

29<sup>th</sup> November, 2019

THE CONTROLLER OF PATENT  
Patent Office Kolkata  
Boudhik Sampada Bhawan  
CP-2 Sector V, Salt Lake City  
Kolkata-700091

**Re: Opposition u/s 25(2) of the Patent act – By SANKALP REHABILITATION TRUST against Indian Patent No. 303371 (Formerly Indian Patent Application No. 637/KOLNP/2013) dated 24<sup>th</sup> November, 2018.**

**Patentee: VIIV HEALTHCARE COMPANY**

Respected Sir,

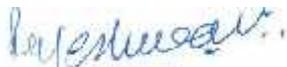
We submit herewith Post-Grant Opposition under Section 25(2) of the Patent Act, 2005 along with evidence and Form 7.

We crave leave of the Controller to submit additional documents or evidence, if necessary to support any averments in the representation as may be necessitated in the proceeding.

The Controller is requested to take the documents on record and proceed further in the matter and keep the Petitioner advised of each and every step taken in the matter.

Lastly, we request the Controller to grant us an opportunity of being heard before the above Opposition is finally decided.

Thanking you,



RAJESHWARI H. IN/PA - 0358  
FOR RAJESHWARI AND ASSOCIATES  
AGENT FOR THE OPPONENT

Encl:

- Form 7;
- Opposition; and
- List of documents.

**BEFORE THE CONTROLLER OF PATENTS, NEW DELHI**

**IN THE MATTER OF:**

The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005, and The Patents Rules, 2003, as amended by The Patents (Amendment) Rules, 2006

AND

IN THE MATTER of Post grant opposition under Section 25(2)

AND

IN THE MATTER of Indian Patent No. 303371

Formerly Indian Patent Application No. 637/KOLNP/2013

**IN THE MATTER OF:**

SANKALP REHABILITATION TRUST

.....OPPONENT

VS.

VIIV HEALTHCARE COMPANY

.....PATENTEE

**POST-GRANT OPPOSITION BY SANKALP REHABILITATION CENTRE**

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Dated this 29<sup>th</sup> day of November, 2019



RAJESHWARI H. IN/PA – 0358  
AGENT FOR THE OPPONENT  
OF RAJESHWARI AND ASSOCIATES

To  
The Controller of Patents  
Patent Office, Kolkata

**FORM 7**  
**THE PATENTS ACT, 1970**  
**(39 OF 1970)**  
**AND**  
**THE PATENTS RULES, 2003**  
**NOTICE OF OPPOSITION**  
**[See Section 25(2) and rule 55A]**

We, **SANKALP REHABILITATION TRUST**, having its registered office at SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002, hereby give Notice of opposition to the grant of patent in respect of Indian Patent No. 303371 (Formerly Indian Patent Application No. 637/KOLNP/2013) dated 24<sup>h</sup> November, 2018 made by VIIV HEALTHCARE COMPANY on the grounds

- (a) Section 25(2)(e): Lack of inventive step
- (b) Section 25(2)(f): Invention is not patentable under section 3(d), 3(e) and 3(i)
- (c) Section 25(2)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
- (d) Section 25(2)(h): Patentee has failed to disclose to the controller the information required by section 8.

**(Detailed grounds are set out in the Opposition)**

Our address for service in India is:

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Dated this 29<sup>th</sup> day of November, 2019



RAJESHWARI H. IN/PA – 0358  
AGENT FOR THE OPPONENT  
OF RAJESHWARI AND ASSOCIATES

To  
The Controller of Patents  
Patent Office, Kolkata

**BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, KOLKATA**

In the matter of Section 25(2) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

AND

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

AND

IN THE MATTER of Indian Patent 303371 date of Grant 24/11/2018 in the name of VIIV HEALTHCARE COMPANY

**REPRESENTATION BY:**

SANKALP REHABILITATION TRUST ..... OPPONENT

VS.

VIIV HEALTHCARE COMPANY ..... PATENTEE

**REPRESENTATION BY WAY OF POST-GRANT OPPOSITION UNDER SECTION 25(2) OF THE PATENTS ACT, 1970**

We, **SANKALP REHABILITATION TRUST**, an Indian citizen, hereby submit my representation by way of opposition of patent in respect of patent no. 303371 granted on 24/11/2018 published on 30/11/2018 entitled "PHARMACEUTICAL COMPOSITIONS" by VIIV HEALTHCARE COMPANY on the following grounds.

**STATEMENT OF CASE OF OPPONENT**

1. The Opponent has learnt that the Indian application 637/KOLNP/2013 has been granted as Indian Patent No. 303371 (hereinafter "the Impugned Patent") on 24/11/2018 and published on 30/11/2018. The Impugned patent was published in the

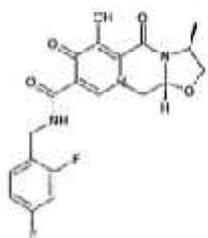
Official Journal of the patent office on 30/11/2018. This Impugned patent is the national phase entry of PCT (PCT/US2011/051713), which was filed on 15/09/2011. The Impugned patent takes the priority of US 61/383,541 (filed on (16.09.2010)). The Impugned patent is entitled "PHARMACEUTICAL COMPOSITIONS" by VIIV HEALTHCARE COMPANY".

2. The impugned patent 303371 has been granted by the Indian patent office on 30/11/2018.
3. The opponent by way of this present post-grant opposition submits that the claims granted on record are not patentable under the provisions provided in this Act. The granted claims on record are annexed herewith as **Annexure-1** and reproduced herein below for ready reference:

**AMENDED**

We Claims:

1. A parenteral pharmaceutical composition comprising a compound of formula (I)



or a pharmaceutically acceptable salt thereof, and a surfactant system comprising a polysorbate and polyethylene glycol.

2. A pharmaceutical composition as claimed in claim 1 for subcutaneous administration.
3. A pharmaceutical composition as claimed in claim 1 for intramuscular administration.
4. A pharmaceutical composition as claimed in any of claims 1 - 3 for once per month administration.
5. A pharmaceutical composition as claimed in any of claims 1 - 3 for administration once every two months.
6. A pharmaceutical composition as claimed in any of claims 1 - 3 for administration once every three months.

7. A pharmaceutical composition as claimed in any of claims 1 – 3 for administration at any interval between 30 and 365 days.
8. A pharmaceutical composition as claimed in any of claims 1 - 7 wherein the amount of a compound of formula (I) is from 10 mg to 500 mg per ml of the dosage form.
9. A pharmaceutical composition as claimed in any of claims 1 - 8 wherein the particle size is less than or equal to 200nm.
10. A pharmaceutical composition as claimed in any of claims 1 - 8 wherein the particle size is in the range of 0.1 – 0.5  $\mu\text{m}$ .
11. A pharmaceutical composition as claimed in any of claims 1 – 10 that can be terminally sterilized by gamma irradiation.

4. **Impugned Patent:** The present post-grant opposition is against Indian Patent 303371, entitled “PHARMACEUTICAL COMPOSITIONS” and is drawn towards a parenteral pharmaceutical composition comprising a compound of Formula 1 (Cabotegravir) or a pharmaceutically acceptable salt thereof, and a surfactant system comprising a polysorbate and polyethylene glycol.
5. **Disclosure in the impugned patent:** As per the Patentee, the present Invention relates to pharmaceutical compositions of (3S,11aR)-N-[(2,4-difluorophenyl)methyl]-2,3,5,7, 1 1, 1 1 a-hexahydro-6-hydroxy-3-methyl-5,7-dioxo-oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide (formula 1) useful in the treatment or prevention of Human Immunodeficiency Virus (HIV) infections. Further, as per the patentee the present invention addresses the issue of non-compliance by formulating the said composition. Further, the pharmaceutical composition for parenteral administration comprising a compound of formula (I) and a surfactant system suitable for commonly known sterilization technologies such as gamma irradiation, electron beam irradiation and autoclave sterilization.

**PRIOR ARTS:**

The opponent wishes to rely on the following prior art as evidence in support of the grounds of opposition.

- i. WO 2006116764 (D1) publication date: November 2, 2006
- ii. US20090163519 (D2) publication date: June 25, 2009
- iii. US2009118354(D3) publication date: May 7, 2009
- iv. 15<sup>th</sup> CROI Conference on Retroviruses and Opportunistic Infections Boston, MA, Feb 3-6, 2008 (D4)
- v. US2005/013386 (D5): publication date: May 6, 2005

Accordingly, the Opponent submits its opposition by way of representation under Section 25(2) in respect of the said Indian Patent 303371 on the following grounds below, which are without prejudice and in the alternative to each other.

6. It is submitted that all claims of the impugned patent are liable to be revoked on following grounds as below:
  - (a) Section 25(2)(e): Lack of inventive step
  - (b) Section 25(2)(f): Invention is not patentable under section 3(d), 3(e) and 3(i)
  - (c) Section 25(2)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
  - (d) Section 25(2)(h): Patentee has failed to disclose to the controller the information required by section 8.

**GROUND 1: LACK OF INVENTIVE STEP**

7. Claim 1-11 are obvious in view of D1 in view of D2 and D3.

8. Claim 1 is drawn towards parenteral composition comprising compound formula 1 and a surfactant system comprising a polysorbate and polyethylene glycol.
9. D1 discloses compound of formula 1 (see page 8-11) and It further discloses that the compounds are useful for treating or preventing various diseases derived from a virus which produces at least integrase such as retrovirus HIV-1, HIV-2. The compound may be used in a joint use therapy by combining another anti-HIV drug having different action mechanism (page 78). D1 further teaches that the compound may be administered orally or parenterally such as in the form of tablet or aqueous suspension injectable (page 78). A dosage form containing the compound may be prepared by mixing the various conventional excipients such as binder, aqueous solvents, emulsifiers, suspending agents, preservatives and stabilizers (page 78).
10. Patentee further admits during the prosecution that D1 discloses the parenteral composition of compound of the formula 1.

Using the first two *John Deere* factors to analyze Johns and Vermeulen, Applicants agree that Johns describes in detail and compound of formula (I) and provides general guidance - a genus of choices - for formulating the compound of formula (I) into an injectable suspension. Applicants also agree that Vermeulen specifically discloses a parenteral formulation using polysorbate, polyethylene glycol, and various additional unclaimed excipients (Table 2), along with a more general disclosure of optional isotonicizing agents which include mannitol (the final claimed excipient).

11. D2 discloses a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations. It further discloses Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension. It specifically discloses the claimed excipients in Table 2.

TABLE 2

Name	Amount Required	
	Per ml	Quantity for 24 L
Paliperidone palmitate (sterile grade)	156 mg	3.744 kg
Polysorbate 20 parenteral	12 mg	288 g
Citric acid monohydrate parenteral	5 mg	120 g
Disodium hydrogen phosphate anhydrous parenteral	5 mg	120 g
Sodium dihydrogen phosphate monohydrate parenteral	2.5 mg	60 g
Sodium Hydroxide all use	2.84 mg	68 g
Polyethylene Glycol 4000 parenteral	30 mg	720 g
Water for injections q.s. ad	1000 µl	24 L

12. D3 discloses a liquid pharmaceutical formulation for parenteral administration composition comprising polyethylene glycol and polysorbate. Example 1 specifically discloses the claimed excipients.

Materials	F1	F2	F3	F4
Docetaxel	10 mg	10 mg	10 mg	10 mg
Polysorbate 80	520 mg	260 mg	260 mg	260 mg
Citric acid	n/a	2 mg	1.6 mg	n/a
Ethanol (absolute)	qs to 1.0 ml	qs to 1.0 ml	0.23 ml	0.25 ml
PEG 300	n/a	n/a	qs to 1 ml	qs to 1 ml

13. Therefore, it would have been obvious for the person skilled in the art to combine D1 in view of D2. D1 specifically discloses claimed compound of formula 1 is formulated in parenteral dosage form and D2 specifically discloses long acting nano suspension comprising polyethylene glycol and polysorbate. Further, at the effective date, it was known that rilpivirine (TMC278) was being developed as long acting parenteral depot preparation as disclosed in D4. It also discloses Injectable long-

acting formulations may provide a new paradigm in ARVuse. It further discloses a novel formulation will contain 300mg/MI of TMC278.

14. Further, cabotegravir has low aqueous solubility and therefore person skilled in the art would be motivated to combine D3 as well which discloses parenteral composition comprising low solubility drug such as docetaxel.
15. Claim 9 and 10 are drawn to particle size less than 200nm. D2 discloses the aqueous formulation would preferably be a nano particle suspension wherein the nano particles would be of an averages size of less than 2000 nm to about 100 nm (Para 0031).
16. Claim 11 is drawn towards the terminal sterilization by gamma irradiation. D5 discloses a pharmaceutical composition that comprise polycyclic compounds that may have a carbaomyl group and is sterilized by gamma radiation specifically Example c (Para 0119-0124)

## **GROUND 2: CLAIMS NOT PATENTABLE UNDERSECTION 25(1)(F)**

17. The Opponent states that the claimed invention clearly falls under the section 3(d) which clearly states that the mere discovery of a **new form of a known substance which does not result in the enhancement of known efficacy of that substance** or the mere discovery of any new property or new use for a known substance or of the mere use of a known process results in a new product or employs at least one new reactant is not patentable under this Act.
18. The Opponent states that the compounds claimed in impugned patent is the new form of the known compound disclosed in D1 and D2 which does not result in

the enhancement of known efficacy and thus not patentable under section 3 (d). Complete specification of the impugned patent does not provide any comparative data to demonstrate enhancement in the therapeutic efficacy with respect to the known efficacy of composition disclosed in D1 and D2. The Opponent states that the patentee miserably failed to provide data demonstrating enhanced 'therapeutic' efficacy as there is no comparative data disclosed in the impugned patent showing improved efficacy of pharmaceutical composition of impugned patent over pharmaceutical composition of D1 and D2.

19. Patentee has also admitted during the US prosecution that D1 and D2 discloses the claimed pharmaceutical composition

Using the first two *John Deere* factors to analyze Johns and Vermeulen, Applicants agree that Johns describes in detail and compound of formula (I) and provides general guidance - a genus of choices - for formulating the compound of formula (I) into an injectable suspension. Applicants also agree that Vermeulen specifically discloses a parenteral formulation using polysorbate, polyethylene glycol, and various additional unclaimed excipients (Table 2), along with a more general disclosure of optional isotonicizing agents which include mannitol (the final claimed excipient).

20. The Opponent thus states that alleged invention claimed in the impugned patent is a mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of 'substances' disclosed in D1 and D2 thus falls under section 3(d) and ought to be rejected in toto under this ground alone.
21. The Opponent states that the claimed invention clearly falls under the section 3(e) which clearly states that the, *a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance* is not considered as an invention unless the functional

interaction between the features of the components achieves a combined technical effect which is greater than the sum of the technical effects of the individual features.

22. Therefore, the present invention is mere an admixture of claimed compound of Formula 1 with polysorbate and polyethylene glycol resulting only in the aggregation of properties of the components thereof. The patentee has failed to demonstrate that the functional interaction between the features of the components achieves a combined technical effect which is greater than the sum of the technical effects of the individual features.
23. The Opponent states that the claimed invention clearly falls under the section 3(i) which clearly states that the, *any process for the medicinal, surgical, curative, prophylactic diagnostic, therapeutic or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products.*

The section clearly states that method for treatment and/or prevention of disease in humans is not patentable subject matter.

Claims 2 to 8 of impugned Patent are directed towards various methods of administration of the claim composition for treatment in humans.

Hence, the subject matter of claims 2 to 8 falls squarely within the purview of Section 3(i) of the Act. Thus, the impugned Patent should be rejected under section 3(i) of the act.

**GROUND 3: INSUFFICIENCY OF DISCLOSURE**

24. The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
25. The claims embrace that the parenteral composition comprising compound of formula 1, polysorbate and polyethylene glycol broadly. However, the examples disclose only one specific amount of polysorbate and polyethylene glycol.. The claimed formulation would be advantageous for all the amount of inactive excipients needs to be established. The person skilled in the art would have to perform undue experimentation to find out whether the claimed formulation would be workable in all the amounts of inactive ingredients specifically polysorbate and polyethylene glycol. Therefore, the claims are broad. Further, the specification does not support i.e. composition without the claimed excipient is not workable.
26. The invention claimed by the impugned patentis not sufficiently disclosed and does not provide enough motivation to a person skilled in the art to understand the invention and reproduce it.

**GROUND 4 -SECTION 25(1)(H): THE PATENTEE HAS FAILED TO DISCLOSE TO THE CONTROLLER THE INFORMATION REQUIRED UNDER SECTION 8.**

27. Section 25(1) (h): Section 25(h) reads as "That the Patentee has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge."

28. The Patentee is required to provide all the information regarding the prosecution of the equivalent applications till the grant of the Indian application to the Controller in writing from time to time and also within the prescribed time. It is observed that Patentee has not updated the status of corresponding application in the Form-3 such as refusal of KR application by Korean patent office which information has not been provided to the learned Controller.
29. Therefore, the Patentee has failed to comply with the requirements of the section 8 of the act and the opponent demands rejection on this ground also. It is submitted that the Patentee has failed to disclose the details of corresponding foreign applications and impugned patent to be revoked.

### **CONCLUSION**

29. In view of the above, the claims are not inventive and insufficient. The post-grant opposition as filed may be allowed and the subject patent may be revoked.

### **PRAYER**

In the fact and circumstances of the case, the Opponent prays as follows:

- a. that the Controller take the present Opposition on record;
- b. that the Indian Patent No. 303371, be rejected under Section 25(2) of the Patents (Amendment) Act, 2005;
- c. that the Opponent may be allowed to file further documents as evidence if necessary to support their averments;
- d. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;

- e. that the Opponent may be allowed to make further submissions in case the Patentee makes any amendments in the claims;
- f. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this the 29<sup>th</sup> day of November, 2019



RAJESHWARI H.

AGENT FOR THE OPPONENT  
RAJESHWARI AND ASSOCIATE

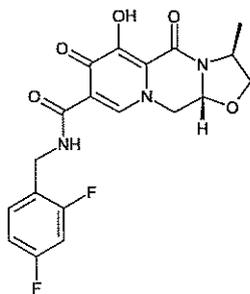
TO  
THE CONTROLLER OF PATENTS  
PATENT OFFICE, KOLKATA

## ANNEXURE - 1

## AMENDED

We Claims:

1. A parenteral pharmaceutical composition comprising a compound of formula (I)



(I)

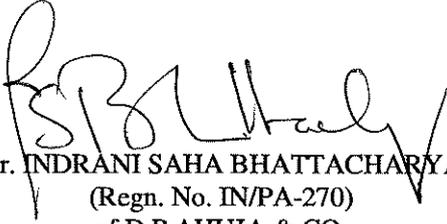
or a pharmaceutically acceptable salt thereof, and a surfactant system comprising a polysorbate and polyethylene glycol.

2. A pharmaceutical composition as claimed in claim 1 for subcutaneous administration.
3. A pharmaceutical composition as claimed in claim 1 for intramuscular administration.
4. A pharmaceutical composition as claimed in any of claims 1 - 3 for once per month administration.
5. A pharmaceutical composition as claimed in any of claims 1 - 3 for administration once every two months.
6. A pharmaceutical composition as claimed in any of claims 1 - 3 for administration once every three months.
7. A pharmaceutical composition as claimed in any of claims 1 - 3 for administration at any interval between 30 and 365 days.
8. A pharmaceutical composition as claimed in any of claims 1 - 7 wherein the amount of a compound of formula (I) is from 10 mg to 500 mg per ml of the dosage form.
9. A pharmaceutical composition as claimed in any of claims 1 - 8 wherein the the particle size is less than or equal to 200nm.
10. A pharmaceutical composition as claimed in any of claims 1 - 8 wherein the the particle size is in the range of 0.1 - 0.5  $\mu$ m.

**AMENDED**

11. A pharmaceutical composition as claimed in any of claims 1 – 10 that can be terminally sterilized by gamma irradiation.

Dated this 7<sup>th</sup> day of March 2013

  
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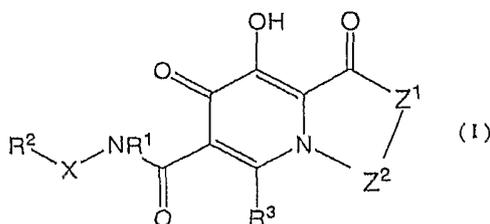
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, 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.

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[Continued on next page]

(54) Title: POLYCYCLIC CARBAMOYLPYRIDONE DERIVATIVE HAVING HIV INTEGRASE INHIBITORY ACTIVITY



(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<sup>1</sup> is NR<sup>4</sup>; R<sup>1</sup> is hydrogen or lower alkyl; X is a single bond, a hetero atom group selected from O, S, SO, SO<sub>2</sub> and NH, or lower alkylene or lower alkenylene in which the hetero atom group may intervene; R<sup>2</sup> is optionally substituted aryl; R<sup>3</sup> is hydrogen, a halogen, hydroxy, optionally substituted lower alkyl etc; and R<sup>4</sup> and Z<sup>2</sup> part taken together forms a ring, to form a polycyclic compound, including e.g., a tricyclic or tetracyclic compound.

WO 2006/116764 A1

**WO 2006/116764 A1**

RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

*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.*

**Published:**

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

## 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  $\gamma$ -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.

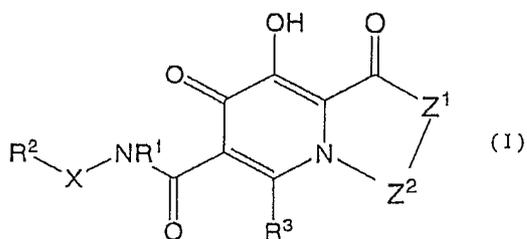
[Means to Solve the Problem]

[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:



(wherein,

Z<sup>1</sup> is NR<sup>4</sup>;

R<sup>4</sup> 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<sub>2</sub>, NR<sup>a</sup> (R<sup>a</sup> is hydrogen or lower alkyl), ·N= and =N-)), O or CH<sub>2</sub>;

Z<sup>2</sup> is optionally substituted lower alkylene or optionally substituted lower alkenylene, each may be intervened by a heteroatom group selected from O, S, SO, SO<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> 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<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is selected independently from the same substituent group as R<sup>4</sup>), ·N= and =N-)), ·N= or =N-

R<sup>1</sup> is hydrogen or lower alkyl;

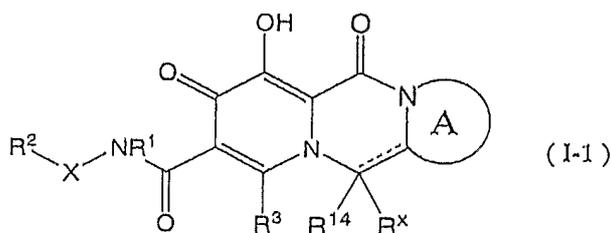
X is a single bond, a heteroatom group selected from O, S, SO, SO<sub>2</sub> and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom;

R<sup>2</sup> is optionally substituted aryl;

R<sup>3</sup> 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):



(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<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is selected independently from the same substituent group as R<sup>4</sup>), -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 aryloxy carbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

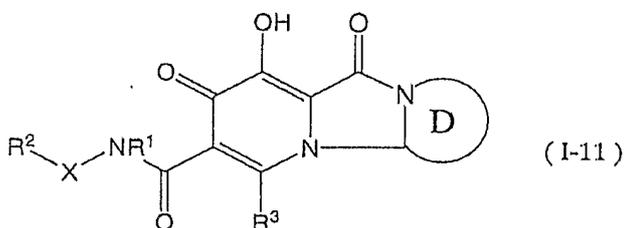
a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, R<sup>X</sup> is not present;

R<sup>1</sup> is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO<sub>2</sub> and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R<sup>2</sup> is optionally substituted aryl;

R<sup>3</sup> 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)



(wherein,

D ring is optionally substituted heterocycle;

R<sup>1</sup> is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO<sub>2</sub> and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R<sup>2</sup> is optionally substituted aryl;

R<sup>3</sup> 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<sup>1</sup> is hydrogen.

(3) A compound according to the above (1), pharmaceutically acceptable salt, or

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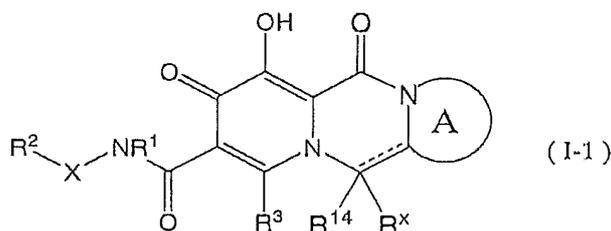
solvate thereof, wherein X is lower alkylene; R<sup>2</sup> is phenyl or phenyl substituted with at least halogen.

(4) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R<sup>3</sup> 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<sup>3</sup> is hydrogen.

(6) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R<sup>1</sup> is hydrogen or lower alkyl; X is lower alkylene; R<sup>2</sup> is phenyl or phenyl substituted with at least halogen; R<sup>3</sup> is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.

(7) A compound of the formula:



(wherein,

A ring is optionally substituted heterocycle;

R<sup>14</sup> and R<sup>x</sup> 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<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is selected independently from the same substituent group as R<sup>4</sup>), -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 aryloxy carbonyl, 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<sup>x</sup> is not present;

R<sup>1</sup> is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO<sub>2</sub> and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R<sup>2</sup> is optionally substituted aryl;

R<sup>3</sup> 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

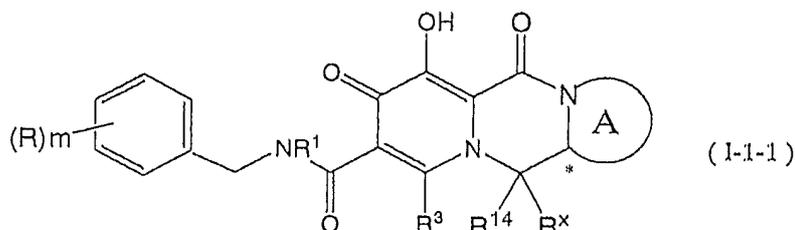
(8) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein R<sup>1</sup> is hydrogen or lower alkyl; X is lower alkylene; R<sup>2</sup> is phenyl or phenyl substituted with at least halogen; R<sup>3</sup> is hydrogen, halogen, hydroxy, lower alkyl, lower 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<sup>x</sup> is hydrogen; R<sup>14</sup> is hydrogen or optionally substituted lower alkyl.

(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:



(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<sup>14</sup> and R<sup>X</sup> 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<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is selected independently from the same substituent group as R<sup>4</sup>), -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;

$R^3$  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

$R^4$  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, S, SO, SO<sub>2</sub>, NR<sup>a</sup> (R<sup>a</sup> 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.

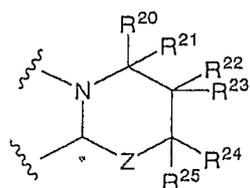
(13) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein  $R^x$  and  $R^{14}$  are independently hydrogen or optionally substituted lower.

(14) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein  $R^x$  and  $R^{14}$  are hydrogens.

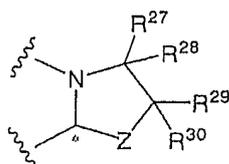
(15) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein  $R^3$  is hydrogen.

(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.

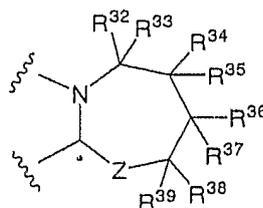
(17) A compound according to the above (7) or (12), pharmaceutically acceptable salt, or solvate thereof, wherein  $A$  ring is any one of the following:



$Z = O$  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 carbocycle 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 ( $R^{39}$  and  $R^{40}$ ), taken together with the neighboring atom, may form an optionally substituted carbocycle 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 alkoxy carbonyl, 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<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is independently selected from the same Substituent group as R<sup>4</sup>), -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<sup>20</sup> to R<sup>40</sup> are each independently hydrogen or substituted lower alkyl, or any two groups of R<sup>20</sup> to R<sup>40</sup>, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7-membered carbocycle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R<sup>20</sup> and R<sup>22</sup>), (R<sup>23</sup> and R<sup>24</sup>), (R<sup>25</sup> and R<sup>26</sup>), (R<sup>27</sup> and R<sup>29</sup>), (R<sup>30</sup> and R<sup>31</sup>), (R<sup>32</sup> and R<sup>34</sup>), (R<sup>35</sup> and R<sup>36</sup>), (R<sup>37</sup> and R<sup>38</sup>), and (R<sup>39</sup> and R<sup>40</sup>), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocycle 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<sup>20</sup> to R<sup>25</sup> 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<sup>20</sup> and R<sup>22</sup>), (R<sup>23</sup> and R<sup>24</sup>), and (R<sup>25</sup> and R<sup>26</sup>), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocycle 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<sup>26</sup>, and R<sup>25</sup> and R<sup>26</sup> 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 carbocycle 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 ( $R^{32}$  and  $R^{34}$ ), ( $R^{35}$  and  $R^{36}$ ), ( $R^{37}$  and  $R^{38}$ ), and ( $R^{39}$  and  $R^{40}$ ), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocycle or optionally substituted 5- to 7- membered heterocycle.

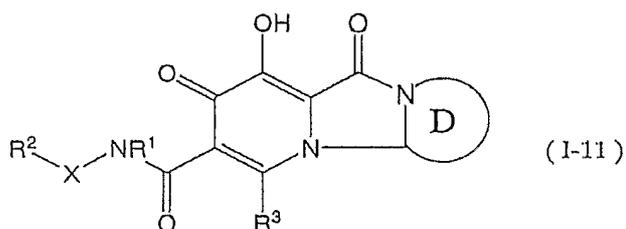
(27) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3);  $Z=NR^{40}$ , and  $R^{39}$  and  $R^{40}$  taken together with the neighboring atom may form an optionally substituted 5- to 7- membered heterocycle.

(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;  $R^s$  is hydrogen; m is 1 to 3 and at least one of  $R_s$  is halogen; A ring is a ring

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  $R_s$  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 carbocycle 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 ( $R^{39}$  and  $R^{40}$ ), taken together with the neighboring carbon atom, may form an optionally substituted 5- to 7- membered carbocycle or optionally substituted 5- to 7- membered heterocycle.

(30) A compound of the formula:



(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

(31) A compound selected from the group consisting of:

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4*aR*,13*aS*)-*N*[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4*a*,5,9,11,13,13*a*-octahydro-1*H*pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3*aS*,13*aS*)-*N*[(2,4-Difluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3*a*,4,5,7,9,13,13*a*-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide;

(4*aS*,13*aR*)-*N*[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4*a*,5,9,11,13,13*a*-octahydro-1*H*pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(4*aS*,13*aR*)-*N*[(4-Fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4*a*,5,9,11,13,13*a*-octahydro-1*H*pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*aS*,13*aS*)-*N*[(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3*a*,4,5,7,9,13,13*a*-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-3-(1,1-Dimethylethyl)-*N*[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11*a*-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-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(5*aR*,14*aR*)-*N*[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5*a*,6,10,12,14,14*a*-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-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide ;

(3*S*,11*aR*)-3-(Cyclohexylmethyl)-*N*[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(5*aR*,14*aS*)-*N*[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-5*a*,6*a*,7,11,13,14*a*-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide;

(2*S*,3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(2*S*,3*R*,11*aR*)-*N*[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4*R*,12*aR*)-*N*[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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(4*R*,12*aR*)-*N*[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-1-(Cyclopropylmethyl)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-1-(2-furanylmethyl)-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*aR*,6*aR*,14*aS*)-*N*[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-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

(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;

(4a*S*,6a*S*,14a*S*)-*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;

(6a*R*,7a*S*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*]benzimidazole-3-carboxamide;

(6a*S*,7a*S*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*]benzimidazole-3-carboxamide;

(5a*S*,14a*S*)-*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;

(4a*R*,14a*R*)-*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*,12*aR*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(3-pyridinylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-1-Cyclopropyl-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methoxy)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;

(3a*S*,5a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-5-(2-methylpropyl)-10,12-dioxo-2,3,3a,4,5,5a,6,10,12,13a-decahydro-1*H*-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]oxazol[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4a*S*,6a*S*,14a*S*)-*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;

(3a*R*,5a*R*,13a*S*)-*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;

(4a*S*,6a*S*,14a*S*)-*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;

(4a*S*,6a*S*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methoxy)ethyl]-11,

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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;

(4a*S*,6a*S*,14a*S*)-6-[2-(Acetylamino)ethyl]-*N*-[(2,4-difluorophenyl)methyl]-12-hydroxy-1,13-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  
;

(4*S*,12a*S*)-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;

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(4*S*,12*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*aS*,6*aS*,14*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-hydroxyethyl)-11,13-dioxo-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-*a*]quinazoline-10-carboxamide;

(4*aS*,6*aS*,14*aS*)-6-Cyclopropyl-*N*-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-*a*]quinazoline-10-carboxamide;

(4*aS*,6*aS*,14*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-6-[2-(1-pyrrolidyl)ethyl]-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-*a*]quinazoline-10-carboxamide;

(4*aS*,14*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4*a*,5,6,8,10,14,14*a*-decahydro-1*H*-pyrido[1,2-*c*]pyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-11-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methoxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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(4*S*,12*aS*)-1-Cyclobutyl-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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-carboxamide;

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mide;

(4*S*,12*aS*)-1-(Cyclopropylmethyl)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*aR*,6*aR*,14*aS*)-*N*[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4*aR*,6*aR*,14*aS*)-*N*[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide ;

4*S*,9*aR*)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9*a*,10-hexahydro-2*H*-1-oxa-4*a*,8*a*-diazanthracene-7-carboxylic acid 2,4,-difluoro-benylamide;

4*R*,9*aS*)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9*a*,10-hexahydro-2*H*-1-oxa-4*a*,8*a*-diazanthracene-7-carboxylic acid 2,4,-difluoro-benylamide;

2*R*,9*aS*)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9*a*,10-hexahydro-2*H*-1-oxa-4*a*,8*a*-diazanthracene-7-carboxylic acid 4-fluoro-benylamide;

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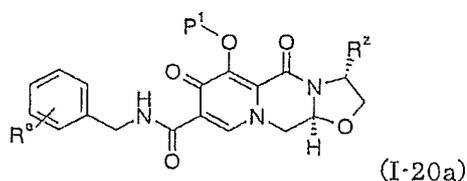
enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.

(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.

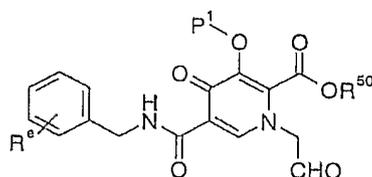
(35) A pharmaceutical composition according to the above (34), which is an anti-HIV agent.

(36) A process for the preparation of a compound of formula (I-20a)



wherein  $R^e$  is one or two halogen;  $R^z$  is  $C_{1-8}$ alkyl,  $C_{6-14}$ aryl $C_{1-8}$ alkyl,  $C_{6-14}$ aryl, or alkoxy; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;

comprising condensing a compound of the formula

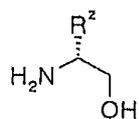


wherein  $R^e$  is one or two halogen;  $R^{50}$  is  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;

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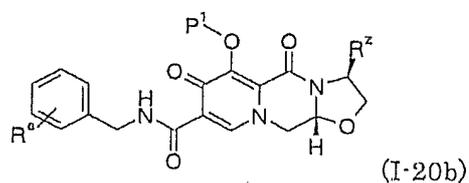
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with a compound of the formula



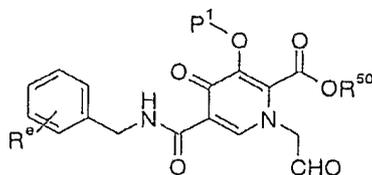
wherein  $R^z$  is  $C_{1-8}$ alkyl,  $C_{6-14}$ aryl $C_{1-8}$ alkyl,  $C_{6-14}$ aryl, or alkoxy;  
to form a compound of formula (I-20a).

(37) A process for the preparation of a compound of formula (I-20b)

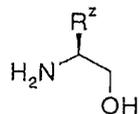


wherein  $R^6$  is one or two halogen;  $R^z$  is  $C_{1-8}$ alkyl,  $C_{6-14}$ aryl $C_{1-8}$ alkyl,  $C_{6-14}$ aryl, or alkoxy; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;

comprising condensing a compound of the formula

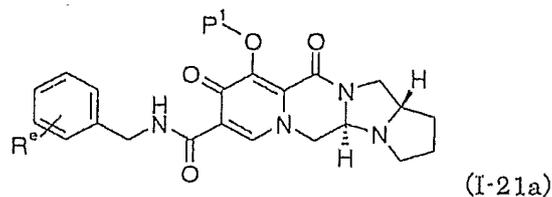


wherein  $R^6$  is one or two halogen;  $R^{50}$  is  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;  
with a compound of the formula



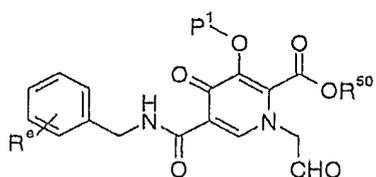
wherein  $R^z$  is  $C_{1-8}$ alkyl,  $C_{6-14}$ aryl $C_{1-8}$ alkyl,  $C_{6-14}$ aryl, or alkoxy;  
to form a compound of formula (I-20b).

(38) A process for the preparation of a compound of formula (I-21a)

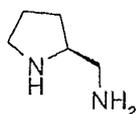


wherein R<sup>6</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;

comprising condensing a compound of the formula

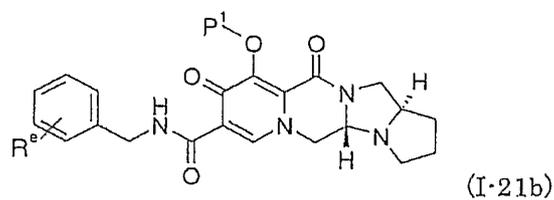


wherein R<sup>6</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
with a compound of the formula



to form a compound of formula (I-21a).

(39) A process for the preparation of a compound of formula (I-21b)

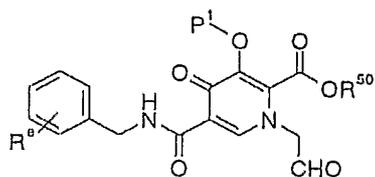


wherein R<sup>6</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;

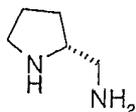
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comprising condensing a compound of the formula

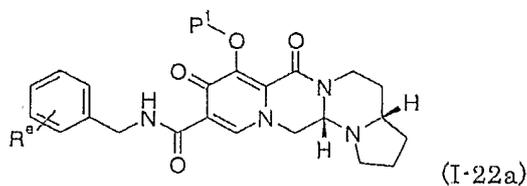


wherein R<sup>0</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
with a compound of the formula

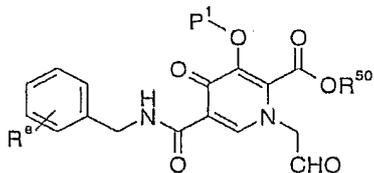


to form a compound of formula (I-21b).

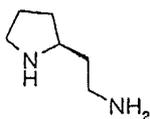
(40) A process for the preparation of a compound of formula (I-22a)



wherein R<sup>0</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
comprising condensing a compound of the formula

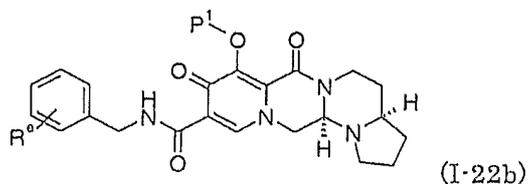


wherein R<sup>0</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
with a compound of the formula

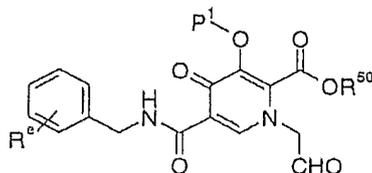


to form a compound of formula (I-22a).

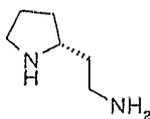
(41) A process for the preparation of a compound of formula (I-22b)



wherein R<sup>6</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
comprising condensing a compound of the formula

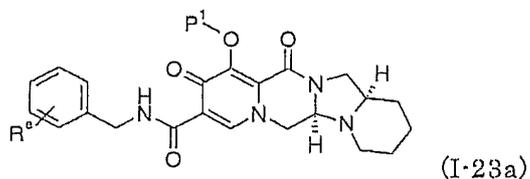


wherein R<sup>6</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
with a compound of the formula



to form a compound of formula (I-22b).

(42) A process for the preparation of a compound of formula (I-23a)

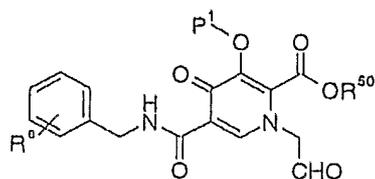


wherein R<sup>6</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;

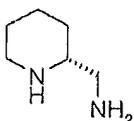
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comprising condensing a compound of the formula

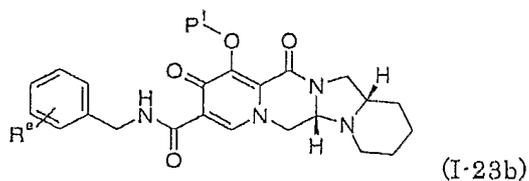


wherein R<sup>a</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
with a compound of the formula

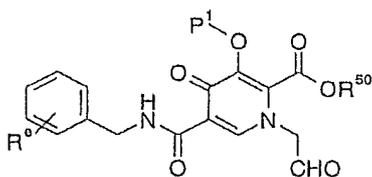


to form a compound of formula (I-23a).

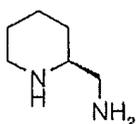
(43) A process for the preparation of a compound of formula (I-23b)



wherein R<sup>a</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
comprising condensing a compound of the formula

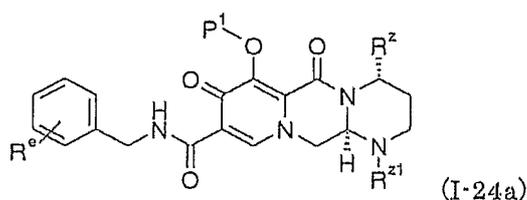


wherein R<sup>a</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl;  
with a compound of the formula



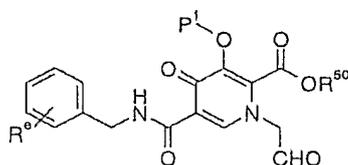
to form a compound of formula (I-23b).

(44) A process for the preparation of a compound of formula (I-24a)

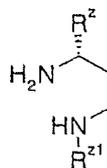


wherein  $R^9$  is one or two halogen;  $R^2$  is  $C_{1-8}$ alkyl;  $R^{21}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_3$ -cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_{6-14}$ aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_{1-8}$ alkyl or  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl/ $C_{1-8}$ alkyl;

comprising condensing a compound of the formula



wherein  $R^9$  is one or two halogen; and  $R^{50}$  is  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl/ $C_{1-8}$ alkyl; with a compound of the formula



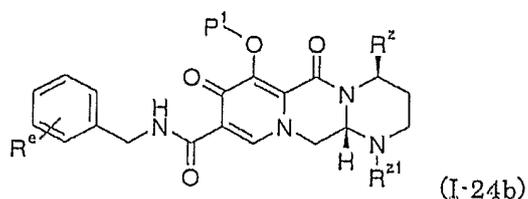
wherein  $R^2$  is  $C_{1-8}$ alkyl;  $R^{21}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_3$ -cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_{6-14}$ aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_{1-8}$ alkyl or  $C_{1-8}$ alkyl;

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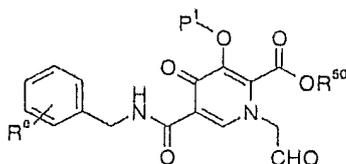
to form a compound of the formula (I-24a).

(45) A process for the preparation of a compound of formula (I-24b)

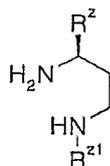


wherein  $R^e$  is one or two halogen;  $R^z$  is  $C_{1-8}$ alkyl;  $R^{z1}$  is hydrogen,  $C_{3-6}$ cycloalkyl, heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_{3-6}$ cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_{6-14}$ aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_{1-8}$ alkyl or  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ 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  $C_{6-14}$ aryl $C_{1-8}$ alkyl; with a compound of the formula



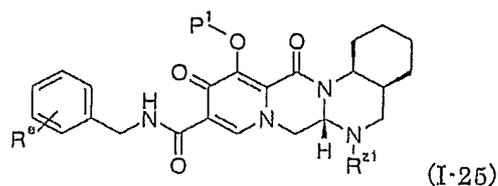
wherein  $R^z$  is  $C_{1-8}$ alkyl; and  $R^{z1}$  is hydrogen,  $C_{3-6}$ cycloalkyl, heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_{3-6}$ cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_{6-14}$ aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_{1-8}$ alkyl or  $C_{1-8}$ alkyl;

to form a compound of the formula (I-24b).

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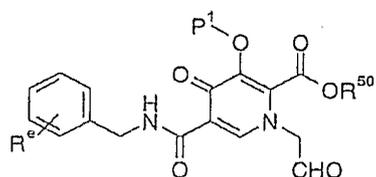
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(46) A process for the preparation of a racemic compound of formula (I-25)

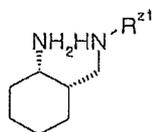


wherein  $R^e$  is one or two halogen;  $R^{z1}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_3$ -cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_{6-14}$ aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_{1-8}$ alkyl or  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;

comprising condensing a compound of the formula



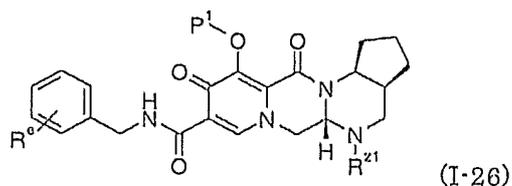
wherein  $R^e$  is one or two halogen; and  $R^{50}$  is  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl; with a racemic compound of the formula



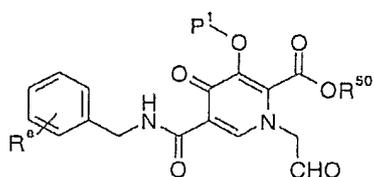
wherein  $R^{z1}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_3$ -cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_{6-14}$ aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_{1-8}$ alkyl or  $C_{1-8}$ alkyl;

to form a racemic compound of the formula (I-25).

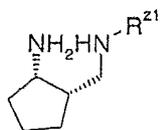
(47) A process for the preparation of a racemic compound of formula (I-26)



wherein R<sup>6</sup> is one or two halogen; R<sup>21</sup> is hydrogen, C<sub>3</sub>-cycloalkyl, heterocycle, or C<sub>1</sub>-alkyl optionally substituted with hydroxy, C<sub>3</sub>-cycloalkyl, alkoxy, heterocycle, heteroaryl, C<sub>6-14</sub>aryl, or amino, wherein said amino may be optionally substituted with -C(O)C<sub>1-8</sub>alkyl or C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl; comprising condensing a compound of the formula



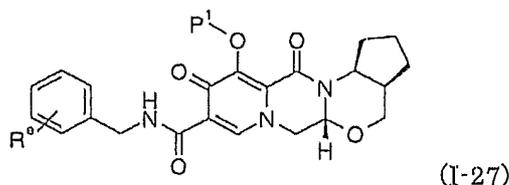
wherein R<sup>6</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl; with a racemic compound of the formula



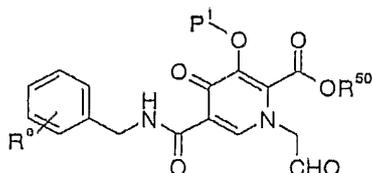
wherein R<sup>21</sup> is hydrogen, C<sub>3</sub>-cycloalkyl, heterocycle, or C<sub>1</sub>-alkyl optionally substituted with hydroxy, C<sub>3</sub>-cycloalkyl, alkoxy, heterocycle, heteroaryl, C<sub>6-14</sub>aryl, or amino, wherein said amino may be optionally substituted with -C(O)C<sub>1-8</sub>alkyl or C<sub>1-8</sub>alkyl;

to form a racemic compound of formula (I-26).

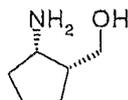
(48) A process for the preparation of a racemic compound of formula (I-27)



wherein  $R^9$  is halogen; and  $P^1$  is  $C_6-14$ aryl $C_1-8$ alkyl;  
comprising condensing a compound of the formula



wherein  $R^9$  is one or two halogen;  $R^{50}$  is  $C_1-8$ alkyl; and  $P^1$  is  $C_6-14$ aryl $C_1-8$ 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<sup>1</sup> 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 term, 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.

When lower alkyl is intervened with "-N=" or "=N-", the lower alkyl may have a double bond to form  $\cdot\text{CH}_2\cdot\text{N}=\text{CH}_2$ ,  $\cdot\text{CH}=\text{N}\cdot\text{CH}_3$  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, cycloheptyl, 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-naphthyl, 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-naphthylmethyl, 2-naphthylmethyl, 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-naphthyloxy, 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-piperidinyl, 2-piperidinyl, 2-morpholinyl, 3-morpholinyl, morpholino, and tetrahydropyranyl. The non-aromatic ring is a

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, quinoxaliny (e.g., 2-quinoxaliny, 5-quinoxaliny, 6-quinoxaliny), cinnoliny (e.g., 3-cinnoliny, 4-cinnoliny, 5-cinnoliny, 6-cinnoliny, 7-cinnoliny, 8-cinnoliny), quinazoliny (e.g., 2-quinazoliny, 4-quinazoliny, 5-quinazoliny, 6-quinazoliny, 7-quinazoliny, 8-quinazoliny), 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, phenandiny (e.g., 1-phenandiny,

2-phenandiny) 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 alkoxy carbonyl", "arylcabonyl", "aryl lower alkylcarbonyl", "aryloxy carbonyl", "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 alkoxy carbonyl", "optionally substituted arylcarbonyl", "optionally substituted aryl lower alkylcarbonyl", "optionally substituted aryloxy carbonyl", "optionally substituted heterocyclecarbonyl", "optionally substituted heterocycle lower alkylcarbonyl", "optionally substituted heterocycleoxy carbonyl", "optionally substituted lower alkylene", "optionally substituted lower alkenylene", "optionally substituted phosphoric acid residue", "optionally substituted carbocycle" or "optionally

substituted heterocycle", each may be substituted with the same or different, 1 to 4 group(s) selected from Substituent group B at any position.

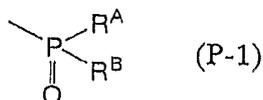
Examples of Substituent group B include hydroxy, carboxy, halogen (F,Cl,Br,I), halo lower alkyl (e.g.,  $\text{CF}_3$ ,  $\text{CH}_2\text{CF}_3$ ,  $\text{CH}_2\text{CCl}_3$ ), halo lower alkoxy (e.g.,  $\text{OCF}_3$ ,  $\text{OCH}_2\text{CF}_3$ ,  $\text{OCH}_2\text{CCl}_3$ ), lower alkyl (e.g., methyl, ethyl, 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, guanidino, 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.,  $\text{CF}_3$ ,  $\text{CH}_2\text{CF}_3$ ,  $\text{CH}_2\text{CCl}_3$ ), halo lower alkoxy (e.g.,  $\text{OCF}_3$ ,  $\text{OCH}_2\text{CF}_3$ ,  $\text{OCH}_2\text{CCl}_3$ ), 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,

ethoxymethyl, ethoxyethyl, isopropoxyethyl), acyl (e.g., formyl, optionally substituted lower alkylcarbonyl (e.g., acetyl, propionyl, butyl, isobutyl, valeryl, isovaleryl, pivaloyl, hexanoyl, octanoyl, methoxyethylcarbonyl, 2,2,2-trifluoroethylcarbonyl, ethoxycarbonylmethylcarbonyl), lower alkoxy lower alkylcarbonyl (e.g., methoxyethylcarbonyl), lower alkylcarbamoyl lower alkylcarbonyl (e.g., methylcarbamoylethylcarbonyl), alkoxyacetyl), optionally substituted arylcarbonyl (e.g., benzoyl, tolyl), 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, trityl), lower alkylaminosulfonyl (e.g., methylaminosulfonyl, dimethylaminosulfonyl), lower alkylaminocarbonyl (e.g., dimethylaminocarbonyl), lower alkoxyacetyl (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 piperidinyl, piperidino, morpholino, pyrrolidino, 2-oxopiperidino, 2-oxopyrrolidino, 4-hydroxymorpholino.

"Phosphoric acid residue" means a group shown of the formula:  $\cdot\text{PO}(\text{OH})_2$ . "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:

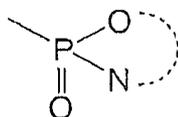


(wherein,  $R^A$  and  $R^B$  each is independently  $OR^C$  or  $NR^D R^E$  (wherein  $R^C$ ,  $R^D$  and  $R^E$  are each independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclic group, or  $R^D$  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 both  $OR^C$ , or one of them is  $OR^C$  and the other is  $NR^D R^E$ .

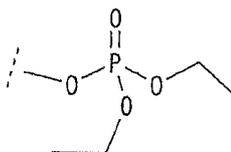
$R^C$ ,  $R^D$  and  $R^E$  each is preferably, independently, lower alkyl (e.g., methyl, ethyl).

The optionally substituted heterocycle formed by  $R^A$  and  $R^B$  taken together with the neighboring P atom may be the following structure:



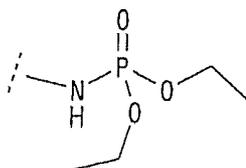
(wherein, the broken line means a part of the ring)

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

alkyls, and more preferably a group of the formula:



[0008]

(More preferable embodiments)

R<sup>1</sup> is hydrogen or lower alkyl, preferably hydrogen.

X is a single bond, a heteroatom group selected from O, S, SO, SO<sub>2</sub> 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<sup>2</sup> neighboring to X.

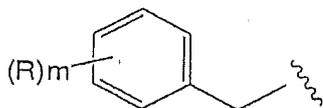
The heteroatom group (M) may be the same or different, and one or more atoms. Examples of that lower alkylene is intervened by a heteroatom group include ·M·CH<sub>2</sub>·, ·CH<sub>2</sub>·M·CH<sub>2</sub>·, ·CH<sub>2</sub>·M·, and ·CH<sub>2</sub>·M·M·CH<sub>2</sub>·.

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<sup>2</sup> 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 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 with a heteroatom group(s) selected from O, S, SO, SO<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is independently selected from the same substituent group for R<sup>4</sup>), -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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup>" is preferably shown by the formula below:

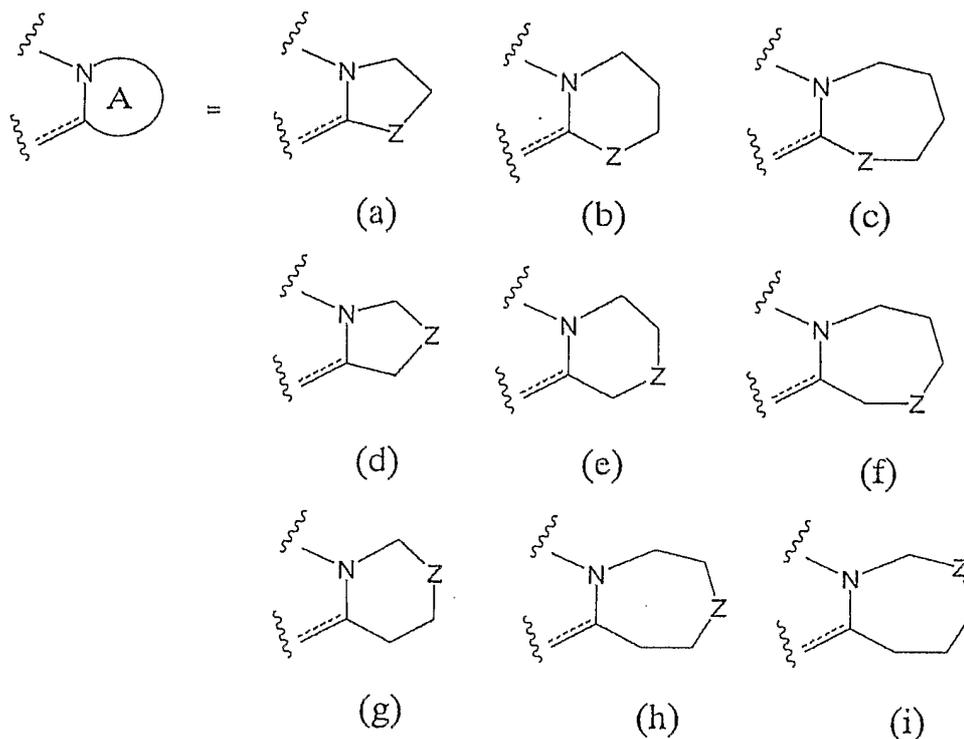


R each is independently a group selected from halogen and Substituent group S1.

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<sub>2</sub>, NR<sup>a</sup> (R<sup>a</sup> 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.



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<sub>2</sub>, O, S, SO, SO<sub>2</sub> or NR<sup>19</sup>)

A ring is preferably a ring of (a), (b), or (c).

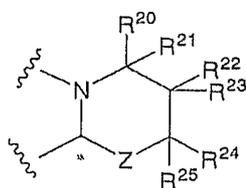
Z is preferably O or NR<sup>19</sup>.

When Z is NR<sup>19</sup>, examples of R<sup>19</sup> 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

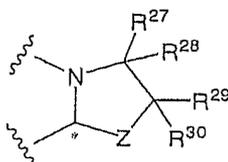
alkylsulfonylamino, lower alkoxy, carbonyl, halogen, thiol, lower alkylthio), 3) lower alkenyl, 4) acyl (e.g., lower alkylcarbonyl), 5) lower alkylsulfonyl.  $R^{19}$  may be selected from Substituent group S2 shown below.

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.

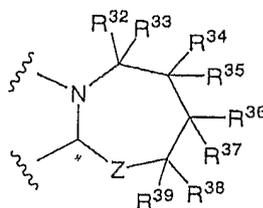
A ring is more preferably any of the following rings:



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 carbocycle 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 ( $R^{39}$  and  $R^{40}$ ), taken together with the neighboring atom, may form an optionally substituted carbocycle 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,

optionally substituted lower alkoxy carbonyl, optionally substituted aryl carbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryl oxycarbonyl, optionally substituted heterocycle carbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycle oxycarbonyl, 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<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is independently selected from the same substitution group as R<sup>4</sup>), -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<sup>20</sup> to R<sup>40</sup> each is preferably hydrogen, optionally substituted lower alkyl (examples of the substituent: OH, lower alkoxy, cycloalkyl, lower alkylthio, lower alkylsulfonyl, heterocyclic group, aryl, optionally substituted amino (examples of the substituent: lower alkyl, acyl)), cycloalkyl, optionally substituted aryl (examples of the substituent: OH, lower alkyl), and optionally substituted heterocyclic group.

In one embodiment, R<sup>20</sup> to R<sup>25</sup>, R<sup>27</sup> to R<sup>30</sup>, and R<sup>32</sup> to R<sup>39</sup>, each is preferably hydrogen, C1-C8 alkyl, C6-C14 aryl C1-C8 alkyl, C6-C14 aryl, or alkoxy.

In one embodiment, R<sup>26</sup>, R<sup>31</sup>, and R<sup>40</sup>, 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

1) When A ring is A-1, preferred is that 1) Z is NR<sup>26</sup> and R<sup>26</sup> and R<sup>24</sup> taken together form heterocycle, and the others are hydrogens; 2) Z is O or NR<sup>26</sup>, (R<sup>20</sup> and R<sup>22</sup>) or

(R<sup>23</sup> and R<sup>24</sup>) 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<sup>27</sup> or R<sup>28</sup> is lower alkyl, and the others are hydrogens; 2) Z is NR<sup>31</sup> and R<sup>30</sup> and R<sup>31</sup> taken together form heterocycle and the others are hydrogens, or R<sup>27</sup> and R<sup>29</sup> taken together form cycloalkyl and the others are hydrogens; 3) Z is O, R<sup>27</sup> and R<sup>29</sup> taken together form cycloalkyl which may be condensed with phenyl, and the others are hydrogens

R<sup>14</sup> and R<sup>x</sup> are each 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, hydroxy, optionally substituted amino, optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryloxy carbonyl, optionally substituted heterocycle carbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxy carbonyl, 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<sub>2</sub>, NR<sup>a</sup> (R<sup>a</sup> is hydrogen or lower alkyl), -N= and =N-).

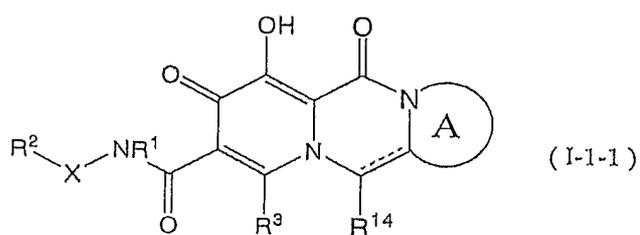
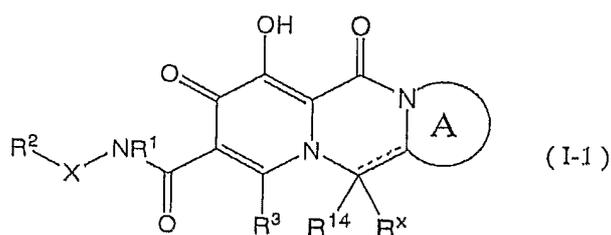
R<sup>14</sup> and R<sup>x</sup> are each independently, preferably, hydrogen, hydroxyl, optionally substituted lower alkyl (the substituent is preferably, e.g., amino, lower alkyl amino, hydroxy, lower alkoxy). R<sup>14</sup> and R<sup>x</sup> are preferably hydrogens.

A broken line in the compound (I-1) represents the presence or absence of a bond,

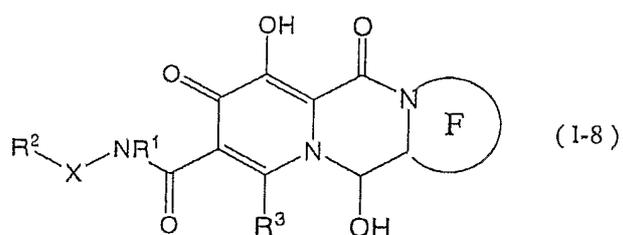
provided that when the broken line represents the presence of a bond, R<sup>x</sup> is not present.

[0009]

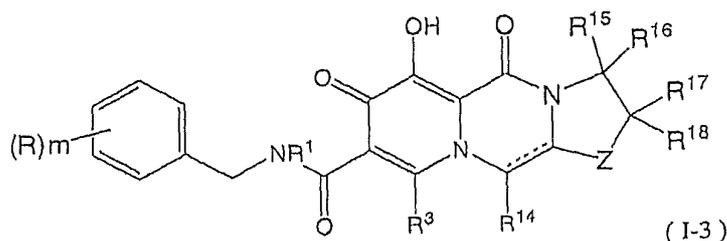
The compound (I) includes the following compounds.



(wherein each symbol is as defined above)



F<sup>r</sup> ring means the same heterocycle as A ring, preferably 5- to 7-membered ring, and the substituents on F<sup>r</sup> ring are the same as those for A ring. The other symbols are as defined above.



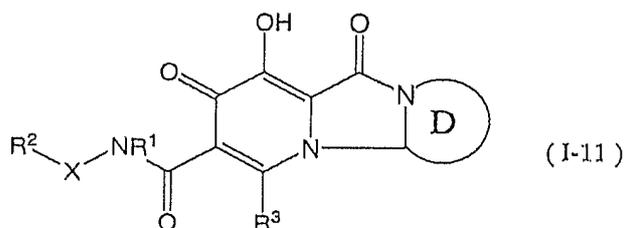
(wherein each symbol is as defined above; Z is O or NR<sup>19</sup>; R<sup>15</sup> to R<sup>19</sup> are each independently hydrogen or a group selected from the above Substituent group S2, or each combination of (R<sup>15</sup> and R<sup>16</sup>), (R<sup>17</sup> and R<sup>18</sup>), (R<sup>16</sup> and R<sup>18</sup>), and (R<sup>18</sup> and R<sup>19</sup>) taken together with the neighboring atom(s), may form an optionally substituted carbocycle (preferably 5- to 6-membered ring) or an optionally substituted heterocycle (preferably 5- to 6-membered ring); or each combination of (R<sup>15</sup> and R<sup>16</sup>) and (R<sup>17</sup> and R<sup>18</sup>) taken together may form oxo)

Compound (I-3) is preferably as follows.

- (1) R<sup>1</sup> is hydrogen; R<sup>3</sup> is hydrogen; m is 1 or 2; R<sup>14</sup> 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<sup>1</sup> is hydrogen; R<sup>3</sup> is hydrogen; R<sup>14</sup> is hydrogen, hydroxyl or lower alkyl optionally substituted with mono- or di- lower alkylamino; Z is O or NR<sup>19</sup> (R<sup>19</sup> 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<sub>3</sub>, -OMe, -OCF<sub>3</sub>, -CH<sub>2</sub>OMe, -CH<sub>2</sub>OH, -CH<sub>2</sub>N(Me)<sub>2</sub>, -CONHMe, -CON(Me)<sub>2</sub>, -CH<sub>2</sub>PO(OEt)<sub>2</sub>, -PO(OEt)<sub>2</sub>, -NHSO<sub>2</sub>Me, or -NMeSO<sub>2</sub>Me; R<sup>1</sup> is hydrogen; R<sup>3</sup> is hydrogen; m is 1 or 2; R<sup>14</sup> is hydrogen, hydroxyl or -CH<sub>2</sub>N(Me)<sub>2</sub>; Z is O or NR<sup>19</sup> (R<sup>19</sup> is hydrogen or -CH(Me)<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>OMe,

$\cdot(\text{CH}_2)_2\text{PO}(\text{OEt})_2$ .

(4)  $\text{R}^{15}$  and  $\text{R}^{16}$  are hydrogens;  $\text{R}^{17}$  and  $\text{R}^{18}$  are hydrogens or taken together with the neighboring atom form a 3- to 7-membered carbocycle; and/or Z is O or NH. This case preferably also satisfies the above (2) or (3).



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 ( $=\text{O}$ ), hydroxyl (OH) and oxo.
- (2) A substituted carbamoyl group ( $-\text{CONR}^1\text{XR}^2$ ) is attached to the position neighboring to the oxo group on the condensed heterocycle.

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  $\text{Z}^1$ ,  $\text{Z}^2$ , and  $\text{R}^3$  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

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.

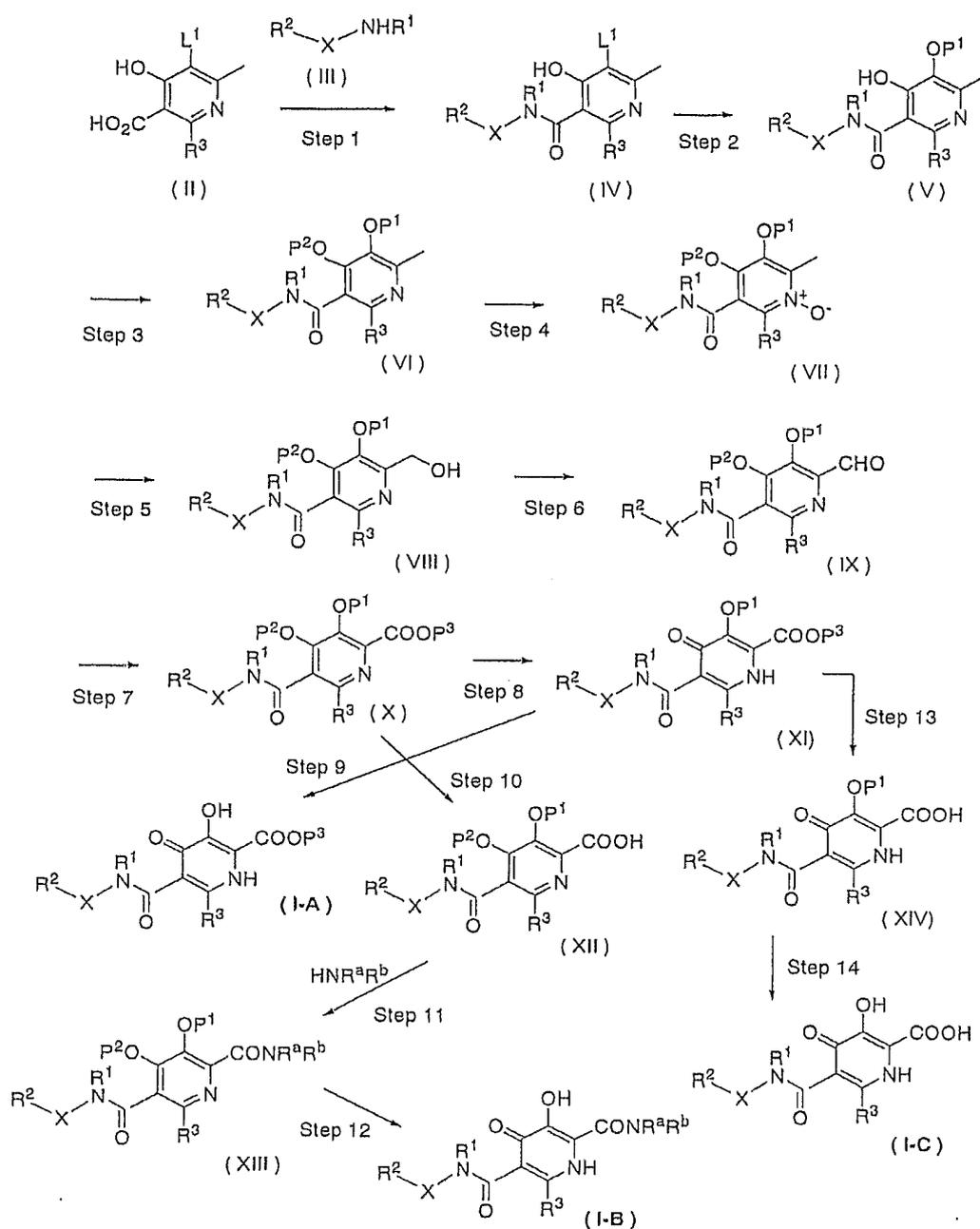
Solvates of a compound of the present invention include alcoholates and hydrates.

[0012]

A general process for producing the present compound will be exemplified below.

(Method of preparing raw material)

[Chemical formula 41]



(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), alkoxy carbonyl (e.g.:

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 alkoxylation 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

(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<sup>2</sup> 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 compound (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.

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<sup>2</sup> 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<sup>1</sup> 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<sup>3</sup>) of a

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<sup>1</sup> and OP<sup>2</sup> 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<sup>3</sup>) of a compound (XI) to synthesize carboxylic acid (XIV). Preferably, hydrolysis with an

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<sup>1</sup> 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.

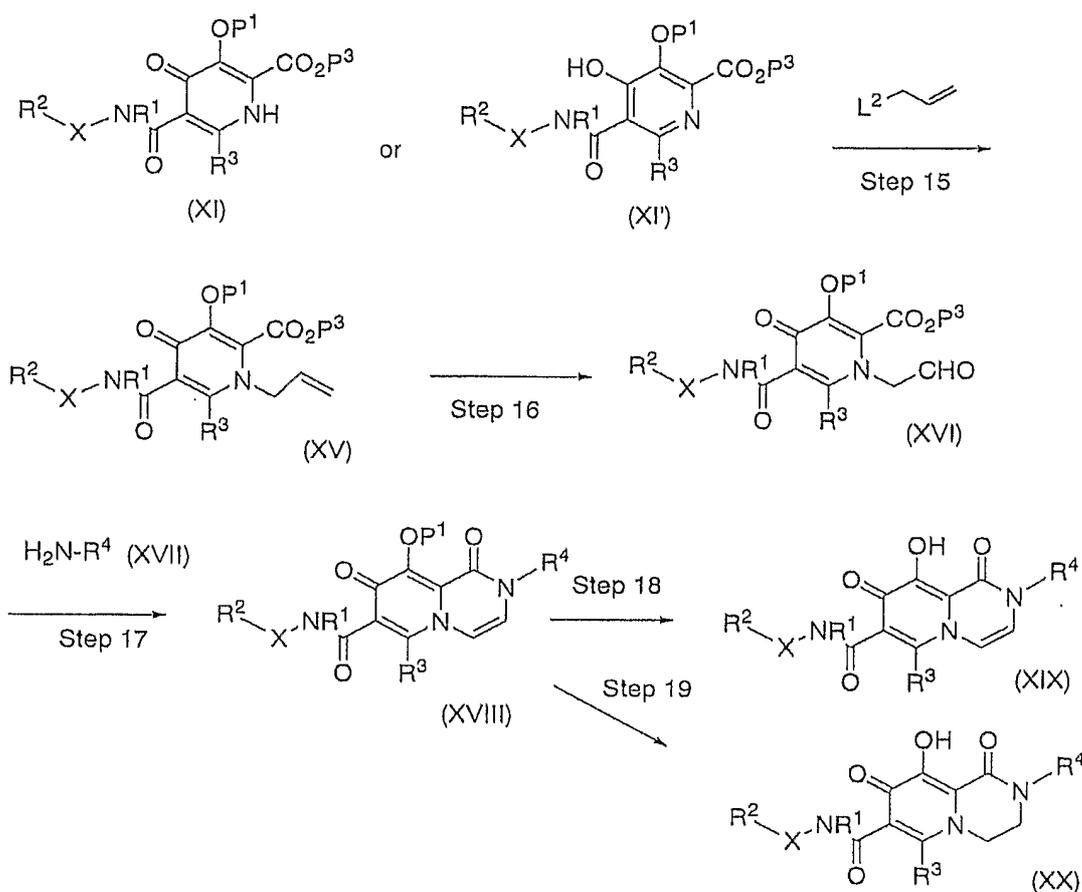
A reaction time is a few minutes to a few tens hours, preferably a few minutes to 5 hours.

[0014]

The monocyclic carbamoylpyridone derivative obtained above is derived into a bicyclic compound by the following method.

(Process 1)

[Chemical formula 42]



(wherein R<sup>1</sup>, X, R<sup>2</sup>, P<sup>1</sup>, P<sup>3</sup> and R<sup>4</sup> are as define above, and L<sup>2</sup> 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 tetroxide and alkali metal osmium tetroxide (e.g.:K<sub>2</sub>OsO<sub>4</sub>) 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, 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<sub>2</sub>/Pd · C and the like are exemplified.

A reaction temperature is 0 to 100°C, preferably 10 to 30°C.

As a reaction solvent, dimethylformamide, methanol, tetrahydrofuran and the like are exemplified.

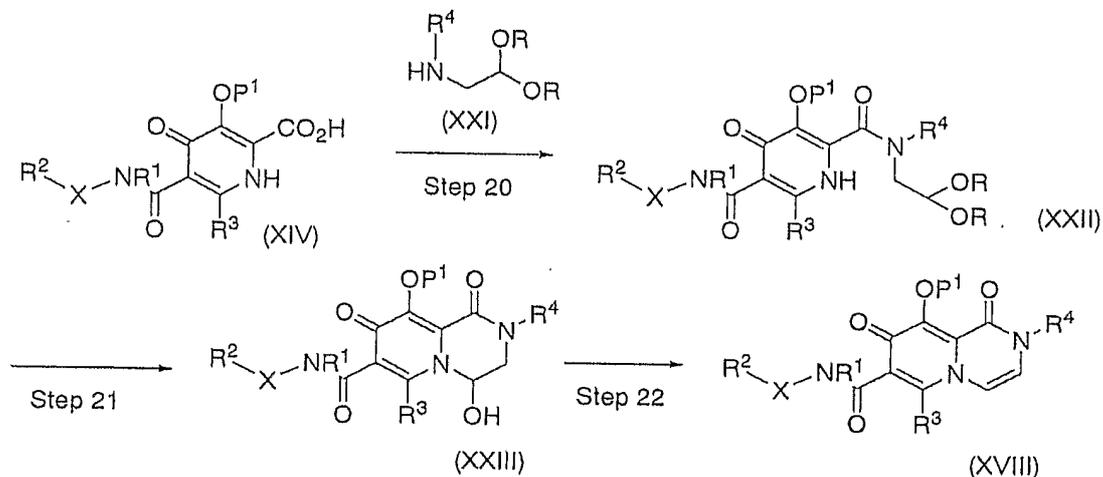
A reaction time is a few minutes to a few tens hours, preferably 5 to 20 hours.

[0015]

(Process 2)

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

synthesize a compound (XXIV). The present reaction may be performed according to the condition for a conventional dehydration reaction.

A reaction temperature is 0 to 100°C, preferably room temperature to 80°C.

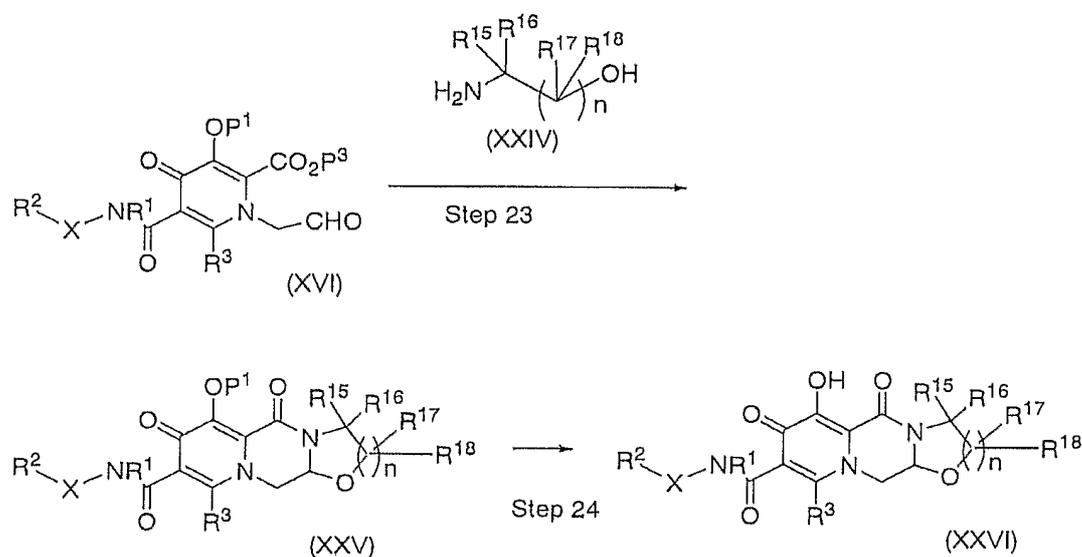
As a reaction solvent, acetonitrile, methylene chloride and the like are exemplified.

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)

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 temperature is 0 to 200°C.

As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.

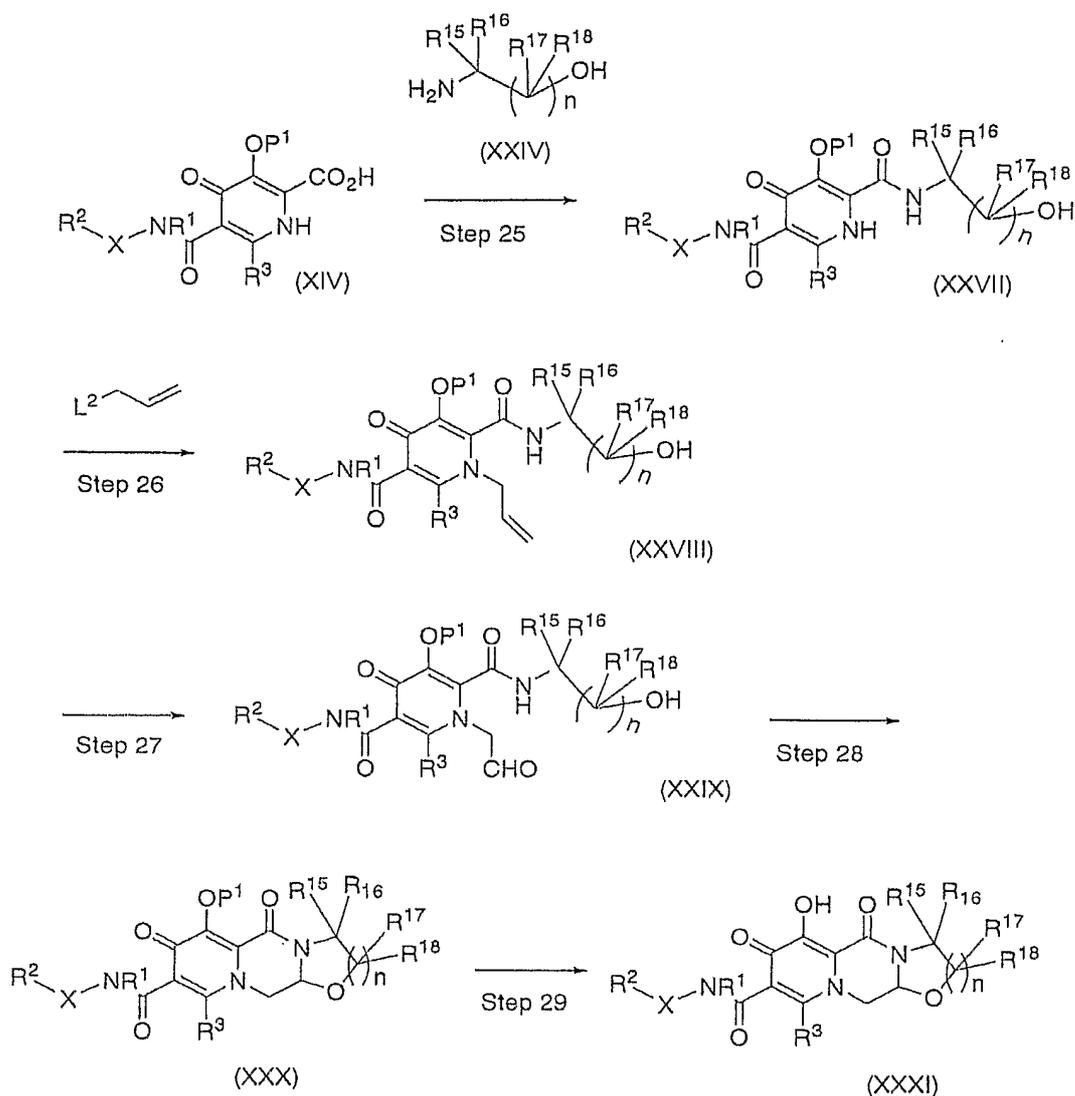
As a reaction solvent, the aforementioned acid and trimethylsilyl iodide are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 hour.

[0017]

(Process 4)

[Chemical formula 45]



(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

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 tetroxide and alkali metal osmium tetroxide (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, preferably 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 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 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.

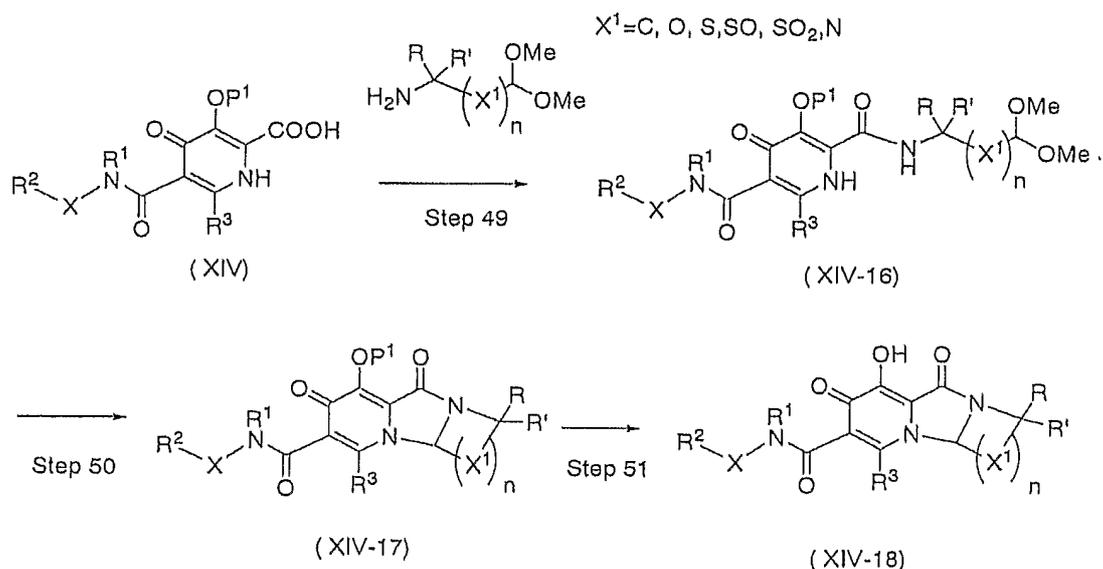
[0018]

(Process 5)

A compound (1-3) in which Z is NR<sup>10</sup> can be synthesized according to the following reaction scheme, according to Process 4.

