HAND DELIVERY

30 September 2014

To
The Controller of Patents
The Patent Office
Boudhik Sampada Bhavan
Plot No. 32, Sector – 14
Dwarka
New Delhi – 110075

Dear Sir,

Sub: Representation by way of opposition by Nai Umang Positive Welfare Society against the Indian Patent Application 5576/DELNP/2008 Titled, "Methods for improving the pharmacokinetics of HIV integrase inhibitors", filed on June 26, 2008 by Gilead Sciences Inc and Japan Tobacco Inc.

Under instruction from our client, Nai Umang Positive Welfare Society, I state as under.

With reference to the publication of Application No. 5576/DELNP/2008 on June 26, 2008, we understand that the said application has not, as yet, been granted a patent.

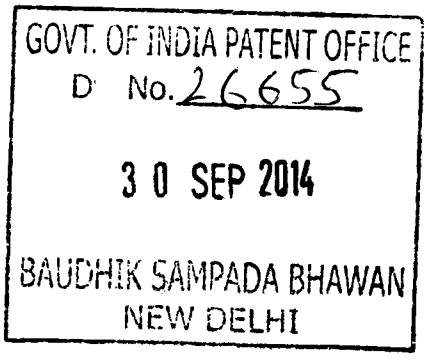
In accordance with section 25(1) of the Patents Act, 1970 (as amended by the Patents (Amendment) Act 2005) and Rule 55(1) of the Patents Rules 2005, please find enclosed a representation by way of opposition against the above application by Nai Umang Positive Welfare Society, supporting Annexures A to Q in two volumes, and Form 26.

Under section 25(1) of the Patents Act, 1970 and Rule 55(1) f the Patents Rules, 2003, the Opponent requests an opportunity to be heard in the above matter and to be kept informed of any reply to the said representation by the Patent Applicant.

Please note that all future correspondence in relation to this opposition should be addressed to **63/2, First Floor, Masjid Road, Jangpura, New Delhi 110014.**

Yours faithfully

Geetanjali Sharma
Advocate
For and behalf of
Nai Umang Positive Welfare Society



Encls:

(i) Representation by way of opposition and Annexures A to Q
(ii) Form 26

Before the Controller of Patents, New Delhi

In the matter of section 25(1) of the Patents Act, 1970;
AND
In the matter of the Patents Rules, 2003
AND
In the matter of Patent Application No. 5576/DELNP/2008 filed by Gilead Sciences Inc and Japan Tobacco Inc. filed on June 26, 2008 titled "Methods for improving the pharmacokinetics of HIV integrase inhibitors"
AND
In the matter of representation by way of opposition by Nai Umang Positive Welfare Society (Opponent)

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4.	**Exhibit C**- WO 2005/112930 titled 'Combinations Comprising A 4- Isoquinolone Derivative and Anti- HIV Agents' published on December 1, 2005	299-398
5.	**Exhibit D**- WO 2005/113508, titled 'Stable Crystal of 4-Oxoquinoline Compound', published on 01.12.2005	399-475
6.	**Exhibit E**- WO 2004/067531, hereinafter WO '531 Application, titled 'HIV-Integrase Inhibitors, Pharmaceutical Compositions, And Methods For Their Use', published on August 12, 2004	476-532
7.	**Exhibit F**- Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients, Robert K. Zeldin *et al,* Journal of Antimicrobial Chemotherapy (2004) 53, 4–9, first published online on December 4, 2003	533-545
8.	**Exhibit G**- "HIV resistance and the effectiveness of combination antiretroviral treatment" by Mugavero *et al* published in December 2004 in Drug Discovery today: Therapeutic Strategies Vol 1, Issue 4, 2004	546-552
9.	**Exhibit H**- "New antiretrovirals: What is on the way?" Robin Wood, published in May 2005 Vol.23 No.5 CME	553-555
10.	**Exhibit I**- "Obstacles to successful antiretroviral treatment of HIV-1 infection; problems & perspectives" Potter *et al* published in Indian J Med Res 119, June 2004, pp 217-237 in June 2004	556-576
11.	**Exhibit J**- "Initial Therapy for Human Immunodeficiency Virus: Broadening the Options" Michael Sension, HIV Clin Trials 2004;5(2):99-111 published in March-April 2004	577-589
12.	**Exhibit K**- WO 2004/101512, titled, 'Naphthyridine Integrase Inhibitors', published on November 25, 2004	590-743

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सत्यमेव जयते

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[redacted]

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FORM 26

THE PATENTS ACT, 1970
&
THE PATENTS RULES, 2003
(sections 127 and 132; rule 135)

1. I, Pradeep Dutta, Indian Inhabitant, President and authorised signatory of Nai Umang Positive Welfare Society having its office at H. No:- 17/353 Than Singh Nagar, Gali No. 2, —Anand Parbat, New Delhi-110005,

Dutta

Statutory Alert:
1. The authenticity of this Stamp Certificate should be verified at "www.shcilestamp.com". Any discrepancy in the details on this Certificate and as available on the website renders it invalid.
2. The onus of checking the legitimacy is on the users of the certificate.
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India, hereby authorise Advocate Geetanjali Sharma, Advocate Apurba Kundu, Advocate Viveka Truman, having their office at First Floor, 63/2 Masjid Road, Jangpura, New Delhi 110 014, to act on our behalf in connection with the pre-grant opposition under section 25(1) by Nai Umang Positive Welfare Society against Application No. 5576/DELNP/2008 titled "Methods for improving the pharmacokinetics of HIV integrase inhibitors" filed on 26th June, 2014 at 14:58:41 at the Delhi Office of the Patent Controller and request that all notices, requisitions and communication relating thereto may be sent to such persons at the above address unless otherwise specified.

2. I hereby revoke all previous authorisations, if any made, in respect of the same matter or proceeding.

3. I hereby assent to the action already taken by the said person in the above matter.

Dated this the 29th day of September, 2014 30 SEP 2014.

Pradeep Dutta
President & Authorised Signatory
Nai Umang Positive Welfare Society

To,
The Controller of Patents,
The Patent Office,
Intellectual Property Office Building,
Plot No. 32, Sector 14,
Dwarka, New Delhi 110075

NOTARY Neelam Sharma

ATTESTED
PUBLIC
COURTS
30 SEP 2014

Before the Controller of Patents, New Delhi

In the matter of section 25(1) of the Patents Act, 1970;

AND

In the matter of the Patents Rules, 2003

AND

In the matter of Patent Application No. 5576/DELNP/2008 filed by Gilead Sciences Inc and Japan Tobacco Inc. filed on June 26, 2008 titled "Methods for improving the pharmacokinetics of HIV integrase inhibitors"

AND

In the matter of representation by way of opposition by Nai Umang Positive Welfare Society (Opponent)

STATEMENT OF FACTS AND EVIDENCE

I. INTRODUCTION

1. Nai Umang Positive Welfare Society (hereinafter referred to as "Nai Umang"), a community based, non-profit organization, registered as a society under the Societies Registration Act, 1860 (Registration Number-S/63727/2008) in 2008 having its operational address at H. No:- 17/353, Gali No. 2, Than Singh Nagar, Anand Parbat, New Delhi-110005, India (hereinafter referred to as the "Opponent") hereby files a representation by way of opposition under section 25(1) of the Patent Act 1970, as amended by the Patents (Amendment) Act, 2005 (hereinafter referred to as the "Patents Act") against Patent Application

titled "Methods for improving the pharmacokinetics of HIV integrase inhibitors" filed on June 26,2008 14:58:41 by Gilead Sciences Inc. and Japan Tobacco, Inc. (hereinafter referred to as the "Patent Applicant"), bearing Indian Patent Application No. 5576/DELNP/2008 (hereinafter referred to as the "present Application"). This representation is proper under section 25(1) of the Patents Act as the present Application has been published but a patent has not yet been granted. Specifically, this pre-grant opposition is brought under section 25(1) of the Patents Act.

2. The present Application was filed at the Patent Office in Delhi, Therefore, the Hon'ble Patent Controller has the jurisdiction to hear and decide this pre-grant opposition in Delhi.

3. Nai Umang is a national level community based organization representing the needs of the people living with HIV/AIDS (hereinafter referred to as "PLHIV"). All of its members are PLHIV who need antiretroviral medicines. Nai Umang represents PLHIV in an attempt to secure systemic changes in critical areas such as care and support, access to treatment and addresses issues of discrimination faced by PLHIV at the local, regional, national and international levels. Because Nai Umang Welfare Society wants to ensure that every PLHIV must be able to enjoy the fundamental right to health, it is concerned about the availability and accessibility of medicines to treat Human Immuno-deficiency Virus (hereinafter referred to as "HIV") at affordable prices. In this context, it is particularly concerned about the impact of product patents on access to safe, effective and affordable medicines to treat HIV, which presently make HIV a chronic but manageable condition for PLHIV in India as well as across the developing and least developing countries. The grant or non-grant of a patent on the dosage form covered by the present Application is of vital concern to the Opponent.

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4. The present Application relates *inter alia* to a composition involving elvitegravir whose pharmacokinetics is improved by ritonavir, which are medicines for treatment for HIV.

5. Presently, elvitegravir is a known pipeline antiretroviral patented by way of Indian patent no. 245833, while ritonavir remains unpatented.

6. Thus, while examining the present Application and the present pre-grant opposition, the Hon'ble Patent Controller must strictly interpret the higher standards of patentability criteria set by the Indian Parliament in order to ensure that pharmaceutical companies are not able to obtain patents over new forms of already known substances and that patents are granted only to genuine inventions.

II. ACCESS TO MEDICINES AND STRICT INTERPRETATION OF PATENTABILITY STANDARDS

7. As mentioned above, the present Application relates to a combination containing an integrase inhibitor and a protease inhibitor and other agents to treat HIV, an epidemic that affects the lives of millions in India and throughout much of the developing world. More particularly, the present Application covers elvitegravir and ritonavir. Elvitegravir is a part of an approved once a week pill combination regimen which has less side effects, approved by the USFDA and ritonavir is a second line antiretroviral (hereinafter referred to as "ARV") medicines to treat HIV.

8. Presently, there is no cure for HIV. While HIV, in part, through the availability of medicines such as the one at issue here, has become a chronic but manageable lifelong condition for many in the developed world, it remains a death sentence for those in the developing and least developing world who cannot afford the treatment. Patent protections granted to medicines to treat HIV only exacerbate this problem. A patent grants a 20-year monopoly to the patentee, during which the

patentee is free to set prices at levels impossibly beyond reach for the vast majority of those who are in desperate need of treatment.

9. Due in large part to the availability of safe, effective and affordable generic medicines to treat HIV, lifesaving treatment has now become a realistic option for millions of people living with HIV in India and across the developing world. Between 2001 and 2006, the prices of first-line ARVs plummeted nearly 100-fold, from around USD 10,000 (Rs. 4,50,000) per person per year to USD 150 (Rs. 6,750) per person per year. Prices have fallen further subsequently. This dramatic decrease in prices is attributable to the absence of product patent protection on medicines in India, which facilitated competition between multiple producers of these lifesaving medicines and which, in turn, led to them being available at a fraction of the price charged by western pharmaceutical companies. This enabled the governments of India and other countries to scale up access to treatment for PLHIV.

10. Although the availability of low-cost first generation medicines from India has extended the lives of millions in India and throughout the developing world, the global battle against HIV is far from over. Eventually, even the most effective of first-line regimens loses its efficacy due to the emergence of drug-resistant strains of HIV within the body. Generally, the first-line ARV treatment comprises of nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. If there is treatment failure, a PLHIV has to be shifted to alternative treatment regimens.

11. Globally, as of end-2011, it is estimated that of approximately 34 million PLHIV across the world, approximately 8 million PLHIV were on ARV treatment. In India, as of December 2012, of the estimated 2.09 million PLHIV (2011 estimates), approximately 1.736 million PLHIV were registered in the Government of India's national ARV roll-out programme. Of these, approximately 6,04,987 PLHIV were

receiving treatment; 5,503 PLHIV were receiving second-line treatment for HIV.

12. Increasingly, in India and throughout the developing world, there is an urgent need to secure an affordable source of alternative better tolerated regimens of ARVs to treat HIV in order to deal with the growing problem of drug-resistance. At the current prices for many of these second-line medicines to treat HIV, however, the goal of providing continued lifesaving treatment to millions of those in need remains far out of reach.

13. The most effective way to lower the cost of these essential medicines is to promote competition. However, in order for there to be any effective generic competition, it is imperative that patents not be granted in India for uninventive, incremental improvements or to inventions that do not meet the strict patentability standards set by India as is the mandate of the Indian Patent law.

14. Although India was constrained by its WTO obligations to introduce product patent protection for pharmaceutical products through the Patents (Amendment) Act of 2005, India retains full sovereignty in determining the standards that must be met with respect to patentability. India is under no obligation to follow the perilous path that many developed nations have taken in setting low standards for novelty and inventive step that result in patent protection for incremental innovations, all too often at the cost of public health. This has been recognised by the Hon'ble Supreme Court of India too in *Novartis AG v. Union of India and others*, (2013) 6 SCC 1.

15. Cognizant of public health concerns and the Doha Declaration on the TRIPS Agreement and Public Health (2001), Parliament introduced certain provisions, while passing the Patents (Amendment) Act, 2005 to amend the Patents Act, 1970 (hereinafter referred to as the "Patents Act"), to ensure that patents are granted only for genuine inventions and to prevent "evergreening", i.e. creation or extension of monopolies

through patent terms by obtaining patents for minor or routine modifications. Indian Parliament also set a higher standard of inventive step.

16. The Patents Act should be interpreted by the Hon'ble Patent Controller in light of all the relevant circumstances surrounding the Amending Act. The Hon'ble Madras High Court, in *Novartis AG v. Union of India and Others*, (2007) 4 MLJ 1153, while upholding section 3(d) against a constitutional challenge, stated: "We have borne in mind the object which the Amending Act wanted to achieve namely, ***to prevent evergreening; to provide easy access to the citizens of this country to life saving drugs and to discharge their Constitutional obligation of providing good health care to its citizens.***" [*see* para 19] (emphasis added). As such, the Opponent submits that the Hon'ble Patent Controller, while considering the present pre-grant opposition and while interpreting the provisions of the Patents Act, must bear in mind the intent of Parliament in enacting the Patents (Amendment) Act, i.e. to ensure India's compliance with its obligations under the Agreement on Trade Related Aspects of Intellectual Property Rights while ensuring that patent protection does not come in the way of India's fundamental duty to provide good health care to its citizens.

17. The Opponent firmly believes that a proper application of the patentability standards set out in section 3(d) of the Patents Act, as well as those embodied in section 2(1)(j) and section 2(1)(ja) of the Patents Act, in a manner that fully carries out the objectives of the Amending Act, will result in the rejection of the present Application. The Opponent, therefore, humbly requests that the Hon'ble Patent Controller scrutinise the present Application with special care, as its decision will determine whether millions of people will have affordable access to lifesaving treatment.

III. BACKGROUND OF ALLEGED INVENTION

18. On 26th June, 2008, the Patent Applicant filed the Indian national phase entry of the International Application no. PCT/US2006/049668 (international Publication No. WO/2007/079260) hereafter referred to as the "'668 Application" with international filing date of December 29, 2006 before the Controller of Patents in India which was subsequently allotted Indian Application Number 5576/DELNP/2008 i.e. the present Application. The said international application claims priority from United States Patent Provisional Patent Applications 60/755,039, filed 30 December 2005; 60/756,631, filed 06 January 2006; and 60/763,901, filed 01 February 2006 (hereafter, '039, '631 and '901 respectively).

III.A. History of relevant patent documents

19. Claiming priority of 30 December 2005 from '039, '631 and '901, the Applicant filed PCT national phase of PCT/US06/49668 on 29 December 2006 in India.

20. On 29 December 2006, the Patent Applicant filed at least two substantially similar patent applications before the United States Patents and Trademarks Office with identical description and claims, claiming priority from the '039, '631 and '901 applications. First of these two applications was assigned a WIPO publication date of WO 2007/079260 and is currently undergoing examination before the United States Patents and Trademarks Office (USPTO).

21. The second substantially similar patent application filed by the patent applicant was designated US application number 12/097,859, hereinafter "US '859 Application", which was rejected by the US patent for double patenting of claims over the US Application no. 11/133,471 titled 'Stable Crystal of 4-Oxoquinoline Compound' (patent no. 7,635,704), for failure in novelty and inventive step requirements. The Applicant substantially amended the claims to satisfy patentability

requirements, but they were rejected. Owing to failure of the patent applicant to respond the final rejection by the USPTO, the Patent Applicant abandoned this application.

22. On 7 December, 2007 the '668 Application was published as WO 2007/079260.

23. On 26 June 2008 the Applicant filed a national phase entry of PCT/US06/49668 claiming priority from '039, '631 and '901 in India. The said national phase entry was allotted Indian Patent Application Number 5576/DELNP/2008 hereinafter referred to as the "576 Patent Application".

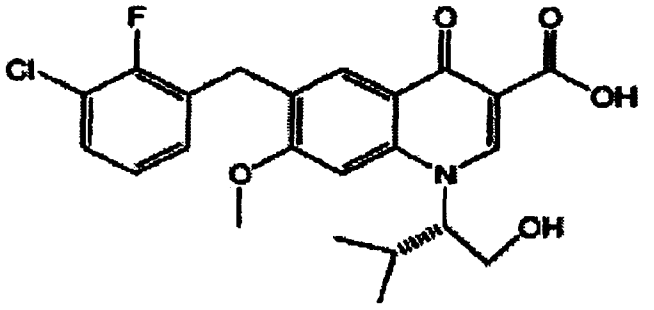
24. The '668 Application is identical to the '576 Patent Application.

25. The '5576 Application is under examination. The examiner has raised objections inter alia relating to lack of novelty, inventive step, clarity, and experimental data to fulfill the requirement of section 3(d), evidence to overcome section 3(e), fulfillment of mandatory requirement under Section 8 of the Patents Act. The Patent Applicant filed part response to the First Examination Report (FER) on 21.04.2014 wherein they submitted certain details including Form 3.

IV. SUMMARY OF CLAIMS

26. The claims of the present Application comprises of 12 claims which can be summarized as follows:

(i) Claims 1 is an independent composition claim which relates to a composition comprising 20 mg to 200 mg of ritonavir with 20 mg to 150 mg of an HIV integrase inhibitor of formula, termed as compound 1:



(1)

(ii) Claim 2 is a composition claim, dependent on claim 1 which relates to the composition of claim 1 administered with food.

(iii) Claim 3-6 are composition claims dependent on claim 1 comprising 50 -100 mg of ritonavir, 80- 150 mg of compound 1, 85 mg of compound 1 and 150 mg of compound 1 respectively.

(iv) Claim 7-9 are a composition claims, each dependent on claim 1 which relate to ritonavir and compound 1 formulated as a single composition, formulated for oral administration and formulated for daily administration, respectively.

(v) Claim 8 & 9 are composition claims dependent on claim 1 wherein compound 1 and ritonavir are formulated for oral administration, and daily administration respectively.

(vi) Claim 10 is a composition claim dependent on claim 1, wherein the composition is in a unit dosage form of a tablet.

(vii) Claim 11 is a composition claim dependent on claim 10 wherein the unit dosage form is a tablet.

(viii) Claim 12 is a composition claim dependent on claim 1, further comprising of stavudine, emtricitabine, tenofovir, abacavir, lamivudine, zudovudine, didanosine, zalcitabine, phosphazide, efavirenz, nevirapine, delavirdine, tipranavir, saquinavir, indinavir, atazanavir, nelfinavir, amprenavir, samprenavir, fosamprenavir, enfuvirtide,

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Fozivudine tidoxil, Alovudine, Dexelvucitabine, Apricitabine, Amdoxovir, Elvucitabine (ACH126443), Racivir (racemic FTC, PSI-5004), MIV-210, KP-1461, fosalvudine tidoxil (HDP 99.0003), AVX756, Dioxolane Thymine (DOT), TMC-254072, INK-20, 4'Ed4T, TMC-125 (etravirine), Capravirine, TMC-278 (rilpivirine), GW-695634, Calanolide A, BILR 355 BS, and VRX 840773, and pharmaceutically acceptable salts thereof.

V. SUMMARY OF GROUNDS

23. The Opponent brings this opposition under the following grounds, amongst others, each of which are without prejudice to one another:

(i) Claims 1 to 12 of the present Application are not new, and anticipated, therefore they lack novelty, and fail under section 2(1)(j) of the Patents Act. Thus, the Opponent brings this opposition under Section 25(1)(b)—that the invention so far as claimed in any claim of the complete specification has been published before the priority date in India or elsewhere in any document;

(ii) Claims 1 to 12 of the present Application lack inventive step, and therefore fail under sections 2(1)(j) and 2(1)(ja) of the Patents Act. Therefore, the Opponent brings this opposition under section 25(1)(e)—that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published before the priority date in India or elsewhere in any document;

(iii) Claims 1 to 12 of the present Application do not satisfy the test of section 3(d) of the Patents Act in as much as the subject matter does not exhibit enhanced therapeutic efficacy over the known substance. Further, they do not satisfy the test of section

3(e) of the Patents Act. Claim 2 &8 of the present Application are drawn to a method of treatment or relate to excluded subject matter under section 3(i) of the Patents Act. Therefore, the Opponent brings this opposition under section 25(1)(f)—that the subject of any claim of the complete specification is not an invention within the meaning of this Act.

(iv) The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed. Therefore, the Opponent brings this opposition under section 25(1)(g) of the Act—that that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed; and

(v) The Patent Applicant has failed to comply with the requirements of section 8 of the Patents Act. Therefore, the Opponent brings this opposition under section 25(1)(h) of the Act—that the Patent Applicant has failed to disclose information required under section 8 or has furnished information which in any material particular was false to his knowledge.

VI. DETAILED GROUNDS

VI.A. Elvitegravir, Ritonavir and combinations were known.

24. Admittedly, as of the priority date, Ritonavir [*see* present Application page 2, paragraph 3], and 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl] 7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, popularly known as elvitegravir were already known substances [*see* present Application, page3, paragraph 2].

25. It was also known that addition of ritonavir to protease inhibitors metabolized by cytochrome P450 monooxygenase can improve the

pharmacokinetics of those protease inhibitors [see present Application, page 2, para 5 and page 3, para 1].

26. At the time of the alleged invention, as will be explained below, the following were well known to the person skilled in the art-

27. Ritonavir and its activity as an inhibitor of the metabolic enzyme cytochrome P450 monooxygenase, leading to increase in the pharmacokinetics of other HIV agents,

28. Ritonavir's role in combinations with other anti- HIV agents, including integrase inhibitors.

VI.B. ***<u>Claims 1-12 are not new, lack novelty, are anticipated by prior publication and, therefore, should be rejected under section 25(1)(b)(ii) of the Patents Act.</u>***

29. Section 2(1)(j) of the Patents Act defines an "invention" as "a ***new*** product or process involving an inventive step and capable of industrial application" (emphasis added). Section 25 (1)(b)(ii) provides a ground for opposition if the alleged invention, in so far as claimed in any claim of the complete specification, is not new, having been published before the priority date of the claim in India or elsewhere, in any other document. Thus, if a publication, published prior to the priority date of a patent application, discloses the claimed invention, then the claims of the patent application are not new, lack novelty, are anticipated by prior publication and must be rejected.

30. "Newness" or novelty is to be determined by comparing the claims of a patent application to the disclosures in the prior art, read in light of the general knowledge available to a person skilled in the art.

31. Without prejudice to other grounds raised herein, claims 1 to 12 of the present Application are not new, lack novelty and are anticipated by prior publication on account of the enabling disclosures of European Patent Application No. EP 1 564210 A1.

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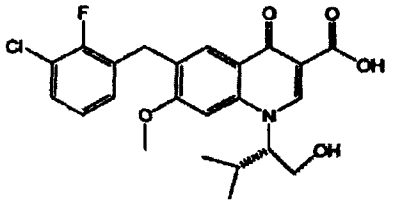
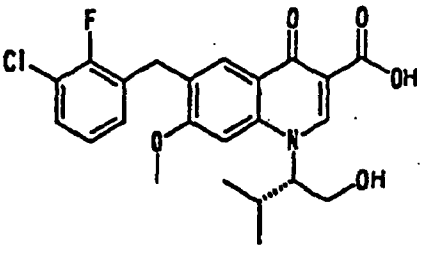
32. Claim 1 of the present Application relates to a composition containing elvitegravir(20 mg to 200 mg) and ritonavir (20 mg to 150 mg) for improving the pharmacokinetics of elvitegravir. The subsequent claims relate compositions comprising to narrower dosages involving 85-100 mg of elvitegravir and 50-100 mg of ritonavir which are formulated together as a single composition which can further comprise other anti-HIV agents, in the form of a tablet to be administered daily with food.

33. European Patent Application No. EP 1 564210 A1, titled '4-Oxoquinoline compounds and utilization thereof as HIV integrase inhibitors' (2003) (hereinafter referred to as the "EP '210 Application"), which was published on 17.08.2005, a copy of which is hereto annexed and marked as "**Exhibit A**", discloses 4-oxoquinoline compounds as compounds having integrase inhibitory action which can be used for treatment of HIV/AIDS. Compound 1 popularly known as elvitegravir is also disclosed specifically paged 1, para 57. [*See* exhibit A, internal page 1, para 57]. The application also discloses combinations with other HIV agents such as protease inhibitors including ritonavir. [*See* exhibit A, internal page 27, para 0104 *placitum* 56].

Structure of elvitegravir in claim 1of present Application	Structure disclosed in EP '210 Application page 1, para 57
 (I)	

34. The EP '210 Application further discloses that while the dose depends on age, body weight, the compound is generally administered in a dosage of 0.01 mg to 1g per i.e. 0.01 mg to 1000 mg administration for an adult. [*See* exhibit A, internal page 27 para 0097]

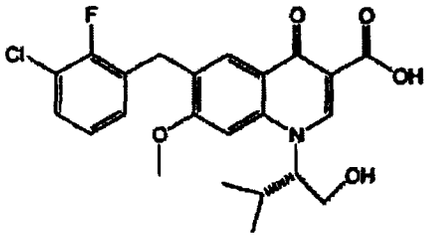
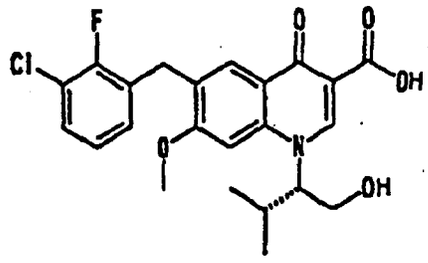
35. As regards dosing and formulating combination regimen, the EP '210 Application incorporates 'Guidelines for the use of Antiretroviral Agents in HIV-Infected Adults and Adolescent' August 13, 2001(hereinafter the "2001 guidelines") [*See* exhibit A, internal page 3, para 009] a copy of which is hereto annexed and marked as **"Exhibit B"**. The 2001 guidelines disclose ritonavir as a boosting agent and a dosage of 100 mg twice daily may be used for boosting of other Protease inhibitors.[*see* exhibit B internal page 16, para 4]

36. It is submitted a narrower range of dosages for elvitegravir (20 mg to 150 mg) and ritonavir (20 mg to 200 mg) is subsumed within and anticipated by the broader range of 0.01 mg to 1000 mg disclosed in the 'EP 210 Patent. It is a matter of routine trial and error for a person skilled in the art to determine the narrower range towards formulating a combination by using pharmacokinetic and pharmacodynamic studies.

37. The dosages of elvitegravir and ritonavir are therefore anticipated by the disclosures made in the EP '210 Application.

38. Below is a summary comparison of claims of present application with the disclosures made in the EP '210 application:

Table 1: Comparison	
'576 Application [Present]	**'EP 210 Patent Application**

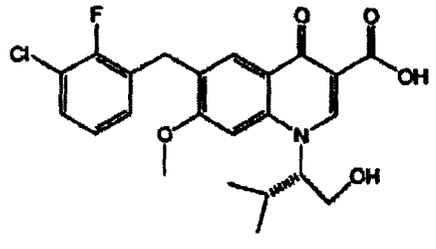
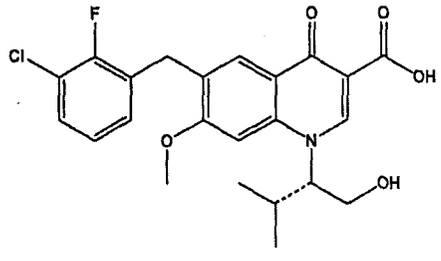
 (I) Claim 1- pharmaceutical composition involving 20-200 mg of ritonavir and 20 to 150 mg of elvitegravir for improving the pharmacokinetics of envitegravir	 Structure disclosed on[para 0348], Table 4, example 4-32, page 91, *placitum* 30 [para 0103, *placitum* 56] discloses ritonavir as a specific example to be used in combination with the above compound.
Claim 2- claimed composition administered with food	It is submitted that administration with food is an inherent administration method excluded from patentability.
Claim 3-11- claimed composition with with 50-100 mg of ritonavir & 85-100 mg of elvitegravir administered in a single composition formulated for oral, daily administration in the form of a tablet.	[para 0098, *placitum* 23-25] disclose generally 0.01 mg to 1 g dosage of the compound per administration, which is given once orally or in a dosage form of an injection. Antiretroviral Agents in HIV-Infected Adults and Adolescent. August 13, 2001 incorporated by reference disclose a boosting dosges for ritonavir.[See page 3, para 009] [para 0097, placitum 20 discloses tablet as a mode of formulation.]
Claim 12 The composition further comprising agents selected from stavudine, emtricitabine,...*et al.*	[para 0103-0111, disclose examples of "other anti- HIV agents" and "other anti- HIV active substance" to be used in multiple drug combination therapy.

39. Therefore, the disclosures in the EP '210 Application constitute enabling disclosures with respect to use of ritonavir with elvitegravir inter alia as claimed in claim 1-12 of the present application.

40. Also, WO 2005/112930, , titled 'Combinations Comprising A 4-Isoquinolone Derivative and Anti- HIV Agents' which was published

on December 1, 2005, hereinafter referred to as the "WO '930" Application', a copy of which is hereto annexed and marked as "**Exhibit C**" destroys novelty of the invention sought to be patented by way of the present Application.

41. The WO '930 Application discloses multiple combination therapy involving combination of an integrase inhibitor, (S)- 6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymehyl-2-methylpropyl1)-7-methoxy-4-oxo,4-dihydroquinoline-3-carbxylic acid with at least one other anti-HIV agents including ritonavir.[See exhibit C, internal page 26, *placitum* 13]

Structure of elvitegravir disclosed in '576 Application [Present]	Structure of integrase inhibitor disclosed in WO 930 Application at internal page 26
 (I)	

42. Further, the application discloses that a combination involving an integrase inhibitor and a protease inhibitor may improve the absolute antiviral effect as a result of attacking the virus through multiple mechanisms. [See exhibit C, internal page 8, paragraph 1, *placitum* 5-7].

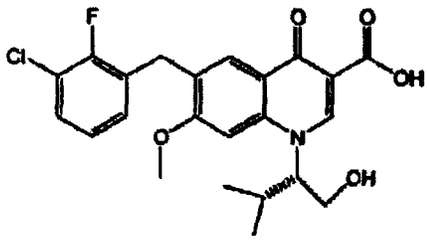
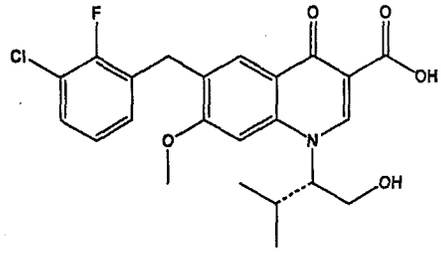
43. An example of the combination involving the compound with at least one protease inhibitor. [See exhibit C, internal page 9, *placitum* 17-18]. The application further teaches both these compositions formulated together as a single composition. [See exhibit C, internal page 10, *placitum* 6-7]

44. The WO '930 application disclosed preferred dosages for administration of the integrase inhibitor. It shows that the integrase inhibitor is generally administered at about 0.01 mg to about 1 g per administration for an adult which may be given once to several times a day. [See exhibit C, internal page 34, paragraph 1, *placitum* 2-5]. Dosages of compound A for combination therapy may be chosen from dosages ranging from about 0.005 mg to about 1000 mg per administration. Further, single administrations of compound A may be 0.01 mg, 0.05 mg, 0.1 mg, 0.5 mg, 1.0 mg, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, **50 mg**, **100 mg**, 200 mg, 300 mg, 400 m, 500 mg, 600 mg, 700 mg, 800 mg, 9000 mg, 1000 mg, per administration. [See exhibit C, internal page 34, paragraph 2, *placitum*, 12-18].

45. The WO '930 Application teaches that the said combination of Compound A and other HIV agents may be administered or simultaneously, orally once a day. [See exhibit C, internal page 34, *placitum* 2-5 & internal page 59-60, claim 7-9]. It further suggests that Compound A and the other agent may be administered in a single composition. [See exhibit C, internal page 63, claim 33, *placitum* 2-8].

