 H), 3.29 (m, 1 H), 2.62 (br, 1 H), 1.98 (m, 1 H), 1.85-1.72 (m, 2 H), 1.58 (m, 1 H).

b) *N*-BOC-(2*S*)-2-({[(4-Methylphenyl)sulfonyl]oxy}methyl)-1-pyrrolidine. To a cold (0 °C) solution of *N*-BOC-(2*S*)-2-(hydroxymethyl)-1-pyrrolidine (350 mg, 1.74 mmol) in dichloromethane (20 mL) was added triethylamine (0.29 mL, 2.08 mmol), and

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toluenesulfonyl chloride (398 mg, 2.08 mmol). *N,N*-demethylaminopyridine (70 mg) was added and the resultant solution was allowed to warm to rt as the bath warmed and stirred for 4 h. Water was added and the layers separated. The aqueous layer was washed with sodium bicarbonate and then with brine. The combined organics were dried over Na_2SO_4, filtered and concentrated followed by flash chromatography purification to give *N*-BOC-(2*S*)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)-1-pyrrolidine (460 mg, 75%) as a clear oil. ^{1}H NMR exists as rotomers ($CDCl_3$) δ 7.77 (d, 2 H), 7.33 (m, 2 H), 4.08 (m, 1 H), 3.97-3.88 (m, 1 H), 3.35-3.25 (m, 2 H), 2.43 (s, 3 H), 1.95-1.79 (m, 4 H), 1.40 and 1.35 (s, 9 H rotomeric BOC *t*-butyl).

c) *N*-BOC-(2*S*)-2-Cyano-1-pyrrolidine. A mixture of *N*-BOC-(2*S*)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)-1-pyrrolidine (460 mg, 1.29 mmol) and KCN (256 mg, 3.88 mmol) were heated at 90 °C in DMSO (10 mL) for 6.5 h. The mixture was cooled to room temperature and EtOAc and water were added. The organics were washed with water twice and then with brine. The aqueous layers were extracted with EtOAc and the combined organics dried over Na_2SO_4, filtered and concentrated followed by flash chromatography purification to give *N*-BOC-(2*S*)-2-cyano-1-pyrrolidine (179 mg, 66%) as an oil. ^{1}H NMR exists as rotomers ($CDCl_3$) δ 3.99 (m, 1 H), 3.43-3.37 (m, 2 H), 2.83-2.51 (m, 2 H), 2.17-1.83 (m, 4 H), 1.46 and 1.44 (s, 9 H rotomeric BOC *t*-butyl).

d) *N*-BOC-(2*S*)-2-(2-Aminoethyl)-1-pyrrolidine. A solution of *N*-BOC-

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(2*S*)-2-cyano-1-pyrrolidine (179 mg, 0.85 mmol) in ethanol saturated with anhydrous ammonia was treated with Raney-Ni (1 mL of 50% aq. Suspension) and 50 psi of H_2 overnight. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (10% CH_3OH/CH_2Cl_2 with 1% NH_4OH gradient elution) through a short plug of silica gel to give *N*-BOC-(2*S*)-2-(2-aminoethyl)-1-pyrrolidine (90 mg, 50%) as a clear oil. ^1H NMR exists as rotomers ($CDCl_3$) δ 3.88-3.77 (m, 1 H), 3.33-3.24 (m, 2 H), 2.66 (m, 2 H), 1.89-1.54 (m, 6 H), 1.40 (s, 9 H).

e) {2-[(2*S*)-2-Pyrrolidinyl]ethyl}amine. A solution of *N*-BOC-(2*S*)-2-(2-aminoethyl)-1-pyrrolidine (90 mg, 0.42 mmol) in THF (6 mL) was treated with 4 *N* HCl (aq) (2 mL) and stirred at room temperature for 3 h. The mixture was concentrated *in vacuo* to give the title compound as its HCl salt. A portion of this material (40 mg) was dissolved in methanol and treated with solid supported carbonate resin (MP-Carbonate, Argonaut Technologies) to freebase the amines. After 30 minutes, the solution was filtered through a fritted tube and the solvents removed carefully *in vacuo* to give {2-[(2*S*)-2-pyrrolidinyl]ethyl}amine (30 mg) as its free base. ^1H NMR ($CDCl_3$) δ 3.06 (m, 1 H), 2.94 (m, 1 H), 2.83 (m, 1 H), 2.79-2.69 (m, 2 H), 1.90-1.56 (m, 6 H).

f)

(3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*d*]pyrimidine-10-carb

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oxamide. A solution of 16a (30 mg, 0.06 mmol), (2-[(2*S*)-2-pyrrolidinyl]ethyl)amine (30 mg, 0.26mmol) and 2 drops of glacial acetic acid were heated under microwave conditions at 140 °C for 10 min. Upon cooling, Celite was added to the mixture and the solvents removed *in vacuo* and the material was purified via silica gel chromatography (2% CH_3OH/CH_2Cl_2 gradient elution) to give (3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*d*]pyrimidine-10-carboxamide. (25 mg, 74%) as a film. ^1H NMR ($CDCl_3$) δ 10.44 (m, 1 H), 8.32 (s, 1 H), 7.59 (m, 2 H), 7.38-7.24 (m, 4 H), 6.80 (m, 2 H), 5.28-5.22 (m, 2 H), 4.67 (dd, *J* = 13.6, 2.8 Hz, 1 H), 4.62 (m, 2 H), 4.26 (m, 1 H), 4.11-4.03 (m, 2 H), 2.91 (m, 1 H), 2.81 (m, 1 H), 2.37 (m, 1 H), 2.24 (m, 1 H), 1.92 (m, 1 H), 1.82-1.76 (m, 3 H), 1.52-1.38 (m, 2 H); ES^+ MS: 535 (M+1).

g)

(3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*d*]pyrimidine-10-carboxamide.