[Chemical formula 46]





(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.

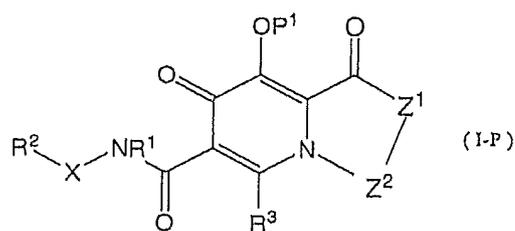
(Fifty-first step)

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)



(P<sup>1</sup> is a hydroxyl-protecting group; the other symbols are as defined above)

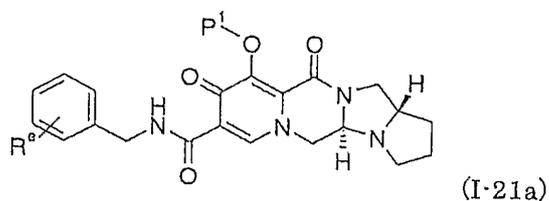
Preferred compounds are shown below. Each P<sup>1</sup> is a hydroxyl-protecting group, such as C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl (e.g., benzyl (=Bn)).



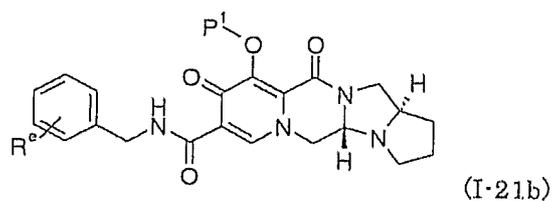
Preferably, wherein R<sup>e</sup> is one or two halogen; R<sup>z</sup> is C<sub>1-8</sub>alkyl, C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl, C<sub>6-14</sub>aryl, or alkoxy; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;



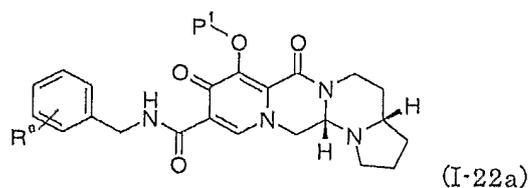
Preferably, wherein R<sup>e</sup> is one or two halogen; R<sup>z</sup> is C<sub>1-8</sub>alkyl, C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl, C<sub>6-14</sub>aryl, or alkoxy; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;



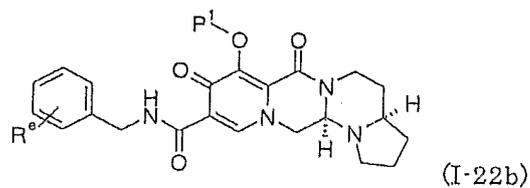
Preferably, wherein R<sup>e</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;



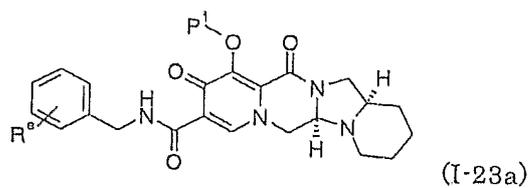
Preferably, wherein R<sup>e</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;



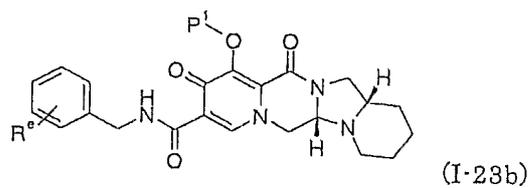
Preferably, wherein R<sup>e</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;



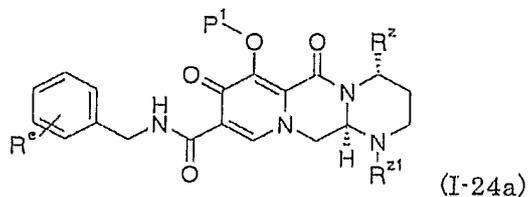
Preferably, wherein R<sup>e</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;



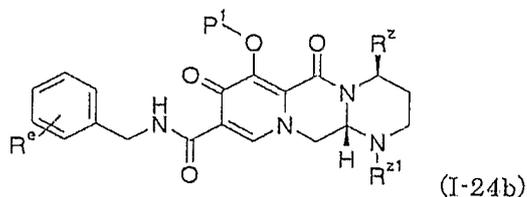
Preferably, wherein R<sup>e</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;



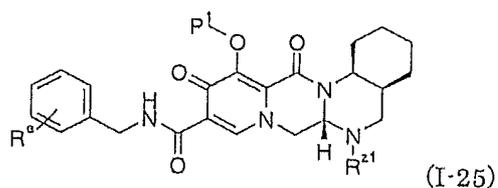
Preferably, wherein R<sup>e</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;



Preferably, wherein  $R^6$  is one or two halogen;  $R^2$  is  $C_{1-8}$ alkyl;  $R^{21}$  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;



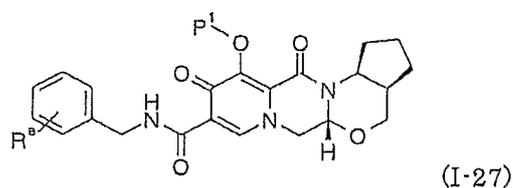
Preferably, wherein  $R^6$  is one or two halogen;  $R^2$  is  $C_{1-8}$ alkyl;  $R^{21}$  is hydrogen,  $C_{3-6}$ cycloalkyl, heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_{3-6}$ cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_{6-14}$ aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_{1-8}$ alkyl or  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;



Preferably, wherein  $R^6$  is one or two halogen;  $R^{21}$  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  $C_{6-14}$ aryl $C_{1-8}$ alkyl;

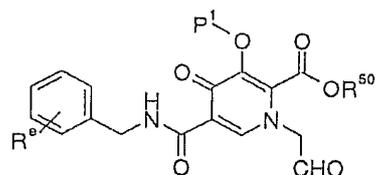


Preferably, wherein R<sup>6</sup> is one or two halogen; R<sup>21</sup> is hydrogen, C<sub>3</sub>-cycloalkyl, heterocycle, or C<sub>1</sub>-8alkyl optionally substituted with hydroxy, C<sub>3</sub>-cycloalkyl, alkoxy, heterocycle, heteroaryl, C<sub>6-14</sub>aryl, or amino, wherein said amino may be optionally substituted with -C(O)C<sub>1</sub>-8alkyl or C<sub>1</sub>-8alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1</sub>-8alkyl;



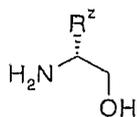
Preferably, wherein R<sup>6</sup> is halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1</sub>-8alkyl;

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:

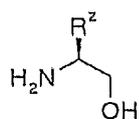


wherein R<sup>6</sup> is one or two halogen; and R<sup>50</sup> is C<sub>1</sub>-8alkyl;

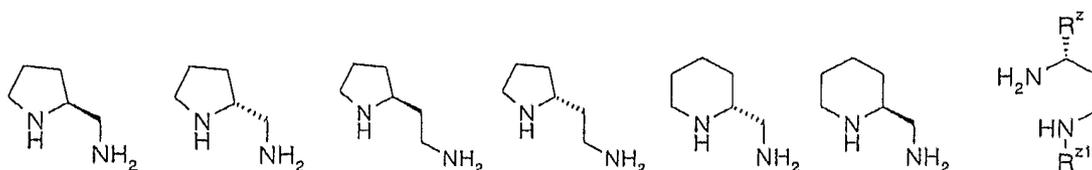
with each amine shown below, respectively:



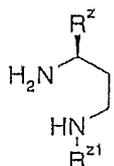
wherein R<sup>Z</sup> is C<sub>1</sub>-8alkyl, C<sub>6-14</sub>arylC<sub>1</sub>-8alkyl, C<sub>6-14</sub>aryl, or alkoxy;



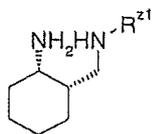
wherein  $R^z$  is  $C_{1-8}$ alkyl,  $C_{6-14}$ aryl $C_{1-8}$ alkyl,  $C_{6-14}$ aryl, or alkoxy;



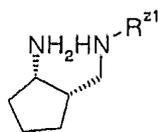
wherein  $R^z$  is  $C_{1-8}$ alkyl;  $R^{z1}$  is hydrogen,  $C_{3-6}$ cycloalkyl, , heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_{3-6}$ cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_{6-14}$ aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_{1-8}$ alkyl or  $C_{1-8}$ alkyl;



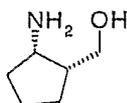
wherein  $R^z$  is  $C_{1-8}$ alkyl;  $R^{z1}$  is hydrogen,  $C_{3-6}$ cycloalkyl, , heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_{3-6}$ cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_{6-14}$ aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_{1-8}$ 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;



wherein  $R^{21}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_{1-8}$ alkyl optionally substituted with hydroxy,  $C_3$ -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 °C, more preferably, 50 to 170°C.

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

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 mechanism such as a reverse transcriptase inhibitor and/or a protease inhibiting agent. Particularly, currently, an integrase inhibitor is not marketed, and it is useful to use in joint use therapy by combining the present compound with a reverse transcriptase inhibitor and/or a protease inhibitor.

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 administered 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 depending on an administration method, an age, a weight and condition of a patient, and a kind of a disease and, usually, in the case of oral administration, about 0.05mg to 3000mg, preferably about 0.1mg to 1000mg may be administered per adult a day, if necessary, by dividing the

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]

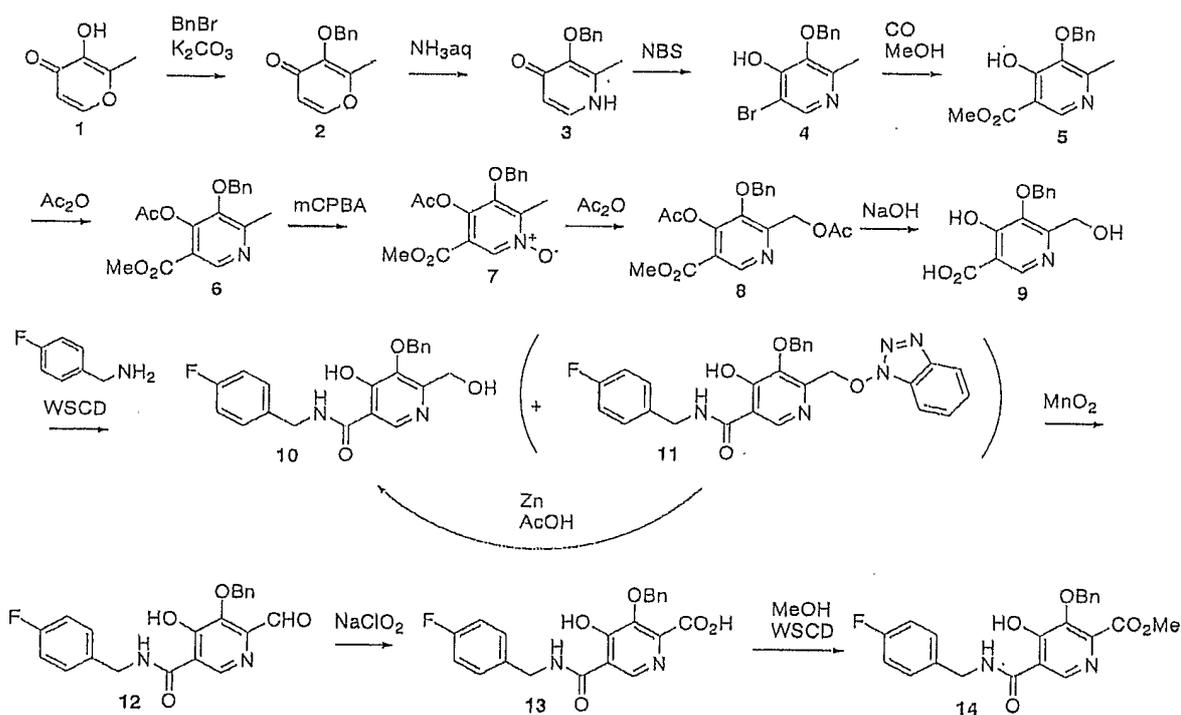
Example A-1)

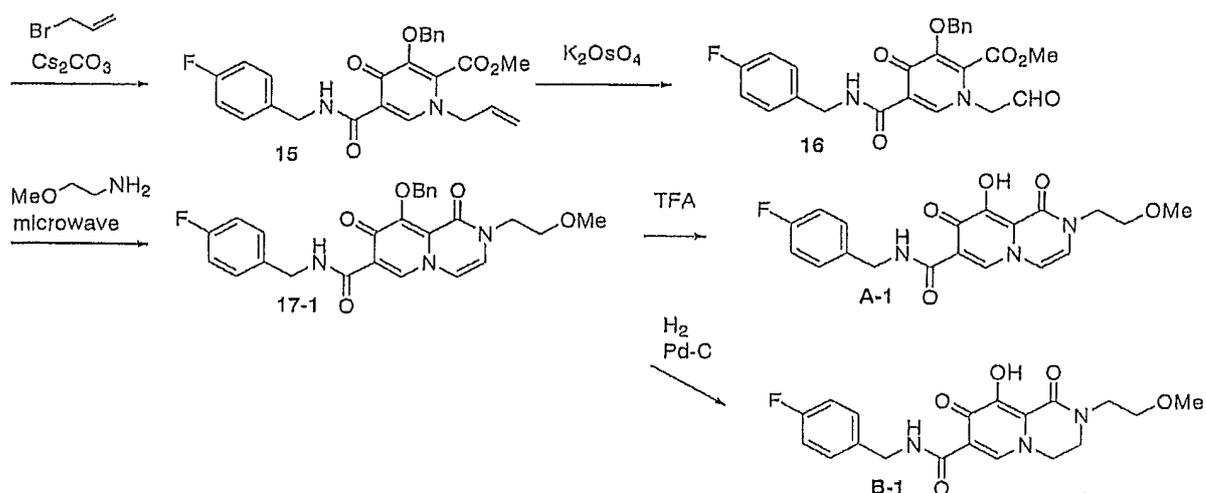
9-Hydroxy-2-(2-methoxy-ethyl)-1,8-dioxo-1,8-dihydro-2H-pyrid[1,2-a]pyrazine-7-carboxylic acid 4-fluoro-benzylamide

Example B-1)

9-Hydroxy-2-(2-methoxy-ethyl)-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrid[1,2-a]pyrazine-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 ( $\text{CDCl}_3$ ) $\delta$ : 2.09(3H, s), 5.15(2H, s), 6.36(1H, d,  $J=5.6\text{Hz}$ ), 7.29-7.41(5H, m), 7.60(1H, d,  $J=5.6\text{Hz}$ ).

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 ( $\text{DMSO-d}_6$ ) $\delta$ : 2.05(3H, s), 5.04(2H, s), 6.14(1H, d,  $J=7.0\text{Hz}$ ), 7.31-7.42(5H, m), 7.46(1H, d,  $J=7.2\text{Hz}$ ), 11.29(1H, brs).

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- $d_6$ ) $\delta$ : 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- $d_6$ ) $\delta$ : 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 $_3$ ) $\delta$ : 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

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<sub>3</sub>) $\delta$ : 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 minutes, and this was stirred for 20 minutes. The solvent 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<sub>3</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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

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 temperature, 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- $d_6$ ) $\delta$ : 4.45(2H, d,  $J=4.3$ Hz), 4.52(2H, d,  $J=5.8$ Hz), 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- $d_6$ ) $\delta$ : 4.53(2H, d,  $J=5.8$ Hz), 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,  $J=5.8$ Hz), 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- $d_6$ ) $\delta$ : 4.52(2H, d,  $J=5.8$ Hz), 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,  $J=4.5$ Hz), 10.44(1H, t,  $J=5.9$ Hz), 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

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- $d_6$ ) $\delta$ : 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<sub>3</sub>)  $\delta$ : 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

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<sub>3</sub>) $\delta$ : 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-methoxyethyl)-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<sub>3</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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

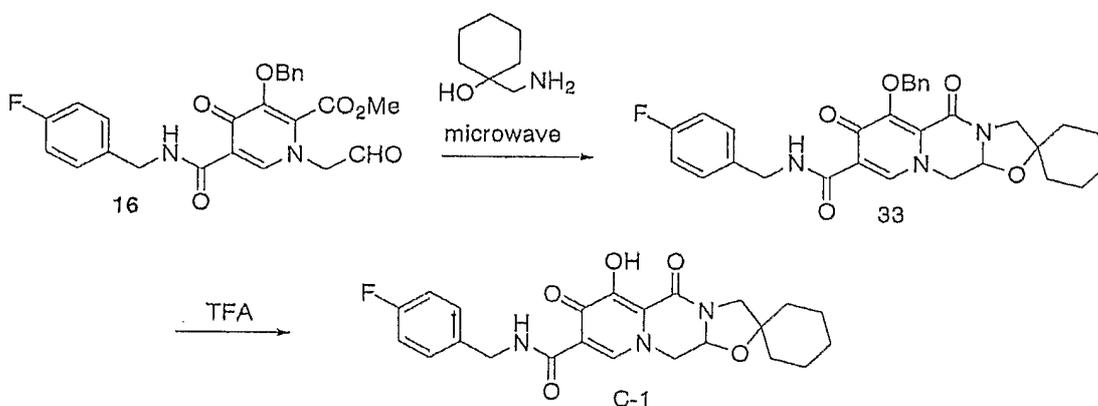
concentrated under reduced pressure. The residue was dissolved in chloroform, this was filtered with Celite again, and the filtrate was concentrated under reduced pressure. The residue was recrystallized with methylene chloride-methanol to obtain Example B-1 (66mg, 52%) as a brown crystal.

melting point: 197-199 °C

NMR (DMSO- $d_6$ ) $\delta$ : 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.  
 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 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

$^1\text{H-NMR}$  (DMSO- $d_6$ ) $\delta$ : 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),

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

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)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-diazacyclopenta[b]naphthalene-7-carboxylic acid 4-fluorobenzylamide

Melting point: 272-274 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)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

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)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-triazacyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 232-234°C

NMR (DMSO-d<sub>6</sub>)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),

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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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-triazacyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 186-187 °C

NMR (DMSO-d<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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- $d_6$ ) $\delta$ : 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]na  
phthalene-3-carboxylic acid 4-fluoro-benzylamide

melting point: 256°C

NMR (DMSO- $d_6$ ) $\delta$ : 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-a  
ntracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 147°C

NMR (DMSO- $d_6$ ) $\delta$ : 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- $d_6$ ) $\delta$ : 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-ant  
hracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 275-277 °C

NMR (DMSO- $d_6$ ) $\delta$ : 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).

## 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<sub>6</sub>) $\delta$ : 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-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid-4-fluoro-benzylamide

melting point: 220 °C

NMR (DMSO-d<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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-Acetyl-amino-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- $d_6$ ) $\delta$ : 1.74(3H, s), 1.49-2.98(9H, m), 3.60(1H, s), 4.25-4.65(7H, m), 7.14(2H, t,  $J=8.4$ Hz), 7.34(2H, m), 7.71(1H, s), 8.26(1H, s), 10.60(1H, s).

## Example C-19)

1-Dimethylcarbamoylmethyl-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- $d_6$ ) $\delta$ : 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,  $J=5.7$ Hz), 4.80(1H, d,  $d=14.4$ Hz), 4.98(1H, s), 7.16(2H, t,  $J=8.4$ Hz), 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- $d_6$ ) $\delta$ : 1.54-1.75(4H, m), 2.80(3H, s), 2.30-3.04(8H, m), 4.45(2H, m), 4.52(2H, d,  $J=5.6$ Hz), 4.75(1H, d,  $J=13.2$ Hz), 6.91(1H, t,  $J=5.6$ Hz), 7.16(2H, t,  $J=8.8$ Hz), 7.36(2H, m), 8.61(1H, s), 10.41(1H, t,  $J=5.6$ Hz), 12.58(1H, s).

## Example C-21)

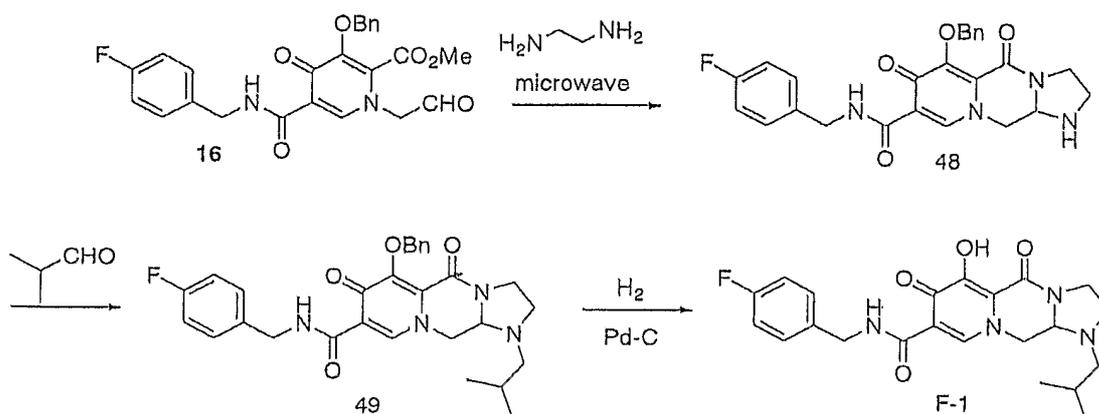
5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-dizazaanthracene-7-carboxylic acid 4-fluorobenzylamide

NMR (CDCl<sub>3</sub>) $\delta$ : 1.27(3H, d,  $J=6.0$ Hz), 1.55-1.78(2H, m), 3.11(1H, td,  $J=12.9, 3.7$ Hz), 3.89-4.00(1H, m), 4.16(1H, dd,  $J=13.8, 3.9$ Hz), 4.34(1H, dd,  $J=13.8, 3.9$ Hz), 4.60(2H, d,  $J=6.0$ Hz), 4.71(1H, ddd,  $J=13.5, 4.8, 1.8$ Hz), 5.08(1H, t,  $J=3.9$ Hz), 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]



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), isobutyraldehyde (39 $\mu$ l, 0.432mmol) and acetic acid (25 $\mu$ l, 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, isobutyraldehyde (20 $\mu$ l) 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 drying, 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%.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 0.96(3H, d,  $J=6.6\text{Hz}$ ), 0.97(3H, d,  $J=6.3\text{Hz}$ ), 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,  $J=9.9, 2.7\text{Hz}$ ), 4.16-4.22(1H, m), 4.57(1H, dd,  $J=15.3, 5.1\text{Hz}$ ), 4.64(1H, dd,  $J=14.7, 5.1\text{Hz}$ ), 5.20(1H, d,  $J=9.9\text{Hz}$ ), 5.38(1H, d,  $J=9.9\text{Hz}$ ), 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).

$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ) $\delta$ : 0.90(3H, d,  $J=6.4\text{Hz}$ ), 0.91(3H, d,  $J=6.0\text{Hz}$ ), 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,  $J=6.0\text{Hz}$ ), 4.94-4.99(1H, m),

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

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)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-triazaanthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 182-184 °C

NMR (DMSO-d<sub>6</sub>)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-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 184-185 °C

NMR (DMSO-d<sub>6</sub>)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<sub>6</sub>)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), 4.83(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).

## 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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).

## 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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-dioxo-3,4,6,9,9a,10-hexahydro-2H-1,4a,8a-triazaanthracene-1-yl]butanoic acid ethyl ester

(CDCl<sub>3</sub>) $\delta$ : 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<sub>3</sub>) $\delta$ : 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), 10.54(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<sub>3</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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-triazanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 242-243°C

(DMSO-d<sub>6</sub>) $\delta$ : 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-triazanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point 214-215°C

(DMSO-d<sub>6</sub>) $\delta$ : 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-triazanthracene-7-carboxylic acid 4-fluorobenzylamide

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PCT/US2006/016604

melting point: 162-164°C

(DMSO-d<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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), 4.40-4.43(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<sub>6</sub>) $\delta$ : 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

melting point: 137-140°C

(DMSO- $d_6$ ) $\delta$ : 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-triazanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 254-256°C

(DMSO- $d_6$ ) $\delta$ : 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-triazacyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide

melting point: 255°C

(DMSO- $d_6$ ) $\delta$ : 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-triazacyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide

melting point: 221-223°C

DMSO- $d_6$ ) $\delta$ : 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-triazacyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide

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melting point: 213°C

DMSO-d<sub>6</sub>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-d<sub>6</sub>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-d<sub>6</sub>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-d<sub>6</sub>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-d<sub>6</sub>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,

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<sub>6</sub>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<sub>6</sub>)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<sub>6</sub>)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), 7.15(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<sub>6</sub>)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).

## 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<sub>6</sub>) $\delta$ : 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), 7.28-4.3(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<sub>6</sub>) $\delta$ : 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), 4.73-4.80(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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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-triazanthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 220°C

NMR (DMSO-d<sub>6</sub>) $\delta$ : 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-triazanthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 151°C

NMR (DMSO-d<sub>6</sub>) $\delta$ : 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-triazanthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 180-182°C

NMR (DMSO-d<sub>6</sub>) $\delta$ : 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)

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- $d_6$ ) $\delta$ : 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- $d_6$ ) $\delta$ : 1.56-1.68(2H, m), 2.54-2.63(1H, m), 2.89-2.99(2H, m), 3.80(2H, dd,  $J=18.4, 33.2$ Hz), 4.37-4.51(3H, m), 4.62(2H, d,  $J=6.0$ Hz), 4.97(1H, d,  $J=15.2$ Hz), 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,  $J=6.0$ Hz), 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- $d_6$ ) $\delta$ : 1.59-1.74(2H, m), 2.76-2.83(1H, m), 2.97-3.08(2H, m), 3.90(1H, d,  $J=16.0$ Hz), 4.36(1H, d,  $J=16.0$ Hz), 4.45-4.69(5H, m), 4.89(1H, d,  $J=14.8$ Hz), 7.18-7.22(1H, m), 7.28-7.31(1H, m), 7.47-7.53(1H, m), 7.54(1H, d,  $J=3.2$ Hz), 7.68(1H, d,  $J=3.2$ Hz), 8.34(1H, s), 10.40(1H, d,  $J=6.0$ Hz), 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- $d_6$ ) $\delta$ : 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,  $J=14.4$ Hz), 4.02(1H, d,  $J=14.8$ Hz), 4.40-4.67(5H, m), 4.85(1H, d,  $J=12.4$ Hz), 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,  $J=6.0$ Hz), 12.58(1H, s).

## 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- $d_6$ ) $\delta$ : 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- $d_6$ ) $\delta$ : 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- $d_6$ ) $\delta$ : 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- $d_6$ ) $\delta$ : 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).

## 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 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<sub>6</sub>) $\delta$ : 0.00-0.10(2H, m), 0.40-0.45(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).

## 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-triazacyclohepta[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

Melting point: 189-190°C

NMR (DMSO- $d_6$ ) $\delta$ : 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-triazacyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide

melting point: 241°C

NMR (DMSO- $d_6$ ) $\delta$ : 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-triazacyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide

melting point: 203°C

NMR (DMSO- $d_6$ ) $\delta$ : 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-triazacyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide

melting point: 182-183°C

NMR (DMSO- $d_6$ ) $\delta$ : 0.00-0.10(2H, m), 0.40-0.45(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).

## 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-tri  
aza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide

melting point: 171-173°C

NMR (DMSO-d<sub>6</sub>) $\delta$ : 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-car  
boxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 276°C

NMR (DMSO-d<sub>6</sub>) $\delta$ : 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-car  
boxylic acid 2,4-difluoro-benzylamide

melting point: 258°C

NMR (DMSO-d<sub>6</sub>) $\delta$ : 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-a  
nthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 193°C

NMR (DMSO-d<sub>6</sub>) $\delta$ : 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).

## 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- $d_6$ ) $\delta$ : 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,  $J=5.2$ Hz), 4.78(1H, d,  $J=13.6$ Hz), 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,  $J=6.0$ Hz), 12.58(1H, s).

## Example F-64)

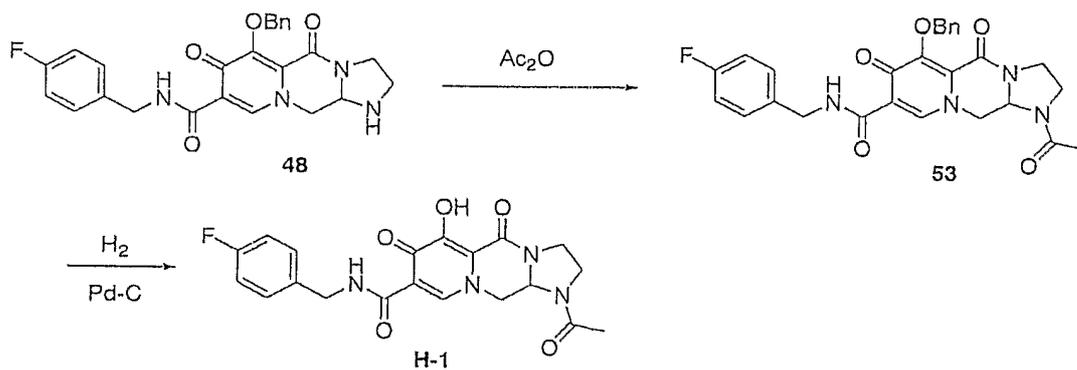
5-Hydroxy-1-(1H-imidazol-4-ylmethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO- $d_6$ ) $\delta$ : 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,  $J=15.2$ Hz), 3.73(1H, d,  $J=15.2$ Hz), 4.34(1H, s), 4.38-4.43(1H, m), 4.47-4.54(3H, m), 5.05(1H, d,  $J=14.0$ Hz), 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,  $J=5.6$ Hz), 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  $\mu$ l, 0.31 mmol), acetic anhydride (29  $\mu$ l, 0.31 mmol), and 4-dimethylaminopyridine (cat.) at room temperature, and the mixture was stirred for 30 minutes. Further, triethylamine (18  $\mu$ l, 0.13 mmol) and acetic anhydride (12  $\mu$ l, 0.13 mmol) were added, and the mixture was stirred for 4 hours. 2N hydrochloric

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- $d_6$ ) $\delta$ : 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

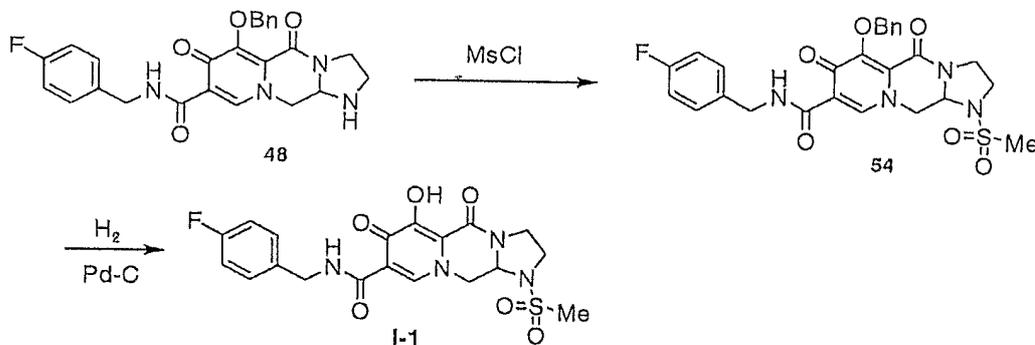
melting point: 290°C

NMR (DMSO- $d_6$ ) $\delta$ : 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<sub>1</sub> (140 mg, 0.30 mmol) in pyridine (1.4 ml) were added methanesulfonyl chloride (28  $\mu$ l, 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*<sub>6</sub>) $\delta$ : 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

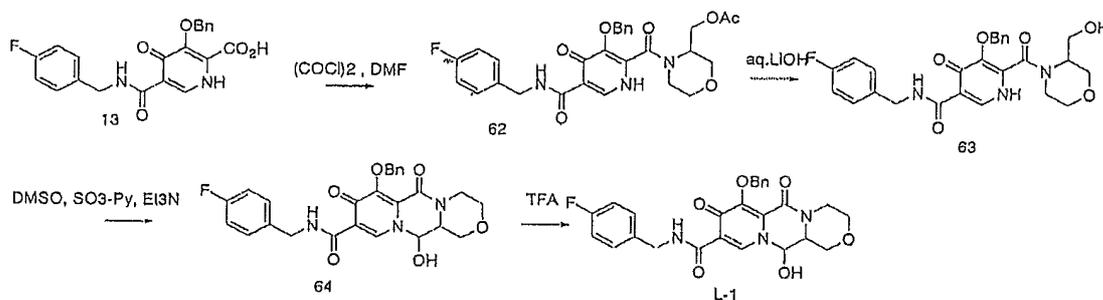
melting point: 257-259°C

NMR (DMSO-*d*<sub>6</sub>) $\delta$ : 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]



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  $\mu$ l, 4.03 mmol), and triethylamine (337  $\mu$ l, 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 %.

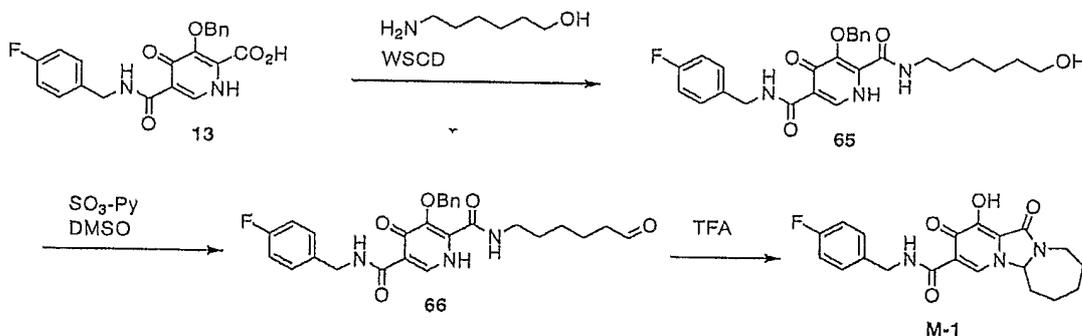
4) Using a compound 64, and according to the method of synthesizing Example A-1, an Example compound L-1 was synthesized.

NMR (DMSO- $d_6$ ) $\delta$ : 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,  $J=8.4$ Hz), 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]

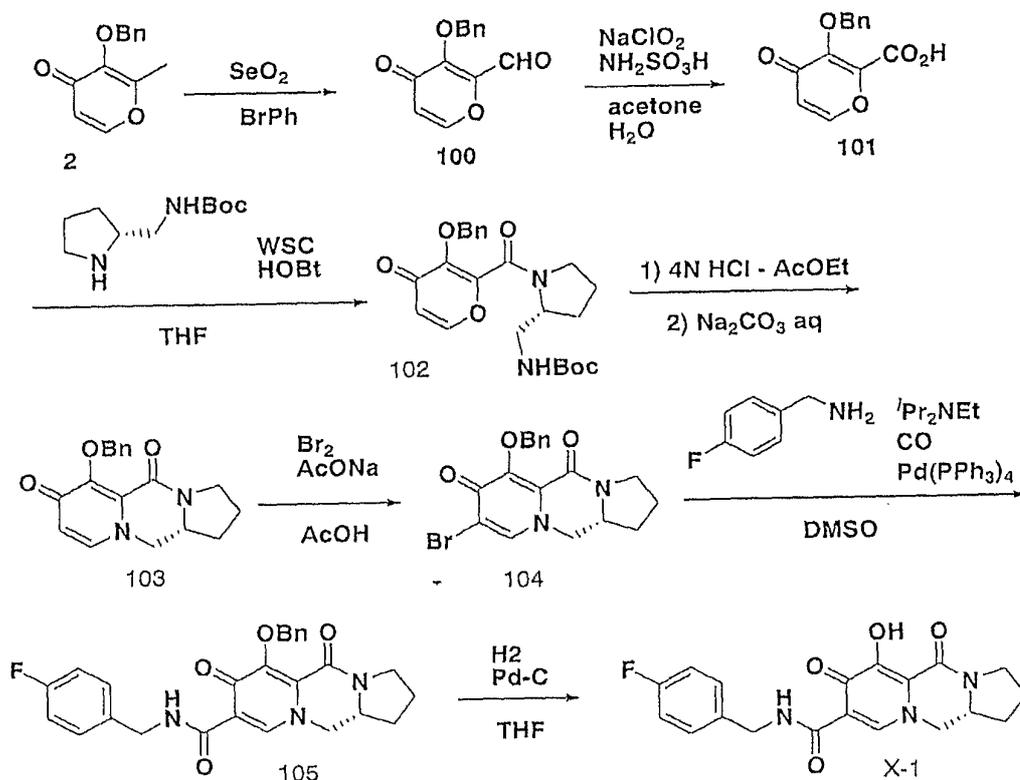


- 1) According to the method of synthesizing a compound 21, a compound 65 (207 mg) was obtained at a yield of 24 % from a compound 13 (250 mg).
- 2) According to the method of synthesizing a compound 64, a compound 66 (313 mg, 67 %) was obtained from a compound 65 (470 mg).
- 3) After trifluoroacetic 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<sub>6</sub>)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]



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  $160^\circ\text{C}$ , 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.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 5.52(1H, s), 6.50(1H, d,  $J=6.0\text{Hz}$ ), 7.36(5H, m), 7.74(1H, d,  $J=6.3\text{Hz}$ ), 9.88(1H, s).

2) Sulfamic acid (1.50g, 15.4mmol) and  $\text{NaClO}_2$  (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.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ) $\delta$ : 5.11(2H, s), 6.55(1H, d,  $J=5.4\text{Hz}$ ), 7.32-7.46(5H, m), 8.21(1H, d,  $J=5.7\text{Hz}$ ).

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 stirring for 16h NaHCO<sub>3</sub> aqueous solution was added to the mixture. The mixture was extracted with EtOAc, which was washed with NH<sub>4</sub>Cl aqueous solution and brine. The organic phase was dried over MgSO<sub>4</sub>. After a filtration the solvent was removed under reduced pressure to obtain compound 102 (694mg, 100%) as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 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 solvent was removed under reduced pressure, diluted with EtOH (16ml) then. A saturated NaHCO<sub>3</sub> aqueous solution was added to the solution to control pH at 9. The mixture was stirred at 50 °C for 2h, then diluted with water. The mixture was extracted with CHCl<sub>3</sub>, washed with brine, and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure to obtain compound 103 (413mg, 68%) as a yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 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<sub>2</sub>Cl<sub>2</sub>, washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure to give compound 104 (390mg, 77%) as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 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 padium (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<sub>4</sub>Cl aqueous solution, extracted with EtOAc then. And the organic phase was washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. The precipitate was purified by silicagel column chromatography, and fractions eluting with MeOH/EtOAc were concentrated

under reduced pressure to obtain compound 105 (115mg, 75%) as a white oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 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 filtration the solvent was removed under reduced pressure to give the example X-1 (57mg, 64%) as a white solid.

Melting point: 274°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) $\delta$ : 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

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) $\delta$ : 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

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) $\delta$ : 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

Melting point: 259°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)δ: 1.33-1.79(6H, m), 2.51(1H, m), 3.88(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-diaz a-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-diaz a-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)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-diaz a-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-diaz a-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)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-diaz a-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

,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 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]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) $\delta$ : 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

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) $\delta$ : 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

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 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

aza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) $\delta$ : 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

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) $\delta$ : 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

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) $\delta$ : 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

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) $\delta$ : 1.15(3H, d, J=6.0Hz), 1.35-1.50(1H, m), 1.75(1H, d, J=12.9Hz),

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).

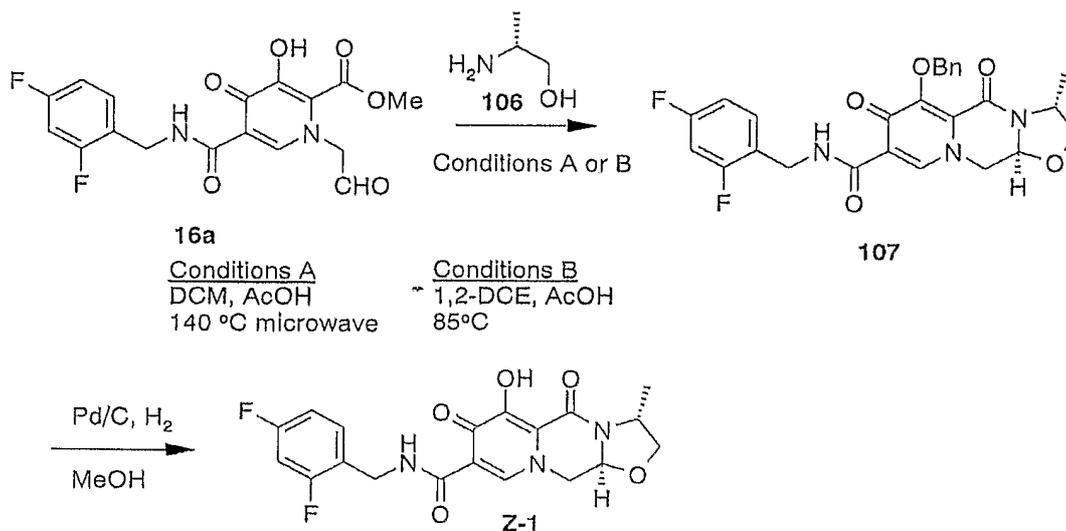
3-Amino-butan-1-ol were prepared according to the method of P. Besse (*Tetrahedron Asymmetry* 10(1999) 2213-2224).

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.

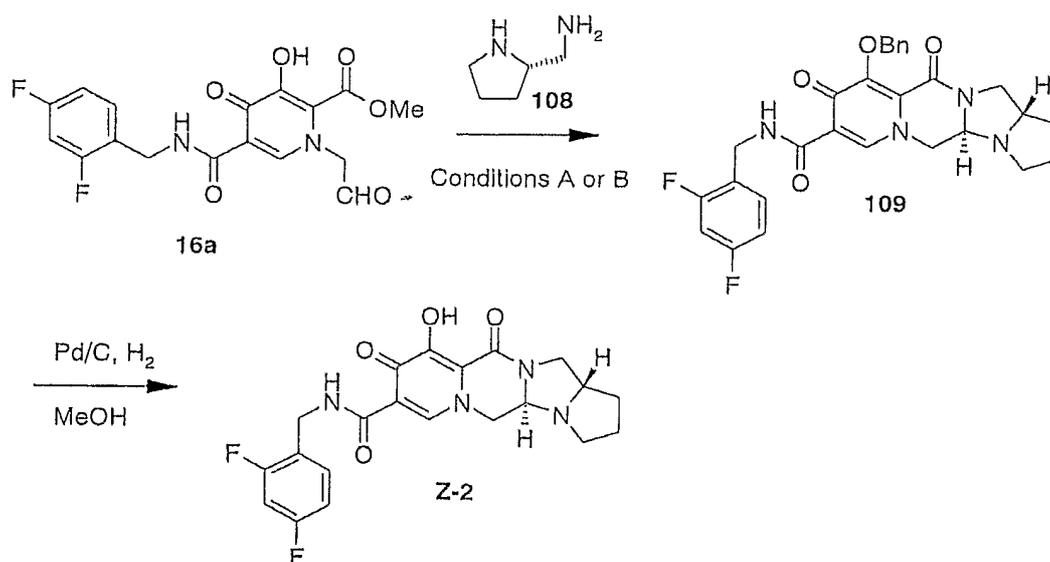
All examples below consist of >95% ee and >6:1 diastereomeric purity unless indicated otherwise. The compounds shown in table ZZ consist of mixtures of diastereomers at the depicted stereocenter in ratios of 1:1 to >10:1. Stereocenters that were formed during the process' below have been assigned using 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

to perform similar transformations and arriving at the same compounds of the general formula or amino alcohol and diamine precursors.

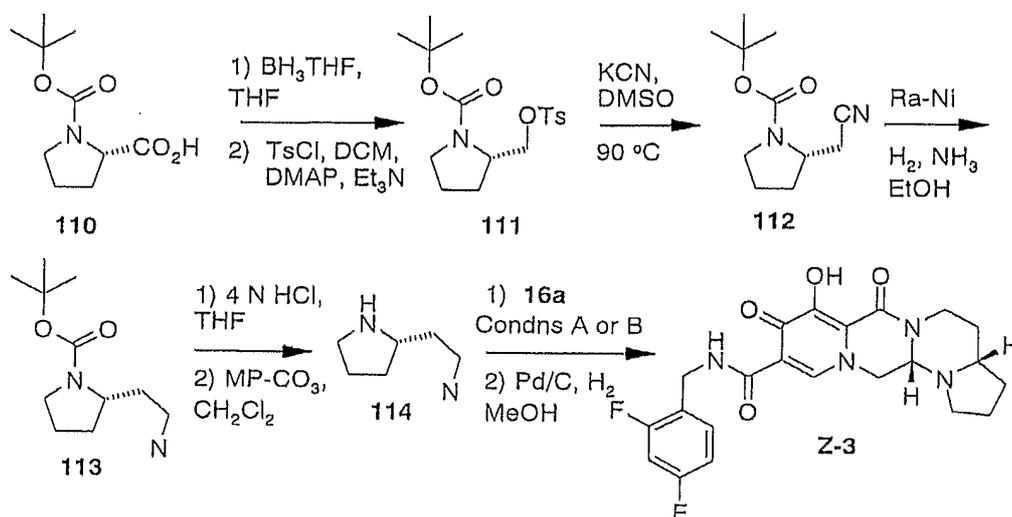
[Chemical formula 68]



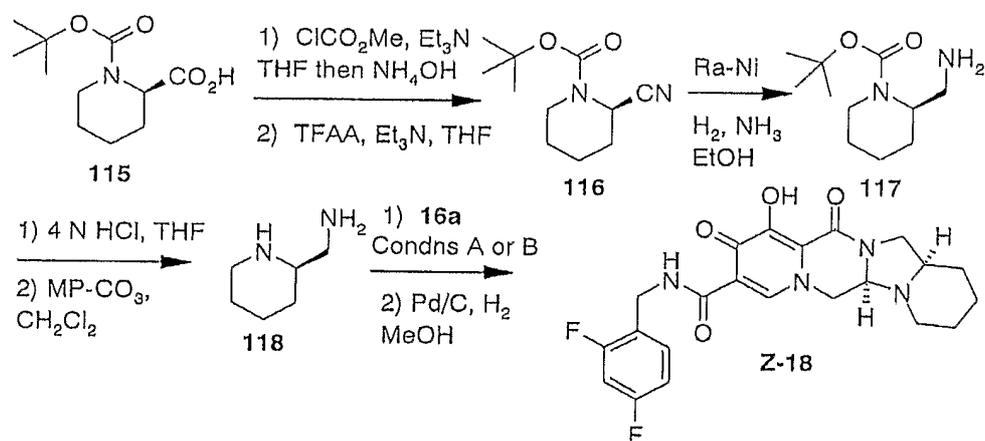
[Chemical formula 69]



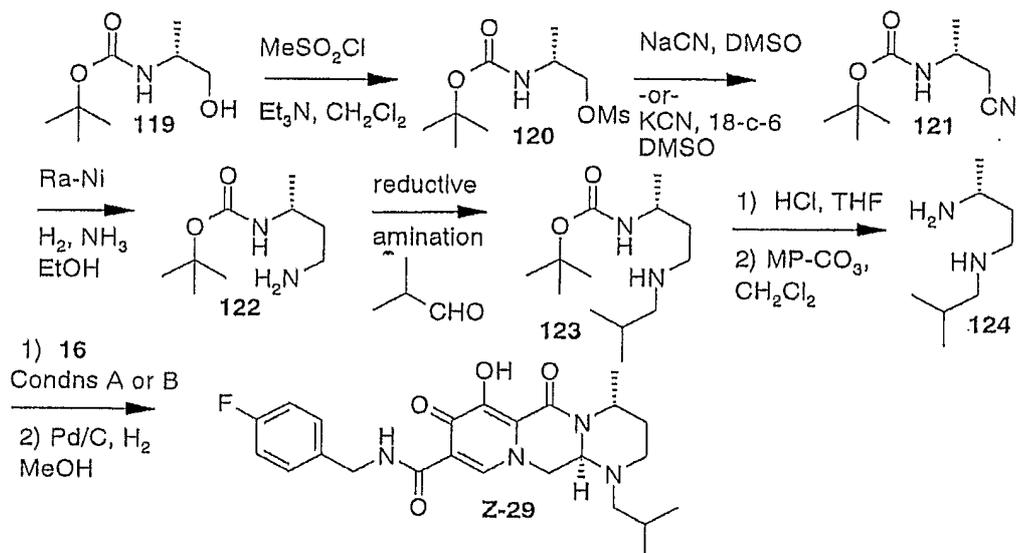
[Chemical formula 70]



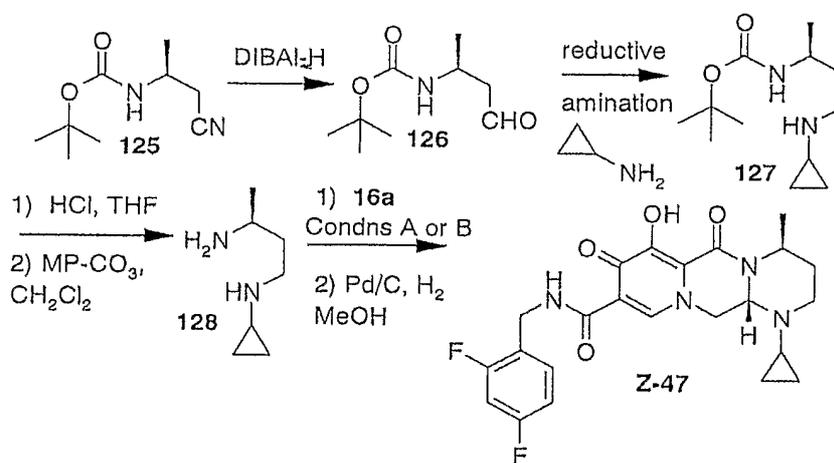
[Chemical formula 71]



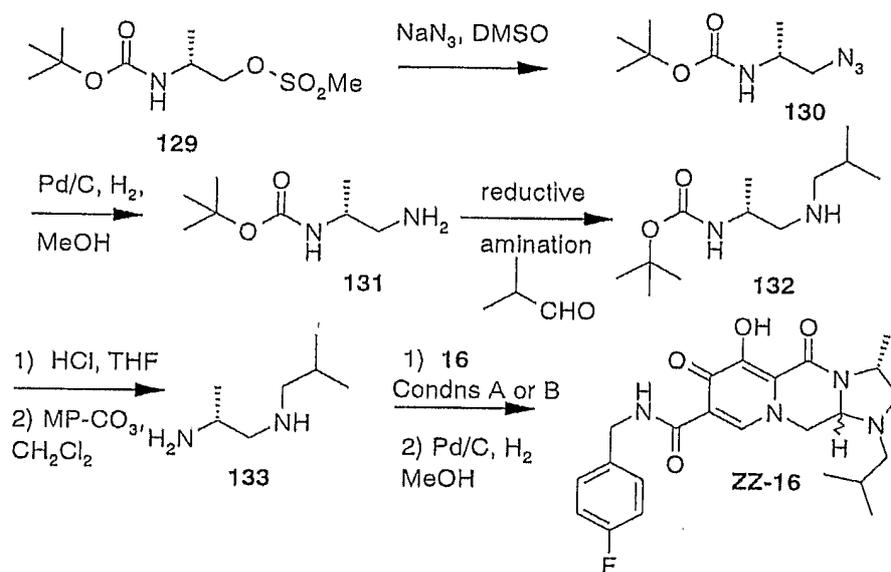
[Chemical formula 72]



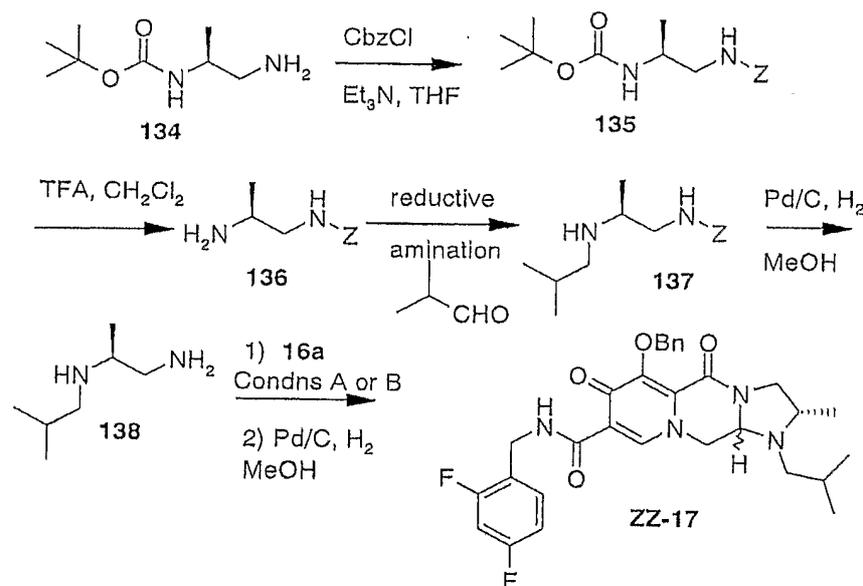
[Chemical formula 73]



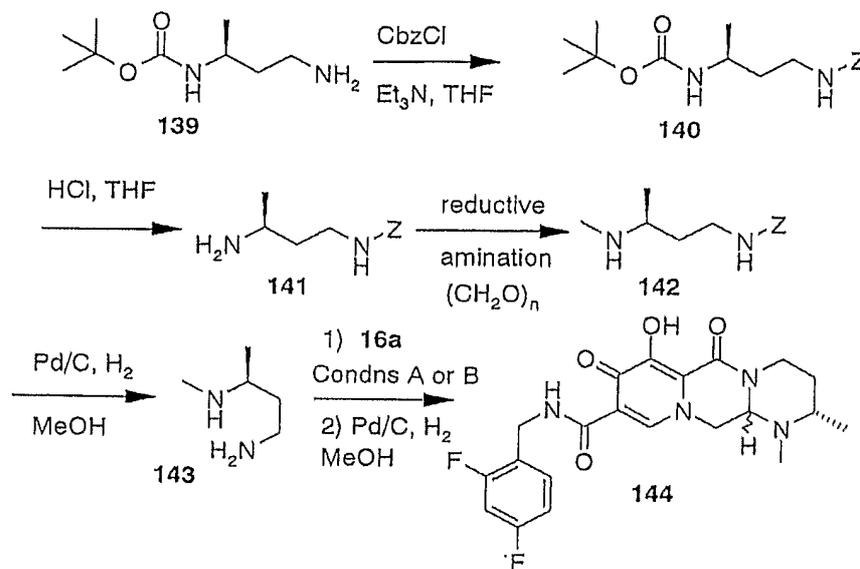
[Chemical formula 74]



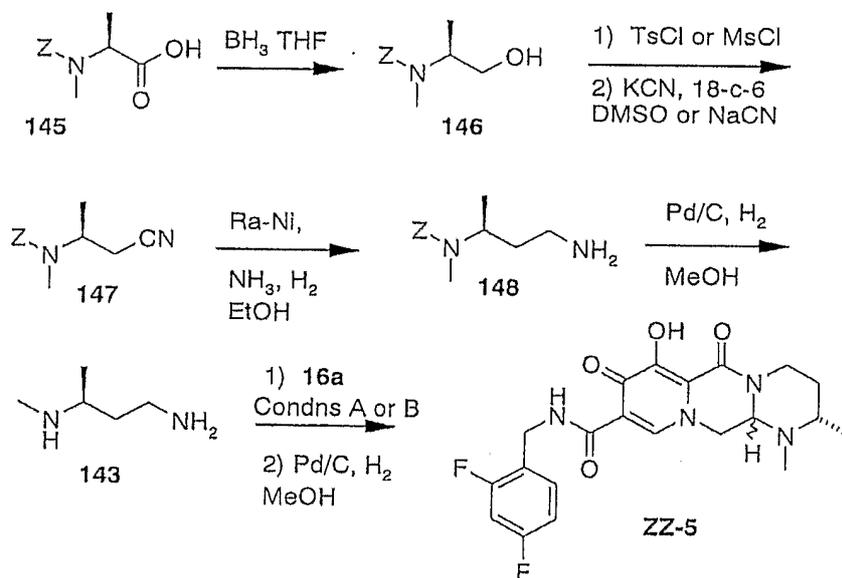
[Chemical formula 74]



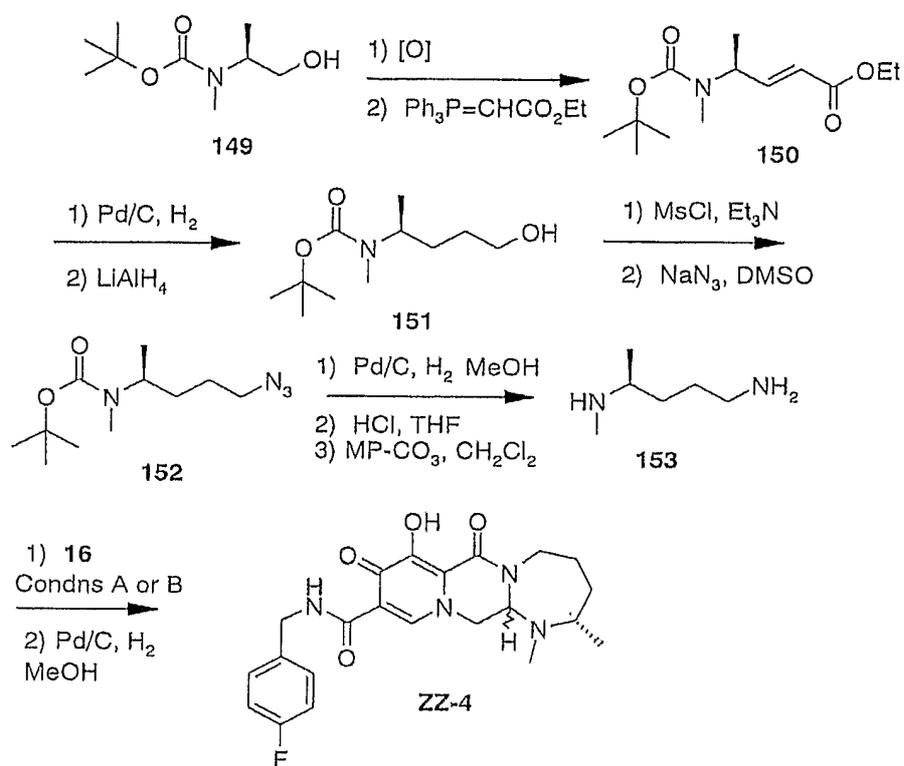
[Chemical formula 75]



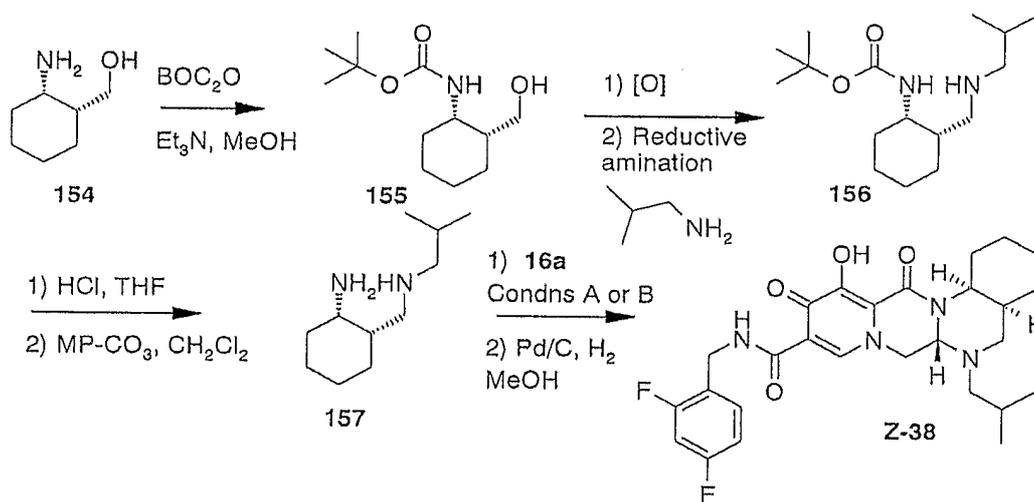
[Chemical formula 76]



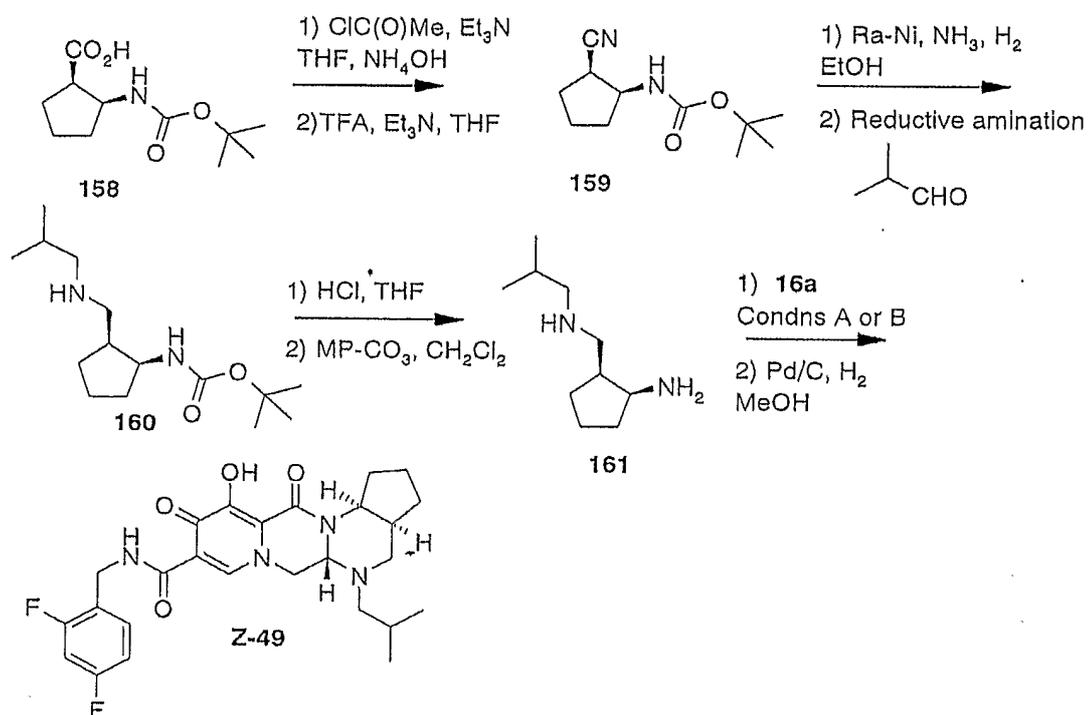
[Chemical formula 77]



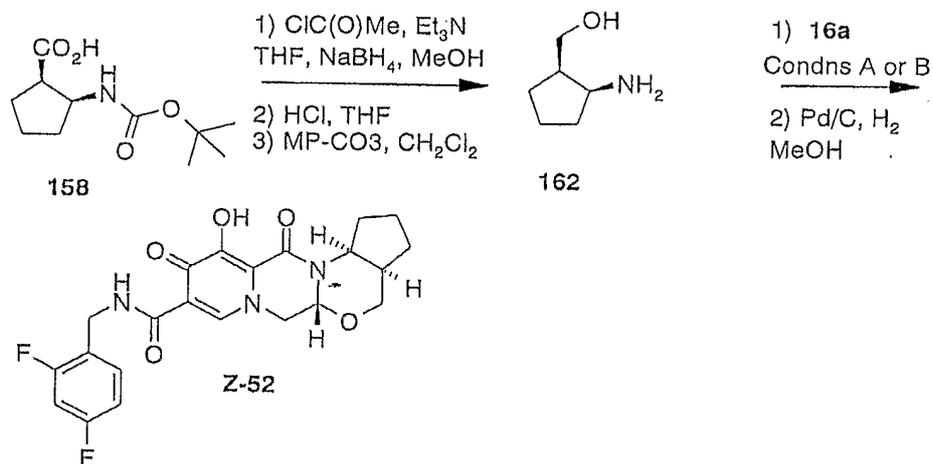
[Chemical formula 78]



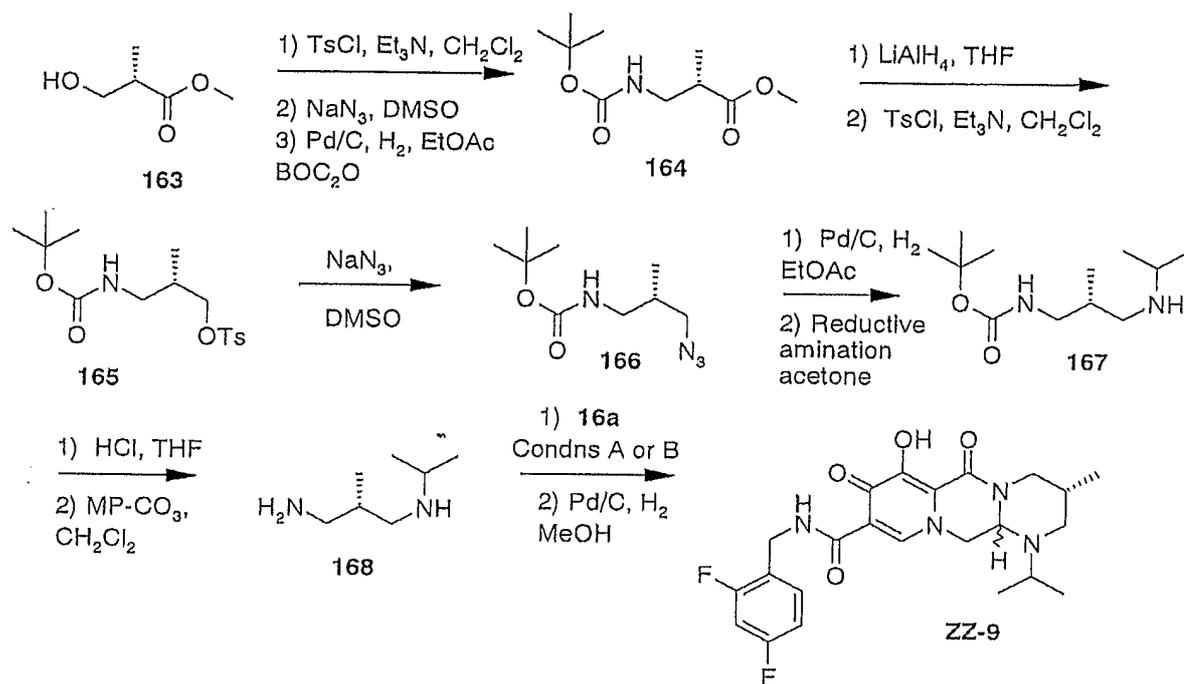
[Chemical formula 79]



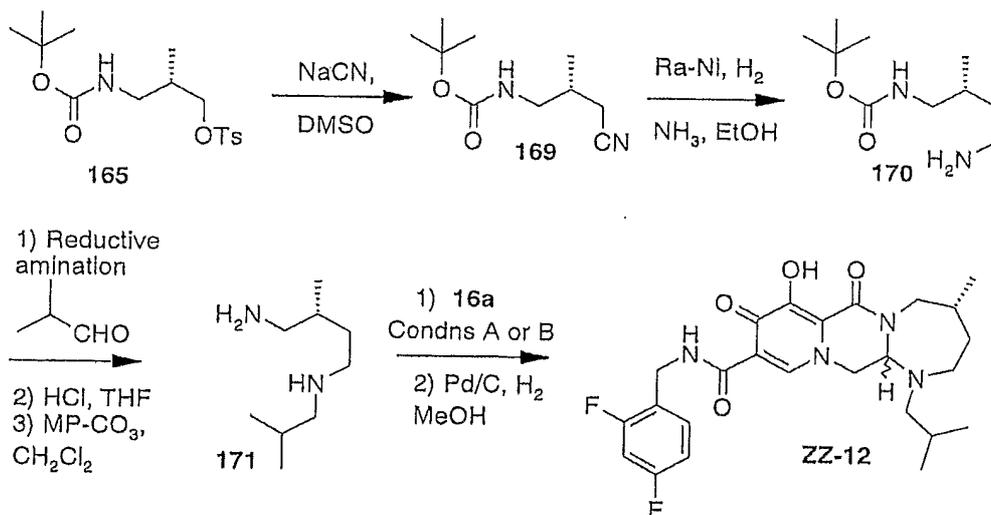
[Chemical formula 80]



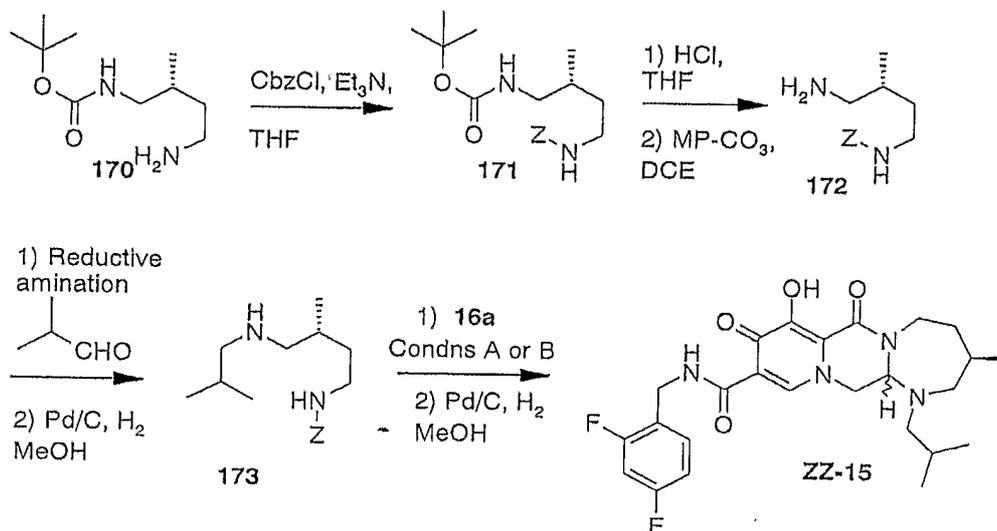
[Chemical formula 81]



[Chemical formula 82]



[Chemical formula 83]

Example Z-1:

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt.



a)

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-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

(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<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> gradient elution) to give (3*R*,11*aS*)-*N*[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (396 mg, 92%) as a glass. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sup>+</sup> MS: 496 (M+1).

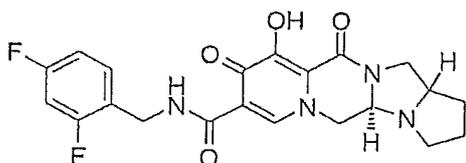
b)

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt. To a solution of (3*R*,11*aS*)-*N*[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-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*,11*aS*)-*N*[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-

hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide as a pink tinted white solid (278 mg, 86%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sup>+</sup> 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%)\*. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) 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:

(4*aR*,13*aS*)-*N*[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4*a*,5,9,11,13,13*a*-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide.



a)

(4*aR*,13*aS*)-*N*[(2,4-Difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4*a*,5,9,11,13,13*a*-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

°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<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sup>+</sup> MS: 521 (M+1).

b)

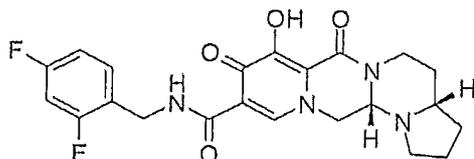
(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide.

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. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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),

3.16-3.08 (m, 2 H), 2.83 (m, 1 H), 2.11-1.65 (m, 4 H); ES<sup>+</sup> 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<sub>3</sub>-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<sub>2</sub>SO<sub>4</sub>, 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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

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  $\text{Na}_2\text{SO}_4$ , 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.  $^1\text{H}$  NMR exists as rotomers ( $\text{CDCl}_3$ )  $\delta$  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  $\text{Na}_2\text{SO}_4$ , filtered and concentrated followed by flash chromatography purification to give *N*-BOC-(2*S*)-2-cyano-1-pyrrolidine (179 mg, 66%) as an oil.  $^1\text{H}$  NMR exists as rotomers ( $\text{CDCl}_3$ )  $\delta$  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-

(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<sub>2</sub> overnight. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (10% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> with 1% NH<sub>4</sub>OH 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. <sup>1</sup>H NMR exists as rotomers (CDCl<sub>3</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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)

(3*aS*,13*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3*a*,4,5,7,9,13,13*a*-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carb

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<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> 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-*c*]pyrimidine-10-carboxamide. (25 mg, 74%) as a film. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sup>+</sup> MS: 535 (M+1).

g)

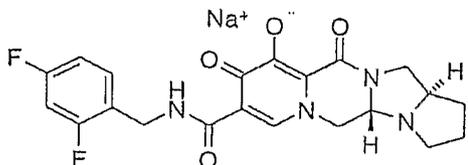
(3a*S*,13a*S*)-*N*[(2,4-Difluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide.

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-*c*]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

white solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  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);  $\text{ES}^+$  MS: 445 ( $\text{M}+1$ ).

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.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  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

,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 16a (435 mg, 0.98 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 (4*aS*,13*aR*)-*N*[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4*a*,5,9,11,13,13*a*-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (321 mg, 67%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sup>+</sup> MS: 521 (M+1).

c)

(4*aS*,13*aR*)-*N*[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4*a*,5,9,11,13,13*a*-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 (4*aS*,13*aR*)-*N*[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4*a*,5,9,11,13,13*a*-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (518 mg, 0.99 mmol) and ~10% Pd/C (35 mg) in methanol (40 mL) was obtained (4*aS*,13*aR*)-*N*[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4*a*,5,9,11,13,13*a*-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. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.73 (m, 1 H), 10.36 (m, 1 H),

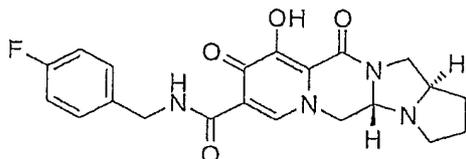
8.32 (s, 1 H), 7.35 (m, 1 H), 6.79 (m, 2 H), 4.64 (m, 2 H), 4.54 (dd,  $J = 10.8, 4.0$  Hz, 1 H), 4.28-4.19 (m, 2 H), 3.90-3.79 (m, 2 H), 3.18-3.10 (m, 2 H), 2.84 (m, 1 H), 2.14-1.92 (m, 3 H), 1.72 (m, 1 H).

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.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ )  $\delta$  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, 1 H), 1.90 (m, 2 H), 1.73 (m, 1 H), 1.60 (m, 1 H).  $\text{ES}^+$  MS: 431 ( $\text{M}+1$ ).

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.

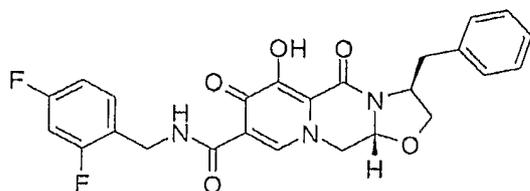


The title compound was made in two steps using a similar process to that described

in example Z-2. 16 (60 mg, 0.13 mmol) and [(2*R*)-2-pyrrolidinylmethyl]amine (100 mg, 1.0 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*aS*,13*aR*)-*N*[(4-fluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4*a*,5,9,11,13,13*a*-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (60 mg, 91%). This material was hydrogenated in a second step as described in example Z-2 to give (4*aS*,13*aR*)-*N*[(4-fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4*a*,5,9,11,13,13*a*-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (21 mg, 42%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.72 (m, 1 H), 1.37 (m, 1 H), 8.33 (s, 1 H), 7.29 (m, 2 H), 6.97 (m, 2 H), 4.57 (m, 2 H), 4.52 (m, 1 H), 4.24-4.19 (m, 2 H), 3.87-3.76 (m, 2 H), 3.14-3.07 (m, 2 H), 2.82 (m, 1 H), 2.11-1.89 (m, 3 H), 1.68 (m, 1 H); ES<sup>+</sup> MS: 413 (M+1).

Example Z-6:

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

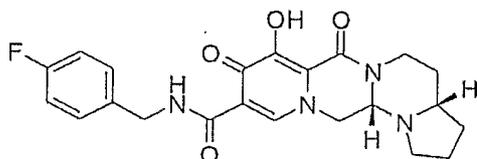


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (37 mg, 0.08 mmol) and (2*S*)-2-amino-3-phenyl-1-propanol (35 mg, 0.24 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11*aR*)-*N*[(2,4-difluorophenyl)methyl]-5,7-dioxo-3-(phenylmethyl)-6-[(phenylmethyl)

loxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (41 mg, 91%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11*aR*)-*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. (25 mg, 75%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.47 (br, 1 H), 10.28 (m, 1 H), 8.35 (m, 1 H), 7.37-7.26 (m, 4 H), 7.18 (m, 2 H), 6.79 (m, 2 H), 5.03 (m, 1 H), 4.64-4.61 (m, 3 H), 4.40 (m, 1 H), 4.23 (apparent t, *J* = 7.2 Hz, 1 H), 3.96 (dd, *J* = 8.8, 6.4 Hz, 1 H), 3.88 (apparent t, *J* = 11.2 Hz, 1 H), 3.37 (dd, *J* = 13.6, 3.2 Hz, 1 H), 2.99 (dd, *J* = 13.2, 8.8 Hz, 1 H); ES<sup>+</sup> MS: 482 (M+1).

Example Z-7:

(3*aS*,13*aS*)-*N*'-[(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3*a*,4,5,7,9,13,13*a*-decahydro[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide.

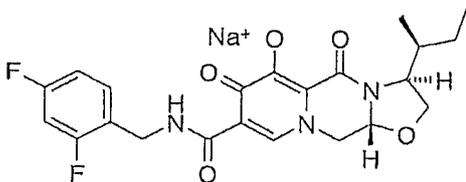


The title compound was made in two steps using a similar process to that described in example Z-2. 16 (84 mg, 0.13 mmol) and {2-[(2*S*)-2-Pyrrolidinyl]ethyl}amine (150 mg, 1.3 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*aS*,13*aS*)-*N*'-[(4-fluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3*a*,4,5,7,9,13,13*a*-decahydro[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide (86 mg, 90%). This material was hydrogenated in a second step as described in

example Z-2 to give (3*aS*,13*aS*)-*N*[(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3*a*,4,5,7,9,13,13*a*-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide. (63 mg, 88%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 10.45 (m, 1 H), 8.23 (s, 1 H), 7.35 (m, 2 H), 6.94 (t, *J* = 8.8 Hz, 2 H), 4.63 (m, 1 H), 4.58-4.48 (m, 2 H), 4.33 (dd, *J* = 13.6, 3.6 Hz, 1 H), 4.21 (m, 1 H), 4.11 (m, 1 H), 2.98 (m, 1 H), 2.85 (td, *J* = 13.2, 3.2 Hz, 1 H), 2.41 (m, 1 H), 2.29 (m, 1 H), 1.92 (m, 1 H), 1.83-1.75 (m, 3 H), 1.54-1.35 (m, 2 H); ES<sup>+</sup> MS: 427 (M+1).

Example Z-8:

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt.



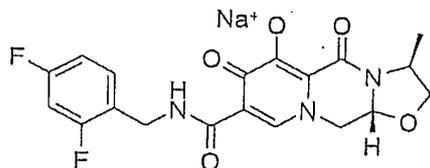
The title compound was made in two steps using a similar process to that described in example Z-1. 16a (417 mg, 0.89 mmol) and L-isoleucinol (259 mg, 2.21 mmol) were reacted in 1,2-dichloroethane (40 mL) with acetic acid to give (3*S*,11*aR*)-*N*[(2,4-difluorophenyl)methyl]-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (426 mg, 90%). This material was hydrogenated in a second step as described in example Z-1 to give

(3*S*,11*aR*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

(376 mg, 99%) as a coarse white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.43 (br, 1 H), 10.27 (br, 1 H), 8.32 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.26 (dd, *J* = 9.6, 4.0 Hz, 1 H), 4.62 (m, 2 H), 4.42-4.35 (m, 2 H), 4.19 (dd, *J* = 8.8, 7.2 Hz, 1 H), 4.01 (dd, *J* = 8.8, 5.6 Hz, 1 H), 3.86 (dd, *J* = 12.0, 10.0 Hz, 1 H), 2.27 (m, 1 H), 1.40 (m, 1 H), 1.15 (m, 1 H), 0.97 (t, *J* = 7.2 Hz, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H); ES<sup>+</sup> MS: 448 (M+1). This material (360 mg, 0.81 mmol) was treated with sodium hydroxide (0.81 mL, 1.0 M, 0.81 mmol) in ethanol (15 mL) as described in example Z-1 to provide its corresponding sodium salt (384 mg, 99%) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.82 (m, 1 H), 7.80 (m, 1 H), 7.33 (m, 1 H), 7.18 (m, 1 H), 7.00 (m, 1 H), 5.14 (m, 1 H), 4.47 (d, *J* = 5.6 Hz, 2 H), 4.31 (m, 1 H), 4.18 (m, 1 H), 3.96 (m, 1 H), 3.84 (m, 1 H), 3.71 (m, 1 H), 3.40 (m, 1 H), 1.88 (m, 1 H), 1.36 (m, 1 H), 1.04 (m, 1 H), 0.85 (t, *J* = 7.2 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H); ES<sup>+</sup> MS: 448 (M+1).

Example Z-9:

(3*S*,11*aR*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt.

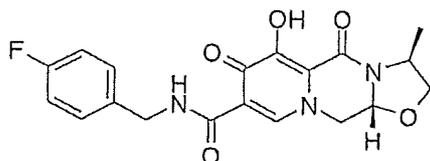


The title compound was made in two steps using a similar process to that described in example Z-1. 16a (510 mg, 1.08 mmol) and (2*S*)-2-amino-1-propanol (0.17 mL,

2.17 mmol) were reacted in 1,2-dichloroethane (20 mL) with acetic acid to give (3*S*,11*aR*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (500 mg, 93%). This material was hydrogenated in a second step as described in example Z-1 to give (3*S*,11*aR*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (386 mg, 94%) as a tinted white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.46 (m, 1 H), 10.28 (m, 1 H), 8.32 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 5.30 (dd, *J* = 10.0, 4.0 Hz, 1 H), 4.63 (m, 2 H), 4.48-4.37 (m, 3 H), 3.91 (dd, *J* = 12.0, 10.0 Hz, 1 H), 3.73 (m, 1 H), 1.48 (d, *J* = 6.0 Hz, 3 H); ES<sup>+</sup> MS: 406 (M+1). This material (385 mg, 0.95 mmol) was treated with sodium hydroxide (0.95 mL, 1.0 M, 0.95 mmol) in ethanol (15 mL) as described in example Z-1 to provide its corresponding sodium salt (381 mg, 94%) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.66 (m, 1 H), 7.93 (s, 1 H), 7.33 (m, 1 H), 7.20 (m, 1 H), 7.01 (m, 1 H), 5.19 (m, 1 H), 4.59 (m, 1 H), 4.48 (m, 2 H), 4.22 (m, 2 H), 3.75 (m, 1 H), 3.57 (m, 1 H), 1.24 (d, *J* = 5.6 Hz, 3 H).

Example Z-10:

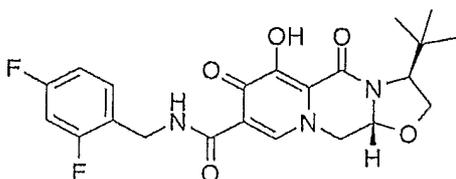
(3*S*,11*aR*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16 (100 mg, 0.22 mmol) and (2*S*)-2-amino-1-propanol (0.10 mL, 1.28 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11*a**R*)-*N*-[(4-fluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (100 mg, 95%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11*a**R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (80 mg, 99%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.43 (br, 1 H), 10.28 (br, 1 H), 8.35 (s, 1 H), 7.28 (m, 2 H), 6.97 (m, 2 H), 5.29 (m, 1 H), 4.55-4.38 (m, 5 H), 3.89 (apparent t, *J* = 10.8 Hz, 1 H), 3.70 (m, 1 H), 1.45 (d, *J* = 5.6 Hz, 3 H); ES-MS: 386 (M-1).

Example Z-11:

(3*S*,11*a**R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

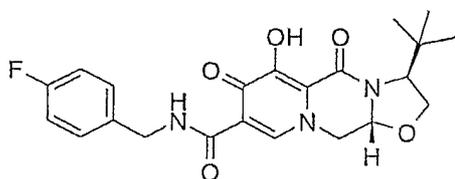


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (41 mg, 0.09 mmol) and freebased *L*-tert-leucinol (59 mg, 0.50 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11*a**R*)-*N*-[(2,4-difluorophenyl)methyl]-3-(1,1-dimethylethyl)-5,7-dioxo-6-[(phenylm

ethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 86%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11*aR*)-*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 (33 mg, 99%) as a tinted white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.29 (s, 1 H), 8.37 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 5.43 (m, 1 H), 4.62 (m, 2 H), 4.36 (m, 2 H), 4.21 (m, 1 H), 3.99 (s, 1 H), 3.81 (m, 1 H), 1.03 (s, 9 H); ES<sup>+</sup> MS: 448 (M+1).