46. Below is a summary comparison of claims of present application with the disclosures made in the WO '930 Application:

Table 2. Comparison	
'576 Application [Present]	**WO '930 Application**

 (I) Claim 1- pharmaceutical composition involving 20-200 mg of ritonavir and 20 to 150 mg of elvitegravir for improving the pharmacokinetics of envitegravir	 Lists agents which can be co-formulated with the integrase inhibitor including ritonavir page 29, paragraph 2, *placitum* 13].
Claim 2- claimed composition administered with food	It is submitted that administration with food is an inherent administration method excluded from patentability.
Claim 3-6- claimed composition with with 50-100 mg of ritonavir& 85-100 mg of elvitegravir	Dosages of compound A for combination therapy may be any dosage ranging from about 0.005 mg to about 1000 mg per administration. Further, single administrations of compound A may be 0.01 mg, 0.05 mg, 0.1 mg, 0.5 mg, 1.0 mg, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, **50 mg**, **100 mg**, 200 mg, 300 mg, 400 m, 500 mg, 600 mg, 700 mg, 800 mg, 9000 mg, 1000 mg, per administration. [See page 34, paragraph 2, placitum, 12-18]. The boosting dosages of ritonavir were widely known in the prior art
Claim 7-11 ritonavir and elvitegravir and ritonavir administered in a single composition formulated for oral, daily administration in the form of a tablet.	The pharmaceutical composition may be administered orally…[Page 16, placitum 21-22],…the composition may be administered as a single composition, page 16, placitum 27- page 17, placitum 1] and can be adminstered daily.[page 17, placitum 4-5]
Claim 12 The composition further comprising agents selected from stavudine, emtricitabine,…*et al*	Lists other agents which can be co-formulated with the integrase inhibitor including page 29, paragraph 2, *placitum* 13].

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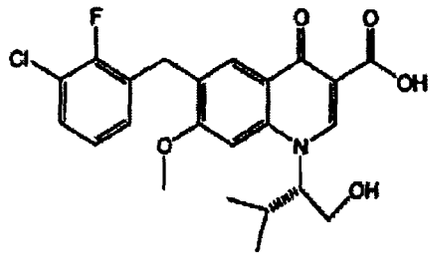
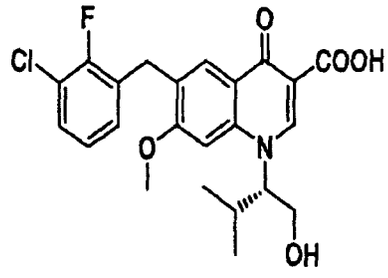
47. Therefore, the disclosures in the WO '930 Application constitute enabling disclosures with respect to use of ritonavir with elvitegravir inter alia as claimed in claim 1-12 of the present application.

48. In addition to this, WO 2005/113508, hereinafter WO '508 Application, titled 'Stable Crystal of 4- Oxoquinoline Compound', which was published on 01.12.2005, a copy of which is hereto annexed and marked as "**Exhibit D**" discloses several stable crystals of 6-(3-chloro-3fluorobenzyl)-1-[(S)-1hydroxymethyl-2-methylpropyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid i.e. elvitegravir.

Structure of elvitegravir disclosed in '576 Application [Present]	Structure of integrase inhibitor disclosed in WO '508 Application at internal page 1
 (1)	

49. The WO '508 application also discloses an anti- HIV composition comprising the crystal of any of the 6-(3-chloro-3fluorobenzyl)-1-[(S)-1hydroxymethyl-2-methylpropyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid is used for, for example, a multiple drug combination therapy of AIDS.[See exhibit D, internal page 7, paragraph 4, *placitum* 22-23]. The WO '508 application further discloses examples of "other anti-HIV active substances" which include ritonvir. [See exhibit D, internal page 8, paragraph 2, *placitum* 24.

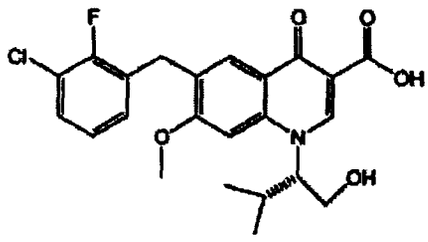
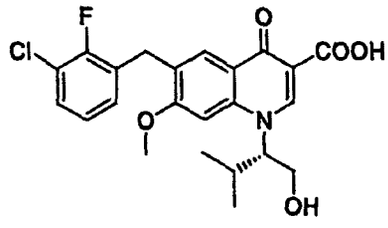
50. Further, the WO '508 application further teaches that the preferred dosage of integrase inhibitor is ususally between 0.1mg to 1000 mg.[See exhibit D, internal page 6, *placitum* 30-35]

51. The WO '508 application also discloses the method of administration which is a daily tablet. [See exhibit D, internal page 6, *placitum* 25-30]

52. It lists specific examples of other agents which can be used in the combination therapy involving integrase inhibitor. [See exhibit D, internal pages 7-11]

53. Below is a summary comparison of claims of present application with the disclosures made in the WO '508 Application:

Table 3. Comparison

'576 Application [Present]	**WO '508 Application**
 (1) Claim 1- pharmaceutical composition involving 20-200 mg of ritonavir and 20 to 150 mg of elvitegravir for improving the pharmacokinetics of envitegravir	 Structure disclosed on internal page 1 The integrase inhibitor compound can be coformulated with ritonavir. [see internal page 8, paragraph, placitum 24]
Claim 2- claimed composition administered with food.	It is submitted that administration with food is an inherent administration method excluded from patentability.
Claim 3-6- claimed composition with with 50-100 mg of ritonavir& 85-100 mg of elvitegravir	Dosage of integrase inhibitor is ususally between 0.1mg to 1000mg. [See internal page 6, *placitum* 30-35]
Claim 7-11 ritonavir and elvitegravir and ritonavir administered in a single	Administration may be oral, daily in the form of a tablet. [See internal

composition formulated for oral, daily administration in the form of a tablet.	page 6, placitum 25-30]
Claim 12 The composition further comprising agents selected from stavudine, emtricitabine,...	Specific examples of other agents which can be used in the combination therapy involving integrase inhibitor can are listed. [See internal pages 7-11]

54. Therefore, the disclosures in the WO '508 Application constitute enabling disclosures with respect to use of ritonavir with elvitegravir inter alia as claimed in claim 1-12 of the present application.

55. In light of this, claim 1 -12 of the present Application are not new, lack novelty and are anticipated by prior publication. Therefore, Claims 1-12 of the present Application should be rejected under section 25(1)(b) of the Patents Act.

VI.C. ***Without* prejudice *to what is stated in respect of anticipation by prior claiming or prior publication, Claims 1 to 12 are obvious, do not involve a technical advance and lack inventive step as defined under section 2(1)(ja) and are, therefore, should be rejected under section 25(1)(e) of the Patents Act.***

56. Section 2(1)(j) defines an "invention" as "a new product or process involving an inventive step and capable of industrial application." (emphasis added). Therefore, all alleged inventions, in order to qualify for a patent, must satisfy the criteria of inventive step. Section 2(1)(ja) of the Patents Act defines an inventive step as "a feature of an invention that involves technical advance as compared to the existing knowledge ... and that makes the invention not obvious to a person skilled in the art".

57. Sub-sections (j) and (ja) of Section 2(1) of the Patents Act thus require a Patent Applicant to show that the feature of the alleged invention involves a technical advance and that it is not obvious to a person

skilled in the art. These requirements are laid down to ensure that patents, which result in a monopoly, are granted only to genuine inventions.

58. Without prejudice to what is stated above under the ground of novelty, it is submitted that in light of the disclosures and teachings made by the '210 Application, WO '508 Application & WO '930 Application the subject matter of the present application is rendered obvious.

59. The integrase inhibitory activity of elvitegravir, including the effect of improvement in pharmacokinetics due to ritonavir was known. Resultantly, combinations involving elvitegravir and ritonavir are rendered obvious. This is further elaborated below:

VI.C.1 CYP3A inhibiting activity of ritonavir in integrase inhibitors was known.

60. Claim 1 relates to a pharmaceutical composition comprising 20 mg to 200 mg of ritonavir or a pharmaceutically acceptable salt thereof and 20 mg to 150 mg of a HIV integrase inhibitor compound 1 for improving the pharmacokinetics of the HIV integase inhibitor in a patient.

61. The use of small quantities of ritonavir as an inhibitor of the metabolic enzyme cytochrome p450 monooxygenase, particularly the 3A4 isoform (CYP 3A4) involved in the metabolic pathway of many drugs is well known and admitted by the patent applicant in the Present Application [*see* present Application, internal page 3 of the specification, para 1]. The present Application claims the use of ritonavir to boost the pharmacokinetics of elvitegravir, an integrase inhibitor.

62. It is submitted that the use of ritonavir to improve the pharmacokinetics of integrase inhibitors was also well known in the prior art at the time of filing of the present application. Firstly, WO 2004/067531,

hereinafter WO '531 Application, titled, 'HIV-Integrase Inhibitors, Pharmaceutical Compositions, And Methods For Their Use', which was published on August 12, 2004, a copy of which is annexed hereto and marked as "**Exhibit E**". The WO '531 application discloses a class of integrase inhibitors and combinations involving them. The application teaches that the activity and exposure of an integrase inhibitor may be enhanced by combining them with agents which are inhibitors of at least one isoform of the cytochrome P-450 (CYP450) enzymes, for example ritonavir. [See exhibit E, internal page 25, para 2, *placitum* 6-10].

VI.C.2 Combination therapy involving elvitegravir and ritonavir are known

63. In another aspect of invention, claims 1-12 relate to formulation of elvitegravir and ritonavir formulated in a single composition further comprising one or more agents.

64. It is submitted that combination regimens were well known at the time of filing of the present Application. Several ritonavir boosted combination regimens involving protease inhibitors were available at the time of the present Application.[*See "Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients"*, Robert K. Zeldin *et al,* Journal of Antimicrobial Chemotherapy (2004) 53, 4–9, first published online on December 4, 2003, which is hereto annexed and marked as "**Exhibit F**"]. Saquinavir and indinavir were first studied in combination twice a day regimens with ritonavir in patients who failed one or more single PI-based regimens and required salvage therapy. Lopinavir/ritonavir was coformulated and approved as a twice a day combination regimen. Saquinavir/ritonavir 600/400 mg provided greater efficacy than ritonavir 600 mg as a single PI (68% versus 40% vRNA < 200 copies/mL), when both were given twice a day with two NRTIs in PI

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naïve patients over 48 weeks. [*See* Exhibit F, internal page 5, column 2, para 5].

65. It is submitted that, Highly Active Antiretroviral Therapy (HAART) had become a widespread practice for the treatment of HIV infection at the time of filing of the present Application. See *"HIV resistance and the effectiveness of combination antiretroviral treatment"* by Mugavero *et al* published in December 2004 in Drug Discovery today: Therapeutic Strategies Vol 1, Issue 4, 2004, which is hereto annexed and marked as **"Exhibit G"** teaches that the use of combination antiviral therapies for treatment of HIV infection is a well- established practice and has been highly effective in reducing associated morbidity and mortality. [See abstract on page 529]. Ritonavir boosting not only enhances pharmacokinetics of the P450 metabolised compounds, but also dimishises the risk of resistance. [See exhibit G, internal page 530, column 2, para 1 *placitum* 7-11].

66. With several new antiretrovirals being developed, including integrase inhibitors, there were substantial reasons for their application in combination regimens. See "*New antiretrovirals: What is on the way*?" Robin Wood, published in May 2005 Vol.23 No.5 CME, which is hereto annexed and marked as **"Exhibit H"** teaches that the use of combination regimens involving integrase inhibitors offers the prospect of robust inhibition of the virus. [See exhibit H internal page 259, column 3, *placitum* 1-4]

67. Further, *"Obstacles to successful antiretroviral treatment of HIV-1 infection; problems & perspectives"* Potter *et al* which was published in Indian J Med Res 119, June 2004, pp 217-237 in June 2004 which has been marked and annexed herewith as **"Exhibit I"** teaches that integrase is required for integration of a double-stranded DNA copy of the viral RNA genome into the host chromosome which is essential for HIV replication and therefore represents an important target for future antiviral design. [*See* Exhibit I, page 219, column 1, para 3]. This

document further teaches how drugs with poor pharmacokinetics can be incorporated in combination regimens. [*See* Exhibit I, page 224, column 2, para 2-3]. The document also strongly motivates a person skilled in the art to investigate combination regiments involving integrase inhibitors with then currently available drugs. The document suggests that such combinations will provide much stronger impediment to the emergence of antiretroviral drug resistance. [See *id.* Page 230, column1 para 3]

68. The motivation for a person skilled in the art to explore integrase as a target for combinations with existing antiretrovirals is abound. For instance, see *"Initial Therapy for Human Immunodeficiency Virus: Broadening the Options" Michael* Sension, HIV Clin Trials 2004;5(2):99-111 which was published in March-April 2004, which is hereto annexed and marked as "**Exhibit J**" teaches that after considerable research, advancements in the therapeutic utility of integrase inhibitors are being achieved and the compounds currently being investigated have demonstrated synergy with NRTIs, NNRTIs, and PIs.[See exhibit J, internal page 107 column 1 para 3] This document therefore, expressly teaches the person skilled in the art to examine combinations involving integrase inhibitors with other agents including protease inhibitors.

69. In light of pharmacokinetic advantage outlined above, this document motivates a person skilled in the art to select a combination regimen involving elvitegravir and ritonavir.

70. Next, the WO '531 application teaches that exposure of certain integrase inhibitors can be enhanced by incorporating them in combinations involving ritonavir. [See internal page 22, paragraph 3-4].

71. In addition to that, WO 2004/101512, titled, 'Naphthyridine Integrase Inhibitors', which was published on 25.11.2004, hereinafter referred to as "WO '512" is annexed herewith and marked as "**Exhibit K**". This application discloses a class of compounds which are useful as HIV

integrase inhibitors for treating of HIV infection. [See exhibit K, internal page 22, *placitum* 24-28]. The application suggests that these integrase inhibitors may be administered in combination with other therapeutic agents including ritonavir owing to its role in inhibition of metabolism of compounds. [See page 26, paragraph 3, *placitum* 27-30]

72. Lastly, Unites States Patent US 6541515, titled 'HIV Integrase Inhibitors', which was granted on April 1, 2003, hereinafter referred to as "US '515" a copy of which is hereto annexed and marked as "**Exhibit L**" teaches compounds useful in the inhibition of integrase and their application in combinations. The US '515 patent further discloses that the integrase inhibitor may be used in combinations with one or more agents including certain protease inhibitors. [See exhibit L, internal Column 13 *placitum* 39-50]

VI.C.3 Lack of clinically significant interactions, dosages between ritonavir and CYP3A metabolized agents were known

73. Physicians' desk references, Edition 51, published in 1997, which is hereto annexed and marked as "**Exhibit M**" teaches that ritonavir can produce large increases in plasma concentrations of highly metabolized drugs. It also teaches that ritonavir has a high affinity for several cytochrome P450 isoforms, the highest being for CYP3A. A dosage is 600 mg twice daily in a monotherapy of ritonavir. It is also disclosed that in combinations with other agents metobolised by CYP3A inhibitors, a reduction in >50% of the dosage maybe required. [See internal page 449, *placitum* 13-40]. It further teaches that in combinations involving ritonavir may significantly improve the gastrointestinal tolerance.[*See* Exhibit M page 451, column 1, *placitum* 19-26]. It is therefore, obvious for a person skilled in the art to choose to combine an agent which is metabolized with CYP3A inhibitor such as elvitegravir. Further, Relative to fasting conditions, the extent of

absorption of ritonavir from capsule formation was observed to be 15% higher when administered with a meal. [*See* Exhibit M page 447, column 3, *placitum* 17-20].

VI.C.4 Claimed dosages of ritonavir and elvitegravir were already known in the prior art

74. Since high doses of ritonavir are known to result in resistance, some ritonavir boosted regimens involve low dose dosages of ritonavir with other protease inhibitors so as to improve pharmacokinetics and ensure the antiviral effect is owing to the boosted drug. [*See* Exhibit F].While contemplating such combinations a person skilled in the art would therefore be motivated to select a relatively lower dose of ritonavir than he would in a combination which desires protease inhibiting antiviral effect as well as boosting effect of ritonavir.[See exhibit F, abstract]

75. Further, according to United States Patent US 6037157 A, titled 'Method For Improving Pharmacokinetics', granted on March 14, 2000, disclosed in the present Application on page 16, para 2, a copy which is annexed hereto and marked as **"Exhibit N"**. According to the US 6037157 patent, dosages of ritonavir to be administered with a drug metabolized with cytochrome P450 monooxygenase is usually 0.1 to 25 mg/kg body weight while the dosage of the drug metabolized by cytochrome P450 monooxygenase to be administered is well known and can be readily determined by person skilled in the art. [See exhibit-N, internal column 12 para 1-2]

76. United States Patent US 6245806 B1, titled 'HIV integrase inhibitors' granted on June 12, 2001, a copy of which is attached hereto and marked **"Exhibit O"**, teaches tetracyclic aromatic ketones useful in the inhibition of HIV integrase which can be used in combinations involving ritonavir [See exhibit O, internal column 14, para 2, *placitum* 44]. The application teaches that while it can be administered orally to

humans in a dosage range of 1 to 1000mg/kg body weight, preferred dosage for oral administration may be provided in the form of tablets containing 1.0 to 1000 mg of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, **50.0**, 75.0, **100.0**, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. Therefore specific dosages of integrase inhibitors to be administered with ritonavir were also known in the prior art. [See exhibit O, internal column 10, para 3]

77. WO 2004/101512 also teaches a dosage of 0.1 to 20 mg per kg body weight of the patient. [See exhibit K, internal page 27, paragraph 2, *placitum* 7]

78. US 6541515 further discloses that such a compound can be administered in a dosage of about 0.01 to about 1000 mg/kg body weight in divided dosages while the preferred dosages include 0.1 to 200 mg/kg body weight. Preferred dosages for oral administration include1.0 to 1000 mg of the active ingredient, particularly, 1.0, 5.0, 10.0, 15.0 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 400.0, 500.0, 600.0, 750.0, 8--.0, 900.0 and 1000.0 mg. [See exhibit L, internal column 13, *placitum* 18-20].

VI.C.5 Effects of food on drug absorption were known

79. Claim 2 of the present specification relates to the formulation of the composition to be administered with food. While the specification does not disclose how the composition is formulated differently, in order to be administered with food. It appears to be guised treatment method claim which will be substantiated further under the relevant ground in section.

80. It is generally known that foods effect drug absorption and it is common practice to prescribe that drugs are administered with food i.e.

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it can cause the drug absorption to be decreased, delayed, or increased, or it may be without effect. However, there is significant indication in the prior art to indicate that for certain drugs, food may have increased absorption and bioavailability for reasons well known. Ingested food tends to decrease stomach emptying due, primarily, to feedback mechanisms from receptors situated in the proximal small intestine. Absorption of most compounds occurs predominantly from the proximal small intestine, so that changes in stomach emptying rate are likely to affect the rate of drug absorption. Prolonged retention in the stomach may increase the percentage of administered drug that is dissolved when it passes into the small intestine and hence increase the absorption efficiency. [See '*Interactions affecting Drug Absorption by Peter G. Welling'*, Clinical Pharmacokinetics, 1984] also mentioned in the present specification on page 38, para 1 which is annexed hereto and marked as "**Exhibit P**".

81. It is further known that food ingestion causes most gastrointestinal tract secretions, including digestive enzymes, hydrochloric acid and bile, to increase. All of these could increase drug availability of the drug or drug formulation. [See exhibit P, *id* 416]. If a drug is taken shortly before a meal, its absorption is likely to be either increased or unaffected. When given after a meal, the degree to which drug absorption is affected in inversely proportional to the time that has elapsed between eating and dosing being inversely proportional to the time that has elapsed between eating and dosing, being maximal if the drug is taken immediately after the meal. [See; exhibit P, *id* page 418]. Increased bioavailability with food of some agents including propanolol, metaprolol, labetolol and hydralazine, which are presystemically metabolized by hydroxylation, glucourodination and acetylation may result from reduced presystemic clearance. It was therefore obvious for a person skilled in the art to conceive of the improved effect of the composition when administered with food.

82. WO 00/74677, titled 'Improved Pharmaceutical Formulations' which was published on December 14, 2000, a copy of which is hereto annexed and marked as "**Exhibit Q**" further discloses use of ritonavir and methods were explored to achieve improvement in bioavailability with effects of food on dosage was determined on dogs. [*see* exhibit Q, internal page 42-43 example 10] signaling motivation for a person skilled in the art to evaluate the effect of food on combinations involving ritonavir.

83. In light of the above, Claims 1-12 of the present Application are obvious to a person skilled in the art. They do not involve any technical advance over the existing knowledge. They, therefore, lack inventive step.

VI.D. Claims 1 to 12 fail under section 3(e), are not an invention within the meaning of this Act and should to be rejected under section 25(1)(f) of the Patents Act.

84. Under section 3(e) of the Patents Act, claims relating to "a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof" are not eligible for a patent.

85. As has been held by the Hon'ble IPAB in *La Renon Health Care Pvt. Ltd.,* versus *Kibow Biotech Inc. and Others*, 261/2013, paragraph 151 clarifies that in case the applicant is attempting to patent a combination of known integers, a surprising/ great technical effect has to be shown by the Applicant.

86. Given that the basis for benefits of combining elvitegravir with ritonavir are well grounded in the prior art as explained above, there is no unexpected synergistic effect disclosed in the specification which merits the subject matter of the present invention to not be considered a 'mere admixture'. Without prejudice to other grounds raised herein, the pharmaceutical dosage forms claimed by the Patent Applicant in

Claims 1 to 12 are substances obtained by a mere admixture. The Patent Applicant has not shown that the compounds claimed exhibit any synergistic effect, whether improved and unexpected or otherwise, over and above the aggregation of the known properties of the components thereof. Therefore, Claims 1 to 12 fail under section 3(e) and should be rejected under section 25(1)(f) of the Patents Act.

VI.E. ***The complete specification does not sufficiently and clearly describe the invention as claimed in claim 1-3 and 31 &32 and should be rejected under section 25(g) of the Act.***

87. Claim 2 relates to the pharmaceutical composition involving elvitegravir and ritonavir which is formulated for administration with food. The specification, however does not support the claim as to how such a combination is formulated differently. In the absence of such information, the said claim is rendered a mere method of treatment wherein the said composition is administered with food.

88. Claim 12 claims relates to the composition of compound 1 and ritonavir further comprising a number of agents, namely stavudine, emtricitabine, tenofovir, abacavir, lamivudine, zudovudine, didanosine, zalcitabine, phosphazide, efavirenz, nevirapine, delavirdine, tipranavir, saquinavir, indinavir, atazanavir, nelfinavir, amprenavir, samprenavir, fosamprenavir, enfuvirtide, Fozivudine tidoxil, Alovudine, Dexelvucitabine, Apricitabine, Amdoxovir, Elvucitabine (ACH126443), Racivir (racemic FTC, PSI-5004), MIV-210, KP-1461, fosalvudine tidoxil (HDP 99.0003), AVX756, Dioxolane Thymine (DOT), TMC-254072, INK-20, 4'Ed4T, TMC-125 (etravirine), Capravirine, TMC-278 (rilpivirine), GW-695634, Calanolide A, BILR 355 BS, and VRX 840773. Without prejudice to what is stated below, under the ground of section 3(d) i.e. section ***VI.F.*** or any other ground in this representation, the specification only reports data for elvitegravir

and ritonavir further comprising tenofovir disoproxil fumarate and zidovudine. The remaining agents are not supported with accompanying data or information on formulation.

89. As such, the Complete Specification does not sufficiently and clearly describe the invention claimed in Claims 1 to 12 of the present Application and their operation and use and fails to meet the requirements of sufficient and clear description and clearly defining the scope of the matter for which protection is sought and should, therefore, be rejected under section 25(1)(g) of the Patents Act.

VI.F. Claims 1-12 fail under section 3(d), are not an invention within the meaning of this Act and should be rejected under section 25(1)(f) of the Patents Act.

90. Section 25(1)(f) of the Patents Act provides a ground for opposition if the subject matter of any claim of the Complete Specification is not an invention within the meaning of the Act.

91. Under section 3(d) of the Patents Act, a new form of a known substance is not an invention unless it results in enhancement of efficacy over the known efficacy of the known substance. The explanation to section 3(d) states that combinations of known substances are to be considered to be the same substance.

92. Section 3(d) of the Patents Act was amended in 2005 to prevent patents on modifications of known substances, such as combinations and salts, esters, ethers and other derivatives of known substances. Under the law, each product claim that relates to a new form of a known substance has to satisfy section 3(d) of the Patents Act.

93. It is an established position of law that section 3(d) has to be satisfied independently of sections 2(1)(j) and 2(1)(ja) [*see Novartis AG v. Union of India and others*, (2013) 6 SCC 1].

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94. As held by the Hon'ble Madras High Court, the burden of proof is on the patent applicant to satisfy the requirements of section 3(d), i.e. that of showing enhanced efficacy [*see Novartis AG and another v. Union of India and others*, (2007) 4 MLJ 1153, para 13]. As held by the Hon'ble Intellectual Property Appellate Board, this data is required to be in the Complete Specification [*Novartis AG v. Union of India and others*, MIPR 2009 (2) 0345, para 9(xvii)].

95. It is also an established position of law that the term "efficacy" in section 3(d) means therapeutic efficacy for pharmaceutical products [*see Novartis AG v. Union of India and others*, (2013) 6 SCC 1].

96. Clearance significantly affects the maintenance of a steady state concentration of a drug in the body. Drugs that are efficiently cleared in the liver fail to maintain a stable concentration and therefore are not available. Maintaining as accessible concentration of the drug in blood or plasma is a direct indicator of the pharmacological effect of drug and is a fundamental tenet of pharmacokinetics.

97. According to Novartis *supra*, improvement in pharmacokinetics does not amount to enhancement in therapeutic efficacy.

98. As regards the increase in antiviral effect reported in table on page 26, arrived at by a two sided Wilcoxon rank sum exact test in example 2 of the present Application, (see present Application, page 23-30) reports an enhancement in antiviral effect of the drug when combined with ritonavir.

99. The data reported for increase in antiviral effect however, when analysed shows that there is no statistically significant difference between the antiviral effect of elvitegravir boosted by ritonavir group versus elvitegravir alone or ritonavir alone. The increase in antiviral effect reported therefore could be due to interpatient variability and therefore cannot be considered.

100. Increase in drug absorption, too does not amount to enhancement of therapeutic efficacy. An enhancement of physical properties, if any does no satisfy the requirement of showing enhanced efficacy.

101. Mere increase in bioavailability also does not amount to increase in therapeutic efficacy.

102. Therefore, without prejudice to other grounds raised herein, Claims 1 to 12 fail under section 3(d) of the Patents Act.

VI.G. Claims 2, 8& 9 fail under section 3(i) for being method of treatment claims and should to be rejected under section 25(1)(f) of the Patents Act.

103. Without prejudice to other grounds raised herein, the Opponent states that certain claims fail for falling within the proscription of method of treatment claims.

104. Section 3(i) of the Patents Act provides that any process for the medicinal, surgical, curative, prophylactic, diagnostic, therapeutic or other treatment of human beings or any process for similar treatment of animals to render them free of disease or to increase their economic value or that of their products is not an invention within the meaning of the Patents Act. Section 25(1)(f) provides a ground for opposition if the subject of the claim is not an invention within the meaning of the Patents Act.

105. Claim 2, 8& 9 relate to the claimed composition being administered with food.

106. Prior to amendments in claims by the Applicant, on 7 May 2014, the earlier claims 1-24, 31-32, 34-37 are drawn as use claims which claim use of ritonavir to increase the pharmacokinetics of an integase inhibitor. Claim 3 was in relation to increase in blood level of integrase inhibitor by co- administration with ritonavir. Effect of a drug cannot be subject matter of invention under the Patents Act, which is probably

why the patent applicant amended the application on his own accord to delete these claims. However, new claims 2, 8 & 9 were introduced by way of amendments which relate to administration of the composition with food [claim 2], oral administration [claim 8] and daily administration [claim 9]. Such claims which relate to the manner in which the drug is administered is sought to be patented clearly indicate an attempt to cover what is impermissible under section 3(i) of the Patents Act by way of crouching them under composition claims. Therefore, Claims 2, 8 & 9 ought to be rejected under section 3(i) of the patents Act.

VI.H. <u>The Patent Applicant has not complied with the requirements of section 8. Therefore, the present Application should be rejected under section 25(1)(h) of the Patents Act.</u>

107. Section 25(1)(h) of the Patents Act provides a ground for opposition if the Patent Applicant has not furnished information required under section 8 of the Patents Act, within the time prescribed by law.

108. Without prejudice to other grounds raised herein, the present Application should be rejected because the Patent Applicant has not complied with the mandatory requirements of section 8 of the Patents Act.

109. Section 8 of the Patents Act read with rule 12(1) of the Patents Rules requires, *inter alia*, a patent applicant, who is prosecuting, either alone or jointly with any other person, an application for a patent in any country outside India in respect of the same or substantially the same invention, to file a statement setting out the particulars of such application (Form 3) within six months of the date of filing of such application in India. Along with such statement, the patent applicant is also required to furnish an undertaking that, up to the grant, it would keep the Controller informed in writing, from time of time, of detailed

particulars of applications filed in other jurisdictions after Form 3 was filed in India within six months of the date of such filing in other jurisdictions. This is done by filing Form 3 as prescribed by the Patents Rules. The Patent Applicant is also required to keep the Hon'ble Patent Controller informed of the developments of the corresponding or similar patent applications in other jurisdictions.

110. The prosecution history for the present Application, available online on the IPAIRS website, shows that the Patent Applicant had not furnished the information required under section 8 of the Patents Act, within the time prescribed by law. Thus, *prima facie*, the Patent Applicant has not complied with the requirements of section 8 of the Patents Act.

111. In the present case, it appears that the Patent Applicant first filed Form 3 on 26 June 2008 and listed only the applications filed in the United States, from which priority is claimed, and the PCT Application. Though several applications had been filed in 2006-07 in other jurisdictions in other countries/ jurisdictions, which had not been designated in the PCT international application, the particulars of these applications were not set out in the Form 3 that was filed in on 26 June 2008. These applications in other jurisdictions include:

Application No.	**Date of filing**	**Country**
2006332664	17.06.2008	Australia
CA 2635468	26.06.2008	Canada
EP1976517	28.07.2008	European Application
P20080313A	01.07.2008	Croatia

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200854878 4	30.06.2008	Japan
MX/a/2008/ 008494	27.06.2008	Mexico
569576	03.07.2008	New Zealand
12097859	20.10.2008	United States of America
11647858	12.29.2006	United States of America
W00200802128	24.06.2008	Indonesia
192208	16.06.2008	Israel

112. Further, it appears from the prosecution history available online that, following the filing of the present Application in August 2007, the Patent Applicant did not even attempt subsequently to comply with the requirements of section 8 of the Patents Act once the corresponding international application entered national phase in other jurisdictions.

113. Even though the Patent Applicant filed the request for examination on 09 November 2009, the Patent Applicant took no step even at or around that time to comply with the requirements of section 8 of the Patents Act.

114. Subsequently, via examination report dated 30.09.2013 the Examiner ordered that regarding the search and/or examination report including claims of the application allowed, as referred to in Rule 12(3) of the Patent Rule, 2003, in respect of same or substantially the same invention filed in all the major Patent offices along with appropriate translation where applicable, should be submitted within a period of six

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months from the date of receipt of this communication as provided under section 8(2) of the Indian Patents Act.

115. It appears that, on or about April 21, 2013, the Patent Applicant tendered Form 3 with a further annexure. This information was not accompanied by any petition to condone the delay or irregularity.

116. Therefore, the Patent Applicant' has failed to comply with the requirements under section 8 of the Patents Act.

117. The Opponent submits that even if the Patent Applicant were to file any petition to condone the delay or irregularity caused by the delay in filing the information required under section 8 of the Patents Act, such petition must be decided in favour of the Patent Applicant only if it provides sufficient and clear and convincing reason for failure to provide the data within the time prescribed by the law. Such delay should not be condoned where the Patent Applicant has failed to exercise due diligence, has been negligent or has delayed the submission of such information in a *mala fide* manner to prevent such information from being available to the Patent Office.

118. Notably the Patent Applicant has chosen not to disclose the fate of US application No. 12/097,859 which was abandoned by the Applicant in view of repeated rejections from the US Patent Office. The Patent Applicant should be put to the strict proof of its pleadings in any such application/petition.

119. In the event that the Patent Applicant furnishes details in response to the first examination report, the Opponent craves leave to raise a further challenge based on this information, if required, under section 25(1)(h) read with section 8 of the Patents Act.

120. Therefore, in view of the fact that the Patent Applicant has evidently not complied with the requirements of section 8 of the Patents Act, the Patent Application should be rejected under section 25(1)(h) of the Patents Act.