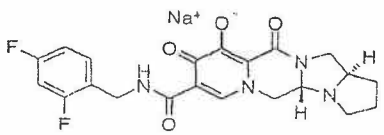
To a solution of (3a*S*,13a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*d*]pyrimidine-10-carboxamide (25 mg, 0.05 mmol) in methanol (8 mL) was added 10% Pd/C (10 mg). Hydrogen was bubbled through the reaction mixture via a balloon for 18 h. The resultant mixture was filtered through Celite with methanol and dichloromethane. The filtrate was concentrated *in vacuo* to give the title compound (14 mg, 67%) as a

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white solid. ^{1}H NMR ($CDCl_3$) δ 12.53 (br, 1 H), 10.44 (s, 1 H), 8.29 (s, 1 H), 7.34 (m, 1 H), 6.78 (m, 2 H), 4.71-4.58 (m, 3 H), 4.29-4.14 (m, 3 H), 2.99 (m, 1 H), 2.88 (m, 1 H), 2.44 (m, 1 H), 2.30 (m, 1 H), 1.97-1.38 (m, 6 H); ES$^+$ MS: 445 (M+1).

Example Z-4:

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide sodium salt.



a) [(2*R*)-2-Pyrrolidinylmethyl]amine. To a solution of *N*-BOC-(2*R*)-2-(aminomethyl)-1-pyrrolidine (1.37 g, 6.85 mmol) in THF (20 mL) was added 4 *N* HCl (aq) (8 mL). The resultant solution was stirred at room temperature overnight. The solvents were removed *in vacuo* and the residue was treated with MP-carbonate resin in methanol and dichloromethane. After 1 h, the resin was removed via filtration through a fritted tube and the volatiles were removed carefully *in vacuo* to produce the free based amine (760 mg crude >100%) as a oil. This material was used without further purification. ^{1}H NMR ($CDCl_3$) δ 3.13 (m, 1 H), 2.92 (m, 1 H), 2.82-2.62 (m, 5 H), 1.88-1.30 (m, 4 H).

b)

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5

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,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carb oxamide. In a similar manner as described in example Z-2 from 16a (435 mg, 0.93 mmol) and [(2*R*)-2-pyrrolidinylmethyl]amine (200 mg, 2.0 mmol) in 1,2-dichloroethane (20 mL) and 15 drops of glacial acetic acid was obtained (4a*S*,13a*R*)-*N*-[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5, 9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carbo xamide (321 mg, 67%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.41 (m, 1 H), 8.35 (s, 1 H), 7.56 (m, 2 H), 7.55-7.24 (m, 4 H), 6.80 (m, 2 H), 5.35 (d, J = 10.0 Hz, 1 H), 5.13 (d, J = 10.0 Hz, 1 H), 4.60 (m, 2 H), 4.38 (dd, J = 10.4, 3.2 Hz, 1 H), 4.21 (dd, J = 12.0, 6.8 Hz, 1 H), 4.04 (dd, J = 12.4, 2.8 Hz, 1 H), 3.77 (apparent t, J = 11.6 Hz, 1 H), 3.68 (m, 1 H), 3.11-3.00 (m, 2 H), 2.75 (m, 1 H), 2.08-1.84 (m, 3 H), 1.65 (m, 1 H); ES$^+$ MS: 521 (M+1).

c)

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a -octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide. In a similar manner as described in example Z-2 from (4a*S*,13a*R*)-*N*-[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5, 9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carbo xamide (518 mg, 0.99 mmol) and 10% Pd/C (35 mg) in methanol (40 mL) was obtained (4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a -octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (430 mg, 99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.73 (m, 1 H), 10.36 (m, 1 H),

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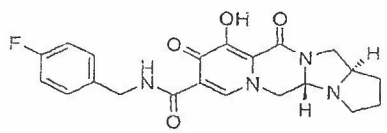
8.32 (s, 1 H), 7.35 (m, 1 H), 6.79 (m, 2 H), 4.64 (m, 2 H), 4.54 (dd, J = 10.8, 4.0 Hz, 1 H), 4.28-4.19 (m, 2 H), 3.90-3.79 (m, 2 H), 3.18-3.10 (m, 2 H), 2.84 (m, 1 H), 2.14-1.92 (m, 3 H), 1.72 (m, 1 H).

d)

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide sodium salt. In a similar manner as described in example Z-1 from (4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (430 mg, 1.0 mmol) and sodium hydroxide (1.0 mL, 1.0 M aq, 1.0 mmol) in 20 mL of ethanol was formed the corresponding sodium salt (425 mg, 94%) as a white solid. ^{1}H NMR (D_2O) δ 7.85 (s, 1 H), 7.23 (m, 1 H), 6.82 (m, 2 H), 4.51-4.46 (m, 3 H), 4.28 (m, 1 H),3.95 (m, 1 H), 3.84 (m, 1 H), 3.62 (m, 1 H), 3.16 (m, 1 H), 2.89 (m, 1 H), 2.84 (m, 1H), 1.90 (m, 2 H), 1.73 (m, 1 H), 1.60 (m, 1 H). ES$^+$ MS: 431 (M+1).

Example Z-5:

(4a*S*,13a*R*)-*N*-[(4-Fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described

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