Example Z-12:

(3*S*,11*aR*)-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.

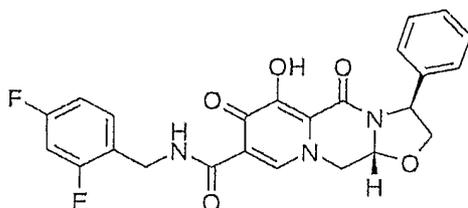


The title compound was made in two steps using a similar process to that described in example Z-2. 16 (41 mg, 0.09 mmol) and freebased *L-tert*-leucinol (59 mg, 0.50 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11*aR*)-3-(1,1-dimethylethyl)-*N*'[(4-fluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 85%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11*aR*)-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 (32 mg, 97%) as a tinted white solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  11.15 (br, 1 H), 10.32 (s, 1 H), 8.38 (s, 1 H), 7.29 (m, 2 H), 6.98 (m, 2 H), 5.43 (m, 1 H), 4.58 (m, 2 H), 4.36 (m, 2 H), 4.21 (m, 1 H), 3.99 (, 1 H), 3.79 (m, 1 H), 1.02 (s, 9 H);  $\text{ES}^+$  MS: 430 ( $\text{M}+1$ ).

Example Z-13:

(3*S*,11*aR*)-*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.

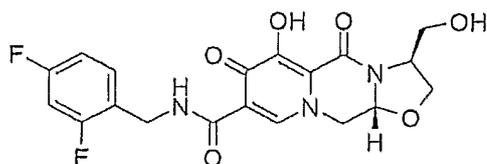


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (33 mg, 0.07 mmol) and L-phenylglycinol (19 mg, 0.14 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11*aR*)-*N*[(4-fluorophenyl)methyl]-5,7-dioxo-3-phenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (37 mg, 95%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11*aR*)-*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 (33 mg, 99%) as a tinted white solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  11.23 (br, 1 H), 10.27 (s, 1 H), 8.39 (s, 1 H), 7.43-7.32 (m, 6 H), 6.80 (m, 2 H), 5.58 (d,  $J = 6.8$  Hz, 1 H), 5.37 (apparent t,  $J = 6.8$  Hz, 1 H), 4.67-4.62 (m, 3 H), 4.54 (d,  $J = 10.4$  Hz, 1 H), 4.11 (m, 1 H), 4.01 (m, 1 H);  $\text{ES}^+$

MS: 468 (M+1).

Example Z-14:

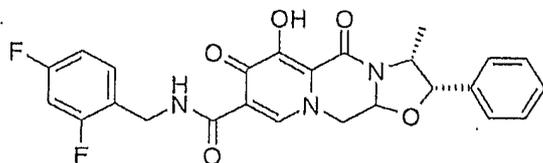
(3*S*,11*a*,*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.10 mmol) and (2*R*)-2-amino-3-[(phenylmethyl)oxy]-1-propanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11*a*,*R*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-3-[(phenylmethyl)oxy]methyl)-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (61 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11*a*,*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (37 mg, 87%) as a tinted white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 8.23 (s, 1 H), 7.32 (m, 1 H), 6.79 (m, 2 H), 5.31 (d, *J* = 7.6 Hz, 1 H), 4.56 (s, 2 H), 4.42-4.36 (m, 3 H), 4.17-4.11 (m, 2 H), 3.85 (m, 1 H), 3.62 (d, *J* = 11.2 Hz, 1 H).

Example Z-15:

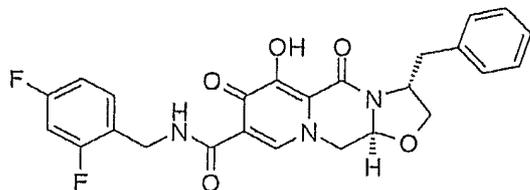
(2*S*,3*R*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (25 mg, 0.05 mmol) and (1*S*,2*R*)-(+)-norephedrine (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (2*S*,3*R*)-*N*[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-2-phenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (30 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (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 (25 mg, 91%) as a white solid. This material is a single diastereomer (>6:1 diastereomeric ratio but unconfirmed relative stereochemistry at the aminal center). <sup>1</sup>H NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 10.28 (m, 1 H), 8.38 (s, 1 H), 7.10-7.30 (m, 6 H), 6.78 (m, 2 H), 5.70 (d, *J* = 7.6 Hz, 1 H), 5.36 (d, *J* = 5.2 Hz, 1 H), 4.82 (m, 1 H), 4.61 (m, 2 H), 4.47 (d, *J* = 10.4 Hz, 1 H), 4.00 (apparent t, *J* = 10.4 Hz, 1 H), 0.94 (d, *J* = 6.4 Hz, 3 H); ES<sup>+</sup> MS: 482 (M+1).

Example Z-16:

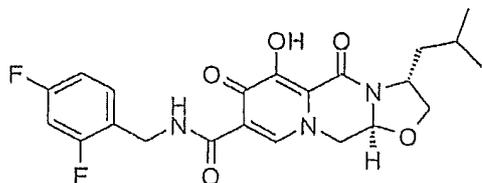
(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,

7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (34 mg, 0.07 mmol) and (2*R*)-2-amino-3-phenyl-1-propanol (D-phenylalaninol) (50 mg, 0.33 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*R*,11a*S*)-*N*[(2,4-difluorophenyl)methyl]-5,7-dioxo-3-(phenylmethyl)-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide (29 mg, 70%). This material was hydrogenated in a second step as described in example Z-2 to give (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 (24 mg, 98%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.46 (br, 1 H), 10.27 (m, 1 H), 8.33 (m, 1 H), 7.32-7.16 (m, 6 H), 6.78 (m, 2 H), 5.02 (m, 1 H), 4.61 (m, 3 H), 4.39 (m, 1 H), 4.22 (m, 1 H), 3.95 (m, 1 H), 3.87 (m, 1 H), 3.36 (m, 1 H), 2.97 (dd, *J* = 13.2 8.8 Hz, 1 H); ES<sup>+</sup> MS: 482 (M+1).

Example Z-17:

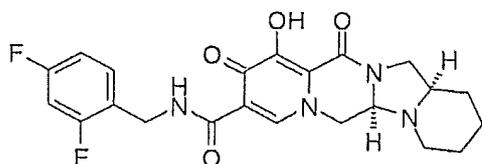
(3*R*,11a*S*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (32 mg, 0.07 mmol) and (2*R*)-2-amino-4-methyl-1-pentanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (3*R*,11*aS*)-*N*-[(2,4-difluorophenyl)methyl]-3-(2-methylpropyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (43 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (3*R*,11*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (32 mg, 90%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.47 (br, 1 H), 10.29 (m, 1 H), 8.35 (s, 1 H), 7.39 (m, 1 H), 6.80 (m, 2 H), 5.31 (m, 1 H), 4.62 (m, 2 H), 4.44 (m, 2 H), 4.37 (m, 1 H), 3.88 (m, 1 H), 3.84 (dd, *J* = 8.0, 5.6 Hz, 1 H), 2.04 (m, 1 H), 1.62 (m, 1 H), 1.41 (m, 1 H), 1.00 (d, *J* = 5.6 Hz, 3 H), 0.99 (d, *J* = 6.0 Hz, 3 H); ES<sup>+</sup> MS: 448 (M+1).

Example Z-18:

(5*aR*,14*aR*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5*a*,6,10,12,14,14*a*-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide.



a) 1,1-Dimethylethyl (2*R*)-2-(aminocarbonyl)-1-piperidinecarboxylate. To a cold (0 °C) solution of (2*R*)-1-[(1,1-dimethylethyl)oxy]carbonyl-2-piperidinecarboxylic acid (1.0 g, 4.36 mmol) in THF (20 mL) was added triethylamine (0.60 mL, 4.36 mmol) followed by slow addition of methyl chloroformate (0.34 mL, 4.36 mmol). After a few minutes a suspension had formed. To this mixture was added concentrated NH<sub>4</sub>OH (1.5 mL) and the solution was allowed to warm to rt as the bath warmed and stirred for a total of 4 h. The mixture was concentrated *in vacuo* and the residue was taken up in EtOAc. The organic layer was washed with citric acid, bicard and then brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and concentration gave 1,1-dimethylethyl (2*R*)-2-(aminocarbonyl)-1-piperidinecarboxylate (1.0 g, 99%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.03 (br, 1 H), 5.45 (br, 1 H), 4.77 (br, 1 H), 4.06 (br, 1 H), 2.82 (m, 1 H), 2.29 (m, 1 H), 1.67-1.43 (m, 13 H).

b) 1,1-Dimethylethyl (2*R*)-2-cyano-1-piperidinecarboxylate. To a cold (0 °C) solution of 1,1-dimethylethyl (2*R*)-2-(aminocarbonyl)-1-piperidinecarboxylate (269 mg, 1.17 mmol) in THF (10 mL) was added triethylamine (0.33 mL, 2.34 mmol) and then trifluoroacetic anhydride (0.17 mL, 1.17 mmol). The mixture was stirred at 0 °C for 1 h and concentrated *in vacuo*. The residue was taken up in EtOAc and washed successively with sodium bicarbonate, 0.5 N HCl and brine. The organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 1,1-dimethylethyl (2*R*)-2-cyano-1-piperidinecarboxylate (255 mg, 99%) as a crystalline solid upon standing. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.23 (br, 1 H), 4.05 (br, 1 H), 2.93 (br, 1 H), 1.93-1.39 (m, 6 H), 1.46 (s, 9 H).

c) 1,1-Dimethylethyl (2*R*)-2-(aminomethyl)-1-piperidinecarboxylate. An ammonia saturated ethanol solution of 1,1-dimethylethyl (2*R*)-2-cyano-1-piperidinecarboxylate (255 mg, 1.19 mmol) was reduced with Raney-Ni in a similar manner to that described in example Z-3 to give after filtration through a short plug of silica, 1,1-dimethylethyl (2*R*)-2-(aminomethyl)-1-piperidinecarboxylate (236 mg, 91%), as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 4.15 (br, 1 H), 3.97 (m, 1 H), 2.96 (m, 1 H), 2.75-2.69 (m, 2 H), 2.23-2.08 (m, 3 H), 1.59-1.55 (m, 3 H), 1.43 (s, 9 H).

d) [(2*R*)-2-Piperidinylmethyl]amine bis HCl salt. A solution of 1,1-dimethylethyl (2*R*)-2-(aminomethyl)-1-piperidinecarboxylate (236 mg, 1.08 mmol) in THF (10 mL) was treated with 4 N HCl (3 mL) as described in example Z-3 to give the bis HCl salt of [(2*R*)-2-Piperidinylmethyl]amine. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.67 (br, 1 H), 9.48 (br, 1 H), 8.48 (br, 2 H), 3.70 (br, 2 H), 3.20 (m, 1 H), 3.04 (m, 1 H), 2.86 (m, 1 H), 1.89-1.41 (m, 6 H).

e)

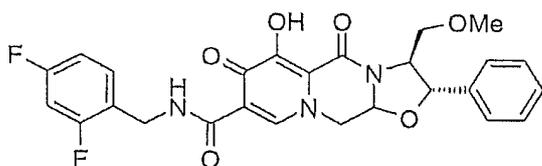
(5*a,R*,14*a,R*)-*N*'-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5*a*,6,10,12,14,14*a*-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.11 mmol) and [(2*R*)-2-Piperidinylmethyl]amine (150 mg, 1.31 mmol) (free based using carbonate resin as described in example Z-3) were reacted in dichloromethane (2 mL) with acetic acid to give

(5a*R*,14a*R*)-*N*-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-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 (50 mg, 88%). This material was hydrogenated in a second step as described in example Z-2 to give (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 (11 mg, 44%) as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD/CDCl<sub>3</sub>) δ 10.46 (m, 1 H), 8.32 (s, 1 H), 7.31 (m, 1 H), 6.80 (m, 2 H), 4.64-4.52 (m, 3 H), 4.14 (dd, *J* = 10.4, 2.8 Hz, 1 H), 3.91-3.82 (m, 2 H), 3.19 (apparent t, *J* = 10.8 Hz, 1 H), 3.08 (d, *J* = 10.4 Hz, 1 H), 2.50 (m, 1 H), 2.27 (m, 1 H), 1.99-1.30 m, 6 H); ES+ MS: 445 (M+1).

Example Z-19:

(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



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (36 mg, 0.07 mmol) and (2*R*)-2-amino-4-methyl-1-pentanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (2*S*,3*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-c



example Z-2 to give (3*S*,11*aR*)-3-(cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (25 mg, 99%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.48 (br, 1 H), 10.28 (s, 1 H), 8.33 (s, 1 H), 7.33 (m, 1 H), 6.78 (m, 2 H), 5.29 (m, 1 H), 4.61 (m, 2 H), 4.47-4.33 (m, 3 H), 3.87-3.81 (m, 2 H), 2.05 (m, 1 H), 1.75-1.64 (m, 6 H), 1.39 (m, 1 H), 1.25-1.14 (m, 3 H), 1.02-0.97 (m, 2 H); ES<sup>+</sup> MS: 488 (M+1).

Example Z-21:

(3*S*,11*aR*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



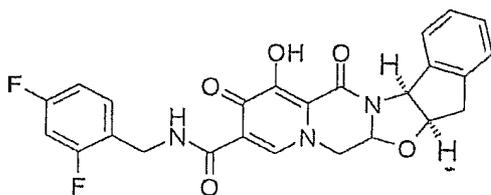
The title compound was made in two steps using a similar process to that described in example Z-1. 16a (42 mg, 0.09 mmol) and (2*S*)-2-amino-3-methyl-1-butanol (0.1 mL) were reacted in 1,2-dichloroethane (8 mL) with acetic acid to give (3*S*,11*aR*)-*N*-[(2,4-difluorophenyl)methyl]-3-(1-methylethyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 86%). This material was hydrogenated in a second step as described in

example Z-1 to give (3*S*,11*aR*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (34 mg,

99%) as a white solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  10.29 (br, 1 H), 8.36 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.29 (d,  $J = 6.4$  Hz, 1 H), 4.61 (m, 2 H), 4.44 (d,  $J = 9.6$  Hz, 1 H), 4.34 (m, 1 H), 4.17 (m, 1 H), 4.02 (dd,  $J = 8.4, 5.2$  Hz, 1 H), 3.86 (m, 1 H), 2.37 (m, 1 H), 0.97 (m, 6 H);  $\text{ES}^+$  MS: 434 ( $\text{M}+1$ ).

Example Z-22:

(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  
e.



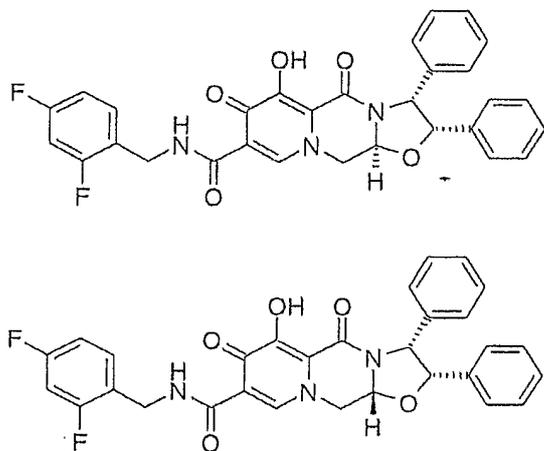
The title compound was made in two steps using a similar process to that described in example Z-1. 16a (42 mg, 0.09 mmol) and (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (100 mg, 0.67 mmol) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (5a*R*,14a*S*)-*N*[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide (55 mg, 99%). This material was hydrogenated in a second step as described in example Z-1 to give (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 (45 mg, 97%) as a white solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  10.28 (m, 1 H), 8.33 (s, 1 H),

7.69 (d,  $J = 7.2$  Hz, 1 H), 7.34-7.19 (m, 4 H), 6.78 (m, 2 H), 5.96 (d,  $J = 6.0$  Hz, 1 H), 5.32 (m, 1 H), 5.22 (m, 1 H), 4.60 (m, 2 H), 4.45 (d,  $J = 9.2$  Hz, 1 H), 3.96 (apparent t,  $J = 10.8$  Hz, 1 H), 3.40 (dd,  $J = 18.0, 6.8$  Hz, 1 H), 3.24 (d,  $J = 17.6$  Hz, 1 H); ES<sup>+</sup> MS: 480 (M+1).

Example Z-23 & Z-24:

(2*S*,3*R*,11*a*,*S*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide &

(2*S*,3*R*,11*a*,*R*)-*N*[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

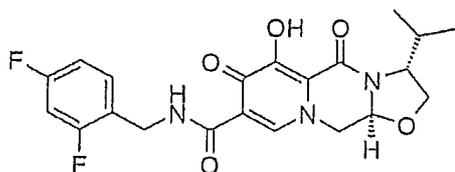


The title compounds were made in two steps using a similar process to that described in example Z-1. 16a (40 mg, 0.09 mmol) and (1*S*,2*R*)-2-amino-1,2-diphenylethanol (50 mg, 0.23 mmol) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (2*S*,3*R*,11*a*,*S*)-*N*[(2,4-difluorophenyl)methyl]-5,7-dioxo-2,3-diphenyl-6-[(phenylmethyl)]

oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (34 mg, 63%) and (2*S*,3*R*,11*a**R*)-*N*[(2,4-difluorophenyl)methyl]-5,7-dioxo-2,3-diphenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (18 mg, 24%). These materials were hydrogenated in a second step as described in example Z-1 to give (2*S*,3*R*,11*a**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 (example Z-23, 29 mg, 99%) as a white solid and (2*S*,3*R*,11*a**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 (example Z-24, 10 mg, 89%) as a white solid respectively. For example Z-23: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.29 (t, *J* = 5.6 Hz, 1 H), 8.55 (s, 1 H), 7.38 (m, 1 H), 7.22 (m, 1 H), 7.11-6.95 (m, 11 H), 6.16 (dd, *J* = 10.4, 3.6 Hz, 1 H), 5.71 (m, 2 H), 4.90 (m, 1 H), 4.54 (m, 2 H), 4.38 (t, *J* = 11.2 Hz, 1 H); ES<sup>+</sup> MS: 544 (M+1). For example Z-24: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.64 (br, 1 H), 10.30 (s, 1 H), 8.45 (s, 1 H), 7.34 (m, 1 H), 7.01-6.90 (m, 10 H), 6.80 (m, 2 H), 5.56 (m, 2 H), 5.42 (d, *J* = 6.4 Hz, 1 H), 4.73 (m, 1 H), 4.63 (m, 2 H), 4.49 (m, 1 H); ES<sup>+</sup> MS: 544 (M+1).

Example Z-25:

(3*R*,11*a**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.



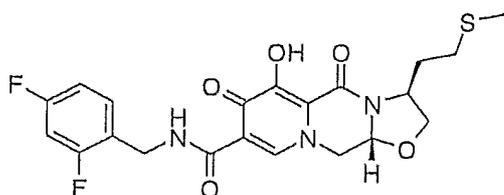
The title compound was made in two steps using a similar process to that described in example Z-1. 16a (40 mg, 0.09 mmol) and (2*R*)-2-amino-3-methyl-1-butanol (0.1 mL) were reacted in 1,2-dichloroethane (8 mL) with acetic acid to give (3*R*,11*aS*)-*N*-[(2,4-difluorophenyl)methyl]-3-(1-methylethyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (41 mg, 92%). This material was hydrogenated in a second step as described in example Z-1 to give

(3*R*,11*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

(32 mg, 94%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.42 (br, 1 H), 10.27 (br, 1 H), 8.34 (s, 1 H), 7.31 (m, 1 H), 6.78 (m, 2 H), 5.28 (d, *J* = 6.0 Hz, 1 H), 4.60 (m, 2 H), 4.42 (m, 1 H), 4.33 (m, 1 H), 4.16 (m, 1 H), 4.01 (dd, *J* = 8.8, 5.2 Hz, 1 H), 3.85 (m, 1 H), 2.37 (m, 1 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.4 Hz, 3 H); ES<sup>+</sup> MS: 434 (M+1).

#### Example Z-26

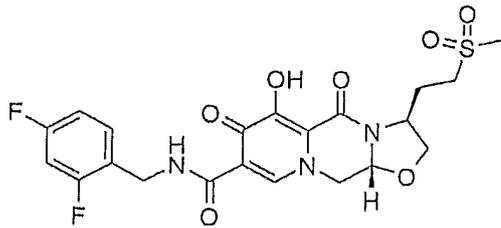
(3*S*,11*aR*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-1. 16a (43 mg, 0.09 mmol) and (2*S*)-2-amino-4-(methylthio)-1-butanol (0.1 mL) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (3*S*,11*a**R*)-*N*[(2,4-difluorophenyl)methyl]-3-[2-(methylthio)ethyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (41 mg, 81%). This material (20 mg, 0.04 mmol) was treated with trifluoroacetic acid (1 mL) in dichloromethane (3 mL) at 0 °C to rt over 6 h. The mixture was concentrated *in vacuo* and subjected to reverse phase preparative HPLC purification to provide (3*S*,11*a**R*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (12 mg, 72%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.35 (br, 1 H), 10.25 (s, 1 H), 8.34 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.32 (m, 1 H), 4.62-4.53 (m, 3 H), 4.43-4.39 (m, 2 H), 3.91-3.87 (m, 2 H), 2.63-2.53 (m, 2 H), 2.39 (m, 1 H), 2.12 (s, 3 H), 1.89 (m, 1 H); ES<sup>+</sup> MS: 466 (M+1).

#### Example Z-27

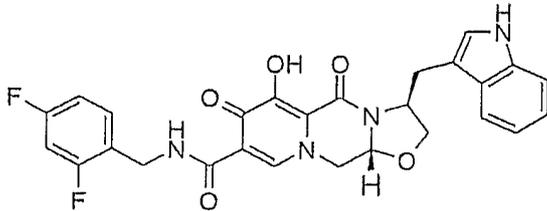
(3*S*,11*a**R*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



To a solution of (3*S*,11*aR*)-*N*-[(2,4-difluorophenyl)methyl]-3-[2-(methylthio)ethyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (20 mg, 0.04 mmol) in dichloromethane (5 mL) at 0 °C was added *m*-CPBA (20 mg, 70%, 0.082 mmol). The resultant solution was allowed to warm as the bath warmed and stirred a total of 3 h. The reaction was quenched by the addition of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (aq) and sodium bicarbonate. The layers were separated and the organic layer washed with brine. The aqueous layer was extracted with dichloromethane and the combined organics dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and concentration provided (3*S*,11*aR*)-*N*-[(2,4-difluorophenyl)methyl]-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (26 mg, 99%) as a white solid. This material was hydrogenated in a second step as described in example Z-1 to give (3*S*,11*aR*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (22 mg, 99%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.00 (br, 1 H), 10.16 (s, 1 H), 8.33 (s, 1 H), 7.36 (m, 1 H), 6.81 (m, 2 H), 5.42 (m, 1 H), 4.62 (m, 3 H), 4.41 (m, 2 H), 3.93 (m, 2 H), 3.31 (m, 2 H), 2.98 (s, 3 H), 2.40 (m, 1 H), 2.28 (m, 1 H); ES<sup>+</sup> MS: 498 (M+1).

Example Z-28:

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



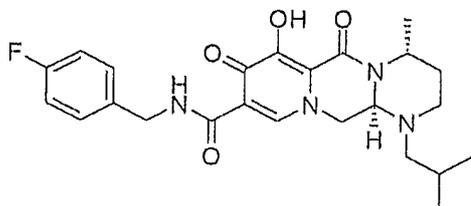
The title compound was made in two steps using a similar process to that described in example Z-1. 16a (43 mg, 0.09 mmol) and (2*S*)-2-amino-3-(1*H*-indol-3-yl)-1-propanol (100 mg, 0.52 mmol) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (3*S*,11*aR*)-*N*[(2,4-difluorophenyl)methyl]-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-6-[(phenyl methyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (36 mg, 64%). This material was hydrogenated in a second step as described in example Z-1 to give (3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (29 mg, 95%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 10.34 (m, 1 H), 8.98 (br, 1 H), 8.24 (s, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.32 (m, 2 H), 7.15-7.01 (m, 3 H), 6.78 (m, 2 H), 4.94 (d, *J* = 6.8 Hz, 1 H), 4.71 (d, *J* = 5.6 Hz, 1 H), 4.59 (m, 2 H), 4.35 (d, *J* = 10.4 Hz, 1 H), 4.22 (m, 1 H), 3.99 (m, 1 H), 3.81 (m, 1 H), 3.40 (dd, *J* = 13.6, 11.6 Hz, 1 H), 3.18 (dd, *J* = 14.0, 8.4 Hz, 1 H); ES<sup>+</sup> MS: 521 (M+1).

Example Z-29:

(4*R*,12*aR*)-*N*[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-

o-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-g]pyrimidine-9-carboxamid

e.



a) (2*R*)-2-(((1,1-Dimethylethyl)oxy)carbonyl)amino)propyl methanesulfonate. To a stirred solution of 1,1-dimethylethyl [(1*R*)-2-hydroxy-1-methylethyl]carbamate (5.00 g, 28.5 mmol) and triethylamine (5.92 mL, 42.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) cooled to 0 °C and under a nitrogen atmosphere was added dropwise a solution of methanesulfonyl chloride (2.43 mL, 31.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL). Stirring was continued for 20 minutes at 0 °C, after which time the reaction was judged complete by TLC analysis (1:1 hexanes/EtOAc). The solution was poured into water and the layers were separated. The organic phase was washed with 0.1 N HCl and then with 5% NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give (2*R*)-2-(((1,1-dimethylethyl)oxy)carbonyl)amino)propyl methanesulfonate (7.08 g, 98%) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.23 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H), 3.03 (s, 3H), 3.97 (m, 1H), 4.15 (dd, *J* = 4.2, 9.8 Hz, 1H), 4.21 (m, 1H), 4.61 (br s, 1H).

b) 1,1-Dimethylethyl [(1*R*)-2-cyano-1-methylethyl]carbamate. To a stirred solution of (2*R*)-2-(((1,1-dimethylethyl)oxy)carbonyl)amino)propyl methanesulfonate (7.08 g, 27.9 mmol) in DMSO (50 mL) was added NaCN (3.78 g, 84.0 mmol). The solution was stirred at 70 °C for 2 hours, over which time the formation of a precipitate was

observed. After cooling at room temperature, water was added and the mixture was extracted with Et<sub>2</sub>O. The ethereal layers were washed with a brine solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 1,1-dimethylethyl [(1*R*)-2-cyano-1-methylethyl]carbamate (3.81 g, 73%) as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.30 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 9H), 2.51 (dd, *J* = 3.8, 16.6 Hz, 1H), 2.73 (m, 1H), 3.93 (m, 1H), 4.63 (br s, 1H).

c) 1,1-Dimethylethyl [(1*R*)-3-amino-1-methylpropyl]carbamate. A solution of 1,1-dimethylethyl [(1*R*)-2-cyano-1-methylethyl]carbamate (1.30 g, 7.1 mmol) in ethanol saturated with anhydrous ammonia was treated with Raney-Ni (1.5 mL of 50% aq. Suspension) and 55 psi of H<sub>2</sub> overnight. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (80:19:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH (37%) gradient elution) through a short plug of silica gel to give 1,1-dimethylethyl [(1*R*)-3-amino-1-methylpropyl]carbamate (1.37 g, 100%) as a clear oil that solidified. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.14 (d, *J* = 6.8 Hz, 3H), 1.43-1.62 (m, 13H), 2.76 (m, 2H), 3.77 (m, 1H), 4.57 (m, 1H).

d) 1,1-Dimethylethyl [(1*R*)-1-methyl-3-[(2-methylpropyl)amino]propyl]carbamate. 1,1-dimethylethyl [(1*R*)-3-amino-1-methylpropyl]carbamate (0.320 g, 1.70 mmol), isobutyraldehyde (150 μL, 1.62 mmol), and sodium triacetoxyborohydride (0.512 g, 2.42 mmol) were stirred in anhydrous dichloroethane (10 mL) at ambient temperature overnight. The reaction was quenched by the addition of saturated NaHCO<sub>3</sub> and

then extracted with dichloromethane. The combined extracts were washed with water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by flash chromatography (80:19:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$  (37%) gradient elution) through a short plug of silica gel to afford 1,1-dimethylethyl  $\{(1R)\text{-}1\text{-methyl-}3\text{-}[(2\text{-methylpropyl})\text{amino}]\text{propyl}\}$ carbamate (0.158 g, 40%) as a clear oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.90 (d,  $J = 6.4$  Hz, 6H), 1.13 (d,  $J = 6.4$  Hz, 3H), 1.42-1.51 (m, 11H), 1.67-1.75 (m, 2H), 2.33-2.42 (m, 2H), 2.58-2.72 (m, 2H), 3.72 (m, 1H), 5.20 (m, 1H).

e)  $[(3R)\text{-}3\text{-Aminobutyl}]\text{(}2\text{-methylpropyl)\text{amine}}$ . An ice cold solution of 1,1-dimethylethyl  $\{(1R)\text{-}1\text{-methyl-}3\text{-}[(2\text{-methylpropyl})\text{amino}]\text{propyl}\}$ carbamate (0.158 g, 0.65 mmol) in THF (8 mL) was treated with 4 *N*HCl (aq) (2 mL) and then stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* to give  $[(3R)\text{-}3\text{-aminobutyl}]\text{(}2\text{-methylpropyl)\text{amine dihydrochloride}}$ . The HCl salt was then dissolved in dichloromethane and a minimal amount of methanol and treated with solid supported carbonate resin (MP-Carbonate, Argonaut Technologies). After 30 minutes, the solution was filtered through a fritted tube and the solvents removed carefully *in vacuo* to give  $[(3R)\text{-}3\text{-aminobutyl}]\text{(}2\text{-methylpropyl)\text{amine}}$  (65 mg).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (d,  $J = 6.0$  Hz, 6H), 1.06 (d,  $J = 5.6$  Hz, 3H), 1.23-1.53 (m, 5H), 1.71-1.74 (m, 1H), 2.39 (m, 2H), 2.65 (m, 2H), 2.97 (m, 1H).

f)

$(4R,12aR)\text{-}N\text{-}[(4\text{-Fluorophenyl})\text{methyl}]\text{-}7\text{-hydroxy-}4\text{-methyl-}1\text{-}(2\text{-methylpropyl})\text{-}6,8\text{-dio}$

oxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16 (40 mg, 0.09 mmol) and [(3*R*)-3-aminobutyl](2-methylpropyl)amine (65 mg, 0.45 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*R*,12*aR*)-*N*'-[(4-fluorophenyl)methyl]-4-methyl-1-(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (29 mg, 60%). This material was hydrogenated in a second step as described in example Z-2 to give (4*R*,12*aR*)-*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 (18 mg, 75%) as a tan solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 1.32 (d, *J* = 7.2 Hz), 1.45-1.49 (m, 1H), 1.57-1.67 (m, 1H), 2.03-2.12 (m, 2H), 2.21-2.27 (m, 1H), 2.73-2.79 (m, 1H), 2.87-2.92 (m, 1H), 4.16-4.24 (m, 2H), 4.45 (s, 1H), 4.54-4.64 (m, 2H), 4.96-4.99 (m, 1H), 6.96-7.00 (m, 2H), 7.29-7.32 (m, 2H), 8.27 (s, 1H), 10.46 (s, 1H), 12.55 (s, 1H); ES<sup>+</sup> MS: 456 (M+1).

Example Z-30:

(4*R*,12*aR*)-*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



a) [(3*R*)-3-Aminobutyl](1-methylethyl)amine. The free diamine was prepared in a similar manner as described in example Z-29. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.04 (d, *J* = 6.4 Hz, 6H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.41-1.58 (m, 5H), 2.62-2.66 (m, 2H), 2.74-2.80 (m, 1H), 2.92-3.00 (m, 1H).

b)

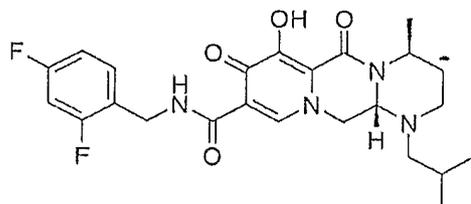
(4*R*,12*aR*)-*N*[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide

e. The title compound was made in two steps using a similar process to that described in example Z-2. 16 (40 mg, 0.088 mmol) and [(3*R*)-3-aminobutyl](1-methylethyl)amine (78 mg, 0.60 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*R*,12*aR*)-*N*[(4-fluorophenyl)methyl]-4-methyl-1-(1-methylethyl)-6,8-dioxo-7-[(phenyl methyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (26 mg, 56%). This material was hydrogenated in a second step as described in example Z-2 to give (4*R*,12*aR*)-*N*[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (21 mg, 90%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.01 (d, *J* = 5.6 Hz, 3H), 1.06 (d, *J* = 6.0 Hz, 3H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.57 (m, 1H), 1.98 (m, 1H),

2.70-2.82 (m, 2H), 3.15 (m, 1H), 4.15-4.19 (m, 1H), 4.30 (m, 1H), 4.48 (s, 1H), 4.54-4.59 (m, 2H), 4.97 (m, 1H), 6.98 (m, 2H), 7.29-7.32 (m, 2H), 8.27 (s, 1H), 10.49 (s, 1H), 12.52 (s, 1H).

Example Z-31:

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) 1,1-Dimethylethyl [(1*S*)-2-cyano-1-methylethyl]carbamate. The nitrile was prepared in two steps using a modified procedure as described in example Z-29. To a stirred solution of (2*S*)-2-([(1,1-dimethylethyl)oxy]carbonyl)amino)propyl methanesulfonate (8.40 g, 33.2 mmol) in DMSO (50 mL) and KCN (6.51 g, 100.0 mmol) cooled to 0 °C was added 18-crown-6 (9.05 g, 34.3 mmol). The solution was allowed to warm to room temperature and then heated to 70 °C for 1 hour. After cooling at room temperature, water was added and the mixture was extracted with Et<sub>2</sub>O. The ethereal layers were washed with a brine solution, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 1,1-dimethylethyl [(1*S*)-2-cyano-1-methylethyl]carbamate (5.37 g, 88%) as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.32 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H), 2.52 (dd, *J* = 4.0, 16.4 Hz, 1H), 2.74 (m, 1H), 3.95 (m, 1H), 4.65 (br s, 1H).

b) [(3*S*)-3-Aminobutyl](2-methylpropyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 0.99 (m, 6H), 1.34 (m, 3H), 2.13-2.27 (m, 3H), 2.76 (m, 2H), 3.07 (m, 2H), 3.47 (m, 1H), 8.22 (m, 1 H), 8.83 (m, <1 H).

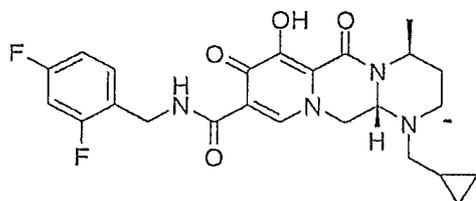
c)

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based [(3*S*)-3-aminobutyl](2-methylpropyl)amine (107 mg, 0.74 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-4-methyl-1-(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (76 mg, 76%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (39 mg, 80%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.76 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.45-1.50 (m, 1H), 1.60-1.69 (m, 1H), 2.03-2.12 (m, 2H), 2.21-2.27 (m, 1H), 2.73-2.79 (m, 1H), 2.87-2.93 (m, 1H), 4.16-4.25 (m, 2H), 4.45 (s, 1H), 4.57-4.68 (m, 2H), 4.96-5.01 (m, 1H), 6.75-6.82 (m, 2H),

7.32-7.38 (m, 1H), 8.26 (s, 1H), 10.45 (s, 1H), 12.56 (s, 1H); ES<sup>+</sup> MS: 475 (M+1).

Example Z-32:

(4*S*,12*aS*)-1-(Cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) 1,1-Dimethylethyl {(1*S*)-3-[(cyclopropylmethyl)amino]-1-methylpropyl}carbamate.

The protected diamine was prepared using a modified procedure as described in example Z-29. 1,1-dimethylethyl [(1*S*)-3-amino-1-methylpropyl]carbamate (0.293 g, 1.56 mmol), cyclopropane carboxaldehyde (96  $\mu$ L, 1.30 mmol), and sodium triacetoxyborohydride (0.439 g, 2.07 mmol) were stirred in a 1:1 mixture of anhydrous dichloroethane and tetrahydrofuran (10 mL) at ambient temperature overnight. The reaction was quenched by the addition of saturated NaHCO<sub>3</sub> and then extracted with EtOAc. The combined extracts were washed with saturated NaHCO<sub>3</sub>, then a solution of brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography (80:19:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH (37% gradient elution) through a short plug of silica gel to afford 1,1-dimethylethyl {(1*S*)-3-[(cyclopropylmethyl)amino]-1-methylpropyl}carbamate (76 mg, 26%) as a clear oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.09-0.13 (m, 2H), 0.44-0.49 (m, 2H), 0.92-0.95 (m, 1H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.43-1.70 (m, 12H), 2.38-2.50 (m, 2H), 2.62-2.73 (m, 2H),

3.74 (m, 1H), 4.88 (m, 1H).

b) [(3*S*)-3-Aminobutyl](cyclopropylmethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 0.40 (m, 2H), 0.64 (m, 2H), 1.15 (m, 1H), 1.34 (m, 3H), 2.12-2.25 (m, 2H), 2.82 (m, 2H), 3.08 (m, 2H), 3.47 (m, 1H), 8.25 (br, < 1H), 9.04 (br, < 1H),

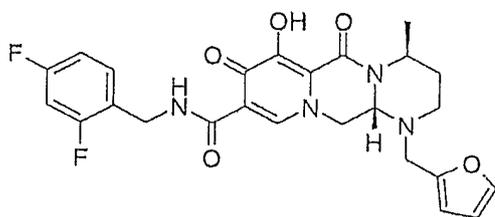
c)

(4*S*,12*aS*)-1-(Cyclopropylmethyl)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.106 mmol) and free based [(3*S*)-3-aminobutyl](cyclopropylmethyl)amine (44 mg, 0.31 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-1-(cyclopropylmethyl)-*N*[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (50 mg, 83%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-1-(cyclopropylmethyl)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (23 mg, 56%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.11 (m, 2H), 0.56-0.59 (m, 2H), 0.77 (m, 1H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.46-1.50 (m, 1H), 2.04-2.13 (m, 1H), 2.30-2.34 (m, 1H), 2.46-2.51 (m, 1H), 2.90-2.96 (m, 1H), 3.16-3.19 (m, 1H),

4.21-4.30 (m, 2H), 4.51 (s, 1H), 4.58-4.67 (m, 2H), 5.00-5.05 (m, 1H), 6.75-6.82 (m, 2H), 7.31-7.37 (m, 1H), 8.28 (s, 1H), 10.46 (s, 1H), 12.55 (br, 1H); ES<sup>+</sup> MS: 473 (M+1).

Example Z-33:

(4*S*,12*aS*)-*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.



a) [(3*S*)-3-Aminobutyl](2-furanylmethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 1.27 (d, *J* = 6.4 Hz, 3H), 1.96-2.05 (m, 1H), 2.14-2.19 (m, 1H), 3.00-3.04 (m, 2H), 3.38-3.39 (m, 1H), 4.11-4.18 (m, 2H), 6.34 (m, 1H), 6.59 (m, 1H), 7.40 (m, 1H), 8.18 (br, <1 H), 9.41 (br, <1 H).

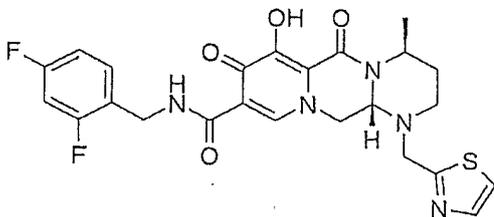
b)

(4*S*,12*aS*)-*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. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (36 mg, 0.076 mmol) and free based [(3*S*)-3-aminobutyl](2-furanylmethyl)amine (70 mg, 0.42 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give

(4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-1-(2-furanylmethyl)-4-methyl-6,8-dioxo-7-[(p-henylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (32 mg, 70%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-1-(2-furanylmethyl)-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (20 mg, 76%), as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.24 (d, *J* = 6.8 Hz, 3H), 1.45-1.49 (m, 1H), 2.04-2.13 (m, 1H), 2.77-2.82 (m, 1H), 2.94-3.01 (m, 1H), 3.65 (d, *J* = 15.6 Hz, 1H), 3.89 (d, *J* = 16.0 Hz, 1H), 4.27-4.31 (m, 1H), 4.39-4.41 (m, 1H), 4.49-4.53 (m, 1H), 4.58-4.66 (m, 1H), 4.98-5.03 (m, 1H), 6.24 (m, 1H), 6.36 (m, 1H), 6.75-6.82 (m, 2H), 7.31-7.39 (m, 1H), 7.40 (m, 1H), 8.26 (s, 1H), 10.47 (m, 1H), 12.50 (br, 1H); ES<sup>+</sup> MS: 499 (M+1).

Example Z-34:

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl](1,3-thiazol-2-ylmethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>·OD) δ 1.28 (d, *J* = 6.4 Hz, 3H), 2.05 (m, 1H), 2.17 (m, 1H), 3.20 (m, 2H), 3.39 (m, 1H),

4.51-4.58 (m, 2H), 7.52 (d, 1H), 7.82 (d, 1H).

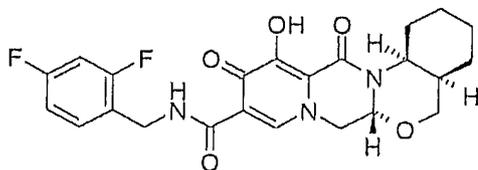
b)

(4*S*,12*aS*)-*N*'[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (35 mg, 0.074 mmol) and free based [(3*S*)-3-aminobutyl](1,3-thiazol-2-ylmethyl)amine were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*'[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (36 mg, 80%) as a film. This material was debenzylated in a second step to in a manner similar to Z-26 to give (4*S*,12*aS*)-*N*'[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (18 mg, 60%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.30 (d, *J* = 7.2 Hz, 3H), 1.49-1.53 (m, 1H), 2.12-2.18 (m, 1H), 2.93-2.96 (m, 1H), 3.07-3.13 (m, 1H), 3.99-4.03 (m, 1H), 4.13-4.17 (m, 1H), 4.24-4.27 (m, 1H), 4.57-4.61 (m, 3H), 5.03-5.06 (m, 1H), 6.75-6.82 (m, 2H), 7.26 (m, 1H), 7.31-7.37 (m, 2H), 7.76 (m, 1H), 7.94 (m, 1H), 10.40 (m, 1H), 12.48 (m, 1H); ES<sup>+</sup> MS: 516 (M+1).

Example Z-35:

*racemic*-(4*aR*,6*aR*,14*aS*)-*N*'[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,

4a,5,6a,7,11,13,14a-decahydro-2H-pyrido[1',2':4,5]pyrazino[1,2-a][3,1]benzoxazine-10-carboxamide



a)

*racemic*-(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-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. *racemic-cis*-2-Hydroxymethyl-1-cyclohexylamine hydrochloride (24 mg, 0.186 mmol) was dissolved in a dichloromethane solution containing a small amount of methanol (to dissolve) and excess MP-Carbonate (Argonaut Technologies) was added, the mixture was stirred for 30 minutes, and the MP-Carbonate was removed by filtration. The free amine solution was transferred to a microwave vessel containing 16a (29 mg, 0.0617 mmol). One drop of glacial acetic acid was added and the solution was heated for 10 minutes at 140 °C. The resultant solution was absorbed on celite and the material was purified by silica gel chromatography (0-12% methanol/dichloromethane gradient elution) to yield the desired product as a white solid (18 mg, 53%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.40 (m, 1 H), 8.35 (s, 1 H), 7.60 (m, 2 H), 7.34-7.26 (m, 4 H), 6.80 (m, 2 H), 5.35-5.23 (m, 2 H), 5.13 (m, 1 H), 4.77 (m, 1 H), 4.70 (m, 2 H), 4.22 (dd, *J* = 13.2, 3.2 Hz, 1 H), 4.07 (dd, *J* = 13.2, 6.4, 1 H), 3.96 (m, 1 H), 3.76 (dd, *J* = 11.2, 4.4, 1 H), 2.22 (m, 1 H), 1.84 (m, 1 H), 1.74-1.40 (m, 6 H), 1.17 (m, 1 H); <sup>-</sup>ES<sup>+</sup> MS: 550 (M + 1).

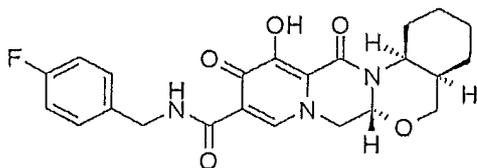
b)

*racemic*-(4*a*,*R*,6*a*,*R*,14*a*,*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide.

*racemic*-(4*a*,*R*,6*a*,*R*,14*a*,*S*)-*N*-[(2,4-Difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide (13 mg, 0.0236 mmol) was dissolved in tetrahydrofuran and 10 w.t.% Pd/C (13 mg) was added. Hydrogen was passed through the solution several times and the mixture was stirred at 1 atm hydrogen for 18 hours until the reaction was determined complete by TLC (5% methanol/dichloromethane). The mixture was filtered through Celite, eluting with methanol/chloroform and the filtrate was concentrated under reduced pressure and purified by HPLC to yield the title compound (7.3 mg, 73%) <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.45 (m, 1 H), 10.38 (s, 1 H), 8.30 (s, 1 H), 7.32 (m, 1 H), 6.83-6.76 (m, 2 H), 5.23 (m, 1 H), 4.75 (m, 1 H), 4.63 (m, 2 H), 4.26 (m, 1 H), 4.12-4.01 (m, 2 H), 3.83 (m, 1 H), 2.30 (m, 1 H), 1.91 (m, 1 H), 1.80 (m, 1 H), 1.67-1.40 (m, 5 H), 1.20 (m, 1 H); ES<sup>+</sup> MS: 460 (M + 1).

Example Z-36:

*racemic*-(4*a*,*R*,6*a*,*R*,14*a*,*S*)-*N*-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide.



a)

*racemic*-(4a*R*,6a*R*,14a*S*)-*N*-[(4-Fluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-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. In a manner similar to that described in example Z-35, from *racemic-cis*-2-Hydroxymethyl-1-cyclohexylamine hydrochloride (50 mg, 0.303 mmol) and 16 (45 mg, 0.0995 mmol) was prepared *racemic*-(4a*R*,6a*R*,14a*S*)-*N*-[(4-fluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-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 (48 mg, 91%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.42 (m, 1 H), 8.37 (s, 1 H), 7.59 (m, 2 H), 7.38-7.24 (m, 5 H), 6.98 (m, 2 H), 5.26-5.18 (m, 2 H), 5.07 (m, 1 H), 4.74 (m, 1 H), 4.62-4.51 (m, 2 H), 4.20 (dd, *J* = 13.6, 4 Hz, 1 H), 4.04 (m, 1 H), 3.91 (m, 1 H), 3.71 (dd, *J* = 11.3, 4.8 Hz, 1 H), 2.18 (m, 1 H), 1.82 (m, 1 H), 1.73-1.63 (m, 2 H), 1.62-1.56 (m, 2 H), 1.48 (s, 1 H), 1.38 (m, 1 H), 1.14 (m, 1 H); ES<sup>+</sup> MS: 532 (M + 1).

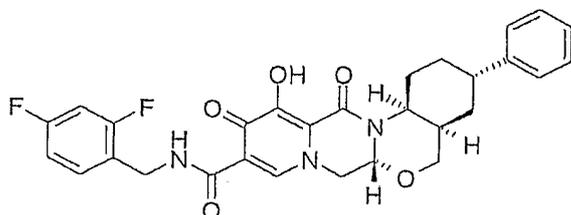
b)

*racemic*-(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. In a manner similar to that described in example Z-37, from *racemic*-(4a*R*,6a*R*,14a*S*)-*N*-[(4-fluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)ox

y]-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2H-pyrido[1',2':4,5]pyrazino[1,2-a][3,1]benzoxazine-10-carboxamide (37 mg, 0.0696 mmol) and 10 w.t. % Pd/C (3 mg) was prepared the title compound (18 mg, 58%) as a white solid after purification by HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.47 (s, 1 H), 10.39 (m, 1 H), 8.32 (s, 1 H), 7.30 (m, 2 H), 6.98 (m, 2 H), 5.22 (m, 1 H), 4.74 (m, 1 H), 4.58 (m, 2 H), 4.28 (dd, *J* = 13.2, 4 Hz, 1 H), 4.12-3.98 (m, 2 H), 3.81 (dd, *J* = 11.6, 4.8 Hz, 1 H), 2.29 (m, 1 H), 1.91-1.19 (m, 8 H); ES<sup>+</sup> MS: 442 (M + 1).

Example Z-37:

*racemic*-(3*S*,4*aR*,6*aR*,14*aS*)-*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.



a)

*racemic*-(3*S*,4*aR*,6*aR*,14*aS*)-*N*[(2,4-Difluorophenyl)methyl]-11,13-dioxo-3-phenyl-12-[(phenylmethyl)oxy]-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. In a manner similar to that described in example Z-35, from *racemic*-[(1*R*,2*S*,5*S*)-2-amino-5-phenylcyclohexyl]methanol hydrochloride (32 mg, 0.160 mmol) and 16a (30 mg, 0.064 mmol) was prepared *racemic*-(3*S*,4*aR*,6*aR*,14*aS*)-*N*[(2,4-difluorophenyl)methyl]-11,13-dioxo-3-phenyl-12-[(phenylmethyl)oxy]-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 (35 mg, 88%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.41 (m, 1 H), 8.38 (s, 1 H), 7.66 (m, 2 H), 7.40-7.26 (m, 6 H), 6.81 (m, 3 H), 5.32-5.25 (m, 2 H), 5.17 (m, 1 H), 4.89 (m, 1 H), 4.66-4.62 (m, 2 H), 4.26 (dd, *J* = 13.6, 4 Hz, 1 H), 4.13-4.04 (m, 2 H), 3.85 (dd, *J* = 11.2, 4.4 Hz, 1 H), 2.56 (m, 1 H), 2.37 (m, 1 H), 2.03-1.64 (m, 6 H); ES<sup>+</sup> MS: 626 (M + 1).

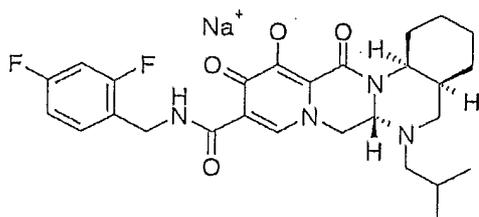
b)

*racemic*-(3*S*,4*aR*,6*aR*,14*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-3-phenyl-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide.

*racemic*-(3*S*,4*aR*,6*aR*,14*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-11,13-dioxo-3-phenyl-12-[(phenylmethyl)oxy]-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide (27 mg, 0.0432 mmol) was suspended in methanol, 10 w.t. % Pd/C (3 mg) was added and hydrogen was bubbled through the system several times until the reaction was determined complete by TLC (5% methanol/dichloromethane). The suspension was filtered through Celite eluting with methanol/chloroform and the filtrate was concentrated under reduced pressure and purified by HPLC to give the title compound (13 mg, 57%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.40 (br s, 1 H), 10.37 (m, 1 H), 8.32 (s, 1 H), 7.37-7.28 (m, 3 H), 7.24-7.15 (m, 4 H), 6.79 (m, 2 H), 5.78 (br s, 1 H), 4.85 (m, 1 H), 4.62 (m, 2 H), 4.29 (m, 1 H), 4.16-4.09 (m, 2 H), 3.92 (dd, *J* = 11.6, 4.8 Hz, 1 H), 2.58 (m, 1 H), 2.46 (m, 1 H), 2.07-1.64 (m, 7 H); ES<sup>+</sup> MS: 536 (M + 1).

Example Z-38:Sodium

*racemic*-(4a*S*,6a*S*,14a*S*)-10-(((2,4-difluorophenyl)methylamino)carbonyl)-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*]quinazolin-12-olate.



a) *racemic*-1,1-Dimethylethyl [(1*S*,2*R*)-2-(hydroxymethyl)cyclohexyl]carbamate. *racemic*-[(1*R*,2*S*,5*S*)-2-Amino-5-phenylcyclohexyl]methanol hydrochloride (800 mg, 4.82 mmol) was dissolved in MeOH (40 mL) and bis(1,1-dimethylethyl) dicarbonate (1.16 g, 5.30 mmol) and triethylamine (4 mL, 28.92 mmol) were added and the mixture was stirred 18 hours at ambient temperature. The solvents were removed under reduced pressure, ethyl acetate and aqueous saturated sodium bicarbonate were added and the product was extracted with ethyl acetate. The combined organics were dried over sodium sulfate and the solvents were removed under reduced pressure. Purification by silica gel chromatography (9:1 hexanes: ethyl acetate to ethyl acetate gradient elution) gave 1,1-dimethylethyl *racemic*-[(1*S*,2*R*)-2-(hydroxymethyl)cyclohexyl]carbamate (934 mg, 85%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.87 (m, 1H), 4.03-3.95 (m, 2 H), 3.26 (m, 1 H), 3.15 (m, 1 H), 1.73-1.48 (m, 5 H), 1.38 (s, 9 H), 1.27-1.15 (m, 3 H), 0.887 (m, 1 H).

b) *racemic*-1,1-Dimethylethyl [(1*S*,2*R*)-2-Formylcyclohexyl]carbamate. To a

solution of dimethylsulfoxide (0.2 mL, 2.88 mmol) in dichloromethane (3 mL) at -78 °C was added oxalyl chloride (0.72 mL, 1.44 mmol) dropwise. The mixture was stirred 10 minutes and *racemic*-1,1-dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclohexyl]carbamate (220 mg, 0.961 mmol) in dichloromethane was added dropwise and stirred 10 minutes. Triethylamine (0.53 mL, 3.84 mmol) was added slowly and the reaction was stirred at -78 °C for one hour and allowed to warm to ambient temperature. Water was added and product was extracted with dichloromethane. The combined organics were washed with brine and dried over sodium sulfate. Removal of solvents under reduced pressure afforded *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (223 mg, quantitative) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.61 (s, 1 H), 5.19 (m, 1 H), 3.88 (m, 1 H), 2.61 (m, 1 H), 1.85 (m, 1 H), 1.63-1.49 (m, 4 H), 1.37-1.16 (m, 12 H).

c) *racemic*-1,1-dimethylethyl ((1S,2S)-2-[(2-Methylpropyl)amino]methyl)cyclohexyl)carbamate. *racemic*-1,1-Dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (223 mg, 0.982 mmol) was dissolved in dichloroethane and 2-methylpropyl)amine (0.15 mL, 1.47 mmol) and sodium triacetoxyborohydride (290 mg, 1.37 mmol) were added and the reaction was stirred at ambient temperature for 18 hours. Aqueous sodium bicarbonate was added and the product was extracted with dichloromethane. The combined extracts were dried over sodium sulfate and the solvents were removed under reduced pressure. Purification by silica gel chromatography (dichloromethane to 1% ammonium hydroxide 19% methanol 80% dichloromethane gradient elution) afforded

*racemic*-1,1-dimethylethyl

((1*S*,2*S*)-2-((2-methylpropyl)amino)methyl)cyclohexyl)carbamate (112 mg, 40%) as a clear colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.06 (br s, 1 H), 3.76 (br s, 1 H), 2.63 (m, 1 H), 2.43-2.37 (m, 2 H), 2.25 (m, 1 H), 1.81 (m, 1 H), 1.71-1.59 (m, 3 H), 1.44-1.32 (m, 14 H), 1.27-1.19 (m, 2 H), 0.866 (m, 6 H).

d) *racemic*-(1*S*,2*S*)-2-((2-Methylpropyl)amino)methyl)cyclohexanamine hydrochloride.

In a manner similar to that describe in example Z-3, step e, from *racemic*-1,1-dimethylethyl ((1*S*,2*S*)-2-((2-methylpropyl)amino)methyl)cyclohexyl)carbamate (112 mg, 0.394 mmol) was prepared (1*S*,2*S*)-2-((2-methylpropyl)amino)methyl)cyclohexanamine hydrochloride (130 mg, > 100%) as a white solid. <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) δ 8.68-8.28 (m, 1 H), 3.62 (br s, 1 H), 3.26 (m, 1 H), 2.83-2.78 (m, 3 H), 2.54 (br s, 1 H), 2.12 (m, 1 H), 1.82-1.66 (m, 3 H), 1.53-1.39 (m, 5 H), 0.96 (m, 6 H), 0.766 (m, 1 H).

e)

*racemic*-(4*aS*,6*aS*,14*aS*)-N-[(2,4-Difluorophenyl)methyl]-6-(2-methylpropyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5] pyrazino[1,2-*a*]quinazoline-10-carboxamide. In a manner similar to that described in Z-35, from *racemic*-(1*S*,2*S*)-2-((2-methylpropyl)amino)methyl)cyclohexanamine hydrochloride (130 mg, 0.508 mmol) and 16a (55 mg, 0.117 mmol) was prepared

*racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-(2-methylpropyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (44 mg, 62%) with a 12: 1 d.r. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.46 (m, 1H), 8.33 (s, 1 H), 7.59 (m, 2 H), 7.37-7.24 (m, 4 H), 6.79 (m, 2 H), 5.30-5.23 (m, 2 H), 4.75-4.56 (m, 3 H), 4.23-4.09 (m, 3 H), 2.69-2.66 (m, 2 H), 2.21-1.98 (m, 3 H), 1.80 (m, 1 H), 1.71-1.33 (m, 6 H), 1.26-1.19 (m, 2 H), 0.810 (m, 3 H), 0.720 (m, 3 H); ES<sup>+</sup> MS: 605 (M +1).

f)

*racemic*-(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. In a manner similar to that described in example Z-37, from *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-(2-methylpropyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (39 mg, 0.064 mmol) and 10 w.t. % Pd/C (7 mg) was prepared *racemic*-(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 (36 mg, > 100%) as a tan solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.60 (br s, 1 H), 10.43 (br s, 1 H), 8.25 (s, 1 H), 7.35 (m, 1 H), 6.78 (m, 2 H), 4.77 (m, 1 H), 4.63 (m, 2 H), 4.49 (br s, 1 H), 4.30-4.13 (m, 2 H), 3.63-3.40 (m, 2 H), 2.88-2.71 (m, 2 H), 2.32-2.21 (m, 2 H), 2.05 (m, 1 H), 1.88-1.11 (m, 7 H), 0.830 (m, 3 H), 0.760 (m, 3

H); AP+ MS: 515 (M +1).

g) Sodium

*racemic*-(4aS,6aS,14aS)-10-((2,4-Difluorophenyl)methyl)amino}carbonyl)-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]quinazolin-12-olate. In a manner similar to that described in example Z-1, from

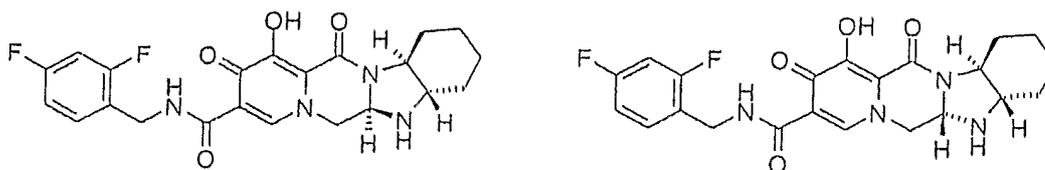
*racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (37 mg, 0.071 mmol) and 1 N sodium hydroxide (0.07 mL) the title compound was prepared as a yellow solid (26 mg, 68 %). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.73 (m, 1 H), 7.94 (s, 1 H), 7.32 (m, 1 H), 7.19 (m, 1 H), 7.00 (m, 1 H), 4.59-4.41 (m, 3 H), 4.28 (m, 2 H), 4.14 (br s, 1 H), 2.63-2.60 (m, 2 H), 1.98-1.61 (m, 5 H), 1.48-1.36 (m, 4 H), 0.997 (m, 3 H), 0.760 (m, 3 H), 0.660 (m, 2 H); AP+ MS: 515 (M +1 of free acid).

Example Z-39:

(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

& Example Z-40:

(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.



a)

(6aR,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido [1',2':4,5] pyrazino[1,2-a] benzimidazole-3-carboxamide and (6aS,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide. In a manner similar to that described in example Z-2, from [(1S,2S)-2-aminocyclohexyl]amine (122 mg, 1.07 mmol) and 16a (200 mg, 0.426 mmol) was prepared (6aR,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido [1',2':4,5] pyrazino[1,2-a] benzimidazole-3-carboxamide (58 mg) and (6aS,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide (10.6 mg) after separation of the diastereomers using silica gel chromatography (0-12% methanol/dichloromethane). (6aR,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido [1',2':4,5] pyrazino[1,2-a] benzimidazole-3-carboxamide (major): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.40 (m, 1 H), 8.33 (s, 1 H), 7.57 (m, 2 H), 7.40-7.25 (m, 4 H), 6.81 (m, 2 H), 5.32 (d, J = 10 Hz, 1 H), 5.13 (d, J

= 10 Hz, 1 H), 4.64-4.58 (m, 3 H), 4.21 (dd,  $J = 12.4, 3.2$  Hz, 1 H), 3.79 (m, 1 H), 3.04 (m, 1 H), 2.73 (m, 1 H), 2.53 (m, 1 H), 2.01-1.79 (m, 4 H), 1.36-1.24 (m, 4 H); ES<sup>+</sup> MS: 535 (M +1).

(6aS,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide (minor diastereomer): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.33 (m, 1 H), 8.28 (s, 1 H), 7.61 (m, 2 H), 7.39-7.28 (m, 3 H), 6.79 (m, 2 H), 5.29 (d,  $J = 9.6$  Hz, 1 H), 5.05 (d,  $J = 9.6$  Hz, 1 H), 4.84 (m, 1 H), 4.60 (m, 2 H), 3.90-3.84 (m, 2 H), 3.07 (m, 1 H), 2.75 (m, 1 H), 2.49 (m, 1 H), 2.07 (m, 1 H), 1.90-1.51 (m, 4 H), 1.33-1.19 (m, 4 H); MS data matches that of its diastereomer.

b) (For example Z-39),

(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.

In a manner similar to that described in example Z-37, from the minor diastereomer prepared in step a

(6aS,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide (7 mg, 0.0131 mmol) and 10 w.t. % Pd/C (catalytic amount) was prepared (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 (2.8 mg, 48%) after purification by HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.15 (br s, 1 H), 10.42 (br s, 1 H), 8.31 (s, 1 H), 7.36 (m, 1 H), 6.80 (m, 2 H), 5.01 (m, 1 H), 4.63 (m, 2

H), 4.16 (m, 1 H), 3.96 (m, 1H), 3.06-2.93 (m, 2 H), 2.61 (m, 1 H), 2.18 (m, 1 H), 1.93 (m, 1 H), 1.60-1.13 (m, 4 H), 0.893-0.840 (m, 2 H); ES+ MS: 445 (M +1).

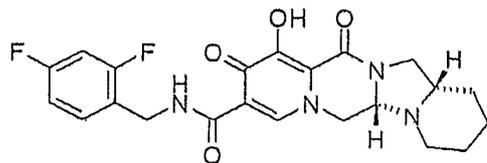
c) (For example Z-40).

(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.

In a manner similar to that described in example Z-37, from the major diastereomer (30 mg, 0.0561 mmol) prepared in step a and 10 w.t. % Pd/C (catalytic amount), (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 was prepared as a white solid (15 mg, 60%) after purification by HPLC. <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) δ 10.41 (m, 1 H), 8.25 (s, 1 H), 7.30 (m, 1 H), 6.77 (m, 2 H), 4.77 (m, 1 H), 4.57 (m, 2 H), 4.45 (m, 1 H), 3.91 (m, 1 H), 3.12 (m, 1 H), 2.67 (m, 1 H), 2.12 (m, 1 H), 1.87-1.84 (m, 2 H), 1.47-1.33 (m, 4 H); ES+ MS: 445 (M +1).

Example Z-41:

(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.



a)

(5aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-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. In a manner similar to that described in example Z-18, from 16a (50 mg, 0.108 mmol) and [(2S)-2-piperidinylmethyl]amine hydrochloride (50 mg, 0.269 mmol, made in a similar manner as described in example Z-18) was prepared (5aS,14aS)-N-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-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 (40 mg, 78 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.43 (m, 1 H), 8.38 (s, 1 H), 7.59 (m, 2 H), 7.59-7.25 (m, 4 H), 6.81 (m, 2 H), 5.38 (d, *J* = 10 Hz, 1 H), 5.19 (d, *J* = 10 Hz, 1 H), 4.65-4.62 (m, 2 H), 4.20 (dd, *J* = 12, 2.8 Hz, 1 H), 4.00 (dd, *J* = 12.4, 2.8 Hz, 1 H), 3.85 (m, 1 H), 3.74 (m, 1 H), 3.27 (m, 1 H), 2.99 (m, 1 H), 2.43 (m, 1 H), 2.24 (m, 1 H), 1.94-1.87 (m, 2 H), 1.77-1.58 (m, 2 H), 1.39-1.24 (m, 2 H); ES<sup>+</sup> MS: 535 (M + 1).

b)

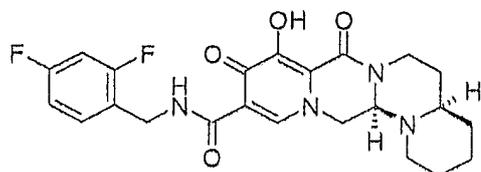
(5aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-a]pyrido[1',2':3,4]imidazo[1,2-d]pyrazine-9-carboxamide.

In a manner similar to that described in example Z-37, from (5aS,14aS)-N-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-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 (18 mg, 0.0337 mmol) and 10 w.t.% Pd/C (catalytic amount) was prepared the title compound as a white solid (13 mg, 87%) after purification by HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.71 (br s, 1 H), 10.36 (br s, 1 H), 8.31 (s, 1 H), 7.34 (m, 1 H), 6.78 (m, 2 H), 4.64-4.57 (m, 2 H), 4.28 (m, 1 H), 4.12 (m, 1 H), 3.92-3.89 (m, 2 H), 3.22 (m, 1 H), 3.04 (m, 1 H), 2.49 (m, 1 H), 2.28 (m, 1 H), 1.97-1.89 (m, 2 H), 1.78 (m, 1 H),

1.66-1.60 (m, 2 H), 1.43-1.36 (m, 2 H); ES<sup>+</sup> MS: 445 (M + 1).

Example Z-42:

(4aR,14aR)-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.



a) Phenylmethyl (2R)-2-(hydroxymethyl)-1-piperidinecarboxylate. In a manner similar to that described in example Z-3a, from (2R)-1-[(phenylmethyl)oxy]carbonyl-2-piperidinecarboxylic acid (4.93 g, 18.75 mmol) was prepared phenylmethyl (2R)-2-(hydroxymethyl)-1-piperidinecarboxylate (2.24 g, 48%) as an oil that solidified upon standing to a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.36-7.26 (m, 5 H), 5.18-5.10 (m, 2 H), 4.37 (m, 1 H), 4.03 (m, 1 H), 3.84 (m, 1 H), 3.63 (m, 1 H), 2.96 (br s, 1 H), 1.71-1.42 (m, 6 H).

b) Phenylmethyl (2R)-2-(cyanomethyl)-1-piperidinecarboxylate. In a manner similar to that described in example Z-3b, from phenylmethyl (2R)-2-(hydroxymethyl)-1-piperidinecarboxylate (1.09g, 4.38 mmol) was prepared phenylmethyl (2R)-2-[(4-methylphenyl)sulfonyl]oxy)methyl)-1-piperidinecarboxylate (1.05g, 59% impure with uncharacterized byproduct) as a clear colorless oil after purification using silica gel chromatography (10-100% ethyl acetate-hexanes). It is

necessary to use this material in the next step as soon as possible or yields deteriorate dramatically. In a manner similar to that described in example Z-3c, from phenylmethyl (2R)-2-((4-methylphenyl)sulfonyloxy)methyl-1-piperidinecarboxylate (1.05 g, 2.61 mmol) and sodium cyanide (383 mg, 7.82 mmol) was prepared phenylmethyl (2R)-2-(cyanomethyl)-1-piperidinecarboxylate (171 mg, 25 %) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35-7.29 (m, 5 H), 5.13 (s, 2 H), 4.65 (m, 1 H), 4.10 (m, 1 H), 2.96 (m, 1 H), 2.60 (m, 2 H), 1.82-1.67 (m, 4 H), 1.54-1.39 (m, 2 H).

d) Phenylmethyl (2R)-2-(2-aminoethyl)-1-piperidinecarboxylate. In a manner similar to that described in example Z-3d, from phenylmethyl (2R)-2-(cyanomethyl)-1-piperidinecarboxylate (171 mg, 0.663 mmol) was prepared phenylmethyl (2R)-2-(2-aminoethyl)-1-piperidinecarboxylate (119 mg, 68%) as a clear colorless residue. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.32-7.25 (m, 5 H), 5.08 (m, 2 H), 4.39 (br s, 1 H), 4.01 (br s, 1 H), 2.78 (m, 1 H), 2.60-2.56 (m, 2 H), 1.95-1.86 (m, 3 H), 1.63-1.35 (m, 6 H).

e) {2-[(2R)-2-Piperidinyl]ethyl}amine. Phenylmethyl (2R)-2-(2-aminoethyl)-1-piperidinecarboxylate (119 mg, 0.454 mmol) was dissolved in methanol and 10 w.t.% Pd/C (120 mg) was added. Hydrogen was bubbled through the solution for 15 minutes and the reaction was stirred under 1 atm hydrogen for 18 hours until determined complete by TLC (1% ammonium hydroxide 19% methanol 80% dichloromethane). The suspension was filtered through Celite eluting with

methanol and the filtrate was carefully concentrated under reduce pressure to yield a clear colorless liquid (58 mg, quantitative). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.99 (m, 1 H), 2.71-2.66 (m, 2 H), 2.57-2.48 (m, 2 H), 1.72 (m, 1 H), 1.61-1.52 (m, 2 H), 1.48-1.42 (m, 2 H), 1.35-1.25 (m, 2 H), 1.05 (m, 1 H).

f)

(4aR,14aR)-N-[(2,4-Difluorophenyl)methyl]-8,10-dioxo-9-[(phenylmethyl)oxy]-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. In a manner similar to that described in example Z-35, from 16a (50 mg, 0.106 mmol) and {2-[(2R)-2-piperidinyl]ethyl}amine (58 mg, 0.454 mmol) was prepared (4aR,14aR)-N-[(2,4-difluorophenyl)methyl]-8,10-dioxo-9-[(phenylmethyl)oxy]-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 (47 mg, 81%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.50 (br s, 1 H), 8.33 (s, 1 H), 7.60 (s, 2 H), 7.38-7.24 (m, 4 H), 6.80 (m, 2 H), 5.29-5.22 (m, 2 H), 4.66-4.56 (m, 3 H), 4.30 (m, 1 H), 4.19 (m, 1 H), 3.78 (br s, 1 H), 2.86-2.80 (m, 2 H), 2.18 (br s, 1 H), 1.94 (m, 1 H), 1.68-1.36 (m, 6 H), 1.23 (br s, 2 H); ES<sup>+</sup> MS: 549 (M + 1).

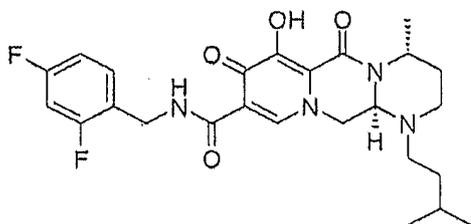
g)

(4aR,14aR)-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. In a manner similar to that described in example Z-37, from (4aR,14aR)-N-[(2,4-difluorophenyl)methyl]-8,10-dioxo-9-[(phenylmethyl)oxy]-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 (47 mg, 0.0857 mmol) and a catalytic amount of 10 w.t.% Pd/C was prepared the title compound as a white solid (19 mg, 54%) after purification by HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.49 (m, 1 H), 8.29 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 4.67-4.56 (m, 3 H), 4.41 (m, 1 H), 4.20 (m, 1 H), 3.93 (s, 1 H), 2.94-2.87 (m, 2 H), 2.28 (br s, 1 H), 2.01 (m, 1 H), 1.68-1.54 (m, 4 H), 1.44 (m, 1 H), 1.29-1.23 (m, 3 H), 0.850 (m, 1 H); ES<sup>+</sup> MS: 459 (M + 1).

Example Z-43:

(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.



a) [(3*R*)-3-Aminobutyl](3-methylbutyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 0.87 (d, *J* = 5.2 Hz, 6H), 1.32 (m, 3H), 1.61 (m, 3H), 2.10-2.20 (m, 2H), 2.90-3.04 (m, 4H), 3.45 (m, 1H), 8.23 (br, < 1 H), 8.96 (br, < 1 H).\_\_\_

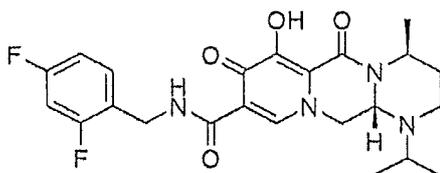
b)

(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-carboxam

ide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.085 mmol) and free [(3*R*)-3-aminobutyl](3-methylbutyl)amine (46 mg, 0.35 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*R*,12*aR*)-*N*[(2,4-difluorophenyl)methyl]-4-methyl-1-(3-methylbutyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (44 mg, 90%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*R*,12*aR*)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (11 mg, 30%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.84 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 1.24-1.36 (m, 5H), 1.47-1.53 (m, 2H), 2.02-2.11 (m, 1H), 2.36-2.43 (m, 1H), 2.54-2.61 (m, 1H), 2.77-2.92 (m, 2H), 4.16-4.26 (m, 2H), 4.44 (m, 1H), 4.62-4.64 (m, 2H), 4.95-5.02 (m, 1H), 6.75-6.81 (m, 2H), 7.31-7.37 (m, 1H), 8.27 (s, 1H), 10.43 (m, 1H), 12.54 (s, 1H); ES<sup>+</sup> MS: 489 (M+1).

Example Z-44:

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl](1-methylethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 1.20-1.25 (m, 9H), 1.98-2.02 (m, 2H), 2.92 (m, 2H), 3.20-3.29 (m, 2H), 8.04 (br, < 1 H), 8.64 (br, < 1 H).

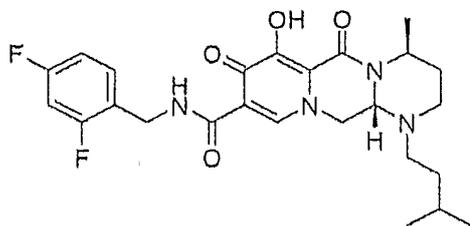
b)

(4*S*,12*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (60 mg, 0.13 mmol) and free based [(3*S*)-3-aminobutyl](1-methylethyl)amine (55 mg, 0.42 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-1-(1-methylethyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (40 mg, 57%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (17 mg, 50%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.02 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.55-1.58 (m, 1H), 1.94-2.03 (m, 1H), 2.70-2.77 (m, 1H), 2.81-2.86 (m, 1H), 3.11-3.18 (m, 1H), 4.17 (dd, *J* = 3.0, 13.8 Hz, 1H), 4.32 (dd, *J* = 3.2, 14.0 Hz, 1H), 4.48 (m, 1H), 4.59-4.69 (m, 2H), 4.97-5.00 (m, 1H), 6.77-6.83 (m, 2H), 7.33-7.39 (m, 1H), 8.28 (s, 1H), 10.50 (m, 1H), 12.55 (s, 1H);

ES+ MS: 461 (M+1).

Example Z-45:

(4*S*,12*aS*)-*N*'-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl](3-methylbutyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 0.86 (d, *J* = 5.6 Hz, 6H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.58 (m, 3H), 2.03-2.14 (m, 2H), 2.87-2.99 (m, 4H), 3.38 (m, 1H), 8.15 (br, < 1 H), 8.87 (br, < 1 H).

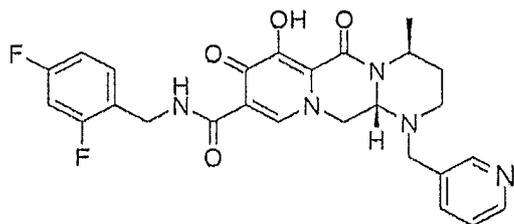
b)

(4*S*,12*aS*)-*N*'-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (0.100 g, 0.21 mmol) and free based [(3*S*)-3-aminobutyl](3-methylbutyl)amine (0.104 g, 0.66 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*'-[(2,4-difluorophenyl)methyl]-4-methyl-1-(3-methylbutyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine

-9-carboxamide (88 mg, 72%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (55 mg, 74%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.84 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H), 1.24-1.37 (m, 5H), 1.45-1.53 (m, 2H), 2.02-2.11 (m, 1H), 2.37-2.44 (m, 1H), 2.56-2.63 (m, 1H), 2.80-2.92 (m, 2H), 4.22-4.29 (m, 2H), 4.45 (s, 1H), 4.62-4.63 (m, 2H), 4.97-5.00 (m, 1H), 6.75-6.82 (m, 2H), 7.31-7.37 (m, 1H), 8.37 (s, 1H), 10.48 (m, 1H), 12.53 (br, 1H); ES<sup>+</sup> MS: 489 (M+1).

Example Z-46:

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(3-pyridinylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) 1,1-Dimethylethyl ((1*S*)-1-methyl-3-[(3-pyridinylmethyl)amino]propyl)carbamate. The protected diamine was prepared using a modified procedure as described in example Z-32. A solution of 1,1-dimethylethyl [(1*S*)-3-amino-1-methylpropyl]carbamate (0.296 g, 1.6 mmol) and 3-pyridinecarboxaldehyde (120 μL, 1.3 mmol) in a 1:1 mixture of anhydrous dichloroethane and tetrahydrofuran (10 mL) was treated with acetic acid (374 μL, 6.6

mmol) and stirred for 30 minutes. Sodium triacetoxyborohydride (0.444 g, 2.1 mmol) was added and the solution was stirred for 2 hours. The resultant was subjected to a workup and purification procedure as described in example Z-32 to give 1,1-dimethylethyl ((1*S*)-1-methyl-3-[(3-pyridinylmethyl)amino]propyl)carbamate (0.245 g, 66%) as a clear oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.12 (d, *J* = 6.4 Hz, 3H), 1.42 (s, 9H), 1.46-1.54 (m, 1H), 1.68 (m, 1H), 2.61-2.75 (m, 2H), 3.73-3.80 (m, 3H), 4.86 (m, 1H), 7.22-7.24 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 8.48 (m, 1H), 8.53 (m, 1H).

b) [(3*S*)-3-Aminobutyl](3-pyridinylmethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29.

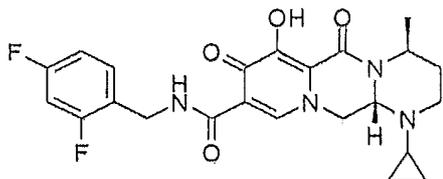
c)

(4*S*,12*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(3-pyridinylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (60 mg, 0.13 mmol) and free based [(3*S*)-3-aminobutyl](3-pyridinylmethyl)amine (83 mg, 0.47 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1-(3-pyridinylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (72 mg, 95%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(3-pyridinyl

methyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (34 mg, 56%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.37 (d, *J* = 6.8 Hz, 3H), 1.43-1.47 (m, 1H), 2.12 (m, 1H), 2.60-2.92 (m, 2H), 3.53 (d, *J* = 14.0 Hz, 1H), 3.82 (d, *J* = 14.4 Hz, 1H), 4.23-4.31 (m, 2H), 4.55-4.64 (m, 3H), 5.06-5.11 (m, 1H), 6.75-6.82 (m, 2H), 7.20-7.23 (m, 1H), 7.31-7.36 (m, 1H), 7.50 (m, 1H), 7.92 (s, 1H), 8.48 (s, 1H), 10.39 (m, 1H), 12.5 (br, 1H); ES<sup>+</sup> MS: 510 (M+1).

Example Z-47:

(4*S*,12*aS*)-1-Cyclopropyl-*N*'-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) 1,1-Dimethylethyl [(1*S*)-1-methyl-3-oxopropyl]carbamate. To a stirred solution of 1,1-dimethylethyl [(1*S*)-2-cyano-1-methylethyl]carbamate (0.656 g, 3.56 mmol) in anhydrous ether cooled to -40 °C was added dropwise a 1.0 M solution of diisobutylaluminum hydride in hexanes (14.2 mL, 14.2 mmol) over 20 minutes. Stirring was continued at this temperature for an additional 20 minutes. The yellow solution was quenched with Rochelle's salt and the resultant stirred at room temperature for 1 hour. The solids were filtered off through celite and rinsed with EtOAc. The organics were washed with brine, concentrated, and flash chromatographed (10-100% EtOAc/hexanes) to give 1,1-dimethylethyl [(1*S*)-1-methyl-3-oxopropyl]carbamate (0.193 g, 30 %) as a clear oil. <sup>1</sup>H NMR (400

MHz, CDCl<sub>3</sub>) δ 1.22 (d, *J* = 6.8 Hz, 3H), 1.41 (s, 9H), 2.53-2.65 (m, 2H), 4.08-4.13 (m, 1H), 4.63 (m, 1H), 9.74-9.75 (m, 1H).

b) 1,1-Dimethylethyl [(1*S*)-3-(cyclopropylamino)-1-methylpropyl]carbamate. The protected diamine was prepared using a modified procedure as described in example Z-32. A solution of 1,1-dimethylethyl [(1*S*)-1-methyl-3-oxopropyl]carbamate (0.178 g, 0.95 mmol) and cyclopropylamine (197 μL, 2.85 mmol) in anhydrous dichloroethane (10 mL) was treated with acetic acid (272 μL, 4.8 mmol) and stirred for 30 minutes. Sodium triacetoxyborohydride (0.444 g, 2.1 mmol) was added and the solution was stirred for 20 hours. The resultant was subjected to a workup and purification procedure as described in example Z-32 to give 1,1-dimethylethyl [(1*S*)-3-(cyclopropylamino)-1-methylpropyl]carbamate (0.136 g, 63%) as a clear oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.32-0.42 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.39-1.51 (m, 10H), 1.58-1.92 (m, 2H), 2.05-2.10 (m, 1H), 2.67-2.80 (m, 2H), 3.71 (m, 1H), 4.78 (m, 1H).

c) [(3*S*)-3-Aminobutyl]cyclopropylamine dihydrochloride was prepared in a similar manner as described in example Z-29. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 0.70-0.75 (m, 2H), 0.90-0.94 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.84-1.94 (m, 1H), 1.97-2.05 (m, 1H), 2.49-2.54 (m, 1H), 2.99-3.04 (m, 2H), 3.23-3.28 (m, 1H).

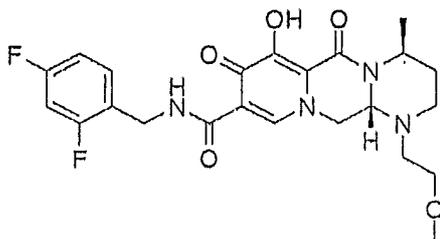
d)

(4*S*,12*aS*)-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. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based [(3*S*)-3-aminobutyl]cyclopropylamine (75 mg, 0.59 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-1-cyclopropyl-*N*[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (74 mg, 80%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-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 (32 mg, 52%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.37-0.54 (m, 3H), 0.64-0.70 (m, 1H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.45-1.49 (m, 1H), 1.76-1.80 (m, 1H), 2.03-2.12 (m, 1H), 2.86-2.93 (m, 1H), 2.99-3.04 (m, 1H), 4.30 (dd, *J* = 4.0, 13.6 Hz, 1H), 4.49-4.67 (m, 4H), 5.00-5.07 (m, 1H), 6.75-6.82 (m, 2H), 7.32-7.36 (m, 1H), 8.28 (s, 1H), 10.49 (m, 1H), 12.53 (s, 1H); ES<sup>+</sup> MS: 459 (M+1).

Example Z-48:

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)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.



a) [(3*S*)-3-Aminobutyl][2-(methoxy)ethyl]amine dihydrochloride. The protected diamine, 1,1-dimethylethyl ((1*S*)-1-methyl-3-[[2-(methoxy)ethyl]amino]propyl)carbamate was prepared in a similar manner as described in example Z-47. Subsequently, [(3*S*)-3-aminobutyl][2-(methoxy)ethyl]amine dihydrochloride was prepared in a similar manner as described in example Z-29. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 1.21 (d, *J* = 5.6 Hz, 3H), 1.93 (m, 1H), 2.04 (m, 1H), 2.98-3.05 (m, 4H), 3.22 (m, 2H), 3.26-3.31 (m, 4H), 8.06 (br, < 1 H), 8.81 (br, < 1 H).