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VII. HEARING REQUESTED

121. The Opponent hereby requests a hearing under section 25(1) of the Patents Act and rule 55 of the Patents Rules.

VIII. CONCLUSION

122. Given all of the foregoing, the Opponents humbly pray:

(i) For an order rejecting patent application 5576/DELNP/2008 for reasons as stated above:

(ii) For such further and other orders as may become necessary in the facts and circumstances of the case or in the interest of justice, equity and good conscience.

Drafted by: Ms. Geetanjali Sharma, Advocate

Settled by: Mr. Anand Grover, Senior Advocate

Place: New Delhi

Date: 29 September, 2014

On Behalf of PDutta

(Pradeep Dutta, President, Authorised signatory, Nai Umang Welfare Society)

Exhibit-A

40

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

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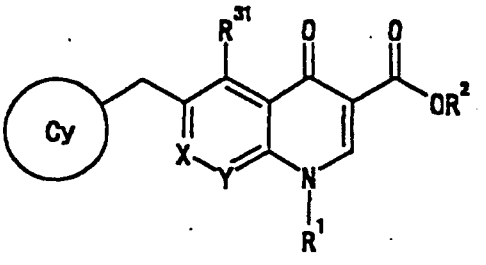
(71) Applicant: **Japan Tobacco Inc.**
Tokyo 105-8422 (JP)

(72) Inventors:
- **SATOH, Motohide, Japan Tobacco Inc.**
  Takatsuki-shi, Osaka 569-1125 (JP)
- **KAWAKAMI, Hiroshi, Japan Tobacco Inc.**
  Takatsuki-shi, Osaka 569-1125 (JP)
- **ITOH, Yoshiharu, Japan Tobacco Inc.**
  Takatsuki-shi, Osaka 569-1125 (JP)
- **SHINKAI, Hisashi, Japan Tobacco Inc.**
  Takatsuki-shi, Osaka 569-1125 (JP)
- **MOTOMURA, Takahisa, Japan Tobacco Inc.**
  Takatsuki-shi, Osaka 569-1125 (JP)
- **ARAMAKI, Hisateru, Japan Tobacco Inc.**
  Takatsuki-shi, Osaka 569-1125 (JP)
- **MATSUZAKI, Yuji, Japan Tobacco Inc.**
  Takatsuki-shi, Osaka 569-1125 (JP)
- **WATANABE, Wataru, Japan Tobacco Inc.**
  Takatsuki-shi, Osaka 569-1125 (JP)
- **WAMAKI, Shuichi, Japan Tobacco Inc.**
  Takatsuki-shi, Osaka 569-1125 (JP)

(74) Representative:
von Kreisler, Alek, Dipl.-Chem. et al
Deichmannhaus am Dom,
Postfach 10 22 41
50462 Köln (DE)

(54) 4-OXOQUINOLINE COMPOUNDS AND UTILIZATION THEREOF AS HIV INTEGRASE INHIBITORS

(57) An anti-HIV agent containing, as an active ingredient, a 4-oxoquinoline compound represented by the following formula [I]



[I]

wherein each symbol is as defined in the specification, or a pharmaceutically acceptable salt thereof. The compound

EP 1 564 210 A1

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of the present invention has HIV integrase inhibitory action and is useful as an anti-HIV agent for the prophylaxis or therapy of AIDS. Moreover, by a combined use with other anti-HIV agents such as protease inhibitors, reverse transcriptase inhibitors and the like, the compound can become a more effective anti-HIV agent. Since the compound has high inhibitory activity specific for integrases, it can provide a safe pharmaceutical agent with a fewer side effects for human.

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Description

Technical Field

[0001] The present invention relates to a novel 4-oxoquinoline compound useful as an anti-HIV agent and a pharmaceutically acceptable salt thereof. The present invention also relates to a novel use of a certain 4-oxoquinoline compound and a pharmaceutically acceptable salt thereof as anti-HIV agents. More particularly, the present invention relates to an anti-HIV agent containing a 4-oxoquinoline compound that particularly shows an anti-HIV action based on an integrase inhibitory activity thereof, or a pharmaceutically acceptable salt thereof.

Background Art

[0002] HIV (Human Immunodeficiency Virus (type 1)) belonging to retrovirus is a causative virus of AIDS (Acquired Immunodeficiency Syndrome).

[0003] HIV targets CD4 positive cell groups such as helper T cell, macrophage and dendritic cell and destroys these immunocompetent cells to cause immunodeficiency.

[0004] Accordingly, a pharmaceutical agent that eradicates HIV in the body or suppresses its growth is effective for the treatment or prophylaxis of AIDS.

[0005] HIV possesses a bimolecular RNA gene in a core protein, and which is covered with an envelope protein. The RNA codes for several enzymes (protease, reverse transcriptase, integrase) characteristic of the virus and the like, and has translated reverse transcriptase and integrase in the core, as well as protease inside and outside the core.

[0006] HIV attaches to and invades a host cell, causes uncoating, and releases a complex of RNA and integrase, and the like into the cytoplasm. From the RNA, DNA is transcribed by reverse transcriptase, and a full length double stranded DNA is produced. The DNA is imported into the nucleus of the host cell and integrated by integrase into the DNA of the host cell. The integrated DNA is converted to an mRNA by polymerase of the host cell, from which mRNA various proteins necessary for forming a virus are synthesized by HIV protease and the like, and a virus particle is finally formed, which then undergoes budding and its release.

[0007] These virus specific enzymes are considered to be essential for the growth of HIV. These enzymes are drawing attention as the target of the development of antiviral agents, and several anti-HIV agents have been already developed.

[0008] For example, zidovudine, didanosine, lamivudine and the like have been already on the market as reverse transcriptase inhibitors, and indinavir, nelfinavir and the like as protease inhibitors.

[0009] In addition, a multiple drug combination therapy concurrently using these pharmaceutical agents has been employed. For example, a combined use of two reverse transcriptase inhibitors (zidovudine and didanosine), and a combined use of three agents of reverse transcriptase inhibitors (zidovudine and lamivudine) and a protease inhibitor (nelfinavir) and the like have been clinically applied. Such multiple drug combination therapy is becoming a mainstream of AIDS therapy (see, e.g., Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adlescent. August 13, 2001).

[0010] However, some of these pharmaceutical agents are known to cause side effects such as liver function failure, central nervous disorders (e.g., vertigo), and the like. In addition, acquisition of resistance to a pharmaceutical agent causes a problem. Even worse, emergence of an HIV that shows multiple drug resistance in a multiple drug combination therapy has been known.

[0011] Under the circumstances, a further development of a novel pharmaceutical agent, particularly a development of an anti-HIV agent based on a new mechanism, has been desired, wherein a development of an anti-HIV agent having an integrase inhibitory activity is expected, because an integrase characteristic of retrovirus is an essential enzyme for the growth of HIV.

[0012] Nevertheless, an effective integrase inhibitor has not been found as yet.

[0013] Known compounds comparatively similar to the anti-HIV agent of the present invention are described in the following.

[0014] WO02/0704865 describes the following compounds [A], [B] and the like as anti-HIV agents having an integrase inhibitory activity (see WO02/0704865 p. 118, Example I-62, p. 203, Example I-152).

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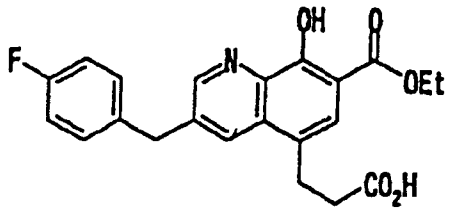
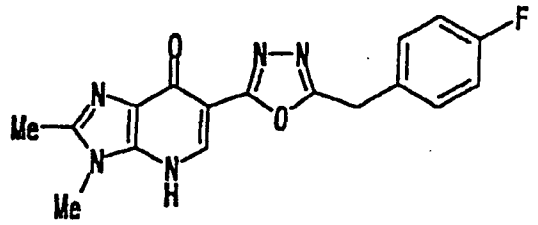
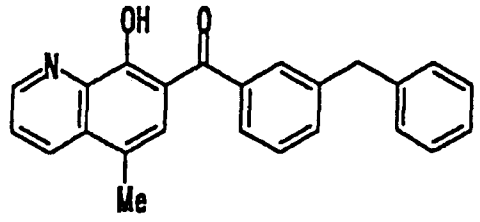


Compound [A]



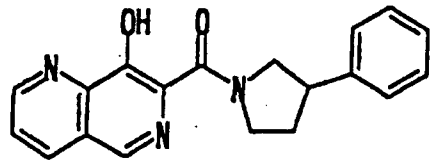
Compound [B]

[0015] In addition, WO02/36734 describes the following compound [C] and the like as anti-HIV agents having an integrase inhibitory activity (see WO02/36734, p. 106, Ex. 3).



Compound [C]

[0016] Moreover, WO02/55079 describes the following compound [D] and the like as anti-HIV agents having an integrase inhibitory activity (see WO02/055079, p. 79, Ex. 1).

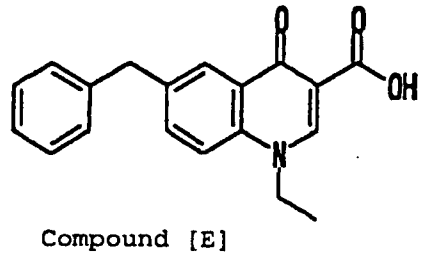


Compound [D]

[0017] However, these publications do not include the 4-oxoquinoline compound disclosed in the present specification, or any description suggestive thereof.

[0018] The compounds comparatively similar to the compound of the present invention are described in the following.

[0019] US3,472,859 describes the following compound [E] and the like as antibacterial agents or antimicrobial agents (see US3,4.72,859, column 11, line 10).



Compound [E]

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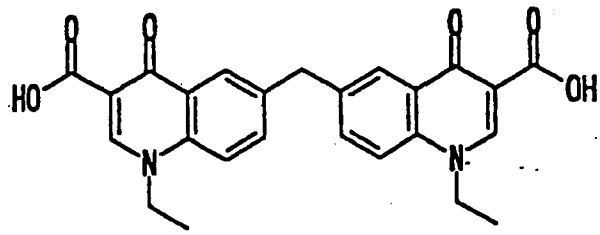
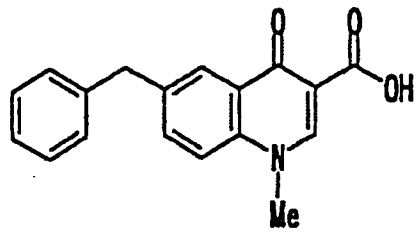
[0020] In addition, JP-A-48-26772 describes the following compound [F] and the like as compounds having an antibacterial activity (see, e.g., JP-A-48-26772, p. 6, Example 9; KYUSHU KYORITSU UNIVERSITY, Memoirs Department of Engineering, No. 14, pp. 21-32, March 1990; Memoirs Kyushu Inst. Tech. (Eng.) No.14, pp. 13-16, 1984).



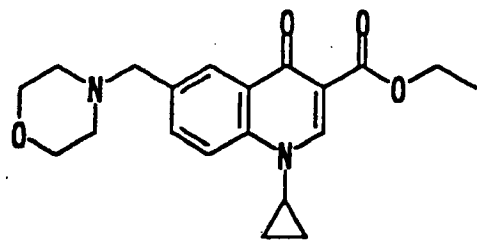
Compound [F]

[0021] As dehydrogenase inhibitors, moreover, the following compound [G] and the like have been pharmacologically evaluated (see Journal of Medicinal Chemistry, table 1, vol. 15, No. 3, pp. 235-237, 1972).



Compound [G]

[0022] In addition, JP-A-2002-534416 (patent family: WO00/40561, US6,248,739, EP1140850) describes the following compound [H] and the like as synthetic intermediates for compounds having an antiviral activity (see JP-A-2002-534416, p. 141, compound 60).



Compound [H]

[0023] JP-A-2002-534417 (patent family: WO00/40563, US6,248,736, EP1140851) also describes the following compound [J] and the like as synthetic intermediates for compounds having an antiviral activity (see JP-A-2002-534417, p. 34, compound 18).

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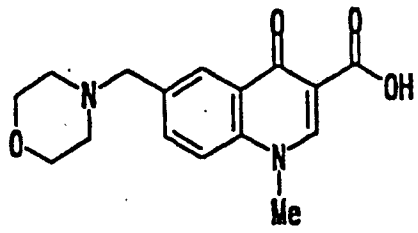
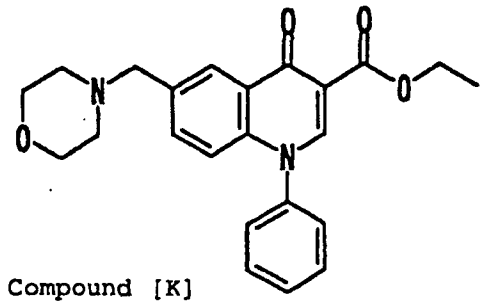


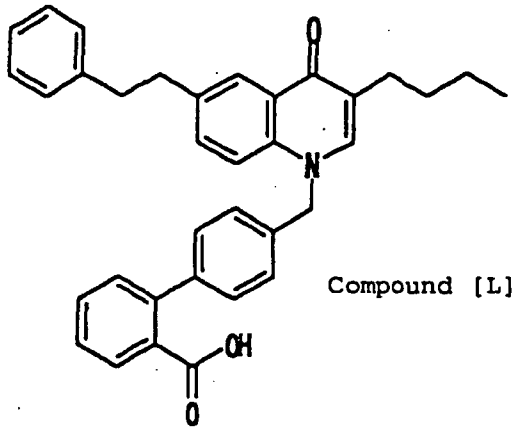
Compound [J]

[0024] Moreover, WO01/98275 (patent family: US2001/103220) also describes the following compound [K] and the like as synthetic intermediates for compounds having an antiviral activity (see WO01/98275, p. 39, line 29).



Compound [K]

[0025] Furthermore, JP-A-4-360872 (patent family: US5,985,894, EP498721B1) describes the following compound [L] and the like as compounds having an antagonistic action against anti-angiotensin II receptor (see JP-A-4-360872, p. 64, Table 1)).



Compound [L]

Disclosure of the Invention

[0026] From the findings based on the pharmacological researches and clinical results obtained so far, an anti-HIV agent is effective for the prophylaxis of the onset of AIDS and the treatment thereof, and particularly a compound having an integrase inhibitory action can provide an effective anti-HIV agent.

[0027] It is therefore an object of the present invention to provide a pharmaceutical agent having an anti-HIV action, particularly a pharmaceutical agent having an integrase inhibitory action.

[0028] *The present inventors have conducted intensive studies in an attempt to find a compound having an anti-HIV* action, particularly a compound having an integrase inhibitory action, and completed the present invention.

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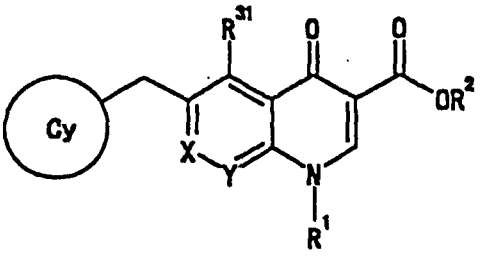
[0029] Accordingly, the present invention is shown in the following (1) to (41).

(1) An anti-HIV agent containing a 4-oxoquinoline compound represented by the following formula [I] or a pharmaceutically acceptable salt thereof as an active ingredient:



[I]

wherein

ring Cy is a C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the following group A or a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group A

wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom (s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom, group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group and R^{a3} is C_{1-4} alkyl group;

R^1 is a substituent selected from the following group B or a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B

wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A;

R^2 is a hydrogen atom or a C_{1-4} alkyl group;

R^{31} is a hydrogen atom, a cyano group, a hydroxy group, an amino group, a nitro group, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a C_{1-4} alkylsulfanyl group, a halo C_{1-4} alkyl group or a halo C_{1-4} alkyloxy group;

X is a C-R^{32} or a nitrogen atom; and

Y is a C-R^{33} or a nitrogen atom

wherein R^{32} and R^{33} are the same or different and each is hydrogen atom, cyano group, nitro group, halogen atom, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, $-OR^{a7}$, $-SR^{a7}$, $-NR^{a7}R^{a8}$, $-NR^{a7}COR^{a9}$, $-COOR^{a10}$ or $-N=CH-NR^{a10}R^{a11}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, R^{a9} is C_{1-4} alkyl group, and R^{a10} and R^{a11} are the same or different and each is hydrogen atom or C_{1-4} alkyl group.

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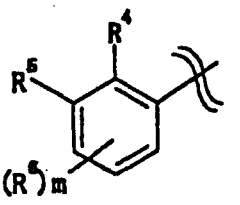
(2) The anti-HIV agent of the above-mentioned (1), wherein X is C-R^{32} and Y is C-R^{33}.
(3) The anti-HIV agent of the above-mentioned (1), wherein ring Cy is



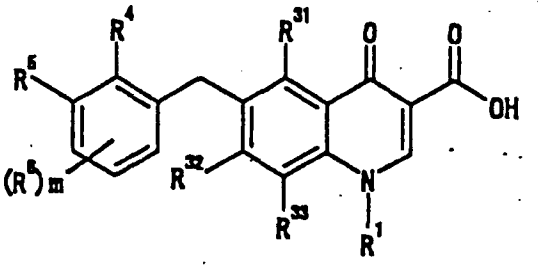
wherein

R^4 and R^6 are the same or different and each is a substituent selected from the following group A
wherein group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$
wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group and R^{a3} is C_{1-4} alkyl group;

R^5 is a substituent selected from hydrogen atom and group A, and R^4 and R^5 may form a fused ring together with a benzene ring they substitute; and

m is 0 or an integer of 1 to 3, and when m is 2 or 3, then R^6 of each m may be the same or different.

(4) The anti-HIV agent of the above-mentioned (1), wherein R^2 is a hydrogen atom.
(5) A 4-oxoquinoline compound represented by the following formula [II] or a pharmaceutically acceptable salt thereof:



[II]

wherein

R^4 and R^6 are the same or different and each is a substituent selected from the following group A
wherein group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$
wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group and R^{a3} is C_{1-4} alkyl group;

R^5 is a substituent selected from hydrogen atom and the above-mentioned group A, and R^4 and R^5 may form a fused ring together with a benzene ring they substitute;

m is 0 or an integer of 1 to 3, and when m is 2 or 3, then R^6 of each m may be the same or different;

R^1 is a substituent selected from the following group B or a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B
wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least

one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A;

R^{31} is a hydrogen atom, a cyano group, a hydroxy group, an amino group, a nitro group, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a C_{1-4} alkylsulfanyl group, a halo C_{1-4} alkyl group or a halo C_{1-4} alkyloxy group; and

R^{32} and R^{33} are the same or different and each is a hydrogen atom, a cyano group, a nitro group, a halogen atom, a C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, a heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, OR^{a7}, $-SR^{a7}$, $-NR^{a7}R^{a8}$, $-NR^{a7}COR^{a9}$, $-COOR^{a10}$ or $-N=CH-NR^{a10}R^{a11}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, R^{a9} is C_{1-4} alkyl group, and R^{a10} and R^{a11} are the same or different and each is hydrogen atom or C_{1-4} alkyl group.

(6) The 4-oxoquinoline compound of the above-mentioned (5), wherein R^{31} is a hydrogen atom, a cyano group, a hydroxy group or a C_{1-4} alkoxy group, or a pharmaceutically acceptable salt thereof.

(7) The 4-oxoquinoline compound of the above-mentioned (6), wherein R^{31} is a hydrogen atom, or a pharmaceutically acceptable salt thereof.

(8) The 4-oxoquinoline compound of the above-mentioned (5), wherein

R^{32} and R^{33} are the same or different and each is a hydrogen atom, a cyano group, a halogen atom, a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group A

wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group and R^{a3} is C_{1-4} alkyl group,

a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B

wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A,

$-OR^{a7}$, $-SR^{a7}$, $-NR^{a7}R^{a8}$, $-NR^{a7}COR^{a9}$, $-COOR^{a10}$ or $-N=CH-NR^{a10}R^{a11}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, R^{a9} is C_{1-4} alkyl group, and R^{a10} and R^{a11} are the same or different and each

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is hydrogen atom or C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

(9) The 4-oxoquinoline compound of the above-mentioned (5), wherein

R^{32} is a hydrogen atom, a cyano group, a halogen atom, a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B

wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom (s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a7}$, $-SR^{a7}$, $-NR^{a7}R^{a8}$, $-NR^{a7}COR^{a9}$ or $-COOR^{a10}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, R^{a9} is C_{1-4} alkyl group, and R^{a10} is hydrogen atom or C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

(10) The 4-oxoquinoline compound of the above-mentioned (9), wherein R^{32} is a hydrogen atom, $-OR^{a7}$ or $-NR^{a7}R^{a8}$ *wherein* R^{a7} *and* R^{a8} *are the same or different and each is hydrogen atom, group B or* C_{1-10} *alkyl group* optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, or a pharmaceutically acceptable salt thereof.

(11) The 4-oxoquinoline compound of the above-mentioned (8), wherein

R^{33} is a hydrogen atom, a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B

wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a7}$ or $-NR^{a7}R^{a8}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group, optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B,

or a pharmaceutically acceptable salt thereof.

(12) The 4-oxoquinoline compound of the above-mentioned (11), wherein

R^{33} is a hydrogen atom, $-OR^{a7}$ or $-NR^{a7}R^{a8}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B,

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or a pharmaceutically acceptable salt thereof.

(13) The 4-oxoquinoline compound of any of the above-mentioned (8) to (12), wherein

R^{a7} and R^{a8} are the same or different and each is a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A,

or a pharmaceutically acceptable salt thereof.

(14) The 4-oxoquinoline compound of the above-mentioned (5), wherein

R^4 and R^5 are the same or different and each is a substituent selected from cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a2}COOR^{a3}$ and $-COOR^{a1}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group, and R^{a3} is C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

(15) The 4-oxoquinoline compound of the above-mentioned (14), wherein

R^4 is a phenyl group, a halogen atom, a C_{1-4} alkyl group, a halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$ or $-COOR^{a1}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group, and R^{a3} is C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

(16) The 4-oxoquinoline compound of the above-mentioned (15), wherein R^4 is a halogen atom,

or a pharmaceutically acceptable salt thereof.

(17) The 4-oxoquinoline compound of the above-mentioned (5), wherein

R^5 is a hydrogen atom, a cyano group, a phenyl group, a nitro group, a halogen atom, a C_{1-4} alkyl group, a halo C_{1-4} alkyl group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$ or $-NR^{a1}COR^{a3}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group, and R^{a3} is C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

(18) The 4-oxoquinoline compound of the above-mentioned (5), wherein R^6 is a halogen atom,

or a pharmaceutically acceptable salt thereof.

(19) The 4-oxoquinoline compound of the above-mentioned (5), wherein m is 0 or 1,

or a pharmaceutically acceptable salt thereof.

(20) The 4-oxoquinoline compound of the above-mentioned (5), wherein

R^1 is a C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the following group A

wherein group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or

benzyl group and R^{a3} is C_{1-4} alkyl group,
a substituent selected from $-NR^{a4}R^{a5}$, $-NR^{a4}COR^{a6}$, $-NR^{a4}SO_2R^{a6}$ and $-NR^{a5}COOR^{a6}$.
wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, or
a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B
wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO^2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$ (wherein R^{a4}, R^{a5}, R^{a6} and group A are as defined above),

or a pharmaceutically acceptable salt thereof.

(21) The 4-oxoquinoline compound of the above-mentioned (20), wherein

R^1 is a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B
wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$
wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A,

or a pharmaceutically acceptable salt thereof.

(22) The 4-oxoquinoline compound of the above-mentioned 5, which is selected from the group consisting of the following compounds:

6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-1),
6-(2,3-Dichlorobenzyl)-8-fluoro-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-2),
6-(2,3-Dichlorobenzyl)-1-(2-methanesulfonylaminoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-3),
6-(2,3-Dichlorobenzyl)-1-(2-imidazol-1-ylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-4),
6-(2,3-Dichlorobenzyl)-1-dimethylcarbamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-5),
6-(2,3-Dichlorobenzyl)-1-methylcarbamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-6),
1-Carbamoylmethyl-6-(2,3-Dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-7),
6-(2,3-Dichlorobenzyl)-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-8),
6-(2,3-Dichlorobenzyl)-4-oxo-1-sulfamoylmethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 1-9),
1-(2-Carboxyethyl)-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-10),
1-(2-Hydroxyethyl)-6-naphthalen-1-ylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-11),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methyl ester (Example 1-12),
1-(2-Carbamoylethyl)-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-13),
6-(2,3-Dichlorobenzyl)-4-oxo-1-(2-oxopropyl)-1,4-dihydroquinoline-3-carboxylic acid (Example 1-14),
1-Benzyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-15),
6-(2,3-Dichlorobenzyl)-4-oxo-1-phenethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 1-16),
6-(2,3-Dichlorobenzyl)-1-(3-phenylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-17),

6-(2,3-Dichlorobenzyl)-1-isobutyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-18),
6-(2,3-Dichlorobenzyl)-1-(4-phenylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-19),
1-Biphenyl-2-ylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-20),
6-(2,3-Dichlorobenzyl)-1-(4-hydroxybutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-21),
1-Benzo[b]thiophen-2-ylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-22),
6-(2,3-dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-23),
6-(2,3-Dichlorobenzyl)-1-(2-dimethylaminoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-24),
6-(2,3-Dichlorobenzyl)-1-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-25),
6-(2,3-Dichlorobenzyl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-26),
6-(2,3-Dichlorobenzyl)-1-(2,2,2-trifluoroethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-27),
1-Carboxymethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-28),
6-(2,3-Dichlorobenzyl)-1-[2-(4-methylthiazol-5-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-29),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-30),
6-(2,3-Dichlorobenzyl)-1-(2-methylsulfanylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-32),
6-(2-Chloro-6-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-33),
6-(2,3-Dichlorobenzyl)-1-(5-hydroxypentyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-34),
6-(2,3-dichlorobenzyl)-1-(2-morpholin-4-ylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-35),
6-(2,3-Dichlorobenzyl)-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-36),
6-(2,3-Dichlorobenzyl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-37),
6-(2,3-Dichlorobenzyl)-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylic acid (Example 1-38),
1-Butyl-6-(2,3-Dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-39),
1-Cyclopentylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-40),
6-(2,3-Dichlorobenzyl)-1-(2-methanesulfonylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-41),
1-Cyclohexylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-42),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxy-2-phenylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-43),
6-(2,3-Dichlorobenzyl)-1-(2-fluoroethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-44),
6-(2,3-Dichlorobenzyl)-4-oxo-1-(2-pyridin-2-ylethyl)-1,4-dihydroquinoline-3-carboxylic acid (Example 1-45),
1-(2-Aminoethyl)-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-46),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxy-2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-47),
1-(2-Acetylaminoethyl)-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-48),
6-(2,3-Dichlorobenzyl)-1-(2-ethoxycarbonylaminoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-49),
6-(2,3-Difluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-50),
6-(2-Chloro-4-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-51),
6-(2-Chlorobenzyl)-4-oxo-1-phenethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 1-65),
6-(2-Chloro-3-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-66),
6-(2,3-Dichlorobenzyl)-1-methylsulfanylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-68),
6-(2,3-Dichlorobenzyl)-1-methanesulfonylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-69),
1-tert-Butylsulfamoylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-70),
6-(2,3-Dichlorobenzyl)-1-methylsulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-71),
6-(2,3-Dichlorobenzyl)-1-dimethylsulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-72),
6-(2-Chloro-3,6-difluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-73),
6-(2,3-Dichlorobenzyl)-1-(2,3-Dihydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-74),
6-(2-Chloro-6-fluorobenzyl)-1-sulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-75),
6-(2-Chloro-6-fluorobenzyl)-1-methylsulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example

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1-76),
6-(2-Chloro-6-fluorobenzyl)-1-dimethylsulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-77),
6-(2-Chloro-3-methylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-79),
6-(2-Bromobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-80),
6-(2-Chloro-3-methoxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-82),
1-(2-Hydroxyethyl)-6-(2-methanesulfonylbenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-85),
6-Biphenyl-2-ylmethyl-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-86),
6-(2-Chlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-87),
6-(2-Chloro-5-methylsulfanylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-92),
1-(2-Hydroxyethyl)-4-oxo-6-(2-trifluoromethyloxybenzyl)-1,4-dihydroquinoline-3-carboxylic acid (Example 1-93),
6-(2-Chloro-5-methylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-97),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-99),
6-(3-Chloro-2,6-difluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-100),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-101),
1-Cyclopropyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-102),
1-Amino-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-1),
6-(2,3-Dichlorobenzyl)-1-methoxycarbonylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-2),
1-Acetylamino-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-3),
6-(2,3-Dichlorobenzyl)-1-methanesulfonylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-4),
6-(2,3-Dichlorobenzyl)-1-(N-methanesulfonyl-N-methylamino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-5),
6-(2,3-Dichlorobenzyl)-1-dimethylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-6),
6-(2,3-Dichlorobenzyl)-1-methylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-7),
6-(2,3-Dichlorobenzyl)-1-ethylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-8),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-5-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-1),
6-(3-Chloro-2-methylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-2),
6-(3-Chloro-2-methoxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-3),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-4),
6-(2,3-Dichlorobenzyl)-5-hydroxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-5),
6-(2,3-Dichlorobenzyl)-7-hydroxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-6),
1-(2-Hydroxyethyl)-6-(2-methylaminobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-7),
6-(2-Dimethylaminobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-8),
6-(2,3-Dichlorobenzyl)-4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylic acid (Example 3-9),
6-(2,3-Dichlorobenzyl)-1-[2-hydroxy-1-(hydroxymethyl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-10),
1-Cyclobutyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-12),
1-Cyclopentyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-13),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-14),
6-(2-Dimethylsulfamoylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-16),
6-(3-Chloro-2,4-difluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-17),

6-(2-Carboxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-18),
1-(2-Hydroxyethyl)-6-(2-methylsulfamoylbenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-19),
6-(2,3-Dichlorobenzyl)-7-ethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-20),
7-Chloro-6-(2,3-dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-21),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-7-trifluoromethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 3-22),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-23),
(R)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-24),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-8-trifluoromethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 3-25),
6-(3-Chloro-2-fluorobenzyl)-1-[2-hydroxy-1-(hydroxymethyl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-26),
7-Cyano-6-(2,3-dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-27),
6-(2-Ethylmethylaminobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-28),
6-[2-(N-Methyl-N-propylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-29),
6-[2-(N-Benzyl-N-methylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-30),
6-[2-(N-Methanesulfonyl-N-methylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-31),
6-[2-(N-Isopropyl-N-methylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-32),
1-tert-Butyl-6-(3-Chloro-2-fluorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-33),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-34),
8-Amino-6-(3-chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-35),
7-Carboxy-6-(2,3-dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-36),
6-(3-Chloro-2,6-difluorobenzyl)-1-(2-hydroxyethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-37),
6-(3-Chloro-2-fluorobenzyl)-8-dimethylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-38),
8-Acetylamino-6-(3-chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-39),
5-Cyano-6-(2,3-dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-40),
6-[2-(N-Acetyl-N-methylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-41),
6-(2-Diethylaminobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-42),
6-(3-Chloro-2-fluorobenzyl)-1-(1,1-dimethyl-2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-43),
6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-44),
6-(3-Chloro-2-fluorobenzyl)-7,8-dimethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-45),
6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-47),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-8-methylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-48),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-7-propyloxy-1,4-dihydroquinoline-3-carboxylic acid

(Example 3-49),
6-(3-Chloro-2-fluorobenzyl)-7-(dimethylaminomethyleneamino)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-50),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methyl ester (Example 3-51),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-8-phenoxy-1,4-dihydroquinoline-3-carboxylic acid (Example 3-52),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-53),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-8-propylamino-1,4-dihydroquinoline-3-carboxylic acid (Example 3-54),
6-(3-Chloro-2-fluorobenzyl)-8-ethylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-55),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-56),
(S)-6-(3-Chloro-2,6-difluorobenzyl)-1-(2-hydroxy-1-methylethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-57),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-8-propyloxy-1,4-dihydroquinoline-3-carboxylic acid (Example 3-58),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-59),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-60),
(S)-6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-61),
6-(3-Chloro-2-fluorobenzyl)-7-dimethylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-62),
6-(3-Chloro-2-fluorobenzyl)-7-cyclohexylmethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-63),
6-(3-Chloro-2-fluorobenzyl)-8-diethylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-64),
6-(3-Chloro-2-fluorobenzyl)-7-methylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-65),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-7-pyrrolidin-1-yl-1,4-dihydroquinoline-3-carboxylic acid (Example 3-66),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-67),
(S) -6- (3-Chloro-2-fluorobenzyl) -7-ethoxy-1- [1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-68),
6-(3-Chloro-2-fluorobenzyl)-8-cyclohexylmethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-69),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-70),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-3-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-71),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-72),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-73),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-7-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-74),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-75),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-(2-hydroxyethyloxy)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-76),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-(3-hydroxypropyloxy)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-77),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-8-(2-hydroxyethylamino)-4-oxo-1,4-dihydroquinoline-3-car-

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boxylic acid (Example 3-78),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-79),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-dimethylamino-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-80),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-phenylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-81),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-82),
6-(3-Chloro-2-fluorobenzyl)-1-((1S,2S)-1-hydroxymethyl-2-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-83),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-84),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-benzyl-2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-85),
6-(2-Chloro-5-methanesulfonylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-1),
6-(2-Ethylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-4),
6-(2-Chloro-5-methylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-5),
6-(2-Chloro-5-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-6),
6-(5-Bromo-2-chlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-7),
6-(2,3-Dichlorobenzyl)-7-fluoro-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-9),
6-(2-Chloro-5-hydroxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-11),
6-(2,3-Dichlorobenzyl)-5-fluoro-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-12),
6-(2-Ethoxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-13),
6-(2-Hydroxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-14),
6-(2,3-Dichlorobenzyl)-7-methyl-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-15),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-16),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-17),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-18),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-19),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-20),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-[1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-21),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2-cyclohexyl-1-(hydroxymethyl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-22),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-3-methylbutyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-23),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-24),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-3-methylbutyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-25),
(S)-6-(3-Chloro-2-fluorobenzyl)-[2,2-dimethyl-1-(hydroxymethyl)propyl]-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-26),
6-(3-Chloro-2-fluorobenzyl)-1-((1S,2S)-1-hydroxymethyl-2-methylbutyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-27),
6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-((1S,2S)-1-hydroxymethyl-2-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-28),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-7-methylsulfanyl-4-oxo-1,4-dihydroquinoline-

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3-carboxylic acid (Example 4-29),
(S)-6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-(1-hydroxymethyl-2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-30),
(S)-6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-31),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-32),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-33),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-34),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-35),
(S)-6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-[1-(hydroxymethyl)butyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-36),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-37),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-38),
6-(3-Chloro-2-fluorobenzyl)-1-((1S,2S)-1-hydroxymethyl-2-methylbutyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-39),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-40),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-8-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-41),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-42),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-7-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-43),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-44),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-(1-hydroxymethyl-2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-45),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-46),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-47),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-[1-(hydroxymethyl)butyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-48),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-49),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-50) and
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-52),

or a pharmaceutically acceptable salt thereof.

(23) A pharmaceutical composition comprising a 4-oxoquinoline compound of any of the above-mentioned (5) to (22), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(24) An integrase inhibitor comprising a 4-oxoquinoline compound of any of the above-mentioned (1) to (22), or a pharmaceutically acceptable salt thereof, as an active ingredient.

(25) An antiviral agent comprising a 4-oxoquinoline compound of any of the above-mentioned (5) to (22), or a pharmaceutically acceptable salt thereof, as an active ingredient.

(26) An anti-HIV agent comprising a 4-oxoquinoline compound of any of the above-mentioned (5) to (22), or a pharmaceutically acceptable salt thereof, as an active ingredient.

(27) An anti-HIV composition comprising a 4-oxoquinoline compound of any of the above-mentioned (1) to (22), or a pharmaceutically acceptable salt thereof, and other one or more kinds of anti-HIV active substance as an active ingredient.

(28) An anti-HIV agent comprising a 4-oxoquinoline compound of any of the above-mentioned (1) to (22), or a pharmaceutically acceptable salt thereof, as an active ingredient, for multiple drug therapy with other anti-HIV agent(s).

(29) Use of a 4-oxoquinoline compound of any of the above-mentioned (5) to (22) or a pharmaceutically acceptable salt thereof, for the production of an anti-HIV agent.

(30) Use of a 4-oxoquinoline compound of any of the above-mentioned (5) to (22) or a pharmaceutically acceptable salt thereof, for the production of an integrase inhibitor.

(31) Use of a 4-oxoquinoline compound of any of the above-mentioned (5) to (22) or a pharmaceutically acceptable salt thereof, for the production of an antiviral agent.

(32) A method for the prophylaxis or treatment of an HIV infectious disease, which comprises administering an effective amount of a 4-oxoquinoline compound of any of the above-mentioned (5) to (22) or a pharmaceutically acceptable salt thereof to a mammal.

(33) The method for the prophylaxis or treatment of an HIV infectious disease according to the above-mentioned (32), which further comprises administering an effective amount of at least one different anti-HIV active substance to said mammal.

(34) A method for inhibiting integrase, which comprises administering an effective amount of a 4-oxoquinoline compound of any of the above-mentioned (5) to (22) or a pharmaceutically acceptable salt thereof to a mammal.

(35) A method for the prophylaxis or treatment of a virus infectious disease, which comprises administering an effective amount of a 4-oxoquinoline compound of any of the above-mentioned (5) to (22) or a pharmaceutically acceptable salt thereof to a mammal.

(36) An anti-HIV composition comprising a 4-oxoquinoline compound of any of the above-mentioned (5) to (22) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(37) A pharmaceutical composition for inhibiting integrase, which comprises a 4-oxoquinoline compound of any of the above-mentioned (5) to (22) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(38) An antiviral composition comprising a 4-oxoquinoline compound of any of the above-mentioned (5) to (22) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(39) A commercial package comprising the composition of the above-mentioned 36 and a written matter associated therewith, the written matter stating that the composition can or should be used for the prophylaxis or treatment of an HIV infectious disease.

(40) A commercial package comprising the composition of the above-mentioned (37) and a written matter associated therewith, the written matter stating that the composition can or should be used for inhibiting integrase.

(41) A commercial package comprising the composition of the above-mentioned (38) and a written matter associated therewith, the written matter stating that the composition can or should be used for the prophylaxis or treatment of a viral infectious disease.

[0030] The definitions of each substituent and each moiety used in the present specification are as follows.

[0031] The "halogen atom" means fluorine atom, chlorine atom, bromine atom or iodine atom, preferably fluorine atom, chlorine atom or bromine atom.

[0032] As R^{32}, R^{33}, R^4, R^5, R^6, $R^{6'}$, $R^{6''}$, $R^{6'''}$ and group A, fluorine atom and chlorine atom are particularly preferable, as R^{32} and R^5, chlorine atom is more preferable, and as R^{31}, R^{33}, R^4, $R^{6'}$, $R^{6'''}$ and the halogen atom of the "$C_{1\text{-}10}$ alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B", fluorine atom is more preferable.

[0033] The "$C_{1\text{-}4}$ alkyl group" means a straight chain or branched chain alkyl group having 1 to 4 carbon atoms, which is specifically methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group or tert-butyl group.

[0034] As R^2, R^{31} and R^{a6}, methyl group and ethyl group are preferable, as R^4, R^5, R^6, $R^{6'}$, $R^{6''}$, $R^{6'''}$ and group A, methyl group, ethyl group and isopropyl group are preferable, methyl group is more preferable, as R^{a1} and R^{a2}, methyl group, ethyl group, propyl group and isopropyl group are preferable, methyl group is more preferable, as R^{a3}, R^{a9}, R^{a10}, R^{a11} and group A, methyl group is preferable, and as R^{a4} and R^{a5}, methyl group, ethyl group and tert-butyl group are preferable.

[0035] The "halo $C_{1\text{-}4}$ alkyl group" is "$C_{1\text{-}4}$ alkyl group" defined above, which is substituted by 1 to 9, preferably 1 to 3, "halogen atom" defined above.

[0036] Specific examples thereof include 2-fluoroethyl group, 2-chloroethyl group, 2-bromomethyl group, 3-fluoropropyl group, 3-chloropropyl group, 4-fluorobutyl group, 4-chlorobutyl group, trifluoromethyl group, 2,2,2-trifluoroethyl group, 3,3,3-trifluoropropyl group, 4,4,4-trifluorobutyl group, pentafluoroethyl group, 2,2,2-trifluoro-1-trifluoromethylethyl group and the like.

[0037] As R^{31}, R^4, R^5, R^6, $R^{6'}$, $R^{6''}$, $R^{6'''}$ and group A, trifluoromethyl group is preferable.

[0038] "The "C_{1-4} alkoxy group" is an alkyloxy group wherein its alkyl moiety is "C_{1-4} alkyl group" defined above, which is specifically exemplified by methoxy group, ethoxy group, propoxy group, isopropyloxy group, butoxy group, isobutyloxy group, tert-butyloxy group and the like.

[0039] It is preferably methoxy group for R^{31}.

[0040] The "C_{1-4} alkylsulfanyl group" is an alkylsulfanyl group wherein its alkyl moiety is "C_{1-4} alkyl group" defined above. Specific examples thereof include methylsulfanyl group, ethylsulfanyl group, propylsulfanyl group, isopropylsulfanyl group, butylsulfanyl group, isobutylsulfanyl group, tert-butylsulfanyl group and the like.

[0041] It is preferably methylsulfanyl group for R^{31}.

[0042] The "halo C_{1-4} alkyloxy group" is a halo C_{1-4} alkyloxy group wherein its haloalkyl moiety is "halo C_{1-4} alkyl group" defined above.

[0043] Specific examples thereof include 2-fluoroethyloxy group, 2-chloroethyloxy group, 2-bromomethyloxy group, 3-fluoropropyloxy group, 3-chloropropyloxy group, 4-fluorobutyloxy group, 4-chlorobutyloxy group, trifluoromethyloxy group, 2,2,2-trifluoroethyloxy group, 3,3,3-trifluoropropyloxy group, 4,4,4-trifluorobutyloxy group, pentafluoroethyloxy group, 2,2,2-trifluoro-1-trifluoromethylethyloxy group and the like.

[0044] It is preferably trifluoromethyloxy group for R^{31}, R^4, R^5, R^6, $R^{6'}$, $R^{6''}$, $R^{6'''}$ and group A.

[0045] The "C_{3-10} carbon ring group" is a saturated or unsaturated cyclic hydrocarbon group having 3 to 10 carbon atoms, which is specifically exemplified by aryl group, cycloalkyl group, cycloalkenyl group or a fused ring thereof.

[0046] Specific examples of the "aryl group" include phenyl group, naphthyl group, pentalenyl group, azulenyl group and the like, preferably phenyl group and naphthyl group, particularly preferably phenyl group.

[0047] Specific examples of the "cycloalkyl group" include cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, adamantyl group, norbornanyl group and the like, preferably cyclopropyl group, cyclobutyl group, cyclopentyl group and cyclohexyl group.

[0048] The "cycloalkenyl group" contains at least one, preferably 1 or 2 double bonds, and is specifically exemplified by cyclopropenyl group, cyclobutenyl group, cyclopentenyl group, cyclopentadienyl group, cyclohexenyl group, cyclohexadienyl group (2,4-cyclohexadien-1-yl group, 2,5-cyclohexadien-1-yl group and the like), cycloheptenyl group and cyclooctenyl group and the like.

[0049] Specific examples of the fused ring of these "aryl group", "cycloalkyl group" and "cycloalkenyl group" include indenyl group, indanyl group, 1,4-dihydronaphthyl group, 1,2,3,4-tetrahydronaphthyl group (1,2,3,4-tetrahydro-2-naphthyl group, 5,6,7,8-tetrahydro-2-naphthyl group and the like), perhydronaphthyl group and the like. Preferably, it is a fused ring of phenyl group and a different ring, which is exemplified by indenyl group, indanyl group, 1,4-dihydronaphthyl group, 1,2,3,4-tetrahydronaphthyl group and the like, and indanyl group is particularly preferable.

[0050] The "C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from group A" is a "C_{3-10} carbon ring group" defined above, which is optionally substituted by 1 to 5, preferably 1 to 3, substituents selected from the following group A, and includes non-substituted "C_{3-10} carbon ring group".

[0051] The "group A" is a group constituting of cyano group, phenyl group, nitro group, "halogen atom" defined above, "C_{1-4} alkyl group" defined above, "halo C_{1-4} alkyl group" defined above, "halo C_{1-4} alkyloxy group" defined above, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$, wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, "C_{1-4} alkyl group" defined above or benzyl group, and R^{a3} is "C_{1-4} alkyl group" defined above.

[0052] Specific examples of "$-OR^{a1}$" include hydroxy group, methoxy group, ethoxy group, propoxy group, isopropyloxy group, tert-butoxy group and the like,

specific examples of "$-SR^{a1}$" include mercapto group, methylsulfanyl group, ethylsulfanyl group, propylsulfanyl group, isopropylsulfanyl group, tert-butylsulfanyl group and the like,

specific examples of "$-NR^{a1}R^{a2}$" include amino group, methylamino group, ethylamino group, propylamino group, isopropylamino group, tert-butylamino group, dimethylamino group, diethylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-isopropyl-N-methylamino group, N-benzyl-N-methylamino group and the like,

specific examples of "$-CONR^{a1}R^{a2}$" include carbamoyl group, methylaminocarbonyl group, ethylaminocarbonyl group, propylaminocarbonyl group, isopropylaminocarbonyl group, tert-butylaminocarbonyl group, dimethylaminocarbonyl group, diethylaminocarbonyl group, N-methyl-N-ethylaminocarbonyl group and the like,

specific examples of "$-SO_2NR^{a1}R^{a2}$" include sulfamoyl group, methylaminosulfonyl group, ethylaminosulfonyl group, propylaminosulfonyl group, isopropylaminosulfonyl group, tert-butylaminosulfonyl group, dimethylaminosulfonyl group, diethylaminosulfonyl group, N-methyl-N-ethylaminosulfonyl group and the like,

specific examples of "$-COR^{a3}$" include acetyl group, propionyl group, butyryl group, isobutyryl group, pivaloyl group and the like,

specific examples of "$-NR^{a1}COR^{a3}$" include acetylamino group, propionylamino group, butyrylamino group, isobutyrylamino group, pivaloylamino group, N-acetyl-N-methylamino group and the like,

specific examples of "$-SO_2R^{a3}$" include methylsulfonyl group, ethylsulfonyl group, propylsulfonyl group, isopropylsulfonyl group, tert-butylsulfonyl group and the like,

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specific examples of "-$NR^{a1}SO_2R^{a3}$" include methylsulfonylamino group, ethylsulfonylamino group, propylsulfonylamino group, isopropylsulfonylamino group, tert-butylsulfonylamino group, N-methyl-N-(methylsulfonyl)amino group and the like,

specific examples of "-$COOR^{a1}$" include carboxyl group, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropyloxycarbonyl group, tert-butoxycarbonyl group and the like, and

specific examples of "$NR^{a2}COOR^{a3}$" include methoxycarbonylamino group, ethoxycarbonylamino group, propoxycarbonylamino group, isopropyloxycarbonylamino group, tert-butoxycarbonylamino group and the like.

[0053] As group A, cyano group, phenyl group, nitro group, fluorine atom, chlorine atom, bromine atom, methyl group, ethyl group, isopropyl group, trifluoromethyl group, trifluoromethyloxy group, hydroxy group, methoxy group, ethoxy group, propoxy group, methylsulfanyl group, amino group, methylamino group, ethylamino group, isopropylamino group, dimethylamino group, diethylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-isopropyl-N-methylamino group, N-benzyl-N-methylamino group, carbamoyl group, methylaminocarbonyl group, dimethylaminocarbonyl group, sulfamoyl group, methylaminosulfonyl group, dimethylaminosulfonyl group, acetyl group, acetylamino group, N-acetyl-N-methylamino group, methylsulfonyl group, methylsulfonylamino group, N-methyl-N-(methylsulfonyl)amino group, carboxyl group, methoxycarbonyl group, carboxyamino group and methoxycarbonylamino group are preferable.

[0054] As group A, cyano group, phenyl group, nitro group, fluorine atom, chlorine atom, bromine atom, methyl group, trifluoromethyl group, trifluoromethyloxy group, hydroxy group, methoxy group, ethoxy group, methylsulfanyl group, amino group, methylamino group, dimethylamino group, diethylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-isopropyl-N-methylamino group, N-benzyl-N-methylamino group, dimethylaminocarbonyl group, methylaminosulfonyl group, dimethylaminosulfonyl group, acetylamino group, N-acetyl-N-methylamino group, methylsulfonyl group, N-methyl-N-(methylsulfonyl)amino group and carboxyl group are particularly preferable, and fluorine atom and chlorine atom are more preferable.

[0055] The number of substituents is preferably 1 to 3, and when "C_{3-10} carbon ring group" is phenyl group, ring Cy is preferably monosubstituted at the 2-position, monosubstituted at the 3-position, disubstituted at the 2,3-positions, disubstituted at the 2,4-positions, disubstituted at the 2,5-positions, disubstituted at the 2,6-positions, trisubstituted at the 2,3,4-positions, trisubstituted at the 2,3,5-positions, trisubstituted at the 2,3,6-positions, particularly preferably disubstituted at the 2,3-positions.

[0056] Specific examples of the "C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from group A" include phenyl group, naphthyl group, 2-fluorophenyl group, 2-chlorophenyl group, 2-bromophenyl group, 3-fluorophenyl group, 3-chlorophenyl group, 3-bromophenyl group, 4-fluorophenyl group, 2-nitrophenyl group, 3-nitrophenyl group, 2-cyanophenyl group, 3-cyanophenyl group, 2-methylphenyl group, 3-methylphenyl group, 4-methylphenyl group, 2-ethylphenyl group, 3-ethylphenyl group, 2-isopropylphenyl group, 3-isopropylphenyl group, 2-trifluoromethylphenyl group, 3-trifluoromethylphenyl group, 2-hydroxyphenyl group, 3-hydroxyphenyl group, 4-hydroxyphenyl group, 2-methoxyphenyl group, 3-methoxyphenyl group, 2-ethoxyphenyl group, 3-ethoxyphenyl group, 2-propoxyphenyl group, 3-propoxyphenyl group, 2-(trifluoromethyl)phenyl group, 3-(trifluoromethyl)phenyl group, 2-(trifluoromethyloxy)phenyl group, 3-(trifluoromethyloxy)phenyl group, 2-methylsulfamoylphenyl group, 3-methylsulfamoylphenyl group, 2-aminophenyl group, 3-aminophenyl group, 2-(methylamino)phenyl group, 3-(methylamino)phenyl group, 2-(dimethylamino)phenyl group, 3-(dimethylamino)phenyl group, 2-(acetylamino)phenyl group, 3-(acetylamino)phenyl group, 2-biphenyl group, 3-biphenyl group, 2-(methylsulfonyl)phenyl group, 3-(methylsulfonyl)phenyl group, 2-sulfamoylphenyl group, 3-sulfamoylphenyl group, 2-(methylaminosulfonyl)phenyl group, 3-(methylaminosulfonyl)phenyl group, 2-(dimethylaminosulfonyl)phenyl group, 3-(dimethylaminosulfonyl)phenyl group, 2-(dimethylsulfonyl)phenyl group, 2-(methylsulfonylamino)phenyl group, 3-(methylsulfonylamino)phenyl group, 2-carbamoylphenyl group, 3-carbamoylphenyl group, 2-(methylcarbamoyl)phenyl group, 3-(methylcarbamoyl)phenyl group, 2-(dimethylcarbamoyl)phenyl group, 3-(dimethylcarbamoyl)phenyl group, 2,3-difluorophenyl group, 2,3-dichlorophenyl group, 2,3-dibromophenyl group, 2,4-difluorophenyl group, 2,4-dichlorophenyl group, 2,5-dichlorophenyl group, 2,6-dichlorophenyl group, 2-chloro-3-fluorophenyl group, 2-chloro-4-fluorophenyl group, 2-chloro-5-fluorophenyl group, 2-chloro-6-fluorophenyl group, 3-chloro-2-fluorophenyl group, 5-chloro-2-fluorophenyl group, 5-bromo-2-chlorophenyl group, 2-chloro-5-nitrophenyl group, 2-chloro-3-methylphenyl group, 2-chloro-5-methylphenyl group, 2-chloro-3-(trifluoromethyl)phenyl group, 2-chloro-5-(trifluoromethyl)phenyl group, 2-chloro-3-hydroxyphenyl group, 2-chloro-5-hydroxyphenyl group, 2-chloro-3-methoxyphenyl group, 2-chloro-5-methoxyphenyl group, 2-chloro-3-methylsulfamoylphenyl group, 2-chloro-5-methylsulfamoylphenyl group, 2-chloro-3-aminophenyl group, 2-chloro-5-aminophenyl group, 2-chloro-3-(methylamino)phenyl group, 2-chloro-5-(methylamino)phenyl group, 2-chloro-3-(dimethylamino)phenyl group, 2-chloro-5-(dimethylamino)phenyl group, 2-chloro-3-(acetylamino)phenyl group, 2-chloro-5-(acetylamino)phenyl group, 2-chloro-3-(methylsulfonyl)phenyl group, 2-chloro-5-(methylsulfonyl)phenyl group, 2-chloro-3-(methylsulfonylamino)phenyl group, 2-chloro-5-(methylsulfonylamino)phenyl group, 2,3,4-trifluorophenyl group, 2-chloro-3,4-difluorophenyl group, 2-chloro-3,5-difluorophenyl group, 2-chloro-3,6-difluorophenyl group, 2-chloro-4,5-difluorophenyl group, 2-chloro-4,6-difluorophenyl group, 3-chloro-2,4-difluorophenyl group, 3-chloro-2,5-difluorophenyl group, 3-chloro-2,6-difluor-

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ophenyl group, 2,3-dichloro-4-fluorophenyl group, 3-chloro-2-fluoro-5-trifluoromethylphenyl group, 2-chloro-3,5,6-trifluorophenyl group, 3-chloro-2,4,5-trifluorophenyl group, 3-chloro-2,4,6-trifluorophenyl group, 2,3-dichloro-4,5,6-trifluorophenyl group, 3,5-dichloro-3,4,6-trifluorophenyl group, 2,6-dichloro-3,4,5-trifluorophenyl group, perfluorophenyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, 2-hydroxycyclopropyl group, 3-hydroxycyclobutyl group, 3-hydroxycyclopentyl group, 2-hydroxycyclohexyl group, 3-hydroxycyclohexyl group, 4-hydroxycyclohexyl group, 4-indanyl group and 1H-inden-4-yl group.

[0057] The ring Cy is preferably phenyl group, naphthyl group, 2-chlorophenyl group, 3-chlorophenyl group, 2-bromophenyl group, 3-bromophenyl group, 2-ethylphenyl group, 3-ethylphenyl group, 2-hydroxyphenyl group, 2-ethoxyphenyl group, 3-(trifluoromethyloxy)phenyl group, 3-(methylsulfonyl)phenyl group, 2,3-difluorophenyl group, 2,3-dichlorophenyl group, 2-chloro-3-fluorophenyl group, 2-chloro-4-fluorophenyl group, 2-chloro-5-fluorophenyl group, 2-chloro-6-fluorophenyl group, 3-chloro-2-fluorophenyl group, 5-bromo-2-chlorophenyl group, 2-chloro-5-methylphenyl group, 2-chloro-5-hydroxyphenyl group, 2-chloro-5-(methylsulfonyl)phenyl group, 2-chloro-3,6-difluorophenyl group, 3-chloro-2,4-difluorophenyl group, 3-chloro-2,6-difluorophenyl group, 2-chloro-3-methylphenyl group, 3-chloro-2-methylphenyl group, 2-chloro-3-methoxyphenyl group, 3-chloro-2-methoxyphenyl group, 3-nitrophenyl group, 3-cyanophenyl group, 4-methylphenyl group, 3-trifluoromethylphenyl group, 2-(trifluoromethyloxy)phenyl group, 3-hydroxyphenyl group, 3-ethoxyphenyl group, 3-aminophenyl group, 2-(methylamino)phenyl group, 2-(dimethylamino)phenyl group, 2-(diethylamino)phenyl group, 2-(N-ethyl-N-methylamino)phenyl group, 2-(N-isopropyl-N-methylamino)phenyl group, 2-(N-benzyl-N-methylamino)phenyl group, 2-(N-acetyl-N-methylamino)phenyl group, 2-(N-methyl-N-methylsulfonylamino)phenyl group, 3-(methylamino)phenyl group, 2-carboxyphenyl group, 3-(dimethylaminocarbonyl)phenyl group, 3-(acetylamino)phenyl group, 2-biphenyl group, 2-(methylsulfonyl)phenyl group, 2-chloro-5-methylsulfanylphenyl group, 2-chloro-5-methylphenyl group, 2-(methylaminosulfonyl)phenyl group, 2-(dimethylaminosulfonyl)phenyl group or 3-(dimethylaminosulfonyl)phenyl group, particularly preferably 2-chlorophenyl group, 2-bromophenyl group, 2-ethylphenyl group, 2-hydroxyphenyl group, 2-ethoxyphenyl group, 2,3-difluorophenyl group, 2,3-dichlorophenyl group, 2-chloro-3-fluorophenyl group, 3-chloro-2-fluorophenyl group, 2-chloro-4-fluorophenyl group, 2-chloro-5-fluorophenyl group, 2-chloro-6-fluorophenyl group, 5-bromo-2-chlorophenyl group, 2-chloro-5-hydroxyphenyl group, 2-chloro-5-(methylsulfonyl)phenyl group, 2-chloro-3,6-difluorophenyl group, 3-chloro-2,6-difluorophenyl group, 2-chloro-3-methylphenyl group, 2-chloro-3-methoxyphenyl group, 2-trifluoromethylphenyl group, 2-(methylsulfonyl)phenyl group, 2-chloro-5-methylsulfanylphenyl group, 2-chloro-5-methylphenyl group or 2-(dimethylaminosulfonyl)phenyl group, and more preferably 2,3-dichlorophenyl group, 2,3-difluorophenyl group, 2-chloro-3-fluorophenyl group or 3-chloro-2-fluorophenyl group.

[0058] R^1 and group B are preferably phenyl group, 3,4-dichlorophenyl group, 2-biphenyl group, cyclopropyl group, 2-hydroxycyclopropyl group, cyclobutyl group, 2-hydroxycyclobutyl group, 3-hydroxycyclobutyl group, cyclopentyl group, 2-hydroxycyclopentyl group, 3-hydroxycyclopentyl group, cyclohexyl group, 2-hydroxycyclohexyl group, 3-hydroxycyclohexyl group and 4-hydroxycyclohexyl group, particularly preferably phenyl group, 3,4-dichlorophenyl group, 2-biphenyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group and cyclohexyl group.

[0059] As R^{32}, R^{33}, R^1 and group B, phenyl group and cyclohexyl group are preferable.

[0060] The "heterocyclic group" means a saturated or unsaturated (inclusive of partially unsaturated and completely unsaturated ones) monocyclic 5- or 6-membered heterocycle containing, besides carbon atom, at least one, preferably 1 to 4, heteroatoms selected from nitrogen atom, oxygen atom and sulfur atom, a fused ring of these heterocycles, or a fused ring of C_{3-10} carbon ring and heterocycle, wherein the carbon ring is selected from benzene, cyclopentane and cyclohexane.

[0061] Examples of the "saturated monocyclic heterocyclic group" include pyrrolidinyl group, tetrahydrofuryl group, tetrahydrothienyl group, imidazolidinyl group, pyrazolidinyl group, 1,3-dioxolanyl group, 1,3-oxathiolanyl group, oxazolidinyl group, thiazolidinyl group, piperidinyl group, piperazinyl group, tetrahydropyranyl group, tetrahydrothiopyranyl group, dioxanyl group, morpholinyl group, thiomorpholinyl group, 2-oxopyrrolidinyl group, 2-oxopiperidinyl group, 4-oxopiperidinyl group, 2,6-dioxopiperidinyl group and the like. Preferably, it is pyrrolidinyl group, piperidinyl group or morpholinyl group.

[0062] Examples of the "unsaturated monocyclic heterocyclic group" include pyrrolyl group, furyl group, thienyl group, imidazolyl group, 1,2-dihydro-2-oxoimidazolyl group, pyrazolyl group, diazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, isothiazolyl group, 1,2,4-triazolyl group, 1,2,3-triazolyl group, tetrazolyl group, 1,3,4-oxadiazolyl group, 1,2,4-oxadiazolyl group, 1,3,4-thiadiazolyl group, 1,2,4-thiadiazolyl group, furazanyl group, pyridyl group, pyrimidinyl group, 3,4-dihydro-4-oxopyrimidinyl group, pyridazinyl group, pyrazinyl group, 1,3,5-triazinyl group, imidazolinyl group, pyrazolinyl group, oxazolinyl group (2-oxazolinyl group, 3-oxazolinyl group, 4-oxazolinyl group), isoxazolinyl group, thiazolinyl group, isothiazolinyl group, pyranyl group, 2-oxopyranyl group, 2-oxo-2,5-dihydrofuranyl group and 1,1-dioxo-1H-isothiazolyl group. Preferable examples include pyrrolyl group, furyl group, thienyl group, imidazolyl group, pyrazolyl group, oxazolyl group, isooxazolyl group, thiazolyl group, isothiazolyl group, pyridyl group, 2-oxo-2,5-dihydrofuranyl group and 1,1-dioxo-1H-isothiazolyl group.

[0063] As a "heterocyclic group, which is a fused ring", indolyl group (e.g., 4-indolyl group, 7-indolyl group and the

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like), isoindolyl group, 1,3-dihydro-1,3-dioxoisoindolyl group, benzofuranyl group (e.g., 4-benzofuranyl group, 7-benzofuranyl group and the like), indazolyl group, isobenzofuranyl group, benzothiophenyl group (e.g., 4-benzothiophenyl group, 7-benzothiophenyl group and the like), benzoxazolyl group (e.g., 4-benzoxazolyl group, 7-benzooxazolyl group and the like), benzimidazolyl group (e.g., 4-benzimidazolyl group, 7-benzimidazolyl group and the like), benzothiazolyl group (e.g., 4-benzothiazolyl group, 7-benzothiazolyl group and the like), indolizinyl group, quinolyl group, isoquinolyl group, 1,2-dihydro-2-oxoquinolyl group, quinazolinyl group, quinoxalinyl group, cinnolinyl group, phthalazinyl group, quinolizinyl group, puryl group, pteridinyl group, indolinyl group, isoindolinyl group, 5,6,7,8-tetrahydroquinolyl group, 1,2,3,4-tetrahydroquinolyl group, 2-oxo-1,2,3,4-tetrahydroquinolyl group, benzo [1,3] dioxolyl group, 3,4-methylenedioxypyridyl group, 4,5-ethylenedioxypyrimidinyl group, chromenyl group, chromanyl group, isochromanyl group and the like can be mentioned.

[0064] It is preferably a fused ring of monocyclic 5- or 6-membered heterocycle and benzene ring. Specific examples thereof include indolyl group, benzofuranyl group, benzothiophenyl group, benzimidazolyl group, benzoxazolyl group, benzothiazolyl group and benzo[1,3]dioxolyl group and the like.

[0065] The "heterocyclic group optionally substituted by 1 to 5 substituents selected from group A" is a "heterocyclic group" defined above, which is optionally substituted by 1 to 5, preferably 1 to 3, substituents selected from "group A" defined above and includes non-substituted "heterocyclic group".

[0066] The "heterocyclic group" is preferably a monocyclic heterocycle containing 1 or 2 heteroatoms, or a heterocycle which is a fused ring thereof with a benzene ring.

[0067] Specific examples of "heterocyclic group optionally substituted by 1 to 5 substituents selected from group A" include pyrrolidinyl group, piperidinyl group, morpholino group, pyrrolyl group, 2-pyrrolyl group, 3-pyrrolyl group, 2-furyl group, 3-furyl group, 2-thienyl group, 3-thienyl group, 4,5-dichlorothiophen-3-yl group, 2-oxo-2,5-dihydrofuran-3-yl group, 1,1-dioxo-1H-isothiazol-5-yl group, 4-methylthiazol-5-yl group, imidazolyl group, 2-imidazolyl group, 3-imidazolyl group, 4-imidazolyl group, pyrazolyl group, 2-oxazolyl group, 3-isoxazolyl group, 2-thiazolyl group, 3-isothiazolyl group, 3-fluoropyridin-2-yl group, 3-chloropyridin-2-yl group, 3-chloro-4-fluoropyridin-2-yl group, 3,5-dichloropyridin-2-yl group, 3-pyridyl group, 2-fluoropyridin-3-yl group, 2-chloropyridin-3-yl group, 2-chloro-4-fluoropyridin-3-yl group, 2-chloro-5-fluoropyridin-3-yl group, 2,5-dichloropyridin-3-yl group, 2-chloro-6-fluoropyridin-3-yl group, 2,6-dichloropyridin-3-yl group, 4-pyridyl group, 2-fluoropyridin-4-yl group, 2-chloropyridin-4-yl group, 2-chloro-3-fluoropyridin-4-yl group, 2,3-difluoropyridin-4-yl group, 2,3-dichloropyridin-4-yl group, 2,5-dichloropyridin-4-yl group, 2-chloro-6-fluoropyridin-4-yl group, 2,6-dichloropyridin-4-yl group, 2-chloro-3,6-difluoropyridin-4-yl group, 2-chloro-3,5-difluoropyridin-4-yl group, 2,3,6-trifluoropyridin-4-yl group, 2,3,5,6-tetrafluoropyridin-4-yl group, 2-indolyl group, 3-indolyl group, 4-indolyl group, 7-indolyl group, 2-benzofuranyl group, 4-benzofuranyl group, 7-benzofuranyl group, 2-benzothiophenyl group, 4-benzothiophenyl group, 7-benzothiophenyl group, 2-benzimidazolyl group, 4-benzimidazolyl group, 2-benzoxazolyl group, 4-benzoxazolyl group, 7-benzoxazolyl group, 2-benzothiazolyl group, 4-benzothiazolyl group, 7-benzothiazolyl group, 2-benzo[1,3]dioxolyl group, 4-benzo [1,3] dioxolyl group, 5-benzo[1,3]dioxolyl group and the like.