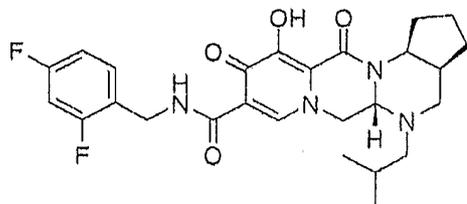
b)

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methoxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (60 mg, 0.13 mmol) and free based [(3*S*)-3-aminobutyl][2-(methoxy)ethyl]amine (53 mg, 0.37 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-4-methyl-1-[2-(methoxy)ethyl]-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (47 mg, 63%) as a film. This material was hydrogenated in a

second step as described in example Z-2 to give (4*S*,12*aS*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methoxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (38 mg, 97%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.34 (d, *J* = 7.2 Hz, 3H), 1.49 (m, 1H), 2.03-2.12 (m, 1H), 2.67-2.70 (m, 1H), 2.81-2.92 (m, 2H), 3.06-3.15 (m, 1H), 3.30-3.37 (m, 4H), 3.58-3.63 (m, 1H), 4.20 (dd, *J* = 3.4, 14.2 Hz, 1H), 4.50-4.59 (m, 1H), 4.62-4.65 (m, 3H), 5.00-5.03 (m, 1H), 6.75-6.81 (m, 2H), 7.31-7.37 (m, 1H), 8.27 (s, 1H), 10.46 (s, 1H), 12.54 (s, 1H); ES<sup>+</sup> MS: 477 (M+1).

Example Z-49:

*racemic*-(3*aS*,5*aS*,13*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-5-(2-methylpropyl)-10,12-dioxo-2,3,3*a*,4,5,5*a*,6,10,12,13*a*-decahydro-1*H*-cyclopenta[*e*]pyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) *racemic*-(1*S*,2*S*)-2-([(2-Methylpropyl)amino]methyl)cyclopentanamine hydrochloride.

In a manner similar to example Z-18*a-c*, from *racemic*-(1*R*,2*S*)-2-([(1,1-dimethylethyl)oxy]carbonyl)aminocyclopentanecarboxylic acid (255 mg, 1.11 mmol) was prepared *racemic*-1,1-dimethylethyl [(1*S*,2*S*)-2-(aminomethyl)cyclopentyl]carbamate (153 mg, 64 % over 3 steps) as a white green residue. Reductive amination with isobutyraldehyde followed by deprotection

as described in Z-38 steps c and d respectively, gave *racemic*-(1S,2S)-2-[(2-methylpropyl)amino]methylcyclopentanamine hydrochloride (105 mg, 39% over 5 steps from amino acid). <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) 8.90 (br s, <1 H), 8.64 (br s, <1 H), 8.28 (m, 1 H), 3.97 (br s, 1 H), 3.37 (m, 1 H), 2.83-2.69 (m, 3 H), 2.18-1.69 (m, 7 H), 0.996 (m, 6 H).

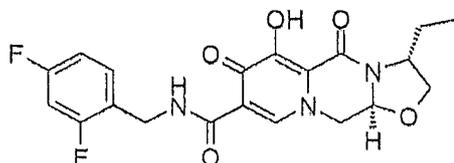
b)

*racemic*-(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. In a manner similar to that described in example Z-35, from *racemic*-(1S,2S)-2-[(2-methylpropyl)amino]methylcyclopentanamine hydrochloride (105 mg, 0.434 mmol) and 16a (56 mg, 0.119 mmol) was prepared *racemic*-(3aS,5aS,13aS)-N-[(2,4-difluorophenyl)methyl]-5-(2-methylpropyl)-10,12-dioxo-11-[(phenylmethyl)oxy]-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 (52 mg, 74%). This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-(3aS,5aS,13aS)-N-[(2,4-difluorophenyl)methyl]-5-(2-methylpropyl)-10,12-dioxo-11-[(phenylmethyl)oxy]-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 (48 mg, 0.081 mmol) and 10% Pd/C (catalytic amount), the title compound was prepared as a white solid after purification by HPLC (30 mg, 75%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 12.59 (s, 1 H), 10.42 (s, 1 H), 8.28 (s, 1 H),

7.34 (m, 1 H), 6.79 (m, 2 H), 4.83 (s, 1 H), 4.63-4.58 (m, 3 H), 4.29 (m, 1 H), 4.14 (m, 1 H), 2.91 (m, 1 H), 2.46-2.32 (m, 3 H), 2.15-2.09 (m, 2 H), 1.85-1.61 (m, 5 H), 1.39 (m, 1 H), 0.88 (m, 6 H); ES<sup>+</sup> MS: 501 (M + 1).

Example Z-50:

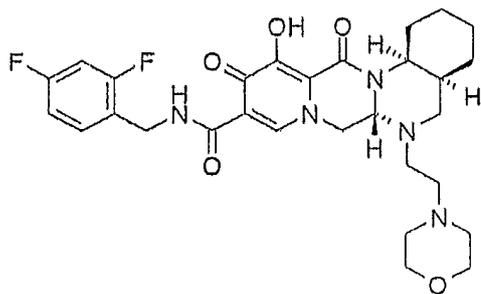
(3*R*,11*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and (2*R*)-2-amino-1-butanol (0.02 mL, 0.21 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*R*,11*aS*)-*N*-[(2,4-difluorophenyl)methyl]-3-ethyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 93%). This material was hydrogenated in a second step as described in example Z-2 to give (3*R*,11*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (30 mg, 91%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.49 (br, 1 H), 10.28 (m, 1 H), 8.35 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 ), 5.30 (m, 1 H), 4.62 (m, 2 H), 4.45-4.32 (m, 3 H), 3.93-3.86 (m, 2 H), 2.11 (m, 1 H), 1.65 (m, 1 H), 0.98 (t, *J* = 7.6 Hz, 3 H); ES<sup>+</sup> MS: 420 (M + 1).

Example Z-51:

*racemic*-(4a*S*,6a*S*,14a*S*)-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]pyrazin  
o[1,2-*a*]quinazoline-10-carboxamide.



- a) *racemic*-1,1-Dimethylethyl [(1*S*,2*R*)-2-formylcyclohexyl]carbamate. An alternative procedure from the one given in example Z-38b follows: To a solution of Dess-Martin Periodane (564 mg, 1.33 mmol) in dichloromethane was added *racemic*-1,1-dimethylethyl [(1*S*,2*R*)-2-(hydroxymethyl)cyclohexyl]carbamate (305 mg, 1.33 mmol, see example Z-38a) dropwise as a solution in dichloromethane. The reaction was stirred 1 hour at ambient temperature until judged complete by TLC (1:1 hexanes: ethyl acetate KMnO<sub>4</sub> stain). The reaction was quenched with aqueous sodium bicarbonate and sodium thiosulfate solutions, extracted with dichloromethane, and the combined organics were dried over sodium sulfate. Silica gel chromatography (0-50% ethyl acetate/ hexanes gradient elution) gave *racemic*-1,1-dimethylethyl [(1*S*,2*R*)-2-formylcyclohexyl]carbamate (280, 93%). See example Z-38b for NMR data.
- b) *racemic*-{[(1*S*,2*S*)-2-Aminocyclohexyl]methyl}[2-(4-morpholinyl)ethyl]amine

hydrochloride. In a manner similar to that described in example Z-38c-d from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (78 mg, 0.344 mmol, prepared using the procedure from example Z-38b) and [2-(4-morpholinyl)ethyl]amine (67 mg, 0.515 mmol) was prepared *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}[2-(4-morpholinyl)ethyl]amine hydrochloride (95 mg, 78% over 2 steps) as a white solid. <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) 8.18 (br s, 1 H), 3.84-3.493 (m, 11 H), 3.19-3.119 (m, 5 H), 2.42 (m, 1 H), 2.11 (br s, 2 H), 1.87-1.17 (m, 10 H).

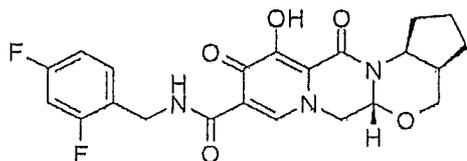
c)

*racemic*-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. In a manner similar to that described in example Z-35, from *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}[2-(4-morpholinyl)ethyl]amine hydrochloride (95 mg, 0.272 mmol) and 16a (45 mg, 0.0957 mmol) was prepared *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-[2-(4-morpholinyl)ethyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (27 mg, 43%). This material was deprotected in a second step similar to the procedure described in example Z-37. From *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-[2-(4-morpholinyl)ethyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':

4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (27 mg, 0.0408 mmol) and 10% Pd/C (1 mg) the title compound was prepared as a white solid after purification by HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 12.30 (br s, <1 H), 10.41 (br s, 1 H), 8.29 (s, 1 H), 7.34 (m, 2 H), 6.78 (m, 2 H), 4.76 (m, 1 H), 4.62-4.54 (m, 3 H), 4.29 (m, 2 H), 3.65 (m, 4 H), 3.01 (m, 1 H), 2.76 (m, 2 H), 2.58-2.42 (m, 7 H), 2.21 (m, 1 H), 1.89-1.23 (m, 8 H); ES<sup>+</sup> MS: 572 (M + 1).

Example Z-52:

*racemic*-(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.



a) *racemic*-1,1-Dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclopentyl]carbamate, *racemic*-(1R,2S)-2-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)cyclopentanecarboxylic acid (22 mg, 0.096 mmol) was dissolved in tetrahydrofuran and placed in an ice-water bath. Triethylamine was added, followed by the slow addition of methyl chloroformate. The reaction was stirred ten minutes in the ice-bath and sodium borohydride was added. Methanol was then added slowly and stirring was continued for two hours while the ice-bath expired. 1 M Potassium hydrogen sulfate was added, the reaction was partially concentrated, and product was extracted with dichloromethane. The combined organics were washed with sodium bicarbonate, brine, and dried over sodium sulfate. Removal of solvents under reduced pressure

afforded *racemic*-1,1-dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclopentyl]carbamate (25 mg, >100%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 4.50 (br s, 1 H), 4.06 (m, 1 H), 3.54 (m, 1 H), 3.37 (m, 1 H), 2.09 (m, 1 H), 1.96 (m, 1 H), 1.64 (m, 3 H), 1.52 (m, 1 H), 1.43 (s, 9 H), 1.11 (m, 2 H).

b) *racemic*-[(1R,2S)-2-Aminocyclopentyl]methanol hydrochloride. In a manner similar to that described in example, from *racemic*-1,1-dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclopentyl]carbamate and 4 N HCl was prepared *racemic*-[(1R,2S)-2-aminocyclopentyl]methanol hydrochloride (20 mg, quantitative). <sup>1</sup>H NMR (methanol-d<sub>4</sub>-CDCl<sub>3</sub>) 7.76 (br s, <1 H), 3.73 (m, 1 H), 3.61-3.28 (m, 3 H), 2.27 (br s, 1 H), 2.01 (m, 2.01 (m, 1 H), 1.74-1.70 (m, 2 H), 1.56-1.42 (m, 2 H), 1.16 (br s, 1 H), 1.05 (br s, 1 H).

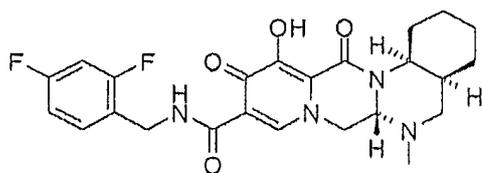
c)

*racemic*-(3aR,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. In a manner similar to that described in example Z-35, from *racemic*-[(1R,2S)-2-aminocyclopentyl]methanol hydrochloride (20 mg, 0.132 mmol) and 16a (24 mg, 0.051 mmol) was prepared *racemic*-(3aR,13aS)-N-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-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 (7 mg, 26 %) as a white solid. This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from

*racemic*-(3aR,13aS)-N-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-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 (7 mg, 0.012 mmol) and 10% Pd/C (1 mg), *racemic*-(3aR,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 (4 mg, 72%) white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 12.20 (br s, 1 H), 10.37 (br s, 1 H), 8.31 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 5.16 (m, 1 H), 4.77 (m, 1 H), 4.64 (m, 2 H), 4.28 (m, 1 H), 4.09 (m, 1 H), 3.97 (m, 1 H), 3.45 (m, 1 H), 2.49-2.20 (m, 2 H), 1.89-1.58 (m, 4 H), 0.936-0.840 (m, 1 H); ES<sup>+</sup> MS: 446 (M + 1).

Example Z-53:

*racemic*-(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.



a) *racemic*-{[(1S,2S)-2-Aminocyclohexyl]methyl}methylamine hydrochloride. In a manner similar to that described in example Z-38c-d from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (0.410 mmol) and methyl amine (0.5 mL of a 2 M tetrahydrofuran solution) was prepared *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}methylamine hydrochloride in two steps as a white solid (46 mg, 53% 2 steps). <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) 9.05 (br s, <1

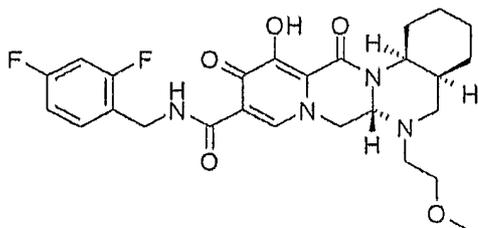
H), 8.72 (br s, < 1 H), 8.24 (br s, 1 H), 3.34 (m, 1 H), 3.29 (m, 1 H), 2.85 (br s, 1H), 2.66 (br s, 4 H), 2.38 (br s, 1 H), 2.07-1.83 (m, 2 H), 1.67-1.14 (m, 6 H).

b)

*racemic*-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-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. In a manner similar to that described in example Z-35, from *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}methylamine hydrochloride (46 mg, 0.215 mmol) and 16a (35 mg, 0.0744 mmol) was prepared *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-methyl-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (17 mg, 41%) as a white solid. This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-methyl-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (17 mg, 0.0302 mmol) and 10% Pd/C (1 mg) was prepared the title compound as a white solid (9 mg, 64%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 10.44 (m, 1 H), 8.29 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 4.78 (m, 1 H), 4.62 (br s, 2 H), 4.29 (br s, 2 H), 3.41 (s, 1 H), 2.92 (m, 1 H), 2.66 (m, 1 H), 2.35-2.25 (m, 4 H), 1.90-1.74 (m, 2 H), 1.67-1.24 (m, 6 H); ES<sup>+</sup> MS: 473(M+1).

Example Z-54:

*racemic*-(4*aS*,6*aS*,14*aS*)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methoxy)ethyl]-11,13-dioxo-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-*a*]quinazoline-10-carboxamide.



a) *racemic*-{[(1*S*,2*S*)-2-Aminocyclohexyl]methyl}[2-(methoxy)ethyl]amine hydrochloride.

In a manner similar to that described in example Z-38c-d from *racemic*-1,1-dimethylethyl [(1*S*,2*R*)-2-formylcyclohexyl]carbamate (93 mg, 0.410 mmol) and [2-(methoxy)ethyl]amine (0.05 mL, 0.615 mmol) was prepared in two steps *racemic*-{[(1*S*,2*S*)-2-aminocyclohexyl]methyl}[2-(methoxy)ethyl]amine hydrochloride (63 mg, 60% 2 steps) as a white solid. <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) 9.02 (br s, <1 H), 8.78 (br s, <1, H), 8.29 (br s, 1 H), 3.69 (br s, 2 H), 3.46 (s, 3 H), 3.36-3.18 (m, 4 H), 2.97 (br s, 1 H), 2.46 (br s, 1 H), 1.86-1.40 (m, 8 H).

b)

*racemic*-4*aS*,6*aS*,14*aS*)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methoxy)ethyl]-11,13-dioxo-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-*a*]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from *racemic*-{[(1*S*,2*S*)-2-aminocyclohexyl]methyl}[2-(methoxy)ethyl]amine hydrochloride (63mg, 0.244 mmol) and 16a (40 mg, 0.0851 mmol) was prepared



hydrochloride. In a manner similar to that described in example Z-38c-d from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (93 mg, 0.41 mmol) and N-(2-aminoethyl)acetamide (63 mg, 0.615 mmol), *racemic*-N-[2-(((1S,2S)-2-aminocyclohexyl)methyl)amino]ethyl]acetamide hydrochloride was prepared in two steps as a white solid (82 mg), 71% 2 steps). <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) 8.86 (br s, 1 H), 8.29 (br s, 1 H), 3.62-3.51 (m, 3 H), 3.40-3.28 (m, 4 H), 3.22-2.93 (m, 3 H), 2.47 (m, 1 H), 2.08-2.06 (m, 4 H), 1.83-1.75 (m, 2 H), 1.56-1.44 (m, 3 H), 1.23 (m, 1 H).

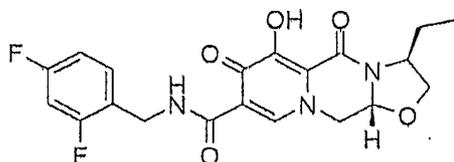
b)

*racemic*-4aS,6aS,14aS)-6-[2-(Acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-11,13-dihydroxy-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. In a manner similar to that described in example Z-35, from *racemic*-N-[2-(((1S,2S)-2-aminocyclohexyl)methyl)amino]ethyl]acetamide hydrochloride (82 mg, 0.349 mmol) and 16a (50 mg, 0.106 mmol) was prepared the title compound (24 mg, 36%). This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-4aS,6aS,14aS)-6-[2-(acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (24 mg, 0.0379 mmol) and 10% Pd/C (1 mg) was prepared the title compound as a white solid after purification by HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 12.59 (s, 1 H), 10.44 (s, 1 H), 8.35 (s, 1 H), 7.32 (m, 1 H), 6.79 (m, 2 H), 5.86

(s, 1 H), 4.78 (m, 1 H), 4.61-4.50 (m, 3 H), 4.30 (m, 1 H), 3.35 (m, 1 H), 3.18 (m, 1 H), 2.96 (m, 1 H), 2.76 (m, 2 H), 2.48 (m, 1 H), 2.19 (m, 1 H), 1.89-1.23 (m, 12 H); ES<sup>+</sup> MS: 544 (M + 1).

Example Z-56:

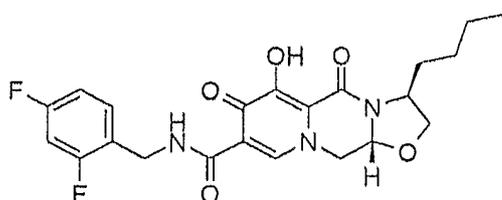
(3*S*,11*a**R*)-*N*[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and (2*S*)-2-amino-1-butanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11*a**R*)-*N*[(2,4-difluorophenyl)methyl]-3-ethyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (39 mg, 90%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11*a**R*)-*N*[(2,4-difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (37 mg, 99%) as a tinted white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.47 (br, 1 H), 10.26 (m, 1 H), 8.35 (s, 1 H), 7.32 (m, 1 H), 6.77 (m, 2 ), 5.29 (m, 1 H), 4.60 (m, 2 H), 4.47-4.32 (m, 3 H), 3.93-3.85 (m, 2 H), 2.08 (m, 1 H), 1.68 (m, 1 H), 0.95 (t, *J* = 7.6 Hz, 3 H); ES<sup>+</sup> MS: 420 (M + 1).

Example Z-57:

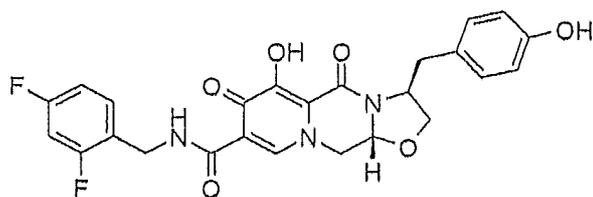
(3*S*,11*a**R*)-3-Butyl-*N*'[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*g*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and (2*S*)-2-amino-1-hexanol (100 mg) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11*a**R*)-3-butyl-*N*'[(2,4-difluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (43 mg, 94%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11*a**R*)-3-butyl-*N*'[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (33 mg, 92%) as a tinted white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.48 (br, 1 H), 10.27 (br, 1 H), 8.36 (br, 1 H), 7.81 (m, 1 H), 6.77 (m, 2), 5.28 (m, 1 H), 4.59-4.36 (m, 5 H), 3.83 (m, 2 H), 2.08 (m, 1 H), 1.58 (m, 1 H), 1.39-1.23 (m, 4 H), 0.90 (t, *J* = 6.8 Hz, 3 H); ES<sup>+</sup> MS: 448 (M+1).

Example Z-58:

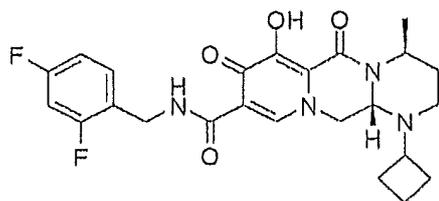
(3*S*,11*a**R*)-*N*'[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(4-hydroxyphenyl)methyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and 4-[(2*S*)-2-amino-3-hydroxypropyl]phenol (43 mg, 0.21 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11*aR*)-*N*[(2,4-difluorophenyl)methyl]-3-[(4-hydroxyphenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (10 mg, 20%). This material was hydrogenated in a second step as described in example Z-2 and purified via preparative HPLC to give (3*S*,11*aR*)-*N*[(2,4-difluorophenyl)methyl]-6-hydroxy-3-[(4-hydroxyphenyl)methyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (7 mg, 63%) as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 10.43 (m, 1 H), 8.34 (s, 1 H), 7.33 (m, 1 H), 7.00 (d, *J* = 8.4 Hz, 2 H), 6.82 (m, 2 H), 6.71 (d, *J* = 8.4 Hz, 2 H), 5.05 (m, 1 H), 4.67-4.57 (m, 4 H), 4.21 (dd, *J* = 8.8, 7.2 Hz, 1 H), 3.94 (dd, *J* = 8.8, 6.4 Hz, 1 H), 3.21 (dd, *J* = 13.2, 3.2 Hz, 1 H), 2.90 (dd, *J* = 13.6, 8.8 Hz, 1 H); ES<sup>+</sup> MS: 498 (M+1).

Example Z-59:

(4*S*,12*aS*)-1-Cyclobutyl-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl]cyclobutylamine dihydrochloride was prepared in a similar manner as described in example Z-47. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 1.23 (d, *J* = 6.4 Hz, 3H), 1.69-2.26 (m, 8H), 2.83 (m, 2H), 3.31-3.33 (m, 1H), 3.55 (m, 1H), 8.08 (br, <1H), 9.07 (br, <1H).

b)

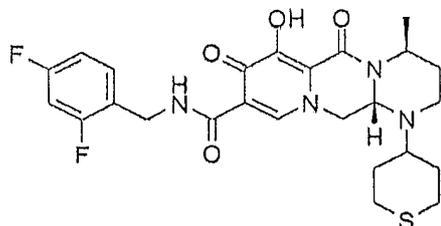
(4*S*,12*aS*)-1-Cyclobutyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based [(3*S*)-3-aminobutyl]cyclobutylamine (96 mg, 0.68 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-1-cyclobutyl-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (68 mg, 70%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-1-cyclobutyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (57 mg, 100%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.31 (d, *J* = 6.8 Hz, 3H), 1.46-1.70 (m, 4H), 1.91-2.12 (m, 4H), 2.52 (m, 1H), 2.90-2.93 (m, 1H), 3.06 (m,

1H), 4.16-4.29 (m, 3H), 4.57-4.66 (m, 2H), 4.99-5.05 (m, 1H), 6.75-6.82 (m, 2H), 7.32-7.38 (m, 1H), 8.20 (s, 1H), 10.44 (s, 1H), 12.51 (s, 1H); ES<sup>+</sup> MS: 473 (M+1).

Example Z-60:

(4*S*,12*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl]tetrahydro-2*H*-thiopyran-4-ylamine dihydrochloride was prepared in a similar manner as described in example Z-47. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 1.21 (d, *J* = 6.4 Hz, 3H), 1.65-1.75 (m, 2H), 1.90-2.10 (m, 2H), 2.35 (m, 2H), 2.56-2.61 (m, 4H), 2.92-2.98 (m, 3H), 3.27-3.31 (m, 1H), 8.05 (br, <1H), 8.90 (br, <1H).

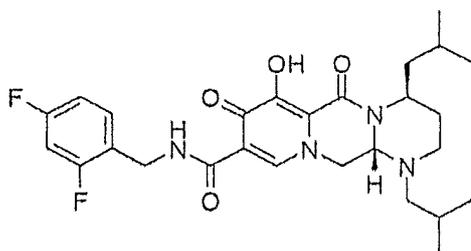
b)

(4*S*,12*aS*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based [(3*S*)-3-aminobutyl]tetrahydro-2*H*-thiopyran-4-ylamine (108 mg, 0.58 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give

(4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1-(tetrahydro-2*H*thiopyran-4-yl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (56 mg, 54%) as a film. This material was debenzylated in a second step to in a manner similar to Z-26 to give (4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*thiopyran-4-yl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (56 mg, >100%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.30 (d, *J* = 6.8 Hz, 3H), 1.54-1.58 (m, 1H), 1.72-1.82 (m, 3H), 1.97-2.11 (m, 2H), 2.60-2.76 (5H), 2.86 (m, 2H), 4.17-4.30 (m, 2H), 4.62-4.66 (m, 3H), 4.92-4.96 (m, 1H), 6.75-6.82 (m, 2H), 7.32-7.38 (m, 1H), 8.31 (s, 1H), 10.46 (s, 1H), 12.48 (s, 1H); ES<sup>+</sup> MS: 519 (M+1).

Example Z-61:

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Amino-5-methylhexyl](2-methylpropyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ 0.87 (d, *J* = 6.4 Hz, 6H), 0.97 (d, *J* = 6.8 Hz, 6H), 1.34-1.41 (m, 1H), 1.45-1.52 (m, 1H), 1.58-1.66 (m, 1H), 2.01-2.13 (m, 2H), 2.72-2.73 (m, 2H), 3.03-3.06

(m, 2H), 3.29 (m, 2H), 8.07 (br, <1H), 8.71 (br, <1H).

b)

(4*S*,12*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.

The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based

[(3*S*)-3-amino-5-methylhexyl](2-methylpropyl)amine (117 mg, 0.63 mmol) were

reacted in dichloromethane (2 mL) with acetic acid to give

(4*S*,12*aS*)-*N*-[(2,4-difluorophenyl)methyl]-1,4-bis(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (68 mg, 66%) as a film. This material was hydrogenated in a second step

as described in example Z-2 to give

(4*S*,12*aS*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide

(56 mg, 97%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.74 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.97-1.00 (m, 6H), 1.37-1.83 (m, 5H), 2.03-2.12 (m, 2H),

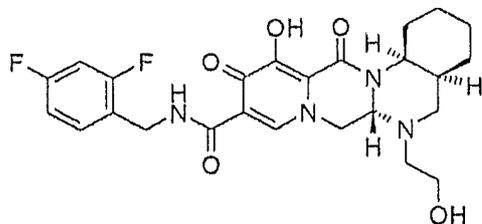
2.21-2.28 (m, 1H), 2.77 (m, 1H), 2.90-2.93 (m, 1H), 4.19-4.40 (m, 3H), 4.59-4.70 (m, 2H), 4.96-4.97 (m, 1H), 6.77-6.83 (m, 2H), 7.33-7.39 (m, 1H), 8.28 (s, 1H), 10.47 (s, 1H),

12.59 (br, 1H); ES<sup>+</sup> MS: 517 (M+1).

Example Z-62:

*racemic*-(4*aS*,6*aS*,14*aS*)-*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.



a) *racemic*-2-(((1*S*,2*S*)-2-Aminocyclohexyl)methyl)amino)ethanol hydrochloride.

In a manner similar to that described in example Z-55a, from *racemic*-1,1-dimethylethyl [(1*S*,2*R*)-2-formylcyclohexyl]carbamate (112 mg, 0.497 mmol) and 2-aminoethanol (0.04 mLm 0.746 mmol) was prepared *racemic*-2-(((1*S*,2*S*)-2-aminocyclohexyl)methyl)amino)ethanol bis-hydrochloride in two steps (102 mg, 84% over 2 steps). <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) 8.81-8.40 (m, < 2 H), 8.16 (br s, 1 H), 4.02-3.93 (m, 2 H), 3.80 (br s, 2 H), 3.53 (m, 1 H), 3.36-2.93 (m, 6 H), 2.41 (br s, 1 H), 2.05 (m, 1 H), 1.75-1.41 (m, 4 H).

b)

*racemic*-(4*aS*,6*aS*,14*aS*)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-hydroxyethyl)-11,13-dioxo-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from 16a (45 mg, 0.0957 mmol) and *racemic*-2-(((1*S*,2*S*)-2-aminocyclohexyl)methyl)amino)ethanol hydrochloride (102 mg, 0.418 mmol) was prepared *racemic*-(4*aS*,6*aS*,14*aS*)-N-[(2,4-difluorophenyl)methyl]-6-(2-hydroxyethyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyra

zino[1,2-a]quinazoline-10-carboxamide (7 mg, 12 %) as a white solid after silica gel chromatography (1-12% methanol/dichloromethane gradient elution). This material was deprotected in a second step similar to the procedure described in example Z-37.

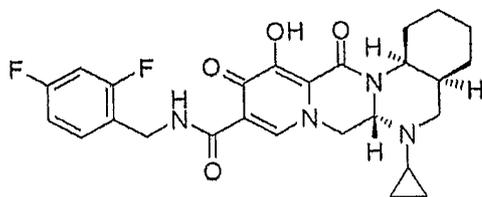
Thus,

from

*racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-(2-hydroxyethyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (7 mg, 0.0118 mmol) the title compound was prepared after purification by HPLC (3 mg, 50 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 12.57 (br s, 1 H), 10.45 (m, 1 H), 8.29 (s, 1 H), 7.34 (m, 1 H), 6.78 (m, 2 H), 4.80 (m, 1 H), 4.71 (s, 1 H), 4.62 (m, 2 H), 4.44 (m, 1 H), 4.33 (m, 1 H), 3.75 (m, 1 H), 3.62-3.20 (m, 3 H), 3.13 (m, 1 H), 2.74-2.71 (m, 2 H), 2.24 (m, 1 H), 1.90-1.37 (m, 12 H), 1.27-1.23 (m, 3 H) 1.12 (m, 1 H); ES<sup>+</sup> MS: 503 (M+1).

Example Z-63:

*racemic*-(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.



a) *racemic*-(1S,2S)-2-[(Cyclopropylamino)methyl]cyclohexanamine hydrochloride.

In a manner similar to that described in example Z-55a, from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (112 mg, 0.497

mmol) and cyclopropylamine (0.05 mL, 0.746 mmol) was prepared *racemic*-(1*S*,2*S*)-2-[(cyclopropylamino)methyl]cyclohexanamine bis hydrochloride salt in two steps (102 mg, 86% over 2 steps). This material was used without further purification. <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) 8.31 (br s, 1 H), 3.75 (br s, 1 H), 3.54 (m, 1 H), 2.96 (m, 1 H), 2.71 (m, 1 H), 2.27 (m, 1 H), 1.94 (m, 1 H), 1.76-1.15 (m, 8 H), 0.88-0.78 (m, 3 H).

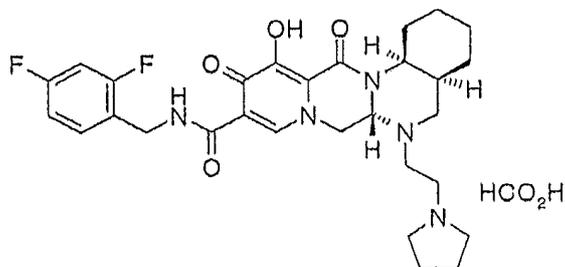
b)

*racemic*-(4*aS*,6*aS*,14*aS*)-6-cyclopropyl-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-*a*]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from 16a (45 mg, 0.0957 mmol) and *racemic*-(1*S*,2*S*)-2-[(cyclopropylamino)methyl]cyclohexanamine hydrochloride (102 mg, 0.425 mmol) was prepared *racemic*-(4*aS*,6*aS*,14*aS*)-6-cyclopropyl-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-*a*]quinazoline-10-carboxamide as a white solid after silica gel chromatography (1-12% methanol/dichloromethane gradient elution). This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-(4*aS*,6*aS*,14*aS*)-6-cyclopropyl-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-*a*]quinazoline-10-carboxamide (56 mg, 0.0949 mmol) the title compound was prepared as a white solid (41 mg, 81%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 12.10 (br s, < 1 H), 10.45

(m, 1 H), 8.27 (s, 1 H), 7.33 (m, 1 H), 6.88 (m, 2 H), 4.77 (m, 1 H), 4.61-4.49 (m, 4 H), 4.33 (m, 1 H), 2.94 (m, 1 H), 2.79 (m, 1 H), 2.17 (m, 1 H), 1.86-0.86 (m, 10 H), 0.658 (m, 1 H), 0.499-0.32 (m, 2 H); ES<sup>+</sup> MS: 499 (M + 1).

Example Z-64:

*racemic*-(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-dodecahydropyridol[1',2':4,5]pyrazin  
o[1,2-a]quinazoline-10-carboxamide formic acid salt



a) *racemic*-(1S,2S)-2-({[2-(1-Pyrrolidinyl)ethyl]amino}methyl)cyclohexanamine hydrochloride. In a manner similar to that described in example Z-55a, from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (112 mg, 0.497 mmol) and 2-(1-pyrrolidinyl)ethanamine (0.09 mL, 0.746 mmol) was prepared *racemic*-(1S,2S)-2-({[2-(1-pyrrolidinyl)ethyl]amino}methyl)cyclohexanamine (88 mg, 60% 2 steps) as the bis hydrochloride salt in two steps as a white solid. <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) 9.68 (br s, < 1 H), 9.24 (br s, < 1 H), 8.25 (br s, 1 H), 3.75-3.04 (m, 11 H), 2.37 (br s, 1 H), 2.06-1.20 (m, 12 H).

b)

*racemic*-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dio

oxo-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 formic acid salt.

In a manner similar to that described in example Z-35, from 16a (30 mg, 0.0638 mmol) and

*racemic*-(1S,2S)-2-({[2-(1-pyrrolidinyl)ethyl]amino)methyl)cyclohexanamine

hydrochloride (88 mg, 0.296 mmol) was prepared

*racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-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 as a white solid (31 mg, 76%) after

silica gel chromatography (1-12% methanol/dichloromethane gradient elution). This

material was deprotected in a second step similar to the procedure described in

example Z-37. Thus, from

*racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-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 (31 mg, 0.048 mmol) the title

compound was prepared as a yellow solid after purification by HPLC (18 mg, 66%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 10.39 (br s, 1 H), 8.56 (br s, 1 H), 8.39 (br s, 1 H), 7.34 (m, 1 H),

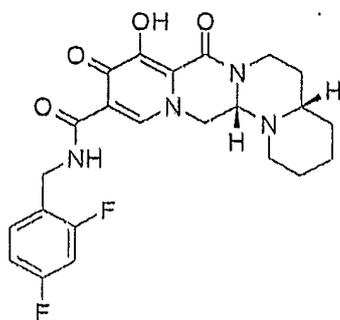
6.78 (m, 2 H), 4.76-4.40 (m, 6 H), 3.26-2.89 (m, 7 H), 2.73 (m, 1 H), 2.15 (m, 1 H),

2.02-1.18 (m, 14 H); ES<sup>+</sup> MS: 556 (M + 1).

#### Example Z-65:

(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-carboxami

de.



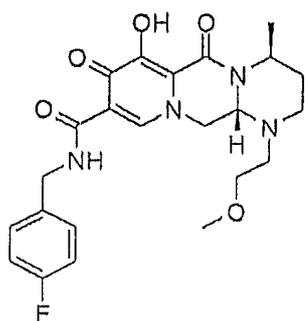
a) {2-[(2S)-2-Piperidinylethyl]amine. This compound was prepared in a similar manner as its enantiomer described in example Z-42a.

b)

(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. In a manner similar to that described in example Z-35, from {2-[(2S)-2-piperidinyl]ethyl}amine (28 mg, 0.218 mmol) and 16a (30 mg, 0.0638 mmol) was prepared (4aS,14aS)-N-[(2,4-difluorophenyl)methyl]-8,10-dioxo-9-[(phenylmethyl)oxy]-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 (29 mg, 82%). This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a white solid (26 mg, quantitative). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.44 (br s, 1 H), 10.48 (s, 1 H), 8.26 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 4.68-4.57 (m, 2 H), 4.38 (m, 1 H), 4.20 (m, 1 H), 3.93 (s, 1H), 3.63-3.39 (m, 2 H), 2.91 (m, 2 H), 2.29 (br s, 1 H), 2.02 (m, 1 H), 1.69-1.45 (m, 4 H), 1.30-1.24 (m, 2 H), 1.12 (br s, 1 H); ES<sup>+</sup> MS: 459 (M+1).

Example Z-66:

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methoxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide.



a) [(3S)-3-Aminobutyl][2-(methoxy)ethyl]amine bis hydrochloride. In a manner similar to that described in example Z-47, from 1,1-dimethylethyl [(1S)-1-methyl-3-oxopropyl]carbamate (76 mg, 0.406 mmol) and 2-(methoxy)ethylamine (0.05 mL, 0.609 mmol) was prepared [(3S)-3-aminobutyl][2-(methoxy)ethyl]amine as the bis hydrochloride salt in two steps (19 mg, quantitative). <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) δ 9.02 (< 1 H), 8.24 (< 1 H), 3.68 (br s, 2 H), 3.49 (br s, 1 H), 3.34 (br s, 4 H), 3.15 (br s, 4 H), 2.26-2.11 (m, 2 H), 1.35 (br s, 3 H).

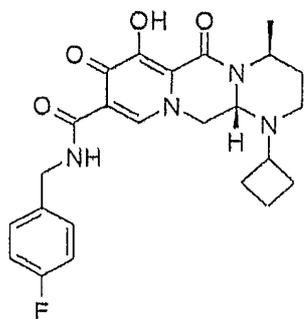
b)

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methoxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide. In a manner similar to that described in example Z-35, from 16 (15

mg, 0.034 mmol) and [(3S)-3-Aminobutyl][2-(methoxy)ethyl]amine bis hydrochloride (19 mg, 0.087 mmol), (4S,12aS)-N-[(4-fluorophenyl)methyl]-4-methyl-1-[2-(methoxy)ethyl]-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide was prepared as a white solid after silica gel chromatography (1-12% methanol/dichloromethane). This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a yellow solid (9 mg, 60 %, 2 steps). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.56 (s, 1 H), 10.51 (m, 1 H), 8.29 (s, 1 H), 7.32 (m, 2 H), 6.98 (m, 2 H), 5.03 (m, 1 H), 4.65-4.59 (m, 2 H), 4.53 (m, 1 H), 4.21 (m, 1 H), 3.61-3.40 (m, 2 H), 3.34-3.13 (m, 3 H), 3.08 (m, 1 H), 2.94-2.84 (m, 2 H), 2.68 (m, 1 H), 2.07 (m, 1 H), 1.50 (m, 1 H), 1.35 (d, *J* = 7.2 Hz, 3 H), 1.14 (m, 1 H); ES<sup>+</sup> MS: 459 (M+1).

Example Z-67:

(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.



a) [(3S)-3-Aminobutyl]cyclobutylamine bis-hydrochloride. In a manner similar to that described in example Z-47, from 1,1-dimethylethyl

[(1S)-1-methyl-3-oxopropyl]carbamate (76 mg, 0.406 mmol) and cyclobutylamine (0.05 mL, 0.609 mmol) was prepared [(3S)-3-Aminobutyl]cyclobutylamine bis-hydrochloride in two steps (23 mg, 27%). <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) δ 8.86 (s, < 1 H), 7.97 (s, < 1 H), 3.46 (m, 1 H), 3.21 (m, 1 H), 2.74 (m, 2 H), 2.14-2.08 (m, 4 H), 1.94-1.62 (m, 5 H), 1.13 (d, *J* = 6 Hz, 1 H).

b)

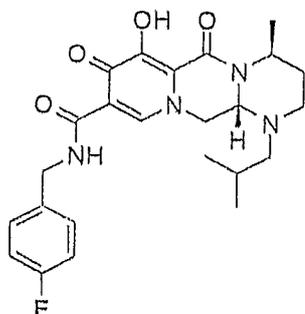
(4S,12aS)-1-Cyclobutyl-N-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide. In a similar manner to that described in example Z-35a, from 16 (18 mg, 0.39 mmol) and [(3S)-3-Aminobutyl]cyclobutylamine bis-hydrochloride (23 mg, 0.107 mmol),

(4S,12aS)-1-cyclobutyl-N-[(4-fluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide was prepared as a white solid. This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a white solid after purification by HPLC (4.5 mg, 25 % 2 steps). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.54 (s, 1 H), 10.48 (s, 1 H), 8.20 (s, 1 H), 7.31 (m, 2 H), 6.98 (m, 2 H), 5.02 (m, 1 H), 4.61-4.57 (m, 2 H), 4.26-4.14 (m, 3 H), 3.05 (m, 1 H), 2.90 (m, 1 H), 2.49 (m, 1 H), 2.12 (m, 1 H), 2.05-1.87 (m, 3 H), 1.84-1.61 (m, 3 H), 1.46 (m, 1 H), 1.32 (m, 3 H); ES<sup>+</sup> MS: 455 (M+1).

Example Z-68:

(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-carboxamid

e



a) [(3S)-3-Aminobutyl](2-methylpropyl)amine bis-hydrochloride. In a manner similar to that described in example Z-47, this compound was prepared from 1,1-dimethylethyl [(1S)-1-methyl-3-oxopropyl]carbamate (76 mg, 0.406 mmol) and (2-methylpropyl)amine (0.06 mL, 0.609 mmol) in two steps as the bis-hydrochloride salt (22 mg, 25 %). <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>/CDCl<sub>3</sub>) δ 3.25 (br s, 1 H), 2.91 (br s, 2 H), 2.64 (m, 2 H), 2.02-1.93 (m, 3 H), 1.17 (m, 3 H), 0.88 (m, 6 H).

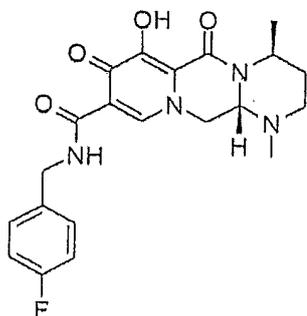
b)

(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. In a similar manner to that described in example Z-35, from 16 (16 mg, 0.035 mmol) and [(3S)-3-Aminobutyl](2-methylpropyl)amine bis-hydrochloride (20 mg, 0.0925 mmol), (4S,12aS)-N-[(4-fluorophenyl)methyl]-4-methyl-1-(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-

carboxamide was prepared as a white solid. This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a tan solid (13 mg, 68% 2 steps).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  12.57 (s, 1 H), 10.46 (s, 1 H), 8.27 (s, 1 H), 7.32 (m, 2 H), 6.99 (m, 2 H), 4.98 (m, 1 H), 4.63-4.54 (m, 2 H), 4.45 (m, 1 H), 4.26-4.16 (m, 2 H), 2.91 (m, 1 H), 2.77 (m, 1 H), 2.24 (m, 1 H), 2.14-2.03 (m, 2 H), 1.68 (m, 1 H), 1.48 (m, 1 H), 1.33 (m, 3 H), 1.09 (m, 1 H), 0.850 (m, 3 H), 0.789 (m, 3 H);  $\text{ES}^+$  MS: 457 (M+1).

Example Z-69:

(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.



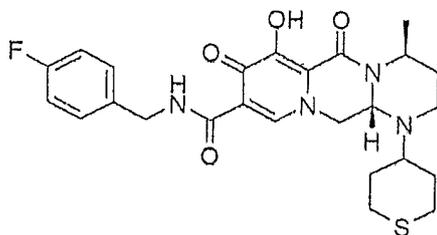
a) [(3S)-3-Aminobutyl]methylamine bis-hydrochloride. In a manner similar to that described in example Z-47, this compound was prepared from 1,1-dimethylethyl [(1S)-1-methyl-3-oxopropyl]carbamate (76 mg, 0.409 mmol) and excess methylamine (2 M in tetrahydrofuran) in two steps as the bis hydrochloride salt (17% 2 steps).  $^1\text{H}$  NMR (methanol- $d_4$ / $\text{CDCl}_3$ )  $\delta$  3.16 (m, 1 H), 3.08 (s, 2 H), 2.83 (m, 2 H), 2.45 (s, 3 H), 1.88 (m, 1 H), 1.75 (m, 1 H), 1.09 (m, 3 H).

b) .

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. In a similar manner to that described in example Z-35, from 16 (18 mg, 0.0398 mmol) and [(3*S*)-3-aminobutyl]methylamine bis-hydrochloride (19 mg, 0.109 mmol, (4*S*,12*aS*)-*N*-[(4-fluorophenyl)methyl]-1,4-dimethyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide was prepared as a white solid. This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a tan solid (7 mg, 44% 2 steps). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.53 (s, 1 H), 10.47 (s, 1 H), 8.29 (s, 1 H), 7.32 (m, 2 H), 6.99 (m, 2 H), 5.04 (1 H), 4.60 (m, 2 H), 4.23 (s, 3 H), 2.83-2.80 (m, 2 H), 2.32 (s, 3 H), 2.13 (m, 1 H), 1.48 (m, 1 H), 1.34 (m, 3 H); ES<sup>+</sup> MS: 415 (M+1).

Example Z-70:

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.

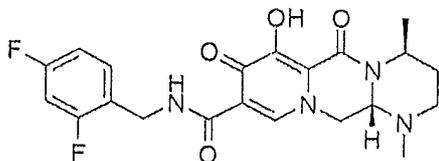


The title compound was made in two steps using a similar process to that described in example Z-2. 16 (25 mg, 0.055 mmol) and free based [(3*S*)-3-aminobutyl]tetrahydro-2*H*-thiopyran-4-ylamine (48 mg, 0.26 mmol) were

reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*[(4-fluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (16 mg, 49%) as a film. This material was debenzylated in a second step in a manner similar to Z-26 to give (4*S*,12*aS*)-*N*[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (8 mg, 59%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.30 (d, *J* = 7.2 Hz, 3H), 1.53-1.58 (m, 1H), 1.72-2.10 (m, 5H), 2.56-2.76 (m, 5H), 2.84-2.87 (m, 2H), 4.18 (dd, *J* = 2.8, 14.0 Hz, 1H), 4.26 (dd, *J* = 3.4, 14.2 Hz, 1H), 4.92-4.97 (m, 1H), 6.96-7.00 (m, 2H), 7.29-7.36 (m, 2H), 8.31 (s, 1H), 10.48 (m, 1H), 12.48 (br, 1H); ES<sup>+</sup> MS: 501 (M+1).

Example Z-71:

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



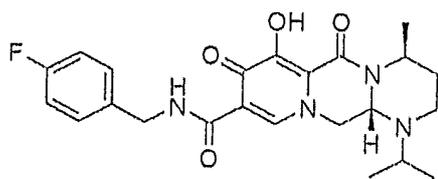
a) [(3*S*)-3-Aminobutyl]methylamine dihydrochloride was prepared in a similar manner as described in example Z-47. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.18 (d, *J* = 6.8 Hz, 3H), 1.82-1.91 (m, 1H), 1.94-2.03 (m, 1H), 2.53 (s, 3H), 2.89-2.93 (m, 2H), 3.22-3.30 (m, 1H), 8.02 (br, <1H), 8.81 (br, <1H).

b)

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.085 mmol) and free based [(3*S*)-3-aminobutyl]methylamine (24 mg, 0.23 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-1,4-dimethyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (39 mg, 89%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (32 mg, 97%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.33 (d, *J* = 6.4 Hz, 3H), 1.46-1.50 (m, 1H), 2.12-2.14 (m, 1H), 2.32 (s, 3H), 2.83 (m, 2H), 4.24 (m, 3H), 4.62 (m, 2H), 5.02 (m, 1H), 6.77-6.79 (m, 2H), 7.33 (m, 1H), 8.30 (s, 1H), 10.43 (s, 1H), 12.50 (br, 1H); ES<sup>+</sup> MS: 433 (M+1).

Example Z-72:

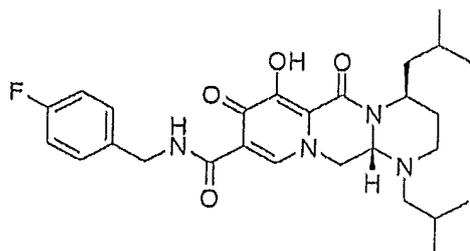
(4*S*,12*aS*)-*N*[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16 (27 mg, 0.060 mmol) and free based [(3S)-3-aminobutyl](1-methylethyl)amine (67 mg, 0.51 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*[(4-fluorophenyl)methyl]-4-methyl-1-(1-methylethyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (18 mg, 56%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-*N*[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (15 mg, >100%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.02 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.54-1.58 (m, 1H), 1.94-2.03 (m, 1H), 2.71-2.76 (m, 1H), 2.82-2.88 (m, 1H), 3.13-3.16 (m, 1H), 4.16-4.19 (m, 1H), 4.30-4.33 (m, 1H), 4.48 (m, 1H), 4.55-4.65 (m, 2H), 4.97-5.00 (m, 1H), 6.97-7.01 (m, 2H), 7.30-7.34 (m, 2H), 8.28 (s, 1H), 10.51 (m, 1H), 12.55 (s, 1H); ES<sup>+</sup> MS: 443 (M+1).

Example Z-73:

(4*S*,12*aS*)-*N*[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



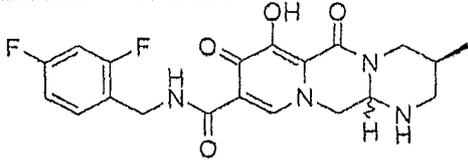
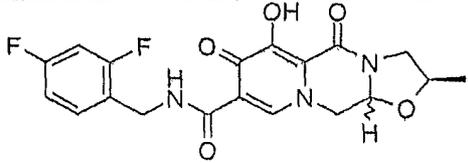
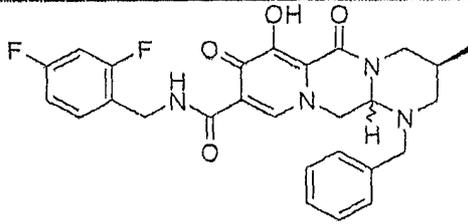
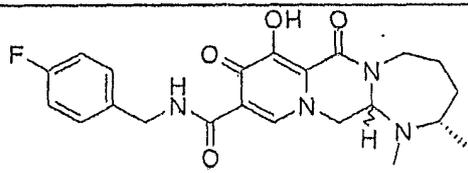
The title compound was made in two steps using a similar process to that described in example Z-2. 16 (25 mg, 0.055 mmol) and free based [(3*S*)-3-amino-5-methylhexyl](2-methylpropyl)amine (21 mg, 0.11 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12*aS*)-*N*'[(4-fluorophenyl)methyl]-1,4-bis(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (8 mg, 25%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12*aS*)-*N*'[(4-fluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (5 mg, 78%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.74 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.97-1.00 (m, 6H), 1.37-1.66 (m, 5H), 1.75-1.82 (m, 1H), 2.05-2.09 (m, 2H), 2.21-2.26 (m, 1H), 2.72-2.79 (m, 1H), 2.87-2.93 (m, 1H), 4.16-4.26 (m, 2H), 4.38 (m, 1H), 4.55-4.66 (m, 2H), 4.93-4.99 (m, 1H), 6.97-7.02 (m, 2H), 7.31-7.34 (m, 2H), 8.27 (s, 1H), 10.49 (m, 1H), 12.61 (s, 1H); ES<sup>+</sup> MS: 499 (M+1).

#### Example ZZ-1 to ZZ-24

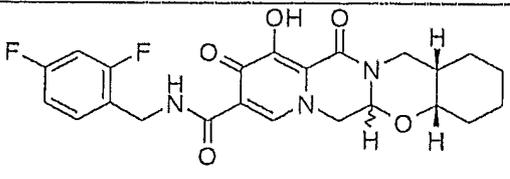
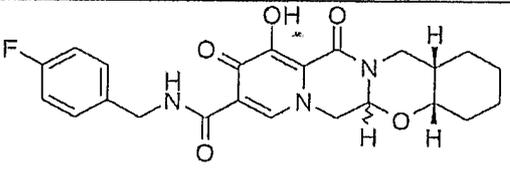
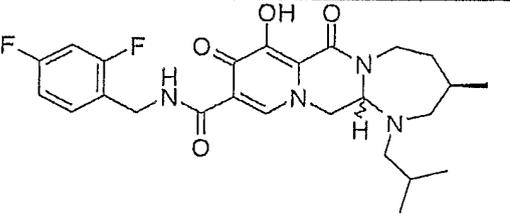
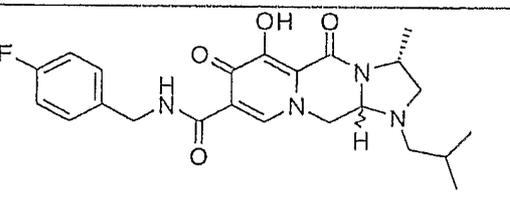
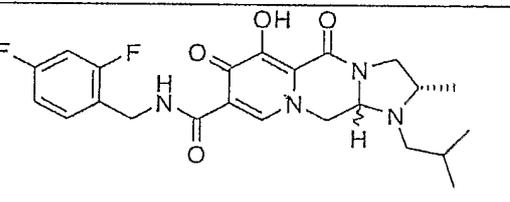
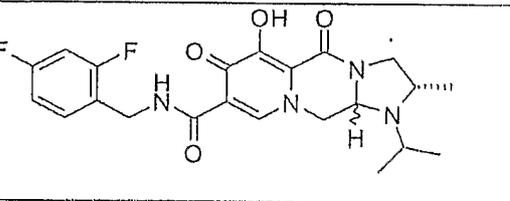
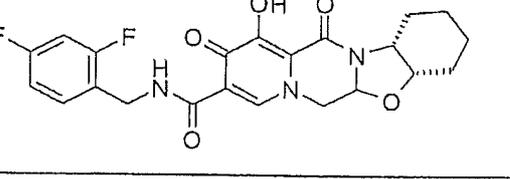
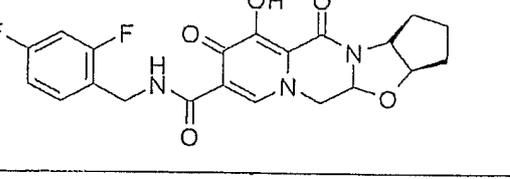
Examples in table below were isolated as a mixture of diastereomers ranging from 1:1 to >10:1 ratios of stereoisomers at the center indicated as undefined.

Characterization data reported herein consists of observed mass spectral signals for molecular ions (M+1) of the compounds using electrospray ionization methods in the positive mode using LC/MS techniques well known in the field. Reported retention times refer to observed UV peaks confirmed by NMR methods for the examples below using the following gradient on a phenomenex C18 reverse phase HPLC column (150 mmX4.6 mm 5 micron). Solvent A = water w/ 0.1% formic acid, solvent B = acetonitrile w/ 0.1% formic acid. Gradient = 10%B for 1 min, gradient from 10% to 90% B from 1 to 9 min, ramping to 100% B at 9.01 min and holding at 100% B for 2 min. In several cases the diastereomers were not separable by the standard HPLC conditions reported above and thus reported as a single retention time.

[Table A]

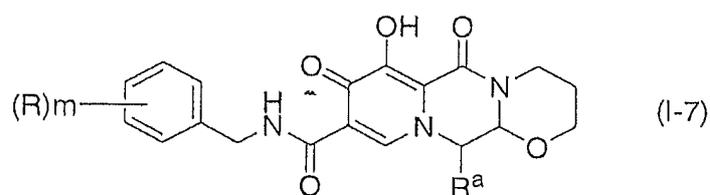
Example No.	Structure	Observed LC/MS or HPLC data
ZZ-1		ES+ MS: 419 (M + 1)
ZZ-2		ES+ MS: 406 (M + 1)
ZZ-3		ES+ MS: 509 (M + 1)
ZZ-4		ES+ MS: 429 (M + 1)

ZZ-5		ES+ MS: 415 (M + 1)
ZZ-6		ES+ MS: 491 (M + 1)
ZZ-7		ES+ MS: 509 (M + 1)
ZZ-8		ES+ MS: 443 (M + 1)
ZZ-9		ES+ MS: 461 (M + 1)
ZZ-10		ES+ MS: 501 (M + 1)
ZZ-11		ES+ MS: 475 (M + 1)
ZZ-12		ES+ MS: 489 (M + 1)

ZZ-13		ES <sup>+</sup> MS: 460 (M + 1)
ZZ-14		ES <sup>+</sup> MS: 442 (M + 1)
ZZ-15		ES <sup>+</sup> MS: 489 (M + 1)
ZZ-16		8.174 & 8.295 min.
ZZ-17		ES <sup>+</sup> MS: 461 (M + 1)
ZZ-18		ES <sup>+</sup> MS: 447 (M + 1)
ZZ-19		ES <sup>+</sup> MS: 446 (M + 1)
ZZ-20		ES <sup>+</sup> MS: 432 (M + 1)

ZZ-21		7.368 min
ZZ-22		7.150 min
ZZ-23		ES+ MS: 447 (M +1)
ZZ-24		ES+ MS: 447 (M +1)

The present invention further includes the following compounds.



[Table B]

No	(R) m	R <sup>a</sup>
1	4 - F	- CH <sub>3</sub>
2	4 - F	- CH(CH <sub>3</sub> ) <sub>2</sub>
3	4 - F	- CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>
4	2, 4 - F	- CH <sub>3</sub>
5	2, 4 - F	- CH(CH <sub>3</sub> ) <sub>2</sub>
6	2, 4 - F	- CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>
7	2 - F, 3 - Cl	- CH <sub>3</sub>
8	2 - F, 3 - Cl	- CH(CH <sub>3</sub> ) <sub>2</sub>
9	2 - F, 3 - Cl	- CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>

### Experimental Example 1

The HIV integrase inhibitory activity was investigated based on the following assay method.

#### (1) Preparation of DNA solution

By the same method as that described in Experimental Example 1 of WO 2004/024693, a substrate DNA solution (2 pmol/ $\mu$ l) and a target DNA solution (5 pmol/ $\mu$ l) were prepared. After each target DNA solution was once boiled, a temperature was slowly lowered to anneal complementary chains, which was used. Each sequence of a substrate DNA and a target DNA is as described in the same Experimental Example.

#### (2) Measurement of inhibition rate ( $IC_{50}$ value)

Streptavidin (manufactured by Vector Laboratories) was dissolved in a 0.1M carbonate buffer solution (composition: 90 mM  $Na_2CO_3$ , 10 mM  $NaHCO_3$ ) to a concentration of 40  $\mu$ g/ml. Each 50  $\mu$ l of this solution was added to a well of an immunoplate (manufactured by NUNC), this is allowed to stand at 4°C overnight to adsorb. Then, each well was washed with a phosphate buffer (composition: 13.7 mM NaCl, 0.27 mM KCl, 0.43 mM  $Na_2HPO_4$ , 0.14 mM  $KH_2PO_4$ ) two times, and 300  $\mu$ l of a phosphate buffer containing 1 % skim milk to block it for 30 minutes. Further, each well was washed with a phosphate buffer two times, 50  $\mu$ l of a substrate DNA solution (2 pmol/ $\mu$ l) was added to adsorb at room temperature for 30 minutes while shaking, and this was washed with a phosphate buffer two times and, then, distilled water once.

Then, to each well prepared as described above were added 12  $\mu$ l of a buffer (composition: 150 mM MOPS (pH7.2), 75 mM  $MnCl_2$ , 50 mM 2-mercaptoethanol, 25% glycerol, 500  $\mu$ g/ml bovine serum albumin-fraction V), and 51  $\mu$ l of a reaction solution prepared from 39  $\mu$ l of distilled water. Then, 9  $\mu$ l of an integrase solution (30 pmol) was added, and the mixture was mixed well. To a well as a negative control (NC) was added 9  $\mu$ l of a diluting solution (composition: 20 mM MOPS (pH7.2), 400 mM potassium glutamate, 1 mM EDTA, 0.1% NP-40, 20% glycerol, 1 mM DTT, 4 M urea), and this was mixed well using a plate mixer.

After the plate was incubated at 30°C for 60 minutes, the reaction solution was discarded, followed by washing with 250  $\mu$ l of a washing buffer (composition: 150 mM MOPS (pH7.2), 50 mM 2-mercaptoethanol, 25% glycerol, 500  $\mu$ g/ml bovine serum albumin-fraction V) three times.

Then, to each well were added 12  $\mu$ l of a buffer (composition: 150 mM MOPS

(pH7.2), 75 mM MgCl<sub>2</sub>, 50 mM 2-mercaptoethanol, 25% glycerol, 500 µg/ml bovine serum albumin-fraction V), and 53 µl of a reaction solution prepared from 41 µl of distilled water. Further, 6 µl of a solution of a test compound in DMSO was added to each well, and 6 µl of DMSO was added to a well as a positive control (PC), followed by mixing well using a plate mixer. After the plate was incubated at 30°C for 30 minutes, 1 µl of a target DNA (5 pmol/µl) was added, and this was mixed well using a plate mixer.

After each plate was incubated at 30°C for 10 minutes, the reaction solution was discarded, followed by washing with a phosphate buffer two times. Then, an anti-digoxigenin antibody labeled with alkaline phosphatase (sheep Fab fragment: manufactured by Boehringer) was diluted 2000-fold with an antibody diluting solution, 100 µl of the diluent was added to bind at 30°C for 1 hour, and this was washed successively with a phosphate buffer containing 0.05 % Tween20 two times, and a phosphate buffer once. Then, 150 µl of an alkaline phosphatase coloring buffer (composition: 10 mM paranitrophenyl phosphate (manufactured by Vector Laboratories), 5 mM MgCl<sub>2</sub>, 100 mM NaCl, 100 mM Tris-HCl (pH 9.5)) was added to react at 30°C for 2 hours, 50 µl of a 1N NaOH solution was added to stop the reaction, an absorbance (OD<sub>405 nm</sub>) of each well was measured, and an inhibition rate (IC<sub>50</sub>) was obtained according to the following calculation equation.

$$\text{Inhibition rate (\%)} = 100[1 - \{(C \text{ abs.} - NC \text{ abs.}) / (PC \text{ abs.} - NC \text{ abs.})\}]$$

C abs.: absorbance of well of compound

NC abs.: absorbance of NC

PC abs.: absorbance of PC

Results are shown below.

[Table 1]

Example No.	Integrase inhibitory activity (IC <sub>50</sub> , ng/ml)
C-2	3.3
F-2	3.8
H-2	3.2

The present compound showed the strong integrase inhibitory activity against HIV.

#### Experimental Example 2

A derivative of 293T cells expressing an attachment factor to improve adherence to plastic were used for the assay. A VSV-g pseudotyped HIV vector that expresses luciferase (herein referred to as PHIV) was produced by transfection of cells with the pGJ3-Luci vector plasmid (Jármay, G. et al., *J. Medical Virology*, 64:223-231, 2001) and pVSV-g (Clontech). Cells were mixed with the PHIV vector and then mixed with serially diluted compounds. After incubation at 37°C and 5% CO<sub>2</sub> for two days, the plates were read by using Steady Glo luciferase assay reagent (Promega) as recommended by the manufacturer. To assess non-HIV specific inhibition, a similar assay was performed, except that cell/PHIV vector mixture was replaced by cells which had been previously transduced and constitutively expressed luciferase.

[Table 2]

Example number	PHIV IC <sub>50</sub> *=<10 nM, **=10-100 nM, ***>100 nM
Z-1	*
Z-2	*
Z-3	*
Z-4	*
Z-5	*
Z-6	*
Z-7	*
Z-8	**
Z-9	*
Z-10	*
Z-11	*
Z-12	*
Z-13	**
Z-14	**
Z-15	*
Z-16	*
Z-17	*
Z-18	*
Z-19	*
Z-20	**
Z-21	*
Z-22	*
Z-23	*

Z-24	*
Z-25	*
Z-26	*
Z-27	***
Z-28	*
Z-29	*
Z-30	*
Z-31	*
Z-32	*
Z-33	*
Z-34	*
Z-35	*
Z-36	*
Z-37	*
Z-38	**
Z-39	*
Z-40	*
Z-41	*
Z-42	*
Z-43	*
Z-44	*
Z-45	*
Z-46	*
Z-47	*
Z-48	*
Z-49	*
Z-50	*
Z-51	*
Z-52	*
Z-53	*
Z-54	*
Z-55	**
Z-59	*
Z-60	*

#### Formulation Example

A term "active ingredient" means the present compound, a tautomer thereof, a pharmaceutically acceptable thereof, or a solvate thereof.

(Formulation Example 1)

A hard gelatin capsule is prepared using the following ingredients:

	dose (mg/capsule)
Active ingredient	250
Starch (dried)	200
Magnesium stearate	10

WO 2006/116764

PCT/US2006/016604

Total 460mg

(Formulation Example 2)

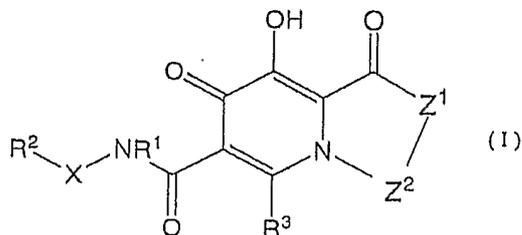
A tablet is prepared using the following ingredients:

	dose (mg/tablet)
Active ingredient	250
Cellulose (microcrystalline)	400
Silicon dioxide (fumed)	10
Stearic acid	5
Total	665mg

Ingredients are mixed, and compressed to obtain tablets, each weighing 665 mg.

[Name of Document] Scope of Claims

1. A compound of the formula:



(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),  $\cdot N=$  and  $=N\cdot$ )), 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,  $SO_2$ ,  $NR^b$  ( $R^b$  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,  $SO_2$ ,  $NR^b$  ( $R^b$  is selected independently from the same substituent group as  $R^4$ ),  $\cdot N=$  and  $=N\cdot$ )),  $\cdot N=$  or

=N·;

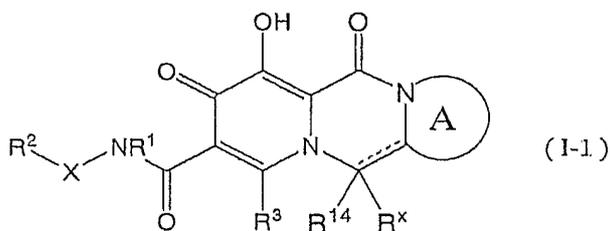
R<sup>1</sup> is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO<sub>2</sub> and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom;

R<sup>2</sup> is optionally substituted aryl;

R<sup>3</sup> 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<sup>4</sup> and Z<sup>2</sup> part taken together forms a ring, where the compound (I) is represented by the following formula (I-1), or (I-11):



(wherein,

A ring is optionally substituted heterocycle;

R<sup>14</sup> and R<sup>x</sup> 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<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is selected independently from the same substituent group as R<sup>4</sup>), -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 aryloxy carbonyl, optionally substituted heterocyclecarbonyl, optionally substituted

heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

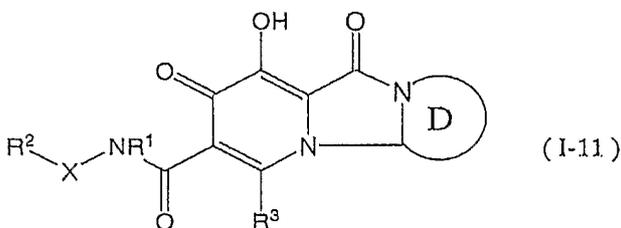
a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, R<sup>x</sup> is not present;

R<sup>1</sup> is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO<sub>2</sub> and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R<sup>2</sup> is optionally substituted aryl;

R<sup>3</sup> 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)



(wherein,

D ring is optionally substituted heterocycle;

R<sup>1</sup> is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO<sub>2</sub> and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R<sup>2</sup> is optionally substituted aryl;

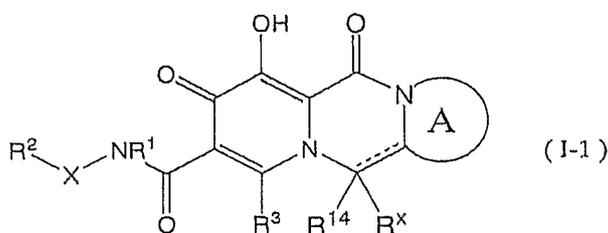
R<sup>3</sup> is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino));

or a pharmaceutically acceptable salt, or solvate thereof.

2. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein R<sup>1</sup> is hydrogen.

3. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein X is lower alkylene; R<sup>2</sup> is phenyl or phenyl substituted with at least halogen.

4. A compound according to Claim 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 Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein  $R^3$  is hydrogen.
6. A compound according to Claim 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:



(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,  $SO_2$ ,  $NR^5$  ( $R^5$  is selected independently from the same substituent group as  $R^4$ ),  $\cdot N=$  and  $=N\cdot$ ), 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 aryloxy carbonyl, 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<sub>2</sub> 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);

or a pharmaceutically acceptable salt, or solvate thereof

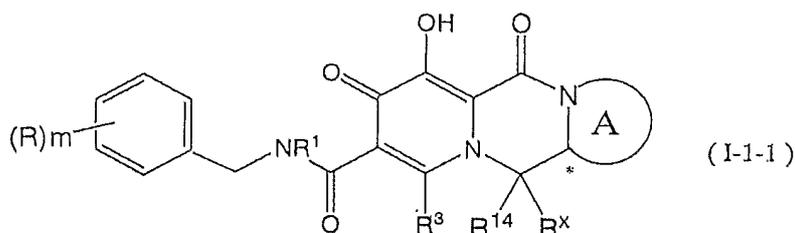
8. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein  $R^1$  is hydrogen or lower alkyl; X is lower alkylene;  $R^2$  is phenyl or phenyl substituted with at least halogen;  $R^3$  is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.

9. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein a broken line represents the absence of a bond.

10. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein  $R^x$  is hydrogen;  $R^{14}$  is hydrogen or optionally substituted lower alkyl.

11. A compound according to Claim 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:



(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<sup>14</sup> and R<sup>X</sup> 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<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is selected independently from the same substituent group as R<sup>4</sup>), -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 aryloxy carbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

R<sup>3</sup> 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<sup>1</sup> 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<sub>2</sub>, NR<sup>a</sup> (R<sup>a</sup> 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);

or a pharmaceutically acceptable salt, or solvate thereof.

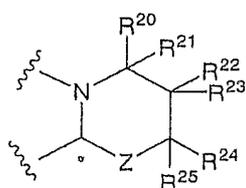
13. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein  $R^X$  and  $R^{14}$  are independently hydrogen or optionally substituted lower alkyl.

14. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein  $R^X$  and  $R^{14}$  are hydrogens.

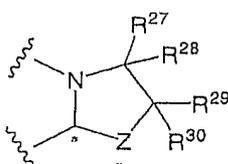
15. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein  $R^3$  is hydrogen.

16. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein m is 0, or 1 to 3 and at least one of R is halogen.

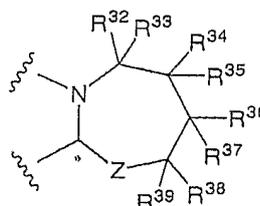
17. A compound according to Claim 7 or 12, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is any one of the followings:



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 carbocycle 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 ( $R^{39}$  and  $R^{40}$ ), taken together with the neighboring atom, may form an optionally substituted carbocycle 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 alkoxy carbonyl, 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<sub>2</sub>, NR<sup>5</sup> (R<sup>5</sup> is independently selected from the same Substituent group as R<sup>4</sup>), ·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 Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein R<sup>20</sup> to R<sup>40</sup> are each independently hydrogen or substituted lower alkyl, or any two groups of R<sup>20</sup> to R<sup>40</sup>, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7- membered carbocycle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R<sup>20</sup> and R<sup>22</sup>), (R<sup>23</sup> and R<sup>24</sup>), (R<sup>25</sup> and R<sup>26</sup>), (R<sup>27</sup> and R<sup>29</sup>), (R<sup>30</sup> and R<sup>31</sup>), (R<sup>32</sup> and R<sup>34</sup>), (R<sup>35</sup> and R<sup>36</sup>), (R<sup>37</sup> and R<sup>38</sup>), and (R<sup>39</sup> and R<sup>40</sup>), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocycle or optionally substituted 5- to 7- membered heterocycle.

19. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); one of R<sup>20</sup> to R<sup>25</sup> is optionally substituted lower alkyl and the others are hydrogens.

20. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); one of (R<sup>20</sup> and R<sup>22</sup>), (R<sup>23</sup> and R<sup>24</sup>), and (R<sup>25</sup> and R<sup>26</sup>), taken together with the neighboring atom, may form an

optionally substituted 5- to 7- membered carbocycle or optionally substituted 5- to 7- membered heterocycle.

21. A compound according to Claim 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 Claim 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 Claim 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 carbocycle or optionally substituted 5- to 7- membered heterocycle.

24. A compound according to Claim 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 Claim 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 Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); one of ( $R^{32}$  and  $R^{34}$ ), ( $R^{35}$  and  $R^{36}$ ), ( $R^{37}$  and  $R^{38}$ ), and ( $R^{39}$  and  $R^{40}$ ), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocycle or optionally substituted 5- to 7- membered heterocycle.

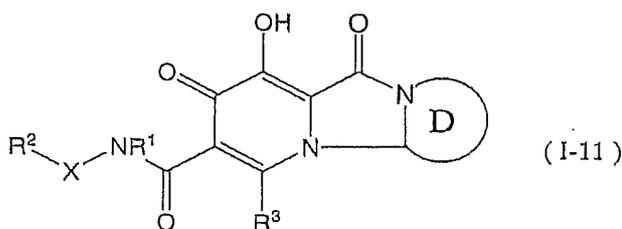
27. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3);  $Z=NR^{40}$ , and  $R^{39}$  and  $R^{40}$  taken together with the neighboring atom may form an optionally substituted 5- to 7- membered heterocycle.

28. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein  $R^x$  is hydrogen;  $R^{14}$  is hydrogen or optionally substituted lower;  $R^3$  is hydrogen; m is 1 to 3 and at least one of Rs is halogen; A ring is a ring described in

Claim 17.

29. A compound according to Claim 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  $R$  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 carbocycle 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 ( $R^{39}$  and  $R^{40}$ ), taken together with the neighboring carbon atom, may form an optionally substituted 5- to 7- membered carbocycle or optionally substituted 5- to 7- membered heterocycle.

30. A compound of the formula:



(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<sub>2</sub> 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);

or a pharmaceutically acceptable salt, or solvate thereof

31. A compound selected from the group consisting of:

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-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-he

hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-3-(1,1-Dimethylethyl)-*N*[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11*a*-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-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11*aS*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(5*aR*,14*aR*)-*N*[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5*a*,6,10,12,14,14*a*-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-[(methoxy)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;

(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*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11*aR*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4*R*,12*aR*)-*N*[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*R*,12*aR*)-*N*[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-1-(Cyclopropylmethyl)-*N*[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*[(2,4-Difluorophenyl)methyl]-1-(2-furanylmethyl)-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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(4*S*,12*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*aR*,6*aR*,14*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4*aR*,6*aR*,14*aS*)-*N*-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide ;

(3*S*,4*aR*,6*aR*,14*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-3-phenyl-1,3,4,4*a*,5,6*a*,7,11,13,14*a*-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4*aS*,6*aS*,14*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4*a*,5,6,6*a*,7,11,13,14*a*-dodecahydropyrido[1',2':4,5]pyrazino[1,2-*a*]quinazoline-10-carboxamide;

(6*aR*,7*aS*,11*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6*a*,7,7*a*,8,9,10,11,11*a*,13-decahydro-6*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*]benzimidazole-3-carboxamide;

(6*aS*,7*aS*,11*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6*a*,7,7*a*,8,9,10,11,11*a*,13-decahydro-6*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*]benzimidazole-3-carboxamide;

(5a*S*, 14a*S*)-*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;

(4a*R*, 14a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,14a-decahydro-1*H*-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-

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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]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(3a*S*,5a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-5-(2-methylpropyl)-10,12-dioxo-2,3,3a,4,5,5a,6,10,12,13a-decahydro-1*H*-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;

(4a*S*,6a*S*,14a*S*)-*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;

(3a*R*,5a*R*,13a*S*)-*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;

(4a*S*,6a*S*,14a*S*)-*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;

(4a*S*,6a*S*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methyloxy)ethyl]-11,

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1,3-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;

(4a*S*,6a*S*,14a*S*)-6-[2-(Acetylamino)ethyl]-*N*-[(2,4-difluorophenyl)methyl]-12-hydroxy-1,13-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 ;

(4*S*,12a*S*)-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-pyrrolidiny)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-(methoxy)ethyl]-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)-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;

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(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12*aS*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12*a*-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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-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;

(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;

mide;

(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

;

4*S*,9a*R*)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2*H*-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benylamide;

4*R*,9a*S*)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2*H*-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benylamide;

2*R*,9a*S*)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2*H*-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benylamide;

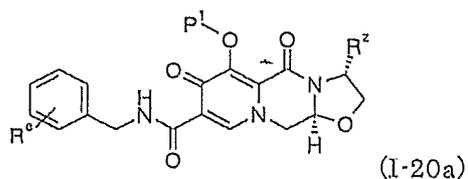
enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.

33. A compound according to claims 31 or 32 wherein the pharmaceutically acceptable salt is a sodium salt.

34. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 33, or a pharmaceutically acceptable salt, or solvate thereof.

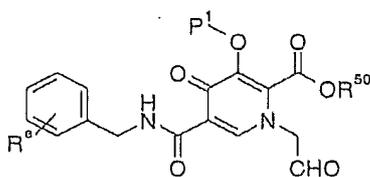
35. A pharmaceutical composition according to Claim 34, which is an anti-HIV agent.

36. A process for the preparation of a compound of formula (I-20a)

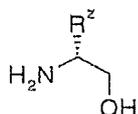


wherein  $R^e$  is one or two halogen;  $R^z$  is  $C_{1-8}$ alkyl,  $C_{6-14}$ aryl $C_{1-8}$ alkyl,  $C_{6-14}$ aryl, or alkoxy; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;

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  $C_{6-14}$ aryl $C_{1-8}$ alkyl; with a compound of the formula



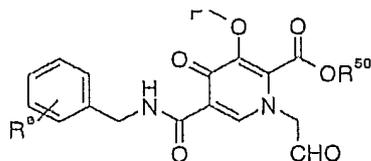
wherein  $R^z$  is  $C_{1-8}$ alkyl,  $C_{6-14}$ aryl $C_{1-8}$ alkyl,  $C_{6-14}$ aryl, or alkoxy; to form a compound of formula (I-20a).

37. A process for the preparation of a compound of formula (I-20b)

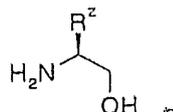


wherein  $R^e$  is one or two halogen;  $R^z$  is  $C_{1-8}$ alkyl,  $C_{6-14}$ aryl $C_{1-8}$ alkyl,  $C_{6-14}$ aryl, or alkoxy; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;

comprising condensing a compound of the formula

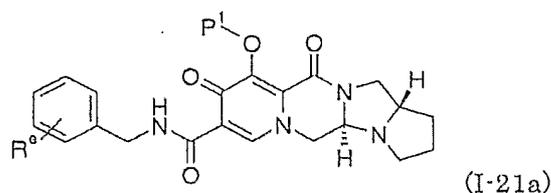


wherein R<sup>e</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
with a compound of the formula



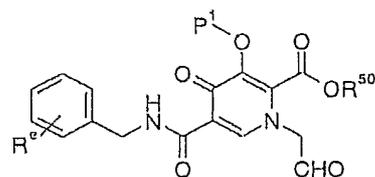
wherein R<sup>z</sup> is C<sub>1-8</sub>alkyl, C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl, C<sub>6-14</sub>aryl, or alkoxy;  
to form a compound of formula (I-20b).

38. A process for the preparation of a compound of formula (I-21a)

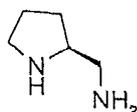


wherein R<sup>e</sup> is one or two halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;

comprising condensing a compound of the formula

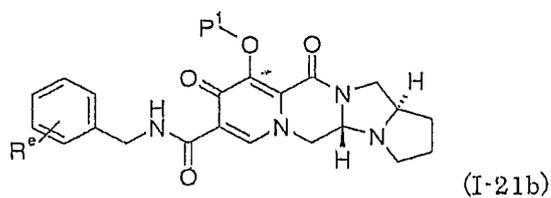


wherein R<sup>e</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
with a compound of the formula



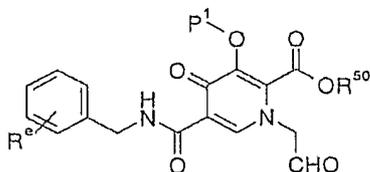
to form a compound of formula (I-21a).

39. A process for the preparation of a compound of formula (I-21b)

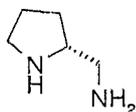


wherein  $R^e$  is one or two halogen; and  $P^1$  is  $C_6-14$ aryl $C_1-8$ alkyl;

comprising condensing a compound of the formula

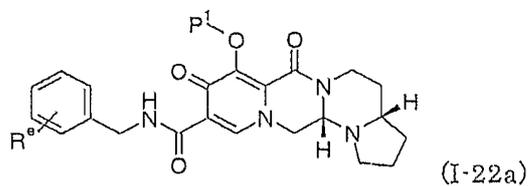


wherein  $R^e$  is one or two halogen;  $R^{50}$  is  $C_1-8$ alkyl; and  $P^1$  is  $C_6-14$ aryl $C_1-8$ alkyl;  
with a compound of the formula

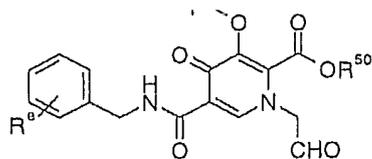


to form a compound of formula (I-21b).

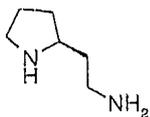
40. A process for the preparation of a compound of formula (I-22a)



wherein  $R^e$  is one or two halogen; and  $P^1$  is  $C_6-14$ aryl $C_1-8$ alkyl;  
comprising condensing a compound of the formula:

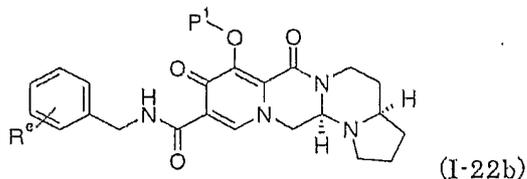


wherein  $R^o$  is one or two halogen;  $R^{50}$  is  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;  
with a compound of the formula

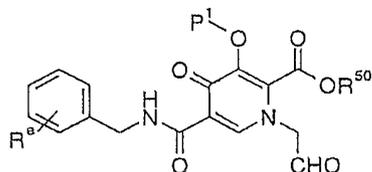


to form a compound of formula (I-22a).

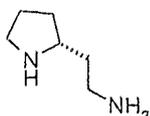
41. A process for the preparation of a compound of formula (I-22b)



wherein  $R^o$  is one or two halogen; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;  
comprising condensing a compound of the formula

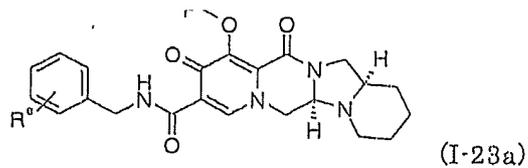


wherein  $R^o$  is one or two halogen;  $R^{50}$  is  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;  
with a compound of the formula

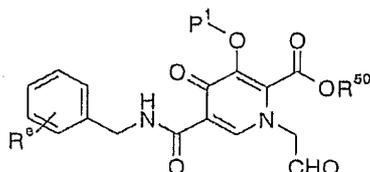


to form a compound of formula (I-22b).

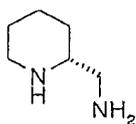
42. A process for the preparation of a compound of formula (I-23a)



wherein  $R^e$  is one or two halogen; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;  
comprising condensing a compound of the formula

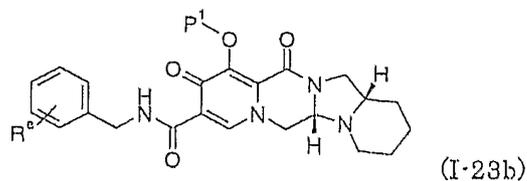


wherein  $R^e$  is one or two halogen;  $R^{50}$  is  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;  
with a compound of the formula

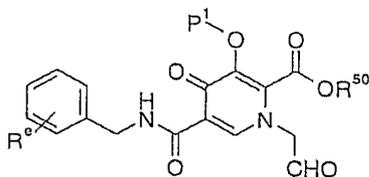


to form a compound of formula (I-23a).