[0068] As ring Cy, 2-pyridyl group and 4-pyridyl group are preferable,
as R^1 and group B, imidazolyl group, 2-pyridyl group, 2-benzothiophenyl group, morpholino group and 4-methylthiazol-5-yl group are preferable, and
as R^{32} and R^{33}, pyrrolidinyl group is preferable.

[0069] The "C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B" is a C_{1-10} alkyl group optionally substituted by the substituent group selected from the "halogen atom" defined above and the "group B" defined below, and may be a non-substituted alkyl group. The alkyl moiety is straight chain or branched chain alkyl group having 1 to 10 carbon atoms. Specific examples thereof include methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, 1-methylbutyl group, 1-ethylpropyl group, 2-ethylpropyl group, 1,1-dimethylpropyl group, 1,2-dimethylpropyl group, tert-pentyl group, hexyl group, isohexyl group, 1-methylpentyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, 1,3-dimethylbutyl group, 1-ethylbutyl group, 1-ethyl-1-methylpropyl group, 1-ethyl-2-methylpropyl group, 1,1,2-trimethylpropyl group, 1,2,2-trimethylpropyl group, 1-ethyl-1-methylpropyl group, heptyl group, isoheptyl group, 1-methylhexyl group, 1,1-dimethylpentyl group, 1,2-dimethylpentyl group, 1,3-dimethylpentyl group, 1,4-dimethylpentyl group, 1,1,2-trimethylbutyl group, 1,1,3-trimethylbutyl group, 1,2,2-trimethylbutyl group, 1,2,3-trimethylbutyl group, 1,3,3-trimethylbutyl group, 1-ethylpentyl group, 1-ethyl-2-methylbutyl group, 1-ethyl-3-methylbutyl group, 2-ethyl-1-methylbutyl group, 1-propylbutyl group, 1-ethyl-2,2-dimethylpropyl group, 1-isopropyl-2-methylpropyl group, 1-isopropyl-1-methylpropyl group, 1,1-diethylpropyl group, 1,1,2,2-tetramethylpropyl group, 1-isopropylbutyl group, 1-ethyl-1-methylbutyl group, octyl group, nonyl group, decanyl group and the like, with preference given to straight chain or branched chain alkyl group having 1 to 6 carbon atoms, particularly preferably branched chain alkyl group having 1 to 6 carbon atoms.

[0070] The "group B" is a group consisting of the "C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from group A" defined above, the "heterocyclic group optionally substituted by 1 to 5 substituents selected from group A" defined above, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$,

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$-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$.

[0071] As used herein, R^{a4} and R^{a5} are the same or different and each is a hydrogen atom, a "C_{1-4} alkyl group" defined above, a "C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from group A" defined above or a "heterocyclic group optionally substituted by 1 to 5 substituents selected from group A" defined above, and R^{a6} is a "C_{1-4} alkyl group" defined above, a "C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from group A" defined above or a "heterocyclic group optionally substituted by 1 to 5 substituents selected from group A" defined above.

[0072] Specific examples of $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$ $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$ include substituents recited in the definitions of "$-OR^{a1}$", "$-SR^{a1}$", "$-NR^{a1}R^{a2}$", "$-CONR^{a1}R^{a2}$", "$-SO_2NR^{a1}R^{a2}$", "COR^{a3}", "$-NR^{a1}COR^{a3}$", "$-SO_2R^{a3}$", "$-NR^{a1}SO_2R^{a3}$", "$-COOR^{a1}$" and "$-NR^{a2}COOR^{a3}$" for "group A", respectively, and the like.

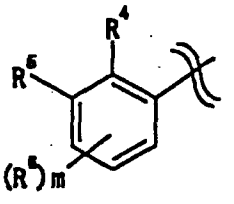
[0073] Specific examples of "C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B" include methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, 1-methylbutyl group, 1-ethylpropyl group, 2-ethylpropyl group, 1,1-dimethylpropyl group, 1,2-dimethylpropyl group, tert-pentyl group, hexyl group, isohexyl group, 1-methylpentyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, 1,3-dimethylbutyl group, 1-ethylbutyl group, 1-ethyl-1-methylpropyl group, 1-ethyl-2-methylpropyl group, 1,1,2-trimethylpropyl group, 1,2,2-trimethylpropyl group, 1-ethyl-1-methylpropyl group, heptyl group, isoheptyl group, 1-methylhexyl group, 1,1-dimethylpentyl group, 1,2-dimethylpentyl group, 1,3-dimethylpentyl group, 1,4-dimethylpentyl group, 1,1,2-trimethylbutyl group, 1,1,3-trimethylbutyl group, 1,2,2-trimethylbutyl group, 1,2,3-trimethylbutyl group, 1,3,3-trimethylbutyl group, 1-ethylpentyl group, 1-ethyl-2-methylbutyl group, 1-ethyl-3-methylbutyl group, 2-ethyl-1-methylbutyl group, 1-propylbutyl group, 1-ethyl-2,2-dimethylpropyl group, 1-isopropyl-2-methylpropyl group, 1-isopropyl-1-methylpropyl group, 1,1-diethylpropyl group, 1,1,2,2-tetramethylpropyl group, 1-isopropylbutyl group, 1-ethyl-1-methylbutyl group, fluoromethyl group, trifluoromethyl group, chloroethyl group, 2-fluoroethyl group, 2-chloroethyl group, 3-fluoropropyl group, 2-chloropropyl group, 2,2,2-trifluoroethyl group, 2-hydroxyethyl group, 2-hydroxypropyl group, 2-hydroxy-1-methylethyl group, 2-hydroxy-1,1-dimethylethyl group, 1-(hydroxymethyl)propyl group, 3-hydroxypropyl group, 2-hydroxybutyl group, 4-hydroxybutyl group, 2-hydroxypentyl group, 5-hydroxypentyl group, 2,3-dihydroxypropyl group, 2,3-dihydroxybutyl group, 2-hydroxy-1-(hydroxymethyl)ethyl group, 2-hydroxy-2-methylpropyl group, 1-(hydroxymethyl)butyl group, 1-(hydroxymethyl)-2-methylpropyl group, 1-(hydroxymethyl)-2,2-dimethylpropyl group, 1-(hydroxymethyl)-2-methylbutyl group, 2-hydroxy-1-phenylethyl group, 2-hydroxy-2-phenylethyl group, 1-(hydroxymethyl)-2-phenylethyl group, 3-methyl-1-(hydroxymethyl)butyl group, 2-ethyl-1-(hydroxymethyl)butyl group, 3-hydroxy-1-methylpropyl group, 1,1-dimethyl-3-hydroxypropyl group, 1,2-dimethyl-3-hydroxypropyl group, 1-isopropyl-3-hydroxypropyl group, 2,2-dimethyl-1-(2-hydroxyethyl)propyl group, 1-ethyl-3-hydroxypropyl group, 2-hydroxy-1-isopropylpropyl group, 1-ethyl-1-(hydroxymethyl)propyl group, 1,1-dimethyl-2-hydroxypropyl group, 1,2-dimethyl-2-hydroxypropyl group, 1-ethyl-2-hydroxypropyl group, 4-hydroxy-1-methylbutyl group, 2-ethyl-1-(hydroxymethyl)-2-methylbutyl group, 3,3-dimethyl-1-(hydroxymethyl)butyl group, 1-(hydroxymethyl)pentyl group, 4-methyl-1-(hydroxymethyl)pentyl group, methoxymethyl group, 2-methoxyethyl group, methylsulfanylmethyl group, 2-(methylsulfanyl)ethyl group, 2-aminoethyl group, 2-(dimethylamino)ethyl group, carboxymethyl group, 2-carboxyethyl group, 2-carboxypropyl group, 3-carboxypropyl group, carbamoylmethyl group, 2-carbamoylethyl group, methylaminocarbonylmethyl group, dimethylaminocarbonylmethyl group, 2-(phenylaminocarbonyl)ethyl group, 2-oxopropyl group, methylsulfonylmethyl group, 2-(methylsulfonyl)ethyl group, sulfamoylmethyl group, methylaminosulfonylmethyl group, dimethylaminosulfonylmethyl group, tert-butylaminosulfonylmethyl group, 2-(acetylamino)ethyl group, 2-(methylsulfonylamino)ethyl group, 2-(ethoxycarbonylamino)ethyl group, benzyl group, phenethyl group, 3-phenylpropyl group, 4-phenylbutyl group, 2-biphenylmethyl group, 3,4-dichlorobenzyl group, 2-hydroxy-2-phenylethyl group, cyclopentylmethyl group, cyclohexylmethyl group, 2-cyclohexylethyl group, 1-cyclohexyl-2-hydroxyethyl group, 1-cyclohexylmethyl-2-hydroxyethyl group, phenylaminocarbonylmethyl group, 2-pyridin-2-ylethyl group, 2-imidazol-1-ylethyl group, 2-benzothiophen-2-ylethyl group, 2-morpholinoethyl group, 2-(4-methylthiazolin-5-yl)ethyl group, 1-carboxyethyl group, 1-carbamoylethyl group, 1-carboxy-2-methylpropyl group, 1-carbamoyl-2-methylpropyl group, 2-hydroxy-1-(hydroxymethyl)propyl group, 1-(hydroxymethyl)-2-mercaptoethyl group, 1-(hydroxymethyl)-3-(methylsulfanyl)propyl group, 2-carboxy-1-(hydroxymethyl)ethyl group, 2-carbamoyl-1-(hydroxymethyl)ethyl group, 2-(indol-3-yl)-1-(hydroxymethyl)ethyl group, 2-(imidazol-4-yl)-1-(hydroxymethyl)ethyl group, 2-(4-hydroxyphenyl)-1-(hydroxymethyl)ethyl group, 3-carbamoyl-1-(hydroxymethyl)propyl group, 5-amino-1-(hydroxymethyl)pentyl group and the like.

[0074] R^1 is preferably methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, tert-butyl group, 2-fluoroethyl group, 2, 2, 2-trifluoroethyl group, 2-hydroxyethyl group, 2-hydroxypropyl group, 3-hydroxypropyl group,4-hydroxybutyl group, 5-hydroxypentyl group, 2,3-dihydroxypropyl group, 2-hydroxy-1-methylethyl group, 2-hydroxy-1,1-dimethylethyl group, 2-hydroxy-1-(hydroxymethyl)ethyl group, 1-(hydroxymethyl)propyl group, 2-hydroxy-2-methylpropyl group, 1-(hydroxymethyl)butyl group, 1-(hydroxymethyl)-2-methylpropyl group, 1-(hydroxymethyl)-2,2-dimethylpropyl group, 1-(hydroxymethyl)-2-methylbutyl group, 1-(hydroxymethyl)-3-methylbutyl group, 2-hy-

droxy-1-phenylethyl group, 2-hydroxy-2-phenylethyl group, 1-(hydroxymethyl)-2-phenylethyl group, 2-methoxyethyl group, methylsulfanylmethyl group, 2-(methylsulfanyl)ethyl group, 2-aminoethyl group, 2-(dimethylamino)ethyl group, carboxymethyl group, 2-carboxyethyl group, 3-carboxypropyl group, carbamoylmethyl group, 2-carbamoylethyl group, methylaminocarbonylmethyl group, dimethylaminocarbonylmethyl group, 2-(phenylaminocarbonyl)ethyl group, 2-oxopropyl group, methylsulfonylmethyl group, 2-(methylsulfonyl)ethyl group, sulfamoylmethyl group, methylaminosulfonylmethyl group, dimethylaminosulfonylmethyl group, tert-butylaminosulfonylmethyl group, 2-(acetylamino)ethyl group, 2-(methylsulfonylamino)ethyl group, 2-(ethoxycarbonylamino)ethyl group, benzyl group, phenethyl group, 3-phenylpropyl group, 4-phenylbutyl group, 2-biphenylmethyl group, 3,4-dichlorobenzyl group, cyclopentylmethyl group, cyclohexylmethyl group, 1-cyclohexyl-2-hydroxyethyl group, 1-cyclohexylmethyl-2-hydroxyethyl group, 2-pyridin-2-ylethyl group, 2-imidazol-1-ylethyl group, 2-morpholinoethyl group, 2-(4-methylthiazolin-5-yl)ethyl group or benzothiophen-2-ylmethyl group, particularly preferably alkyl group branched at the 1-position and/or alkyl group substituted by hydroxy group. Specific examples thereof include 2-hydroxy-1-methylethyl group, 1-(hydroxymethyl)-2-methylpropyl group, 1-(hydroxymethyl)-2,2-dimethylpropyl group, 1-(hydroxymethyl)-2-methylbutyl group, 2-hydroxy-1-(hydroxymethyl)ethyl group and 2-phenyl-1-(hydroxymethyl)ethyl group. When these particularly preferable substituents are in optically active forms, S form is more preferable.

[0075] R^{32} and R^{33} are preferably methyl group, ethyl group and trifluoromethyl group, and R^{a7} and R^{a8} are preferably methyl group, ethyl group, propyl group, isopropyl group, 2-hydroxyethyl group, 3-hydroxypropyl group and cyclohexylmethyl group, more preferably methyl group, ethyl group and isopropyl group, and particularly preferably methyl group.

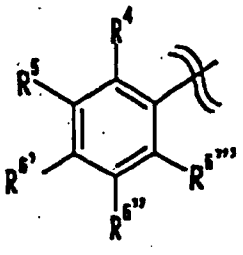
[0076] The ring Cy in the formula [I] is preferably a "C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from group A" defined above, more preferably



wherein R^4, R^5, R^6 and m are as defined above. A more preferable embodiment here is the same as the 4-oxoquinoline compound represented by the formula [II], wherein m is preferably 0 or 1, more preferably 0.

[0077] The group A for ring Cy is preferably cyano group, phenyl group, nitro group, "halogen atom" defined above, "C_{1-4} alkyl group" defined above, "halo C_{1-4} alkyl group" defined above, "halo C_{1-4} alkyloxy group" defined above, "$-OR^{a1}$" defined above, "$-SR^{a1}$" defined above, "$-NR^{a1}R^{a2}$" defined above, "$-CONR^{a1}R^{a2}$" defined above, "$-SO_2NR^{a1}R^{a2}$" defined above, "$-NR^{a1}COR^{a3}$" defined above, "$-SO_2R^{a3}$" defined above or "$-NR^{a1}SO_2R^{a3}$" defined above, more preferably cyano group, phenyl group, nitro group, "halogen atom", "C_{1-4} alkyl group", "halo C_{1-4} alkyl group", "halo C_{1-4} alkyloxy group", "$-OR^{a1}$", "SR^{a1}", "$-NR^{a1}R^{a2}$", "$-SO_2R^{a3}$", "$-SO_2NR^{a1}R^{a2}$" or "$-NR^{a1}COR^{a3}$", and particularly preferably "halogen atom" defined above.

[0078] The ring Cy is more preferably



wherein $R^{6'}$, $R^{6''}$ and $R^{6'''}$ are substituents selected from hydrogen atom and "group A" defined above, and R^4 and R^5 are as defined above.

[0079] R^4 is preferably phenyl group, "halogen atom" defined above, "C_{1-4} alkyl group" defined above, "halo C_{1-4} alkyloxy group" defined above, "$-OR^{a1}$", defined above, "$-NR^{a1}R^{a2}$" defined above, "$-SO_2NR^{a1}R^{a2}$" defined above, "$-NR^{a1}COR^{a3}$" defined above, "$-SO_2R^{a3}$" defined above, "$-COOR^{a1}$" defined above or"$-NR^{a1}SO_2R^{a3}$" defined above,

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more preferably "halogen atom", "C_{1-4} alkyl group", "halo C_{1-4} alkyloxy group", "-OR^{a1}" or "-$NR^{a1}R^{a2}$", and particularly preferably "halogen atom" defined above,

R^5 is preferably hydrogen atom, cyano group, nitro group, "halogen atom" defined above, "C_{1-4} alkyl group" defined above, "halo C_{1-4} alkyl group" defined above, "-OR^{a1}" defined above, "-SR^{a1}" defined above, "-$NR^{a1}R^{a2}$" defined above, "-$CONR^{a1}R^{a2}$" defined above, "-$SO_2NR^{a1}R^{a2}$" defined above or "-$NR^{a1}COR^{a3}$" defined above, more preferably hydrogen atom, "halogen atom" or "C_{1-4} alkyl group", and particularly preferably "halogen atom".

[0080] R^6 is preferably "halogen atom", "C_{1-4} alkyl group" defined above, "-SO_2R^{a3}" defined above, "-OR^{a1}" defined above or "-SR^{a1}" defined above, more preferably "halogen atom".

[0081] $R^{6'}$ and $R^{6''}$ are preferably the same or different and each is hydrogen atom or "halogen atom" defined above, $R^{6''}$ is preferably hydrogen atom, "halogen atom" defined above, "C_{1-4} alkyl group" defined above, "-SO_2R^{a3}" defined above, "-OR^{a1}" defined above or "-SR^{a1}" defined above, more preferably, hydrogen atom, "halogen atom", "C_{1-4} alkyl group" defined above or "-SR^{a1}" defined above, and more preferably hydrogen atom.

[0082] R^1 is preferably "C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from group A" defined above, "heterocyclic group optionally substituted by 1 to 5 substituents selected from group A" defined above, "-OR^{a4}" defined above (here, it is concretely preferably methoxy group), "-$NR^{a4}R^{a5}$" defined above (here, it is concretely preferably amino group, methylamino group, ethylamino group or dimethylamino group), "-$NR^{a4}COR^{a6}$" defined above (here, it is concretely preferably acetylamino group), "-$NR^{a4}SO_2R^{a6}$" defined above (here, it is concretely preferably, methylsulfonylamino group or N-methyl-N-(methylsulfonyl)amino group), "-$NR^{a5}COOR^{a6}$" defined above (here, it is concretely preferably methoxycarbonylamino group) or "C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B" defined above, more preferably, "C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from group A" defined above or "C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B", more preferably "C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B" defined above.

[0083] R^2 is preferably hydrogen atom.

[0084] R^{31} is preferably hydrogen atom, cyano group, "halogen atom" defined above, hydroxy group or "C_{1-4} alkoxy group" defined above, more preferably hydrogen atom, cyano group, "halogen atom" defined above or "C_{1-4} alkoxy group" defined above, more preferably hydrogen atom, cyano group or "C_{1-4} alkoxy group" defined above, particularly preferably hydrogen atom.

[0085] R^{32} is preferably hydrogen atom, cyano group, "halogen atom" defined above, "heterocyclic group optionally substituted by 1 to 5 substituents selected from group A" defined above, "C_{1-10}alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B" defined above, "-OR^{a7}" defined above, "-SR^{a7}" defined above, "-$NR^{a7}R^{a8}$" defined above, "-$COOR^{a10}$" defined above or "-$N{=}CH\text{-}NR^{a10}R^{a11}$" defined above, more preferably hydrogen atom, "-OR^{a7}" defined above, "-SR^{a7}" defined above or "-$NR^{a7}R^{a8}$" defined above, more preferably hydrogen atom or "-OR^{a7}" defined above, particularly preferably "-OR^{a7}".

[0086] R^{33} is preferably hydrogen atom, "C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B" defined above, "-OR^{a7}" defined above or "-$NR^{a7}R^{a8}$" defined above, more preferably hydrogen atom, "-OR^{a7}" defined above or "-$NR^{a7}R^{a8}$" defined above, more preferably hydrogen atom or "-OR^{a7}" defined above, particularly preferably hydrogen atom.

[0087] It is preferable that one of R^{32} and R^{33} be hydrogen atom, and the other be "OR^{a7}" defined above.

[0088] It is preferable that R^{31} be hydrogen atom and R^{32} or R^{33} be other than hydrogen atom.

[0089] The "pharmaceutically acceptable salt thereof" may be any as long as it forms a non-toxic salt with a compound of the above-mentioned formula [I] or [II]. For example, it can be obtained by reaction with an inorganic acid such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; an organic acid such as oxalic acid, malonic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoroacetic acid, gluconic acid, ascorbic acid, methylsulfonic acid, benzylsulfonic acid and the like; an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and the like; an organic base such as methylamine, diethylamine, triethylamine, triethanolamine, ethylenediamine, tris(hydroxymethyl) methylamine, guanidine, choline, cinchonine and the like; or an amino acid such as lysin, arginine, alanine and the like. The present invention encompasses water-containing products, hydrates and solvates of each compound.

[0090] In addition, the compounds represented by the above-mentioned formulas [I] and [II] have various isomers. For example, E form and Z form are present as geometric isomers, and when an asymmetric carbon atom exists, enantiomer and diastereomer are present as stereoisomers based thereon, and tautomer can be present. Accordingly, the present invention encompasses all these isomers and mixtures thereof. The compound of the present invention is preferably isolated and purified from various isomers, byproducts, metabolites or prodrugs, where one having a purity of 90% or above is preferable and one having a purity of 95% or above is more preferable.

[0091] The present invention also encompasses prodrugs and metabolites of each compound.

[0092] By the "prodrug" is meant a derivative of the compound of the present invention, which has a chemically or metabolically decomposable group and which, after administration to a body, restores to the original compound to show

its inherent efficacy, including a complex and a salt free of covalent bond.

[0093] The prodrug is utilized for, for example, improving absorption by oral administration or targeting of a target site.

[0094] As the site to be modified, highly reactive functional groups in the compound of the present invention, such as hydroxyl group, carboxyl group, amino group, thiol group and the like, are mentioned.

[0095] Examples of the hydroxyl-modifying group include acetyl group, propionyl group, isobutyryl group, pivaloyl group, benzoyl group, 4-methylbenzoyl group, dimethylcarbamoyl group, sulfo group and the like. Examples of the carboxyl-modifying group include ethyl group, pivaloyloxymethyl group, 1-(acetyloxy)ethyl group, 1-(ethoxycarbonyloxy)ethyl group, 1-(cyclohexyloxycarbonyloxy)ethyl group, carboxylmethyl group, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group, phenyl group, o-tolyl group and the like. Examples of the amino-modifying group include hexylcarbamoyl group, 3-methylthio-1-(acetylamino)propylcarbonyl group, 1-sulfo-1-(3-ethoxy-4-hydroxyphenyl)methyl group, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group and the like.

[0096] The compound of the present invention can be administered to a mammal (human, mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, swine and the like) as an anti-HIV agent, an integrase inhibitor, an antiviral agent and the like.

[0097] When the compound of the present invention is used as a pharmaceutical preparation, it is admixed with pharmaceutically acceptable carriers, excipients, diluents, extending agents, disintegrants, stabilizers, preservatives, buffers, emulsifiers, flavoring agents, coloring agents, sweetening agents, thickeners, correctives, dissolution aids, and other additives, that are generally known *per se*, such as water, vegetable oil, alcohol (e.g., ethanol or benzyl alcohol etc.), polyethylene glycol, glycerol triacetate, gelatin, carbohydrate (e.g., lactose, starch etc.), magnesium stearate, talc, lanolin, petrolatum and the like, formed into tablet, pill, powder, granule, suppository, injection, eye drop, liquid, capsule, troche, aerosol, elixir, suspension, emulsion, syrup and the like by a conventional method, and administered systemically or topically, and orally or parenterally.

[0098] While the dose varies depending on age, body weight, symptom, treatment effect, administration method and the like, it is generally 0.01 mg to 1 g per administration for an adult, which is given once to several times a day orally or in a dosage form of an injection such as intravenous injection and the like.

[0099] An anti-HIV agent is generally required to sustain its effect for a long time, so that can be effective not only for temporal suppression of viral growth but also for prohibition of viral re-growth. This means that a long term administration is necessary and that a high single dose may be frequently inevitable to sustain effect for a longer period through the night. Such long term and high dose administration increases the risk of causing side effects.

[0100] In view of this, one of the preferable modes of the 4-oxoquinoline compound of the present invention is such compound permitting high absorption by oral administration, and such compound capable of maintaining blood concentration of the administered compound for an extended period of time.

[0101] By the "prophylaxis of AIDS" is meant, for example, administration of a pharmaceutical agent to an individual who tested HIV positive but has not yet developed the disease state of AIDS, administration of a pharmaceutical agent to an individual who shows an improved disease state of AIDS after treatment but who carries HIV still to be eradicated and whose relapse of AIDS is worried, and administration of a pharmaceutical agent before the infection of HIV out of a fear of possible infection.

[0102] Examples of the "other anti-HIV agents" and "other anti-HIV active substance" to be used for a multiple drug combination therapy include an anti-HIV antibody, an HIV vaccine, immunostimulants such as interferon and the like, an HIV ribozyme, an HIV antisense drug, a reverse transcriptase inhibitor, a protease inhibitor, an inhibitor of bond between a bond receptor (CD4, CXCR4, CCR5 and the like) of a host cell recognized by virus and the virus, and the like.

[0103] Specific examples of the HIV reverse transcriptase inhibitor include Retrovir(R) (zidovudine), Epivir(R) (lamivudine), Zerit(R) (sanilvudine), Videx(R) (didanosine), Hivid(R) (zalcitabine), Ziagen(R) (abacavir sulfate), Viramune (R) (nevirapine), Stocrin(R) (efavirenz), Rescriptor(R) (delavirdine mesylate), Combivir(R) (zidovudine+lamivudine), Trizivir(R) (abacavir sulfate+lamivudine+zidovudine), Coactinon(R) (emivirine), Phosphonovir(R), Coviracil(R), alovudine (3'-fluoro-3'-deoxythymidine), Thiovir (thiophosphonoformic acid), Capravirin (5-[(3,5-dichlorophenyl)thio]-4-isopropyl-1-(4-pyridylmethyl)imidazole-2-methanol carbamic acid), Tenofovir disoproxil fumarate ((R)-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis(isopropoxycarbonyloxymethyl)ester fumarate), DPC-083 ((4S)-6-chloro-4-[(1E)-cyclopropylethenyl]-3,4-dihydro-4-trifluoromethyl-2(1H)-quinazolinone), DPC-961 ((4S)-6-chloro-4-(cyclopropylethynyl)-3,4-dihydro-4-(trifluoromethyl)-2(1H)-quinazolinone), DAPD ((-)-β-D-2,6-diaminopurine dioxolane), Immunocal, MSK-055, MSA-254, MSH-143, NV-01, TMC-120, DPC-817,GS-7340, TMC-125, SPD-754, D-A4FC, capravirine, UC-781, emtricitabine, alovudine, Phosphazid, UC-7.81, BCH-10618, DPC-083, Etravirine, BCH-13520, MIV-210,Abacavir sulfate/lamivudine, GS-7340, GW-5634, GW-695634 and the like, wherein (R) means a registered trademark (hereinafter the same) and the names of other pharmaceutical agents are general names.

[0104] Specific examples of the HIV protease inhibitor include Crixivan(R) (indinavir sulfate ethanolate), saquinavir, Invirase(R) (saquinavir mesylate), Norvir (R) (ritonavir), Viracept(R) (nelfinavir mesylate), lopinavir, Prozei(R) (amprenavir), Kaletra(R) (ritonavir+lopinavir), mozenavir dimesylate ([4R-(4α,5α,6β)]-1-3-bis[(3-aminophenyl)methyl]-hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one dimethanesulfonate), tipranavir (3'-[(1R)-1-[(6R)-

5,6-dihydro-4-hydroxy-2-oxo-6-phenylethyl-6-propyl-2H-pyran-3-yl]propyl]-5-(trifluoromethyl)-2-pyridinesulfonamide), lasinavir (N-[5(S)-(tert-butoxycarbonylamino)-4(S)-hydroxy-6-phenyl-2(R)-(2,3,4-trimethoxybenzyl)hexanoyl]-L-valine 2-methoxyethylenamide), KNI-272 ((R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl]amino-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide), GW-433908, TMC-126, DPC-681, buckminsterfullerene, MK-944A (MK944 (N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-[4-(2-benzo[b]furanylmethyl)-2(S)-(tert-butylcarbamoyl)piperazin-1-yl]pentanamide)+indinavir sulfate), JE-2147 ([2(S)-oxo-4-phenylmethyl-3(S)-[(2-methyl-3-oxy)phenylcarbonylamino]-1-oxabutyl]-4-[(2-methylphenyl)methylamino]carbonyl-4(R)-5,5-dimethyl-1,3-thiazole), BMS-232632 ((3S,8S,9S,12S)-3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedicarboxylic acid dimethyl ester), DMP-850 ((4R,5S,6S,7R)-1-(3-amino-1H-indazol-5-ylmethyl)-4,7-dibenzyl-3-butyl-5,6-dihydroxyperhydro-1,3-diazepin-2-one), DMP-851, RO-0334649, Nar-DG-35, R-944, VX-385, TMC-114, Tipranavir, Fosamprenavir sodium, Fosamprenavir calcium, Darunavir, GW-0385, R-944, RO-033-4649, AG-1859 and the like.

[0105] The HIV integrase inhibitor is exemplified by S-1360, L-870810 and the like, the DNA polymerase inhibitor or DNA synthesis inhibitor is exemplified by Foscavir(R), ACH-126443 (L-2',3'-didehydro-dideoxy-5-fluorocytidine), entecavir ((1S,3S,4S)-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine), calanolide A ([10R-(10α,11β,12α)]-11,12-dihydro-12-hydroxy-6,6,10,11-tetramethyl-4-propyl-2H,6H,10H-benzo[1,2-b:3,4-b':5,6-b"]tripyran-2-one), calanolide B, NSC-674447 (1,1'-azobisformamide), Iscador (viscum alubm extract), Rubutecan and the like, the HIV antisense drug is exemplified by HGTV-43, GEM-92 and the like, the anti-HIV antibody or other antibody is exemplified by NM-01, PRO-367, KD-247, Cytolin(R), TNX-355 (CD4 antibody), AGT-1, PRO-140 (CCR5 antibody), Anti-CTLA-4 MAb and the like, the HIV vaccine or other vaccine is exemplified by ALVAC(R), AIDSVAX(R), Remune(R), HIV gp41 vaccine, HIV gp120 vaccine, HIV gp140 vaccine, HIV gp160 vaccine, HIV p17 vaccine, HIV p24 vaccine, HIV p55 vaccine, AlphaVax Vector System, canarypox gp160 vaccine, AntiTat, MVA-F6 Nef vaccine, HIV rev vaccine, C4-V3 peptide, p2249f, VIR-201, HGP-30W, TBC-3B, PARTICLE-3B and the like, Antiferon (interferon-α vaccine) and the like, the interferon or interferon agonist is exemplified by Sumiferon(R), MultiFeron(R), interferon-τ, Reticulose, Human leukocyte interferon alpha and the like, the CCR5 antagonist is exemplified by SCH-351125 and the like, the pharmaceutical agent acting on HIV p24 is exemplified by GPG-NH2 (glycyl-prolyl-glycinamide) and the like, the HIV fusion inhibitor is exemplified by FP-21399 (1,4-bis[3-[(2,4-dichlorophenyl)carbonylamino]-2-oxo-5,8-disodium sulfonyl]naphthyl-2,5-dimethoxyphenyl-1,4-dihydrazone), T-1249, Synthetic Polymeric Construction No3, pentafuside, FP-21399, PRO-542, Enfuvirtide and the like, the IL-2 agonist or antagonist is exemplified by interleukin-2, Imunace(R), Proleukin (R), Multikine(R), Ontak(R) and the like, the TNF-α antagonist is exemplified by Thalomid(R) (thalidomide), Remicade (R) (infliximab), curdlan sulfate and the like, the α-glucosidase inhibitor is exemplified by Bucast(R) and the like, the purine nucleoside phosphorylase inhibitor is exemplified by peldesine (2-amino-4-oxo-3H,5H-7-[(3-pyridyl)methyl]pyrrolo[3,2-d]pyrimidine) and the like, the apoptosis agonist or inhibitor is exemplified by Arkin Z(R), Panavir(R), Coenzyme Q10 (2-deca(3-methyl-2-butenylene)-5,6-dimethoxy-3-methyl-p-benzoquinone) and the like, the cholinesterase inhibitor is exemplified by Cognex(R) and the like, and the immunomodulator is exemplified by Imunox (R), Prokine(R), Met-enkephalin (6-de-L-arginine-7-de-L-arginine-8-de-L-valinamide-adrenorphin), WF-10 (10-fold dilute tetrachlorodecaoxide solution), Perthon, PRO-542, SCH-D, UK-427857, AMD-070, AK-602 and the like.

[0106] In addition, Neurotropin(R), Lidakol(R), Ancer 20(R), Ampligen(R), Anticort(R), Inactivin(R) and the like, PRO-2000, Rev M10 gene, HIV specific cytotoxic T cell (CTL immunotherapy, ACTG protocol 080 therapy, CD4-ζ gene therapy), SCA binding protein, RBC-CD4 complex, Motexafin gadolinium, GEM-92, CNI-1493, (±)-FTC, Ushercell, D2S, BufferGel(R), VivaGel(R), Glyminox vaginal gel, sodium lauryl sulfate, 2F5, 2F5/2G12, VRX-496, Ad5gag2, BG-777, IGIV-C, BILR-255 and the like are exemplified.

[0107] As the "other anti-HIV agents" and "other anti-HIV active substance" to be used for a multiple drug combination therapy with the compound of the present invention, preferred are a reverse transcriptase inhibitor and a protease inhibitor. Two or three, or even a greater number of pharmaceutical agents can be used in combination, wherein a combination of pharmaceutical agents having different action mechanisms is one of the preferable embodiments. In addition, selection of pharmaceutical agents free of side effect duplication is preferable.

[0108] Specific combination of pharmaceutical agents include a combination of a group consisting of Efavirenz, Tenofovir, Emtricitabine, Indinavir, Nelfinavir, Atanazavir, Ritonavir+Indinavir, Ritonavir+Lopinavir, Ritonavir+Saquinavir, Didanosine+Lamivudine, Zidovudine+Didanosine, Stavudine+Didanosine, Zidovudine+Lamivudine, Stavudine+Lamivudine, and Emtriva and the 4-oxoquinoline compound [I] of the present invention (Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. August 13, 2001). Particularly preferably, two drug therapy by the combination with Efavirenz, Indinavir, Nelfinavir, Tenofovir, Emtricitabine, Zidovudine and Lamivudine, and three drug therapy by the combination with Zidovudine+Lamivudine, Tenofovir+Lamivudine, Tenofovir+Zidovudine, Tenofovir+Efavirenz, Tenofovir+Nelfinavir, Tenofovir+Indinavir, Tenofovir+Emtricitabine, Emtricitabine+Lamivudine, Emtricitabine+Zidovudine, Emtricitabine+Efavirenz, Emtricitabine+Nelfinavir, Emtricitabine+Indinavir, Nelfinavir+Lamivudine, Nelfinavir+Zidovudine, Nelfinavir+Efavirenz, Nelfinavir+Indinavir, Efavirenz+Lamivudine, Efavirenz+Zidovudine, and Efavirenz+Indinavir can be mentioned.

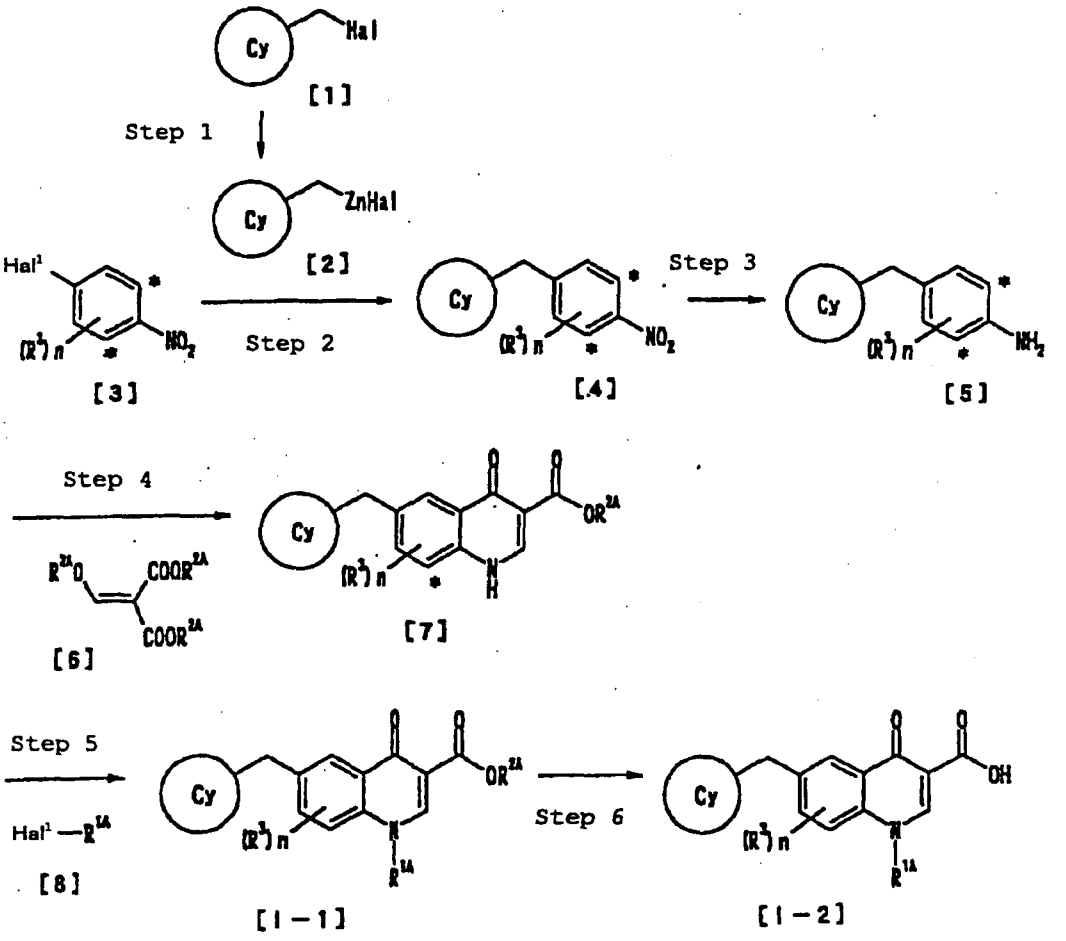
[0109] Some examples of the production methods of the compounds used for embodiment of the present invention are shown in the following. However, the production method of the compounds of the present invention is not limited to these examples.

[0110] Even in the absence of description in the production method, efficient production can be afforded, where necessary, by introducing a protecting group into a functional group followed by deprotection in a subsequent step, by using a compound with a functional group as a precursor in each step and converting the group to a desired functional group in a suitable step, by exchanging the order of respective production methods and steps, or by other method.

[0111] The workup in each step can be applied by a typical method, wherein isolation and purification is performed by selecting or combining conventional methods as necessary, such as crystallization, recrystallization, distillation, partitioning, silica gel chromatography, preparative HPLC and the like.

Production Method 1-1

[0112]



wherein Hal is a halogen atom such as chlorine atom, bromine atom and the like; Hal^1 is a halogen atom such as bromine atom, iodine atom and the like; R^{1A} is "C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B" defined above; R^{2A} is "C_{1-4} alkyl group" defined above, which is preferably methyl group or ethyl group; in compound [6], each R^{2A} may be different but preferably the same; $(R^3)_n$ is a substituent of any of R^{31}, R^{32} and R^{33}, which may be the same or different; n is an integer of 1 to 3; where the substituent R^3 does not simultaneously substitute at both of the * positions, and other symbols are as defined above.

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Step 1

[0113] Under an argon or nitrogen stream, zinc powder and 1,2-dibromoethane are reacted in a solvent with heating, and trimethylsilyl chloride is added to allow reaction. Then, to the reaction solution is added a solution of compound [1] to allow reaction to give compound [2].

[0114] As preferable solvents, ether solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran (THF) and the like; hydrocarbon solvents such as benzene, toluene, hexane, xylene and the like; and the like can be mentioned.

Step 2

[0115] The compound [2] is reacted with compound [3] in a solvent in the presence of a catalyst and, where necessary, a ligand such as triphenylphosphine, tri(2-furyl)phosphine and the like, and under an argon or nitrogen stream with cooling or with heating to give compound [4].

[0116] As the catalyst, palladium catalysts such as bis(dibenzylideneacetone)palladium, tris (dibenzylideneacetone) dipalladium, dichlorobis (triphenylphosphine) palladium; dichlorobis (benzonitrile) palladium, dichloroethylenediamine palladium, palladium acetate, tetrakis(triphenylphosphine)palladium and the like, nickel catalyst and the like can be mentioned.

[0117] As preferable solvents, ether solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran (THF) and the like; hydrocarbon solvents such as benzene, toluene, hexane, xylene and the like and the like can be mentioned.

Step 3

[0118] The compound [4] is reduced by a conventional method such as reduction with zinc or iron under neutral or alkaline conditions; iron and acid; tin or tin(II) chloride and conc. hydrochloric acid; alkali sulfide; alkaline hydrosulfite and the like, catalytic reduction under a hydrogen atmosphere, and the like to give compound [5].

[0119] For example, to compound [4] are added acetic acid and zinc powder with cooling, and the mixture is reacted at room temperature to give compound [5]. Alternatively, palladium-carbon is added to a solution of compound [4] in a mixed solvent of THF and methanol and the mixture is reacted under a hydrogen atmosphere at room temperature to give compound [5].

Step 4

[0120] The compound [5] is reacted with compound [6] in a solvent with heating.

[0121] As preferable solvents, alcohol solvents such as methanol, ethanol, n-propanol, isopropanol and the like; hydrocarbon solvents such as benzene, toluene, hexane, xylene and the like; halogenated solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; ether solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and the like and a mixed solvents thereof can be mentioned.

[0122] Then, after removal of the solvent, the residue is reacted in a solvent such as diphenyl ether or a mixture of diphenyl ether and diphenyl, such as Dowtherm A (trademark, Fluka) and the like, with heating to give compound [7].

Step 5

[0123] The compound [7] is reacted with compound [8] in a solvent in the presence of a base to give compound [I-1].

[0124] As the base, potassium carbonate, sodium carbonate, lithium hydride, sodium hydride, potassium hydride and the like can be mentioned, with preference given to potassium carbonate.

[0125] As the solvents, hydrocarbon solvents such as benzene, toluene, hexane, xylene and the like; ether solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and the like; polar solvents such as dimethylformamide, dimethyl sulfoxide, acetonitrile and the like and a mixed solvent thereof can be mentioned.

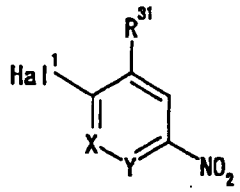
Step 6

[0126] The compound [I-1] is subjected to hydrolysis in a solvent at room temperature or with heating under basic conditions with sodium hydroxide, potassium hydroxide, lithium hydroxide and the like, or under acidic conditions with hydrochloric acid, sulfuric acid and the like to give compound [I-2].

[0127] As the solvents, alcohol solvents such as methanol, ethanol, n-propanol, isopropanol and the like; hydrocarbon solvents such as benzene, toluene, hexane, xylene and the like; halogenated solvents such as dichloromethane,

carbon tetrachloride, 1,2-dichloroethane and the like; ether solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and the like; polar solvents such as dimethylformamide, dimethyl sulfoxide, acetonitrile and the like; water and a mixed solvent thereof can be mentioned.

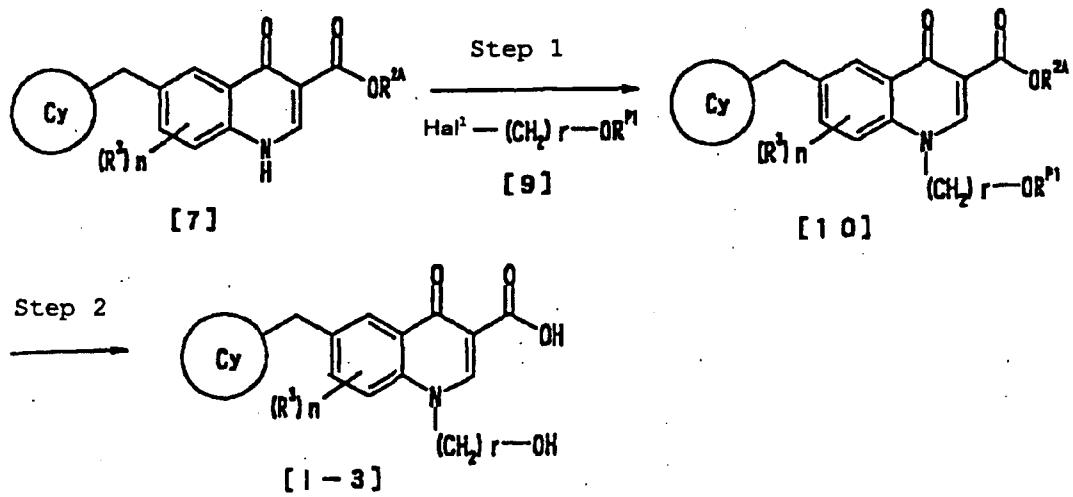
[0128] By a reaction in the same manner as in Production Method 1-1 using compound [20] represented by



instead of compound [3], compound [I] can be obtained.

Production Method 1-2 Example of production method using compound [9] in which a hydroxyl-protecting group has been introduced

[0129]



wherein r is an integer of 1 to 6, R^{P1} is a hydroxyl-protecting group, and other symbols are as defined above.

Step 1

[0130] The compound [7] obtained in the same manner as in Production Method 1-1 and compound [9] are reacted in the same manner as in Production Method 1-1, Step 5 to give compound [10].

Step 2

[0131] The compound [10] is deprotected by a conventional method to give compound [I-3].

[0132] As the hydroxyl-protecting group, acetyl group, methyloxycarbonyl group, methoxymethyl group, methoxyethoxymethyl group, trimethylsilyl group, tert-butyldimethylsilyl group, tert-butyldiphenylsilyl group and the like can be mentioned.

[0133] For example, when R^{P1} is acetyl group or methyloxycarbonyl group, a reaction with heating in the presence of a base such as sodium hydroxide, potassium hydroxide and the like achieves deprotection. A treatment comprising addition of conc. hydrochloric acid and heating, heating in conc. ammonia and the like may be applied.

[0134] For example, when R^{P1} is tert-butyldimethylsilyl group, deprotection can be achieved by a treatment with

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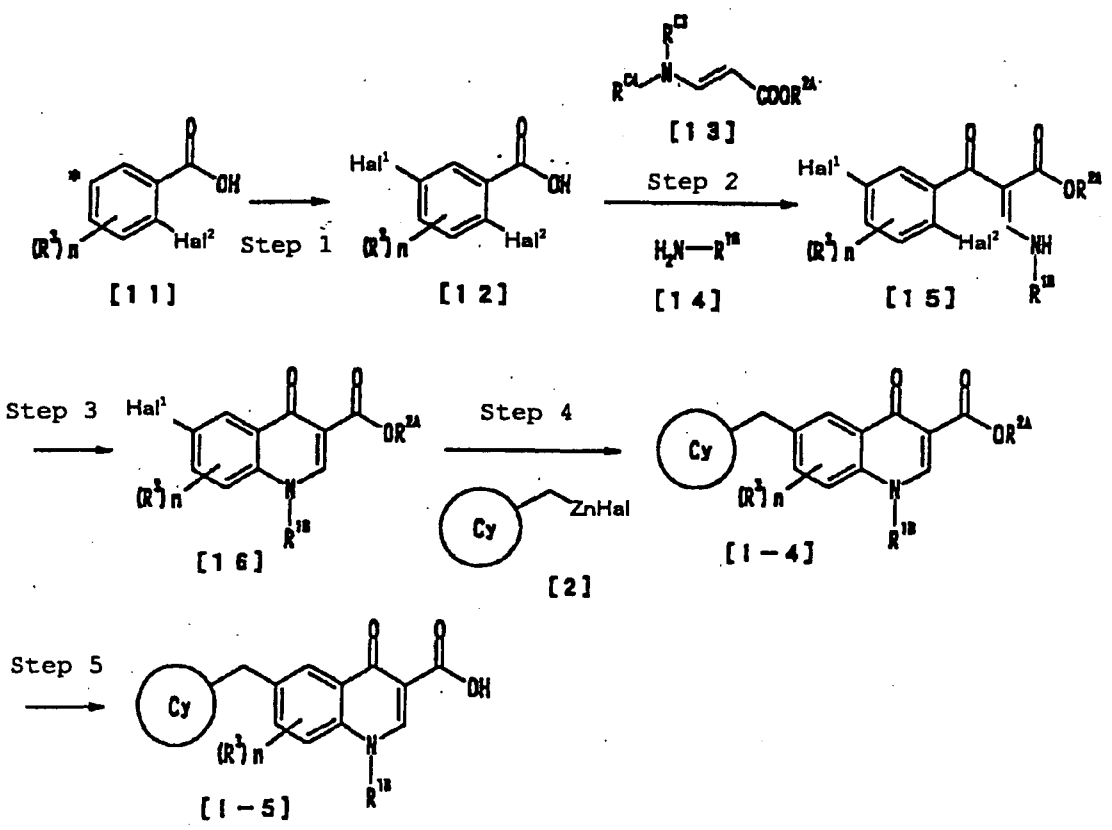
tetrabutylammonium fluoride in THF at room temperature, a treatment in the presence of sodium hydroxide in THF with heating, a treatment with acetic acid-water-THF at room temperature or with heating, and the like. In this step, the deprotection of R^{P1} and hydrolysis of R^{2A} can be performed in two stages.

Production Method 2-1

[0135]



wherein Hal^2 is a halogen atom and preferably a fluorine atom or a chlorine atom, R^{C3} and R^{C4} are the same or different and each is a lower alkyl group such as methyl group, ethyl group and the like, R^{1B} is a "C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B" defined above, a "C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from group A" defined above, a "heterocyclic group optionally substituted by 1 to 5 substituents selected from group A" defined above or "-OR^{a4}" defined above, and other symbols are as defined above, wherein the substituent R^3 is not substituted at the * position.

Step 1

[0136] Here, Hal^1 is preferably bromine or iodine, and compound [12] can be obtained by conventional halogenation.

[0137] For example, compound [11] is reacted with a halogenating agent such as N-bromosuccinimide, N-iodosuccinimide and the like in a solvent such as trifluoromethanesulfonic acid, acetic acid, conc. sulfuric acid, DMF and the like at room temperature or with heating to give compound [12].

Step 2

[0138] An acid halide is obtained by a conventional method by, for example, reacting compound [12] with heating with a halogenating agent such as oxalyl chloride, thionyl chloride and the like, in a solvent such as hydrocarbon solvents (e.g., toluene, xylene etc.); halogenated solvent (e.g., dichloromethane, carbon tetrachloride, 1,2-dichlo-

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roethane etc.); ethyl acetate and the like.

[0139] Here, for example, when thionyl chloride is used as a halogenating agent, a catalytic amount of DMF may be added.

[0140] Then, compound [13] is added to allow reaction in a solvent in the presence of a base such as triethylamine, diisopropylethylamine, potassium carbonate, pyridine and the like at room temperature or with heating, after which the resulting compound is reacted with compound [14] at room temperature or with heating to give compound [15].

[0141] As the solvent, hydrocarbon solvents such as benzene, toluene, hexane, xylene and the like; halogenated solvents such as dichloromethane, carbon tetrachloride, 1,2-dichloroethane and the like; ether solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and the like; polar solvents such as acetonitrile and the like, ethyl acetate and a mixed solvent thereof can be mentioned.

Step 3

[0142] The compound [15] is reacted in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium tert-butoxide, sodium hydride, potassium hydride and the like, in a solvent to give compound [16].

[0143] As one of the preferable production methods, compound [15] may be reacted in the presence of 1,8-diazacyclo [5.4.0]-7-undecene in a solvent at room temperature or with heating to give compound [16].

[0144] As the solvent, hydrocarbon solvents such as benzene, toluene, hexane, xylene and the like; halogenated solvents such as dichloromethane, carbon tetrachloride, 1,2-dichloroethane and the like; ether solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and the like; polar solvents such as dimethylformamide, dimethyl sulfoxide, acetonitrile and the like and a mixed solvent thereof can be mentioned.

Step 4

[0145] The compound [16] is reacted with compound [2] in the same manner as in Production Method 1-1, Step 2 to give compound [I-4].

Step 5

[0146] The compound [I-4] is subjected to hydrolysis in the same manner as in Production Method 1-1, Step 6 to give compound [I -5].

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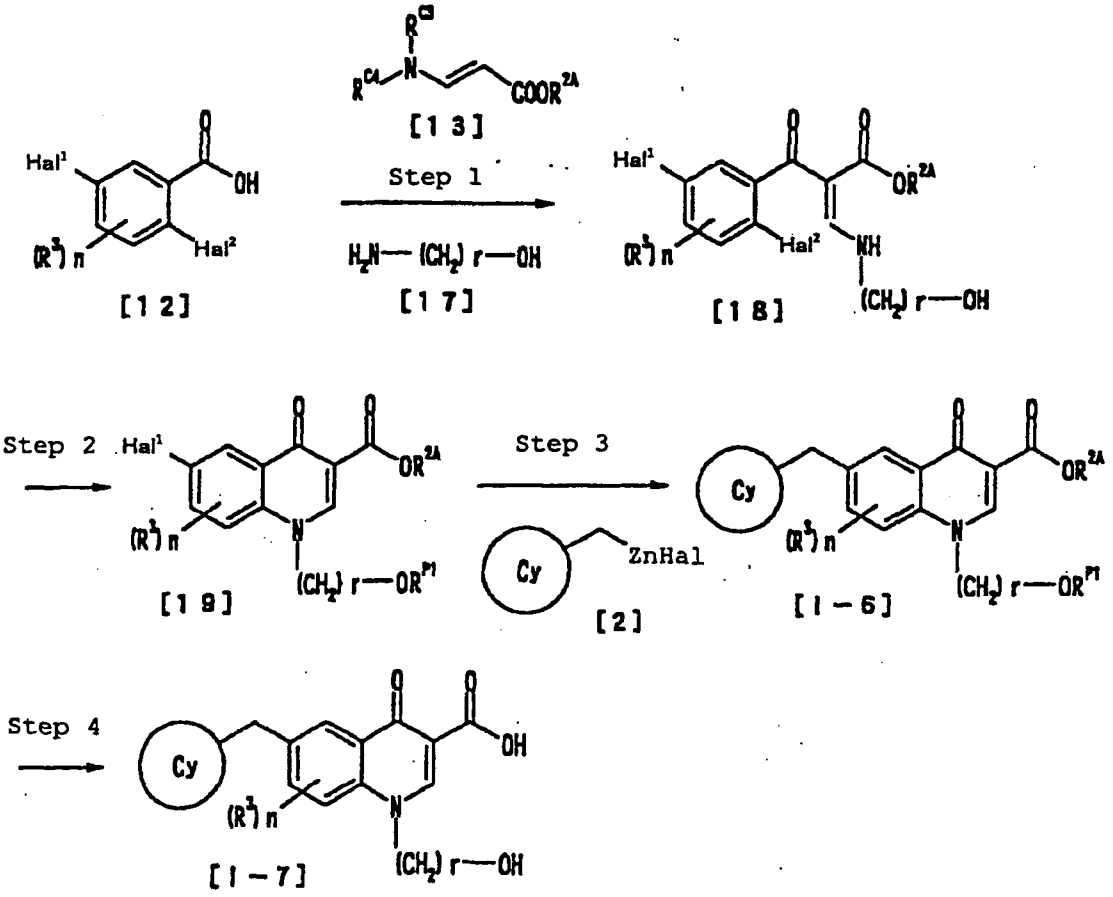
Production Method 2-2 Example of production method comprising introduction and removal of hydroxyl-protecting group

[0147]



wherein each symbol is as defined above.

Step 1

[0148] The compound [12] obtained in the same manner as in Production Method 2-1, Step 1 is reacted with compound [13] and compound [17] in the same manner as in Production Method 2-1, Step 2 to give compound [18].

Step 2

[0149] A protecting group is introduced into hydroxyl group of compound [18] by a conventional method and then the compound is cyclized in the same manner as in Production Method 2-1, Step 3 to give compound [19].

[0150] Alternatively, compound [18] is cyclized in the same manner as in Production Method 2-1, Step 3 and then a protecting group is introduced into hydroxyl group by a conventional method to give compound [19].

[0151] For example, when R^{P1} is a tert-butyldimethylsilyl group, compound [18] may be reacted with imidazole and tert-butyldimethylsilyl chloride in a solvent such as DMF and toluene at room temperature.

[0152] When R^{P1} is a methoxycarbonyl group, compound [18] may be reacted with pyridine and methyl chlorocarbonate in a solvent such as chloroform with cooling or at room temperature.

[0153] A similar production method can be used for NH_2-R^{1A}, wherein R^{1A}, is a $C_{1\text{-}10}$ alkyl group optionally substituted by at least one hydroxyl group instead of compound [17].

Step 3

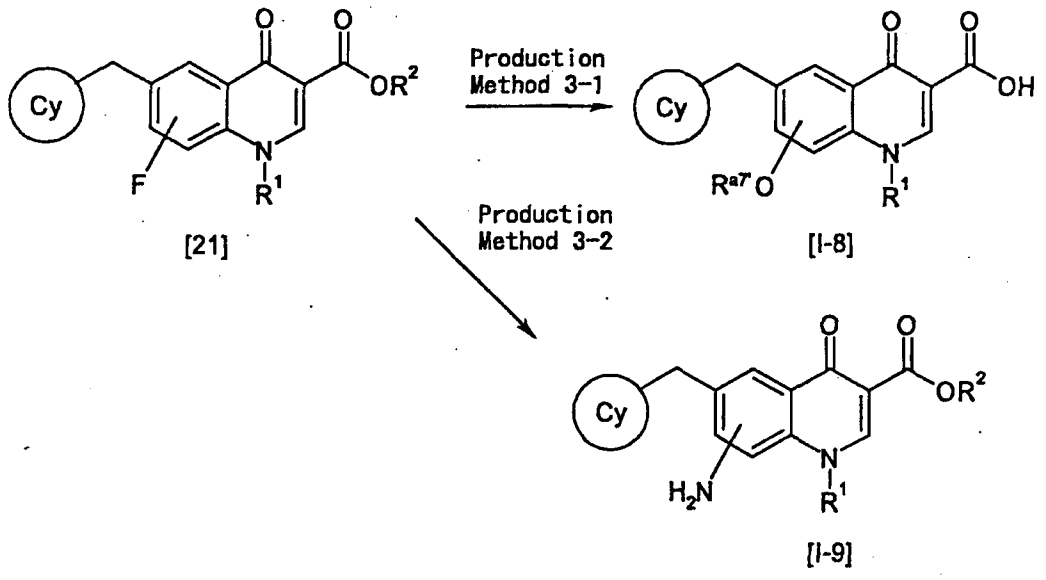
[0154] The compound [19] is reacted with compound [2] in the same manner as in Production Method 1-1, Step 2 to give compound [I-6].

Step 4

[0155] The compound [I-6] is subjected to hydrolysis by a conventional method in the same manner as in Production Method 1-2, Step 2 to give compound [I-7]. In this step, the deprotection of R^{P1} and hydrolysis of R^{2A} can be performed in two stages.

Production Method 3

[0156]



wherein $R^{a7'}$ is a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B, and other symbols are as defined above.

[0157] The fluorine atom on 4-oxoquinoline can be converted to $-OR^{a7}$, $-SR^{a7}$ or $-NR^{a7}R^{a8}$ by a reaction with nucleophilic agent by a conventional method. They can be further converted to $-NR^{a7}COR^{a9}$ or $-N=CH-NR^{a10}R^{a11}$ by a conventional method.

[0158] This production method is suitable for introducing a substituent into the 7-position on 4-oxoquinoline.

Production Method 3-1

[0159] An alkoxy group is introduced into compound [21] by a conventional method to give compound [I-8].

[0160] For example, compound [I-8] can be obtained by reaction with metal alkoxide with heating in an alcohol solvent such as methanol, ethanol, propanol, butanol and the like, and then hydrolysis.

[0161] A solvent and a metal alkoxide need to be determined corresponding to a desired alkoxy group. In the case of a methoxy group, sodium methoxide or potassium methoxide is reacted in methanol, and in the case of an ethoxy group, sodium ethoxide or potassium ethoxide is reacted in ethanol.

Production Method 3-2

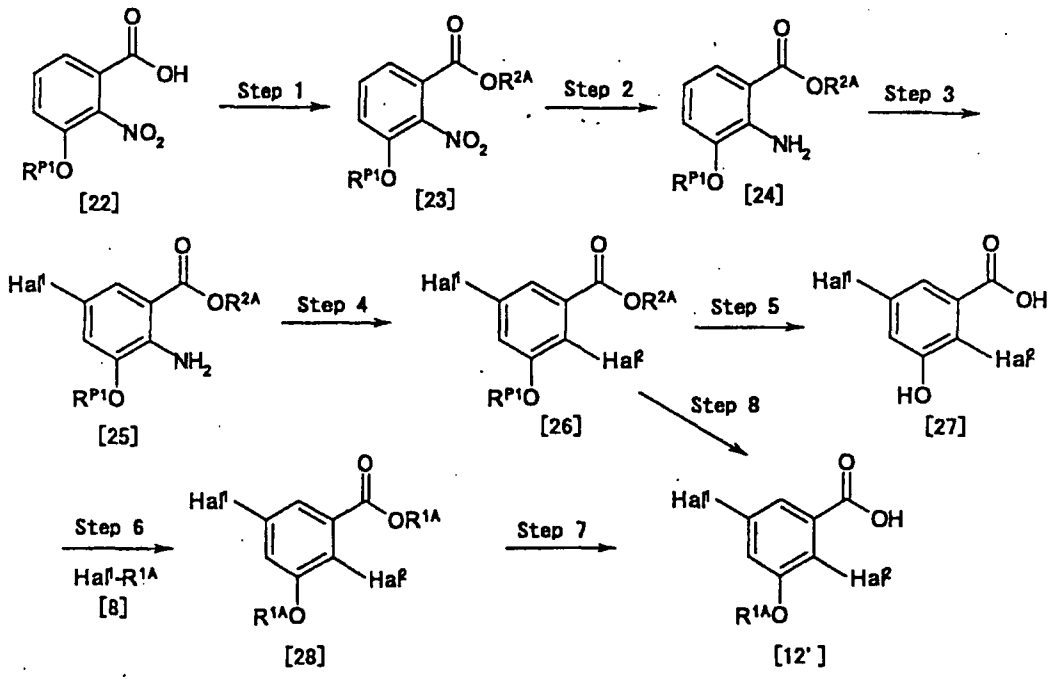
[0162] The compound [21] is subjected to amination by a conventional method to give compound [I-9].

[0163] For example, compound [I-9] can be obtained by a reaction with an amine in an inactive organic solvent such as THF, dioxane, chloroform, dichloromethane, methanol, ethanol, pyridine and the like with heating.

[0164] In addition, compound [I-9] can be also obtained by a reaction with an amine with microwave irradiation in DMF.

Production Method 4

[0165] Examples of the production methods of intermediate compound [12] are shown below.



wherein each symbol is as defined above.

Step 1

[0166] A protecting group is introduced into carboxylic acid of compound [22] by a conventional method to give compound [23].

[0167] In the case of esterification, for example, compound [23] can be obtained by a reaction with an alkylating agent such as methyl iodide and the like in a solvent such as DMF, THF, toluene and the like in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydride, potassium hydride and the like.

Step 2

[0168] The compound [23] is reduced by a conventional method in the same manner as in Production Method 1-1, Step 3 to give compound [24].

Step 3

[0169] The compound [24] is subjected to halogenation by a conventional method in the same manner as in Production Method 2-1, Step 1 to give compound [25].

Step 4

[0170] The compound [25] is subjected to diazotization with sodium nitrite and hydrochloric acid or sulfuric acid in water or an inactive organic solvent such as THF, dioxane, ethyl acetate, chloroform, dichloromethane, methanol, ethanol, pyridine and the like with cooling or at room temperature, and then subjected to halogenation with cuprous halide such as copper chloride and the like and conc. hydrochloric acid with cooling or with heating to give compound

[26]. Here, Hal^2 is preferably a chlorine atom.

Step 5

[0171] The hydroxyl group of compound [26] is deprotected by a conventional method to give compound [27].

[0172] For example, when R^{P1} is a methyl group, compound [27] can be obtained by reaction with boron tribromide in dichloromethane with cooling.

Step 6

[0173] The compound [27] is reacted with compound [8] in the presence of a base in a solvent to give compound [28].

[0174] As compound [8], for example, an alkylating agent such as ethyl iodide and the like can be mentioned.

[0175] As the base, potassium carbonate, sodium carbonate, lithium hydride, sodium hydride, potassium hydride and the like can be mentioned, with preference given to potassium carbonate.

[0176] As the solvent, alcohol solvents such as methanol, ethanol, n-propanol, isopropanol and the like; hydrocarbon solvents such as benzene, toluene, hexane, xylene and the like; halogenated solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; ether solvents such as 1,4-dioxane, diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran and the like; polar solvents such as dimethylformamide, dimethyl sulfoxide, acetonitrile and the like; water and a mixed solvent thereof can be mentioned.