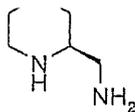
43. A process for the preparation of a compound of formula (I-23b)



wherein  $R^e$  is one or two halogen; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;  
comprising condensing a compound of the formula

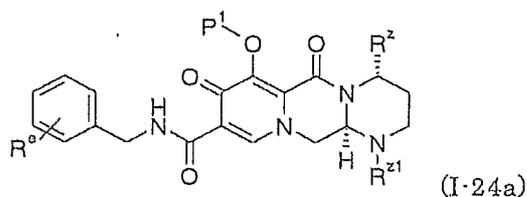


wherein  $R^e$  is one or two halogen;  $R^{50}$  is  $C_{1-8}$ alkyl; and  $P^1$  is  $C_{6-14}$ aryl $C_{1-8}$ alkyl;  
with a compound of the formula \*



to form a compound of formula (I-23b).

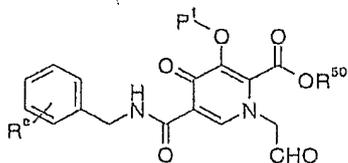
44. A process for the preparation of a compound of formula (I-24a)



wherein R<sup>a</sup> is one or two halogen; R<sup>z1</sup> is hydrogen, C<sub>3</sub>-cycloalkyl, heterocycle, or C<sub>1</sub>-alkyl optionally substituted with hydroxy, C<sub>3</sub>-cycloalkyl, alkoxy, heterocycle, heteroaryl, C<sub>6-14</sub>aryl, or amino, wherein said amino may be optionally substituted with -C(O)C<sub>1-8</sub>alkyl or C<sub>1-8</sub>alkyl;

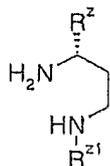
and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;

comprising condensing a compound of the formula



wherein R<sup>a</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;

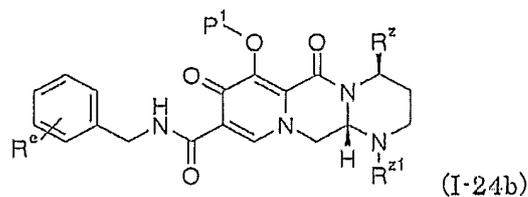
with a compound of the formula



wherein R<sup>z</sup> is C<sub>1-8</sub>alkyl; R<sup>z1</sup> is hydrogen, C<sub>3</sub>-cycloalkyl, , heterocycle, or C<sub>1</sub>-alkyl optionally substituted with hydroxy, C<sub>3</sub>-cycloalkyl, alkoxy, heterocycle, heteroaryl, C<sub>6-14</sub>aryl, or amino, wherein said amino may be optionally substituted with -C(O)C<sub>1-8</sub>alkyl or C<sub>1-8</sub>alkyl;

to form a compound of the formula (I-24a).

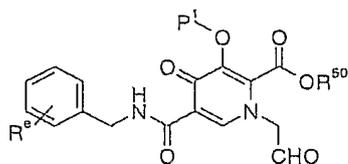
45. A process for the preparation of a compound of formula (I-24b)



wherein  $R^e$  is one or two halogen;  $R^{z1}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_1$ -alkyl optionally substituted with hydroxy,  $C_3$ -cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_6$ -14aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_1$ -8alkyl or  $C_1$ -8alkyl;

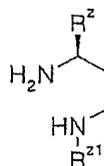
and  $P^1$  is  $C_6$ -14aryl $C_1$ -8alkyl;

comprising condensing a compound of the formula



wherein  $R^e$  is one or two halogen;  $R^{50}$  is  $C_1$ -8alkyl; and  $P^1$  is  $C_6$ -14aryl $C_1$ -8alkyl;

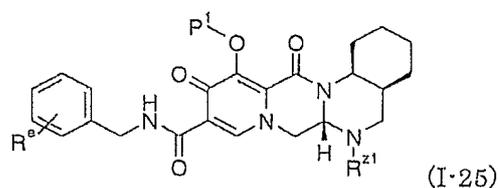
with a compound of the formula



wherein  $R^z$  is  $C_1$ -8alkyl;  $R^{z1}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_1$ -8alkyl optionally substituted with hydroxy,  $C_3$ -cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_6$ -14aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_1$ -8alkyl or  $C_1$ -8alkyl;

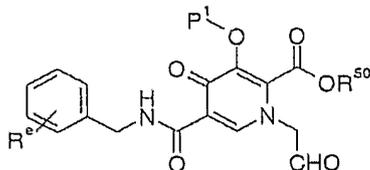
to form a compound of the formula (I-24b).

46. A process for the preparation of a racemic compound of formula (I-25)

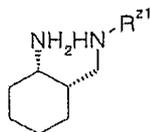


wherein  $R^e$  is one or two halogen;  $R^{z1}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_1$ -salkyl optionally substituted with hydroxy,  $C_3$ -cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_6$ -14aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_1$ -salkyl or  $C_1$ -salkyl; and  $P^1$  is  $C_6$ -14aryl $C_1$ -salkyl;

comprising condensing a compound of the formula



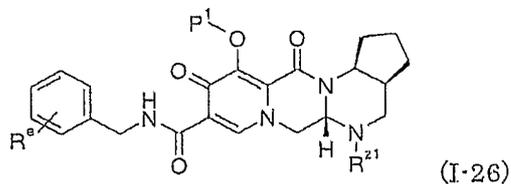
wherein  $R^e$  is one or two halogen;  $R^{50}$  is  $C_1$ -salkyl; and  $P^1$  is  $C_6$ -14aryl $C_1$ -salkyl; with a racemic compound of the formula



wherein  $R^{z1}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_1$ -salkyl optionally substituted with hydroxy,  $C_3$ -cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_6$ -14aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_1$ -salkyl or  $C_1$ -salkyl;

to form a racemic compound of the formula (I-25).

47. A process for the preparation of a racemic compound of formula (I-26)



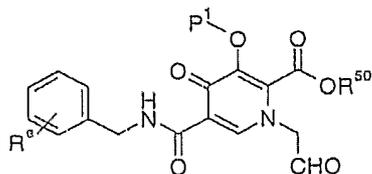
(I-26)

wherein  $R^e$  is one or two halogen;  $R^{z1}$  is hydrogen,  $C_3$ -cycloalkyl, heterocycle, or  $C_1$ -salkyl optionally substituted with hydroxy,  $C_3$ -cycloalkyl, alkoxy, heterocycle, heteroaryl,  $C_6$ -14aryl, or amino, wherein said amino may be optionally substituted with  $-C(O)C_1$ -salkyl or  $C_1$ -salkyl; and  $P^1$  is  $C_6$ -14aryl $C_1$ -salkyl;

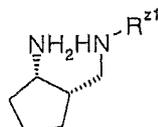
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comprising condensing a compound of the formula



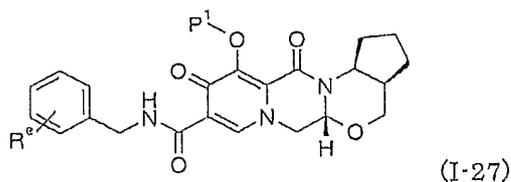
wherein R<sup>e</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
with a racemic compound of the formula



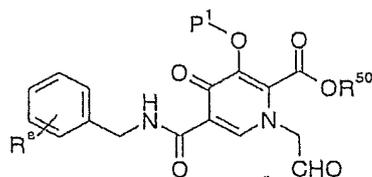
wherein R<sup>z1</sup> is hydrogen, C<sub>3-6</sub>cycloalkyl, heterocycle, or C<sub>1-8</sub>alkyl optionally substituted with hydroxy, C<sub>3-6</sub>cycloalkyl, alkoxy, heterocycle, heteroaryl, C<sub>6-14</sub>aryl, or amino, wherein said amino may be optionally substituted with -C(O)C<sub>1-8</sub>alkyl or C<sub>1-8</sub>alkyl;

to form a racemic compound of formula (I-26).

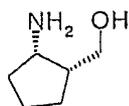
48. A process for the preparation of a racemic compound of formula (I-27)



wherein R<sup>e</sup> is halogen; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
comprising condensing a compound of the formula



wherein R<sup>e</sup> is one or two halogen; R<sup>50</sup> is C<sub>1-8</sub>alkyl; and P<sup>1</sup> is C<sub>6-14</sub>arylC<sub>1-8</sub>alkyl;  
with a racemic compound of the formula



to form a racemic compound of formula (I-27).

49. A method of treatment of an HIV infection in a human comprising administering to said human an antiviral effective amount of a compound according to any of claims 1 to 33.

50. A compound as claimed in any of claims 1 to 33 for use in medical therapy.

51. Use of a compound as claimed in any of claims 1 to 33 in the manufacture of a medicament for the treatment or prophylaxis of an HIV infection.

52. A compound of formula (I-20a) described in Claim 36, formula (I-20b) described in Claim 37, formula (I-21a) described in Claim 38, formula (I-21b) described in Claim 39, formula (I-22a) described in Claim 40, formula (I-22b) described in Claim 41, formula (I-23a) described in Claim 42, formula (I-23b) described in Claim 43, formula (I-24a) described in Claim 44, formula (I-24b) described in Claim 45, formula (I-25) described in Claim 46, formula (I-26) described in Claim 47, or formula (I-27) described in Claim 48, or a pharmaceutically acceptable salt thereof.

53. A compound of formula (I-20a) described in Claim 36, formula (I-20b) described in Claim 37, formula (I-21a) described in Claim 38, formula (I-21b) described in Claim 39, formula (I-22a) described in Claim 40, formula (I-22b) described in Claim 41, formula (I-23a) described in Claim 42, formula (I-23b) described in Claim 43, formula (I-24a) described in Claim 44, formula (I-24b) described in Claim 45, formula (I-25) described in Claim 46, formula (I-26) described in Claim 47, or formula (I-27) described in Claim 48, or a pharmaceutically acceptable salt thereof, wherein each P<sup>1</sup> is hydrogen.

54. A pharmaceutical composition according to claim 34 wherein said composition comprises at least one additional therapeutic agent selected from reverse transcriptase inhibitors and protease inhibitors.

55. A method of treatment of an HIV infection in a human comprising administering to said human a composition comprising a compound according to any of claims 1 to

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33 and another therapeutic agent.

56. The method according to claim 55 wherein said therapeutic agent is selected from reverse transcriptase inhibitors and protease inhibitors.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US06/16604

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC: A01N 43/58( 2006.01), 43/60( 2006.01); A61K 31/50( 2006.01), 31/495( 2006.01); C07D 239/00( 2006.01), 241/36( 2006.01), 471/00( 2006.01), 487/00( 2006.01), 495/00( 2006.01), 497/00( 2006.01)		
USPC: 514/250; 544/247, 250, 251, 343, 346		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/250; 544/247, 250, 251, 343, 346		
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) STN: structure search was conducted in file REGISTRY, answer set cross-referenced into file CAPLUS.		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/0054645 (MIYAZAKI et al) 10 March 2005 (10.03.2005), page 105 compound #180, page 108 compound #196, page 111 compounds #213 and #214, 114 compound #234, page 116 compound #273, page 125 compound #372, page 126 compounds #377 and #378, page 127 compound #380 and page 135 compound #428.	1-6
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> 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	" 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	
" E" earlier application or patent published on or after the international filing date	" 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	
" 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)	" 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	
" O" document referring to an oral disclosure, use, exhibition or other means	" &" document member of the same patent family	
" P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 21 August 2006 (21.08.2006)	Date of mailing of the international search report 18 SEP 2006	
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Zachary C. Tucker Telephone No. (571) 272-1600	

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/16604

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos. :  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos. : 52 and 53  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Please See Continuation Sheet
  
3.  Claims Nos. : 34,35,49-51 and 54-56  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
  3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
  4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
- Remark on Protest**
- The additional search fees were accompanied by the applicant' s protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant' s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/US06/16604

Continuation of Box II Reason 2:

Claims 52 and 53 lack antecedent basis in the claims from which they depend. Claims 52 and 53 are drawn to compounds, while the claims from which they depend are drawn to methods. Thus, no meaningful search can be carried out for claims 52 and 53



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D2

(19) **United States**  
(12) **Patent Application Publication**  
**Vermeulen et al.**

(10) **Pub. No.: US 2009/0163519 A1**  
(43) **Pub. Date: Jun. 25, 2009**

(54) **DOSING REGIMEN ASSOCIATED WITH  
LONG ACTING INJECTABLE  
PALIPERIDONE ESTERS**

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**Alfons Wouters**, Beerse (BE)

Correspondence Address:  
**PHILIP S. JOHNSON**  
**JOHNSON & JOHNSON**  
**ONE JOHNSON & JOHNSON PLAZA**  
**NEW BRUNSWICK, NJ 08933-7003 (US)**

(21) Appl. No.: **12/337,144**

(22) Filed: **Dec. 17, 2008**

**Related U.S. Application Data**

(60) Provisional application No. 61/014,918, filed on Dec. 19, 2007, provisional application No. 61/120,276, filed on Dec. 5, 2008.

**Publication Classification**

(51) **Int. Cl.**  
**A61K 31/519** (2006.01)  
**A61P 25/18** (2006.01)

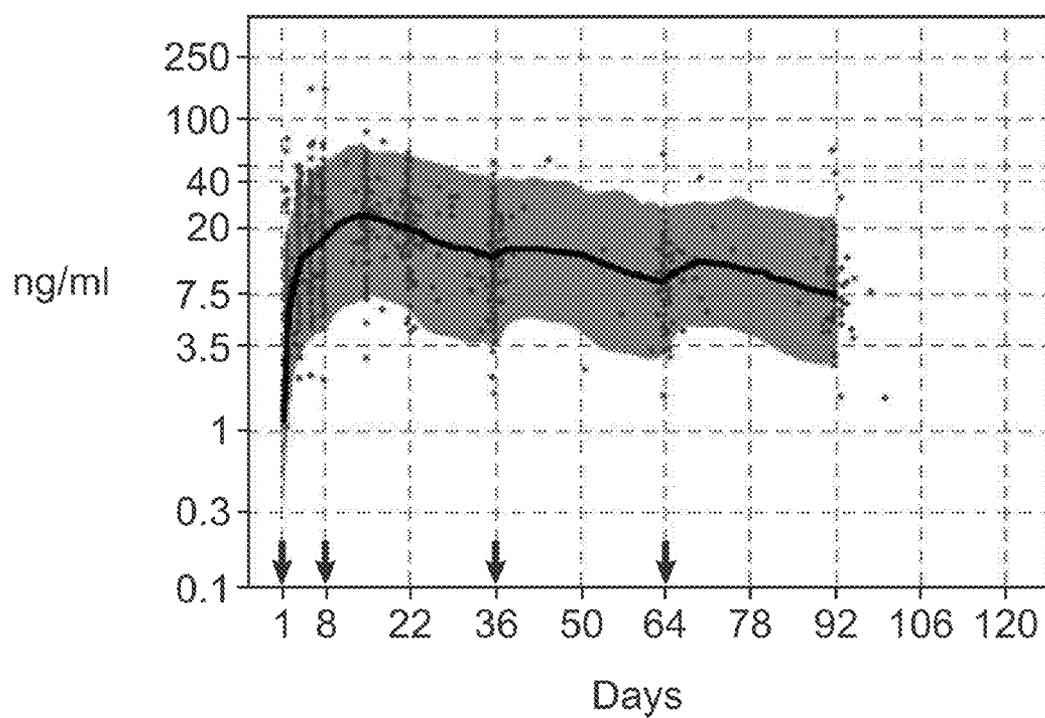
(52) **U.S. Cl.** ..... **514/259.41; 977/915**

(57) **ABSTRACT**

The present invention provides a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations.

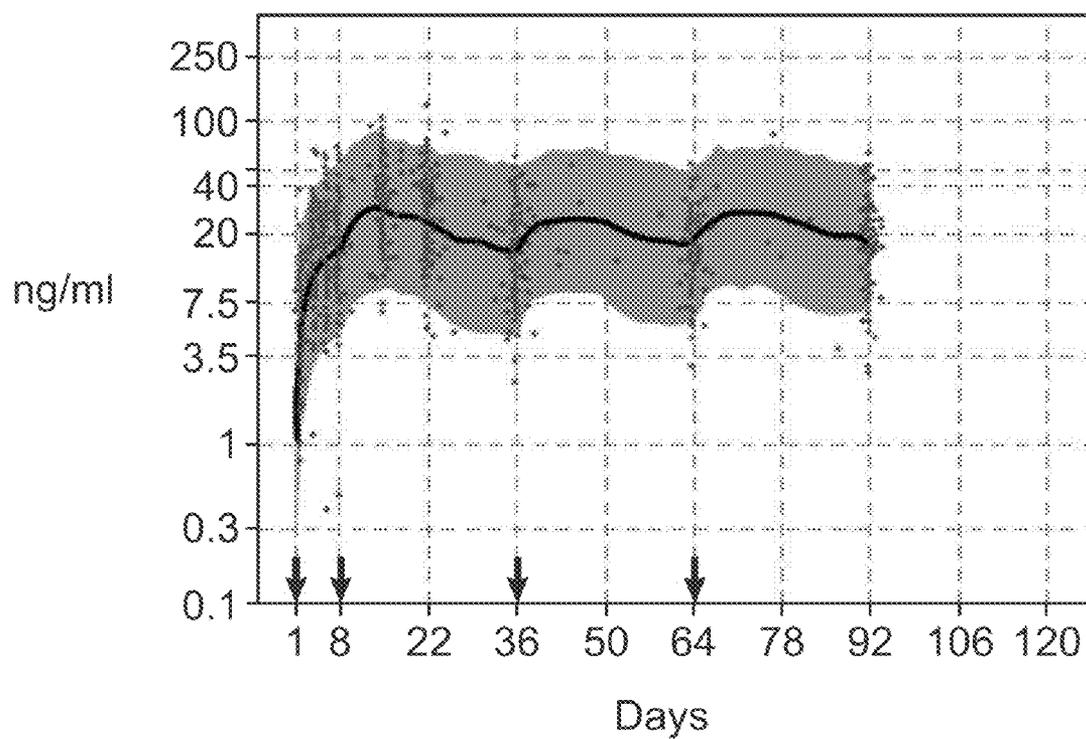
**FIG. 1**

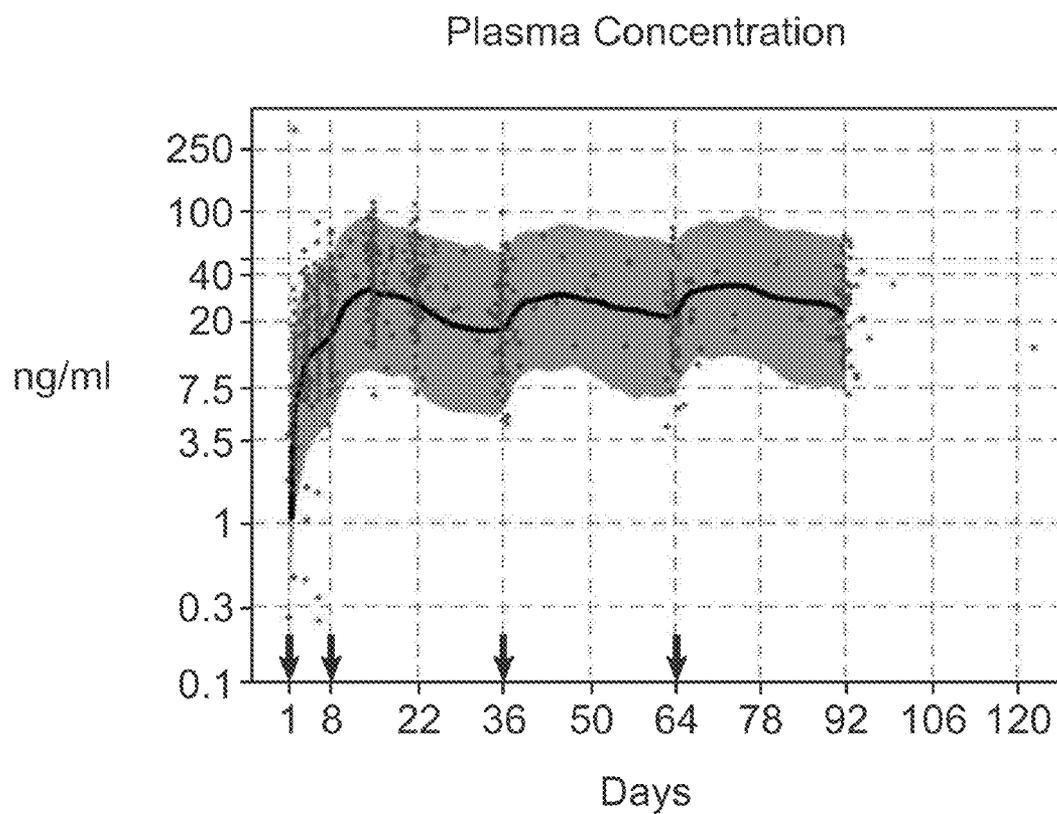
Plasma Concentration



**FIG. 2**

Plasma Concentration



**FIG. 3**

**DOSING REGIMEN ASSOCIATED WITH  
LONG ACTING INJECTABLE  
PALIPERIDONE ESTERS**

FIELD OF THE INVENTION

[0001] This invention relates to a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations.

BACKGROUND OF THE INVENTION

[0002] Antipsychotic medications are the mainstay in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorders. Conventional antipsychotics were introduced in the mid-1950s. These typical or first generation drugs are usually effective in controlling the positive symptoms of schizophrenia, but are less effective in moderating the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, typified by risperidone and olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia.

[0003] Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine D<sub>2</sub> and serotonin (5-hydroxytryptamine type 2A) antagonism of the second-generation, atypical antipsychotic drugs. Paliperidone is the major active metabolite of risperidone. Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) for the treatment of schizophrenia and maintenance of effect.

[0004] Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension for the treatment of schizophrenia and other diseases that are normally treated with antipsychotic medications. Because of extreme low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly after an i.m. injection before being hydrolyzed to paliperidone and made available in the systemic circulation.

[0005] Many patients with these mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have difficulty adhering to a daily oral treatment regimen, i.e. compliance problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies.

[0006] Paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly, which may greatly enhance compliance with dosing. Paliperidone palmitate was formulated as an aqueous nano suspension as is described in U.S. Pat. Nos. 6,577,545 and 6,555,544. However, after the data was analyzed from the clinical trials of this formulation it was discovered that the absorption of paliperidone from these injections was far more complex than was originally anticipated. Additionally, attaining a potential therapeutic plasma level of paliperidone in patients was discovered to be dependent on the site of injection until steady state concentration is reached. Due to the challenging nature of ensuring an optimum plasma concentration-time profile for treating

patients with paliperidone it is desirable to develop a dosing regimen that fulfills this goal in patients in need of treatment.

SUMMARY OF THE INVENTION

[0007] In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation on between about the 34<sup>th</sup> and about the 38th day of treatment.

[0008] In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation approximately monthly from the date of the second loading dose.

[0009] In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose from about 100 mg-eq. to about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on between about the 34th day and the 38th day of treatment.

[0010] In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a

maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

**[0011]** In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

**[0012]** In yet another embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a renally impaired psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 mg-eq. to about 75 mg-eq of paliperidone as a paliperidone palmitate in a sustained release formulation on between about the 34<sup>th</sup> and about the 38th day of treatment.

**[0013]** In yet another embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a renally impaired psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 100 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 mg-eq. to about 75 mg-eq of paliperidone as a paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

**[0014]** In a further embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 75 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a mainte-

nance dose of from about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th day and the 38th day of treatment.

**[0015]** In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; thereafter administering intramuscularly a second maintenance dose of from about 25 mg-eq. to about 100 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 100 mg-eq. of paliperidone as a paliperidone palmitate in a sustained release formulation on between about the 34<sup>th</sup> and about the 38th day of treatment.

**[0016]** In a further embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose from about 150 mg-eq. of paliperidone as a paliperidone palmitate ester in a sustained release formulation on the first day of treatment; thereafter administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th day and the 38th day of treatment.

**[0017]** This and other objects and advantages of the present invention may be appreciated from a review of the present applications.

#### BRIEF DESCRIPTION OF THE FIGURES

**[0018]** FIG. 1 shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 25 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

**[0019]** FIG. 2 shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 100 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

**[0020]** FIG. 3 shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 150 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

#### DETAILED DESCRIPTION

**[0021]** We have discovered after extensive analysis of the clinical data that paliperidone palmitate due to its dissolution rate-limited absorption exhibits flip-flop kinetics, where the apparent half-life is controlled by the absorption rate constant. Additionally the volume of injected drug product also

impacts the apparent rate constant. It was also discovered that deltoid injections result in a faster rise in initial plasma concentration, facilitating a rapid attainment of potential therapeutic concentrations. Consequently, to facilitate patients' attaining a rapid therapeutic concentration of paliperidone it is preferred to provide the initial loading dose of paliperidone palmitate in the deltoids. The loading dose should be from about 100 mg-eq. to about 150 mg-eq. of paliperidone provided in the form of paliperidone palmitate. After the first or more preferably after the second loading dose injection patients will be approaching a steady state concentration of paliperidone in their plasma and may be injected in either the deltoid or the gluteal muscle thereafter. However, it is preferred that the patients receive further injections in the gluteal muscle.

**[0022]** In view of these discoveries the recommended dosing regimen for patients to attain a therapeutic plasma level of paliperidone is for patients to receive the first dose of paliperidone palmitate on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment or monthly  $\pm 7$  days after the second dose. More preferably the patients will be administered a first dose on day 1, a second dose on day 8 and a third dose on or about day 36 of treatment or approximately monthly  $\pm 3$  days after the second dose. The first two doses will preferably be injected in the deltoid muscle. Thereafter paliperidone palmitate will be administered by injection approximately once a month (e.g. monthly  $\pm 7$  days or approximately once every four weeks) thereafter. To assure that a potential therapeutic plasma level of paliperidone is attained at least a first loading dose of 150 mg-eq of paliperidone as a paliperidone palmitate ester should be administered on day one of treatment. Preferably the first two doses will be loading dose of between from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate ester to assure that a potential therapeutic plasma level of paliperidone is attained by the patient. The subsequent doses thereafter will drop to a therapeutic maintenance dose of from about 25 mg-eq. to 150 mg-eq. per month ( $\pm 7$  days). Preferably the maintenance dose will be from about 25 mg eq. to about 100 mg eq; more preferably the maintenance dose will be from about 25 mg eq. to about 75 mg eq; and most preferably the maintenance dose initially will be about 50 mg eq., or more preferably the maintenance dose initially will be about 75 mg eq. which may be administered intramuscularly into the deltoid or gluteal muscle, but more preferably will be administered in the gluteal muscle. Those of ordinary skill in the art will understand that the maintenance dose may be titrated up or down in view of the patients condition (response to the medication and renal function).

**[0023]** Since paliperidone is mainly eliminated through the kidneys, patients with renal impairment will have a higher total exposure to paliperidone after i.m. injections of paliperidone palmitate. For patients with renal impairment it would be desirable to adjust the loading doses to account for the increased exposure levels of patients with renal impairment. For patients with mild renal impairment the loading doses should be reduced to 75 mg-eq. for the first two loading doses. The maintenance doses should range from about 25 mg-eq. to about 75 mg-eq. and more preferably with range from about 25 mg-eq. to about 50 mg-eq. The doses would be administered on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment. More preferably the patients will

be administered a first dose on day 1, a second dose on day 8 and a third dose on day 36 of treatment. The first two doses will preferably be injected in the deltoid muscle. Thereafter paliperidone palmitate will be administered by injection approximately once a month (e.g. one a month  $\pm 7$  days or once every four weeks) thereafter. For the purpose of this patent application renal function is estimated by glomerular filtration rate (GFR) usually measured by the creatinine clearance (best calculated from a 24-hour urine collection). Creatinine clearance may be estimated by the Cockcroft and Gault method based on serum creatinine concentration, as described in Prediction of creatinine clearance from serum creatinine. Nephron 1976; vol 16. pages 31-41. Patients with mild renal impairment have a creatinine clearance of 50 to  $< 80$  mL/minute.

**[0024]** It is recommended that the second initiation dose of paliperidone palmitate be given about one week (6-10 days) after the first dose. To avoid a missed dose, patients may be given the second dose 2 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

**[0025]** After initiation, the recommended injection cycle of paliperidone palmitate is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilized dose should be administered as soon as possible, followed by injections at monthly intervals.

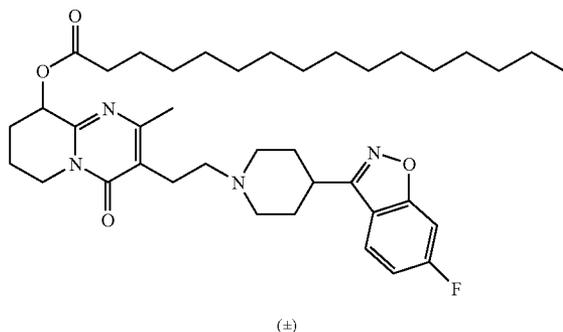
**[0026]** If more than 6 weeks have elapsed since the last injection, reinitiation with the same dose the patient was previously stabilized to should be resumed in the following manner: 1) a deltoid injection as soon as practically possible, followed by 2) another deltoid injection one week later, and 3) resumption of either deltoid or gluteal dosing at monthly intervals.

**[0027]** If more than 6 months have elapsed since the last injection, it is recommended to re-initiate dosing as described above.

**[0028]** Additionally, in this patient population needle length and BMI index are two related variables that need to be considered to assure patients attain therapeutic concentration of paliperidone in the desired time frame. Patients with high BMI had lower plasma concentration of paliperidone and a lessened treatment response. The lower initial plasma concentration in high BMI patients was likely due to unintended partial or complete injection into adipose tissue, instead of deep injection into muscle. However, once steady-state plasma concentration are attained BMI no longer influenced plasma concentrations or clinical efficacy. From these observations it was determined that for patients weighing  $< 90$  kg ( $< 200$  lb) a 1-inch needle will be of adequate length to use in injections to reach the muscle tissue for deltoid injections with preferably a 23 gauge needle. However, for patients with high BMIs,  $\geq 90$  kg ( $\geq 200$  lb) a 1.5-inch needle should be used for deltoid injections. For gluteal muscle injections a 1.5-inch needle should be used. Preferably the 1.5-inch needle will be a 22-gauge needle.

**[0029]** Paliperidone esters are psychotic agents belonging to the chemical class of benzisoxazole derivatives, which contains a racemic mixture of (+)- and (-)-paliperidone, which are described in U.S. Pat. No. 5,254,556 (incorporated herein by reference). The chemical name for paliperidone palmitate is (+)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-

piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate. The structural formula is:



**[0030]** Paliperidone esters may be formulated with pharmaceutical excipients into injectable dosage forms as described in U.S. Pat. No. 5,254,556 and U.S. Pat. No. 6,077,843 (incorporated herein by reference). Injectable formulations may be formulated in aqueous carriers.

**[0031]** Currently it is preferred to administer paliperidone palmitate in a once monthly aqueous depot. Suitable aqueous depot formulations are described in U.S. Pat. No. 6,077,843 (incorporated herein by reference). The aqueous formulation would preferably be a nano particle suspension of wherein the nano particles would be of an average size of less than 2000 nm to about 100 nm. Preferably the nano particles would have an average particle size (d50) of from about 1600 nm to 400 nm and most preferably about 1400 nm to 900 nm. Preferably the d90 will be less than about 5000 nm and more preferably less than about 4400 nm. As used herein, an effective average particle size (d50) of less than 2,000 nm means that at least 50% of the particles have a diameter of less than 2,000 nm when measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation. With reference to the effective average particle size, it is preferred that at least 90%, e.g. 5,000 nm. Most preferably, 90% of the particles have a size of less than 4,400 nm.

**[0032]** Suitable aqueous nano particle depot formulations are described in U.S. Pat. No. 6,555,544 (incorporated herein by reference). In one embodiment of the present invention the formulation would comprise nanoparticles, a surfactant, a suspending agent, and optionally one or more additional ingredients selected from the group consisting of preservatives, buffers and an isotonicizing agents. Useful surface modifiers are believed to include those that physically adhere to the surface of the active agent but do not chemically bond thereto.

**[0033]** Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethyl-

ene sorbitan fatty acid esters, e.g., the commercially available TWEENS™, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), poloxamers, tyloxapol and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

**[0034]** Particularly preferred surface modifiers include polyvinylpyrrolidone; tyloxapol; poloxamers, such as PLURONIC™ F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide available from BASF; poloxamines, such as TETRONIC™ 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF; dextran; lecithin; Aerosol OT™ (AOT) which is a dioctyl ester of sodium sulfosuccinic acid available from Cytec Industries; DUPONOL P which is a sodium lauryl sulfate available from DuPont; TRITON X-200 which is an alkyl aryl polyether sulfonate available from Rohm and Haas; TWEEN™, 20, 40, 60 and 80 which are polyoxyethylene sorbitan fatty acid esters available from ICI Specialty Chemicals; SPAN™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids; ARLACEL™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids available from Hercules, Inc.; CARBOWAX™ 3550 and 934 which are polyethylene glycols available from Union Carbide; CRODESTA™ F110 which is a mixture of sucrose stearate and sucrose distearate available from Croda Inc.; CRODESTA™ SL-40 which is available from Croda, Inc.; hexyldecyl trimethyl ammonium chloride (CTAC); bovine serum albumin and SA90HCO which is C<sub>18</sub>H<sub>17</sub>CH<sub>2</sub>(CON(CH<sub>3</sub>)CH<sub>2</sub>(CHOH)<sub>4</sub>CH<sub>2</sub>O)<sub>2</sub>. The surface modifiers which have been found to be particularly useful include tyloxapol and a poloxamer, preferably, Pluronic™ F108 and Pluronic™ F68.

**[0035]** Pluronic™ F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula HO[CH<sub>2</sub>CH<sub>2</sub>O]<sub>x</sub>[CH(CH<sub>3</sub>)CH<sub>2</sub>O]<sub>y</sub>[CH<sub>2</sub>CH<sub>2</sub>O]<sub>z</sub>H in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag NONIONIC™ 1108-F available from Hodag, and SYNPERONIC™ PE/F108 available from ICI Americas.

**[0036]** The optimal relative amount of paliperidone palmitate and the surface modifier depends on various parameters. The optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the antipsychotic agent, etc. The specific surface modifier preferably is present in an amount of 0.1 to 1 mg per square meter surface area of the paliperidone palmitate. It is preferred in the case of paliperidone palmitate (9-hydroxyrisperidone palmitate) to use PLURONIC™ F 108 as a surface modifier, a relative amount (w/w) of both ingredients of approximately 6:1 is preferred.

**[0037]** The particles of this invention can be prepared by a method comprising the steps of dispersing paliperidone palmitate in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the antipsychotic agent to an effective average particle size of less than 2,000 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

**[0038]** A general procedure for preparing the particles of this invention includes (a) obtaining paliperidone palmitate in micronized form; (b) adding the micronized paliperidone palmitate to a liquid medium to form a premix; and (c) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the effective average particle size.

**[0039]** The paliperidone palmitate in micronized form may be prepared using techniques known in the art. It is preferred that the particle size of the micronized paliperidone palmitate be less than about 100  $\mu\text{m}$  as determined by sieve analysis. If the particle size of the micronized paliperidone palmitate is greater than about 100  $\mu\text{m}$ , then it is preferred that the particles of paliperidone palmitate be reduced in size to less than 100  $\mu\text{m}$ .

**[0040]** The micronized paliperidone palmitate can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of paliperidone palmitate in the liquid medium (weight by weight percentage) can vary widely and depends on the selected antipsychotic agent, the selected surface modifier and other factors. Suitable concentrations of paliperidone palmitate in compositions vary between 0.1 to 60%, preferably is from 0.5 to 30%, and more preferably, is approximately 7% (w/v). It is currently preferred to use a concentration of about 100 mg eq of paliperidone per ml or about 156 mg of paliperidone palmitate per ml.

**[0041]** A more preferred procedure involves the addition of a surface modifier to the premix prior to its subsection to mechanical means to reduce the effective average particle size. The concentration of the surface modifier (weight by weight percentage) can vary from 0.1% to 90%, preferably from 0.5% to 80%, and more preferably is approximately 7% (w/v).

**[0042]** The premix can be used directly by subjecting it to mechanical means to reduce the effective average particle size in the dispersion to less than 2,000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the antipsychotic agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation such as, for example, a roller mill or a Cowles type mixer, until a homogeneous dispersion is achieved.

**[0043]** The mechanical means applied to reduce the effective average particle size of the antipsychotic conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills—such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is anywhere between 0.1 and 1 Pa·s. For ball milling, the apparent viscosity of the premix preferably is anywhere between 1 and 100 mPa·s.

**[0044]** The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than 3 mm and,

more preferably, less than 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of the material for the grinding media is believed not to be critical. However, 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are acceptable for the preparation of pharmaceutical compositions. Further, other media, such as polymeric beads, stainless steel, titania, alumina and 95% ZrO stabilized with yttrium, are useful. Preferred grinding media have a density greater than 2.5 g/cm<sup>3</sup> and include 95% ZrO stabilized with magnesia and polymeric beads.

**[0045]** The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For rolling mills, processing times of up to two days or longer may be required.

**[0046]** The particles must be reduced in size at a temperature which does not significantly degrade the antipsychotic agent. Processing temperatures of less than 30° C. to 40° C. are ordinarily preferred. If desired, the processing equipment may be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process.

**[0047]** The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed by, for example, shaking vigorously. Optionally, the dispersion can be subjected to a sonication step using, for example, a ultrasonic power supply.

**[0048]** Aqueous compositions according to the present invention conveniently further comprise a suspending agent and a buffer, and optionally one or more of a preservative and an isotonicizing agent. Particular ingredients may function as two or more of these agents simultaneously, e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonicizing agent.

**[0049]** Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylene- and polyoxypropylene ethers. Preferably sodium carboxymethyl cellulose is used in a concentration of 0.5 to 2%, most preferably 1% (w/v). Suitable wetting agents for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate. Preferably polysorbate 20 is used in a concentration of 0.5 to 3%, more preferably 0.5 to 2%, most preferably 1.1% (w/v).

**[0050]** Suitable buffering agents are salt of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to pH 8.5), preferably in the pH range of 7 to 7.5. Particularly preferred is the use of a mixture of disodium hydrogen phosphate (anhydrous) (typically about 0.9% (w/v)) and sodium dihydrogen phosphate monohydrate (typically about 0.6% (w/v)). This buffer also renders the dispersion isotonic and, in addition, less prone to flocculation of the ester suspended therein.

**[0051]** Preservatives are antimicrobials and anti-oxidants which can be selected from the group consisting of benzoic

acid, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-gamma-piccolinium chloride, phenylmercuric acetate and thimerosal. In particular, it is benzyl alcohol which can be used in a concentration up to 2% (w/v), preferably up to 1.5% (w/v).

**[0052]** Isotonizing agents are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. The suspensions conveniently comprise from 0 to 10% (w/v) isotonicizing agent. Mannitol may be used in a concentration from 0 to 7% More preferably, however, from about 1 to about 3% (w/v), especially from about 1.5 to about 2% (w/v) of one or more electrolytes are used to render the suspension isotonic, apparently because ions help to prevent flocculation of the suspended ester. In particular, electrolytes of the buffer serve as isotonicizing agent.

**[0053]** A particularly desirable feature for an injectable depot formulation relates to the ease with which it can be administered. In particular such an injection should be feasible using a needle as fine as possible in a span of time which is as short as possible. This can be accomplished with the aqueous suspensions of the present invention by keeping the viscosity below about 75 mPa·s, preferably below 60 mPa·s. Aqueous suspensions of such viscosity or lower can both easily be taken up in a syringe (e.g. from a vial), and injected through a fine needle (e.g. a 21 G 1½ inch, 22 G 2 inch, 22 G 1¼ inch or 23 G 1 inch needle). The preferred needles for injection are 22 G 22 G 1½ inch regular wall and 23 G 1½ inch regular wall needles.

**[0054]** Ideally, aqueous suspensions according to the present invention will comprise as much prodrug as can be tolerated so as to keep the injected volume to a minimum, and as little of the other ingredients as possible. In particular, such a composition will comprise by weight based on the total volume of the composition: (a) from 3 to 20% (w/v) of the prodrug; (b) from 0.5 to 2% (w/v) of a wetting agent; (c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5); (d) from 0.5 to 2% (w/v) of a suspending agent; (e) up to 2% (w/v) preservatives; and (f) water q.s. ad 100%. Preferably the aqueous suspension will be made under sterile conditions and no preservatives will be used. Appropriate methods to aseptically prepare paliperidone palmitate are described in WO 2006/114384 which is hereby incorporated by reference herein.

**[0055]** The preferred aqueous dosage form contains inactive ingredients that are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection. The mg of compound delivered in such a dosage form to the patient may be from 25 to about 150 mg (e.g. 25 mg, 50 mg, 75 mg, 100 mg, 150 mg) injectable dosage form.

**[0056]** The term "psychiatric patient" as used herein, refers to a human, who has been the object of treatment, or experiment for a "mental disorder" and "mental illness" refer to those provided in the Diagnostic and Statistical Manual (DSM IV), American Psychological Association (APA). Those of ordinary skill in the art will appreciate that paliperidone esters (e.g. paliperidone palmitate), can be administered to psychiatric patients for all the known uses of risperidone. These mental disorders include, but are not limited to, schizophrenia; bipolar disorder or other disease states in which psychosis, aggressive behavior, anxiety or depression is evi-

denced. Schizophrenia refers to conditions characterized as schizophrenia, schizoaffective disorder and schizophreniform disorders, in DSM-IV-TR such as category 295.xx. Bipolar Disorder refers to a condition characterized as a Bipolar Disorder, in DSM-IV-TR such as category 296.xx including Bipolar I and Bipolar Disorder II. The DSM-IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. Pathologic psychological conditions, which are psychoses or may be associated with psychotic features include, but are not limited to the following disorders that have been characterized in the DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The numbers in parenthesis refer to the DSM-IV-TR categories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress. Examples of pathologic psychological conditions which may be treated include, but are not limited to, Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusions (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delu-

sions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder,

Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

**[0057]** The following non-limiting examples are provided to further illustrate the present invention.

**[0058]** 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 human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

**[0059]** Those of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above. In general it is contemplated that an effective amount of paliperidone for the treatment of mental disorders would be from about 0.01 mg/kg to about 2 mg/kg body weight. For the present invention it is preferred to dose patients with 25 mg-eq. to about 150 mg eq. paliperidone. The amount of paliperidone palmitate is provided in sufficient amount to provide the equivalent dose of paliperidone after the palmitic acid moiety is removed from the ester (e.g. 156 mg corresponds to paliperidone 100 mg). In one embodiment of present invention wherein paliperidone palmitate is administered by intramuscular injection once per month is preferred.

#### Example 1

##### Paliperidone Palmitate Formulations

###### a) Crystallization in Stainless Steel Reactor of 50 L

**[0060]** All equipment was sterilized using dry heat sterilization.

**[0061]** A stainless steel reactor was charged with 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one palmitate ester and ethanol parenteral grade (8 L/kg) and heated to reflux temperature (78-79° C.) while stirring. The product dissolved at about 70° C. The solution was filtered at 76° C. over a sterile 0.22 µm filter into a sterile crystallization reactor. The sterile filter was then washed with heated ethanol (1 L/kg).

**[0062]** The filtrate was reheated to reflux and then cooled to room temperature whereupon the product crystallized. The thus obtained suspension was reheated again. The solution was cooled using differing cooling gradients (in consecutive experiments, the mixture was reheated and cooled again; after each cooling gradient, a sample was taken and isolated using a filter. The crystals were dried in vacuo at 50° C. in Tyvek bags so as to prevent dust formation and the particle characteristics were determined.

**[0063]** Different batches were run, yielding product with a particle size distribution measured by laser diffraction as shown in Table 1.

TABLE 1

Crystallization								
Cooling rate	Calculated cooling gradient (° C./min)	Tmax Treactor	start at . . .		start cooling (° C.) Treactor	Particle size distribution		
			(° C.) Treactor	(° C.) Tjacket		d110 (µm)	d150 (µm)	d190 (µm)
1° C./min	0.95	78	63.5	60.2	77.5	156	65	16
ASAP	3.2	75.7	61.2	17.5	75	119	36	9.2
0.5° C./min	0.48	75.7	63.8	62.7	75	192	80	20
0.5° C./min	0.48	75.7	63.8	62.7	75	189	81	23
0.7° C./min	0.81	75.7	61.7	58.9	75	113	41	11
1° C./min	0.92	75.7	62.1	54.9	75	128	52	13

## b) Formulation of Composition

**[0064]** Table 2 provides the formulation for the F013 formulation. The F011 formulation contained the same ingredients, with the exception of citric acid and NaOH, which were not present in the F011 formulation. Since the F011 formulation does not contain NaOH or citric acid, they are not part of the aqueous phase that is added to the milled concentrate of the F011 formulation. Therefore, the concentration of buffer salts in the aqueous phase of the F011 formulation is slightly different to make the formulation isotonic.

TABLE 2

Name	Amount Required	
	Per ml	Quantity for 24 L
Paliperidone palmitate (sterile grade)	156 mg	3.744 kg
Polysorbate 20 parenteral	12 mg	288 g
Citric acid monohydrate parenteral	5 mg	120 g
Disodium hydrogen phosphate anhydrous parenteral	5 mg	120 g
Sodium dihydrogen phosphate monohydrate parenteral	2.5 mg	60 g
Sodium Hydroxide all use	2.84 mg	68 g
Polyethylene Glycol 4000 parenteral	30 mg	720 g
Water for injections q.s. ad	1000 µl	24 L

## Equipment

- [0065]** stainless steel (SS) containers
- [0066]** Grinding media (Zirconium beads)+stainless steel (SS) grinding chamber
- [0067]** 0.2 µm filters
- [0068]** 40 µm filter
- [0069]** Filling unit
- [0070]** Autoclave
- [0071]** Dry heat oven

## Manufacturing

**[0072]** Zirconium beads were cleaned and rinsed using water for injections and then depyrogenised by dry heat (120 min at 260° C.). Water for injections was transferred into a SS container. Polysorbate 20 was added and dissolved by mixing. The solution was sterilized by filtration through a sterile 0.2 µm filter into a sterilized SS container. Paliperidone palmitate ester (sterile grade) as prepared in the previous examples was dispersed into the solution and mixed until

homogeneous. The suspension was milled aseptically in the grinding chamber using Zirconium beads as grinding media until the required particle size was reached. The suspension was filtered aseptically through a 40 µm filter into a sterilized SS container

**[0073]** Water for injections was transferred into a SS container, citric acid monohydrate parenteral, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide all use, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through a sterile 0.2 µm filter and transferred aseptically into the suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes. The target dose volume was between 0.25 ml and 1.50 ml depending on the dose needed.

TABLE 3

Dose volume	Target limit	lower limit	upper limit
0.25 ml-1.00 ml	identical to dose volume	target limit – (target limit × 0.05)	target limit × 1.05
1.25 ml-1.50 ml	identical to dose volume	target limit – (target limit × 0.025)	target limit × 1.025

## Sterilization

**[0074]** All aseptic manipulations and sterilization processes were carried out according to FDA and European regulatory guidelines.

## Apparatus

- [0075]** Sterilization was done by steam sterilization (F<sub>0</sub> ≧ 15 of following equipment:
- [0076]** SS containers
- [0077]** Zirconium beads+grinding chamber
- [0078]** 0.2 µm filters
- [0079]** 40 µm filter
- [0080]** filling pump
- [0081]** Immediate Container
- [0082]** 1 ml long transparent plastic (COC) syringe with luer lock.
- [0083]** rubber tip cap, FM257/2 dark grey
- [0084]** rubber plunger stopper, 1 ml long, 4023/50, Fluorotec B2-40

**[0085]** 2.25 ml transparent plastic (COC) syringe with luer lock.

**[0086]** rubber tip cap, FM257/2 dark grey

**[0087]** rubber plunger stopper, 1-3 ml, 4023/50, Fluorotec B2-40

**[0088]** The empty syringes with pre-assembled tip-caps were sterilized by gamma-irradiation (dose  $\cong$  25 kGy). The rubber plunger stoppers were sterilized by means of steam sterilization ( $F_0 \cong 1$ □).

#### Example 2

##### Evaluation of the Pharmacokinetic Profile of Gluteal Versus Deltoid Intramuscular Injections of Paliperidone Palmitate 100 mg Equivalent in Patients with Schizophrenia

**[0089]** This study was performed to characterize and compare the pharmacokinetic profile of paliperidone palmitate (formulated as described above) following four intramuscular injections in the deltoid or gluteal muscle.

#### Method

**[0090]** In this multiple-dose, open-label, parallel-group study, patients with schizophrenia were randomized to receive four consecutive intramuscular injections (days 1, 8, 36 and 64) of paliperidone palmitate 100 mg-eq. administered into either the deltoid (n=24) or gluteal muscle (n=25). Plasma samples for pharmacokinetic analyses were collected. The total paliperidone concentration was calculated as the sum of both enantiomers.

#### Results

**[0091]** The median  $C_{max}$  for paliperidone was higher in the deltoid versus the gluteal muscle after the second (31.3 versus 24.1 ng/mL) and fourth (23.7 versus 22.3 ng/mL) injections. After four injections, median  $AUC_{\infty}$  was similar for both injection sites;  $C_{max}$  and  $AUC_{\tau}$  for paliperidone were 30% (90% CI=100.56%-168.93%) and 20% (90% CI=93.09%-154.69%) higher in deltoid versus gluteal muscle, respectively. Median  $T_{max}$  was similar between injection sites after the second (10 day versus 10 day) and fourth injections (5 versus 6.5 days). After four injections, the median peak-to-trough ratio was higher (2.3 versus 1.9), with a larger inter-subject variability for deltoid versus gluteal injection. An increase in median predose plasma concentration between days 8, 36 and 64 for both sites suggested subjects were not completely at steady state after four injections. Relative exposure after the fourth injection was slightly lower than after the second injection in both the deltoid and gluteal muscle. Most commonly reported adverse events (combined injection sites) were orthostatic hypotension (24%), hypotension (14%), diastolic hypotension (12%) and injection site pain (14%). There were four serious adverse events (worsening of psychosis) that led to discontinuations. There were no deaths in the study. Paliperidone palmitate was well tolerated with more favorable local tolerability profile in the gluteal versus deltoid; mean injection site pain VSA score was 3.3 for gluteal versus 10.8 for deltoid muscle (day 1, 8 hours after injection).

#### Conclusion

**[0092]** Paliperidone palmitate 100 mg-eq. injections resulted in an increased  $AUC_{\tau}$ , higher  $C_{max}$ , greater FI, but

similar  $T_{max}$  following four consecutive injections into the deltoid versus gluteal muscle. Paliperidone palmitate 100 mg-eq. was systemically and locally well tolerated in this study.

#### Example 3

##### Assessment of the Dose Proportionality of Paliperidone Palmitate 25, 50, 100, and 150 mg eq. Following Administration in the Deltoid or Gluteal Muscles

**[0093]** This study evaluated dose proportionality of paliperidone palmitate injections when administered into either the gluteal or deltoid muscle.

#### Method

**[0094]** A single-dose, open label, parallel-group study of 201 randomized schizophrenia subjects was performed. The subjects were assigned into eight treatment groups: paliperidone palmitate 25 (n=48), 50 (n=50), 100 (n=51) or 150 (n=52) mg-eq. injected into either the deltoid or gluteal muscle. Serial plasma samples were collected for pharmacokinetic evaluation over 126-day period. The total paliperidone concentration was calculated as the sum of both enantiomers. Dose proportionality was assessed by linear regression model, for each injection site, with log-transformed dose-normalized  $AUC_{\infty}$  and  $C_{max}$  as dependent variables and log-transformed dose as predictor, respectively of  $C_{max}$  and  $AUC_{\infty}$  ratios of the enantiomers were documented.

#### Results

**[0095]** Slopes for log-transformed dose-normalized  $AUC_{\infty}$  were not significantly different from zero for deltoid (slope -0.06; p=0.036) and gluteal injections (slope -0.02; p=0.760) indicating a dose-proportional increase in  $AUC_{\infty}$ ,  $T_{max}$ , was comparable between doses but slightly earlier for deltoid (13-14 days) versus gluteal injections (13-17 days). Median  $C_{max}$  was higher with deltoid (range 5.3-11.0 ng/mL) versus gluteal (range 5.1-8.7 ng/mL) injections except for the 100 mg-eq. deltoid (slope -0.22, p=0.0062) and gluteal (slope -0.31; p<0.0001) injections, indicating a less than dose-proportional increase in  $C_{max}$ . Results of  $C_{max}$  and  $AUC_{\infty}$  were confirmed using pairwise comparisons. Plasma concentrations of (+)-enantiomer were consistently higher than (-)-enantiomer; (+)/(-) plasma concentrations ratio was approximately 2.4 shortly after administration and decreased to ~1.7 for both injection sites, independent of dose. After a single dose of paliperidone palmitate, subjects received concomitant oral antipsychotics. Treatment-emergent AEs (TEAs) included tachycardia (10%), headache (7%), schizophrenia (6%), insomnia (5%). Only 2% of subjects discontinued due to TEAs. No deaths were reported.

#### Conclusion

**[0096]**  $AUC_{\infty}$  increased proportionality with increasing paliperidone palmitate doses (5-150 mg-eq.), regardless of gluteal or deltoid injection. Overall, deltoid injection was associated with a higher  $C_{max}$  (except for 100 mg-eq.) and slightly earlier  $T_{max}$  compared with gluteal injections.

#### Example 4

##### Comparison of the PK Profile in the Deltoid to that in the Gluteal

**[0097]** The plasma concentration-time profile of paliperidone after single i.m. injection of the paliperidone palmitate formulation at 25-150 mg-eq. has been documented in several studies (Table 4). Details of how the comparison of injection sites study and the dose proportionality studies were performed are provided in Examples 2 and 3.

TABLE 4

Table of Clinical Studies Summarized	
Study	Design/Treatment/PK Objective
PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R092670-INT-12 (dose-proportionality)	S.D., OL, parallel group/single i.m. injection of F011*, 25, 50, 100 or 150 mg eq./document PK of the F011* formulation at different doses, enantiomer disposition
R092670-USA-3	M.D., OL, randomized, parallel groups/2 i.m. injections of R092670 (F011*) 25 or 150 mg eq., gluteal or deltoid, separated by 1 week/compare the PK after deltoid and gluteal injections, explore the relationship between R092670 PK parameters and CYP P450 genotypes
R092670-PSY-1001 (comparison of injection site)	M.D., OL, randomized, parallel groups/4 i.m. injections of R092670 (F013) 100 mg eq. in the gluteal or deltoid muscle (on Day 1, 8, 36 and 64)/compare the PK at steady state between deltoid and gluteal injection sites
R092670-PSY-1004 (dose-proportionality)	S.D., OL, randomized, parallel groups/single i.m. injection of R092670 (F013) 25, 50, 100 or 150 mg eq. in the gluteal or deltoid muscle/evaluate dose proportionality of F013 formulation over a dose range of 25-150 mg eq., compare the PK after deltoid and gluteal injections

S.D.: single dose; M.D.: multiple dose; OL: open-label; DB: double blind; PK: pharmacokinetic; PC: placebo-controlled; AC: active-controlled; pali ER: paliperidone extended release; pali IR: paliperidone immediate release  
 F011\*: Sterilized by gamma-irradiation. Otherwise, sterilized by aseptic crystallization.

**[0098]** The total exposure ( $AUC_{\infty}$ ) of paliperidone increased proportionally with dose after single-dose injections of 25 to 150 mg eq. paliperidone palmitate in both the deltoid and gluteal muscle. The increase in  $C_{max}$  was slightly less than dose proportional for both injection sites at doses greater than 50 mg eq. The apparent half-life (reflecting the absorption rate for this type of formulations) increased with dose from 25 days (median) after the 25 mg eq. dose to 40-49 days (median) after the 100 and 150 mg eq. dose, for both injection sites. The  $C_{max}$  of paliperidone was generally higher after single-dose injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (geometric mean ratio ranging from 108.75% to 164.85%) whereas this was much less pronounced for  $AUC_{\infty}$  (geometric mean ratio ranging from 103.00% to 117.83%). The median apparent half-life was comparable between injection sites.

#### Example 5

##### Description of the PK Profile in the Gluteal After Multiple Administrations

**[0099]** Paliperidone palmitate is a long-acting i.m. injectable, intended to release over a period of 1 month. In order to attain this long injection interval, an ester of paliperidone was prepared that has a limited solubility in a physiological environment. The ester was subsequently formulated as an aqueous suspension for i.m. injection. The rate of dissolution is governed by the particle size distribution whereby it was experimentally determined that an optimal particle size range is contained within xx-yy microm ( $d_{50v}$ ). In fact, the rate of dissolution (and thus the particle size distribution) fully determines the in vivo behaviour, as was nicely demonstrated in study PSY-1002. It was found that the median  $C_{max}$  increases and  $t_{max}$  shortens with decreasing particle size, which is consistent with the hypothesis that particle size is driving the release rate. The point estimates suggest that paliperidone exposure ( $AUC$ ,  $C_{max}$ ) after injection of paliperidone palmitate is similar between the to-be-marketed formulation F013 and formulation F011.

TABLE 5

Table of Clinical Studies Summarized in Module 2.7.2	
Study	Design/Treatment/PK Objective
PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R092670-BEL-4 (pilot, dose-proportionality)	M.D., OL, sequential, parallel groups/4-6 monthly i.m. injections of F004, 50 mg eq. or 100 mg eq. or 150 mg eq./explore M.D. PK and dose-proportionality
R092670-BEL-7 (dosing regimen)	M.D., OL, parallel groups/F004 formulation: Panel I: 100 mg eq. i.m. followed by 3 monthly i.m. injections of 50 mg eq.; Panel II: 200 mg eq. i.m. followed by 3 monthly i.m. injections of 100 mg eq.; Panel III: 300 mg eq. i.m. followed by 3 monthly i.m. injections of 150 mg eq.; Panel IV: 50 mg eq. i.m. followed by 1 week later by 4 monthly i.m. injections of 50 mg eq.; Panel V: 150 mg eq. i.m. followed by 1 week later by 4 monthly i.m. injections of 150 mg eq./explore the M.D. PK with various dosing regimens

TABLE 5-continued

Table of Clinical Studies Summarized in Module 2.7.2	
Study	Design/Treatment/PK Objective
PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R092670-INT-11 (compare F004 and F011)	M.D., DB, randomized, 4-group 2-way cross-over/4 monthly i.m. injections of F004 or F011*, 2 × 50 and 2 × 150 mg eq./compare PK of F004 and F011* formulations; compare S.D. and M.D. PK of both formulations
R092670-PSY-1002 (IVIVC)	S.D., OL, randomized, parallel groups/single i.m. injections of 1 mg paliperidone IR, followed by single i.m. injection of 50 mg eq. R092670: 1 of 4 F013 formulations with different particle sizes, or F011 formulation with medium particle size/explore IVIVC of 4 F013 formulations, compare the PK of F011 and F013 formulations
R092670-PSY-1001 (comparison of injection site)	M.D., OL, randomized, parallel groups/4 i.m. injections of R092670 (F013) 100 mg eq. in the gluteal or deltoid muscle (on Day 1, 8, 36 and 64)/compare the PK at steady state between deltoid and gluteal injection sites

S.D.: single dose; M.D.: multiple dose; OL: open-label; DB: double blind; PK: pharmacokinetic; PC: placebo-controlled; AC: active-controlled; pali ER: paliperidone extended release; pali IR: paliperidone immediate release  
F011\*: Sterilized by gamma-irradiation. Otherwise, sterilized by aseptic crystallization.

**[0100]** Pharmacokinetic theory also implies that for a formulation with such a long apparent half-life it takes 4-5 times this half-life for steady-state to be achieved. For individual patients, this means that following the first few injections, only subtherapeutic plasma concentrations are achieved. In order to overcome this problem, a loading dose regimen was developed (BEL-7), that was subsequently used in phase 2 and 3 of drug development. The dosing regimen consisting of two initial i.m. injections separated by one week followed by subsequent doses at monthly intervals resulted in a faster attainment of apparent steady state compared with a dosing regimen of one initial injection of twice the monthly dose followed by subsequent doses at monthly intervals. Somewhat higher peak-to-through fluctuations were observed with the first dosing regimen as compared with the latter one. The dosing regimen consisting of two initial i.m. injections separated by one week followed by subsequent doses at monthly intervals was selected for further studies and is also the recommended regimen for treatment.

#### Example 6

##### Description of the Exposure Range Needed for Efficacy Using Invega Data

**[0101]** All antipsychotic drugs currently on the market have one feature in common: they antagonize the D<sub>2</sub> receptor at the level of the brain. It has been empirically derived and is currently widely accepted that 65-70% occupancy is needed for antipsychotics to show clinical efficacy (Farde et al.), i.e. improvement on the PANSS scale. A too high occupancy (80-85%) will typically increase the risk to develop EPS. In order to determine the central D<sub>2</sub> occupancy, PET trials in human healthy volunteers are typically performed. Two such studies have been done for paliperidone: SWE-1 and SIV-101, showing that the K<sub>D</sub><sup>app</sup> for D<sub>2</sub> occupancy was ranging from 4.4 to 6.4 ng/mL. Using the 65-85% occupancy window, it can be calculated that the exposure range for efficacy without an increased risk to develop EPS as compared to placebo (<5% difference in probability) is contained in the window of 7.5-40 ng/mL.

**[0102]** In addition, based on the results of the phase 3 program of 6 mg paliperidone ER, in which plasma samples

were collected at several time points, a plasma concentration of 7.5 ng/mL was identified as the cut-off value above which 90% of the plasma concentrations were observed. The risk to develop EPS was clearly higher for dose above 9 mg Invega. Calculating back, this roughly corresponds to an exposure level of 35-40 ng/mL at steady-state. This implies that there is ample evidence to support a target exposure efficacy range of 7.5-40 ng/mL. This should be the target exposure range for paliperidone after injection of the paliperidone palmitate formulation.

#### Example 7

##### Optimal Way of Dosing

**[0103]** During the development of paliperidone palmitate, as the result of an extensive population PK analysis (refer to popPK report for paliperidone palmitate), several factors were found to slow down the release of paliperidone from the formulation, resulting in a slower build-up of plasma concentrations at the start of therapy and in more time required to reach steady-state. One factor was body mass index: the higher the BMI, the slower the dissolution (probably related to local physiological factors such as diminished blood flow at the site of injection); the other one being volume administered: the higher the volume injected, the slower the dissolution (probably related to the nonlinear relationship between surface area and volume). This has resulted in a lower than expected exposure using the originally proposed loading dose regimen, and the need to come up with an improved loading dose scheme for all patients irrespective of BMI in order to avoid drop-out due to lack of efficacy at the start of therapy. The aim was to get patients as quickly as possible above the 7.5 ng/mL, certainly after 1 week for all doses considered (25 mg-eq. and above).

**[0104]** Simulation scenarios with the statistically significant covariates from the population PK analysis revealed the following features about the paliperidone PK after injection of paliperidone palmitate:

**[0105]** Compared to deltoid injections, repeated administration in the gluteal muscle resulted in a delayed time to achieve steady-state (~4 wk longer), but did not influ-

ence the overall exposure (in terms of steady-state concentrations) to paliperidone.

**[0106]** Deltoid injections resulted in a faster rise in initial plasma concentrations, facilitating a rapid attainment of potential therapeutic plasma concentrations. The deltoid injection site is therefore recommended as the initiation site for dosing paliperidone palmitate.

**[0107]** Higher doses, associated with larger injection volumes, increased the apparent half-life of paliperidone, which in turn increased the time to achieve steady-state.

**[0108]** Needle length was an important variable for the absorption kinetics from the deltoid injection-site and it is recommended to use a longer 1.5-inch needle for deltoid administration in heavy subjects ( $\geq 90$  kg). Simulations indicated that the use of a longer needle in the deltoid muscle for the heavy individuals might be associated with an initial faster release of paliperidone into the systemic circulation, which could help overcome the slower absorption observed in heavier individuals described below.

**[0109]** The body size variable BMI was another important covariate for paliperidone palmitate. A slower rise in initial concentrations was observed in the obese population, which possibly occurred due to the reduced speed of initial influx from the injection site. Initiating the first two injections in the deltoid muscle and using a longer 1.5-inch needle for deltoid injection in heavy subjects can mitigate this effect. These observations are consistent with the expectation that in heavy subjects, administration into the adipose layer of the deltoid muscle can be avoided with the use of a longer injection needle.

Summarize what the optimized loading dose regimens would be here:

**[0110]** 150 deltoid (day 1), 100 mg deltoid (day 8), then every 4 weeks maintenance (gluteal or deltoid) (PSY-3006, simulations—popPK report palmitate)

**[0111]** 100 deltoid (day 1), 100 mg deltoid (day 8), then every 4 weeks maintenance (gluteal or deltoid) (simulations—popPK report palmitate, proposed for the label)

**[0112]** 150 mg deltoid day 1, maintenance dose day 8 and then every 4 weeks (gluteal or deltoid) (PSY-3007)

#### Example 8

**[0113]** TITLE OF STUDY: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia

Phase of Development: Phase 3

**[0114]** OBJECTIVES: The primary objectives of this study were to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate administered intramuscularly (i.m.) after an initial dose of 150 mg equivalent (eq.) in the deltoid muscle followed by either deltoid or gluteal injections for a total of 13 weeks of treatment as compared with placebo in subjects with schizophrenia. The secondary objectives were to:

**[0115]** Assess the benefits in personal and social functioning (key secondary endpoint) associated with the use of paliperidone palmitate compared with placebo;

**[0116]** Assess the global improvement in severity of illness associated with the use of paliperidone palmitate compared with placebo;

**[0117]** Assess the dose-response and exposure-response relationships of paliperidone palmitate.

**[0118]** METHODS: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-response study of men and women, 18 years of age and older, who had a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of schizophrenia. The study included a screening period of up to 7 days and a 13-week double-blind treatment period. The screening period included a washout of disallowed psychotropic medications.

**[0119]** Subjects without source documentation of previous exposure to at least 2 doses of oral risperidone or paliperidone extended-release (ER), at least 1 dose of i.m. RISPERDAL® CONSTA® or paliperidone palmitate, or who were not currently receiving an antipsychotic medication were given 4 to 6 days of paliperidone ER 6 mg/day (or the option of oral risperidone 3 mg/day for subjects in Malaysia) for tolerability testing. Subjects who had source documentation of previous exposure to the above medications and were currently taking another antipsychotic regimen continued their current treatment through Day-1. At the beginning of the double-blind treatment period, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 treatment groups: placebo or paliperidone palmitate 25 mg eq., 100 mg eq., or 150 mg eq. Study medication was administered as 4 doses: an initial i.m. injection of 150 mg eq. of paliperidone palmitate or placebo followed by 3 fixed i.m. doses of placebo or paliperidone palmitate [25, 100, or 150 mg eq.] on Days 8, 36, and 64. The initial injection of study medication was given in the deltoid muscle. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator. Randomized subjects were to remain in the study for 28 days after the last injection on Day 64 with the end of study visit scheduled for Day 92 during the double-blind period. The entire study, including the screening period, lasted approximately 14 weeks. Samples for pharmacokinetic (PK) evaluation were collected on Day 1, prior to the first injection and on Days 2, 4, 6, 8, 15, 22, 36, 64 and 92. Efficacy and safety were evaluated regularly throughout the study. A pharmacogenomic blood sample (10 mL) was collected from subjects who gave separate written informed consent for this part of the study. Participation in the pharmacogenomic research was optional. Approximately 105 to 115 mL of whole blood was collected during the study.

**[0120]** Number of Subjects (Planned and Analyzed): It was planned to include approximately 644 men and women in this study. A total of 652 eligible subjects from 72 centers in 8 countries were randomized and received at least 1 dose of double-blind study medication (safety analysis set); 636 subjects had both baseline and post baseline efficacy data (intent-to-treat analysis set).

**[0121]** Diagnosis and Main Criteria for Inclusion: Male or female subjects  $\geq 18$  years of age who met the DSM-IV diagnostic criteria for schizophrenia for at least 1 year before screening, had a Positive and Negative Syndrome Scale (PANSS) total score at screening of between 70 and 120, inclusive, and at baseline of between 60 and 120, inclusive, and had a body mass index (BMI) of  $>17.0$  kg/m<sup>2</sup> to  $<40$  kg/m<sup>2</sup> were eligible.

**[0122]** Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER was supplied as a 6-mg capsule-

shaped tablet for the oral tolerability test (batch number 0617714/F40). Paliperidone palmitate was supplied as 25, 100, or 150 mg eq. injectable suspension (batch numbers 06K22/F13 and 07D23/F13). For the oral tolerability test, a 6-mg tablet of paliperidone ER (or the option of oral risperidone 3 mg/day for subjects in Malaysia) was administered daily for 4 to 6 days. On Day 1 of the double-blind treatment period, 150 mg eq. of paliperidone palmitate was injected in the deltoid muscle followed by 25, 100, or 150 mg eq. i.m. injections of paliperidone palmitate on Days 8, 36, and 64, injected into the deltoid or gluteal muscle at the investigator's discretion.

**[0123]** Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as 20% Intralipid (200 mg/mL) injectable emulsion (batch numbers 06K14/F00 and 07F12/F00). An injection was given on Days 1, 8, 36 and 64.

**[0124]** Duration of Treatment: The study consisted of a screening and washout phase of 7 days and a double-blind treatment period of 13 weeks, starting with the first injection in the deltoid muscle followed by a second injection 1 week later. All injections after Day 1 were given in either the deltoid or the gluteal muscle at the discretion of the investigator. Two subsequent injections were given at 4-week intervals.

#### Criteria for Evaluation:

**[0125]** Pharmacokinetic Evaluations: A sparse blood sampling procedure was followed to study the paliperidone concentration-time profiles. Paliperidone plasma concentration-time data were subject to population PK analysis using nonlinear mixed-effects modeling, and details are described in a separate report.

**[0126]** Efficacy Evaluations/Criteria: The primary endpoint was the change in the PANSS total score from baseline (i.e., the start of double-blind treatment, Day 1) to the end of the double-blind treatment period (i.e., Day 92 or the last post baseline assessment). The key secondary efficacy endpoint was the change in the Personal and Social Performance Scale (PSP) from baseline to the end of the double-blind treatment period. The other secondary efficacy endpoint was the change in the Clinical Global Impression-Severity (CGI-S) scores from baseline to the end of the double-blind treatment period. Other endpoints included the change from baseline in subject ratings of sleep quality and daytime drowsiness using a visual analogue scale (VAS), the onset of therapeutic effect, responder rate, and the change from baseline to end point in PANSS subscales and Marder factors.

**[0127]** Safety Evaluations: Safety was monitored by the evaluation of adverse events, extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], Simpson and Angus Rating Scale [SAS]) scores, clinical laboratory test results, vital signs measurements, electrocardiograms (ECGs), and physical examination findings. In addition, the tolerability of injections was assessed; the investigators evaluated injection sites and the subjects assessed injection pain.

**[0128]** STATISTICAL METHODS: All randomized subjects who received at least 1 dose of double-blind study drug and had both baseline and at least one post baseline efficacy measurement (PANSS, PSP, or CGI-S) during the double-blind treatment period were included in the intent-to-treat efficacy analyses. The overall type 1 error rate for testing all paliperidone palmitate doses versus placebo for both the primary endpoint (change in PANSS total score at end point) and

the key secondary efficacy endpoint (change in PSP total score at end point) was controlled at the 2-sided 0.05 significance level. The 2 families of hypotheses (in each family, 3 comparisons for each of the paliperidone palmitate doses versus placebo) were tested using a parallel gatekeeping procedure that adjusts for multiplicity using Dunnett's method in each family of hypotheses and using Bonferroni's inequality between different families of hypotheses. This procedure is referred to as the Dunnett-Bonferroni-based parallel gatekeeping procedure.

**[0129]** The change from baseline in PANSS total score at each visit and at end point was analyzed using an analysis of covariance (ANCOVA) model. The last observation carried forward (LOCF) method was used. The model included treatment and country as factors and baseline PANSS total score as a covariate. Treatment effect was based on the difference in least-squares mean change. Dunnett's test was used to adjust for multiple comparisons of the 3 paliperidone palmitate dosages versus placebo. Unadjusted 2-sided 95% confidence intervals were presented for the difference in least-squares mean change of each paliperidone palmitate dosage group compared with placebo. Treatment-by-country and treatment-by-baseline PANSS total score interactions were explored using the same ANCOVA model as the one for the analysis of the primary endpoint. If either term was statistically significant at the predefined 2-sided significance level of 0.10, further evaluations of the effect of other covariates were to be performed to assess the nature of the interaction and identify possible causes. In addition, to address the dose-response relationship and to facilitate the discussion of dosage selection, an analysis to compare the 3 active paliperidone palmitate dosages with each other was performed without adjustment for multiple comparisons.

**[0130]** The analysis of the key secondary endpoint, change in PSP score at end point, was conducted by means of an ANCOVA model with treatment and country as factors and the baseline score as the covariate. The Dunnett-Bonferroni-based parallel gatekeeping approach was used to adjust for multiple testing.

**[0131]** Between-group comparisons of CGI-S were performed by using an ANCOVA model on the ranks of change from baseline, with treatment and country as factors and the baseline score as the covariate.

**[0132]** Change from baseline over time (observed case) in the PANSS total score was explored using mixed effects linear models for repeated measures with time, treatment, country, and treatment-by-time as factors and baseline score as a covariate.

**[0133]** The number and percentage of subjects with treatment-emergent adverse events were summarized. Adverse events of potential clinical interest were summarized separately, including events related to EPS or changes in serum glucose or prolactin levels.

**[0134]** Changes from baseline in clinical laboratory tests, vital sign measurements, ECGs, body weight, BMI, and EPS scale scores were summarized by treatment group. Prolactin levels were summarized by sex. Subjects with potentially abnormal values or changes in clinical laboratory tests, vital signs, orthostatic parameters, and ECG parameters were summarized based on predefined criteria. Frequency distributions were presented for the investigator's evaluation of the injec-

tion site, and descriptive statistics were presented for VAS scores corresponding to the subject's evaluation of injection pain.

#### Results:

**[0135]** The majority of subjects in the paliperidone palmitate treatment groups (56%-61%) received all 4 injections compared with 48% of the placebo-treated subjects. Completion rates were also higher for the paliperidone palmitate groups (52%-55%) than for the placebo group (43%). More subjects were discontinued for lack of efficacy in the placebo group (27%) compared with the paliperidone palmitate groups (14%-19%).

**[0136]** Demographic and Baseline Characteristics: The double-blind treatment groups were well matched with respect to demographic and baseline disease characteristics and psychiatric history. The 636 subjects who comprised the intent-to-treat analysis set were mainly male (67%), racially diverse (54% White, 30% Black, 14% Asian, 1% other races), and predominately between the ages of 26 and 50 years (75%). Most subjects had a primary diagnosis of paranoid schizophrenia (88%), and were highly symptomatic as indicated by a mean PANSS total score of 87.1 at baseline. There were notable differences between countries with respect to BMI and gender, with subjects enrolled at centers in the U.S. being more likely to be male and obese (i.e.,  $BMI \geq 30 \text{ kg/m}^2$ ) than those from centers in other countries.

**[0137]** Pharmacokinetics: A total of 488 subjects who were randomly assigned to receive paliperidone palmitate treat-

ment had scheduled pharmacokinetic blood samples taken over the course of the study. The median paliperidone predose concentration for the 25 mg eq. treatment group was highest on Day 8, which is the result of the initial 150 mg eq. dose on Day 1. After Day 8, paliperidone concentrations decreased and seemed to reach steady state levels on Day 92 based on visual inspection. The median paliperidone predose concentration for the 100 mg eq. treatment group remained in the same range from Day 8 onwards. The median predose concentration for the 150 mg eq. treatment group seemed to increase up to the last study day, Day 92. The median paliperidone plasma concentrations on Day 8 were lower in subjects with high BMI ( $\geq 25$  to  $<30 \text{ kg/m}^2$  and  $\geq 30 \text{ kg/m}^2$ ; overweight/obese) compared to subjects with low BMI ( $<25 \text{ kg/m}^2$ ) for the 3 dose groups. After Day 8, no consistent trends were observed for the 3 paliperidone palmitate dose groups with respect to paliperidone plasma concentrations as a function of baseline BMI classification.

**[0138]** The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. treatment group were approximately 2-fold higher than those for the 25 mg eq. treatment group. Thus, the PK profile for the 25 mg eq. and 100 mg eq. dose groups appeared to be less than dose proportional, which is the result of the initial paliperidone palmitate 150 mg eq. injection on Day 1 in all active treatment groups. The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. dose were apparently dose proportional compared to the 150 mg eq. dose. A high inter-subject variability was observed in the paliperidone plasma concentrations on Days 1 and 2 with a % CV of 118.9% (Day 1) and 153.1% (Day 2). After Day 2, the inter-subject variability decreased and the % CV ranged from 50.4 to 83.4%.

**[0139]** Primary Efficacy Analysis: Adult subjects with schizophrenia achieved statistically significant improvements in the PANSS total score (primary efficacy endpoint) with all 3 doses of paliperidone palmitate compared to placebo (25 mg eq.:  $p=0.034$ ; 100 mg eq.:  $p<0.001$ ; 150 mg eq.:  $p<0.001$ ) based on the intent-to-treat LOCF analysis and the Dunnett's test to control for multiplicity.

Positive and Negative Syndrome Scale for Schizophrenia (PANSS)  
Total Score - Change from Baseline to End Point-LOCF with the  
Dunnett-Bonferroni-Based Parallel Gatekeeping Procedure  
(Study R092670-PSY-3007: Intent-to-Treat Analysis Set)

	Placebo (N = 160)	R092670 25 mg eq. (N = 155)	R092670 100 mg eq. (N = 161)	R092670 150 mg eq. (N = 160)
Baseline Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)
End point Mean (SD)	83.9 (21.44)	78.8 (19.88)	74.6 (18.06)	75.2 (18.59)
Change from Baseline Mean (SD)	-2.9 (19.26)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
P-value (minus Placebo) <sup>a</sup>		0.034	<0.001	<0.001
Diff of LS Means (SE)		-5.1 (2.01)	-8.7 (2.00)	-9.8 (2.00)

<sup>a</sup>Based on analysis of covariance (ANCOVA) model with treatment (Placebo, R092670 25 mg eq., R092670 100 mg eq., R092670 150 mg eq.) and country as factors, and baseline value as a covariate. P-values were adjusted for multiplicity for comparison with placebo using Dunnett's test.

Note:

Negative change in score indicates improvement.

ment had scheduled pharmacokinetic blood samples taken over the course of the study. The median paliperidone predose concentration for the 25 mg eq. treatment group was highest on Day 8, which is the result of the initial 150 mg eq. dose on Day 1. After Day 8, paliperidone concentrations decreased and seemed to reach steady state levels on Day 92 based on visual inspection. The median paliperidone predose concentration for the 100 mg eq. treatment group remained in the same range from Day 8 onwards. The median predose concentration for the 150 mg eq. treatment group seemed to increase up to the last study day, Day 92. The median paliperidone plasma concentrations on Day 8 were lower in subjects with high BMI ( $\geq 25$  to  $<30 \text{ kg/m}^2$  and  $\geq 30 \text{ kg/m}^2$ ; overweight/obese) compared to subjects with low BMI ( $<25 \text{ kg/m}^2$ ) for the 3 dose groups. After Day 8, no consistent trends were observed for the 3 paliperidone palmitate dose groups with respect to paliperidone plasma concentrations as a function of baseline BMI classification.

**[0140]** Other Efficacy Results: There was a dose-response pattern with respect to the primary efficacy variable, with the mean decreases (improvement) in the PANSS total score at end point (LOCF).

**[0141]** Prespecified treatment-by-country and treatment-by-baseline PANSS total score interactions in the primary efficacy model were not statistically significant at the 0.10 level. An exploratory analysis additionally provided no statistical evidence for a BMI effect on treatment.

**[0142]** All 3 paliperidone palmitate dose groups showed a statistically significant improvement over placebo in the

change in PANSS total score as of Day 22 and at every subsequent time point, and as early as Day 8 in the paliperidone palmitate 25 mg eq. and 150 mg eq. groups.

**[0143]** The mean improvements in the PSP score from baseline to end point, the key secondary efficacy outcome measure, showed a dose response among the 3 paliperidone palmitate groups (25 mg eq.: 2.9; 100 mg eq.: 6.1; 150 mg eq.: 8.3); all were numerically higher than the mean improvement

injections at fixed doses of 25 mg eq., 100 mg eq., or 150 mg eq. on Days 8, 36, and 64, was generally well tolerated by adult subjects with schizophrenia during this 13-week study. Overall, the safety and tolerability results were consistent with previous clinical studies involving paliperidone palmitate, and no new safety signals were detected.

**[0148]** The overall summary of treatment-emergent adverse events is given below.

Overall Summary of Treatment-Emergent Adverse Events (Study R092670-PSY-3007: Safety Analysis Set)					
	Placebo (N = 164) n (%)	R092670 25 mg eq. (N = 160) n (%)	R092670 100 mg eq. (N = 165) n (%)	R092670 150 mg eq. (N = 163) n (%)	Total (N = 652) n (%)
TEAE	107 (65.2)	101 (63.1)	99 (60.0)	103 (63.2)	410 (62.9)
Possibly related TEAE <sup>a</sup>	47 (28.7)	45 (28.1)	49 (29.7)	51 (31.3)	192 (29.4)
TEAE leading to death	0	0	0	1 (0.6)	1 (0.2)
1 or more serious TEAE	23 (14.0)	15 (9.4)	22 (13.3)	13 (8.0)	73 (11.2)
TEAE leading to permanent stop	11 (6.7)	10 (6.3)	10 (6.1)	13 (8.0)	44 (6.7)

<sup>a</sup>Study drug relationships of possible, probable, and very likely are included in this category. Adverse events are coded using MedDRA version 10.1

in the PSP score seen in the placebo group (1.7). Based on the intent-to-treat LOCF analysis of this key secondary efficacy variable, using the Dunnett-Bonferroni-based parallel gate-keeping procedure to adjust for multiplicity, the improvement in the paliperidone palmitate 100 and 150 mg eq. treatment groups reached statistical significance (100 mg eq.:  $p=0.007$ ; 150 mg eq.:  $p<0.001$ ) when compared with the placebo group.

**[0144]** The paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significantly superior to placebo in improving the CGI-S scores from baseline to end point (LOCF) (without multiplicity adjustment, 100 mg eq.:  $p=0.005$ ; 150 mg eq.:  $p<0.001$ ). Significantly more subjects treated with paliperidone palmitate 25 mg eq. (33.5%;  $p=0.007$ ), 100 mg eq. (41.0%;  $p<0.001$ ), and 150 mg eq. (40.0%,  $p<0.001$ ) achieved responder status (30% or larger decrease on PANSS total scores) than with placebo (20.0%).

**[0145]** Based on the intent-to-treat LOCF analysis of the change from baseline to end point without statistical adjustment for multiplicity, the paliperidone palmitate 100 and 150 mg eq. groups were statistically significantly superior to the placebo group for all 5 PANSS Marder factors ( $p<0.010$ ). The improvements in both negative symptoms and disorganized thoughts factor scores were statistically significantly greater in the paliperidone palmitate 25 mg eq. group compared with placebo ( $p=0.032$ ).

**[0146]** Based on the intent-to-treat LOCF analysis using an ANCOVA model with no adjustment for multiplicity, the mean improvement in sleep quality in the paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significant ( $p<0.001$  and  $p=0.026$ , respectively) when compared with placebo. The mean changes in daytime drowsiness in the paliperidone palmitate treatment groups were not statistically significantly different from that in the placebo group (25 mg eq.:  $p=0.541$ ; 100 mg eq.:  $p=0.340$ ; 150 mg eq.:  $p=0.261$ ).

**[0147]** Safety Results Paliperidone palmitate, injected at a dose of 150 mg eq. into the deltoid muscle followed by 3 i.m.

**[0149]** There was 1 death in a subject in the paliperidone palmitate 150 mg eq. group after withdrawal from the study due to an adverse event (cerebrovascular accident) that began during the study. This subject received 2 injections of study medication, with the last injection administered approximately 2 weeks before the subject died. While this event was assessed as doubtfully related to study treatment by the investigator, an unblinded review by the sponsor assessed this event to be possibly related to study treatment.