Step 7

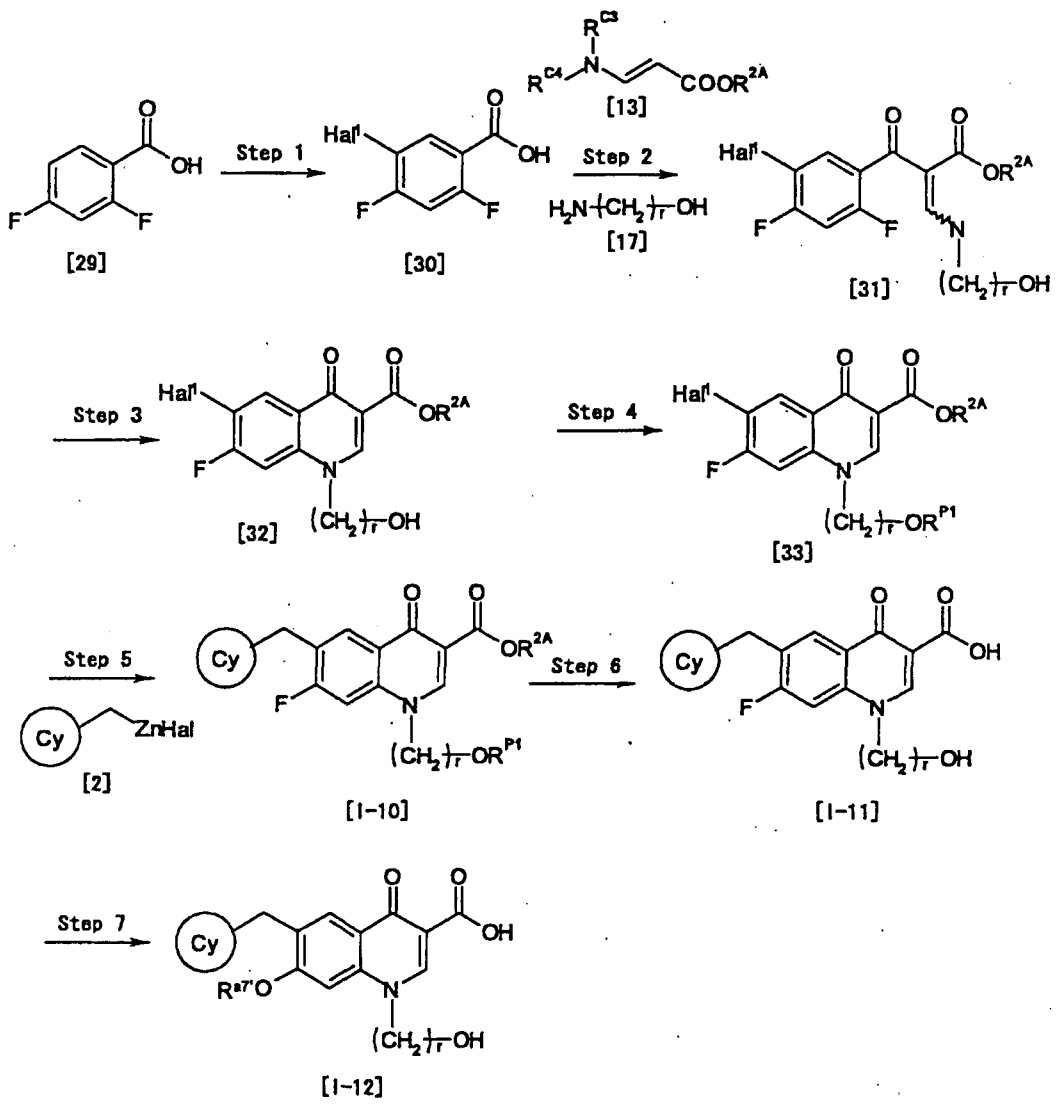
[0177] The compound [28] is subjected to hydrolysis by a conventional method in the same manner as in Production Method 1-1, Step 6 to give compound [12'].

Step 8

[0178] When R^{P1} in compound [26] is a desired substituent, compound [12'] can be obtained in the same manner as in Step 7.

Production Method 5

[0179]



wherein each symbol is as defined above.

Step 1

[0180] The compound [29] is subjected to halogenation by a conventional method in the same manner as in Production Method 2-1, Step 1 to give compound [30].

Step 2

[0181] The compound [30] is reacted with compound [13] and compound [17] in the same manner as in Production Method 2-1, Step 2 to give compound [31].

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Step 3

[0182] The compound [31] is reacted in the same manner as in Production Method 2-1, Step 3 to give compound [32].

Step 4

[0183] The compound [32] is reacted in the same manner as in Production Method 2-2, Step 2 to give compound [33].

Step 5

[0184] The compound [33] is reacted with compound [2] in the similar as in Production Method 1-1, Step 2 to give compound [I-10].

Step 6

[0185] The compound [I-10] is subjected to hydrolysis in the same manner as in Production Method 1-2, Step 2 to give compound [I-11] .

Step 7

[0186] The compound [I-12] can be obtained by introducing an alkoxy group into compound [I-11] by a conventional method in a similar manner as in Production Method 3-1.

[0187] The 4-oxoquinoline compound represented by the formula [I] of the present invention, a pharmaceutically acceptable salt thereof and a production method are explained in detail by referring to Examples, which are not to be construed as limitative.

Reference Example 1

Preparation of a solution of 2,3-dichlorobenzylzinc chloride in THF

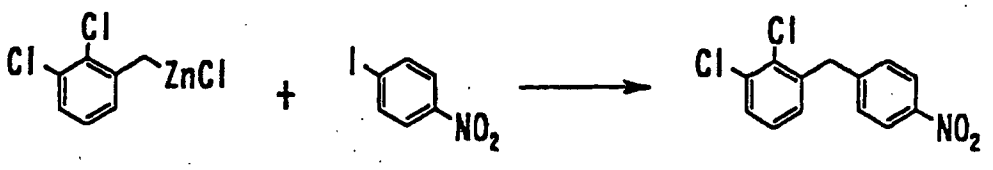
[0188]

[0189] Under an argon stream, to a suspension of zinc powder (55.1 g, 843 mmol) in tetrahydrofuran (THF; 56 ml) was added 1,2-dibromoethane (2.9 ml, 33.8 mmol) and the mixture was heated under reflux for 5 min. Then, trimethylsilyl chloride (8.6 ml, 67.5 mmol) was added at 0°C and the mixture was stirred at 0°C for 5 min, after which a solution of 2,3-dichlorobenzyl chloride (82.4 g, 421.7 mmol) in THF (330 ml) was added dropwise with ice-cooling. After completion of the dropwise addition, the mixture was warmed to room temperature and stirred for 1 hr to give a solution of 2,3-dichlorobenzylzinc chloride in THF.

Example 1-1 Synthesis of 6-(2,3-dichlorobenzyl)-1,4-dihydro-1-(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylic acid

Step 1 Synthesis of 1,2-dichloro-3-(4-nitrobenzyl)benzene

[0190]



[0191] Under an argon stream, bis (dibenzylideneacetone)palladium (0) (3.2 g, 5.6 mmol) and tri (2-furyl)phosphine (2.6 g, 11.2 mmol) were dissolved in THF (310 ml). To this solution was added dropwise a solution of 2,3-dichlorobenzylzinc chloride (421.7 mmol) in THF obtained in Reference Example 1 with ice-cooling through a cannula, and then a solution of 4-iodonitrobenzene (70.0 g, 281 mmol) in THF (700 ml) was added dropwise. After stirring at room temperature for 2 hrs, saturated aqueous ammonium chloride solution was added to the reaction solution and the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the solid precipitated during the concentration was collected by filtration. The filtrate was again concentrated under reduced pressure and the solid precipitated during the concentration was collected by filtration. The solids obtained by filtration were combined, washed with n-hexane and vacuum-dried to give an object product (60.2 g, yield 76%) as a pale-brown solid.
^{1}H NMR ($CDCl_3$ 400MHz) (δ) ppm: 4.24 (2H, s), 7.09 (1H,d,J=7.7Hz), 7.18 (1H, dd, J=7.8Hz, 7.9Hz), 7.32(2H,d, J=8.9Hz), 7.40 (1H, d, J=8.0Hz), 8.15 (2H, d, J=8.7Hz)
MS (ESI): M- 280

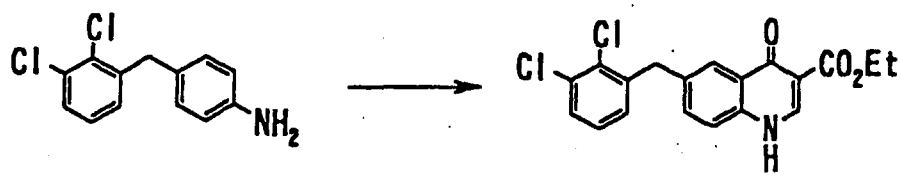
Step 2 Synthesis of 4-(2,3-dichlorobenzyl)phenylamine

[0192]

[0193] 1,2-Dichloro-3-(4-nitrobenzyl)benzene (25.0 g, 88.6 mmol) obtained in Step 1 was dissolved in acetic acid (400 ml) and zinc powder (70 g, 1.1 mol) was added by portions at 0°C. The mixture was stirred at room temperature for 1 hr. The reaction mixture was filtered through Celite and washed with ethanol. The filtrate was concentrated under reduced pressure and the solid precipitated during concentration was collected by filtration. The solid obtained by the filtration was washed with diethyl ether, and dissolved in ethyl acetate (500 ml) and water (500 ml). A 4N aqueous sodium hydroxide solution was added to neutralize the aqueous layer. The organic layer was separated, and the aqueous layer was further extracted with ethyl acetate. The organic layers were combined, washed with water and saturated brine, and dried over sodium sulfate. After the filtration, the filtrate was concentrated under reduced pressure and the solid precipitated during the concentration was collected by filtration. The solid obtained by filtration was washed with n-hexane and vacuum-dried to give an object product (18.1 g, yield 81%) as a pale-brown solid.
^{1}H NMR ($CDCl_3$ 400MHz) (δ) ppm: 3.52 (2H, brs), 4.01 (2H, s), 6.63 (2H, d, J=8.2Hz), 6.97 (2H,d,J=8. 1Hz), 7.02 (1H, d, J=7.6Hz), 7.09 (1H, dd, J=7.8Hz, 7.8Hz), 7.31 (1H, d, J=7.8Hz)
MS(ESI): M+ 252

Step 3 Synthesis of ethyl 6-(2,3-dichloroberizyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylate

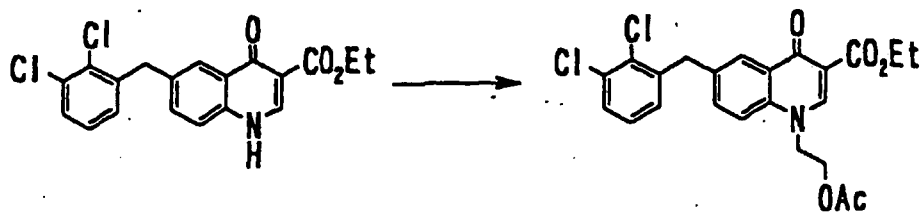
[0194]



[0195] 4-(2,3-Dichlorobenzyl)phenylamine (10.0 g, 39.7 mmol) obtained in Step 2 was dissolved in toluene (100 ml) and diethyl ethoxymethylenemalonate (8.8 ml, 43.7 mmol) was added. The mixture was heated under reflux for 3 hrs. The reaction solution was concentrated under reduced pressure, and diphenyl ether (100 ml) was added to dissolve the residue. The mixture was stirred with heating at 250°C for 3 hrs. After allowing the mixture to cool, n-hexane was added to the reaction solution and the precipitate was collected by filtration, washed with chloroform and vacuum-dried to give an object product (10.1 g, yield 68%) as a pale-yellow solid.
^{1}H NMR(DMSO-d_6 400MHz) (δ) ppm: 1.27 (3H, t,J=7.1Hz), 4.20 (2H,q,J=7.1Hz), 4.27 (2H,s), 7.34-7.41(2H,m), 7.55-7.57(3H,m), 7.90 (1H,s), 8.49(1H,d,J=6.6Hz), 12.26(1H,brs)
MS(ESI): M+ 376

Step 4 Synthesis of ethyl 1-(2-acetoxyethyl)-6-(2,3-dichlorobenzyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylate

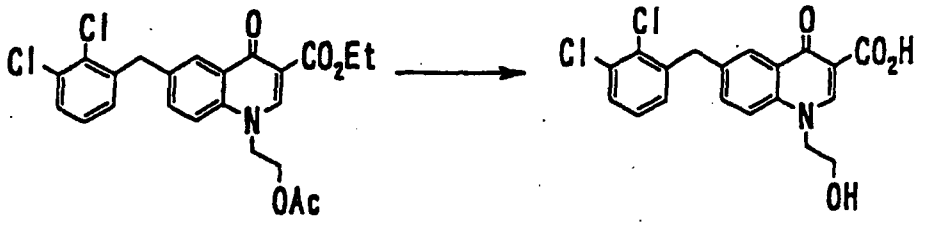
[0196]



[0197] Ethyl 6-(2,3-dichlorobenzyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylate obtained in Step 3 (400 mg, 1.1 mmol) was suspended in dimethylformamide (DMF; 8 ml) and 2-bromoethyl acetate (152 µl, 1.4 mmol) and potassium carbonate (440 mg, 3.2 mmol) were added. The mixture was stirred with heating at 80°C. During the stirring, 2-bromoethyl acetate (152 µl, 1.4 mmol) was added twice and the mixture was stirred with heating at 80°C for the total of 1.5 hrs. After allowing the mixture to cool, saturated aqueous ammonium chloride was added to the reaction solution, and the precipitate was collected by filtration, washed with water and vacuum-dried to give an object product (468 mg, yield 95%) as a white solid.
^{1}H NMR(DMSO-d_6 400MHz) (δ) ppm: 1.25(3H,t,J=9.3Hz), 1.88(3H,s), 4.20(2H,q,J=9.3Hz), 4.27 (2H,s), 4.33-4.41 (2H, m), 4.59-4.62(2H,m), 7.32-7.41 (3H,m), 7.54(1H,dd,J=2.9Hz.10.2Hz), 7.64 (1H,dd,J=2.4Hz,11.2Hz), 7.81 (1H,d, J=11.7Hz), 7.88(1H,d,J=2.4Hz), 8.57 (1H, s)

Step 5 Synthesis of 6-(2,3-dichlorobenzyl)-1,4-dihydro-1-(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylic acid

[0198]

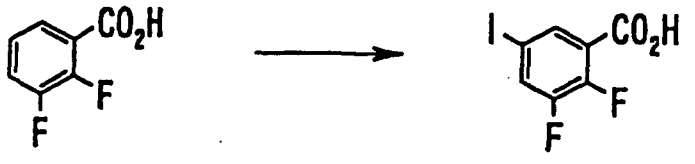


[0199] Ethyl 1-(2-acetoxyethyl)-6-(2,3-dichlorobenzyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylate obtained in Step 4 (6.0 g, 13.0 mmol) was suspended in ethanol (480 ml) and 4N aqueous sodium hydroxide solution (84 ml, 21 mmol) was added. The mixture was heated under reflux for 30 min. After allowing the mixture to cool, the reaction solution was partly concentrated under reduced pressure. Hydrochloric acid was added and the precipitate was collected by filtration, washed with water and ethanol and vacuum-dried to give an object product (4.5 g, yield 85%) as a white solid.
^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.75(2H, t, J=4.7Hz), 4.36(2H, s), 4.60(2H, t, J=4.8Hz), 4.98(1H, brs), 7.37-7.39 (1H, m), 7.45(1H, dd, J=1.4, 7.6Hz), 7.57(1H, dd, J=1.5, 8.0Hz), 7.81(1H, dd, J=2.1, 8.9Hz), 8.02 (1H, d, J=8.8Hz), 8.15 (1H, d, J=1.8Hz), 8.86(1H, s), 15.18 (1H, brs)
MS (ESI): M+ 392
m.p.: 247-249°C

Example 1-2 Synthesis of 6-(2,3-dichlorobenzyl)-1,4-dihydro-8-fluoro-1-(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylic acid

Step 1 Synthesis of 2,3-difluoro-5-iodobenzoic acid

[0200]

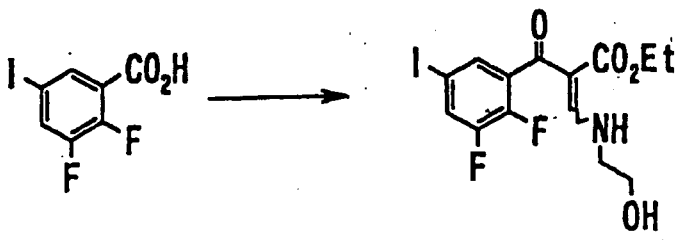


[0201] 2,3-Difluorobenzoic acid (5.0 g, 31.6 mmol) was dissolved in trifluoromethanesulfonic acid (25 ml), and N-iodosuccinimide (8.55 g, 38.0 mmol) was added by portions at 0°C under an argon stream. The mixture was stirred at room temperature for 3 hrs., and the reaction solution was poured into sodium sulfite in ice water. The mixture was stirred and the precipitate was collected by filtration, washed with water and vacuum-dried to give an object product (7.5 g, yield 84%) as a pale-pink solid.
^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: 7.74 (1H,m), 8.11 (1H,m)
MS(ESI): M- 283

B2

Step 2 Synthesis of ethyl 2-(2,3-difluoro-5-iodobenzoyl)-3-(2-hydroxyethylamino)acrylate

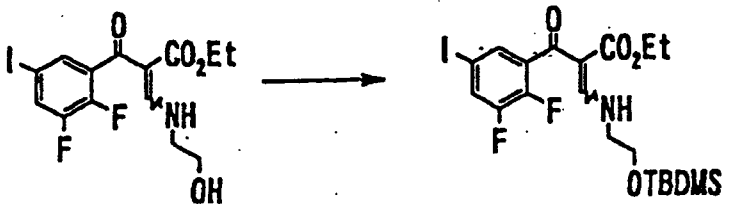
[0202]



[0203] 2,3-Difluoro-5-iodobenzoic acid (3.0 g, 10.6 mmol) obtained in Step 1 was dissolved in toluene, and thionyl chloride (3.0 ml, 41.1 mmol) and DMF (catalytic amount) were added. The mixture was heated under reflux for 3 hrs. The reaction solution was concentrated under reduced pressure and THF (15 ml) was added to dissolve the residue. The resulting solution was added dropwise to a solution of ethyl 3-dimethylaminoacrylate (1.66 g, 11.6 mmol) and triethylamine (1.77 ml, 12.7 mmol) in THF (10 ml) and the mixture was stirred with heating at 50°C for 2.5 hrs. After allowing the mixture to cool, the reaction mixture was filtered and washed with THF (10 ml). Aminoethanol (0.77 ml, 12.7 mmol) was added to the filtrate and the mixture was stirred with heating at 40°C for 1 hr. After allowing the mixture to cool, water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=2:1) to give an object product (3.8 g, yield 85%) of a mixture of E form and Z form as a yellow solid.
^{1}H NMR($CDCl_3$ 400MHz) (δ) ppm: 0.91-1.09 (3H,m), 1.80-1.89 (1H, m), 3.52-3.63 (2H, m), 3.83-3.91 (2H,m), 3.98-4.09 (2H, m), 7.36-7.52(2H,m), 8.15 (1H, d, J=14.4Hz), 9.6(0.22H,brs), 11.0 (0.78H, brs)
MS(ESI): M+ 426

Step 3 Synthesis of ethyl 2-(2,3-difluoro-5-iodobenzoyl)-3-[2-(tert-butyldimethylsilyloxy)ethylamino]acrylate

[0204]

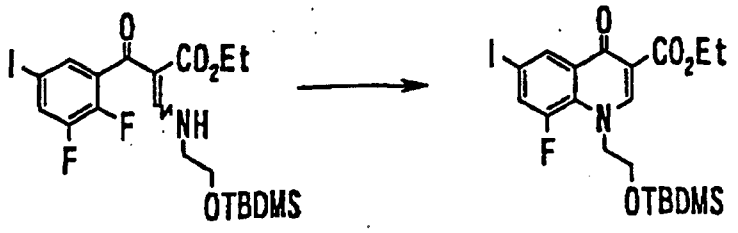


[0205] Ethyl 2-(2,3-difluoro-5-iodobenzoyl)-3-(2-hydroxyethylamino)acrylate (2.0 g, 4.7 mmol) obtained in Step 2 was dissolved in DMF (10 ml), imidazole (705 mg, 10.4 mmol) and tert-butyldimethylsilyl chloride (1.49 g, 9.9 mmol) were added, and stirred at room temperature for 4 hrs. Water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:4) to give an object product (2.3 g, yield 91%) as a white solid.
^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: 0.07 (6H, s), 0.90 (9H,s), 1.07 (3H, t, J=7.1Hz), 3.45-3.55(2H,m), 3.70-3.80 (2H, m), 4.04 (2H, q, J=7.1Hz), 7.30-7.50 (2H, m), 8.14 (1H, d, J=14.1Hz), 10.80-11.10 (1H, m)
MS(ESI): M+ 540

83

Step 4 Synthesis of ethyl 1,4-dihydro-8-fluoro-6-iodo-1-[2-(tert-butyldimethylsilyloxy)ethyl]-4-oxo-3-quinolinecarboxylate

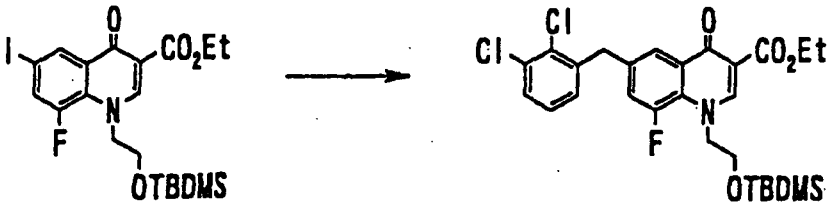
[0206]



[0207] Ethyl 2-(2,3-difluoro-5-iodobenzoyl)-3-[2-(tert-butyldimethylsilyloxy)ethylamino]acrylate (2.3 g, 4.3 mmol) obtained in Step 3 was dissolved in THF (25 ml) and sodium hydride (256 mg, 6.4 mmol) was added with ice-cooling. The mixture was stirred at 0°C for 1 hr. 1N Hydrochloric acid (6.4 ml, 6.4 mmol) was added to neutralize the reaction solution. Water was further added and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:2 to ethyl acetate:hexane=2:1) to give an object product (2.0 g, yield 92%) as a white solid.
^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: -0.12 (6H, s), 0. 79 (9H, s), 1.38(3H,t,J=7.1Hz), 3.90-4.00(2H,m), 4.37(2H,q, J=7.1Hz), 4.40-4.50(2H,m), 7.69(1H,dd,J=2:0Hz,13.7Hz), 8.40(1H,s), 8.69(1H,d,J=2.0Hz)
MS (ESI) : M+ 520

Step 5 Synthesis of ethyl 6-(2,3-dichlorobenzyl)-1,4-dihydro-8-fluoro-1-[2-(tert-butyldimethylsilyloxy)ethyl]-4-oxo-3-quinolinecarboxylate

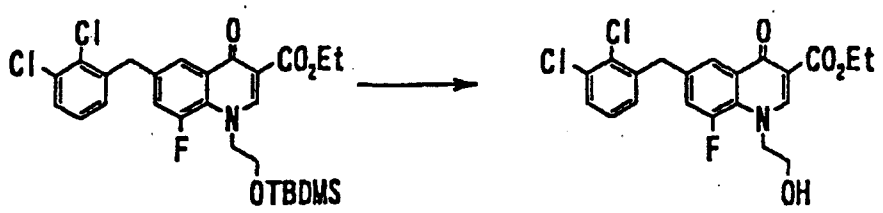
[0208]



[0209] Under an argon stream, 1M solution (2.9 ml, 2.9 mmol) of 2,3-dichlorobenzylzinc chloride in THF obtained in the same manner as in Reference Example 1 was added to THF (20 ml), and then bis(dibenzylideneacetone)palladium (0) (22 mg, 0.039 mmol), tri(2-furyl)phosphine (18 mg, 0.077 mmol) and ethyl 1,4-dihydro-8-fluoro-6-iodo-1-[2-(tert-butyldimethylsilyloxy)ethyl]-4-oxo-3-quinolinecarboxylate (1.0 g, 1.9 mmol) obtained in Step 4 were added. The mixture was stirred at room temperature for 17 hrs, and then a solution (1.0 ml, 1.0 mmol) of 2,3-dichlorobenzylzinc chloride in THF was added. The mixture was heated under reflux for 1 hr. After allowing the mixture to cool, saturated aqueous ammonium chloride solution was added to the reaction solution and insoluble materials were filtered off with Celite. The filtrate was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:1), and then by PTLC (ethyl acetate:chloroform=1:2) to give an object product (562 mg, yield 53%) as a pale-yellow oil.
^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: -0.13 (6H, s), 0. 79 (9H, s), 1.38 (3H, t, J=7.1Hz), 3.90-4.00(2H,m), 4.23(2H,s), 4.37 (2H, q, J=7.1Hz), 4.40-4.50 (2H,m), 7.10-7.50 (4H, m), 8.20-8.30 (1H, m), 8.39 (1H, s)
MS(ESI): M+ 552

Step 6 Synthesis of ethyl 6-(2,3-dichlorobenzyl)-1,4-dihydro-8-fluoro-1-(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylate

[0210]



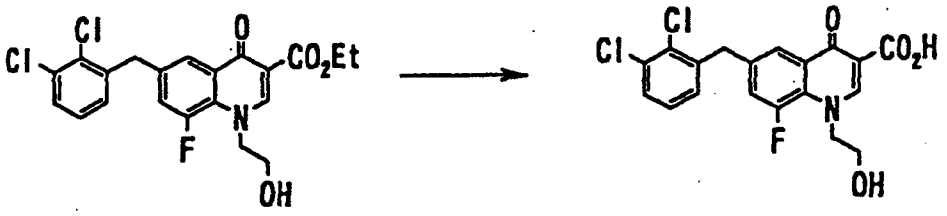
[0211] Ethyl 6-(2,3-dichlorobenzyl)-1,4-dihydro-8-fluoro-1-[2-(tert-butyldimethylsilyloxy)ethyl]-4-oxo-3-quinolinecarboxylate (350 mg, 0.63 mmol) obtained in Step 5 was dissolved in THF (25 ml) and tetrabutylammonium fluoride (1M THF solution; 1.9 ml, 1.9 mmol) was added. The mixture was stirred at room temperature for 1 hr. Water was added to the reaction solution and the precipitate was collected by filtration, washed with water and vacuum-dried to give an object product (279 mg, yield quant) as a pale-yellow solid.

^{1}H NMR(DMSO-d_6 300MHz) (δ) ppm: 1.27 (3H, t, J=7.1Hz), 3.65-3.80(2H,m), 4.21 (2H, q, J=7.1Hz), 4.40-4.50 (2H, m), 4.99 (1H, m), 7.30-7.90(5H,m), 8.47 (1H, s)

MS(ESI): M+ 438

Step 7 Synthesis of 6-(2,3-dichlorobenzyl)-1,4-dihydro-8-fluoro-1-(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylic acid

[0212]



[0213] Ethyl 6-(2,3-dichlorobenzyl)-1,4-dihydro-8-fluoro-1-(2-hydroxyethyl)-4-oxo-3-quinolinecarboxylate (80 mg, 0.18 mmol) obtained in Step 6 was dissolved in a mixture of ethanol (2 ml) and THF (1 ml), and 1N aqueous sodium hydroxide solution (1 ml, 1.0 mmol) was added. The mixture was stirred with heating at 60°C for 1 hr. After allowing the mixture to cool, 10% aqueous citric acid solution was added to the reaction solution. The precipitate was collected by filtration, washed with 30% aqueous ethanol and vacuum-dried to give an object product (70 mg, yield 93%) as a white solid.

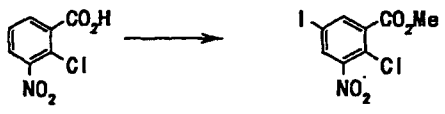
^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.78 (2H, m), 4.35 (2H, s), 4.64 (2H, m), 5.00 (1H, m), 7.39 (2H, m), 7.47 (1H, m), 7.58 (1H, m), 8.00 (1H, m), 8.81 (1H, s), 14.80 (1H, s)

MS (ESI): M+409

Example 3-38

Step 1

[0214]



[0215] 2-Chloro-3-nitrobenzoic acid (6.00 g, 29.77 mmol) was dissolved in trifluoromethanesulfonic acid (40 ml) and N-iodosuccinimide (7.37 g, 32.76 mmol) was added by portions at 0°C. The mixture was stirred at 40°C for 4 hrs and the reaction solution was added to ice water. After stirring, the precipitate was collected by filtration, washed with water and vacuum-dried. The obtained solid was dissolved in methanol (50 ml), conc. sulfuric acid (catalytic amount) was added, and the mixture was heated under reflux for 5.5 hrs. The reaction solution was concentrated under reduced pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:4) to give an object product (5.35 g, yield 53%) as a pale-yellow solid.
1H NMR ($CDCl_3$ 300MHz) (δ) ppm: 3.98 (3H, s), 8.11 (1H, d, J=2.1Hz), 8.24 (1H, d, J=2.1Hz)

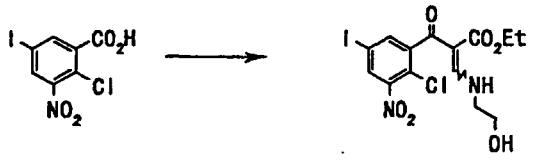
Step 2

[0216]

[0217] The compound (5.35 g, 15.67 mmol) obtained in Step 1 was dissolved in methanol (25 ml) and 4N aqueous potassium hydroxide solution (10.00 ml, 4.00 mmol) was added. The mixture was heated under reflux for 30 min. After allowing the mixture to cool, 1N hydrochloric acid was added to the reaction solution and the precipitated solid was collected by filtration and vacuum-dried to give an object product (4.99 g, yield 97%) as a white solid.
^1H NMR($CDCl_3$ 300MHz) (δ) ppm: 8.14 (1H, d, J=2.0Hz), 8.39 (1H, d, J=2.1Hz)

Step 3

[0218]



[0219] The compound (4.99 g, 15.24 mmol) obtained in Step 2 was dissolved in toluene (50 ml), and thionyl chloride (5.00 ml, 68.54 mmol) and dimethylformamide (catalytic amount) were added. The mixture was heated under reflux for 1 hr. The reaction solution was concentrated under reduced pressure and tetrahydrofuran (80 ml) was added to dissolve the residue. The resulting solution was added dropwise to a solution of ethyl 3,3-dimethylaminoacrylate (2.29 g, 16.00 mmol) and triethylamine (2.55 ml, 18.30 mmol) in tetrahydrofuran (50 ml) and the mixture was stirred with heating at 50°C for 10 hrs. After allowing the mixture to cool, aminoethanol (1.10 ml, 18.23 mmol) was added to the reaction mixture and the mixture was stirred with heating at 40°C for 1.5 hrs. After allowing the mixture to cool, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=2:1) to give an object product (5.35 g, yield 75%) of a mixture of E form and Z form as a yellow solid.
^1H NMR($CDCl_3$ 300MHz) (δ) ppm: 0.82-1.01 (3H, m), 3.63 (2H, br), 3.85-4.06 (4H, m), 7.65-7.68 (1H, m), 8.02-8.06 (1H, m), 8.21-8.36 (1H, m), 9.78 (0.16H, br), 11.15 (0.84H, br)

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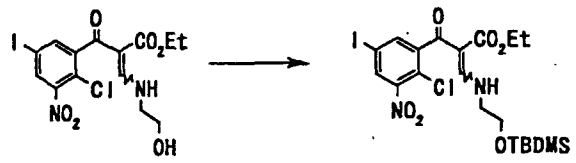
Step 4

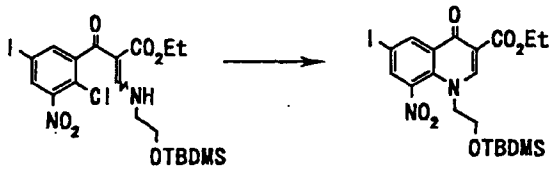
[0220]



[0221] The compound (5.35 g, 11.42 mmol) obtained in Step 3 was dissolved in dimethylformamide (50 ml), and imidazole (1.71 g, 25.12 mmol) and tert-butyldimethylsilyl chloride (3.62 g, 24.02 mmol) were added. The mixture was stirred at room temperature for 30 min. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, concentration under reduced pressure gave a crude product (7.10 g) as a pale-yellow solid.