**[0150]** The number of subjects who experienced treatment-emergent serious adverse events was higher in the placebo group than in any of the paliperidone palmitate groups (see table above). Most serious adverse events in all treatment groups were psychiatric disorders (e.g., schizophrenia, psychotic disorder) that were likely the result of the natural course of the underlying schizophrenia. Adverse events leading to study discontinuation occurred at a similar low incidence across treatment groups.

**[0151]** Common treatment-emergent adverse events ( $\geq 2\%$  of subjects in any treatment group) that occurred more frequently in the total paliperidone palmitate group (all 3 active dose groups combined) than in the placebo-treated subjects (i.e.,  $\geq 1\%$  difference between the combined paliperidone palmitate group and the placebo group) were: injection site pain, dizziness, sedation, pain in extremity, and myalgia. An examination of treatment-emergent adverse events of potential clinical importance revealed no reports of seizure or convulsion, tardive dyskinesia, dermatologic events, neuroleptic malignant syndrome, hyperthermia, anaphylactic reaction, rhabdomyolysis, syndrome of inappropriate secretion of antidiuretic hormone, ventricular tachycardia, ventricular fibrillation, or torsades de pointes.

**[0152]** In general, the type and incidence of treatment-emergent adverse events did not differ as a function of baseline BMI categories (normal:  $<25 \text{ kg/m}^2$ ; overweight:  $\geq 25$  to  $<30 \text{ kg/m}^2$ ; obese:  $\geq 30 \text{ kg/m}^2$ ).

**[0153]** The incidence of treatment-emergent EPS-related adverse events was low and comparable to placebo. Akathisia

was the most frequently reported EPS-related adverse event (4.9% for the placebo group and 1.3%, 4.8%, 5.5% for the paliperidone palmitate 25, 100, and 150 mg eq. groups, respectively). None of the EPS-related adverse events reported in subjects receiving paliperidone palmitate were serious or treatment limiting, and only 1 was severe (musculoskeletal stiffness). Results of EPS rating scales and use of anti-EPS medication were consistent in indicating that paliperidone palmitate was associated with a low incidence of EPS.

**[0154]** No clinically relevant mean changes from baseline to end point in supine or standing pulse rates were apparent for any of the paliperidone palmitate doses. A similar, low percentage of subjects had pulse rate of  $\geq 100$  bpm with an increase of  $\geq 15$  bpm in the placebo and paliperidone palmitate groups (6% to 11% for standing measurements; 2% to 5% for supine measurements).

**[0155]** Assessment of ECG data did not demonstrate evidence of clinically significant QTc prolongation with paliperidone palmitate at doses up to 150 mg eq. No subject had a maximum QTcLD value  $>480$  ms or a maximal change in QTcLD  $>60$  ms during the study.

**[0156]** The increases in body weight with paliperidone palmitate over the 13-week double-blind treatment period were modest in a dose-related manner, averaging 0.4, 0.7, and 1.4 kg for the 25 mg eq., 100 mg eq., and 150 mg eq. groups, respectively ( $-0.2$  kg for placebo); corresponding mean changes in BMI from baseline to end point were 0.1, 0.3, and  $0.5$  kg/m<sup>2</sup>, respectively ( $-0.1$  kg/m<sup>2</sup> for placebo). A clinically relevant weight increase of at least 7% relative to baseline was seen in 13% of subjects receiving the highest dose of paliperidone palmitate (compared with 5% for placebo).

**[0157]** Consistent with the known pharmacology of paliperidone, increases in prolactin levels were observed with greater frequency in subjects who received paliperidone palmitate, with the largest increase seen in the 150 mg eq. group. Overall, there was a low incidence of potentially prolactin-related adverse events, despite the known propensity of paliperidone palmitate to increase serum prolactin levels. This suggests that the clinical importance of this increase in serum prolactin levels is of questionable clinical significance.

**[0158]** Based on mean changes from baseline to end point and the occurrence of treatment-emergent markedly abnormal laboratory test values and adverse events related to abnormal laboratory analyte findings, except for prolactin, the effects of paliperidone palmitate on the results of chemistry and hematology laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) did not show clinically relevant differences from those of placebo.

**[0159]** Local injection site tolerability was good. Occurrences of induration, redness, or swelling as assessed by blinded study personnel were infrequent, generally mild, decreasing over time, and similar in incidence for the paliperidone palmitate and placebo groups. Investigator ratings of injection pain were similar for the placebo and paliperidone palmitate groups.

**[0160]** STUDY LIMITATIONS: This study investigated the efficacy and safety of paliperidone palmitate for acute treatment of schizophrenia over 13 weeks and does not provide information on longer term treatment. The study was not designed to detect differences between doses of paliperidone palmitate; thus, dose-related trends in efficacy and safety can only be described descriptively. The study was also not designed to demonstrate efficacy for specific subgroups of

subjects, such as those from a particular country. An independent, centralized blinded rating service was used for performing all ratings of PANSS, PSP and CGI-S for all subjects enrolled at U.S. sites. The investigators at these sites did not complete any of the ratings, which would have provided a reference for ratings provided by the rating service. Thus, data from this study cannot be used to fully evaluate the utility of using blinded independent raters for detecting treatment differences.

**[0161]** CONCLUSION: All 3 doses of paliperidone palmitate tested in this study—25, 100, and 150 mg eq.—were efficacious in adult subjects with schizophrenia who were experiencing acutely exacerbated schizophrenia. Specifically, the results of the primary efficacy endpoint (change from baseline to end point in PANSS total score) demonstrated statistical superiority of paliperidone palmitate 25 mg eq., 100 mg eq., and 150 mg eq. over placebo. Significantly greater improvement in subjects' personal and social functioning (as measured by the PSP score) was also seen for the paliperidone palmitate 100 mg eq. and 150 mg eq. doses compared with placebo, and global improvement was validated by a favorable and statistically significant CGI-S change for these 2 dose groups. There was a dose response in the primary and secondary efficacy endpoints (PANSS, PSP, and CGI-S). All 3 doses of paliperidone palmitate, including the highest dose of 150 mg eq., were well tolerated, suggesting a positive benefit-risk ratio across the dose range currently studied. No new safety signal was detected.

#### FIGURES

**[0162]** FIGS. 1-3 graphically presents the observed versus population pharmacokinetics model simulation for plasma paliperidone concentrations. The line indicates the median values calculated from population pharmacokinetic simulation. The shading indicates 90% prediction interval representing the between and within subject, variability obtained using the population pharmacokinetic simulation. The circles indicate observed plasma paliperidone concentrations. The arrows indicate the days when paliperidone palmitate injection was given. As is apparent from the Figures the plasma profiles provided by initiating paliperidone with 150 mg eq. followed by a subsequent dose of 100 or 150 for days 1-36 provide a rapid rise to a therapeutic dose levels. Most preferably the dosing of paliperidone to patients should be maintained within  $\pm 25\%$ , preferably 20% of the median plasma concentrations provided in these figures for days 1-36. For patients whose dosing continues at 100 mg eq. the preferably the dosing of paliperidone to patients should be maintained within  $\pm 25\%$ , preferably 20% of the median plasma concentrations provided in FIG. 2 for days 1-64. For patients whose dosing continues at 150 mg eq. the preferably the dosing of paliperidone to patients should be maintained within  $\pm 25\%$ , preferably 20% of the median plasma concentrations provided in FIG. 3 for days 1-64.

We claim:

1. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising
  - (1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
  - (2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of

- from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6<sup>th</sup> to about 10th day of treatment; and
- (3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.
2. The method of claim 1 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30<sup>th</sup> day of treatment.
3. The method of claim 1 wherein the sustained release formulation is an aqueous nanoparticle suspension.
4. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising
- (a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
- (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and
- (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.
5. The method of claim 4 wherein the sustained release formulation is an aqueous nanoparticle suspension.
6. The method of claim 4 wherein the first loading dose is 150 mgs-eq. of paliperidone as paliperidone palmitate.
7. The method of claim 4 wherein the first loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.
8. The method of claim 4 wherein the second loading dose is 150 mg-eq. of paliperidone as paliperidone palmitate.
9. The method of claim 4 wherein the second loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.
10. The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg-eq. of paliperidone as paliperidone palmitate.
11. The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg of paliperidone as paliperidone palmitate.
12. The method of claim 4 wherein the psychiatric patient is in need of treatment for psychosis.
13. The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.
14. The method of claim 4 wherein the psychiatric patient is in need of treatment for bipolar disorder.
15. The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxi-

olytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

**17.** A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

- (a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
- (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6<sup>th</sup> to about 10th day of treatment; and
- (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance

dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

**18.** The method of claim **17** wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30<sup>th</sup> day of treatment.

**19.** The method of claim **17** wherein the sustained release formulation is an aqueous nanoparticle suspension.

**20.** A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

- (a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
- (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and
- (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

**21.** The method of claim **20** wherein the sustained release formulation is an aqueous nanoparticle suspension.

**22.** The method of claim **20** wherein the psychiatric patient is in need of treatment for psychosis.

**23.** The method of claim **4** wherein the psychiatric patient is in need of treatment for schizophrenia.

**24.** The method of claim **4** wherein the psychiatric patient is in need of treatment for bipolar disorder.

**25.** The method of claim **4** wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or

Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somato-

form Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar TI Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

**26.** A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

- (a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
- (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6<sup>th</sup> to about 10th day of treatment; and
- (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

**27.** The method of claim 26 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30<sup>th</sup> day of treatment.

**28.** The method of claim 26 wherein the sustained release formulation is an aqueous nanoparticle suspension.

**29.** A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

- (a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

- (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and
- (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.
- 30.** The method of claim **29** wherein the sustained release formulation is an aqueous nanoparticle suspension.
- 31.** The method of claim **29** wherein the psychiatric patient is in need of treatment for psychosis.
- 32.** The method of claim **29** wherein the psychiatric patient is in need of treatment for schizophrenia.
- 33.** The method of claim **29** wherein the psychiatric patient is in need of treatment for bipolar disorder.
- 34.** The method of claim **29** wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed,

Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar

II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

\* \* \* \* \*



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FORMULATIONS OF DOCETAXEL**(86) PCT No.: **PCT/AU2006/000843**

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(2), (4) Date: **Dec. 12, 2007**(75) Inventors: **Aikun Julie Liu**, Victoria (AU);  
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**A61K 31/337** (2006.01)(52) **U.S. Cl.** ..... **514/449**(57) **ABSTRACT**(73) Assignee: **MAYNE PHARMA LIMITED**,  
Mt Waverley (AU)There is provided a liquid pharmaceutical formulation for  
parenteral administration comprising: docetaxel or a pharma-  
ceutically acceptable salt thereof; one or more glycols; and a pharma-  
ceutically acceptable nonaqueous solvent system;  
wherein the formulation has a pH meter reading in the range  
of from 2.5 to 7.(21) Appl. No.: **11/922,165**(22) PCT Filed: **Jun. 16, 2006**

## LIQUID PHARMACEUTICAL FORMULATIONS OF DOCETAXEL

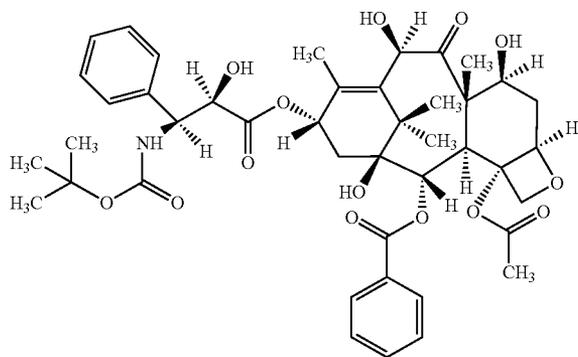
### FIELD OF THE INVENTION

[0001] The invention relates to liquid pharmaceutical formulations comprising docetaxel that are able to be used as single dose or multi-dose formulations, and to their uses in medicaments and to methods for treating cancer.

### BACKGROUND OF THE INVENTION

[0002] In this specification, where a document, act or item of knowledge is referred to or discussed, this reference or discussion is not an admission that the document, act or item of knowledge or any combination thereof was at the priority date, publicly available, known to the public, part of common general knowledge; or known to be relevant to an attempt to solve any problem with which this specification is concerned.

[0003] Docetaxel (CAS 114977-28-5) is an antineoplastic agent belonging to the taxoid family which was identified in 1986 as an alternative to paclitaxel. It is prepared by a semi-synthetic process beginning with a precursor extracted from the needles of yew plants (*Taxus baccata*). The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butylester, 13 ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2 benzoate, and it has the following chemical structure:



[0004] Docetaxel is a white to almost white powder with an empirical formula of  $C_{43}H_{53}NO_{14}$ . It is very lipophilic and practically insoluble in water. The first patent family relating to docetaxel includes U.S. Pat. No. 4,814,470 (AU 591,309).

[0005] Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubules without normal function and to the stabilization of microtubules which results in the inhibition of mitosis (replication) in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

[0006] The commercial product marketed by Aventis is called Taxotere® and it was first approved in 1996. It is now approved for a number of different indications throughout the world, as set out below:

Indication	USA	EU	AU	CA
2 <sup>nd</sup> line breast cancer	✓	✓	✓	✓
Breast cancer in combination with capecitabine after anthracycline failure	x	✓	✓	✓
Breast cancer: adjuvant treatment of patients with node positive breast cancer in combination with doxorubicin and cyclophosphamide, potentially followed by prophylactic G-CSF	✓	✓	✓	x
Breast cancer: combination with doxorubicin with potentially life threatening disease	x	x	x	✓
Breast cancer: combination with trastuzumab for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease	x	✓	x	x
2 <sup>nd</sup> line ovarian cancer	x	x	✓	✓
NSCLC, including those where platinum compound has failed	✓	✓	✓	✓
NSCLC: combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition	✓	✓	x	✓
Prostate cancer; androgen independent (hormone refractory)	✓ (in combination with prednisone)	✓ (in combination with prednisone or prednisolone)	✓	x
Squamous cell carcinoma of the head and neck; monotherapy or combination after previous failure	x	x	x	✓

[0007] As such, it is widely understood that docetaxel is a useful and efficacious oncology agent, either alone or in combination with other agents.

[0008] Taxotere® is formulated as a concentrate for dilution. It is a clear-yellow to brownish-yellow viscous solution. Each millilitre contains 40 mg docetaxel and 1040 mg polysorbate 80. The diluent for Taxotere® is 13% ethanol in water for injection. It comes in two presentations:

Strength	Labelled Fill	Diluent (13% ethanol in Water for Injection)
Taxotere ® 80	80 mg docetaxel per 2 ml polysorbate 80	6 ml
Taxotere ® 20	20 mg docetaxel per 0.5 ml polysorbate 80	1.5 ml

[0009] The medical practitioner must aseptically withdraw the entire contents of the diluent vial, transfer it to the vial containing the docetaxel concentrate and mix the components to produce a solution containing 10 mg/ml docetaxel. That

mixture must be repeatedly inverted for 45 seconds in order to mix the solutions adequately. It cannot be shaken, as that leads to foaming and the potential loss of potency. This intermediate solution is then diluted in an infusion bag, typically 250 ml, containing either 0.9% sodium chloride solution or 5% dextrose solution to produce a concentration of 0.3 to 0.74 mg/ml of docetaxel.

**[0010]** Due to the fact that docetaxel is practically insoluble in water, there have been a number of other attempts to develop appropriate injectable formulations. For example, docetaxel is known to be soluble in ethanol and one of the first such other formulations was 50% ethanol and 50% Emulphor EL® (a non-ionic solubilizer and emulsifier manufactured by reacting castor oil with ethylene oxide).

**[0011]** U.S. Pat. No. 5,403,858 (AU 666,859; EP593 601; EP522 937) discloses a formulation for docetaxel which reduces the ethanol concentration, or eliminates the ethanol from the solution completely. The formulations comprise a surfactant, such as a polysorbate (eg Tween®), a polyoxyethylene glycol ester (eg. Emulphor®) or an ester of polyethylene glycol and castor oil (eg Cremophor EL®); and are virtually free from ethanol.

**[0012]** U.S. Pat. No. 5,714,512 is also part of this patent family and relates to formulations consisting essentially of docetaxel dissolved in a surfactant selected from polysorbate, polyoxyethylated vegetable oil and polyethoxylated castor oil which are essentially free of ethanol. U.S. Pat. No. 5,698,582 is also part of this patent family and relates to formulations comprising docetaxel dissolved in a surfactant selected from polysorbate or polyethoxylated castor oil which is essentially free of ethanol.

**[0013]** AU691476 (EP 0 671 912) discloses a two part injectable composition. This two part composition involves preparing an intermediate solution using the stock solution, prior to the addition of this intermediate solution to infusion bag. The intermediate solution contains an additive which promotes the dissolution of the stock solution in the aqueous infusion solution by breaking or avoiding the formation of a gelled phase between the surfactant in the stock solution and the water of the infusion solution. The additives have a molecular weight equal to or less than 200 and have at least one hydroxyl functional group or one amine functional group, for example, ethanol, glucose, glycerol, propylene glycol, glycine, sorbitol, mannitol, benzyl alcohol and polyethylene glycols. The additives may also be inorganic salts such as sodium chloride.

**[0014]** There are a number of other patent applications which have been made for formulations of docetaxel. However, none of these attempted formulations has resulted in a successful commercial product to compete with Taxotere® to date. There is thus still a need for alternative docetaxel formulations which have the necessary physicochemical properties, bioavailability and shelf life.

**[0015]** One of the difficulties with the currently commercially available formulation of docetaxel, Taxotere®, is that the administration process is complex and involves many steps. As described above, the person administering the drug must first create an intermediate solution before then administering that intermediate solution into the infusion bag. As docetaxel is extremely toxic, all steps should be taken to minimise the handling that is required in administering the drug.

**[0016]** In making that intermediate solution, the medical practitioner must manually invert the vial for 45 seconds. The

prescribing information for Taxotere® gives very clear instructions not to shake the vial. This is due to the foaming that can occur, potentially resulting in potency loss.

**[0017]** A further difficulty of the Taxotere® product is that the intermediate solution must be added to the infusion bag within 8 hours of making that admixture. Accordingly, the current commercially available presentation of docetaxel is a single use vial only.

**[0018]** Further, once added to the infusion bag, it has a limited stability in the infusion bag. The prescribing information for Taxotere®D states it is only stable for four hours and must be used within this period.

#### SUMMARY OF THE INVENTION

**[0019]** It has surprisingly been found that a docetaxel formulation comprising the combination of pH modification and a glycol in a non-aqueous solvent has the following advantages:

**[0020]** (a) comparative stability of the formulation when compared to the Taxotere® concentrate (ie pre-dilution);

**[0021]** (b) suitable for use as a multi-dose product due to the increased alcohol content;

**[0022]** (c) it is a single vial product ready for introduction directly into the infusion bag without the need for any intermediate solution, therefore requiring less handling by the medical practitioner prior to administration to a patient;

**[0023]** (d) more accurate dosage of the drug as a consequence of the reduced foaming when preparing the product minimising the risk of potency loss; and

**[0024]** (e) comparative stability once the formulation is introduced to the infusion solution.

**[0025]** According to a first aspect of the invention, there is provided a liquid pharmaceutical formulation for parenteral administration comprising:

**[0026]** docetaxel or a pharmaceutically acceptable salt thereof;

**[0027]** one or more glycols; and

**[0028]** a pharmaceutically acceptable nonaqueous solvent system;

wherein the formulation has a pH meter reading in the range of from 2.5 to 7.

**[0029]** According to a second aspect of the invention, there is provided a pharmaceutical liquid formulation for parenteral administration comprising:

**[0030]** docetaxel or a pharmaceutically acceptable salt thereof;

**[0031]** one or more glycols;

**[0032]** an amount of one or more pharmaceutically acceptable acids sufficient to provide the formulation with a pH meter reading in the range of from 2.5 to 7; and

**[0033]** a pharmaceutically acceptable nonaqueous solvent system.

**[0034]** A person skilled in the art will know that pH is a measure of free H<sup>+</sup> ions in a solution. For example, free H<sup>+</sup> will exist in alcohol systems which contain acids. The pH may be measured by placing a pH meter directly into the liquid formulation, such pH meter having been calibrated for the appropriate pH range with standard aqueous buffers. Persons skilled in the art will know of other methods which may be used to measure pH. Such a person will further know that, while the pH meter reading obtained for a substantially non-aqueous formulation may not be a true reflection of the actual

H<sup>+</sup> ion concentration in the solution, it may nonetheless give a meaningful and reproducible measurement that indicates the relative acidity/basicity of the solution as is the case for the docetaxel formulations disclosed herein. Preferably, the pH meter reading is in the range from 3 to 7, more preferably 3 to 6. Most preferably, the pH meter reading is in the range of from 4 to 6. These ranges are for measurements made at room temperature (20 to 25° C.). A person skilled in the art will know that the pH meter reading will vary depending on the temperature.

**[0035]** The pH of a formulation comprising 10 mg docetaxel, 260 mg polysorbate 80, 0.23 ml ethanol and PEG 300 to one ml had a pH reading of 8.2. Polysorbate 80 on its own had a pH reading of 8.

**[0036]** A person skilled in the art will recognise that the pH meter reading of the formulations according to the invention can be achieved by acidifying the formulation itself, or by adjustment of the pH of any of the components of the formulation, for example by purification of the surfactant to remove basic contaminants or acidification of any one of the components prior to the mixing of the formulation.

**[0037]** The acid may be selected from the range of pharmaceutically acceptable acids known to those skilled in the art, which are soluble in the nonaqueous solvent system and which are compatible with docetaxel. A person skilled in the art will know that certain strong acids may react with docetaxel creating degradants and to avoid such acids. For example, epimerisation of the hydroxyl functionality of docetaxel is known to be facilitated by certain strong acids. In some instances, the use of a stabilising agent may counteract any degradative effect of the acid. The acid may be inorganic or organic. Preferably, the pharmaceutically acceptable acids are organic acids. More preferably, the pharmaceutically acceptable acid is selected from carboxylic and dicarboxylic acids. Most preferably, the pharmaceutically acceptable acid is selected from citric acid, tartaric acid, acetic acid and mixtures thereof.

**[0038]** A person skilled in the art will know that the amount of pharmaceutically acceptable acid used will be limited by the particular acid's solubility in the pharmaceutically acceptable nonaqueous solvent system. The amount of acid required will also be further determined by the relative strength of the acid.

**[0039]** Where the pharmaceutically acceptable acid is citric acid, then preferably the citric acid is present at a concentration in the range of from 1.6 to 6 mg/ml, more preferably 4 mg/ml.

**[0040]** The docetaxel used to make the formulation of the invention may be in any form known to those skilled in the art including anhydrous forms, hydrated forms, polymorphs, derivatives and pro-drugs.

**[0041]** The concentration of docetaxel may be any amount up to 90 mg/ml. Preferably, the concentration of docetaxel is in the range of from 5 to 20 mg/ml, more preferably from 8 to 12 mg/ml, and most preferably about 10 mg/ml.

**[0042]** The glycol is preferably selected from the group consisting of polyethylene glycols, propylene glycol, tetra glycol and mixtures thereof. Polyethylene glycol (eg PEG 300 and PEG 400) is an excipient which is widely used in pharmaceutical formulations. Preferably, the polyethylene glycol has a molecular weight in the range from 200 to 600. More preferably, the polyethylene glycol has a molecular weight of about 300 (PEG 300). A person skilled in the art will

know that a polyethylene glycol having a molecular weight above 600 is likely to be solid and can be used in nonaqueous systems.

**[0043]** Propylene glycol and tetra glycol are also used in pharmaceutical formulations as solvents and are approved for parenteral use by the regulatory authorities around the world, including the US Food and Drug Administration and the equivalent European authority.

**[0044]** Preferably, the glycol is present in the formulation in an amount in the range of from 30 to 65% v/v, more preferably about 57%.

**[0045]** The pharmaceutically acceptable nonaqueous solvent system may comprise any pharmaceutically acceptable nonaqueous components known to persons skilled in the art in which the docetaxel is soluble; for example, alcohols and surfactants. Typically, the pharmaceutically acceptable nonaqueous solvent system will comprise one or more alcohols; and one or more non-ionic surfactants selected from the group consisting of polyethoxylene sorbitan fatty acid esters (polysorbates) such as Tween 80®, polyoxyethylene glycol esters such as Emulphor®, and polyethoxylated castor oils such as Cremophor-EL® and mixtures thereof. Preferably, the alcohol is ethanol and the surfactant is a polysorbate.

**[0046]** Preferably, the alcohol is present in an amount in the range of from 10 to 55% v/v of the formulation, more preferably 18 to 26%, and most preferably about 23% v/v.

**[0047]** Preferably, the non-ionic surfactant is present in an amount in the range of from 10 to 50% v/v of the formulation, more preferably 10 to 40%, and most preferably about 25%.

**[0048]** The pharmaceutically acceptable nonaqueous solvent system may include other components such as a solubilising agent, eg benzyl benzoate, or stabilising agents, eg povidone.

**[0049]** The person skilled in the art will understand that whilst the solvent system is described as nonaqueous, this merely indicates that water is not specifically added to the formulation. There is likely to be some water present in the formulation due to its presence in some of the commercial components used (eg surfactants) and water may also be absorbed from the environment into the formulation. Formulations containing these incidental amounts of water are included within the scope of the invention.

**[0050]** A person skilled in the art preparing formulations according to the invention will understand that the proportion of components with respect to each other will vary depending on the specific components used. For example, the use of different surfactants and alcohols will require some straightforward modifications to the proportions depending on the miscibility of a particular surfactant in a particular alcohol. A skilled person will understand that the appropriate relative ratios of each of the excipients have been obtained when a homogeneous solution results from the admixture of all ingredients, and the docetaxel remains in solution.

**[0051]** The pharmaceutical formulation will typically comply with the *International Conference on Harmonisation (ICH) Guidelines*.

**[0052]** In a preferred embodiment, there is provided a liquid formulation for parenteral administration comprising:

**[0053]** docetaxel or a pharmaceutically acceptable salt thereof at a concentration in the range of from 5 to 20 mg/ml;

**[0054]** one or more polyethylene glycols in an amount in the range of from 30 to 65% v/v;

- [0055] one or more pharmaceutically acceptable acids in an amount sufficient to provide the formulation with a pH meter reading in the range of from 3 to 7;
- [0056] one or more alcohols in an amount in the range of from 10 to 55% v/v; and
- [0057] one or more surfactants in an amount in the range of from 10 to 50% v/v.
- [0058] In one preferred embodiment, the pharmaceutical liquid formulation for parenteral administration comprises:
- [0059] 1 docetaxel at a concentration in the range of from 6 to 20 mg/ml;
- [0060] polyethylene glycol 300 in an amount in the range of from 30% to 65% v/v;
- [0061] citric acid at a concentration in the range of from 1.6 to 6 mg/ml;
- [0062] polysorbate 80 in an amount in the range of from 10 to 55% v/v; and
- [0063] ethanol in an amount in the range of from 10 to 50% v/v.
- [0064] In a particularly preferred embodiment, the pharmaceutical liquid formulation for parenteral administration comprises:
- [0065] a concentration of about 10 mg/ml docetaxel;
- [0066] about 57% v/v of polyethylene glycol 300;
- [0067] a concentration of about 4 mg/ml of citric acid;
- [0068] about 25% v/v of polysorbate 80; and
- [0069] about 23% v/v of ethanol.
- [0070] In another preferred embodiment, the pharmaceutical liquid formulation for parenteral administration comprises:
- [0071] docetaxel at a concentration in the range of from 6 to 20 mg/ml;
- [0072] citric acid at a concentration in the range of from 1.6 to 6 mg/ml;
- [0073] polysorbate 80 in an amount in the range of from 10 to 55% v/v;
- [0074] ethanol in an amount in the range of from 10 to 50% v/v; and
- [0075] polyethylene glycol 300 in an amount sufficient to make up the formulation to QS 100%
- [0076] In another particularly preferred embodiment, the pharmaceutical liquid formulation for parenteral administration comprises:
- [0077] a concentration of about 10 mg/ml docetaxel;
- [0078] a concentration of about 4 mg/ml of citric acid;
- [0079] about 25% v/v of polysorbate 80;
- [0080] about 23% v/v of ethanol; and
- [0081] polyethylene glycol 300 in an amount sufficient to make up the formulation to QS 100%
- [0082] According to a third aspect of the invention, there is provided the use of a pharmaceutical formulation according to the first and second aspects in the preparation of a medicament for the treatment of a cancer.
- [0083] According to a fourth aspect of the invention, there is provided a method for treating a cancer which comprises administering a pharmaceutical formulation according to the first and second aspects to a patient in need thereof.
- [0084] According to a fifth aspect of the invention, there is provided an infusion solution produced by the admixture of a pharmaceutical formulation according to the first and second

aspects of the invention and an infusion diluent, typically 0.9% NaCl or 5% dextrose or glucose.

#### DRAWINGS

[0085] Various embodiments/aspects of the invention will now be described with reference to the following drawings in which:

[0086] Table 1 shows the impurity profile of the formulations in Example 1 at the initial time point.

[0087] Table 2 shows the impurity profile of the formulations in Example 1 at one month.

[0088] Table 3 shows the impurity profile of the formulations in Example 1 at two months.

[0089] Table 4 shows the impurity profile of Formulation 3 in Example 1 at 3, 4 and 5 months.

[0090] Table 5 shows the impurity profile of the formulations in Example 2 at the initial time point.

[0091] Table 6 shows the impurity profile of the formulations in Example 2 at one month.

[0092] Table 7 shows the impurity profile of the formulations in Example 3.

[0093] Table 8 shows the impurity profile of the formulations in Example 4.

[0094] Table 9 shows the impurity profile of the formulations in Example 5.

[0095] Table 10 shows the impurity profile of the formulations in Example 6.

[0096] Table 11 shows the impurity profile of the formulations in Example 7.

[0097] Table 12 shows the impurity profile of the formulations in Example 8.

[0098] Table 13 shows the results obtained for NaCl solution in Example 9.

[0099] Table 14 shows the results obtained for glucose solution in Example 9.

[0100] In these tables, the level of impurities is provided as % peak area. The following abbreviations are used in the tables.

ND = not detected	n/t = not tested
N/R = not recorded as peak areas <0.05%	n/a = not applicable

#### EXAMPLES

[0101] Various aspects of the invention will now be described with reference to the following non-limiting examples.

##### Components Used in Formulations

[0102] All components including the docetaxel were standard pharmaceutical grade quality.

[0103] Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycols are stable, hydrophilic substances that are essentially non-irritant to the skin. Although they do not readily penetrate the skin, polyethylene glycols are water soluble and as such are easily removed from the skin by washing; they are therefore useful as ointment bases. Solid grades are generally

employed in topical ointments with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

**[0104]** Propylene glycol is used as an antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; and water-miscible cosolvent. Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anaesthetics.

**[0105]** Citric acid, as either the monohydrate or anhydrous material, is widely used in pharmaceutical formulations and food products primarily to adjust the pH of solutions. Citric acid monohydrate is used in the preparation of effervescent granules while anhydrous citric acid is widely used in the preparation of effervescent tablets.

**[0106]** Tartaric acid is used in beverages, confectionery, food products, and pharmaceutical formulations as an acidulant. It may also be used as an acidifying agent, a sequestering agent, and as an antioxidant synergist. In pharmaceutical formulations, it is widely used in combination with bicarbonates, as the acid component of effervescent granules, powders, and tablets.

**[0107]** Polyethoxylene sorbitan fatty acid esters (polysorbates) are a series of partial fatty acid esters of sorbitol and its anhydrides co-polymerized with approximately 20, 5 or 4 moles of ethylene oxide for each mole of sorbitol and its anhydrides. The resulting product is a mixture of molecules of different sizes. Polysorbates are used as solubilising agents for a variety of substances including oil-soluble vitamins and as wetting agents in the formulation of oral and parenteral suspensions. Polysorbate 80 is approved by the FDA, EMEA and TGA for parenteral use.

**[0108]** Ethanol is commonly used as a solvent, anti-microbial preservative, disinfectant and penetration enhancer. Ethanol and aqueous ethanol solutions of various concentrations are widely used in pharmaceutical formulations and cosmetics. Although ethanol is primarily used as a solvent it is also employed in solutions as an antimicrobial preservative.

**[0109]** Benzyl benzoate is used as a plasticizer; solubilising agent; solvent; and therapeutic agent. Benzyl benzoate is used as a solubilising agent and nonaqueous solvent in intramuscular injections at concentrations between 0.01 to 46.0% v/v. It is also used as a solvent and plasticizer for cellulose and nitrocellulose. However, the most widespread pharmaceutical use of benzyl benzoate is as a topical therapeutic agent in the treatment of scabies.

#### Formulations

**[0110]** All formulations referred to in the following examples have been prepared using the following mixing process.

**[0111]** Add required amount of ethanol into a clean, dry beaker mixing vessel.

**[0112]** Add acid into the vessel containing absolute alcohol. Mix until all dissolved.

**[0113]** Add docetaxel active ingredient and mix until solution becomes clear.

**[0114]** Add polysorbate 80 (pre-flushed with nitrogen) into above solution, mixed until solution becomes homogeneous.

**[0115]** Make up the solution to final volume using PEG 300.

**[0116]** Mixed and flushed with nitrogen for at least 10 minutes.

**[0117]** Close and seal the solution and kept at room temperature until filtration and filling.

**[0118]** Filter the bulk solution through a suitable sterile filter.

**[0119]** Fill the solution into a clear type I glass vial, and capped with a rubber stopper that is suitable for parenteral and compatible with docetaxel solution.

**[0120]** Two stoppers and 1 type of clear Type 1 glass vials were tested, and were found satisfactory. A person skilled would know to avoid stoppers and vials that were subject to materials being extracted from the stopper and vials by the formulation components contained therein.

#### Methods

**[0121]** Each of the formulations prepared was subjected to accelerated stability testing at 40° C.

#### pH Measurement

**[0122]** The pH reading was taken using a standard laboratory pH meter and method. The pH meter used was a pH 330 pocket pH/mV meter with electrode model SenTix 81, both of which are manufactured by WTW. The pH meter was calibrated using standard aqueous buffers at pH 7.0 and 3.0. The pH meter electrode was inserted directly into the undiluted solution. After the initial fluctuation in the reading resolved, the pH meter reading was taken. A person skilled in the art would recognise that there is some fluctuation in the initial reading of a pH meter with both aqueous and non-aqueous solutions, but that the reading will resolve and stabilise in a period of time between 30 seconds and 5 minutes, typically one minute. Whilst the fluctuation may be greater in a non-aqueous system, stabilisation does still occur.

#### Impurity Analysis

**[0123]** The analysis of the impurities was undertaken using reverse phase High Performance Liquid Chromatography (HPLC). HPLC is a technique that is widely used and well known in the art. HPLC can be used to measure the potency of the docetaxel where potency is defined as a percentage of the initial concentration of docetaxel. HPLC can also be used to measure the relative proportions of known and unknown impurities in a docetaxel formulation. Any suitable HPLC method which will separate the impurities may be used.

**[0124]** Impurity levels were calculated by peak area normalisation.

#### Example 1

**[0125]** The following formulations were prepared.

Materials	F1	F2	F3	F4
Docetaxel	10 mg	10 mg	10 mg	10 mg
Poly-sorbate 80	520 mg	260 mg	260 mg	260 mg

-continued

Materials	F1	F2	F3	F4
Citric acid	n/a	2 mg	1.6 mg	n/a
Ethanol (absolute)	qs to 1.0 ml	qs to 1.0 ml	0.23 ml	0.25 ml
PEG 300	n/a	n/a	qs to 1 ml	qs to 1 ml

**[0126]** Formulation F1 replicates the formulation which was used in the docetaxel clinical trials by Aventis. Formulation F2 contains an acid but no PEG 300. Formulation F4 contains PEG 300 but no acid. Formulation F3 contains both acid and PEG 300.

#### Control Formulations

**[0127]** Taxotere® 20 (Aventis, B/No: 4 D404/4B057, Expiry: 10/2005) was tested as the control. The product as purchased commercially was tested, that is, the two vial sys-

not sufficient to reduce the level of impurities to a level that would be satisfactory for a commercial pharmaceutical formulation. These results show plainly that the combination of PEG 300, polysorbate 80, alcohol and acidification leads to a more stable docetaxel formulation.

**[0130]** From the results at the one month time point, it was decided to only continue with Formulation F3. The results at two months (Table 3) show that Formulation F3 has a lower level of total impurities than that of the Taxotere® 20 control.

**[0131]** The results for Formulation F3 at 3, 4 and 5 months is shown in Table 4.

**[0132]** In summary, the impurity results indicate that formulation F3 was observed to have at least comparative stability with the Taxotere® 20 presentation.

#### Example 2

**[0133]** In this example, further formulations according to the invention were tested.

**[0134]** The following formulations were prepared.

Formulation	Composition
F5	10 mg docetaxel, 260 mg polysorbate 80, 2.0 mg citric acid, 0.23 ml ethanol (absolute) and PEG 300 QS to 1 ml. Filled under nitrogen.
F6	10 mg docetaxel, 260 mg polysorbate 80, 2.0 mg citric acid, 0.20 ml ethanol (absolute) and PEG 300 QS to 1 ml.
F7	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 0.20 ml ethanol (absolute) and PEG 300 QS to 1 ml.
F8	10 mg docetaxel, 260 mg polysorbate 80, 6.0 mg citric acid, 0.20 ml ethanol (absolute) and PEG 300 QS to 1 ml.
F9	10 mg docetaxel, 260 mg polysorbate 80, 2.0 mg citric acid, 0.25 ml ethanol (absolute) and PEG 300 QS to 1 ml.
F10	10 mg docetaxel, 520 mg polysorbate 80, 2.0 mg citric acid, 0.10 ml ethanol (absolute) and PEG 300 QS to 1 ml.
F11	10 mg docetaxel, 260 mg polysorbate 80, 2.0 mg tartaric acid, 0.20 ml ethanol (absolute) and PEG 300 QS to 1 ml.
F12	20 mg docetaxel, 260 mg polysorbate 80, 2.0 mg citric acid, 0.20 ml ethanol (absolute) and PEG 300 QS to 1 ml.
F13	20 mg docetaxel, 520 mg polysorbate 80, 2.0 mg citric acid, 0.20 ml ethanol (absolute) and PEG 300 QS to 1 ml.
F14	10 mg docetaxel, 520 mg polysorbate 80, 2.0 mg citric acid, 0.10 ml ethanol (absolute) and PEG 300 QS to 1 ml.

tem was subjected to the accelerated stability trials. However, the two vials of the Taxotere were only combined at the time of testing the sample for pH measurement and colour. The potency and impurities described in this example were determined using the storage form of Taxotere®, namely the single vial containing the docetaxel prior to the combining of the two vials.

#### Results & Discussion

**[0128]** At the initial time point (Table 1), Formulation F3 did not produce any significant impurities when compared with the unformulated docetaxel active ingredient which had been stored at 2 to 8° C. Formulation F3 was observed to have less impurities than Taxotere® 20.

**[0129]** From the results at one month (Table 2), it is clear that formulation F3 was significantly more stable than formulation F2 and the key difference between these two formulations was the PEG 300. This indicates that PEG 300 has a stabilising effect on docetaxel. However, it is apparent from the results for formulation F4 that the use of PEG 300 alone is

**[0135]** The formulations were subjected to accelerated stability trials and the pH, potency and impurities were tested as per Example 1.

#### Results and Discussion

**[0136]** The initial impurity profile is shown in Table 5 with the results at one month in Table 6. There was not enough sample remaining at one month to take the pH measurement so the pH at 2 months is provided.

**[0137]** The results show that formulations according to the invention with varying amounts of the docetaxel, acid, ethanol and polysorbate or with different acids are stable.

#### Example 3

**[0138]** This example investigated the stability of formulations according to the invention which contain different glycols.

**[0139]** The following formulations were prepared and potency assay and related substances compared at time 0 and 1 month for 25 and 40° C.

Formulation	Composition
C1	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 0.23 ml ethanol and PEG-300 QS to 1 ml
F15	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 0.23 ml ethanol and propylene glycol QS to 1 ml
F16	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 0.23 ml ethanol and tetra glycol QS to 1 ml

#### Results and Discussion

**[0140]** The results are in Table 7. The impurity profile for all F16T=0 and 1 month samples look nearly identical and within experimental error. Interestingly, in contrast to C1, the amounts of some impurities in F16 do not increase under the accelerated stability conditions.

**[0141]** For F17, only very minor known and unknown impurities appear in the impurity profile as the stability experiment progressed.

**[0142]** These results clearly show that a range of different glycols can be used in the formulation according to the invention. It would therefore be understood by the person skilled in the art that other glycols are readily substitutable in the invention.

#### Example 4

**[0143]** This example investigated the stability of formulations according to the invention which contain different pharmaceutically acceptable acids.

**[0144]** The following formulations were prepared and potency assay and related substances compared at time 0 and 1 month for 25 and 40° C.

**[0145]** The pH adjustment for F18 was made by reference to the pH of acidified ethanol with citric acid. The pH reading of the citric acid acidified ethanol used in C1 was recorded following its addition to docetaxel. For F18, sufficient acetic acid was added to obtain that pH reading obtained for C1 after the addition of the 4.0 mg of citric acid and the 10 mg of docetaxel to the ethanol.

Formulation	Composition
C1	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 0.23 ml ethanol and PEG-300 QS to 1 ml
F17	10 mg docetaxel, 260 mg polysorbate 80, 0.23 ml ethanol pH adjusted using acetic acid followed by addition of PEG-300 QS to 1 ml

#### Results and Discussion

**[0146]** The results are in Table 8. Acetic acid in F18 causes minor increases in known and unknown impurities in this formulation when compared to the control, but is within the range of what would be considered pharmaceutically acceptable stability.

**[0147]** When combined with the results for the tartaric acid seen above in Example 2 (formulation F11, these results

clearly show that different organic acids can be used in the formulation according to the invention.

#### Example 5

**[0148]** This example investigated the stability of formulations according to the invention which contain different non-ionic surfactants in the nonaqueous solvent system. As noted previously, a person skilled in the art will recognise that the use of different components, including a different surfactant, may require adjustments to be made to the relative ratios of the components of the formulation.

**[0149]** The following formulations were prepared and potency assay and related substances compared at time 0 and 1 week for 25 and 40° C.

Formulation	Composition
C1	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 0.23 ml ethanol and PEG-300 QS to 1 ml
F18	10 mg docetaxel, 315 mg Cremophor®, 5.2 mg citric acid, 0.3 mL ethanol and PEG-300 QS to 1 mL

#### Results and Discussion

**[0150]** The results are in Table 9.

**[0151]** These results clearly show that different non-ionic surfactants in a suitable non-aqueous solvent system vehicle can be used in the formulation according to the invention.

#### Example 6

**[0152]** This example demonstrates that other pharmaceutically acceptable excipients may be included within the formulation according to the invention.

**[0153]** The following formulations were prepared and potency assay and related substances compared at time 0 and 1 month for 25 and 40° C.

Formulation	Composition
C1	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 0.23 ml ethanol and PEG-300 QS to 1 ml
F19	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 4.0 mg povidone 12F, 0.23 ml ethanol and PEG-300 QS to 1 ml

#### Results and Discussion

**[0154]** The results are in Table 10. F19 has a similar stability profile to that observed for the control C1.

**[0155]** These results clearly show that other stabilising agents (eg povidone) can be used in a suitable nonaqueous solvent system in the formulation according to the invention.

#### Example 7

**[0156]** This example demonstrates that other pharmaceutically acceptable solvents may be included within the formulation according to the invention.

**[0157]** The following formulations were prepared and potency assay and related substances compared at time 0 and 1 month for 25 and 40° C.

Formulation	Composition
C1	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 0.23 ml ethanol and PEG-300 QS to 1 ml
F20	10 mg docetaxel, 260 mg polysorbate 80, 4.0 mg citric acid, 0.10 ml ethanol, 0.13 benzyl benzoate and PEG-300 QS to 1 ml

#### Results and Discussion

[0158] The results are in Table 11. The impurity profile for F20 is consistent as time and temperature increases. The major impurity at RRT=0.9 (>0.5%) is believed to be associated with the excipient benzyl benzoate and not a degradation product of docetaxel.

[0159] These results clearly show that other solvents can be used in a suitable nonaqueous solvent system in the formulation according to the invention.

#### Example 8

[0160] The following formula according to the invention was prepared and its stability investigated.

Component	Amount
Docetaxel	10.67 mg
Polysorbate 80	260 mg
Citric Acid	4 mg
Absolute alcohol (ethanol)	0.23 ml
PEG 300	qs to 1 ml
Headspace	Nitrogen

#### Results

[0161] The results obtained after storage at 25° C. and 40° C. for 15 weeks are in Table 12.

#### Example 9

[0162] This example investigated the stability of formulations according to the invention when diluted in infusion bags as they would be prior to administration.

[0163] The formulation according to the invention used in this example is as follows:

Component	Formula
Docetaxel (anhydrous)	10 mg
Polysorbate 80	260 mg
Citric Acid	4 mg
Absolute alcohol	0.23 ml
PEG 300 qs to	1 ml
Headspace	Nitrogen

[0164] As a control, infusion bags containing the current commercial product Taxotere® were also prepared. The infusion bags were prepared according to the Taxotere® instructions for both the Taxotere® and the formulation according to the invention to produce a solution having a final concentration of docetaxel of 0.74 mg/ml. Infusion bags were prepared using both 0.9% NaCl solution and 5% glucose solution.

[0165] The infusion bags were analysed for clarity, particulates and chemical stability.

#### Results

[0166] Table 13 includes the results obtained for the 0.9% NaCl solution, where:

[0167] N-clear colourless solution free from visible matter

[0168] N\*-Slightly cloudy solution, no visible matter observed

[0169] N\*\*-Cloudy solution, visible matter observed

[0170] Table 14 includes the results obtained for the 5% glucose solution, where:

[0171] N-clear colourless solution free from visible matter

[0172] N\*-Slightly cloudy solution, no visible matter observed

[0173] N\*\*-Cloudy solution, visible matter observed

[0174] "OOS" in these tables indicates the measurement was "outside of specification", that is, no longer considered suitable for administration.

[0175] "Particulates complies" in these tables indicates that the formulation complies with the Particulates Test Acceptance Criteria (USP/BP/Ph.Eur requirement).

Fill Volume	Particle Sizes	Acceptance Criteria
Small Volume Injections (<100 mL)	= 10 um = 20 um	<6000 counts/container <600 counts/container

#### Discussion

[0176] For an infusion bag solution to be considered stable and suitable for use, it must remain a clear, colourless solution free from visible matter and particulates. If the solution becomes cloudy, it is no longer suitable for use, particularly where an in-line filter is used during administration.

[0177] From the results generated with 0.9% sodium chloride bags, Taxotere® was observed to be stable in the bag for up to four hours. The formulation according to the invention was observed to be stable for at least four hours.

[0178] From the results generated using the 5% glucose bags, the formulation according to the invention was clear and colourless up to 6 hours. The particulates test for the formulation according to the invention also complied with stability requirements for up to six hours. Unfortunately due to lack of sample, the formulation according to the invention could not be tested for particulates at six hours as approximately 25 ml of sample is required for each test point. At 7.5 hours, the formulation according to the invention's physical stability seemed to change dramatically wherein the appearance of solution was seen to be cloudy with visible matter observed and therefore all other associated testing was not carried out.

[0179] From the results generated using the 5% glucose bags, Taxotere® was found to go cloudy at four hours with particulate counts 25 µm higher at three hours (6398) compared to the formulation according to the invention at four hours (633). The pH did not change between testing initially

to five hours, however, no other testing was carried out at five hours due to the cloudiness of the Taxotere® solution indicating instability.

### CONCLUSION

**[0180]** From this study, it can be concluded that the formulation according to the invention is stable for at least four hours in the NaCl infusion bag and at least six hours in the glucose bag. Based on these results, therefore, it can be concluded that the formulation according to the invention is at least as physically stable as Taxotere® in the infusion bag, and appears to have improved stability (particularly in a glucose solution).

**[0181]** The word ‘comprising’ and forms of the word ‘comprising’ as used in this description and in the claims does not limit the invention claimed to exclude any variants or additions.

**[0182]** Modifications and improvements to the invention will be readily apparent to those skilled in the art. Such modifications and improvements are intended to be within the scope of this invention.

TABLE 1

(Example 1)						
Description	Docetaxel	Taxotere 20	F1	F2	F3	F4
Impurity A (RRT = 0.86)	ND	0.09	0.30	0.12	0.06	0.06
Impurity B (RRT = 0.89)	0.08	0.12	N/R	0.07	0.08	0.08
Impurity C (RRT = 1.27)	ND	0.08	0.20	0.08	N/R	N/R
Impurity D (RRT = 1.30)	ND	ND	ND	ND	ND	ND
Impurity E (RRT = 1.33)	0.07	0.25	0.11	0.17	0.07	0.08
Impurity F (RRT = 1.47)	0.10	N/R	0.19	0.09	0.09	0.25
Total Impurities	0.25	0.54	0.96	0.53	0.30	0.55
Potency (mg/ml)	n/t	9.4	9.9	10.9	9.9	10.2
pH	n/t	n/t	7.7	5.8	5.9	7.8

TABLE 2

(Example 1)						
Description	Docetaxel	Taxotere 20	F1	F2	F3	F4
Impurity A (RRT = 0.86)	ND	0.05	0.29	0.05	N/R	0.05
Impurity B (RRT = 0.89)	0.08	0.13	0.11	0.09	0.05	0.07
Impurity C (RRT = 1.27)	ND	0.06	0.23	0.05	N/R	N/R
Impurity D (RRT = 1.30)	ND	ND	ND	ND	ND	ND
Impurity E (RRT = 1.33)	0.07	0.29	0.23	1.39	0.15	0.16
Impurity F (RRT = 1.47)	0.10	0.07	8.58	0.21	0.13	10.84
Total Impurities	0.25	0.71	12.89	2.21	0.33	13.41
Potency (mg/ml)	n/t	10.0	8.3	10.4	9.6	8.6
pH	n/t	3.9	7.7	5.7	5.9	7.8

TABLE 3

(Example 1)		
Description	Taxotere 20	F3
Impurity A (RRT = 0.86)	0.06	0.06
Impurity C (RRT = 1.27)	0.31	0.08
Impurity E (RRT = 1.33)	0.32	0.20
Impurity F (RRT = 1.47)	0.05	0.19
Total Impurities	0.99	0.75
pH	n/t	5.6
Potency (mg/ml)	12.5	10.1

TABLE 4

(Example 1)			
RRT	F3		
	3 M	4 M	5 M
Impurity A (RRT = 0.86)	0.12	0.22	0.32
Impurity B (RRT = 0.89)	0.06	0.10	0.13
Impurity C (RRT = 1.27)	0.31	0.29	0.32
Impurity D (RRT = 1.30)	0.22	0.27	0.31
Impurity E (RRT = 1.33)	ND	0.07	0.09
Impurity F (RRT = 1.47)	0.05	0.12	0.14
Total (% area)	0.86	1.13	1.36
pH	5.65	5.78	

TABLE 5

(Example 2)												
Description	Docetaxel	Taxotere 20	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Impurity A (RRT = 0.87)	ND	0.06	NR	NR	NR	NR	NR	0.08	NR	NR	NR	NR
Impurity B (RRT = 0.89)	NR	0.09	ND									
Impurity C (RRT = 1.24)	ND	0.09	ND									
Impurity D (RRT = 1.30)	ND	0.06	NR	NR	NR	NR	NR	0.06	NR	ND	NR	NR
Impurity E (RRT = 1.34)	0.16	0.34	0.15	0.14	0.15	0.15	0.15	0.14	0.15	0.15	0.13	0.13

TABLE 5-continued

(Example 2)												
Description	Docetaxel	Taxotere 20	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Impurity F (RRT = 1.48)	0.09	NR	0.09	0.09	0.09	0.08	0.09	0.10	0.08	0.11	0.09	0.09
Total Impurities	0.25	0.71	0.29	0.23	0.24	0.23	0.24	0.38	0.23	0.31	0.22	0.27
Potency(mg/ml)	NT	9.65	9.34	10.61	10.47	11.11	10.32	8.49	10.53	20.82	20.47	20.33
pH	NT	NT	4.98	5.34	5.02	4.82	5.25	5.82	5.36	5.09	5.82	5.78

TABLE 6

(Example 2)												
Description	Docetaxel	Taxotere 20	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Impurity A (RRT = 0.87)	ND	0.09	0.09	0.09	NR	0.08	0.09	0.17	0.08	NR	0.09	0.10
Impurity B (RRT = 0.89)	NR	0.11	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Impurity C (RRT = 1.24)	ND	0.26	NR	NR	NR	NR	NR	0.13	0.05	NR	0.11	0.15
Impurity D (RRT = 1.30)	ND	0.09	0.06	NR	NR	0.05	0.05	0.10	NR	NR	0.05	0.05
Impurity E (RRT = 1.34)	0.16	0.32	0.15	0.15	0.15	0.18	0.17	0.13	0.17	0.15	0.14	0.14
Impurity F (RRT = 1.48)	0.09	0.07	0.12	0.12	0.10	0.10	0.12	0.19	0.13	0.12	0.21	0.22
Total Impurities	0.25	0.94	0.42	0.36	0.25	0.41	0.43	0.78	0.43	0.27	0.70	0.78
Potency (mg/ml)	NT	10.66	10.22	10.44	10.34	10.25	10.47	9.23	11.42	20.79	19.80	20.92
pH (40° C. at 2M)	NT	NT	5.6	5.6	5.2	5.0	5.4	5.9	5.5	5.6	6.0	6.1

TABLE 7

(Example 3)				
Name	RRT	% Area T = 0	% Area 25° C., T = 4 weeks	% Area 40° C., T = 4 weeks
C1				
Unknown	0.882	0.03	0.03	0.03
Docetaxel	1	99.83	99.80	99.58
Unknown	1.153			0.05
10 oxo-docetaxel	1.494	0.05	0.03	0.07
Epi-docetaxel	1.817	0.05	0.05	0.09
Unknown	1.968			0.05
Unknown	2.17			0.04
Total Unknown		0.13	0.11	0.33
Formulation 15				
Unknown	0.88	0.03	0.03	0.03
Docetaxel	1	99.79	99.78	99.81
10 oxo-docetaxel	1.50	0.04	0.05	0.04
Epi-docetaxel	1.82	0.06	0.06	0.05
Unknown	2.16		0.03	
Total Unknown		0.13	0.17	0.12
Formulation 16				
Unknown	0.22		0.06	0.16
Unknown	0.88	0.04	0.04	0.03
Docetaxel	1.00	99.78	99.67	99.48
10 oxo-docetaxel	1.50	0.05	0.08	0.18

TABLE 7-continued

(Example 3)				
Name	RRT	% Area T = 0	% Area 25° C., T = 4 weeks	% Area 40° C., T = 4 weeks
Epi-docetaxel	1.82	0.05	0.05	0.06
Unknown	1.97	0.03	0.04	0.04
Total Unknown	1.97	0.17	0.27	0.47

TABLE 8

(Example 4)				
Name	RRT	% Area T = 0	% Area 25° C., T = 4 weeks	% Area 40° C., T = 4 weeks
C1				
Unknown	0.882	0.03	0.03	0.03
Docetaxel	1	99.83	99.80	99.58
Unknown	1.153			0.05
10 oxo-docetaxel	1.494	0.05	0.03	0.07
Epi-docetaxel	1.817	0.05	0.05	0.09
Unknown	1.968			0.05
Unknown	2.17			0.04
Total Unknown		0.13	0.11	0.33

TABLE 8-continued

(Example 4)				
Name	RRT	% Area T = 0	% Area 25° C., T = 4 weeks	% Area 40° C., T = 4 weeks
Formulation 17				
Unknown	0.21	0.06	0.10	0.33
Unknown	0.25	0.04	0.05	0.10
Unknown	0.88	0.03	0.03	0.03
Docetaxel	1.00	99.73	99.63	98.75
Unknown	1.15			0.08
Unknown	1.31			0.25
Unknown	1.43			0.03
10 oxo-docetaxel	1.50	0.05	0.07	0.12
Epi-docetaxel	1.82	0.06	0.05	0.19
Unknown	1.965		0.03	0.06
Total Unknown		0.24	0.33	1.19

TABLE 9

(Example 5)				
Formulation 18				
Name	RRT	% Area T = 0	% Area 25° C., T = 1 week	% Area 40° C., T = 1 week
Docetaxel	0.92	0.05		
	1.00	99.65	99.62	99.58
	1.101		0.14	0.14
	1.15			0.03
	1.19	0.05	0.03	0.03
10 oxo-docetaxel	1.51	0.05	0.05	0.05
Epi-docetaxel	1.83	0.06	0.04	0.05
	1.99	0.14	0.11	0.12
Total Unknown		0.35	0.37	0.42

TABLE 10

(Example 6)				
Name	RRT	% Area T = 0	% Area 25° C., T = 4 weeks	% Area 40° C., T = 4 weeks
C1				
Unknown	0.882	0.03	0.03	0.03
Docetaxel	1	99.83	99.80	99.58
Unknown	1.153			0.05
10 oxo-docetaxel	1.494	0.05	0.03	0.07
Epi-docetaxel	1.817	0.05	0.05	0.09
Unknown	1.968			0.05
Unknown	2.17			0.04
Total Unknown		0.13	0.11	0.33
Formulation 19				
Unknown	0.88	0.03	0.03	0.03
Docetaxel	1.00	99.81	99.78	99.67
Unknown	1.155			0.06
10 oxo-docetaxel	1.49	0.03	0.06	0.08
Epi-docetaxel	1.82	0.05	0.05	0.05
Unknown	1.97	0.03	0.03	0.06
Total Unknown		0.14	0.17	0.28

TABLE 11

(Example 7)				
Name	RRT	% Area T = 0	% Area 25° C., T = 4 weeks	% Area 40° C., T = 4 weeks
C1				
Unknown	0.882	0.03	0.03	0.03
Docetaxel	1	99.83	99.80	99.58
Unknown	1.153			0.05
10 oxo-docetaxel	1.494	0.05	0.03	0.07
Epi-docetaxel	1.817	0.05	0.05	0.09
Unknown	1.968			0.05
Unknown	2.17			0.04
Total Unknown		0.13	0.11	0.33
Formulation 20				
Unknown	0.59			0.03
Unknown	0.61	0.06	0.06	0.07
Unknown	0.65	0.05	0.05	0.05
Unknown	0.69	0.04	0.06	0.03
Unknown	0.82	0.03	0.03	0.03
Unknown	0.90	0.62	0.59	0.52
Docetaxel	1.00	98.99	99.00	99.03
10 oxo-docetaxel	1.49	0.07	0.08	0.09
Unknown	1.726		0.04	0.04
Epi-docetaxel	1.82	0.04	0.05	0.05
Unknown	1.97	0.03	0.05	0.06
Total Unknown		0.94	0.92	0.97

TABLE 12

(Example 8)				
RRT	Docetaxel	Initial	40° C.	25° C.
0.212	ND	ND	NR	NR
0.225	NR	NR	0.06	NR
0.866	0.05	NR	ND	ND
1.162	ND	0.05	0.07	0.05
1.194	ND	ND	NR	ND
1.317	ND	ND	0.11	ND
1.426	ND	ND	0.22	ND
1.505	NR	0.11	0.21	0.13
1.821	0.08	0.07	0.13	0.09
1.943	NR	NR	0.05	0.06
Total impurity	0.13	0.28	0.85	0.33

TABLE 13

(Example 9)					
Sample name/ timepoint	Appearance	pH	Particulates (10 µm)	Particulates (25 µm)	Particulates comments
Invention/T0	N	4.04	150	3115	Particulates complies
Invention/T4	N	4.04	45	1643	Particulates complies
Invention/T6	N**	4.06	N/T	N/T	N/A
Invention/T8	N**	4.05	N/T	N/T	N/A
Taxotere/T0	N	3.20	53	4110	Particulates complies
Taxotere/T4	N*	3.30	551215	43613	OOS
Taxotere/T6	N**	3.19	N/T	N/T	N/A
Taxotere/T8	N**	3.19	N/T	N/T	N/A

TABLE 14

(Example 9)

Sample name/ timepoint	Appearance	pH	Particulates (10 µm)	Particulates (25 µm)	Particulates comments
Invention/T0	N	3.24	53	588	Particulates complies
Invention/T4	N	3.25	63	633	Particulates complies
Invention/T5	N	3.25	6415	7160	Particulates complies
Invention/T6	N	N/T	N/A	N/A	Not tested
Invention/ T7.5	N**	N/T	N/A	N/A	Not tested
Taxotere/T0	N	3.95	32	1578	Particulates complies
Taxotere/T3	N	3.96	73	6398	Particulates complies
Taxotere/T4	N*	N/T	N/T	N/T	N/A
Taxotere/T5	N*	3.95	N/T	N/T	N/A

1-42. (canceled)

43. A liquid pharmaceutical formulation for parenteral administration comprising:

- docetaxel or a pharmaceutically acceptable salt thereof;
- one or more glycols;
- an amount of one or more pharmaceutically acceptable acids sufficient to provide the formulation with a pH meter reading in the range of from 2.5 to 7;
- one or more alcohols; and
- one or more non-ionic surfactants.

44. The liquid pharmaceutical formulation according to claim 43, wherein the glycol is present in an amount in the range of from 30 to 65% v/v.

45. The liquid pharmaceutical formulation according to claim 44, wherein there is about 57% v/v of glycol.

46. The liquid pharmaceutical formulation according to claim 43, wherein the glycol is selected from the group consisting of polyethylene glycols, propylene glycol, tetra glycol and mixtures thereof.

47. The liquid pharmaceutical formulation according to claim 46, wherein the glycol is a polyethylene glycol.

48. The liquid pharmaceutical formulation according to claim 47, wherein the glycol is polyethylene glycol 300.

49. The liquid pharmaceutical formulation according to claim 43, wherein the pharmaceutically acceptable acid is an organic acid.

50. The liquid pharmaceutical formulation according to claim 49, wherein the pharmaceutically acceptable acid is selected from the group consisting of citric acid, tartaric acid, acetic acid and mixtures thereof.

51. The liquid pharmaceutical formulation according to claim 60, wherein the pharmaceutically acceptable acid is citric acid.

52. The liquid pharmaceutical formulation according to claim 51, wherein the citric acid is present at a concentration in the range of from 1.6 to 6 mg/ml.

53. The liquid pharmaceutical formulation according to claim 43, wherein the concentration of docetaxel is an amount up to 90 mg/ml.

54. The liquid pharmaceutical formulation according to claim 53, wherein the concentration of docetaxel is in the range of from 5 to 20 mg/ml.

55. The liquid pharmaceutical formulation according to claim 54, wherein the concentration of docetaxel is about 10 mg/ml.

56. The liquid pharmaceutical formulation according to claim 43, wherein the alcohol is ethanol.

57. The liquid pharmaceutical formulation according to claim 43, wherein the one or more non-ionic surfactants are selected from the group consisting of polyethoxylene sorbitan fatty acid esters, polyoxyethylene glycol esters, polyethoxylated castor oils and mixtures thereof.

58. The liquid pharmaceutical formulation according to claim 43, wherein the alcohol is ethanol and the non-ionic surfactant is one or more polysorbate 80.

59. A pharmaceutical liquid formulation for parenteral administration comprising:

- docetaxel at a concentration of about 10 mg/ml;
- polyethylene glycol 300 in an amount in the range of from 30% to 65% v/v;
- citric acid at a concentration in the range of from 1.6 to 6 mg/ml;
- polysorbate 80 in an amount in the range of from 10 to 57%; and
- ethanol in an amount in the range of from 10 to 50% v/v.

60. The pharmaceutical liquid formulation for parenteral administration according to claim 59 comprising:

- docetaxel at a concentration of about 10 mg/ml;
- about 57% v/v of polyethylene glycol 300;
- citric acid at a concentration of about 4 mg/ml;
- about 25% v/v of polysorbate 80; and
- about 23% v/v of ethanol.

61. A pharmaceutical liquid formulation for parenteral administration comprising:

- docetaxel or a pharmaceutically acceptable salt thereof at a concentration in the range of from 5 to 20 mg/ml;
- one or more pharmaceutically acceptable acids present in an amount sufficient to provide the formulation with a pH meter reading in the range of from 2.5 to 7;
- one or more alcohols in an amount in the range of from 10 to 55% v/v;
- one or more non-ionic surfactants in an amount in the range of from 10 to 50% v/v; and
- one or more polyethylene glycols in an amount sufficient to make up the formulation to QS 100%.

62. The pharmaceutical liquid formulation for parenteral administration according to claim 61 comprising:

- docetaxel at a concentration of about 10 mg/ml;
- citric acid at a concentration in the range of from 1.6 to 6 mg/ml;
- polysorbate 80 in an amount in the range of from 10 to 55%;
- ethanol in an amount in the range of from 10 to 50% v/v;
- polyethylene glycol 300 in an amount sufficient to make up the formulation to QS 100%.

\* \* \* \* \*

 **Conference Reports for NATAP**

D4

15th CROI  
Conference on Retroviruses and  
Opportunistic Infections Boston, MA  
Feb 3-6, 2008

[Back](#) ▶

**Long-acting TMC278, a parenteral depot formulation delivering sustained NNRTI plasma concentrations in preclinical and clinical settings**

Reported by Jules Levin  
15th CROI, Feb 3-6, 2008, Boston

G van't Klooster,<sup>1</sup> R Verloes,<sup>1</sup> L Baert,<sup>1</sup> F van Velsen,<sup>1</sup> M-P Bouche,<sup>2</sup> K Spittaels,<sup>1</sup> J Leempoels,<sup>3</sup> P Williams,<sup>1</sup> G Kraus,<sup>1</sup> P Wigerinck<sup>1</sup> 1Tibotec BVBA, Mechelen, Belgium;  
2Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium;  
3Johnson & Johnson Pharmaceutical Research and Development, Merksem, Belgium

**Long-acting ARV formulations -  
A new paradigm?**

Uses of such formulations could include  
-- once monthly injectable HAART  
-- maintenance of undetectable viral load  
-- prophylaxis

Infrequent parenteral dosing offers potential advantages over daily (oral) treatment:  
-- sustained concentrations of drugs in plasma  
-- may improve adherence to therapy/prophylaxis  
-- may avoid gastro-intestinal adverse events

**CONCLUSIONS & NEXT STEPS**

Injectable long-acting formulations may provide a new paradigm in ARV use

TMC278 LA was demonstrated to be a promising depot formulation  
--single doses gave prolonged TMC278 exposure  
--in humans, PK profiles and exposures were similar after IM and SC administration  
--injections were well tolerated, particularly when administered IM

A novel formulation will contain 300mg/mL TMC278  
--evaluation in a single and repeated dose study in healthy volunteers

**TMC278: a potent and selective NNRTI**

Potent NNRTI in vitro against wild-type and NNRTI-resistant HIV-1, with an increased genetic barrier to development of resistance<sup>1</sup>

Potent and sustained efficacy at all doses (25, 75 and 150mg qd) in ARV-naive patients in Phase IIb<sup>2</sup>

Safe and generally well tolerated<sup>2</sup>

Potential for antiretroviral therapy in one daily pill or fixed-dose combinations with other agents

### Oral TMC278 48-week results in ARV-naïve patients (Phase IIb)

Parameter	TMC278 qd 25mg (N=93)	TMC278 qd 75mg (N=95)	TMC278 qd 150mg (N=91)	EFV (N=89)
Viral load <50 cps/mL, %	81	80	77	81
Mean change from baseline in log <sub>10</sub> viral load	-2.63	-2.65	-2.63	-2.64
Mean trough plasma concentration, ng/mL	93	193	341	ND

● Oral TMC278 program ongoing; Phase III studies starting soon

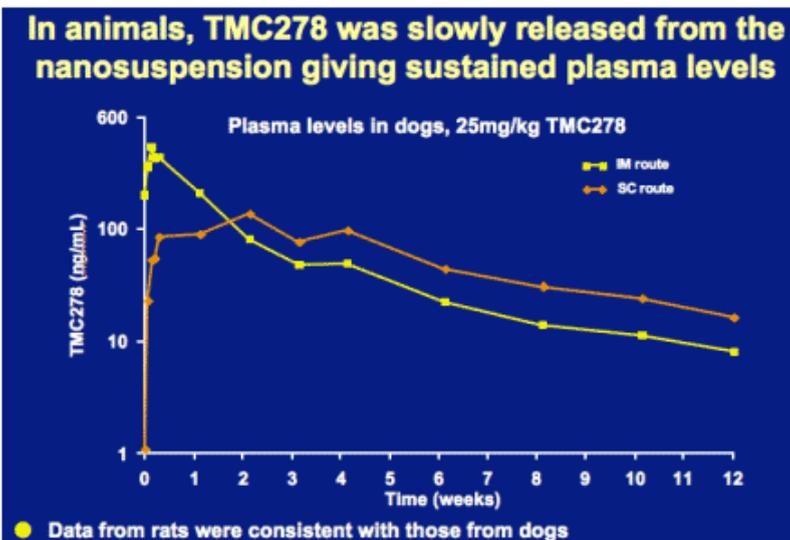
**Formulation and preclinical methods**

**Innovative nanosuspension\***

- 100mg TMC278 base per mL
- particles of pure TMC278, average size of 200nm
- sterile, stable formulation with neutral pH

TMC278 LA single doses, given as intramuscular (IM) and subcutaneous (SC) injections to Sprague-Dawley rats and Beagle dogs

PK and injection-site tolerability were evaluated



### Tissue concentrations in dogs

High concentrations of TMC278 were observed at the injection site up to 12 weeks in dogs

During the first month, high concentrations were observed in lymph nodes draining the injection site

-- these nodes may act as secondary depots, releasing TMC278 directly into the lymph system

By 24 weeks, the release from the depot was complete, as demonstrated by an absolute bioavailability of essentially 100%

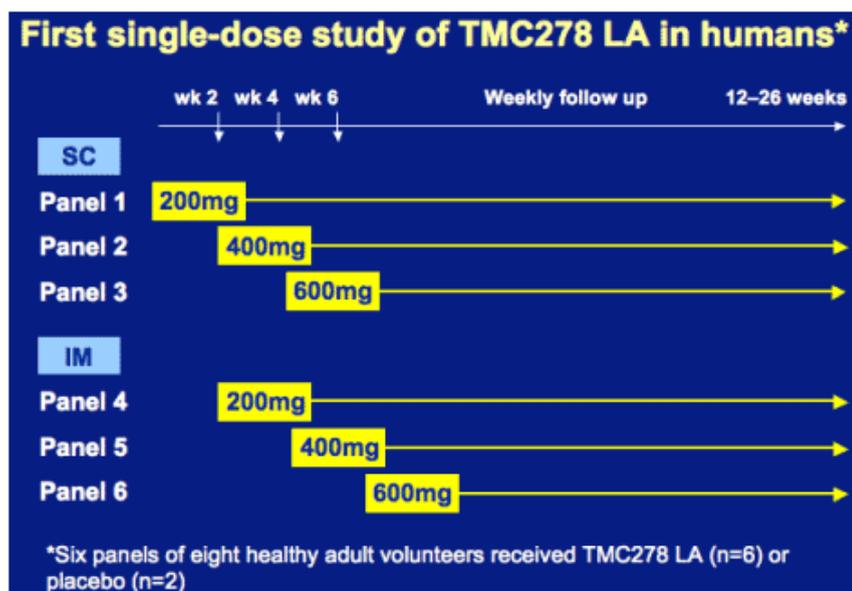
### TMC278 LA intramuscular route was better tolerated than the subcutaneous route in dogs

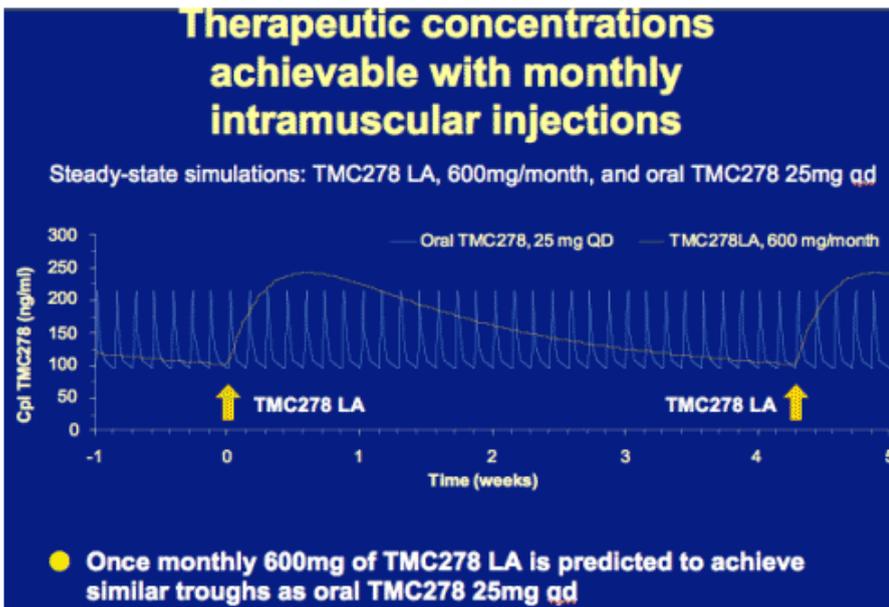
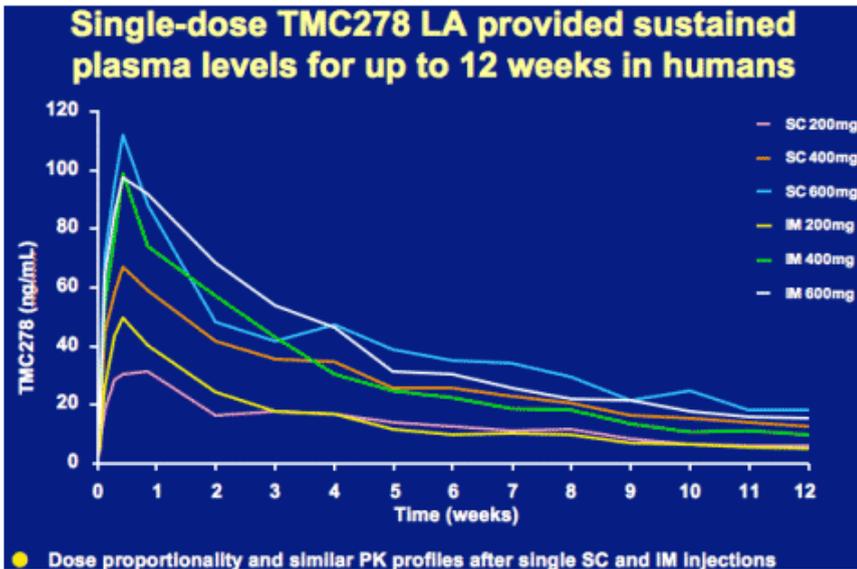
TMC278 LA 200 or 400mg per animal or placebo:

4- and 13-week follow-up

Injection-site reactions (ISRs) were mild to moderate and more frequent with SC than IM administration

Several lymph nodes increased in weight at 4 weeks post dose, consistent with a mild inflammatory response and disproportionate lymph node distribution of nanoparticles





**TMC278 LA intramuscular route was better tolerated than the subcutaneous route**  
**No serious adverse events (AEs) or rash**

ISRs, but no other AEs, were more common after TMC278 than after placebo injections - no dose response for ISRs

Animal model was predictive for humans regarding ISRs

	IM		SC	
	Active (n=18)	Placebo (n=6)	Active (n=18)	Placebo (n=6)
<b>Total number of ISRs</b>				
<b>Induration</b>	1	0	22	1
<b>Pain</b>	13	7	20	4
<b>Redness</b>	0	0	10	4
<b>Bruise</b>	0	0	6	5



(19) **United States**

(12) **Patent Application Publication**  
**Ojard**

(10) **Pub. No.: US 2005/0013386 A1**

(43) **Pub. Date: Jan. 20, 2005**

(54) **MULTI-BAND SINGLE-CARRIER MODULATION**

(52) **U.S. Cl. .... 375/316**

(76) **Inventor: Eric J. Ojard, San Francisco, CA (US)**

(57) **ABSTRACT**

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Multi-band single-carrier modulation. A novel approach is presented by which interference compensation may be performed for signals received by a piconet operable device. The piconet operable device may be implemented within a region that includes two or more SOPs (Simultaneously Operating Piconets). Estimation of the level and location of interference is performed and the input to a decoder (within the piconet operable device) is selectively weighted to ensure that the effect of any existent interference within the signal received by the piconet operable device is minimized. Different interference levels are dealt with differently. For one example, portions of the received signal having undergone a large amount of interference may be simply treated as erasures with respect to the input the decoder. For another example, portions of the received signal having undergone some smaller degree of interference, but some interference nonetheless, may be de-weighted before being provided to the decoder.

(21) **Appl. No.: 10/873,911**

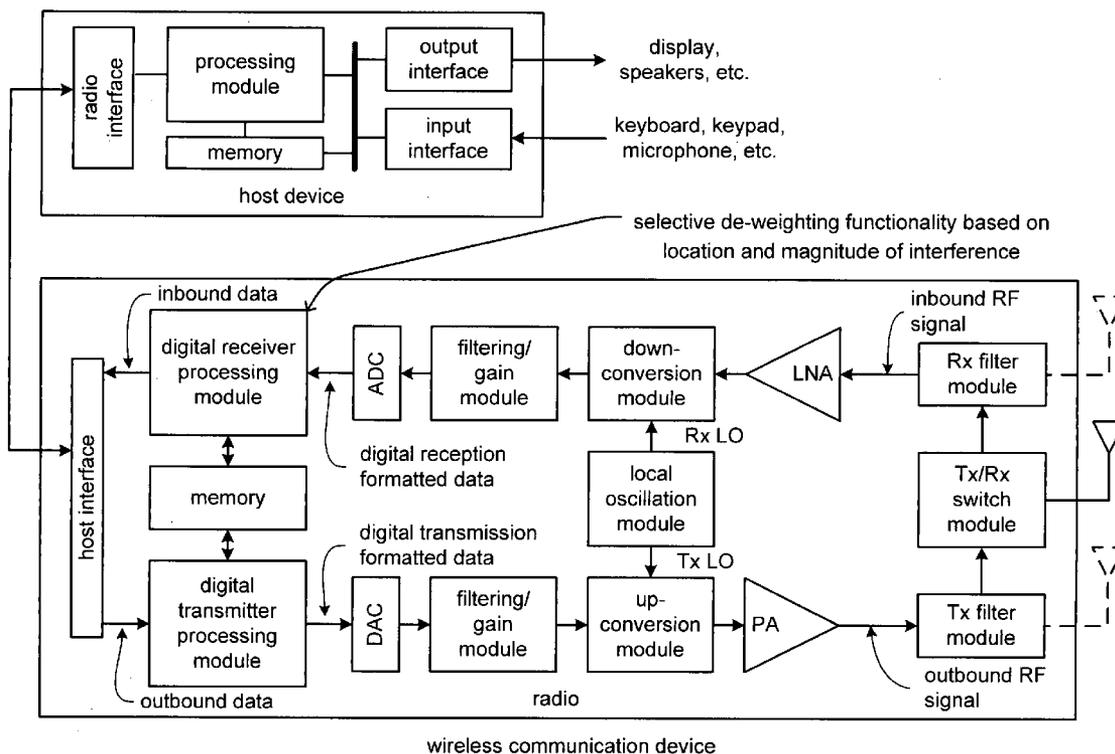
(22) **Filed: Jun. 22, 2004**

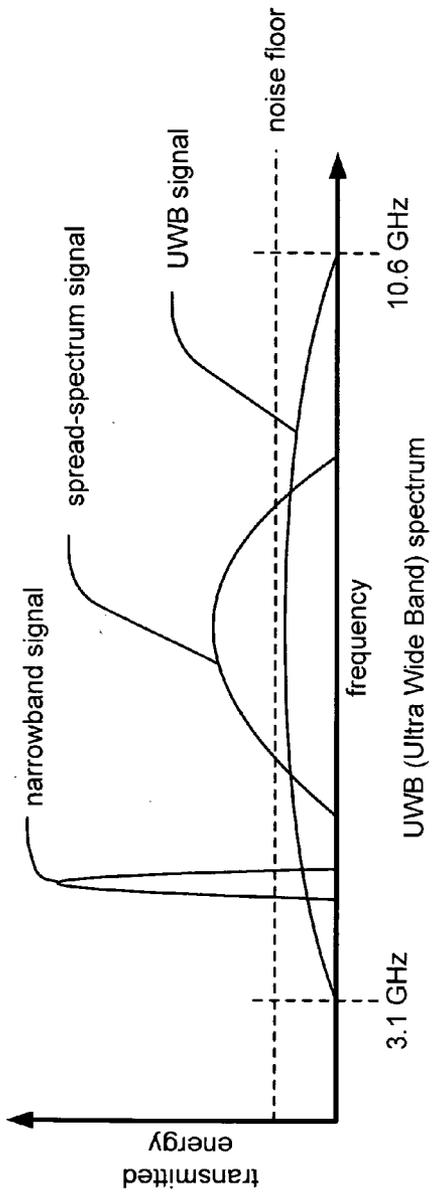
**Related U.S. Application Data**

(60) **Provisional application No. 60/488,623, filed on Jul. 18, 2003. Provisional application No. 60/494,498, filed on Aug. 12, 2003.**

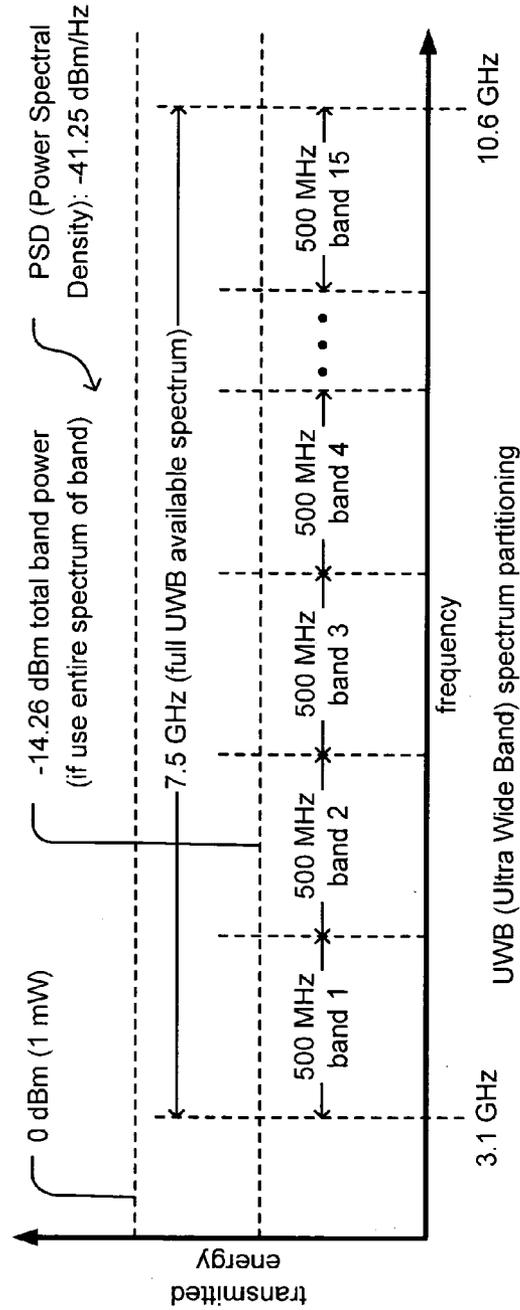
**Publication Classification**

(51) **Int. Cl.<sup>7</sup> ..... H04K 1/00**

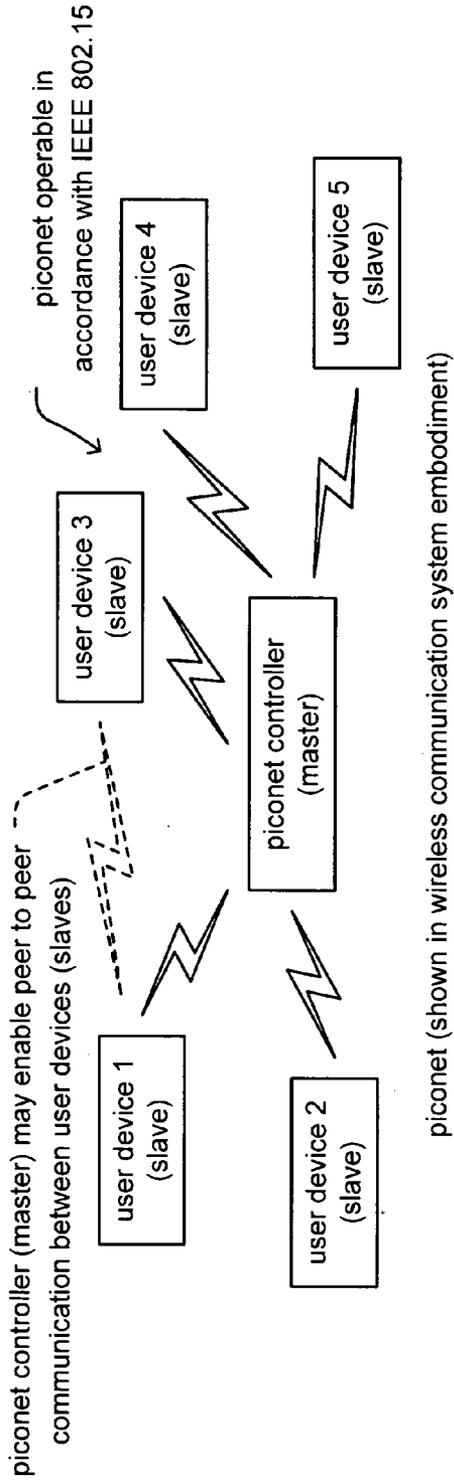




**Fig. 1A**

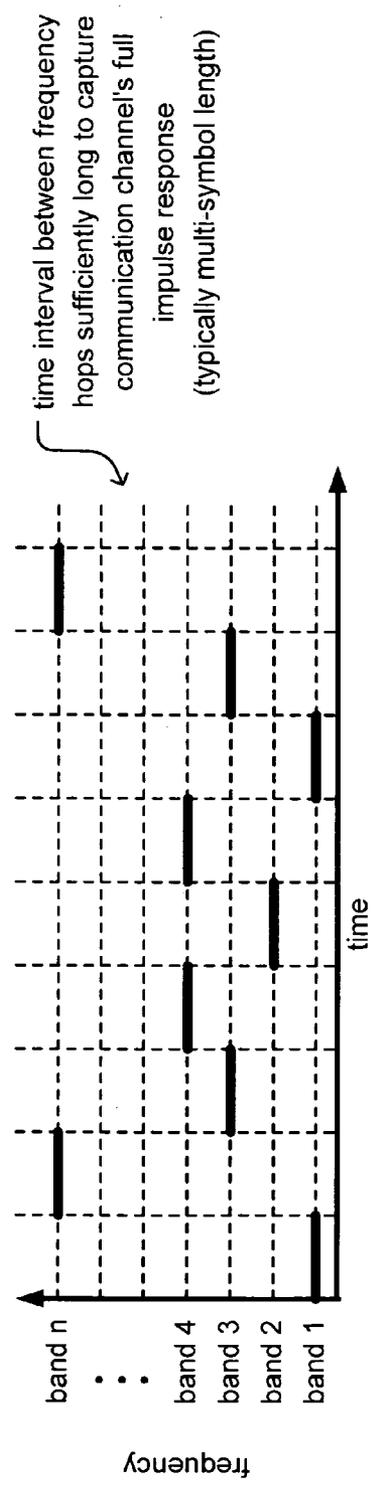


**Fig. 1B**



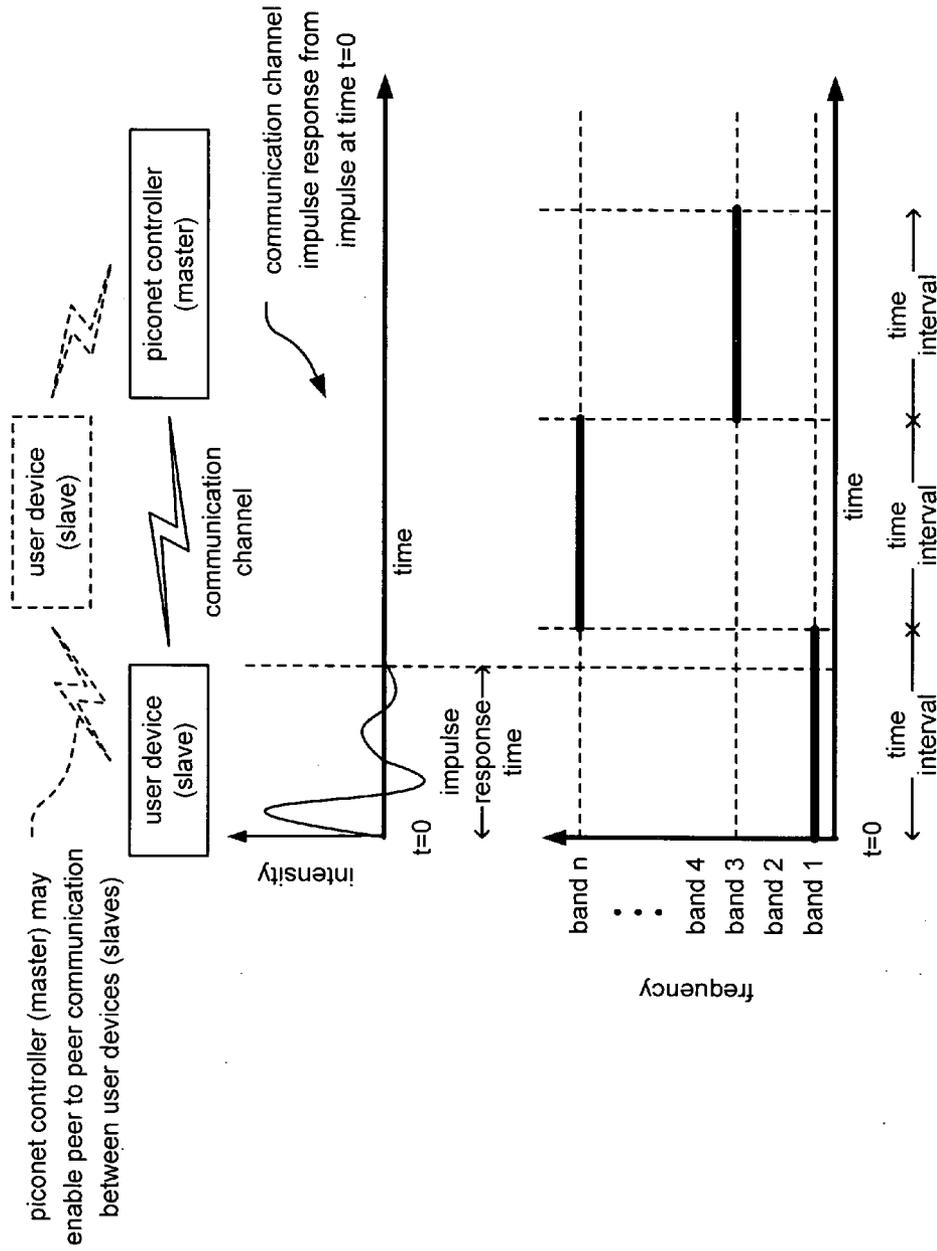
**Fig. 2A**

piconet (shown in wireless communication system embodiment)



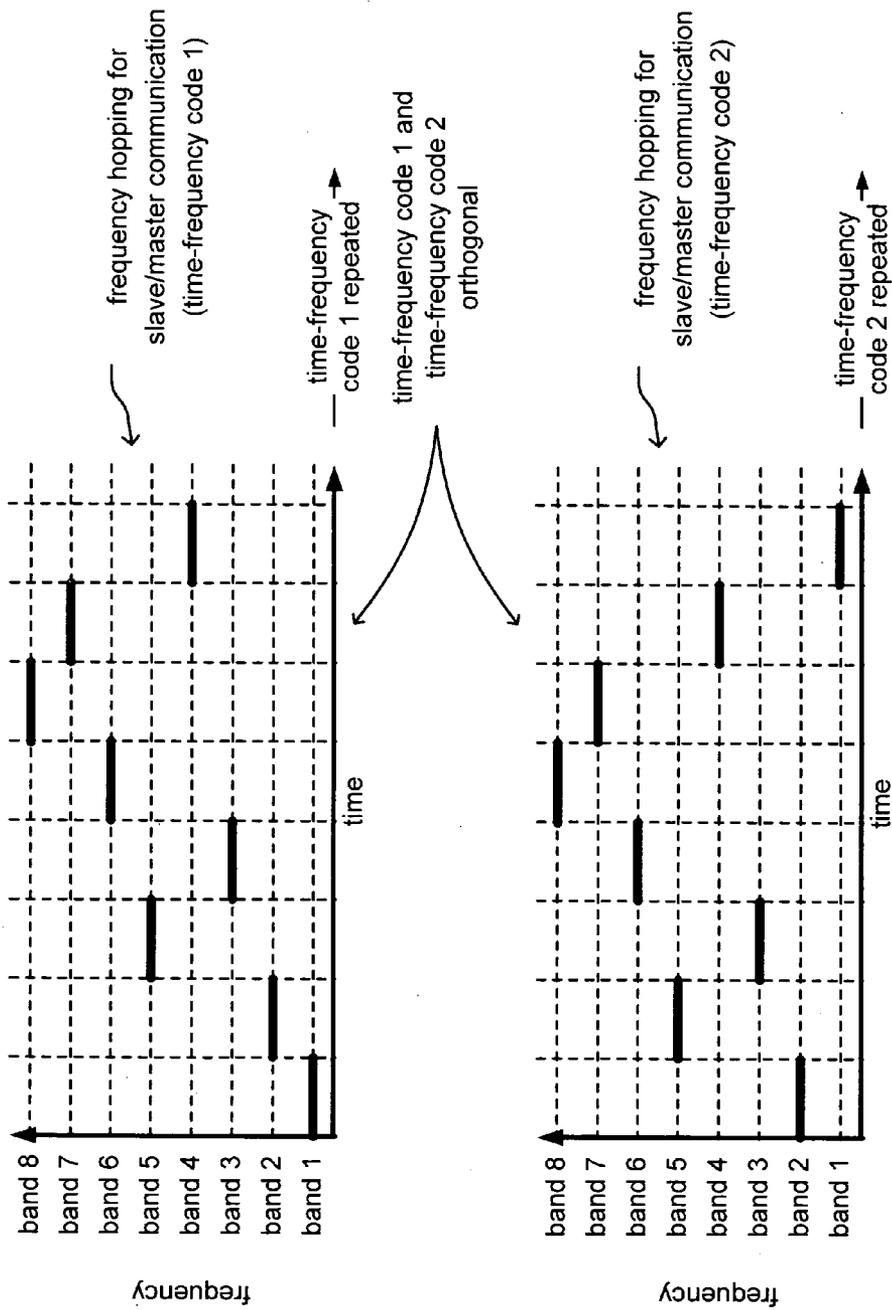
frequency hopping

**Fig. 2B**

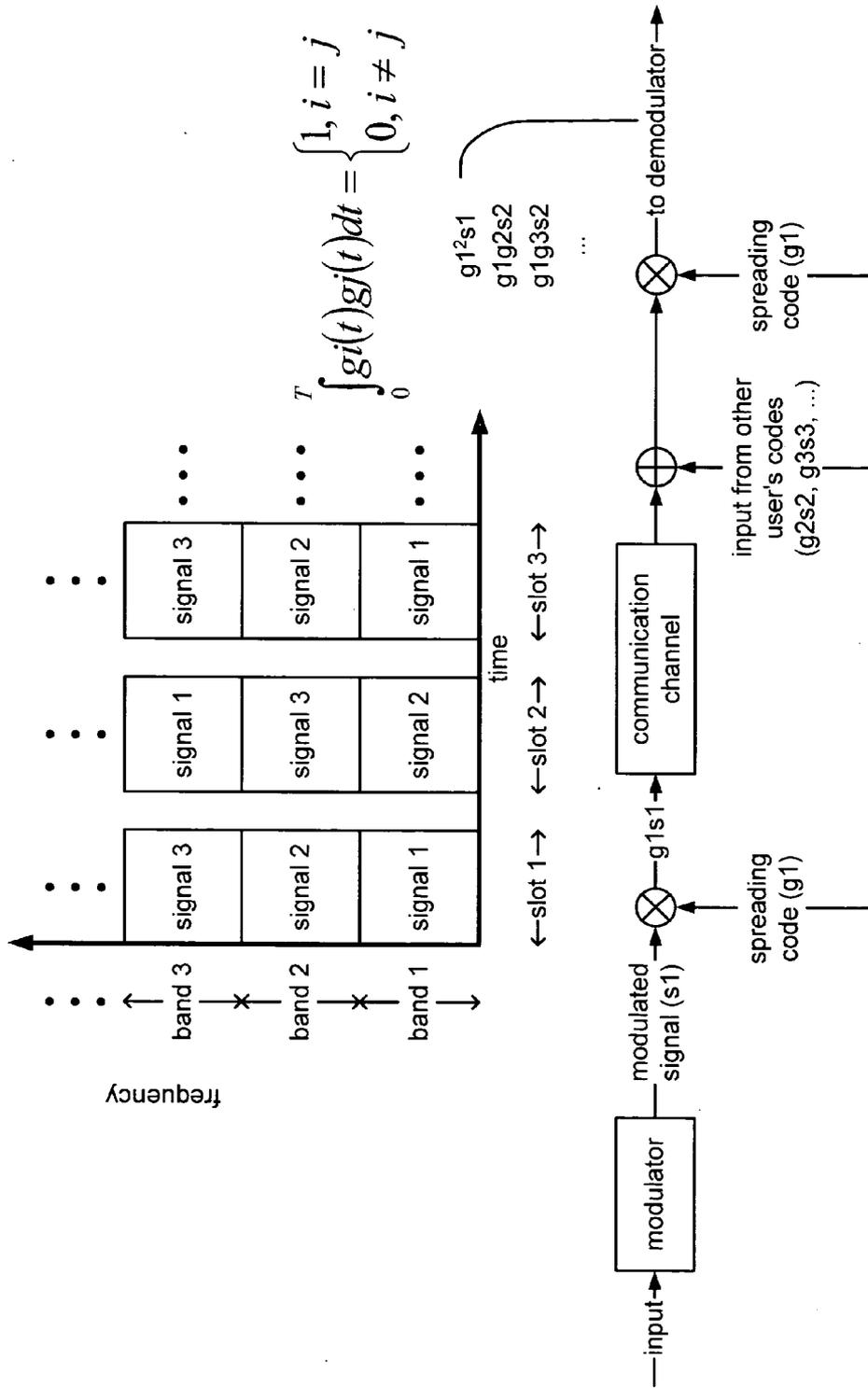


frequency hopping time interval duration compared to communication channel impulse response

Fig. 3

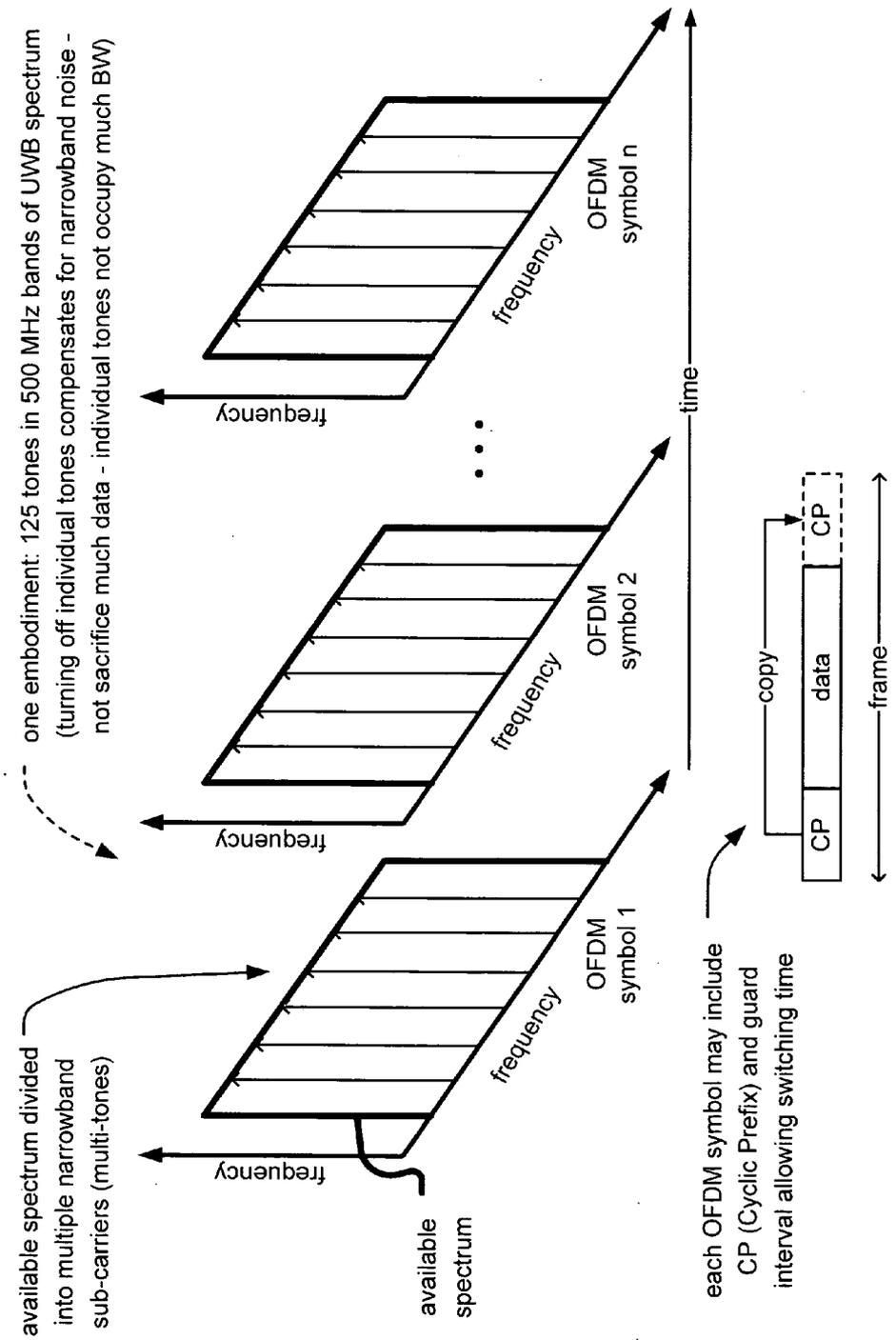


frequency hopping  
**Fig. 4**

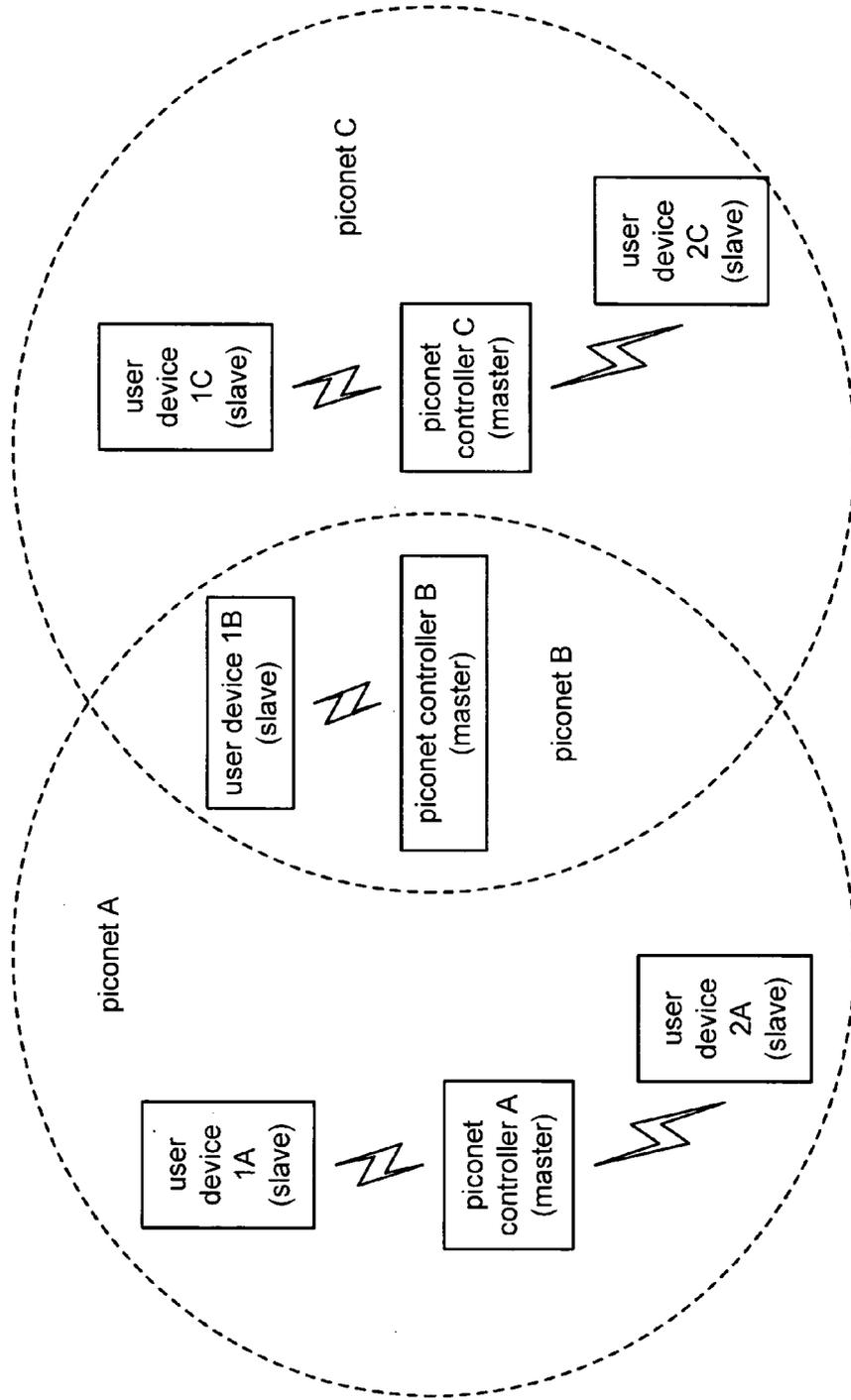


CDMA (Code Division Multiple Access)

**Fig. 5**

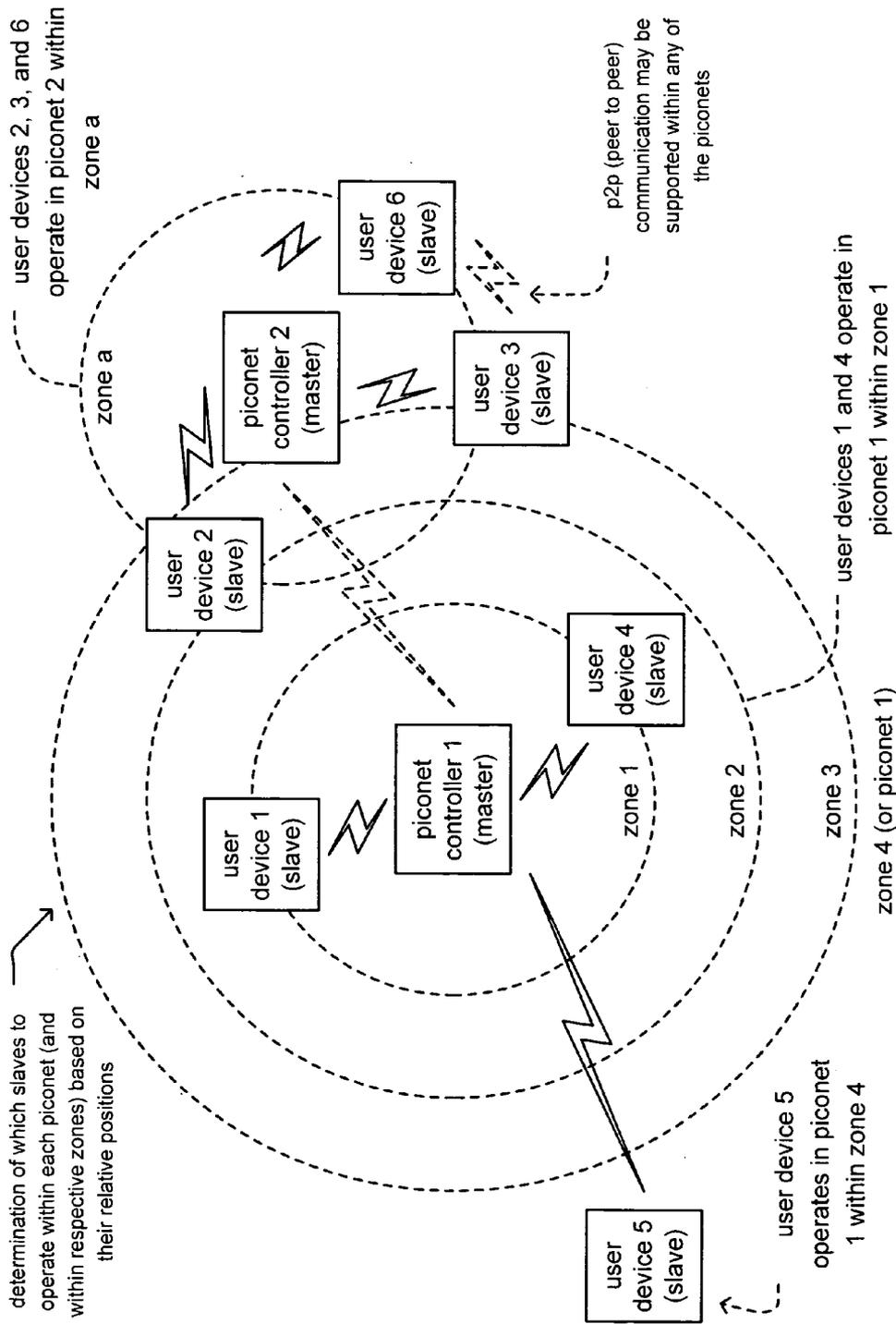


OFDM (Orthogonal Frequency Division Multiplexing) modulation  
**Fig. 6**



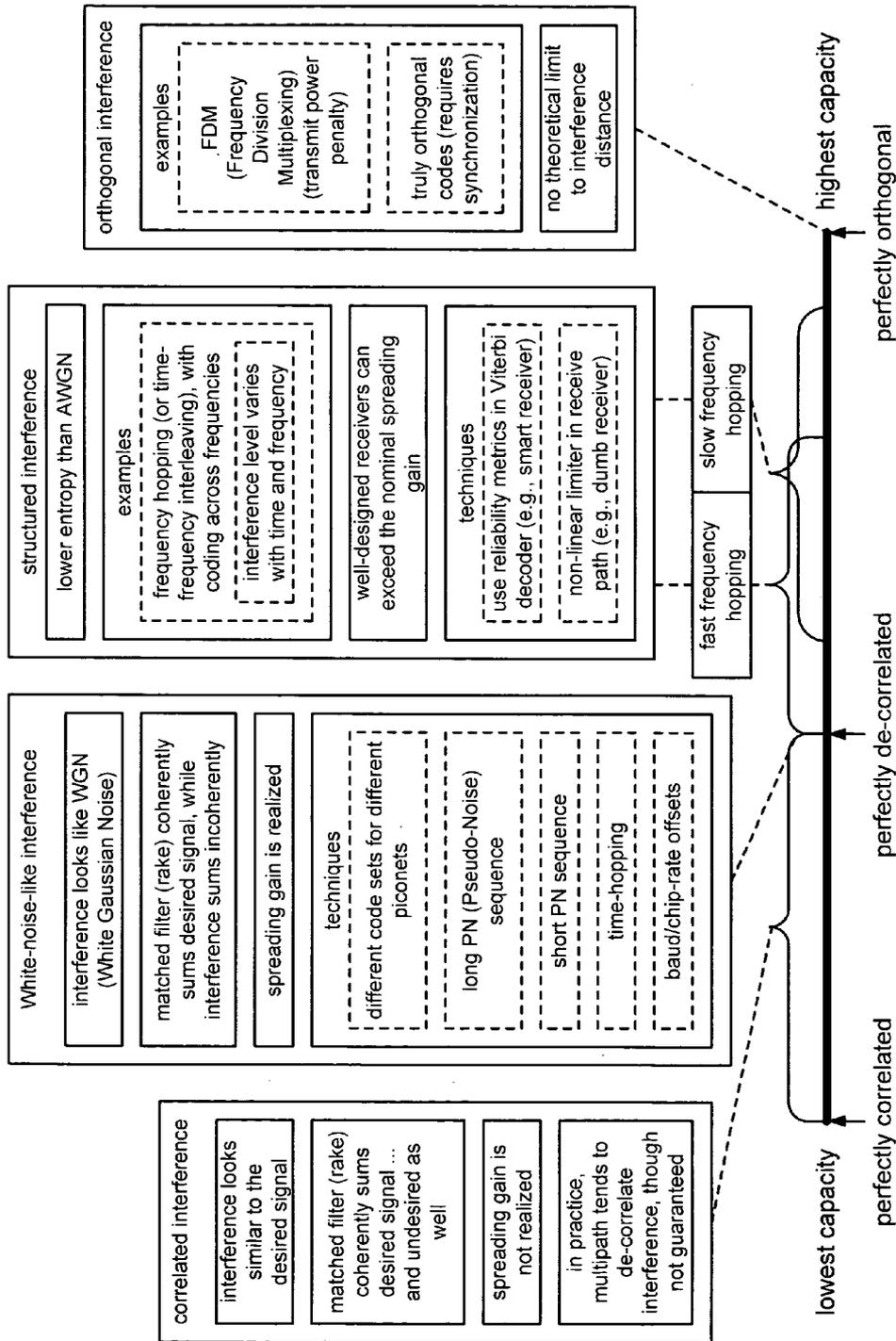
SOPs (Simultaneously Operating Piconets) within relatively close proximity (having some overlap)

**Fig. 7**



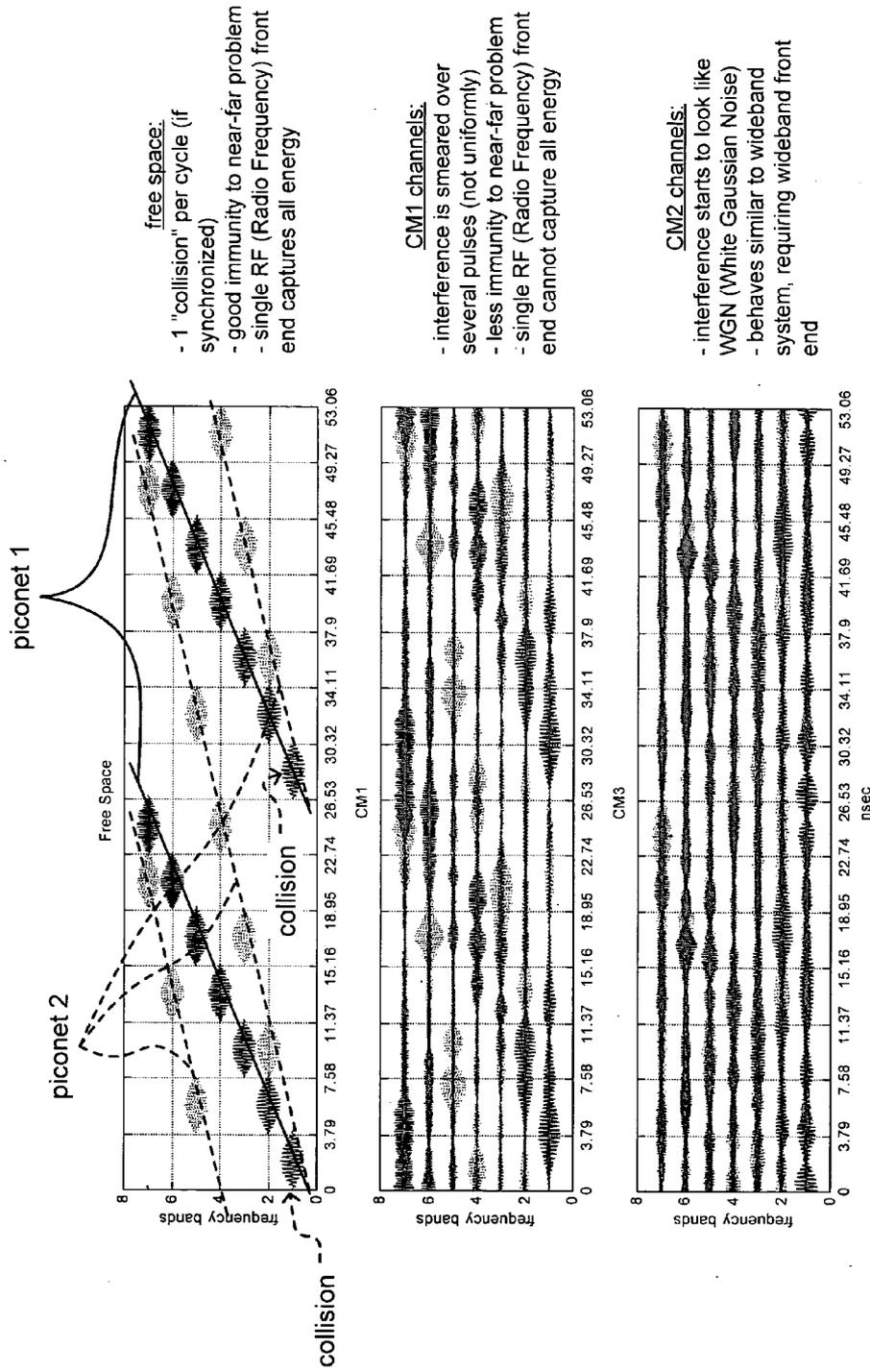
SOPs (Simultaneously Operating Piconets) within relatively close proximity (again, having some overlap)

**Fig. 8**



SOPs (Simultaneously Operating Piconets) interference characteristics

Fig. 9



free space:

- 1 "collision" per cycle (if synchronized)
- good immunity to near-far problem
- single RF (Radio Frequency) front end captures all energy

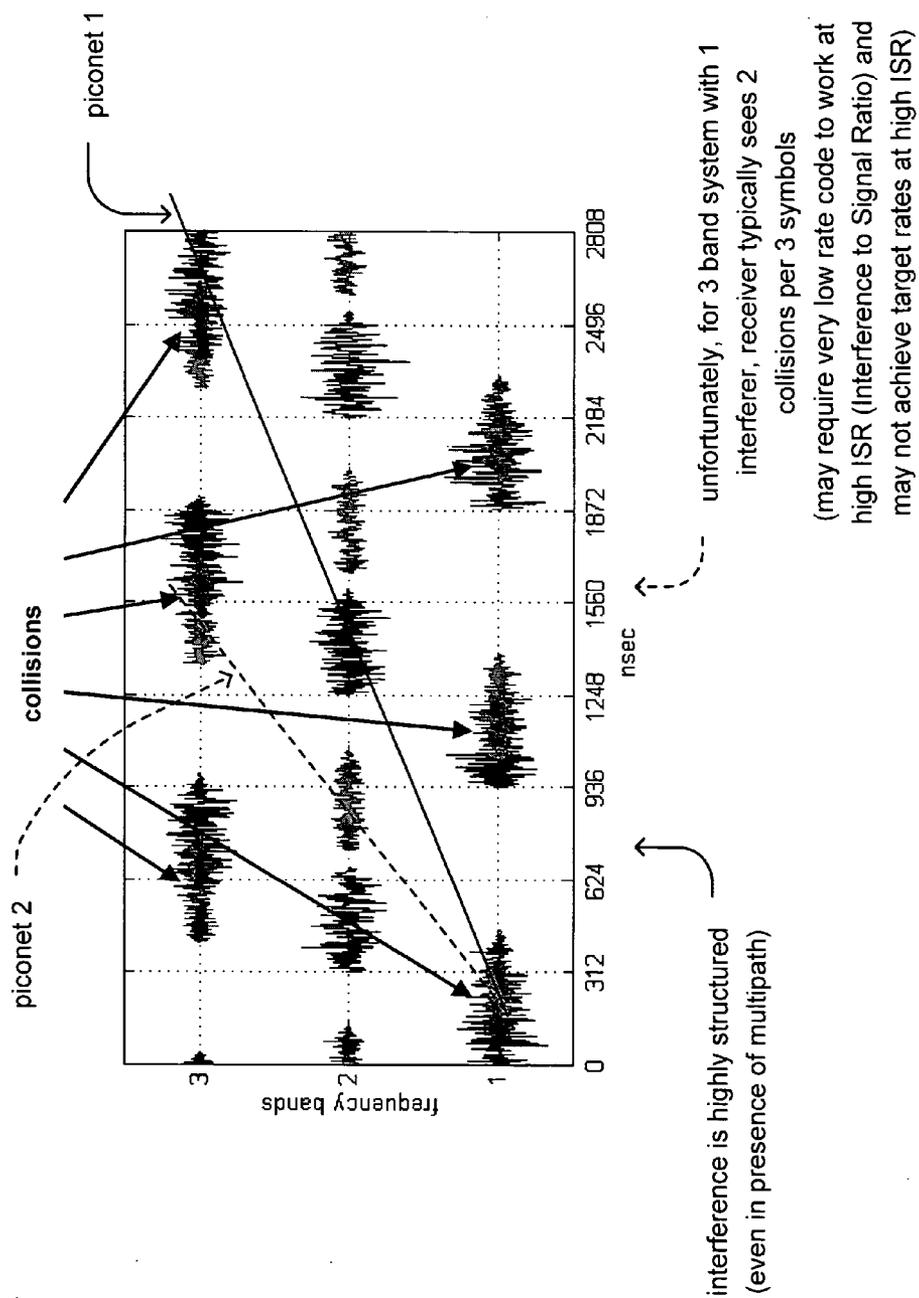
CM1 channels:

- interference is smeared over several pulses (not uniformly)
- less immunity to near-far problem
- single RF (Radio Frequency) front end cannot capture all energy

CM2 channels:

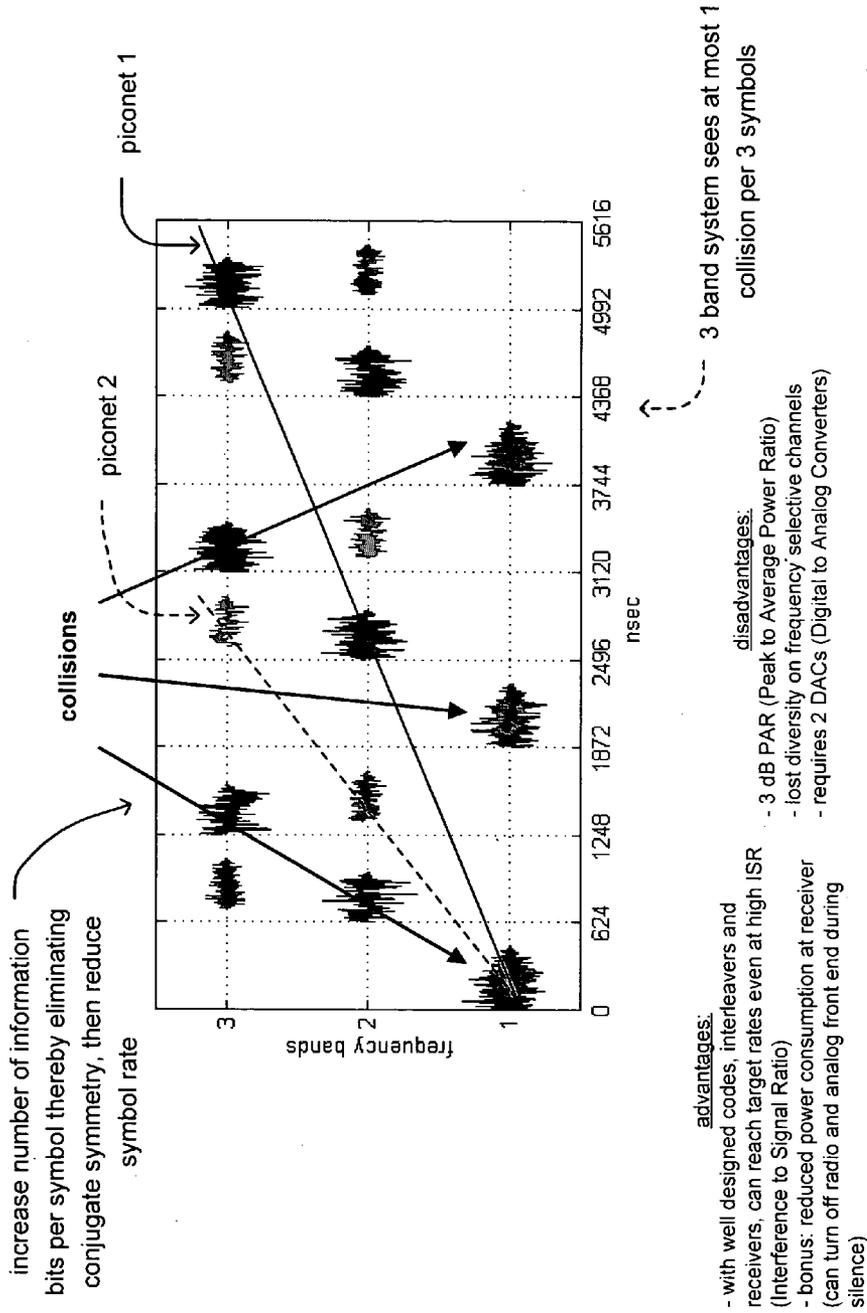
- interference starts to look like WGN (White Gaussian Noise)
- behaves similar to wideband system, requiring wideband front end

fast frequency hopping with multipath and interference  
**Fig. 10**



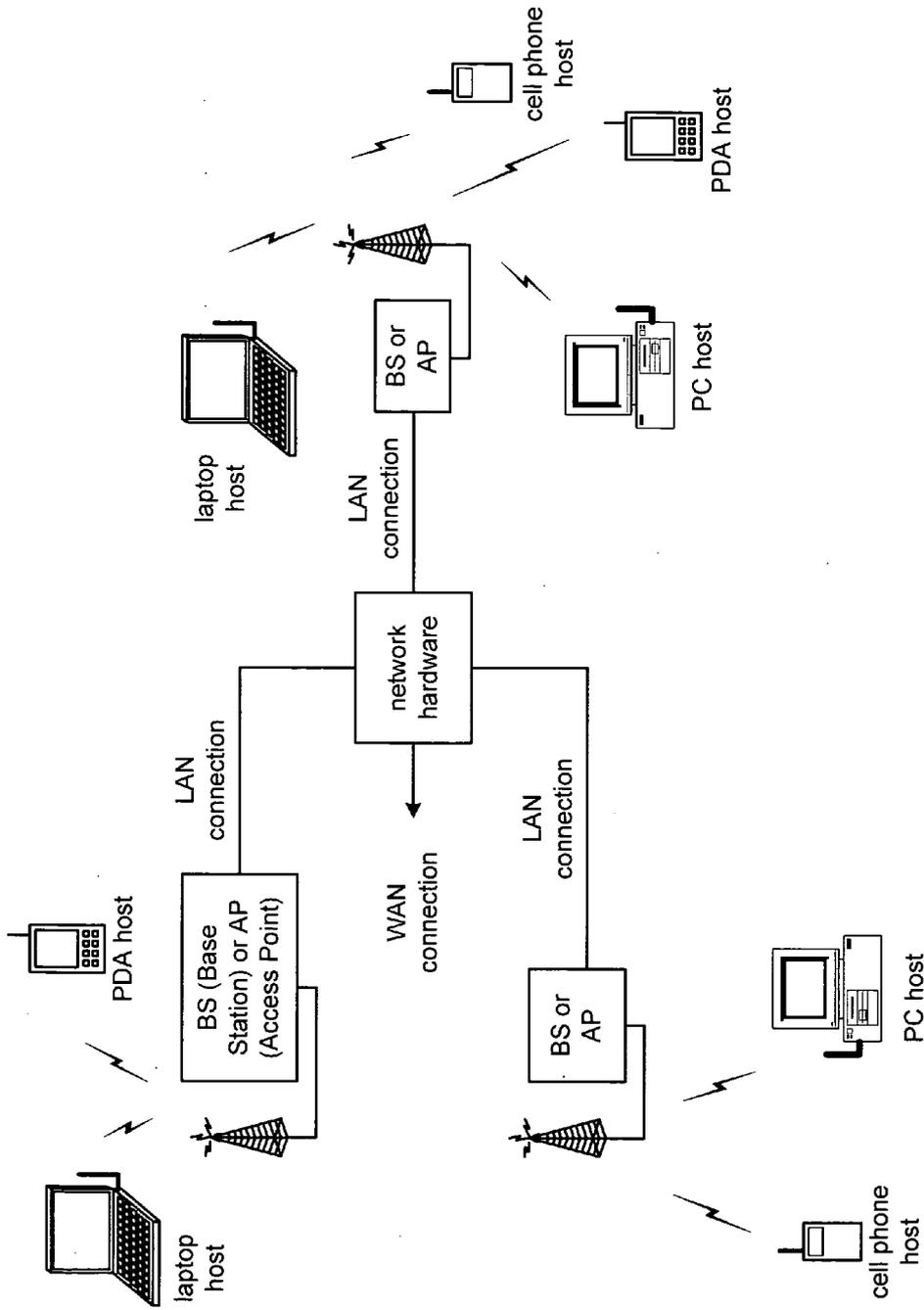
SH-OFDM (Slow Hopping-Orthogonal Frequency Division Multiplexing)

**Fig. 11**

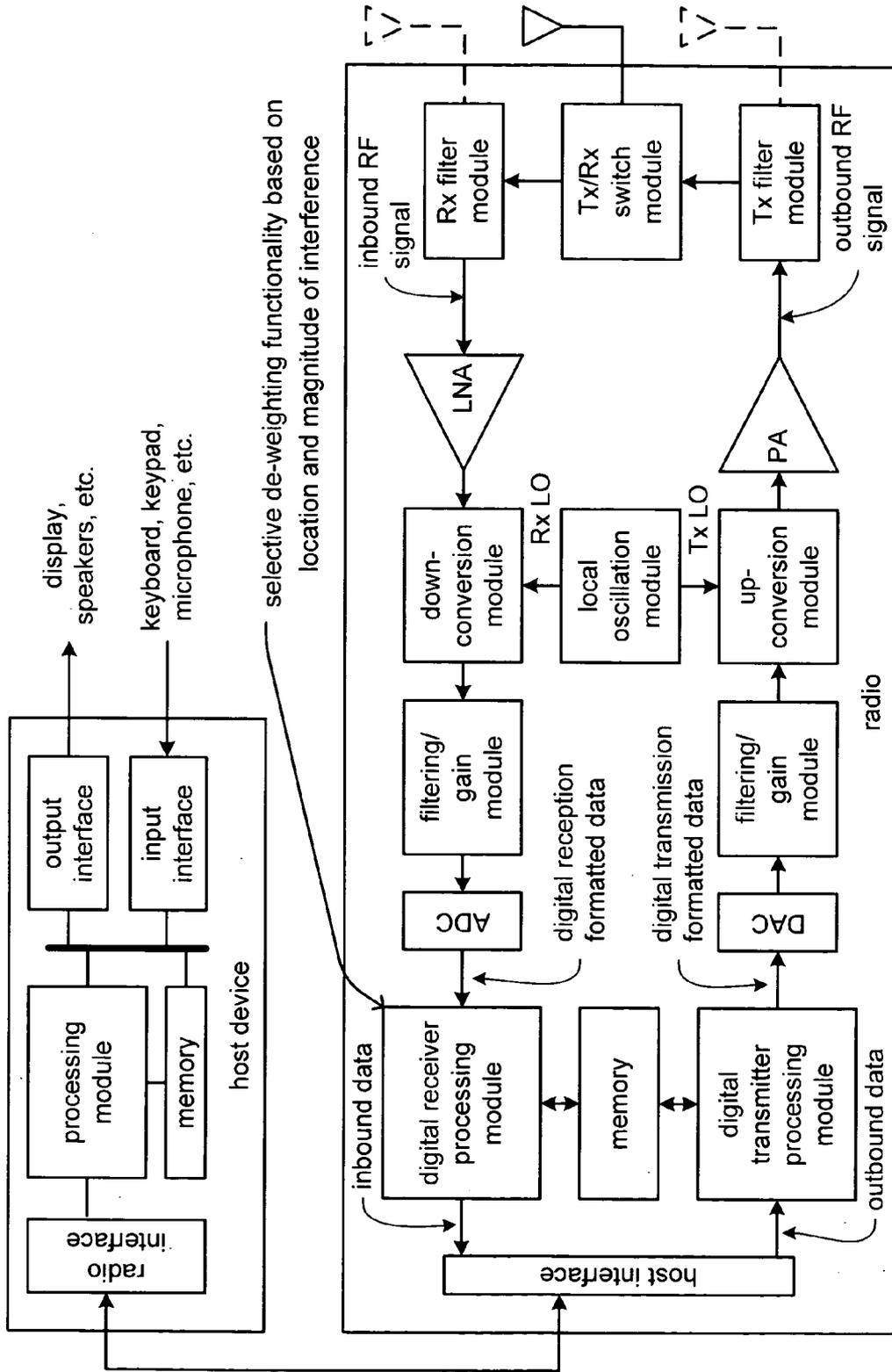


reduced duty cycle SH-OFDM (Slow Hopping-Orthogonal Frequency Division Multiplexing)

Fig. 12

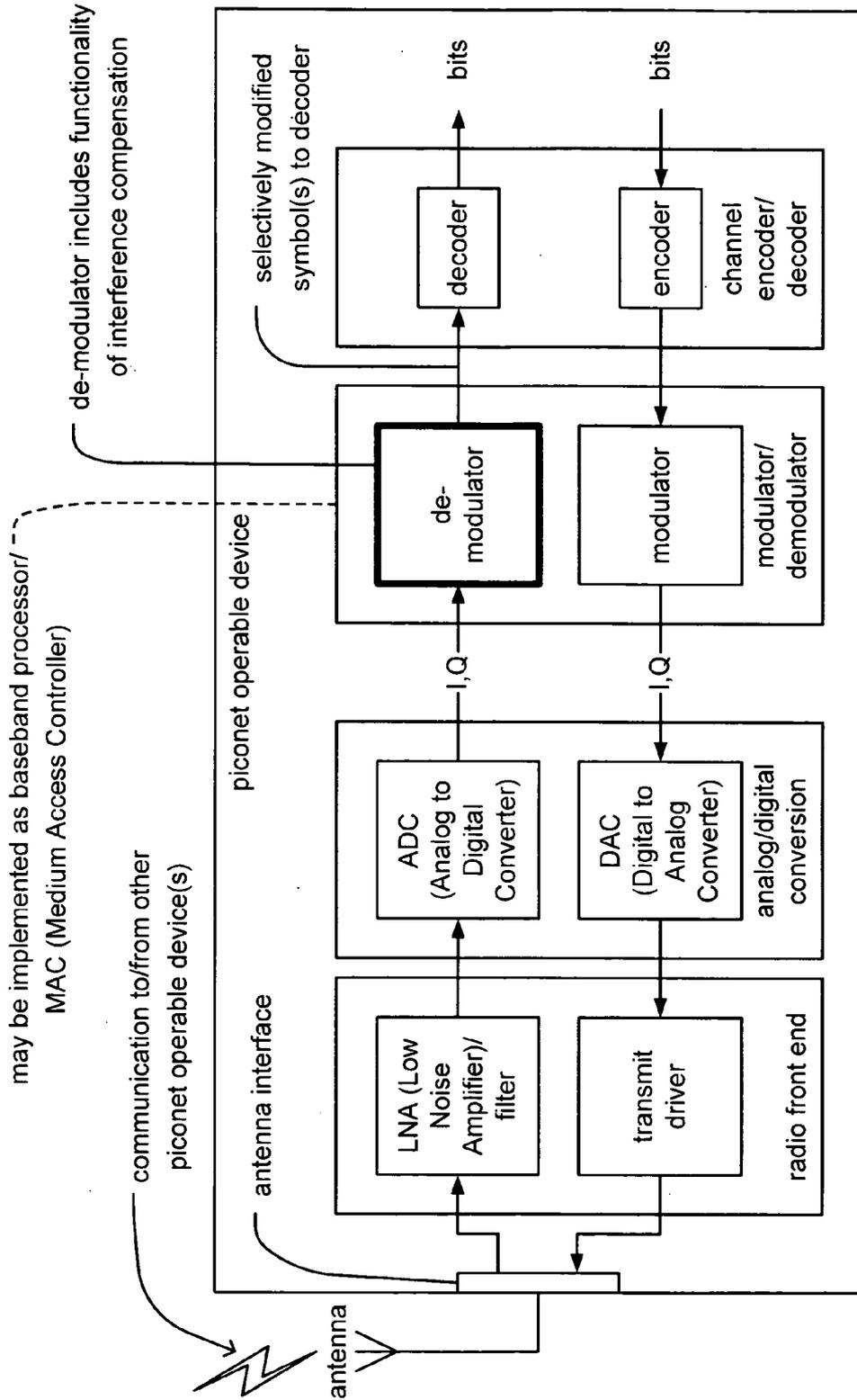


communication system  
**Fig. 13**

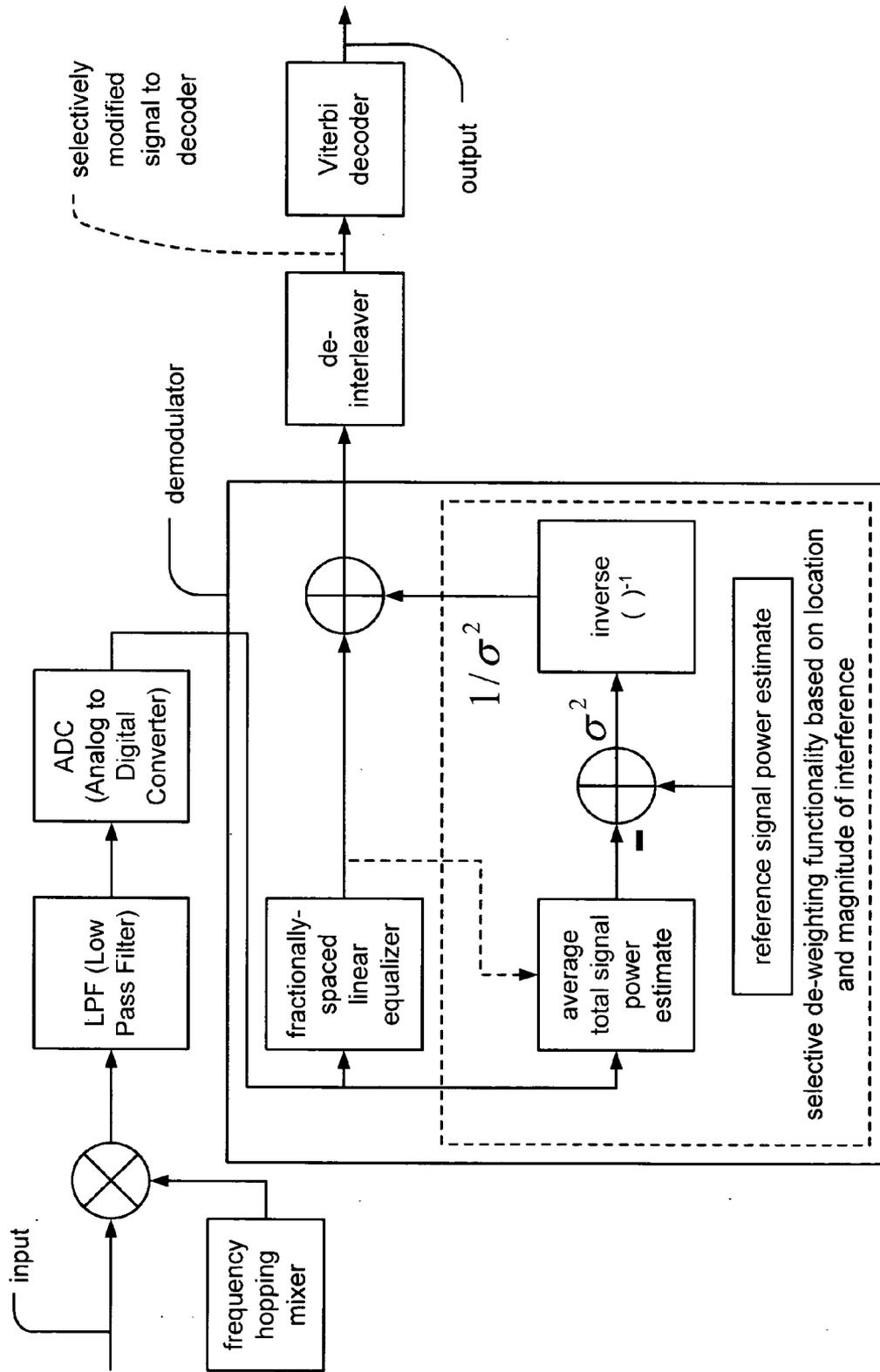


wireless communication device

**Fig. 14**

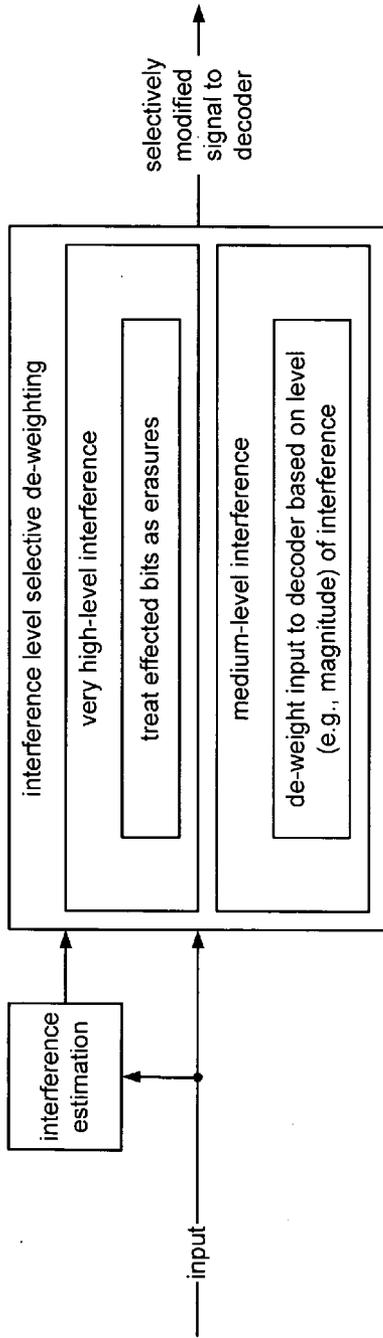


piconet operable device  
**Fig. 15**



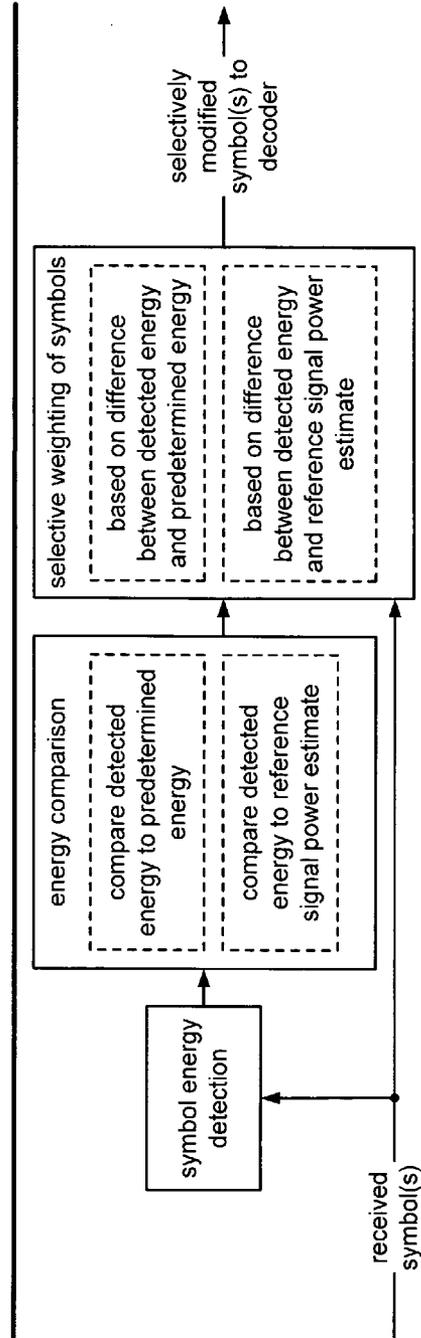
smart receiver structure

**Fig. 16**



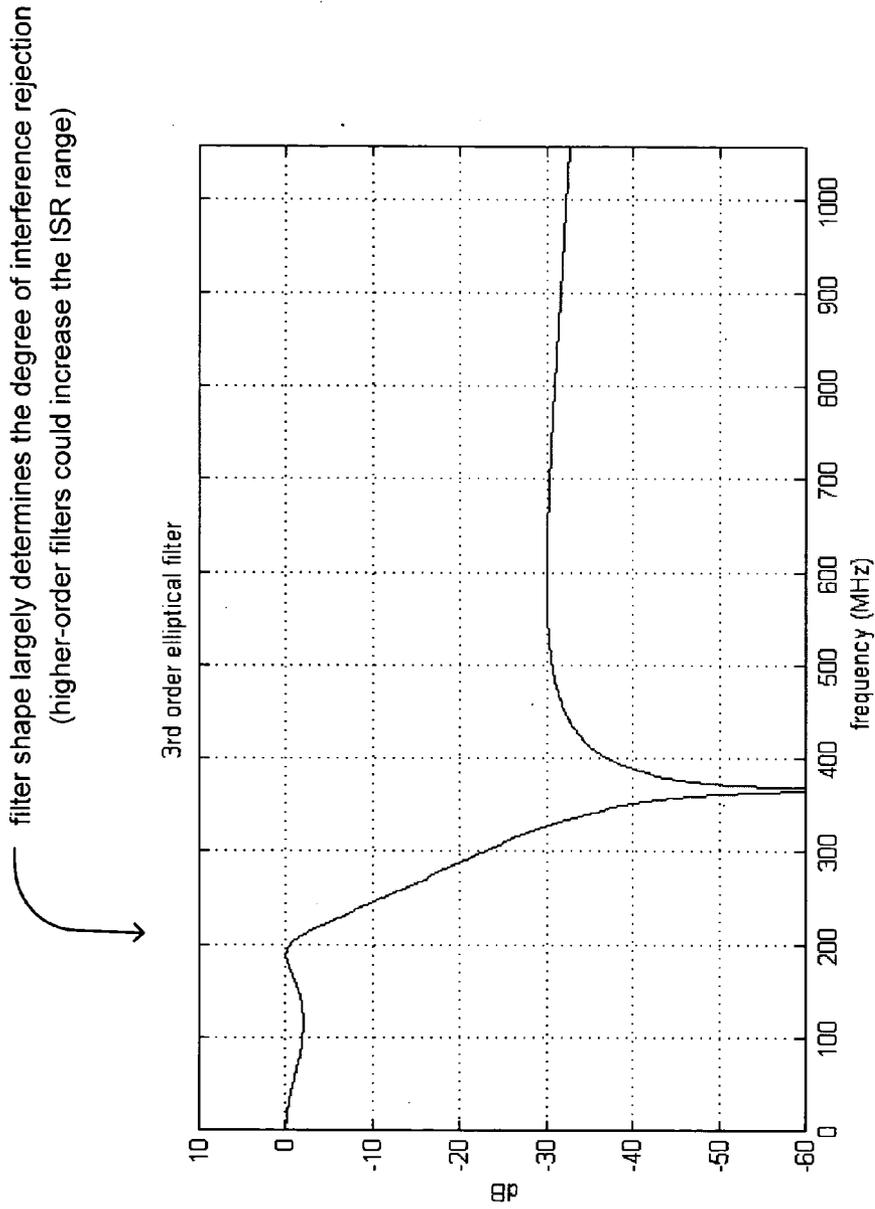
functionality of smart receiver

**Fig. 17A**

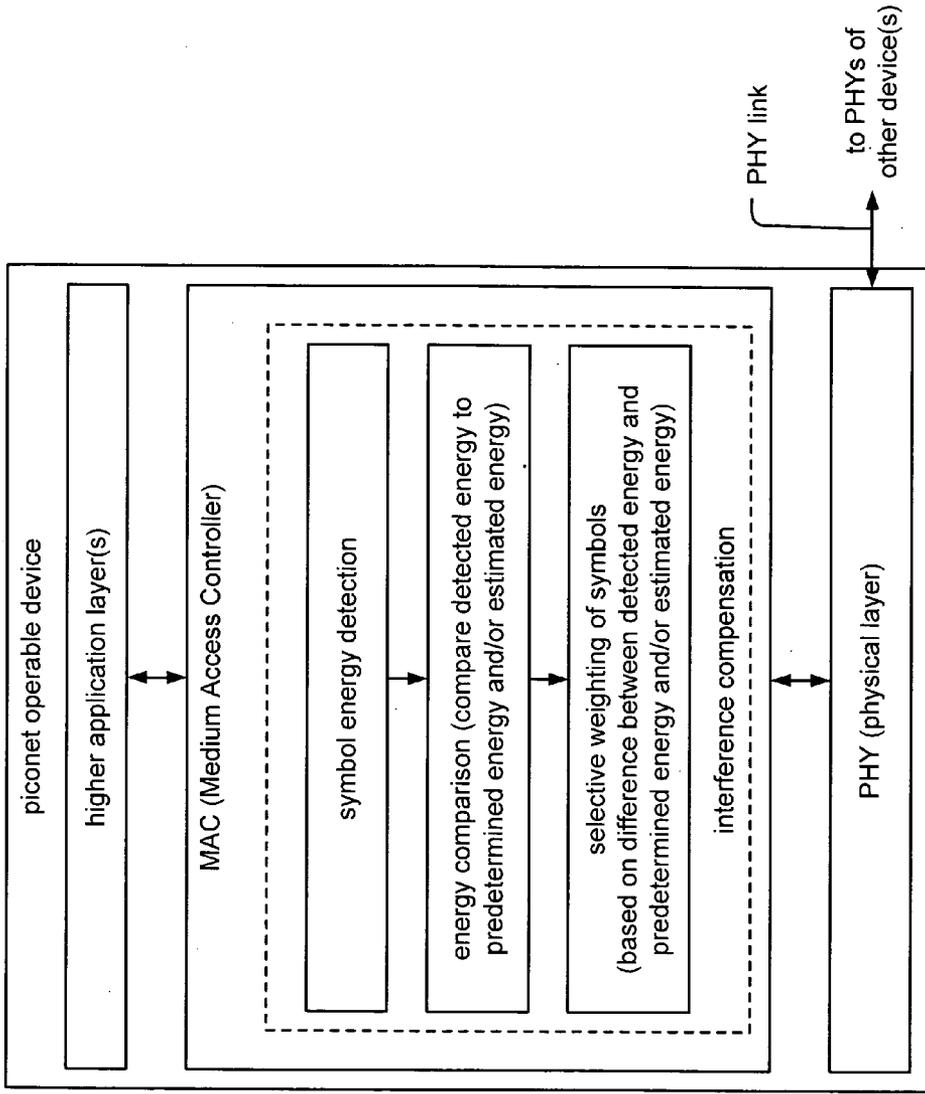


functionality of interference compensation capitalizing on structured interference

**Fig. 17B**

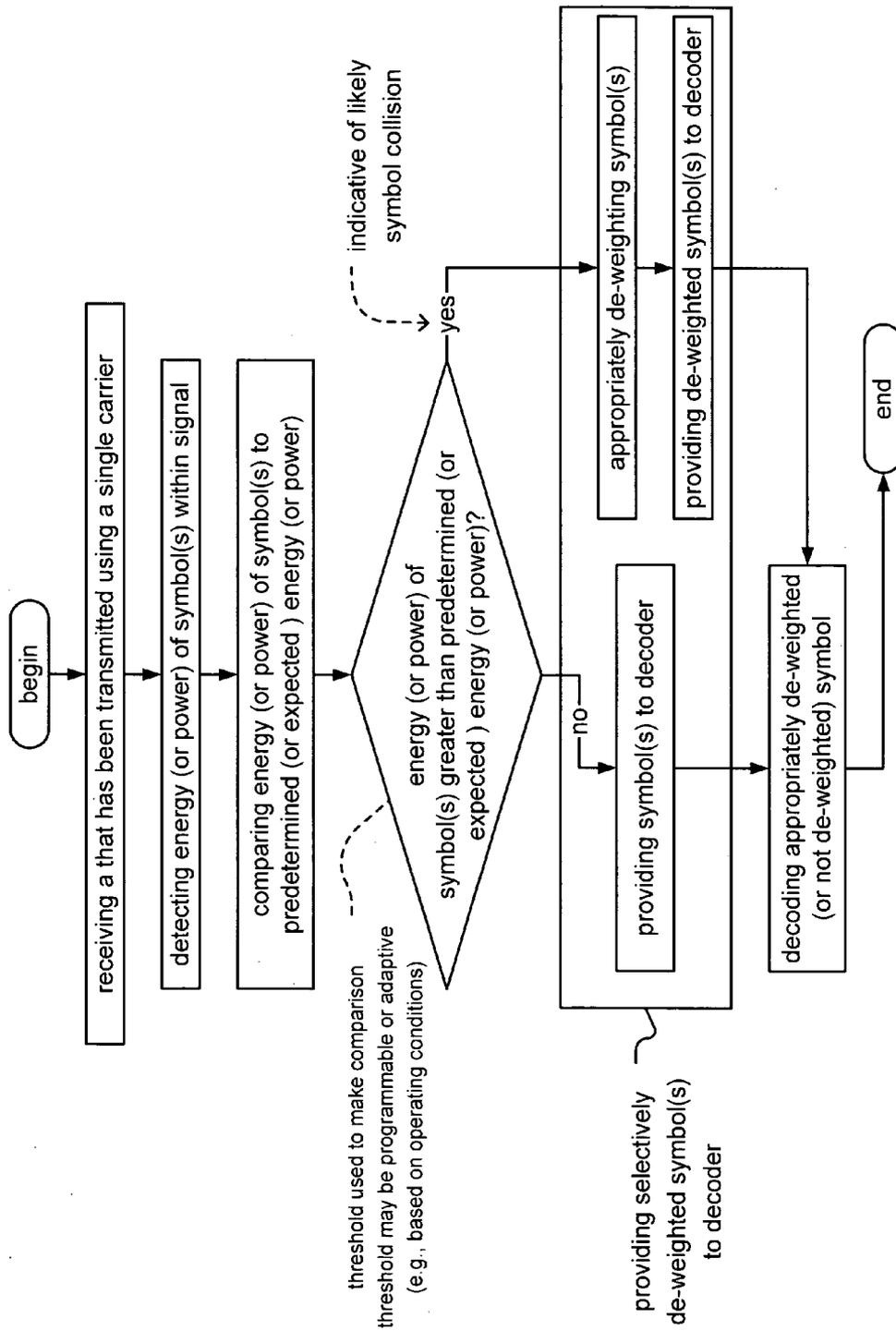


3rd order elliptical LPF (Low Pass Filter) employed at transmitter and receiver (or a transceiver)  
**Fig. 18**



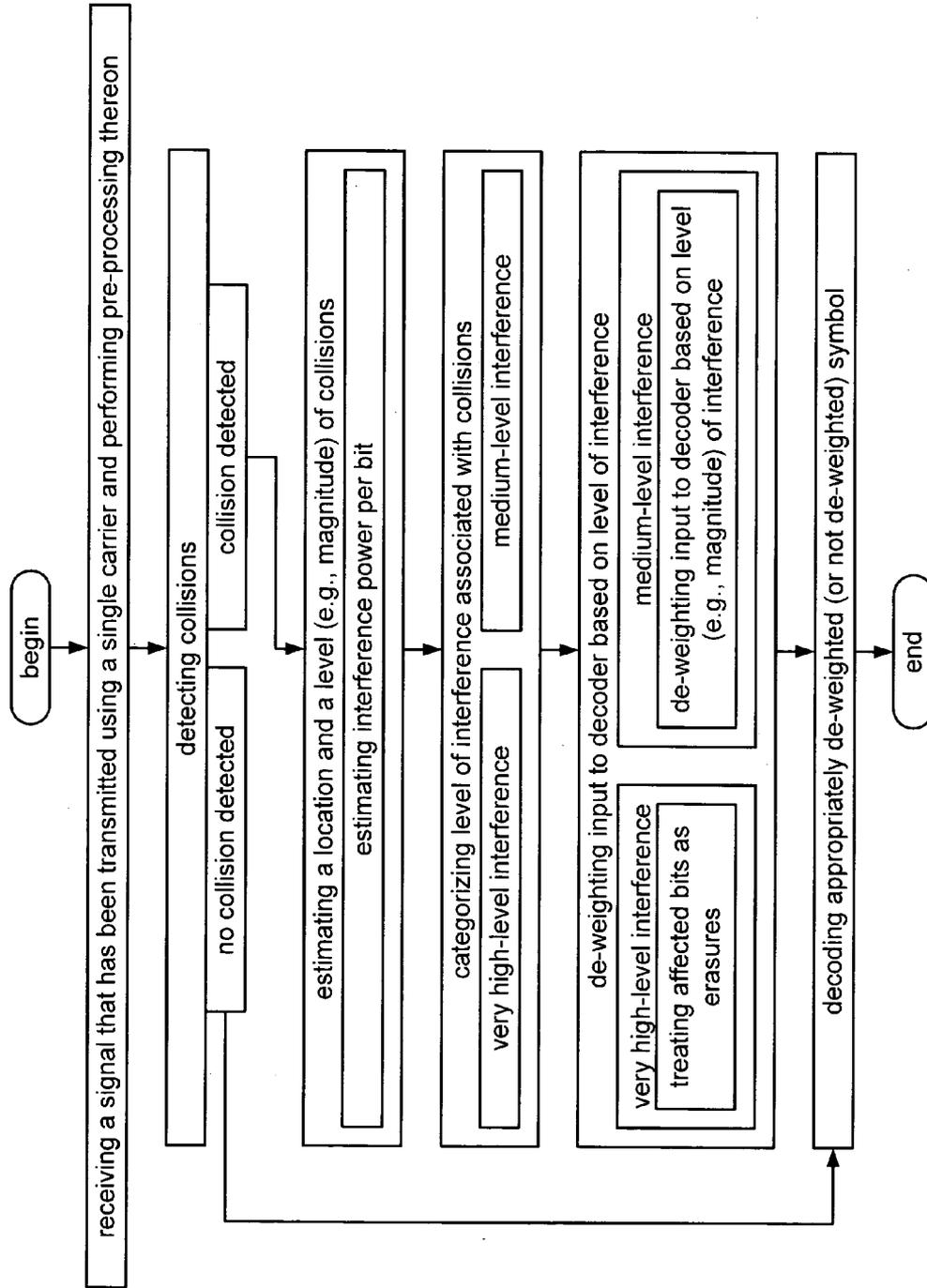
piconet operable device (showing PHY, MAC, and higher protocol layers)

**Fig. 19**



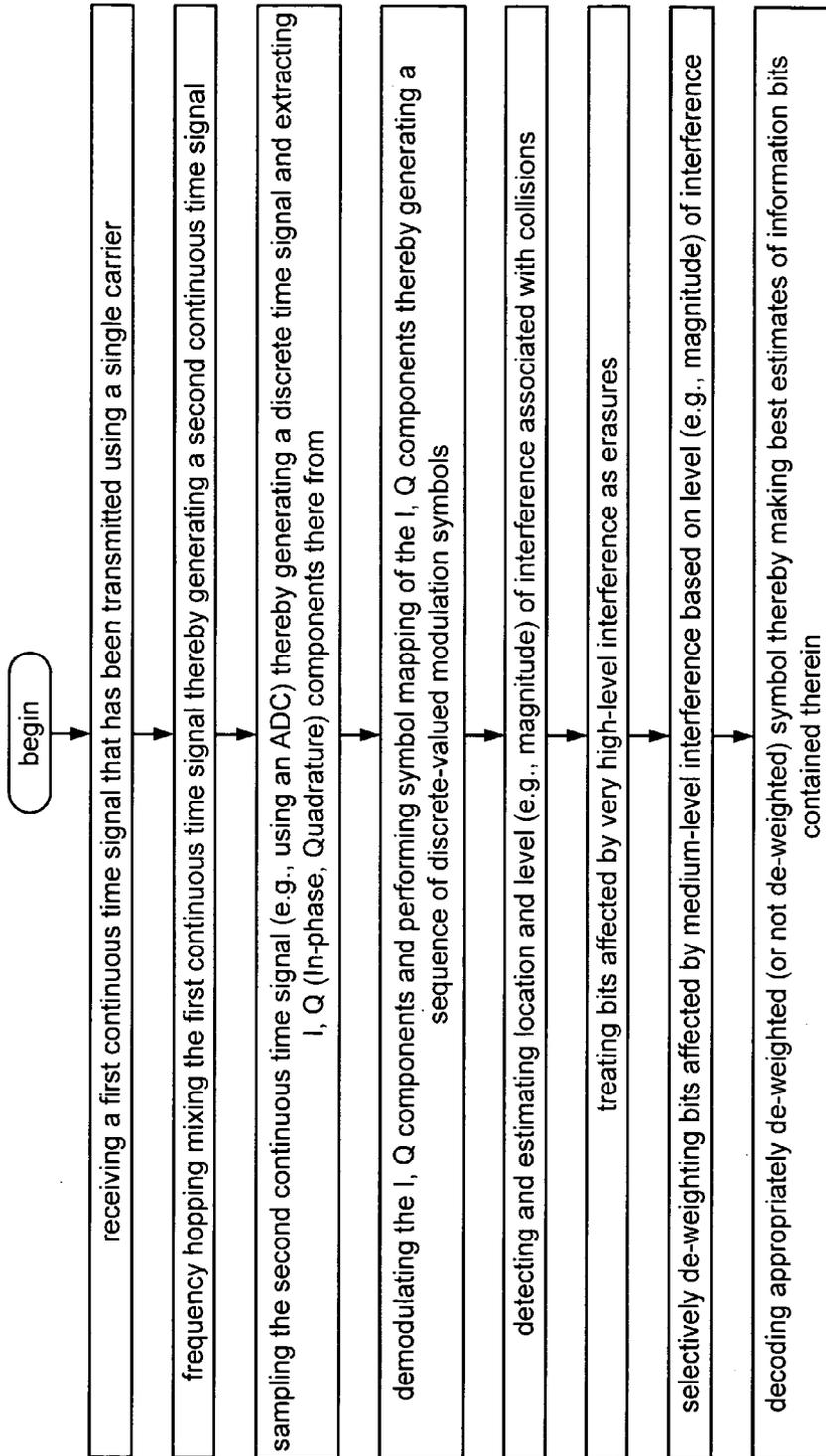
method for receive processing in a piconet operable device

**Fig. 20**



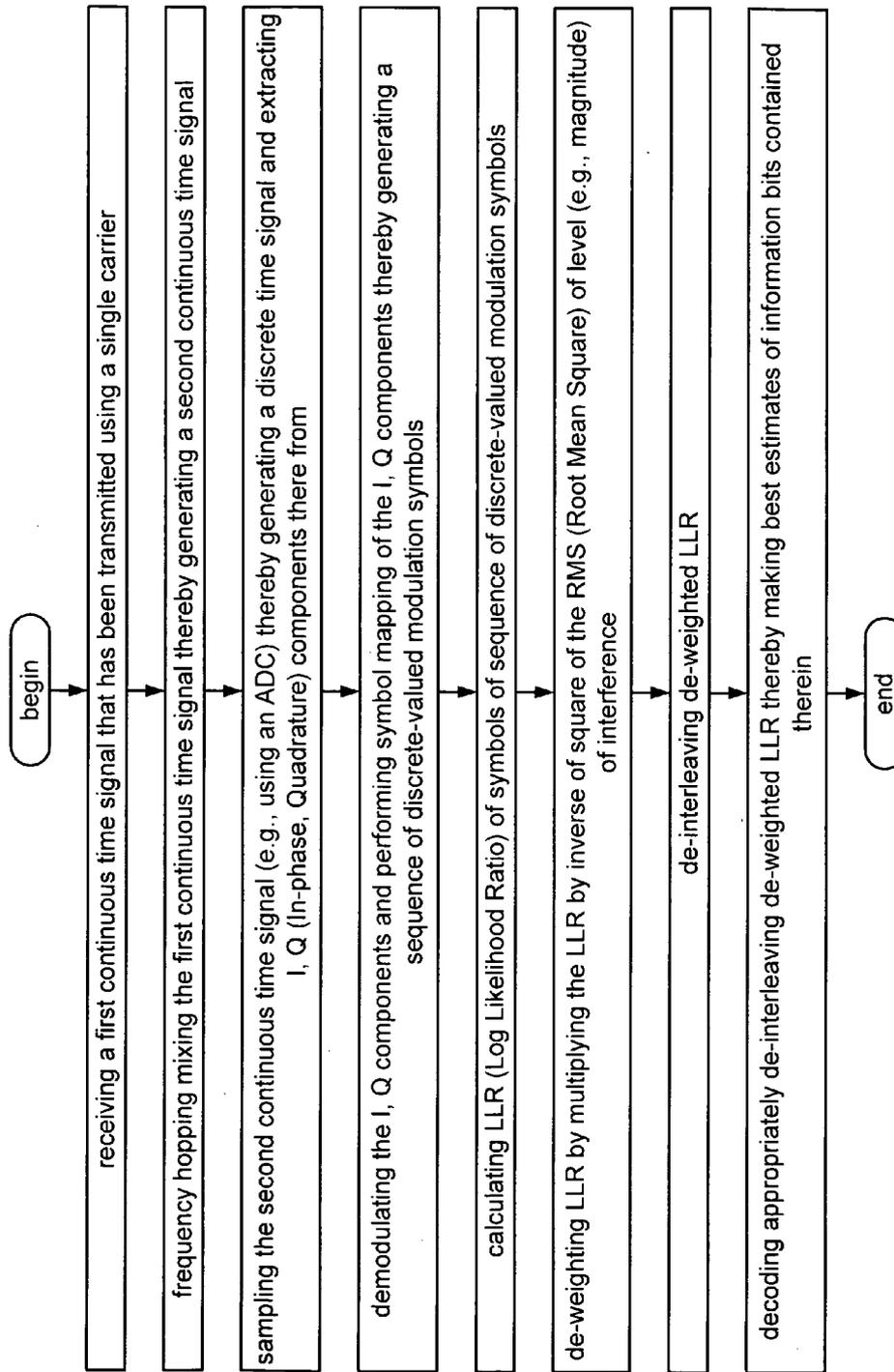
method for receive processing in a piconet operable device

**Fig. 21**



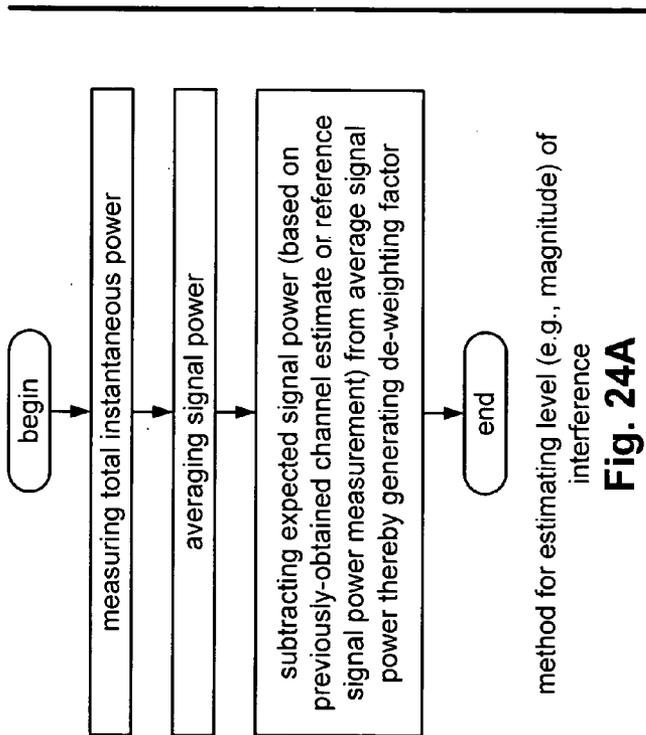
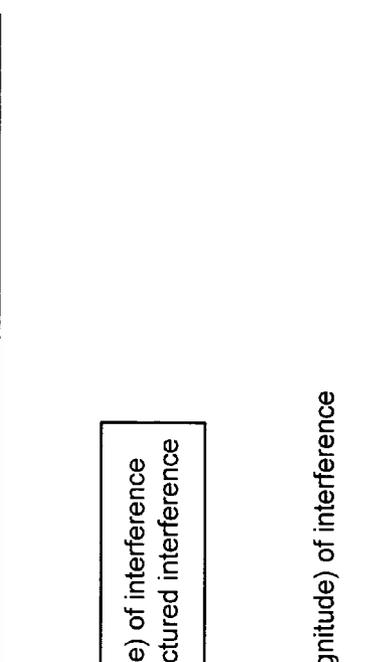
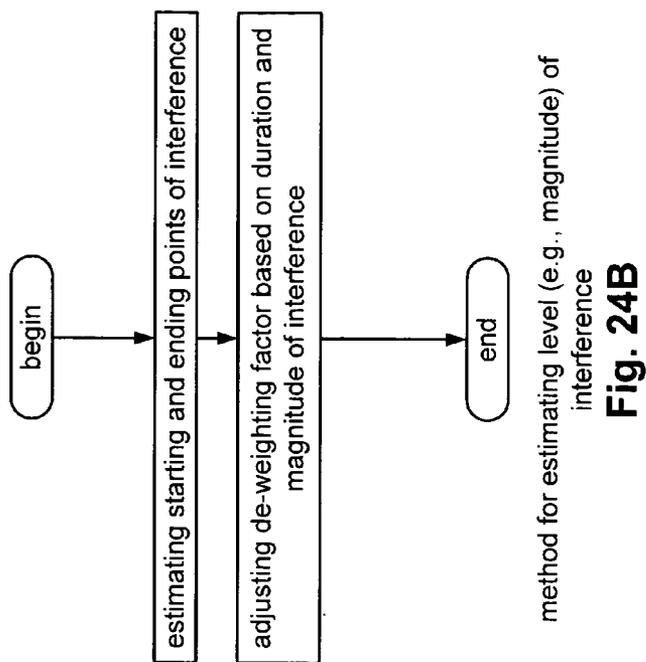
method for receive processing in a piconet operable device

**Fig. 22**



method for receive processing in a piconet operable device

**Fig. 23**



## MULTI-BAND SINGLE-CARRIER MODULATION

### CROSS REFERENCE TO RELATED PATENTS/PATENT APPLICATIONS

[0001] The present U.S. Utility Patent Application claims priority pursuant to 35 U.S.C. § 119(e) to the following U.S. Provisional Patent Applications which are hereby incorporated herein by reference in their entirety and made part of the present U.S. Utility Patent Application for all purposes:

[0002] 1. U.S. Provisional Application Ser. No. 60/488, 623, entitled "UWB (Ultra Wide Band) interference mitigation," (Attorney Docket No. BP3085), filed Jul. 18, 2003 (Jul. 18, 2003), pending.

[0003] 2. U.S. Provisional Application Ser. No. 60/494, 498, entitled "Multi-band single-carrier modulation," (Attorney Docket No. BP3135), filed Aug. 12, 2003 (Aug. 12, 2003), pending.

### BACKGROUND OF THE INVENTION

[0004] 1. Technical Field

[0005] The invention relates generally to communication systems; and, more particularly, it relates to receive processing (demodulation and decoding) of signals received within such communication systems.

[0006] 2. Description of Related Art

[0007] Data communication systems have been under continual development for many years. In recent years, the development of piconet type communication systems has been under increasing development. A piconet may be viewed as a network that is established when two devices connect to support communication of data between themselves. These piconets typically operate within a region having a radius of up to approximately 10 meters. Sometimes, piconets are referred to as PANs (Personal Area Networks), and those piconets that operate using wireless means are often referred to as WPANs (Wireless Personal Area Networks).

[0008] Piconets are often typically discussed in the context of wireless communication systems. Devices operating within the piconet typically operate according to an M/S (Master/Slave) type relationship. Some piconets also include multiple user devices (e.g., slave devices) that interact with a piconet controller (e.g., the master device). In even some other instances, two or more piconets operate such that they share at least one common device in a scatternet implementation. For example, in a scatternet, user devices (slave devices) may interact with two or more separate piconet controllers (master devices). This implementation allows various devices within different piconets that are located relatively far from one another to communicate through the corresponding piconet controllers (master devices) of the scatternet. However, within a scatternet implementation, a problem may arise such that each of the individual piconets must be able to operate in relative close proximity with other piconets without interfering with one another. It is also noted that independently operating piconets, not implemented within a scatternet implementation, may also suffer from deleterious effects of interference with other piconets located within relative close proximity. One such deleterious effect that may arise is when the symbols (or pulses) being

transmitted within the piconets operating within relatively close proximity collide with one another thereby resulting in potentially lost data.

[0009] As is known, the Bluetooth® communication standard is the first such PAN communication standard that has been developed. In accordance with the Bluetooth® communication standard, the communication between the various devices in such a piconet is strictly performed using an M/S (Master/Slave) configuration. Each of the devices within the Bluetooth® piconet is M/S capable. Typically one of the devices, or a first device within the Bluetooth® piconet, transmits a beacon signal (or an access invitation signal) while operating as the "master" device of the Bluetooth® piconet to the other "slave" devices of the Bluetooth® piconet. In other words, the "master" device of the Bluetooth® piconet polls the other "slave" devices to get them to respond.

[0010] Another PAN communication standard that has been developed is that of the IEEE (Institute of Electrical & Electronics Engineers) 802.15 standard. Variations and extensions of the 802.15 standard (e.g., 802.15.1, 802.15.2, 802.15.3, and others that may be developed over time) have also been under development during recent times. Operation according to 802.15.3 differs from that of the Bluetooth® communication standard. According to 802.15.3, one particular device is specially designed to operate as a piconet controller (master) within a piconet; that is to say, every device in such an IEEE 802.15.3 piconet does not operate in an M/S mode. One device within such an IEEE 802.15.3 piconet operates as a piconet controller (master), and the other devices within the IEEE 802.15.3 piconet may be implemented as user devices (slaves). It is also noted that the piconet controller (master) may operate to facilitate the p2p (peer to peer) operation between the various user devices (slaves) within the piconet.

[0011] There has been a great deal of development recently in seeking to enable the simultaneous operation of piconets within relatively close proximity with one another (without suffering significant deleterious effects such as degradation of performance, large numbers of collisions of transmitted symbols within the various piconets, and other such deleterious effects. Currently, there does not exist in the art a sufficient solution that may accommodate the undesirable effects of symbol collisions within such piconets in a satisfactory manner. While there have been some attempts to try to deal with minimizing these undesirable symbol collisions within such piconets, there does not yet exist a satisfactory manner in which symbol collisions (when they do in fact occur) may be dealt with while maintaining a very high level of performance for all of the devices within the piconet.

### BRIEF SUMMARY OF THE INVENTION

[0012] Various aspects of the invention can be found in a communication device that operates within a piconet. This communication device may be viewed as being a piconet operable device. The piconet operable device includes a radio front end, an ADC (Analog to Digital Converter), a demodulator, and a decoder. The radio front end receives and filters a continuous time signal. The ADC samples the received and filtered continuous time signal thereby generating a discrete time signal and extracting I, Q (In-phase,

Quadrature) components there from. The demodulator receives the I, Q components and performs symbol mapping of the I, Q components thereby generating a sequence of discrete-valued modulation symbols. The demodulator estimates at least one of a location and a level of interference associated with a collision within a symbol of the sequence of discrete-valued modulation symbols. The demodulator then categorizes the level of the interference into at least two categories. When the level of the interference is categorized into a first category of the at least two categories, the demodulator treats interference affected bits of the symbol as erasures thereby generating a first demodulator output symbol. However, when the level of the interference is categorized into a second category of the at least two categories, the demodulator also selectively de-weights interference affected bits of the symbol according to a de-weighting factor thereby generating a second demodulator output symbol. The decoder decodes the first demodulator output symbol or the second demodulator output symbol to make best estimates of the at least one information bit contained therein.

[0013] In certain embodiments, the demodulator estimates interference associated with the collision within the symbol on a power per bit basis. The location of interference associated with the collision within the symbol may be used to identify the interference affected bits of the symbol. The demodulator may be implemented in a variety of different ways; one of which is when the demodulator is implemented as a baseband processor/MAC (Medium Access Controller) within the piconet operable device.

[0014] The piconet operable device may be viewed as being a first piconet operable device that operates within a first piconet that substantially occupies a first region, and a second piconet operable device operates within a second piconet that substantially occupies a second region. These two piconets may be viewed as SOPs (Simultaneously Operating Piconets), and sometimes the first region and the second region occupy at least a portion of common space. In this SOP context, the symbol may be viewed as being a first symbol that collides with a second symbol that is received by the second piconet operable device before being received. Collisions between symbols within the first piconet and symbols within the second piconet can occur according to a structured interference pattern. Sometimes, this structured interference pattern is a predetermined structured interference pattern, and the demodulator estimates at least one of the location and the level of interference associated with the collision within the symbol based on the predetermined structured interference pattern.

[0015] In some instances, the demodulator estimates the level of interference associated with the collision within the symbol by measuring a total instantaneous power of the continuous time signal associated with the symbol, averaging a power of the continuous time signal associated with the symbol, and subtracting an expected reference signal power associated with the symbol from a previously obtained channel estimate or power measurement of the continuous time signal associated with the symbol.

[0016] There may be scenarios when the symbol does not include any interference; this may be viewed as being a third category of interference. For example, in such instances, when the level of the interference is categorized into a third

category of the at least two categories, the decoder directly decodes the symbol to make best estimates of the at least one information bit contained therein. That is to say, no de-weighting of the symbol is performed in such instances; the symbol is passed directly through to the decoder for decoding processing.

[0017] The invention envisions any type of communication device that supports the functionality and/or processing described herein. Moreover, various types of methods may be performed to support the functionality described herein without departing from the scope and spirit of the invention as well.

#### BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0018] FIG. 1A is a diagram illustrating an embodiment of the frequency spectrum of a UWB (Ultra Wide Band) signal when compared to some other signal types according to the invention.

[0019] FIG. 1B is a diagram illustrating an embodiment of UWB (Ultra Wide Band) spectrum partitioning into a plurality of sub-bands according to the invention.

[0020] FIG. 2A is a diagram illustrating an embodiment of a piconet or WPAN (Wireless Personal Area Network) (shown as a wireless communication system) that is built according to the invention.

[0021] FIG. 2B is a diagram illustrating an embodiment of frequency hopping that may be performed according to the invention.

[0022] FIG. 3 is a diagram illustrating an embodiment showing comparison of frequency hopping time interval duration compared to a communication channel impulse response according to the invention.

[0023] FIG. 4 is a diagram illustrating another embodiment of frequency hopping that is performed according to the invention.

[0024] FIG. 5 is a diagram illustrating an embodiment of CDMA (Code Division Multiple Access) that may be employed according to the invention.

[0025] FIG. 6 is a diagram illustrating an embodiment of OFDM (Orthogonal Frequency Division Multiplexing) that may be employed according to the invention.

[0026] FIG. 7 is a diagram illustrating an embodiment of SOPs (Simultaneously Operating Piconets) within relatively close proximity to one another (having some overlap) according to the invention.

[0027] FIG. 8 is a diagram illustrating another embodiment of SOPs within relatively close proximity to one another (having some overlap) according to the invention.

[0028] FIG. 9 is a diagram illustrating an embodiment of SOPs interference characteristics according to the invention.

[0029] FIG. 10 is a diagram illustrating an embodiment of fast frequency hopping with multipath and interference according to the invention.

[0030] FIG. 11 is a diagram illustrating an embodiment of SH-OFDM (Slow-Hopping-Orthogonal Frequency Division Multiplexing) according to the invention.

[0031] FIG. 12 is a diagram illustrating an embodiment of reduced duty cycle SH-OFDM according to the invention.

[0032] FIG. 13 is a schematic block diagram illustrating a communication system that includes a plurality of base stations and/or access points, a plurality of wireless communication devices and a network hardware component in accordance with certain aspects of the invention.

[0033] FIG. 14 is a schematic block diagram illustrating a wireless communication device that includes the host device and an associated radio in accordance with certain aspects of the invention.

[0034] FIG. 15 is a diagram illustrating an embodiment of a piconet operable device that supports functionality of interference compensation capitalizing on structured interference according to the invention.

[0035] FIG. 16 is a diagram illustrating an embodiment of smart receiver structure functionality that is built according to the invention.

[0036] FIG. 17A is a diagram illustrating an embodiment of functionality of a smart receiver according to the invention.

[0037] FIG. 17B is a diagram illustrating an embodiment of functionality of interference compensation capitalizing on structured interference according to the invention.

[0038] FIG. 18 is a diagram illustrating an embodiment of a 3<sup>rd</sup> order elliptical LPF (Low Pass Filter) employed at a transmitter and a receiver (or a transceiver) according to the invention.

[0039] FIG. 19 is a diagram illustrating another embodiment of a piconet operable device that supports functionality of interference compensation capitalizing on structured interference (showing PHY (physical layer), MAC (Medium Access Controller), and higher protocol layers) according to the invention.

[0040] FIG. 20, FIG. 21, FIG. 22, and FIG. 23 are flowcharts illustrating various embodiments of methods for receive processing in a piconet operable device according to the invention.

[0041] FIG. 24A, FIG. 24B, and FIG. 24C are flowcharts illustrating various embodiments of methods for estimating a level (e.g., magnitude) of interference of a signal for use in performing interference compensation according to the invention.

#### DETAILED DESCRIPTION OF THE INVENTION

[0042] A novel approach is presented herein by which a piconet, or SOPs (Simultaneously Operating Piconets), may operate in such a manner as to have a minimal amount (if any) of interference between them. A single carrier (e.g., single carrier frequency) solution is provided in place of an OFDM (Orthogonal Frequency Division Multiplexing) solution. A piconet operable device is presented to include intelligence (e.g., smart receiver structure within the piconet operable device) that is able to perform estimation of the location and level (e.g., magnitude) of the interference and to perform appropriate processing to minimize its impact when demodulating and decoding a received signal. For example, this may involve selectively de-weighting only

specific bits of one or more individual symbols of the received and demodulated signal.

[0043] Some background information is initially provided below to acquaint the reader to the particular context of operation of piconet and their use of the UWB (Ultra Wide Band) portion of the frequency spectrum.

[0044] FIG. 1A is a diagram illustrating an embodiment of the frequency spectrum of a UWB (Ultra Wide Band) signal when compared to some other signal types according to the invention. In contradistinction to RF (Radio Frequency) communications that operate by using a narrow-band carrier frequency to transmit information, UWB communications operate by sending pulses of energy across a broad frequency spectrum. For example, an RF signal may be viewed as occupying the range of spectra of a narrowband frequency. Also, in contradistinction to a spread-spectrum signal whose intensity (magnitude) generally rises above the noise floor within an available spectrum and also occupies a relatively narrower portion of the available spectrum, a UWB signal may actually be viewed as pulse shaped noise (that may never exceed the noise floor within the available spectrum). A spread-spectrum signal may be viewed as a signal that occupies a frequency band that is much wider than the minimum bandwidth required by the information signal. For example, a transmitter “spreads” the energy (that is typically originally concentrated in narrowband) across a number of frequency band channels on a wider electromagnetic spectrum. Some benefits of a spread-spectrum signal include improved privacy, decreased narrowband interference, and increased signal capacity.

[0045] However, a UWB signal’s PSD (Power Spectral Density) actually curves across the available spectrum, whereas the PSD of noise generally looks similar across the entire range of the available spectrum. Because of this distinction of shaping of the UWB signal and the noise across the available spectrum, the noise does not fully obliterate a pulse that is transmitted as a UWB signal. It is also important to note that a UWB signal is a function of time, not frequency.

[0046] FIG. 1B is a diagram illustrating an embodiment of UWB (Ultra Wide Band) spectrum partitioning into a plurality of sub-bands (or channels) according to the invention. Relatively recently, the FCC (Federal Communications Commission) has defined the available spectrum for UWB communications as being between 3.1 GHz (Giga-Hertz) and 10.6 GHz. In addition, the FCC defined the minimum spectral width of any sub-band (or channel) within the available UWB spectrum to be 500 MHz (Mega-Hertz).

[0047] Moreover, this FCC definition allows for a PSD across the UWB spectrum of  $-41.25$  dBm/MHz of bandwidth. As a brief review, 0 dBm is the dB (decibel) measure of power of a signal referenced to 1 mW (milli-Watt). This means that the total power that may be employed by a UWB signal is approximately  $-14.26$  dBm in any individual 500 MHz sub-band (or channel) within the entire available UWB bandwidth of 7.5 GHz. In addition, if a pulse is sent using the entire 7.5 GHz of available UWB bandwidth, then the total power that may be employed by a UWB signal is approximately  $-2.5$  dBm.

[0048] FIG. 2A is a diagram illustrating an embodiment of a piconet or WPAN (Wireless Personal Area Network)

(shown as a wireless communication system) that is built according to the invention. As described briefly above, a piconet may be viewed as being the network that is established when any two devices connect to support communication between them. This operation is typically within the context of communication being performed in an M/S (Master/Slave) relationship. The piconet may typically be implemented using a piconet controller (master) and 1 or more user devices (slaves). The user devices (slaves) typically do not communicate directly with one another in this embodiment, but with each other through the piconet controller (master). However, 2 user devices (slaves) may be set up by the piconet controller (master) to communicate directly with one another using p2p (peer to peer) communication. This p2p communication set up for the 2 user devices (slaves) is typically performed by the piconet controller (master).

[0049] To support communication between each of the plurality of user devices (slaves), simultaneously at some times, and the piconet controller (master), the communication must be implemented in such a way that the communication links between each user device (slave) and the piconet controller (master) do not interfere with the other communication links between the other user devices (slaves) and the piconet controller (master). Moreover, when two or more piconets operate within relatively close proximity to one another, the communication within each of the respective piconets must be implemented in such a way that simultaneous operation of the two or more piconets (e.g., the coexistence and operation) may be performed without interfering with one another.

[0050] While it is noted that the user devices (slaves) do not typically communicate directly with one another (that is to say, via the piconet controller (master)), it is also noted that the piconet controller (master) may sometimes operate to enable p2p communication between the 2 user devices (slaves) within the piconet. Moreover, the piconet in this embodiment as well as within other embodiments described herein are all operable in accordance with the conditions and constraints provided by the IEEE (Institute of Electrical & Electronics Engineers) 802.15 standard and may also be implemented such that the piconet is operable in accordance with other wireless communication standards as well. Moreover, this piconet is also operable within the various alternative and subsequent drafts of the IEEE 801.15 standards being developed including the IEEE 802.15 WPAN High Rate Alternative PHY Task Group 3a (TG3a) draft standard.

[0051] FIG. 2B is a diagram illustrating an embodiment of frequency hopping that is performed according to the invention. As a function of time, the frequency band (or channel) that is being used will "hop" from one frequency band (or channel) to another. Frequency hopping is one means of operation that may be used to make a communication channel more robust. For example, when noise, such as background noise, is relatively localized to a particular portion of the spectrum, the frequency hopping will help minimize the effects this frequency specific and frequency localized noise.

[0052] Frequency hopping may be viewed as a repeated switching of the frequency of a signal during transmission. In a communication system, a transmitter and a receiver operate in synchronization so that each operates at the same

frequency at any given time. In this particular embodiment, an available frequency spectrum is sub-divided into  $n$  bands (or  $n$  channels). The communication operates using a band 1 during a first time interval, then operates using a band  $n$  during a second time interval, then operates using a band 3 during a third time interval, and so on as indicated in the diagram.

[0053] It is also noted that the time interval between the various frequency hops may be implemented as being sufficiently long so as to permit the capture of a communication channel's full impulse response at the various piconet operable devices within the piconet (e.g., the piconet controller (master) and the user devices (slaves)). This time interval at which the communication system operates at any given frequency will typically be multi-symbol lengths in duration. Alternatively, very fast frequency hopping may be performed when such considerations are not desired or critical.

[0054] As an example of the operation of frequency hopping, in the context of a UWB signal, the UWB spectrum may be divided into 15 sub-bands of 500 MHz bandwidth, the frequency hopping may be viewed as hopping between the various 500 MHz bandwidth sub-bands (or channels) as a function of time.

[0055] FIG. 3 is a diagram illustrating an embodiment showing comparison of frequency hopping time interval duration compared to a communication channel impulse response according to the invention. The impulse response, as a function of time, is shown for the communication channel between a user device (slave) and a piconet controller (master). This impulse response may be viewed as the response of the communication system when an impulse is provided thereto. The impulse response varies in intensity as a function of time before dissipating. The time that the impulse response takes to dissipate completely may be viewed as the impulse response time of the communication channel.

[0056] When compared to frequency hopping performed according to the invention, the time interval at which the communication system operates using a first frequency band (shown as a band 1 during a first time interval) is longer than the impulse response time of the communication channel. This will allow all of the energy of a pulse to be captured when transmitted and when operating at this frequency band. Similarly, when the operation switches to another frequency band according to the frequency hopping time-frequency code sequence, that corresponding time interval will also be longer than the impulse response time of the communication channel.

[0057] Within some prior art piconet approaches, frequency hopping alone has been implemented such that the time intervals are typically only of a single symbol's length; this is typically much shorter than the impulse response time of the communication channel. Much of the energy of a transmitted pulse may be lost if the frequency hops are performed too quickly. The longer duration over which the frequency hops are performed according to the invention allows for capturing of all of the energy of the transmitted pulse thereby ensuring more robust and more accurate communications. Alternatively, again, very fast frequency hopping may be performed when such considerations are not desired or critical.

[0058] Within the context of the invention, the time-frequency code employed to govern communication between 2 devices within the piconet may be viewed as an operational parameter. This operational parameter may be modified in real time based on a change in another operational parameter that governs communication between the 2 devices. For example, a 1<sup>st</sup> time-frequency code may be employed at one time, and a 2<sup>nd</sup> time-frequency code may be performed subsequently based on a change of another of the operational parameters. Based on a change in the operational parameter of interference of the communication link between 2 devices, as an example, one time-frequency code may more effectively support communication between the 2 devices compared to the other time-frequency codes that are available. As is also described in other of the embodiments of the invention, other operational parameters may also be modified in response to a change in 1 or more of the other operational parameters as well without departing from the scope and spirit of the invention.

[0059] Again, as briefly mentioned above, it is also noted that the piconet controller (master) may enable p2p communication between two separate user devices (slaves) within the piconet. The manner of communication described herein with respect to communication between the piconet controller (master) and any one user device (slave) is also applicable to p2p communication that may be performed between two separate user devices (slaves) within the piconet.

[0060] FIG. 4 is a diagram illustrating another embodiment of frequency hopping that is performed according to the invention. The description of this diagram may be viewed as being a specific example of the operational parameter of the time-frequency codes employed to support communication across various PHY (physical layer) links between the various devices within the piconet.

[0061] This embodiment shows how two separate piconets (or two separate groups of devices within a piconet) may operate using two separate time-frequency codes that are orthogonal to one another. For example, a first piconet (or first group of devices) performs frequency hopping for slave/master communication using a first time-frequency code (time-frequency code 1). In addition, a second piconet (or second group of devices) performs frequency hopping for slave/master communication using a second time-frequency code (time-frequency code 1). During each time interval, the time-frequency code 1 and the time-frequency code 2 each operate using a different band (or channel). For example, when the time-frequency code 1 operates using the band 1, the time-frequency code 2 operates using the band 2. Similarly, when the time-frequency code 1 operates using the band 2, the time-frequency code 2 operates using the band 5. This orthogonal operation of the 2 time-frequency codes continues for the duration of the respective time-frequency code sequences.

[0062] Each of the respective time-frequency code sequences are repeated to support subsequent operation of the respective piconets. This orthogonal operation of employing two time-frequency codes allows more than one piconet to coexist in relative close proximity with one another. In addition it is noted that all of the user devices (slaves) within a respective piconet (or group of devices) will communicate with their corresponding piconet control-

ler (master) using their time-frequency code sequence, and all of the user devices (slaves) within another respective piconet will communicate with their corresponding piconet controller (master) using their corresponding time-frequency code sequence.

[0063] FIG. 5 is a diagram illustrating an embodiment of CDMA (Code Division Multiple Access) that may be employed according to the invention. CDMA may be viewed as the short term assignment of a frequency band to various signal sources. At each successive time slot, the band assignments are reordered either adaptively or according to a predetermined sequence. For example, during a time slot 1, a signal 1 operates using a band 1, a signal 2 operates using a band 2, and a signal 3 operates using a band 3. Then, during a time slot 2, the signal 1 operates using the band 3, the signal 2 operates using the band 1, and the signal 3 operates using the band 2. During a time slot 3, the signal 1 operates using the band 1, the signal 2 operates using the band 2, and the signal 3 operates using the band 3.

[0064] The operation of communication devices (e.g., users) is performed using a PN (Pseudo-Noise) code that is typically orthogonal to the other PNs codes employed by the other communication devices within the communication system. This PN code is oftentimes referred to as a spreading code. A modulated signal is spread using that spreading code and the spread signal is then transmitted across a communication channel (e.g., a PHY (physical layer) link that communicatively couples 2 devices within the piconet). At a receiver end of the communication channel, this same spreading code (e.g., this PN code) is employed to de-spread the code so that data sent from a particular device may be demodulated by the appropriate destination device.

[0065] The operation of CDMA may be better understood when viewed as the transformation of an input signal through a communication system. At a transmitter end of a communication channel, input from a particular user is first provided to a modulator where the data is modulated by a carrier thereby generating a modulated signal (s1). Next, the data-modulated signal is then multiplied by a spreading code (g1) that corresponds to that particular user thereby generating a spread signal (g1s1) that is then provided to the communication channel. This signal may be viewed as a convolution of the frequency spectrum of the modulated signal and the frequency spectrum of the spreading code. Simultaneously, input from other users within the communication system is modulated and spread in an analogous manner.

[0066] At the receiver end of the communication channel, a linear combination of all of the spread signals provided by the other users is received, e.g.,  $g1s1+g2s2+g3s3+ \dots$  and so on for all of the users. At the receiver end, the total received signal is then multiplied by the spreading code (g1) thereby generating a signal that includes  $g1^2s1$  plus a composite of the undesired signal (e.g.,  $g1g2s2+g1g3s3+ \dots$  and so on).

[0067] In CDMA, the spreading codes are typically chosen such that they are orthogonal to one another. That is to say, when any one spreading code is multiplied with another spreading code, the result is zero. This way, all of the undesired signals drop out. Given that the spreading codes  $g1(t)$ ,  $g2(t)$ ,  $g3(t)$  and so on, the orthogonality of the spreading codes may be represented as follows:

$$\int_0^T g_i(t)g_j(t)dt = \begin{cases} 1, & i = j \\ 0, & i \neq j \end{cases}$$

[0068] This final signal is then passed to a demodulator where the input that has been provided at the transmitter end of the communication channel is extracted and a best estimate is made thereof.

[0069] FIG. 6 is a diagram illustrating an embodiment of OFDM (Orthogonal Frequency Division Multiplexing) modulation that may be employed according to the invention. OFDM modulation may be viewed as dividing up an available spectrum into a plurality of narrowband sub-carriers (e.g., lower data rate carriers). Typically, the frequency responses of these sub-carriers are overlapping and orthogonal. Each sub-carrier may be modulated using any of a variety of modulation coding techniques.

[0070] OFDM modulation operates by performing simultaneous transmission of a larger number of narrowband carriers (or multi-tones). Oftentimes a guard interval or guard space is also employed between the various OFDM symbols to try to minimize the effects of ISI (Inter-Symbol Interference) that may be caused by the effects of multi-path within the communication system (which can be particularly of concern in wireless communication systems). In addition, a CP (Cyclic Prefix) may also be employed within the guard interval to allow switching time (when jumping to a new band) and to help maintain orthogonality of the OFDM symbols.

[0071] In one UWB embodiment, 125 OFDM tones may be implemented in any one of the 15 sub-bands of 500 MHz bandwidth within the UWB spectrum. Other benefits are achieved using OFDM. For example, the use of multi-tones allows for an effective solution to deal with narrowband interference. For example, a tone that corresponds to the locality of the narrowband interference may be turned off (to eliminate the susceptibility to this narrowband interference) and still provide for efficient operation. This turning off of these one or few tones will not result in a great loss of bandwidth because each individual tone does not occupy a great deal of bandwidth within the available spectrum employed by the OFDM symbol. Therefore, OFDM modulation provides a solution that may be employed in accordance with invention that provides link quality intelligence from the PHY (physical layer) to the higher protocol layers within devices operating within wireless networks (e.g., piconets as one example).

[0072] FIG. 7 is a diagram illustrating an embodiment of SOPs (Simultaneously Operating Piconets) within relatively close proximity to one another (having some overlap) according to the invention. This embodiment shows how various piconets may operate in such a way that the individual devices within these piconets are sufficiently close to one another that they may sometimes even associate with different piconets at different times. This inherently requires operating the various piconets in such a way that they do not interfere with one another. For example, each piconet may operate using a different frequency hopping approach. Each piconet may employ a different time-frequency code such that undesirable symbol collisions are kept at a relatively

low rate of occurrence. Other operational parameters may alternatively be employed for each of the various piconets. For example, different PN (Pseudo-Noise) codes may be employed to govern the spreading/de-spreading of symbols transmitted within the various piconets. Moreover, even other operational parameters may be implemented such that any undesirable symbol collisions are kept at a relative minimum.

[0073] The manner in which the various devices within the piconet operate may be performed in such a way that when symbol collisions do in fact occur (e.g., when interference does occur) the interference has a particular characteristic, namely, a relatively structured interference. Thereafter, using an understanding of this structured interference, intelligent processing of symbols within the various devices may be made so as to support a much higher level of performance than is provided by communication systems whose high end of performance is limited by the AWGN (Additive White Gaussian Noise) existent within the communication system. The performance of a piconet operating this way will typically be limited only by the out of band roll off and front end range (e.g., the radio front end and the filtering performed therein) of a device operating within such a piconet.

[0074] Various aspects of the invention operate the various devices within a piconet using a combination of SH-OFDM (Slow Hopping-Orthogonal Frequency Division Multiplexing) and a relatively slower PRF (Pulse Repetition Frequency) than is typically performed within prior art piconets. By operating the various devices of the piconet in such a way, when symbol collisions do in fact occur, they will exhibit the structured interference briefly describe above. Several examples are provided below showing more particularly how symbol collisions will exhibit this structured interference. In addition, various embodiments are also described about how this structure interference may be capitalized upon to ensure a high level of performance of the overall piconet.

[0075] As shown within this embodiment, a piconet A includes a piconet controller A (master) and user devices 1A & 2A (slaves). Similarly, a piconet C includes a piconet controller C (master) and user devices 1C & 2C (slaves). In addition, a piconet B includes a piconet controller B (master) and a user device 1B (slave).

[0076] As can be seen, each of these various piconets A, B, and C operate such that they may have a portion of overlap with 1 or more of the other piconets. Some of the devices within these piconets may associate with different piconets at different points in time.

[0077] Again, each of the various devices within the piconets A, B, and C may operate using individually selected time-frequency codes that include appropriate combinations of SH-OFDM and a relatively slower PRFs than are typically performed within prior art piconets. By operating the piconets A, B, and C in such a manner that when symbol collisions in the region, they exhibit a relatively structured type of interference. Having an understanding of the nature of this structured interference allows the implementation of a receiver having some intelligence that may appropriately de-weight symbols that have experienced an undesirable symbol collision.

[0078] FIG. 8 is a diagram illustrating another embodiment of SOPs within relatively close proximity to one

another (having some overlap) according to the invention. However, in contradistinction to the embodiment described above, this embodiment shows how different time-frequency codes may be implemented even within a given piconet. This may be performed in addition to (e.g., in conjunction with) the different time-frequency codes being implemented for different piconets.

[0079] This embodiment shows a number of user devices (slaves) and 2 piconet controllers (masters) within a region. If desired, the locations of the various devices within this region may be ascertained using any number of means. In one such embodiment, both of the piconet controllers 1 & 2 (masters) are operable to perform ranging of all of the user devices (slaves) within the region. Together, the piconet controller (master) 1 and the piconet controller (master) 2 perform this ranging of all of the user devices (slaves), group them accordingly, and also select the appropriate time-frequency codes that are used to govern the communication between the user devices (slaves) and the piconet controllers 1 & 2 (masters). In addition, one or both of the piconet controllers 1 & 2 (masters) may also direct 2 or more of the user devices (slaves) to perform p2p communication between them and perform ranging of the relative distances between them; this information may then be provided to both of the piconet controllers 1 & 2 (masters). In doing so, triangulation may be performed by one or both of the piconet controllers 1 & 2 (masters) to determine the precise location of the user devices (slaves) within the region.

[0080] The distribution of the user devices (slaves) in this embodiment is such that the user devices (slaves) may appropriately be grouped to operate with one particular piconet controller (master) within the region. For example, those user devices (slaves) closer in vicinity to the piconet controller 2 (master) may be grouped within one group; that is to say, user devices 2, 3, & 6 (slaves) may be grouped within a zone whose communication is governed according to one time-frequency code in one piconet (e.g., piconet 2).

[0081] Similarly, the piconet controller 1 (master) services the other user devices 1 & 4 (slaves) (within a zone 1 using another time-frequency code), and the piconet controller 1 (master) services user device 5 (slave) (as being outside a zone 3 using yet another time-frequency code). These user devices (slaves) and the piconet controller 1 (master) may be viewed as being another piconet (e.g., piconet 1).

[0082] Alternatively, the communication between the various groups of user devices (slaves) and their respective piconet controller (master) may be governed using different profiles. Each of these profiles may include information corresponding to the time-frequency code employed, the rate of frequency hopping, and/or the PRF that governs the communication of those devices (among other operational parameters). Generally speaking, this embodiment shows how the communication between various devices may not only be implemented differently within different piconets, but also may be implemented differently between various devices within a given piconet.

[0083] FIG. 9 is a diagram illustrating an embodiment of SOPs interference characteristics according to the invention. The interference regions are shown in this diagram for many different ways of implementing SOPs. A spectrum of lowest capacity of a piconet communication system ranging to a highest capacity is shown for various manners in which a

piconet communication system may be operated. At the lowest capacity end of the spectrum, the interference is perfectly correlated. At the highest capacity end of the spectrum, the interference is perfectly orthogonal. In the interim, there is a region of the spectrum where the interference is perfectly de-correlated. This region may be characterized as unstructured interference. Moving towards the highest capacity portion of the spectrum, there is a portion of the spectrum where the interference may then be characterized as structured interference.

[0084] Starting at the low end of capacity, correlated interference may be characterized as interference that looks similar to the desired signal. To accommodate this type of interference, a matched filter (rake) may be implemented to coherently sum the desired signal. However, such a matched filter (rake) also coherently sums the undesired signal as well as the desired signal, and this typically requires more complex receiver processing. No spreading gain is realized in this type of situation. In practice, multipath typically tends to de-correlate interference, though it is not guaranteed.

[0085] Continuing up the spectrum towards the highest capacity end, White-noise-like interference may be characterized as interference that looks like WGN (White Gaussian Noise). A matched filter (rake) may be implemented that coherently sums the desired signal, while the interference is summed incoherently. For this type of interference, spreading gain is in fact realized. There are a variety of techniques in which this may be implemented. For example, different code sets may be implemented for different piconets. Alternatively, long PN (Pseudo-Noise) sequences (or short PN sequences) may be implemented. Time-hopping may alternatively be performed. In addition, baud/chip-rate offsets may be employed as well.

[0086] Within the context of structured interference, fast or slow frequency hopping may be performed. One embodiment of the invention includes employing combined SH-OFDM (Slow Hopping-Orthogonal Frequency Division Multiplexing) that inherently provides a structured type of interference that may be handled very effectively using a receiver with some embedded intelligence to accommodate any undesirable symbol collisions. One of the reasons that this structure type of interference offers benefits over the WGN (White Gaussian Noise) is that this type of structured interference has lower entropy than interference added via AWGN (Additive White Gaussian Noise). This lower entropy may be deduced when analyzing and comparing these types of interferences. One example that may be implemented to achieve this structured interference is frequency hopping (or time-frequency interleaving), with coding across frequencies. The interference level then varies with time and frequency. Well-designed receivers can exceed the nominal spreading gain that may be achieved using prior art receivers. In addition some techniques in which this may be achieved include using reliability metrics in a Viterbi decoder (e.g., a smart receiver having some embedded intelligence). Alternatively, a non-linear limiter may be implemented in a receive path (e.g., in a dumb receiver).

[0087] Moving to the right hand portion of the spectrum, orthogonal interference may be found that is perfectly orthogonal. Examples of means of operating a communication system to achieve this orthogonal interference FDM

(Frequency Division Multiplexing) that does, however, incur a transmit power penalty. In addition, any truly orthogonal code does require synchronization for proper performance. The advantage of such orthogonal codes is that there exists no theoretical limit to the interference distance of interference that is generated by such codes.

[0088] FIG. 10 is a diagram illustrating an embodiment of fast frequency hopping with multipath and interference according to the invention. This embodiment shows various time-frequency codes implemented within various piconets may suffer symbol collisions.

[0089] At the top of the diagram, free space communication of pulses is shown. As can be seen, 1 symbol "collision" will occur per cycle (if the time-frequency codes are synchronized with one another. This solution does provide good immunity to the near-far problem, and a single RF (Radio Frequency) front end may be implemented such that it captures all of the energy of the received pulses.

[0090] In the middle of the diagram, CM1 channels are shown where the interference is smeared over several pulses (and not uniformly). Unfortunately, this implementation presents less immunity to the near-far problem. Also unfortunately, a single RF (Radio Frequency) front end cannot capture all of the energy of received symbols.

[0091] At the bottom of the diagram, CM2 channels are shown where the interference starts to look like WGN (White Gaussian Noise). This interference behaves more similar to that of a wideband system. Therefore, to accommodate such signaling, a wideband front end need be implemented.

[0092] These various types of interference, generated by SOPs show more clearly and how difficult effective receiver processing may be when trying to deal with interference that does not have a predictable and manageable structure. Various aspects of the invention show how structure (and therefore more manageable) interference may be generated by operating various SOPs in a particular manner. For example, when operating these SOPs using SH-OFDM (Slow Hopping-Orthogonal Frequency Division Multiplexing) combined with a reduced PRF (Pulse Repetition Frequency), when compared to prior art piconets, will allow for the intelligent managing symbol collisions.

[0093] The current proposal for Multi-Band OFDM (MB-OFDM), shown as references [1,2] below, for IEEE 802.15.3a suffers from poor performance in the presence of close SOPs (Simultaneously Operating Piconets).

[0094] The Internet URLs for the above references documents are provided here:

[0095] [1] [http://grouper.ieee.org/groups/802/15/pub/2003/Jul03/03267r5P802-15\\_TG3a-Multi-band-OFDM-CFP-Presentation.ppt](http://grouper.ieee.org/groups/802/15/pub/2003/Jul03/03267r5P802-15_TG3a-Multi-band-OFDM-CFP-Presentation.ppt)

[0096] [2] [http://grouper.ieee.org/groups/802/15/pub/2003/Jul03/03268r0P802-15\\_TG3a-Multi-band-CFP-Documents.doc](http://grouper.ieee.org/groups/802/15/pub/2003/Jul03/03268r0P802-15_TG3a-Multi-band-CFP-Documents.doc)

[0097] Theoretically, a Multi-Band (time-hopping) system can achieve much better performance than a wideband (CDMA (Code Division Multiple Access)) system by exploiting the structured nature of the interference, but the

current proposal fails to do this. In fact, it does not achieve even the nominal interference suppression of a wideband CDMA system.

[0098] FIG. 11 is a diagram illustrating an embodiment of SH-OFDM (Slow-Hopping-Orthogonal Frequency Division Multiplexing) according to the invention. Two (2) separate piconets (e.g., a piconet 1 and a piconet 2) each operate using different time-frequency codes, as can be seen where the frequency bands employed are changed as a function of time. During some instances, a common frequency band is employed by both piconets and undesirable symbol collisions may occur. One such effect is that, when a symbol collision occurs, the energy of such a "symbol" (really a symbol-(collision-modified-symbol) will incur a greater amount of energy (or power).

[0099] However, one advantage of operating in such a way is that the interference is actually highly structured. This is true even in the presence of multipath effects within the piconets. There is a drawback, however, in that, unfortunately, for a 3 band system with 1 interferer, a receiver will typically see 2 collisions per 3 symbols. To compensate for this, the piconet may require a very low rate code to work at a high ISR (Interference to Signal Ratio). Moreover, the piconet may not achieve the target rates at the high ISR.

[0100] This diagram illustrates 2 adjacent piconets in a 3-band system, where the two piconets use different time-frequency codes. As shown, this typically results in 2 partial collisions out of every 3 symbols. Unfortunately, although the partial collisions affect only a portion of each hop in the time-domain, they affect all tones in the frequency domain. Thus, in an OFDM system, all bits are affected by a partial collision. In situations where the interferer is much closer than the transmitter of the desired signal, these collisions will be treated as erasures, and 2 out of every 3 coded bits will be erased.

[0101] However, the fact that the interference is highly structure, even in the presence of multipath, does provide for some operational advantages. In accordance with the SH-OFDM, by dwelling longer on each frequency band, symbol collisions may be confined to a single frequency hop. However, dealing with 2 partial collisions out of every 3 symbols can be extremely problematic for many applications.

[0102] FIG. 12 is a diagram illustrating an embodiment of reduced duty cycle SH-OFDM according to the invention. This diagram shows an alternative embodiment where the number of information bits is increased per symbol thereby eliminating the conjugate symmetry; then the symbol rate is reduced. In other words, the power level of each symbol and the number of bits per tone is increased, and the rate at which symbols are sent is decreased (alternatively, the symbol rate may be decreased). As illustrated in this diagram, this reduces the collision rate by a factor of 2, so that at most 1 out of every 3 coded bits will be erased (versus 2 out of 3 in the embodiment described above).

[0103] This reduced duty cycle MB-OFDM (Multi-band Orthogonal Frequency Division Multiplexing) approach described with respect to this diagram was initially introduced in another pending patent application (Attorney Docket No. BP3085, filed Jul. 18, 2003 (Jul. 18, 2003), pending), and later introduced within a proposal made by the inventor [3].

[0104] The Internet URL for the above referenced document is provided here:

[0105] [3] [http://grouper.ieee.org/groups/802/15/pub/2003/Jul03/03273r0P802-15\\_TG3a-Reduced-Duty-Cycle-MB-OFDM.ppt](http://grouper.ieee.org/groups/802/15/pub/2003/Jul03/03273r0P802-15_TG3a-Reduced-Duty-Cycle-MB-OFDM.ppt)

[0106] This diagram shows an alternative embodiment where the number of information bits is increased per symbol thereby eliminating the conjugate symmetry; then, the symbol rate is reduced.

[0107] Again, as with the embodiment shown above, two (2) separate piconets (e.g., a piconet 1 and a piconet 2) each operate using different time-frequency codes, as can be seen where the frequency bands employed are changed as a function of time. During some instances, a common frequency band is employed by both piconets and undesirable symbol collisions may occur. One such effect is that, when a symbol collision occurs, the energy of such a "symbol" (really a symbol-collision-modified-symbol) will incur a greater amount of energy (or power).

[0108] Within such an embodiment, a 3 band system will see at most 1 collision per 3 symbols. This is a large improvement over the 2 collisions per 3 symbols as shown within the above embodiment.

[0109] Some of the advantages of such a system, implemented using well designed codes, include the fact that such a system can reach the target rates even at high ISR (Interference to Signal Ratio). In addition, there is bonus of such a system, in that, reduced power consumption may be supported at the receiver. The receiver can turn off its radio and analog front end during silence periods.

[0110] However, such a system may be viewed as having some disadvantages. For example, some of the disadvantages of such a system may be characterized to include a 3 dB PAR (Peak to Average Power Ratio) limitation. In addition, there is lost diversity on the frequency selective channels, and the implementation of such a system requires 2 separate DACs (Digital to Analog Converters). Moreover, this scheme suffers from 3 perhaps more significant drawbacks.

[0111] 1. It gives up frequency diversity over fading channels, which results in a penalty of about 1 dB (decibels) at 110 Mbps (Mega-bits per second), and more at higher rates.

[0112] 2. It increases the peak transmitted power by 3 dB, which may require a more expensive transmitter.

[0113] 3. Most importantly, it only works if all piconets within the vicinity operate in this mode. Thus, it requires some mechanism to enforce the use of this mode when close SOPs are present.

[0114] While the advantages of such a system nevertheless do provide an advantage over the prior art, an even improved new mode of operates is presented herein that achieves the goals of reduced duty-cycle MB-OFDM but doesn't suffer from the above-described shortcomings.

[0115] A novel proposed solution consists of transmitting a single-carrier signal in place of the OFDM signal and also implementing a piconet operable device to include smart receiver structure functionality that is capable of estimating the interference power per bit and de-weighting the input to

the Viterbi decoder accordingly. This may be viewed as being an additional mode of operation in an MB-OFDM system that may also employ the same hopping pattern and the same RF architecture.

[0116] Referring to FIG. 11, it can be seen that the partial collisions affect only a portion of each signal (e.g., not the entirety of the signal but only a portion). In this proposed mode of operation using the single carrier, the bits are transmitted in the time domain, so that the only bits affected by collisions are those corresponding to the portion of the signal experiencing the collision. This is a fundamental advantage to using the single carrier approach over using an OFDM approach, where the collisions are undesirably spread across all bits in the frequency-domain.

[0117] The proposed solution dramatically improves performance in the presence of close SOPs, without sacrificing frequency diversity, without increasing the peak transmitted power, and without requiring other piconets to use this mode. In addition, it offers a simple low-power transmission mode suitable for applications where the power of the transmitter must be minimized.

[0118] Certain operational characteristics of a transmitter-capable device (e.g., generically a piconet operable device) that is compatible with a receiver-capable device (e.g., again, another generically a piconet operable device) may be described below.

[0119] There are several possible good choices of operational parameters that may be selected for such a system that is built in accordance with the invention. Some of these are described here. The current MB-OFDM proposal uses an IFFT (Inverse Fast Fourier Transform) output sampling rate of 528 MHz. For synergy with the MB-OFDM components, it is easiest to use a symbol rate which is an integer fraction of the IFFT output sampling rate.

[0120] As such, one good choice of parameters would be as follows:

[0121] Symbol Rate=528/3=176 MHz (Mega-Hertz).

[0122] QPSK (Quadrature Phase Shift Key) modulation.

[0123] Rate  $\frac{1}{3}$  convolutional code: G=[117 155 127].

[0124] Data rate=176 MHz\* $\frac{2}{3}$ =117.33 MHz.

[0125] Because this symbol rate is less than  $\frac{1}{2}$  the bandwidth of the transmitted signal, it results in a frequency-diverse signal (as described in another patent having common inventorship as the present patent application). In other words, the same information is transmitted independently in at least 2 frequency bands spaced 176 MHz apart. This spacing is larger than the coherence bandwidth of the channel, so the two spectral regions experience independent fading.

[0126] The interleaver would be designed such that each output from the convolutional encoder is mapped to a different sub-band. This code was chosen such that if any one output stream is punctured, the resulting rate  $\frac{1}{2}$  code is still a strong code.

[0127] Moreover, there are several other useful choices of parameters. For any set of parameters, it is critical to design

the code and the interleaver such that the code remains a strong code in the presence of erasures that any possible collision pattern can cause.

[0128] The following diagram is provided to show one type of a generic wireless communication system embodiment in which aspects of the invention may be found.

[0129] FIG. 13 is a schematic block diagram illustrating a communication system that includes a plurality of base stations and/or access points, a plurality of wireless communication devices and a network hardware component in accordance with certain aspects of the invention. The wireless communication devices may be laptop host computers, PDA (Personal Digital Assistant) hosts, PC (Personal Computer) hosts and/or cellular telephone hosts. The details of any one of these wireless communication devices is described in greater detail with reference to FIG. 14 below.

[0130] The BSs (Base Stations) or APs (Access Points) are operably coupled to the network hardware via the respective LAN (Local Area Network) connections. The network hardware, which may be a router, switch, bridge, modem, system controller, et cetera, provides a WAN (Wide Area Network) connection for the communication system. Each of the BSs or APs has an associated antenna or antenna array to communicate with the wireless communication devices in its area. Typically, the wireless communication devices register with a particular BS or AP to receive services from the communication system. For direct connections (i.e., point-to-point communications), wireless communication devices communicate directly via an allocated channel.

[0131] Typically, BSs are used for cellular telephone systems and like-type systems, while APs are used for in-home or in-building wireless networks. Regardless of the particular type of communication system, each wireless communication device includes a built-in radio and/or is coupled to a radio. The radio includes a highly linear amplifier and/or programmable multi-stage amplifier as disclosed herein to enhance performance, reduce costs, reduce size, and/or enhance broadband applications.

[0132] FIG. 14 is a schematic block diagram illustrating a wireless communication device that includes the host device and an associated radio in accordance with certain aspects of the invention. For cellular telephone hosts, the radio is a built-in component. For PDA (Personal Digital Assistant) hosts, laptop hosts, and/or personal computer hosts, the radio may be built-in or an externally coupled component.

[0133] As illustrated, the host device includes a processing module, memory, radio interface, input interface and output interface. The processing module and memory execute the corresponding instructions that are typically done by the host device. For example, for a cellular telephone host device, the processing module performs the corresponding communication functions in accordance with a particular cellular telephone standard or protocol.

[0134] The radio interface allows data to be received from and sent to the radio. For data received from the radio (e.g., inbound data), the radio interface provides the data to the processing module for further processing and/or routing to the output interface. The output interface provides connectivity to an output display device such as a display, monitor, speakers, et cetera, such that the received data may be displayed or appropriately used. The radio interface also

provides data from the processing module to the radio. The processing module may receive the outbound data from an input device such as a keyboard, keypad, microphone, et cetera, via the input interface or generate the data itself. For data received via the input interface, the processing module may perform a corresponding host function on the data and/or route it to the radio via the radio interface.

[0135] The radio includes a host interface, a digital receiver processing module, an ADC (Analog to Digital Converter), a filtering/gain module, an IF (Intermediate Frequency) mixing down conversion stage, a receiver filter, an LNA (Low Noise Amplifier), a transmitter/receiver switch, a local oscillation module, memory, a digital transmitter processing module, a DAC (Digital to Analog Converter), a filtering/gain module, an IF mixing up conversion stage, a PA (Power Amplifier), a transmitter filter module, and an antenna. The antenna may be a single antenna that is shared by the transmit and the receive paths as regulated by the Tx/Rx (Transmit/Receive) switch, or may include separate antennas for the transmit path and receive path. The antenna implementation will depend on the particular standard to which the wireless communication device is compliant.

[0136] The digital receiver processing module and the digital transmitter processing module, in combination with operational instructions stored in memory, execute digital receiver functions and digital transmitter functions, respectively. The digital receiver functions include, but are not limited to, digital IF (Intermediate Frequency) to baseband conversion, demodulation, constellation de-mapping, decoding, and/or descrambling. The digital transmitter functions include, but are not limited to, scrambling, encoding, constellation mapping, modulation, and/or digital baseband to IF conversion. The digital receiver and transmitter processing modules may be implemented using a shared processing device, individual processing devices, or a plurality of processing devices. Such a processing device may be a microprocessor, micro-controller, DSP (Digital Signal Processor), microcomputer, CPU (Central Processing Unit), FPGA (Field Programmable Gate Array), programmable logic device, state machine, logic circuitry, analog circuitry, digital circuitry, and/or any device that manipulates signals (analog and/or digital) based on operational instructions. The memory may be a single memory device or a plurality of memory devices. Such a memory device may be a ROM (Read Only Memory), RAM (Random Access Memory), volatile memory, non-volatile memory, static memory, dynamic memory, flash memory, and/or any device that stores digital information. It is noted that when either of the digital receiver processing module or the digital transmitter processing module implements one or more of its functions via a state machine, analog circuitry, digital circuitry, and/or logic circuitry, the memory storing the corresponding operational instructions is embedded with the circuitry comprising the state machine, analog circuitry, digital circuitry, and/or logic circuitry.

[0137] In operation, the radio receives outbound data from the host device via the host interface. The host interface routes the outbound data to the digital transmitter processing module, which processes the outbound data in accordance with a particular wireless communication standard (e.g., IEEE 802.11, Bluetooth®, et cetera) to produce digital transmission formatted data. The digital transmission for-

matted data is a digital base-band signal or a digital low IF signal, where the low IF typically will be in the frequency range of one hundred kHz (kilo-Hertz) to a few MHz (Mega-Hertz).

[0138] The DAC converts the digital transmission formatted data from the digital domain to the analog domain. The filtering/gain module filters and/or adjusts the gain of the analog signal prior to providing it to the IF mixing stage. The IF mixing stage converts the analog baseband or low IF signal into an RF signal based on a transmitter local oscillation provided by local oscillation module. The PA amplifies the RF signal to produce outbound RF signal, which is filtered by the transmitter filter module. The antenna transmits the outbound RF signal to a targeted device such as a base station, an access point and/or another wireless communication device.

[0139] The radio also receives an inbound RF signal via the antenna, which was transmitted by a BS, an AP, or another wireless communication device. The antenna provides the inbound RF signal to the receiver filter module via the Tx/Rx switch, where the Rx filter bandpass filters the inbound RF signal. The Rx filter provides the filtered RF signal to the LNA, which amplifies the signal to produce an amplified inbound RF signal. The LNA provides the amplified inbound RF signal to the IF mixing module, which directly converts the amplified inbound RF signal into an inbound low IF signal or baseband signal based on a receiver local oscillation provided by local oscillation module. The down conversion module provides the inbound low IF signal or baseband signal to the filtering/gain module. The filtering/gain module filters and/or gains the inbound low IF signal or the inbound baseband signal to produce a filtered inbound signal.

[0140] The ADC converts the filtered inbound signal from the analog domain to the digital domain to produce digital reception formatted data. In other words, the ADC samples the incoming continuous time signal thereby generating a discrete time signal (e.g., the digital reception formatted data). The digital receiver processing module decodes, descrambles, demaps, and/or demodulates the digital reception formatted data to recapture inbound data in accordance with the particular wireless communication standard being implemented by radio. The host interface provides the recaptured inbound data to the host device via the radio interface.

[0141] As one of average skill in the art will appreciate, the wireless communication device of FIG. 14 may be implemented using one or more integrated circuits. For example, the host device may be implemented on one integrated circuit, the digital receiver processing module, the digital transmitter processing module and memory may be implemented on a second integrated circuit, and the remaining components of the radio, less the antenna, may be implemented on a third integrated circuit. As an alternate example, the radio may be implemented on a single integrated circuit. As yet another example, the processing module of the host device and the digital receiver and transmitter processing modules may be a common processing device implemented on a single integrated circuit. Further, the memories of the host device and the radio may also be implemented on a single integrated circuit and/or on the same integrated circuit as the common processing modules

of processing module of the host device and the digital receiver and transmitter processing module of the radio.

[0142] FIG. 15 is a diagram illustrating an embodiment of a piconet operable device that supports functionality of interference compensation according to the invention.

[0143] This embodiment of a piconet operable device includes an antenna that is operable to communicate with any 1 or more other piconet operable devices within the piconet. An antenna interface communicatively couples a signal to be transmitted from the piconet operable device or a signal received by the piconet operable device to the appropriate path (be it the transmit path or the receive path).

[0144] A radio front end includes receiver functionality and transmitter functionality. The radio front end communicatively couples to an analog/digital conversion functional block. The radio front end communicatively couples to a modulator/demodulator, and the radio front end communicatively couples to a channel encoder/decoder.

[0145] Along the Receive Path:

[0146] The receiver functionality of the front end includes a LNA (Low Noise Amplifier)/filter. The filtering performed in this receiver functionality may be viewed as the filtering that is limiting to the performance of the device, as also described above. The receiver functionality of the front end performs any down-converting that may be requiring (which may alternatively include down-converting directing from the received signal to a baseband signal). This front end may be viewed as receiving a continuous time signal, and performing appropriate filtering and any down conversion necessary to generate the baseband signal. Whichever manner of down conversion is employed, a baseband signal is output from the receiver functionality of the front end and provided to an ADC (Analog to Digital Converter) that samples the baseband signal (which is also a continuous time signal, though at the baseband frequency) and generates a discrete time signal baseband signal (e.g., a digital format of the baseband signal); the ADC also outputs the digital I, Q (In-phase, Quadrature) components of the discrete time signal baseband signal.

[0147] These I, Q components are provided to a demodulator portion of the modulator/demodulator where any modulation decoding/symbol mapping is performed where the I, Q components of the discrete time signal baseband signal. The appropriate I, Q components are then mapped to an appropriate modulation (that includes a constellation and corresponding mapping). Examples of such modulations may include BPSK (Binary Phase Shift Key), QPSK (Quadrature Phase Shift Key), 8 PSK (8 Phase Shift Key), 16 QAM (16 Quadrature Amplitude Modulation), and even higher order modulation types. In this demodulator portion of the modulator/demodulator, embedded intelligence is included to support the functionality of the interference compensation described within other of the various embodiments. For example, this may include selectively de-weighting those symbols that have undergone a symbol collision. This interference compensation may be performed by capitalizing in the inherent properties of the structured interference supported by operating the piconet in a manner according to the invention. This may also involve treating certain interference affected bits as erasures and appropriately de-weighting other interference affected bits. These selectively

modified symbols are then provided to a decoder portion of the channel encoder/decoder where best estimates of the information bits contained within the received symbols are made.

**[0148]** Along the Transmit Path:

**[0149]** Somewhat analogous and opposite processing is performed in the transmit path when compared to the receive path. Information bits that are to be transmitted are encoded using an encoder of the channel encoder/decoder. These encoded bits are provided to a modulator of the modulator/demodulator where modulation encoding/symbol mapping may be performed according to the modulation of interest. These now I, Q components of the symbols are then passed to a DAC (Digital to Analog Converter) of the analog/digital conversion functional block to transform the I, Q components into a continuous time transmit signal (e.g., an analog signal). The now continuous time transmit signal to be transmitted is then passed to a transmit driver that performs any necessary up-converting/modification to the analog signal (e.g., amplification and/or filtering) to comport it to the communication channel over which the signal is to be transmitted to another piconet operable device via the antenna.

**[0150]** FIG. 16 is a diagram illustrating an embodiment of smart receiver structure functionality that is built according to the invention. This diagram describes a structure of a smart receiver that may effectuate many of the various aspects of the invention. It is noted that this smart receiver structure functionality may be found within any piconet operable device described herein including various transceivers and receivers.

**[0151]** The front end portion of the smart receiver structure functionality receives an input that is a continuous time signal. This received smart receiver structure functionality performs the appropriate mixing using a frequency hopping mixer that uses the same frequency hopping approach used to generate the signal at the transmit end of the communication channel. For example, this may be a reduced duty cycle SH-OFDM approach as described above on an alternative embodiment. This appropriately mixed version of the received continuous time signal is provided to an ADC (Analog to Digital Converter) that samples the received continuous time signal thereby generating a discrete time signal. The ADC may also be implemented to extract the I, Q components of the discrete time signal as well. These I, Q components of the discrete time signal are provided to a demodulator. The demodulator may be implemented using various digital signal processing techniques. The demodulator employs the appropriate functionality to perform selective de-weighting based on the location and magnitude of the level (e.g., magnitude) of interference that the received signal may have experienced when being transmitted from a transmitting piconet operable device to a receiving piconet operable device including this smart receiver structure functionality.

**[0152]** The demodulator also includes functionality to support a fractionally-spaced linear equalizer that is operable to sum over the various spectral regions of a frequency-diverse signal that may have been transmitted from a transmitting piconet operable device. The demodulator also includes various functionality to perform the appropriate estimation and location of the level (e.g., magnitude) of

collisions that may have occurred to the received signal. In other words, the smart receiver structure functionality is operable to characterize the level of the interference so that different types of interference may be dealt with differently and appropriately.

**[0153]** This diagram shows a very general, simplified example of the smart receiver structure functionality that is capable to support various aspects of the invention. This diagram illustrates how the input to the Viterbi decoder is de-weighted based on the estimated interference level. For very high-level interference (e.g., a first level of interference), it is sufficient to treat the affected bits as erasures, but for medium-level interference (e.g., a second level of interference), it is better to de-weight the input to the Viterbi decoder based on the magnitude of the interference.

**[0154]** Specifically, for optimal decoding, the LLR (log-likelihood ratio) input to the Viterbi decoder is de-weighted by multiplying the LLR by the inverse of the square of the RMS (Root Mean Square) interference level. In this illustrated embodiment, the interference level is estimated at the receiver by measuring the total instantaneous signal power, averaging the signal power, and subtracting the expected reference signal power based on the previously-obtained channel estimate or reference signal power measurement. This is shown as being all performed within the demodulator. There are many possible variations on the approach to estimate the interference power level. For one example, instead of using the average signal power that is determined directly, an alternatively embodiment of the smart receiver structure functionality may exploit predetermined knowledge of the inherent structure of the interference (in the SOPs (Simultaneously Operating Piconets) context). For another example, the smart receiver structure functionality could estimate the starting and ending points of the interference and adjust the de-weighting factor accordingly.

**[0155]** In addition, there are several possible equalizer structures that may be implemented in accordance with the invention (e.g., besides the fractionally-spaced linear equalizer that is illustrated). For frequency-diverse modes of operation (e.g. a transmitted signal including the same information transmitted independently over more than one frequency band), a good choice is a fractionally-spaced linear equalizer. A fractionally-spaced equalizer can optimally sum the various spectral regions of the frequency-diverse signal to allow the appropriate subsequent processing thereof.

**[0156]** FIG. 17A is a diagram illustrating an embodiment of functionality of a smart receiver according to the invention. It is noted that this functionality of a smart receiver may be included within any type of piconet operable device that can perform receiver processing including receiver and transceiver type devices. This diagram illustrates generally how an input signal undergoes interference estimation and based on that interference estimate, the input signal may be modified accordingly. For example, the interference may be categorized into at least 2 different types based on the level of the interference (or 3 different types if one considers that little or no interference is a 3<sup>rd</sup> category).

**[0157]** The input to the decoder is selectively de-weighted based on the level of the estimated interference. For a very high-level of interference (e.g., a first level of interference), it is sufficient to treat the affected bits as erasures. However,

for a medium-level of interference (e.g., a second level of interference), it is better to de-weight the input to the decoder based on the magnitude of the interference.

[0158] In addition, if one considers that little or no interference is a 3<sup>rd</sup> category (e.g., a third level of interference or no interference), then for little or no interference, no de-weighting would be performed on the input to the decoder.

[0159] FIG. 17B is a diagram illustrating an embodiment of functionality of interference compensation capitalizing on structured interference according to the invention. This capitalizing may be viewed as being a manner in which receiver processing may be employed is performed in such a way as to operate in an intelligent manner using the intrinsic characteristics and nature of the structured type of interference that may be existent in the received signal. This may be viewed as being performed in such a way that a demodulator, within a communication device, selectively performs interference compensation of a symbol by selectively de-weighting the symbol based on structured interference existent therein. This selective de-weighting of the symbol may include performing no de-weighting in some instances while performing some de-weighting in other instances.

[0160] In this embodiment, one or more symbols are received by this functionality. A symbol energy detection functional block is operable to perform detection of the energy of received symbols.

[0161] After the symbol energy detection functional block performs the detection of the energy of a received symbol, an energy comparison functional block is operable to perform comparison of the detected energy to a predetermined energy. This predetermined energy may be viewed as an expected energy at which the received symbols should be at or is expected to be at.

[0162] When a difference between the detected energy of the symbol exceeds a threshold (that may be programmable or adaptively determined in real time in response to operating conditions or some other inputs), then this interference compensation functionality includes a functional block that is operable to perform selective weighting (as necessary) of symbols (or the individual bits of those symbols). This may be performed based on the difference between the detected energy and the predetermined energy. For example, when the energy is greater than the predetermined energy by a particular threshold, then that may be used to indicate a high likelihood of a symbol collision, and that symbol may be de-weighted before performing decoding processing of the symbol (e.g., in a decoder—one embodiment of which is a Viterbi decoder).

[0163] After the functionality of this diagram has been performed, then the selectively modified symbol(s) and/or bits of those symbols are provided to a decoder for making best estimates of the information bits contained therein. By selective modification, it is noted that some of the symbols (or some of the bits) may not undergo any de-weighting, but rather be passed to the decoder without any modification at all. However, in the presence of some interference, de-weighting may be performed to the symbol or the individual bits of those symbols.

[0164] FIG. 18 is a diagram illustrating an embodiment of a 3<sup>rd</sup> order elliptical LPF (Low Pass Filter) employed at a

transmitter and a receiver (or a transceiver) according to the invention. Above, it is noted that the performance of a piconet operating according to the invention will typically be limited only by the out of band roll off and front end range (e.g., the radio front end and the filtering performed therein) of a device operating within such a piconet. That is to say, the filter shape largely determines the degree of interference rejection. Higher-order filters could substantially increase the ISR range of such a system.

[0165] The LPF shown in this diagram was employed. It is however noted that even better filters that may be designed can be implemented to provide for even better performance.

[0166] FIG. 19 is a diagram illustrating another embodiment of a piconet operable device that supports functionality of interference compensation capitalizing on structured interference (showing PHY (physical layer), MAC (Medium Access Controller), and higher protocol layers) according to the invention. A piconet operable device is included within a piconet. This piconet operable device includes a PHY (physical layer) that communicatively couples to a MAC (Medium Access Controller). The MACs of the devices may also communicatively couple to 1 or more even higher application layers within the piconet operable device. The MAC and the higher application layers may be viewed as being the higher protocol layers (e.g., above the PHY) within the respective piconet operable device. The PHY is operable to support a physical interconnection link to 1 or more other devices within a piconet.

[0167] When compared to a prior art MAC, the MAC of the piconet operable device may be viewed as being a modified protocol layer, in that, the MAC includes functionality to perform interference compensation based on the estimation of the location and level of the interference of the received signal. In an alternative embodiment, the MAC of the piconet operable device may be viewed as being a modified protocol layer, in that, the MAC may include functionality to perform interference compensation that capitalizes on the properties of the structured interference that may result from symbol collisions when operating using the combination of SH-OFDM and reduced PRF (Pulse Repetition Frequency) when compared to prior art piconet systems.

[0168] This interference compensation functionality is operable to perform symbol energy detection of symbols extracted from a signal received by the piconet operable device. After performing the detection of the energy of a received symbol, the detected energy is compared to a predetermined energy and/or estimated energy. When a difference between the detected of the symbol exceeds a threshold (that may be programmable or adaptively determined), then this interference compensation functionality may then perform selective de-weighting of symbol. In one example, when the detected energy of the symbol exceeds a predetermined threshold (e.g., when the detected energy of the symbol is greater than the predetermined energy by the threshold) then the symbol is appropriately de-weighted before being passed to a decoder for decoding processing. In another example, when the interference level is relatively much higher than the threshold, then the interference affected bits may be treated as erasures.

[0169] FIG. 20, FIG. 21, FIG. 22, and FIG. 23 are flowcharts illustrating various embodiments of methods for receive processing in a piconet operable device according to the invention.

[0170] Referring to the FIG. 20, the method involves receiving a signal that has been transmitted using a single carrier (e.g., single carrier frequency). Then, the method involves detecting an energy (or a power) of 1 or more symbol(s) within signal. Then, the method involves comparing the energy (or the power) of 1 or more symbol(s) to a predetermined (or an expected) energy (or power).

[0171] Then, a decision is made. It is then determined whether the energy (or the power) of the 1 or more symbol(s) is greater than the predetermined (or the expected) energy (or power). A threshold may be used to make this comparison, and the threshold may be programmable or adaptive (e.g., based on operating conditions or some other operational parameter).

[0172] If the energy (or the power) of the 1 or more symbol(s) is greater than the predetermined (or the expected) energy (or power), then this is indicative of a likely symbol collision. The symbol's energy (or power) is appropriately de-weighted, and that de-weighted symbol is then provided to a decoder for decoder processing. However, if the energy (or the power) of the 1 or more symbol(s) is not greater than the predetermined (or the expected) energy (or power), then the method involves providing the symbol(s) to decoder for decoder processing.

[0173] This providing of the either the de-weighted symbols or the unmodified symbols to the decoder for decoder processing may be viewed as being providing selectively weighted symbol(s) to decoder. That is to say, some of the symbols are de-weighted and some are not (hence, the term selectively de-weighted symbols). The method then involves decoding the de-weighted symbol or the unmodified symbol to make best estimates of at least one information bit contained within the originally received symbol.

[0174] Referring to the FIG. 21, the method involves receiving a signal that has been transmitted using a single carrier and performing pre-processing thereon. The method then involves detecting collisions within that received and pre-processed signal. When no collision is detected in the received and pre-processed signal, then the received and pre-processed signal is provided to a decoder to perform decoding to make best estimates of at least one information bit contained therein.

[0175] However, when a collision is detected in the received and pre-processed signal, then the method involves estimating a location and a level (e.g., magnitude) of those one or more collisions. This may involve also estimating the interference power per bit of the symbols that have been extracted from that signal during pre-processing. The method then involves categorizing the level of interference associated with collisions. This categorization may be viewed as being into a first level of interference (very high-level interference) and a second level of interference (medium-level interference).

[0176] The method then involves de-weighting the input to decoder based on level of that categorized interference. Two different de-weighting factors may be employed based on the level of interference that has been detected and

categorized. For example, when the difference between the energy of the symbol and the predetermined energy level exceeds a first threshold, then the method may involve selectively de-weighting the symbol according to a first de-weighting factor and providing the de-weighted symbol to a decoder for subsequent decoding. When the difference between the energy of the symbol and the predetermined energy level exceeds a second threshold, then the method may involve selectively de-weighting the symbol according to a second de-weighting factor and providing the de-weighted symbol (according to this different de-weighting factor) to the decoder for subsequent decoding. When the difference between the energy of the symbol and the predetermined energy level does not exceed any threshold, the method may simply involve providing the symbol to the decoder. Moreover, the method may specifically treat these various degrees of interference independently. For example, for the first level of interference (very high-level interference), the method involves treating the affected bits as erasures. For the second level of interference (medium-level interference), the method involves de-weighting input to decoder based on the level (e.g., magnitude) of that interference. It is note that for the second level of interference (medium-level interference), the degree of de-weighting is performance based on the relative degree of that interference (e.g., based on the estimate of the interference). But when the level of interference exceeds a relatively high threshold (which may be selected by a user) such as the first level of interference (very high-level interference), those affected bits are simply treated as erasures and not appropriately de-weighted.

[0177] Referring to the FIG. 22, the method involves receiving a first continuous time signal that has been transmitted using a single carrier. The method then involves frequency hopping mixing the first continuous time signal thereby generating a second continuous time signal. This is performed in accordance with the manner in which a transmitted signal was frequency hopping mixed at a transmit end of a communication channel. The method then involves sampling the second continuous time signal (e.g., using an ADC) thereby generating a discrete time signal and extracting I, Q (In-phase, Quadrature) components there from. The method then involves demodulating the I, Q components and performing symbol mapping of the I, Q components thereby generating a sequence of discrete-valued modulation symbols. The method then involves detecting and estimating the location and the level (e.g., magnitude) of interference associated with collisions. The method then involves treating bits affected by very high-level interference as erasures. The method then involves selectively de-weighting bits affected by medium-level interference based on level (e.g., magnitude) of interference. The method then involves de-interleaving de-weighted LLR. The method then involves decoding the appropriately de-interleaving de-weighted LLR thereby making best estimates of information bits contained therein.

[0178] Referring to the FIG. 23, the method involves receiving a first continuous time signal that has been transmitted using a single carrier. The method then involves frequency hopping mixing the first continuous time signal thereby generating a second continuous time signal. The method then involves sampling the second continuous time signal (e.g., using an ADC) thereby generating a discrete time signal and extracting I, Q (In-phase, Quadrature) com-

ponents there from. The method then involves demodulating the I, Q components and performing symbol mapping of the I, Q components thereby generating a sequence of discrete-valued modulation symbols. The method then involves calculating LLR (Log Likelihood Ratio) of symbols of sequence of discrete-valued modulation symbols. The method then involves de-weighting LLR by multiplying the LLR by inverse of square of the RMS (Root Mean Square) of level (e.g., magnitude) of interference. The method then involves de-interleaving de-weighted LLR. The method then involves decoding appropriately de-interleaving de-weighted LLR thereby making best estimates of information bits contained therein.

[0179] As mentioned above, there are many possible variations on approached and methods to estimate the interference power level. Some of these possible approaches are illustrated in the following diagrams and described below.

[0180] FIG. 24A, FIG. 24B, and FIG. 24C are flowcharts illustrating various embodiments of methods for estimating a level (e.g., magnitude) of interference of a signal for use in performing interference compensation according to the invention.

[0181] Referring to the FIG. 24A, the method involves measuring total instantaneous power. The method then involves averaging signal power. The method then involves subtracting expected signal power (based on previously-obtained channel estimate or reference signal power measurement) from the average signal power thereby generating de-weighting factor that is used in performing interference compensation.

[0182] Referring to the FIG. 24B, the method involves estimating starting and ending points of interference. The method then involves adjusting the de-weighting factor based on duration and magnitude of interference. This is a relatively easier approach to estimating a level of interference of a signal for use in performing interference compensation compared to the approach described just above.,

[0183] Referring to the FIG. 24C, the method is a one step method approach that involves estimating the level (e.g., magnitude) of interference based on prior knowledge of structured nature of the interference itself. As described above in various embodiments, the manner in which the various SOPs (Simultaneously Operating Piconets) operate using frequency hopping approaches, the manner and type of interference they may experience can exhibit a "structured" type nature. Knowledge of this can be used to estimate the level and location of the interference within a signal received by a piconet operable device.

[0184] This is a completely straight-forward approach to estimating a level of interference of a signal for use in performing interference compensation.

[0185] It is also noted that various methods may be performed, in accordance with the invention, in a manner similar to the operation and functionality of the various system and/or apparatus embodiments described above. In addition, such methods may be viewed as being performed within any of the appropriate system and/or apparatus embodiments (communication systems, communication transmitters, communication receivers, communication transceivers, and/or functionality described therein) that are described above without departing from the scope and spirit of the invention.

[0186] The proposed systems and methods provide for a much improved performance when compared to any of the current proposals in the context of SOPs within relatively close proximity with one another. For example, in a 3-band system with 2 SOPs using different hopping sequences, one out of every three bits may be erased. In a 7-band system with 4 SOPs, three out of seven bits may be erased. It is critical to choose codes and interleavers such that after collisions, the surviving bits still employ a strong code. These effects are described in greater detail within the reference [3] mentioned above.

[0187] When compared to the prior art approaches to deal with interference generated by SOPs within relatively close proximity with one another, the proposed system dramatically improves performance in the presence of close SOPs, without sacrificing frequency diversity, without increasing the peak transmitted power, and without requiring other piconets to use this mode. In addition, it offers a simple low-power transmission mode suitable for applications where the power of the transmitter must be minimized.

[0188] In view of the above detailed description of the invention and associated drawings, other modifications and variations will now become apparent. It should also be apparent that such other modifications and variations may be effected without departing from the spirit and scope of the invention.

What is claimed is:

1. A method for operating a piconet operable device, the method comprising:

receiving a signal that includes a symbol;

detecting an energy of the symbol;

comparing the energy of the symbol to a predetermined energy or to an estimated energy;

determining whether a difference between the energy of the symbol and the predetermined energy exceeds at least one threshold from among a plurality of thresholds or whether a difference between the energy of the symbol and the estimated energy exceeds at least one threshold from among a plurality of thresholds;

when the difference exceeds a first threshold of the plurality of thresholds and no other threshold of the plurality of thresholds, selectively de-weighting the symbol according to a first de-weighting factor and providing the de-weighted symbol to a decoder;

when the difference exceeds the first threshold and a second threshold of the plurality of thresholds and no other threshold of the plurality of thresholds, selectively de-weighting the symbol according to a second de-weighting factor and providing the de-weighted symbol to a decoder; and

when the difference does not exceed any threshold of the plurality of thresholds, providing the symbol to the decoder.

2. The method of claim 1, further comprising:

when the difference exceeds the each threshold of the plurality of thresholds, treating interference affected bits of the symbol as erasures.

3. The method of claim 1, wherein:  
 the piconet operable device is a first piconet operable device that operates within a first piconet that substantially occupies a first region;  
 a second piconet operable device operates within a second piconet that substantially occupies a second region; and  
 the first region and the second region occupy at least a portion of common space.
4. The method of claim 3, wherein:  
 the symbol is a first symbol that collides with a second symbol that is received by the second piconet operable device before being received.
5. The method of claim 3., wherein:  
 collisions between symbols within the first piconet and symbols within the second piconet occur according to a structured interference pattern.
6. The method of claim 5, wherein the structured interference pattern is a predetermined structured interference pattern; and further comprising:  
 at least one threshold from among the plurality of thresholds based on the predetermined structured interference pattern.
7. The method of claim 1, further comprising:  
 estimating at least one of a location and a level of interference of the symbol using the detected energy of the symbol.
8. The method of claim 1, further comprising:  
 when the difference exceeds the first threshold of the plurality of thresholds and no other threshold of the plurality of thresholds, selectively de-weighting the symbol according to a first de-weighting factor and de-interleaving the de-weighted symbol before providing the de-weighted symbol to the decoder.
9. The method of claim 1, further comprising:  
 when the difference exceeds the first threshold and the second threshold of the plurality of thresholds and no other threshold of the plurality of thresholds, selectively de-weighting the symbol according to the second de-weighting factor and de-interleaving the de-weighted symbol before providing the de-weighted symbol to the decoder.
10. The method of claim 1, further comprising:  
 when the difference does not exceed any threshold of the plurality of thresholds, de-interleaving the symbol before providing the symbol to the decoder.
11. A piconet operable device, the device comprising:  
 a radio front end that receives and filters a continuous time signal;  
 an ADC (Analog to Digital Converter) that samples the received and filtered continuous time signal thereby generating a discrete time signal and extracting I, Q (In-phase, Quadrature) components there from;  
 a demodulator that receives the I, Q components and performs symbol mapping of the I, Q components thereby generating a sequence of discrete-valued modulation symbols;  
 wherein the demodulator estimates at least one of a location and a level of interference associated with a collision within a symbol of the sequence of discrete-valued modulation symbols;  
 wherein the demodulator categorizes the level of the interference into at least two categories;  
 when the level of the interference is categorized into a first category of the at least two categorizes, the demodulator treats interference affected bits of the symbol as erasures thereby generating a first demodulator output symbol;  
 when the level of the interference is categorized into a second category of the at least two categorizes, the demodulator selectively de-weights interference affected bits of the symbol according to a de-weighting factor thereby generating a second demodulator output symbol; and  
 a decoder that decodes the first demodulator output symbol or the second demodulator output symbol to make best estimates of the at least one information bit contained therein.
12. The device of claim 1, wherein:  
 the demodulator estimates interference associated with the collision within the symbol on a power per bit basis.
13. The device of claim 11, wherein:  
 the location of interference associated with the collision within the symbol is used to identify the interference affected bits of the symbol.
14. The device of claim 11, wherein:  
 demodulator is implemented as a baseband processor/MAC (Medium Access Controller) within the piconet operable device.
15. The device of claim 11, wherein:  
 the piconet operable device is a first piconet operable device that operates within a first piconet that substantially occupies a first region;  
 a second piconet operable device operates within a second piconet that substantially occupies a second region; and  
 the first region and the second region occupy at least a portion of common space.
16. The device of claim 15, wherein:  
 the symbol is a first symbol that collides with a second symbol that is received by the second piconet operable device before being received.
17. The device of claim 15, wherein:  
 collisions between symbols within the first piconet and symbols within the second piconet occur according to a structured interference pattern.
18. The device of claim 17, wherein:  
 the structured interference pattern is a predetermined structured interference pattern; and  
 the demodulator estimates at least one of the location and the level of interference associated with the collision within the symbol based on the predetermined structured interference pattern.

**19.** The device of claim 11, wherein:

the demodulator estimates the level of interference associated with the collision within the symbol by measuring a total instantaneous power of the continuous time signal associated with the symbol, averaging a power of the continuous time signal associated with the symbol, and subtracting an expected reference signal power associated with the symbol from a previously obtained channel estimate or power measurement of the continuous time signal associated with the symbol.

**20.** The device of claim 11, wherein:

when the level of the interference is categorized into a third category of the at least two categorizes, the decoder directly decodes the symbol to make best estimates of the at least one information bit contained therein.

**21.** A piconet operable device, the device comprising:

a radio front end that receives and filters a first continuous time signal that has been transmitted using a single carrier frequency;

a frequency hopping mixer that mixes the first continuous time signal thereby generating a second continuous time signal;

a LPF (Low Pass Filter) that filters the second continuous time signal;

an ADC (Analog to Digital Converter) that samples the filtered, second continuous time signal thereby generating a discrete time signal and extracting I, Q (In-phase, Quadrature) components there from;

a demodulator that receives the I, Q components and performs symbol mapping of the I, Q components thereby generating a sequence of discrete-valued modulation symbols;

wherein the demodulator determines an average total signal power of a symbol of the sequence of discrete-valued modulation symbols;

wherein the demodulator subtracts a reference signal power estimate from the average total signal power of the symbol to generate a de-weighting factor;

the demodulator selectively de-weights interference affected bits of the symbol according to the de-weighting factor thereby generating a demodulator output symbol; and

a decoder that decodes the demodulator output symbol to make best estimates of the at least one information bit contained therein.

**22.** The device of claim 21, wherein:

the demodulator estimates at least one of a location and a level of interference associated with a collision within the symbol of the sequence of discrete-valued modulation symbols;

the demodulator categories the level of the interference into at least two categorizes;

when the level of the interference is categorized into a first category of the at least two categorizes, the demodulator treats interference affected bits of the symbol as erasures thereby generating a first demodulator output symbol; and

when the level of the interference is categorized into a second category of the at least two categorizes.

**23.** The device of claim 22, wherein:

when the level of the interference is categorized into a third category of the at least two categorizes, the decoder directly decodes the symbol to make best estimates of the at least one information bit contained therein.

**24.** The device of claim 22, wherein:

the demodulator estimates interference associated with the collision within the symbol on a power per bit basis.

**25.** The device of claim 22, wherein:

the location of interference associated with the collision within the symbol is used to identify the interference affected bits of the symbol.

**26.** The device of claim 21, wherein:

the piconet operable device is a first piconet operable device that operates within a first piconet that substantially occupies a first region;

a second piconet operable device operates within a second piconet that substantially occupies a second region; and

the first region and the second region occupy at least a portion of common space.

**27.** The device of claim 26, wherein:

the symbol is a first symbol that collides with a second symbol that is received by the second piconet operable device before being received.

**28.** The device of claim 26, wherein:

collisions between symbols within the first piconet and symbols within the second piconet occur according to a structured interference pattern.

**29.** The device of claim 28, wherein:

the structured interference pattern is a predetermined structured interference pattern; and

the demodulator estimates at least one of a location and a level of interference associated with a collision within the symbol of the sequence of discrete-valued modulation symbols based on the predetermined structured interference pattern.

**30.** The device of claim 21, further comprising:

an interleaver that interleaves the demodulator output symbol before the decoder decodes the demodulator output symbol to make best estimates of the at least one information bit contained therein.

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FORM 26  
THE PATENTS ACT, 1970  
(39 of 1970)

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The Patent Rules, 2003

FORM OF AUTHORISATION OF A PATENT AGENT/OR ANY PERSON IN A MATTER OR  
PROCEEDING UNDER THE ACT

[See sections 127 and 132 and rule 135]

We, **SANKALP REHABILITATION TRUST**, having its office at, SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002; hereby authorize Rajeshwari H., Gopalan Deepak Srinivas, Sweety Sharma and Pragya Singh Thakur, all Indian citizens, Advocates / Patent Agents of **RAJESHWARI & ASSOCIATES, AMSOFT BUSINESS CENTRE, UNITECH TRADE CENTRE, Sector 43, Gurgaon- 122 002, Haryana, India**, jointly or severally to act on our behalf for filing an opposition and/or representation by the way of opposition against an invention entitled: **"PHARMACEUTICAL COMPOSITIONS" Indian Patent No. 303371 (having Indian Application No: 637/KOLNP/2013 filed on 07<sup>th</sup> March, 2013)** by **VIIV HEALTHCARE COMPANY** is a National Phase of PCT Application No. PCT/US2011/051713 dated 15.09.2011 under the above mentioned Act and in all matters and proceedings relating to the patent applications before the Controller of Patents or the Government of India in connection therewith or incidental thereto and in general to do all acts or things including filing of representation, statements, replies, extensions, fees, evidence and any or all documents or pleadings, attending hearings and appointment of a substitute or substitutes as the said Agent(s) may deem necessary or expedient and request that all notices, requisitions and communication relating thereto may be sent to such Agent(s) at Rajeshwari & Associates, India.

We hereby revoke all previous authorization, if any made, in respect of same matter or proceeding.

We hereby assent to the action already taken by the said person in the above matter.

Dated this 22<sup>nd</sup> day of November, 2019

For SANKALP Rehabilitation Trust

  
R. TELLIS

(Director)  
Signature:



To  
The Controller of Patents  
The Patent Office, Kolkata