Step 5

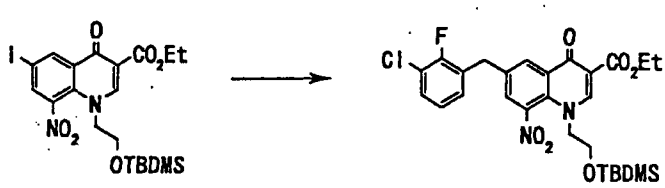
[0222]



[0223] The crude product (7.10 g) obtained in Step 4 was dissolved in tetrahydrofuran (70 ml) and sodium hydride (731 mg, 18.27 mmol) was added with ice-cooling. The mixture was stirred at 0°C for 45 min. 1N Hydrochloric acid (18.3 ml) and water were added to the reaction solution and stirred, after which the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and purified by silica gel chromatography (ethyl acetate:hexane=1:4 to 1:2) to give an object product (5.58 g, yield 84%) as a yellow solid.
^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: -0.14 (6H, s), 0.73 (9H, s), 1.39 (3H, t, J=7.1Hz), 3.74 (2H, t, J=4.6Hz), 4.02 (2H, t, J=4.6Hz), 4.39 (2H, q, J=7.1Hz), 8.13 (1H, d, J=2.2Hz), 8.50 (1H, s), 9.02 (1H, d, J=2.2Hz)

Step 6

[0224]

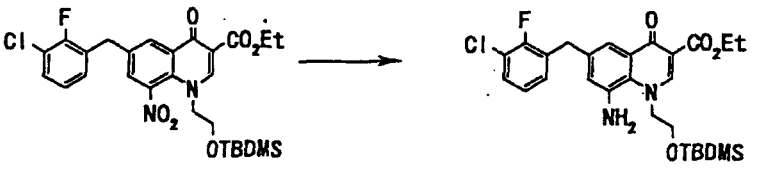


[0225] The compound (5.00 g, 9.15 mmol) obtained in Step 5 was dissolved in tetrahydrofuran (100 ml) and bis (dibenzylideneacetone)palladium(0) (105 mg, 0.18 mmol) and tri(2-furyl)phosphine (85 mg, 0.37 mmol) were added under an argon stream. A solution of 3-chloro-2-fluorobenzylzinc bromide (11.90 mmol) in tetrahydrofuran prepared as mentioned in Example 4-32, Step 4 was added dropwise at 60°C. After completion of the addition, the mixture was heated under reflux for 4 hrs. After allowing the mixture to cool, saturated aqueous ammonium chloride solution was added to the reaction solution and insoluble material was filtered off with Celite. The filtrate was extracted with ethyl acetate, and the organic layer was washed successively with water and saturated brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica

gel chromatography (ethyl acetate:hexane=1:2 to 1:1) to give an object product (2.67 g, yield 52%) as a brown oil. ^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: -0. 19 (6H, s), 0.70 (9H, s), 1.39 (3H, t, J=7.1Hz), 3.73 (2H, t, J=4.6Hz), 4.03 (2H, t, J=4.6Hz), 4.14 (2H, s), 4.38 (2H, q, J=7.1Hz), 7.02-7.14 (2H, m), 7.29-7.35 (1H, m), 7.73 (1H, d, J=2.2Hz), 8.50 (1H, s), 8.59 (1H, s)

Step 7

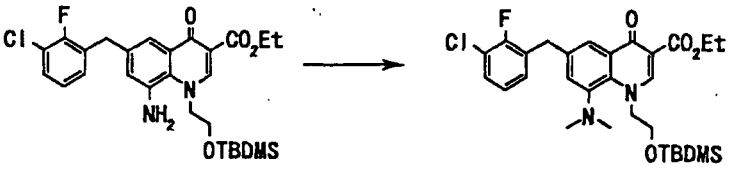
[0226]



[0227] The compound (1.00 g, 1.79 mmol) obtained in Step 6 was dissolved in acetic acid (20 ml) and zinc powder (1.16 g, 17.76 mmol) was added. The mixture was stirred at room temperature for 4 hrs. The reaction mixture was filtered through Celite and saturated aqueous sodium hydrogen carbonate was added to the filtrate. The mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate, water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate). To the residue obtained was added ethyl ether and the mixture was sonicated. After filtration, it was vacuum-dried to give an object product (730 mg, yield 77%) as a pale-orange solid.
^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: -0.06 (6H, s), 0.77 (9H, s), 1.41 (3H, t, J=7.1Hz), 4.01 (2H, s), 4.08 (2H, t, J=4.7Hz), 4.39 (2H, q, J=7.1Hz), 4.50 (2H, brs), 4.75 (2H, t, J=4.7Hz), 6.81 (1H, s), 6.94-7.08 (2H, m), 7.20-7.26 (1H, m), 7.91 (1H, s), 8.34 (1H, s)

Step 8

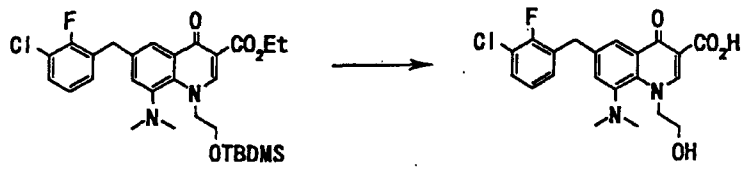
[0228]



[0229] The compound (100 mg, 0.19 mmol) obtained in Step 7 was dissolved in dimethylformamide (2 ml), and methyl iodide (0.029 ml, 0.47 mmol) and sodium hydride (23 mg, 0.56 mmol) were added. The mixture was stirred at room temperature for 2 hrs. A 10% aqueous citric acid solution was added to the reaction mixture, and the mixture was stirred and extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and subjected to silica gel chromatography (ethyl acetate:hexane=2:1) to give a crudely purified product (45 mg) as a pale-red solid. ^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: -0.33 - -0.29 (6H, m), 0.64-0.69 (9H, m), 1.23-1.41(3H, m), 2.66-2.70 (6H, m), 3.55-3.59 (2H, m), 4.36-4.4.2 (4H, m), 4.82-4.96 (2H, m), 6.96-7.11 (2H, m), 7.23-7.30 (2H, m), 8.16-8.15 (1H, m), 8.40-8.66 (1H, m)

Step 9

[0230]

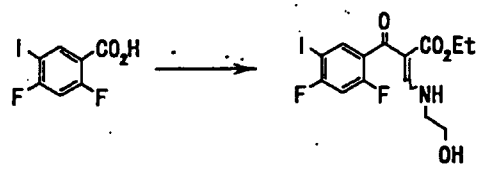


[0231] The crudely purified product (45 mg) obtained in Step 8 was dissolved in tetrahydrofuran (1 ml), and 1M solution of tetrabutylammonium fluoride (1.00 ml, 1.00 mmol) in THF was added. The mixture was stirred at room temperature for 5 min. To the reaction solution were added ethanol (1 ml) and 1N aqueous sodium hydroxide solution (1 ml, 1.00 mmol), and the mixture was heated under reflux for 2 hrs. After allowing the mixture to cool, 10% aqueous citric acid solution was added to the reaction solution. The mixture was stirred and extracted twice with chloroform. The organic layer was washed with saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and subjected to silica gel chromatography (chloroform:methanol:acetic acid=10:1:0.1) to give a crudely purified product. To the crudely purified product was added aqueous ethanol and the mixture was sonicated. After filtration, the filtrate was vacuum-dried to give an object product (22 mg, yield 27%) as a beige solid.
^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.67 (6H, s), 3.39 (2H, m), 4.21 (2H, s), 4.72 (1H, t), 4.97 (2H, t), 7.20-7.22 (1H, m), 7.40-7.50 (2H, m), 7.65 (1H, s), 7.84 (1H, s), 15.10 (1H, s)
MS (ESI) : M+ 419

Example 3-62

Step 1

[0232]



[0233] 2,4-Difluoro-5-iodobenzoic acid (3.00 g, 10.60 mmol) obtained in Example 4-33, Step 1 was dissolved in toluene (10 ml), and thionyl chloride (3.00 ml, 41.10 mmol) and dimethylformamide (catalytic amount) were added. The mixture was heated under reflux for 1.5 hrs. The reaction solution was concentrated under reduced pressure and tetrahydrofuran (15 ml) was added to dissolve the residue. The resulting solution was added dropwise to a solution of ethyl 3,3-dimethylaminoacrylate (1.66 g, 11.60 mmol) and triethylamine (1.77 ml, 12.70 mmol) in tetrahydrofuran (10 ml), and the mixture was stirred with heating at 50°C for 2.5 hrs. After allowing the mixture to cool, the reaction mixture was filtered and washed with tetrahydrofuran (10 ml). To the filtrate was added aminoethanol (0.77 ml, 12.76 mmol) and the mixture was stirred with heating at 40°C for 1 hr. After allowing the mixture to cool, water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=2:1) to give a crudely purified product (3.00 g, yield 67%) of a mixture of E form and Z form as a yellow solid.

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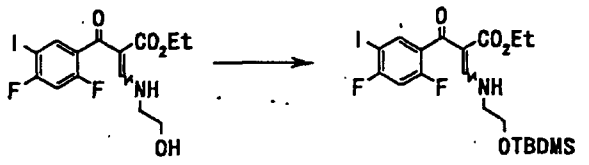
Step 2

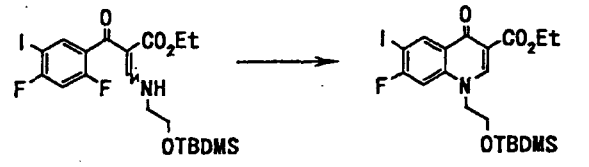
[0234]



[0235] The compound (3.00 g, 7.06 mmol) obtained in Step 1 was dissolved in dimethylformamide (15 ml) and imidazole (1.06 g, 15.52 mmol) and tert-butyldimethylsilyl chloride (2.23 g, 14.82 mmol) were added. The mixture was stirred at room temperature for 14 hrs. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:4) to give an object product (3.22 g, yield 85%) as a white solid.
^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: 0.06 (6H, s), 0.90 (9H, s), 1.08 (3H, t, J=7.1Hz), 3.51 (2H, br), 3.79(2H, t, J=4.9Hz), 4.05(2H, q, J=7.1Hz), 6.78 (1H, dd, J=7.9, 9.4Hz), 7.71 (1H, dd, J=7:3, 7.3Hz), 8.11 (1H, d, J=14.0Hz), 10.91 (1H, br)

Step 3

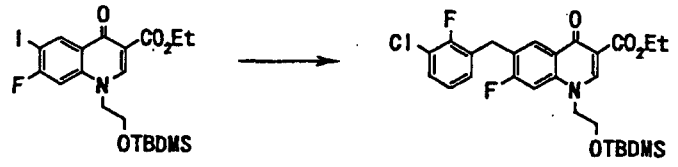
[0236]



[0237] The compound (3.22 g, 5.97 mmol) obtained in Step 2 was dissolved in tetrahydrofuran (35 ml) and sodium hydride (358 mg, 8.95 mmol) was added with ice-cooling. The mixture was stirred at 0°C for 2.5 hrs. 1N Hydrochloric acid (8.90 ml, 8.90 mmol) and water (35 ml) were added to the reaction mixture and the mixture was stirred. The precipitate was collected by filtration, and purified by silica gel chromatography (ethyl acetate:hexane=1:2 to 2:1) to give an object product (2.52 g, yield 81%) as a pale-yellow solid.
^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: -0.11 (6H, s), 0.79 (9H, s), 1.39 (3H, t, J=7.1Hz), 3.96 (2H, t, J=4.8Hz), 4.23 (2H, t, J=4. 8Hz), 4.38(2H, q, J=7.1Hz), 7.14 (1H, d, J=9.3Hz), 8.47 (1H, s), 8.93 (1H, d, J=7.2Hz)

Step 4

[0238]



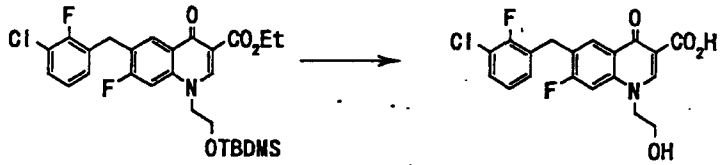
[0239] The compound (1.00 g, 1.93 mmol) obtained in Step 3 was dissolved in tetrahydrofuran (20 ml). Under an argon stream, bis(dibenzylideneacetone)palladium(0) (22 mg, 0.039 mmol) and tri(2-furyl)phosphine (18 mg, 0.077 mmol) were added. To this mixture was added a solution of 3-chloro-2-fluorobenzylzinc bromide (2.89 mmol) in tetrahydrofuran prepared as mentioned above dropwise at 60°C. After completion of the addition, the mixture was heated under reflux for 1 hr. After allowing the mixture to cool, saturated aqueous ammonium chloride solution was added to

the reaction solution. Insoluble material was filtered off with Celite. The filtrate was extracted with ethyl acetate, and the organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=2:1) to give an object product (573 mg, yield 55%) as a pale-yellow solid.

^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: -0.12 (6H, s), 0.78 (9H, s), 1.38 (3H, t, J=7.1Hz), 3.99 (2H, t), 4.13 (2H, s), 4.23 (2H, t), 4.37 (2H, q, J=7.1Hz), 6.96-7.13 (3H, m), 7.25-7.31(1H, m), 8.39 (1H, d), 8.46 (1H, s)

Step 5

[0240]

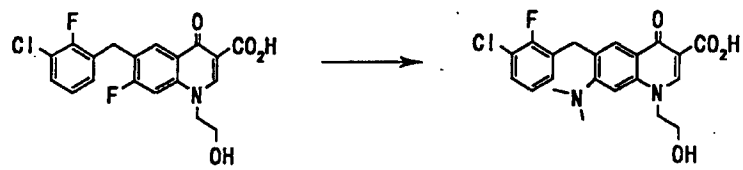


[0241] The compound (170 mg, 0.32 mmol) obtained in Step 4 was dissolved in tetrahydrofuran (1 ml) and 2N aqueous sodium hydroxide solution (4.00 ml, 2.00 mmol) was added. The mixture was heated under reflux for 3.5 hrs. After allowing the mixture to cool, 10% aqueous citric acid solution was added to the reaction solution, and the precipitate was collected by filtration, washed with 50% aqueous ethanol and vacuum-dried to give an object product (117 mg, yield 94%) as a white solid.

^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.73 (2H, br), 4.25 (2H, s), 4.58(2H, br), 4.96 (1H, br), 7.19-7.22 (1H, m), 7.30-7.36 (1H, m), 7.49-7.54 (1H, m), 8.03 (1H, d), 8.30 (1H, d), 8.88 (1H, s), 15.42 (1H, brs)

Step 6

[0242]



[0243] The compound (65 mg, 0.17 mmol) obtained in Step 5 was dissolved in dimethyl sulfoxide (2.5ml) and microwave was irradiated thereon at 50W and 120°C or below for 20 min. After allowing the mixture to cool, 10% aqueous citric acid solution was added to the reaction mixture, and the precipitate was collected by filtration, washed with water and vacuum-dried to give an object product (66 mg, yield 96%) as a white solid.

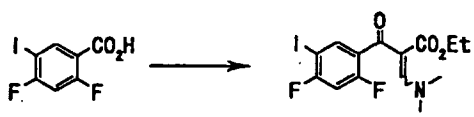
^{1}H NMR(DMSO-d_6 300MHz) (δ) ppm: 2.88 (6H, s), 3.70-3.80 (2H, m), 4.22(2H, s), 4.60-4.70 (2H, m), 5.05 (1H, t), 7.20-7.31 (3H, m), 7.50-7.60 (1H, m), 7.80 (1H, s), 8.78 (1H, s), 15.30-15.40 (1H, brs)

MS (ESI) : M+ 419

Example 3-73

Step 1

[0244]

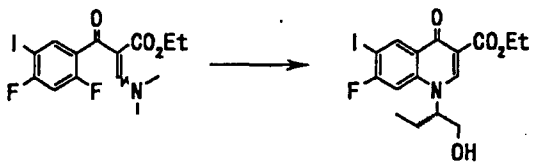


91

[0245] 2,4-Difluoro-5-iodobenzoic acid (5.00 g, 17.60 mol) was dissolved in toluene (25 ml), and oxalyl chloride (2.00 ml, 22.93 mmol) and dimethylformamide (catalytic amount) were added. The mixture was stirred at room temperature for 12 hrs. After filtering the reaction solution, the filtrate was concentrated under reduced pressure and toluene (20 ml) was added. Insoluble material was filtered with Celite. The filtrate was concentrated under reduced pressure and tetrahydrofuran (20 ml) was added to dissolve the obtained residue. The resulting solution was added dropwise to a solution of ethyl 3,3-dimethylaminoacrylate (3.28 g, 22.91 mmol) and triethylamine (3.70 ml, 26.55 mmol) in tetrahydrofuran (20 ml). The mixture was heated under reflux for 1 hr. After allowing the mixture to cool, water and ethyl acetate (50 ml) were added to the reaction mixture. The mixture was stirred and partitioned. The organic layer was washed successively with 1N hydrochloric acid (20 ml) and water (200 ml), and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give a crude product (7.24 g) as a brown oil.

Step 2

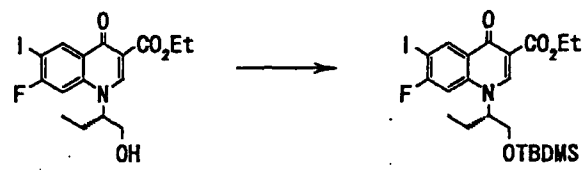
[0246]



[0247] The crude product (7.24 g) obtained in Step 1 was dissolved in tetrahydrofuran (20 ml) and (S)-2-amino-1-butanol (1.89 g, 21.24 mmol) was added. The mixture was stirred with heating at 60°C for 1.5 hrs. After allowing the mixture to cool, the reaction solution was concentrated under reduced pressure and the obtained residue was dissolved in dimethylformamide (20 ml). Potassium carbonate (7.33 g, 53.02 mmol) was added and the mixture was stirred with heating at 70°C for 1 hr. After allowing the mixture to cool, the reaction mixture was concentrated under reduced pressure. Water (150 ml) was added to the residue and the mixture was stirred at room temperature for 30 min. The precipitate was collected by filtration. The obtained solid was washed with water (50 ml), and then with a mixture (50 ml) of hexane:diethyl ether=7:3, and vacuum-dried to give an object product (4.69 g, yield 61%) as a white solid.
^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: 0.97 (3H, t, J=7.4Hz), 1.40(3H, t, J=7.1Hz), 1.95-2.05 (1H, m), 2.11-2.21 (1H, m), 4.05 (1H, br), 4.34-4.39 (5H, m), 5.59 (1H, br), 7.30 (1H, d, J=10.0Hz), 8.04 (1H, d, J=7.1Hz), 8.58(1H, s)

Step 3

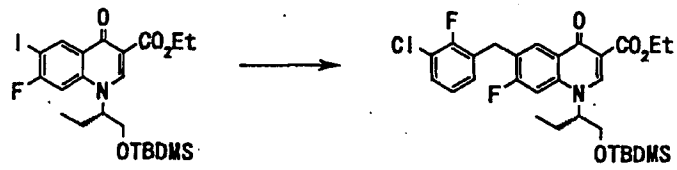
[0248]



[0249] The compound (4.69 g, 10.82 mmol) obtained in Step 2 was dissolved in dimethylformamide (20 ml), and imidazole (950 mg, 13.95 mmol) and tert-butyldimethylsilyl chloride (1.95 g, 12.96 mmol) were added. The mixture was stirred at room temperature for 14.5 hrs. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate (50 ml). The organic layer was washed 3 times with water and then with saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=3:7) to give an object product (5.06 g, yield 86%) as a yellow oil.
^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: -0.08 (3H, s), -0.05 (3H, s), 0.77 (9H, s), 0.98 (3H, t, J=7.5Hz), 1.40 (3H, t, J=7.2Hz), 1.94-2.10(2H, m), 3.90 (2H, br), 4.35-4.43 (3H, m), 7.26 (1H, d, J=9.9Hz), 8.59 (1H, s), 8.95 (1H, d, J=7.2Hz)

Step 4

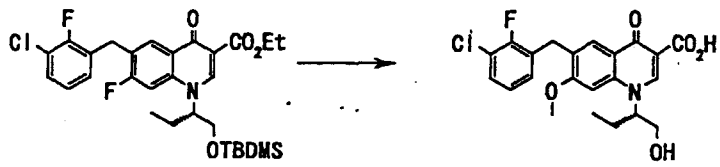
[0250]



[0251] The compound (5.06 g, 9.24 mmol) obtained in Step 3 was dissolved in tetrahydrofuran (20 ml), and bis (dibenzylideneacetone)palladium(0) (266 mg, 0.46 mmol) and tri(2-furyl)phosphine (215 mg, 0.92 mmol) were added under an argon stream. A solution of 3-chloro-2-fluorobenzylzinc bromide (18.50 mmol) in tetrahydrofuran prepared as mentioned above was added dropwise. After completion of the addition, the mixture was stirred with heating at 60°C for 1 hr. After allowing the mixture to cool, water and ethyl acetate were added to the reaction solution and the mixture was stirred and partitioned. The organic layer was washed successively with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (ethyl acetate: hexane=1:1 to 2:1) to give an object product (3.86 g, yield 74%) as a brown oil.
^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: -0.10 (3H, s), -0.06(3H, s), 0.752(9H, s), 0.98(3H, t, J=7.4Hz), 1.403H, t, J=7.1Hz), 1.90-2.12(2H, m), 3.89 (2H, br), 4.12 (2H, s), 4.35-4.49(3H, m), 6.97-7.08 (2H, m), 7.22-7.29 (2H, m), 8.40 (1H, d, J=8.7Hz), 8.58 (1H, s)

Step 5

[0252]

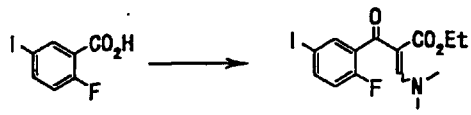


[0253] To the compound (3.86 g, 6.85 mmol) obtained in Step 4 were added 28% sodium methoxide in methanol (40.00 ml, 0.20 mol) and water (2.00 ml, 0.11 mol), and the mixture was heated under reflux for 5.5 hrs. After allowing the mixture to cool, the reaction solution was concentrated under reduced pressure and 6N hydrochloric acid was added to the obtained residue. The mixture was stirred, and extracted twice with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The obtained residue was recrystallized from ethanol (200 ml) to give an object product (2.03 g, yield 68%) as a white solid.
^{1}H NMR(DMSO-d_6 300MHz) (δ) ppm: 0.87 (3H, t, J=7.3Hz), 1.80-2.10 (2H, m), 3.70-3.90 (2H, m), 4.02 (3H, s), 4.11 (2H, s), 5.00-5.19 (2H, m), 7.16-7.24 (2H, m), 7.44-7.48 (2H, m), 8.04 (1H, s), 8.78 (1H, s), 15.44 (1H, s)
MS(ESI): M+ 434

Example 3-75

Step 1

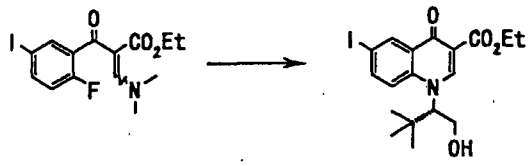
[0254]



[0255] 2-Fluoro-5-iodobenzoic acid (6.60 g, 24.81 mmol) was dissolved in chloroform (70 ml) and oxalyl chloride (4.30 ml, 49.29 mmol) and dimethylformamide (catalytic amount) were added. The mixture was stirred at room temperature for 3 hrs. The reaction solution was concentrated under reduced pressure and chloroform (35 ml), was added to dissolve the residue. The obtained solution was added dropwise to a solution of ethyl 3,3-dimethylaminoacrylate (4.26 g, 29.75 mmol) and triethylamine (5.19 ml, 37.24 mmol) in chloroform (35 ml), and the mixture was stirred at room temperature for 15 hrs. Water was added to partition the reaction solution, and the organic layer was washed with saturated brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:2 to 1:1) to give an object product (6.40 g, yield 66%) of a mixture of E form and Z form as an orange solid.
^{1}H NMR($CDCl_3$ 400MHz) (δ) ppm: 0.94 (3H, t, J=7.2Hz), 2.88 (3H, brs), 3.31 (3H, brs), 3.97 (2H, q), 6.78 (1H, dd, J=8.4, 10.0Hz), 7.65-7.67 (1H, m), 7.78(1H, s), 7,85 (1H, brs)
MS (ESI) : M+ 392

Step 2

[0256]



[0257] The compound (300 mg, 0.77 mmol) obtained in Step 1 was dissolved in tetrahydrofuran (1.5 ml) and (S)-(+)-tert-leucinol (0.12 ml, 0.92 mmol) was added. The mixture was stirred with heating at 60°C for 1 hr. The reaction solution was concentrated under reduced pressure and the obtained residue was dissolved in dimethylformamide (1.2 ml). Potassium carbonate (318 mg, 2.30 mmol) was added and the mixture was stirred with heating at 70°C for 5.5 hrs. After cooling, 1N hydrochloric acid (5 ml) was added to the reaction mixture and the mixture was stirred with ice-cooling for 30 min. The precipitate was collected by filtration and the obtained solid was washed with 30% aqueous ethanol (6 ml), and then with a mixture (5 ml) of hexane:diethyl ether=2:1 and vacuum-dried to give an object product (276 mg, yield 81%) as a pale-yellow solid.
^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: 0.98 (9H, s), 1.41 (3H, t, J=7.0Hz), 4.25-4.41 (4H, m), 4:64=4.70 (1H, m), 5.14 (1H, br), 7.46 (1H, d, J=9.0Hz), 7.89 (1H, dd, J=2.2, 9.1Hz), 8.06 (1H, d, J=2.1Hz), 8.69 (1H, s)

94

Step 3

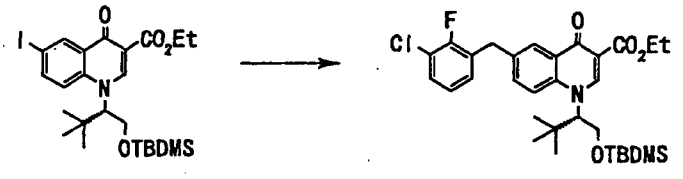
[0258]

[0259] The compound (276 mg, 0.62 mmol) obtained in Step 2 was dissolved in dimethylformamide (1 ml) and imidazole (51 mg, 0.75 mmol) and tert-butyldimethylsilyl chloride (122 mg, 0.81 mmol) were added. The mixture was stirred at room temperature for 30 min. Water was added to the reaction mixture and the mixture was extracted twice with ethyl acetate, and the organic layer was washed twice with water and then with saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=3:5) to give an object product (314 mg, yield 91%) as a white amorphous form.

^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: -0.09 (3H, s), -0.01 (3H, s), 0.66 (9H, s), 1.04 (9H, s), 1.41 (3H, t, J=7.2Hz), 4.10-4.14 (2H, m), 4.40 (2H, q, J=7.0Hz), 4.58-4.63 (1H, m), 7.39(1H, d, J=9.3Hz), 7.89 (1H, dd, J=2.2, 8.8Hz), 8.67 (1H, s), 8.87 (1H, d, J=2.1Hz)

Step 4

[0260]



[0261] The compound (314 mg, 0.56 mmol) obtained in Step 3 was dissolved in tetrahydrofuran (1.2 ml), and bis(dibenzylideneacetone)palladium(0) (16 mg, 0.028 mmol) and tri(2-furyl)phosphine (13 mg, 0.056 mmol) were added under an argon stream. A solution of 3-chloro-2-fluorobenzylzinc bromide (1.13 mmol) in tetrahydrofuran prepared as mentioned above was added dropwise. After completion of the addition, the mixture was stirred with heating at 50°C for 1.5 hrs. After allowing the mixture to cool, water and ethyl acetate were added to the reaction solution and the mixture was stirred. Insoluble material was filtered with Celite. The filtrate was partitioned and the organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:1) to give an object product (283 mg, yield 87%) as a brown amorphous form.

^{1}H NMR($CDCl_3$ 400MHz) (δ) ppm: -0.11 (3H, s), -0.01 (3H, s), 0.63 (9H, s), 1.06 (9H, s), 1.41 (3H, t, J=7.0Hz), 4.08-4.16 (4H, m), 4.38 (2H, q, J=7.0Hz), 4.61-4.67 (1H, m), 6.95-7.08(2H, m), 7.23-7.27 (1H, m), 7.47-7.49 (1H, m), 7.53-7.55 (1H, m), 8.41 (1H, d, J=2.0Hz), 8.68 (1H, s)

95

Step 5

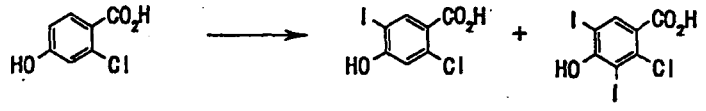
[0262]

[0263] The compound (283 mg, 0.49 mmol) obtained in Step 4 was dissolved in ethanol (2 ml) and 1N aqueous sodium hydroxide solution (1.00 ml, 1.00 mmol) was added. The mixture was heated under reflux for 1 hr. After allowing the mixture to cool, acetic acid (0.35 ml) was added to the reaction solution and the mixture was stirred. The precipitate was collected by filtration and the solid was suspended in diethyl ether (10 ml). After filtration, the mixture was vacuum-dried to give an object product (157 mg, yield 74%) as a white solid.
^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.00 (9H, s), 4.07-4.12 (2H, m), 4.30 (2H, s), 5.12-5.14 (2H, m), 7.20-7.25 (1H, m), 7.40-7.45 (1H, m), 7.51-7.53 (1H, m), 7.87 (1H, d), 8.25 (1H, s), 8.41 (1H, d, J=9.2Hz), 8.85 (1H, s), 15.20-15.21 (1H, br)
MS (ESI) : M+ 432

Example 4-20

Step 1

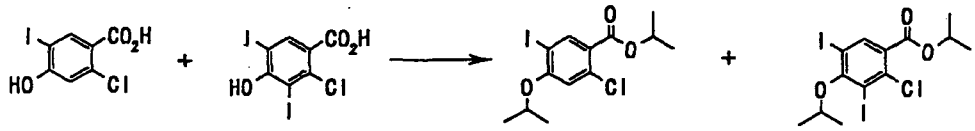
[0264]



[0265] 2-Chloro-4-hydroxybenzoic acid (5.18 g, 30.02 mmol) was dissolved in trifluoromethanesulfonic acid (25 g) and N-iodosuccinimide (6.75 g, 30.00 mmol) was added by portions at 0°C. The mixture was stirred at room temperature for 15 hrs and trifluoromethanesulfonic acid (25 g) was further added. N-Iodosuccinimide (2.02 g, 8.98 mmol) was added by portions at 0°C. The mixture was stirred at room temperature for 13.5 hrs and the reaction mixture was added to ice water (300 ml). The mixture was stirred for 2 hrs. The precipitate was collected by filtration, washed with water and vacuum-dried to give an object product as a mixture of 2-chloro-4-hydroxy-5-iodobenzoic acid and 2-chloro-3,5-di-iodo-4-hydroxybenzoic acid (8:2) (5.76 g).

Step 2

[0266]



[0267] The mixture (3.89 g) obtained in Step 1 was dissolved in dimethylformamide (20 ml) and potassium carbonate (8.97 g, 64.90 mmol) and isopropyl iodide (6.50 ml, 65.15 mmol) were added. The mixture was stirred with heating at 80°C for 2.5 hrs. The reaction mixture was added to 1N hydrochloric acid (100 ml), and toluene (100 ml) was further added. The mixture was stirred and insoluble material was filtered through Celite. The filtrate was partitioned and the organic layer was washed with water three times, and dried over sodium sulfate. After filtration, the filtrate was con-

centrated under reduced pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate: hexane=1:9) to give an object product as a mixture (4.08 g).

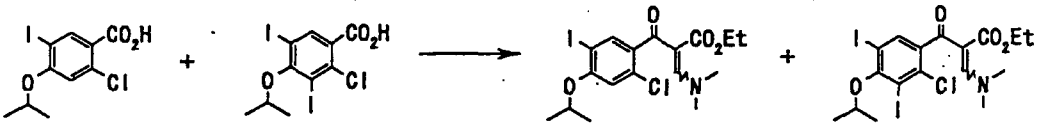
Step 3

[0268]

[0269] The mixture (4.08 g) obtained in Step 2 was dissolved in ethanol (20 ml) and 1N aqueous sodium hydroxide solution (20.00 ml, 20.00 mmol) was added. The mixture was heated under reflux for 24 hrs. After allowing the mixture to cool, 1N hydrochloric acid (30 ml) was added to the reaction solution and the mixture was stirred. The mixture was extracted with ethyl acetate three times. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, concentration under reduced pressure gave an object product as a mixture (3.40 g).

Step 4

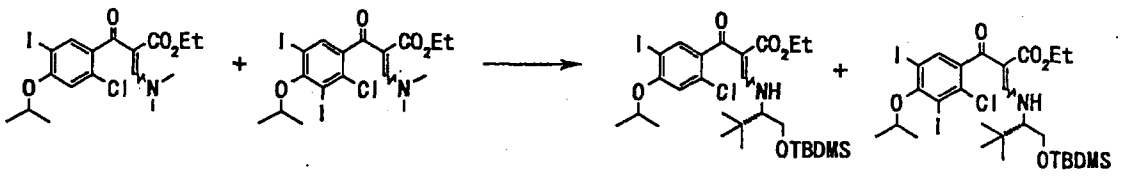
[0270]



[0271] The mixture (3.40 g) obtained in Step 3 was dissolved in toluene (35 ml) and thionyl chloride (3.40 ml, 46.61 mmol) and dimethylformamide (catalytic amount) were added. The mixture was heated under reflux for 1.5 hrs. The reaction solution was concentrated under reduced pressure and tetrahydrofuran (25 ml) was added to dissolve the residue. The obtained solution was added dropwise to a solution of ethyl 3,3-dimethylaminoacrylate (4.29 g, 30.00 mmol) and triethylamine (4.17 ml, 30.00 mmol) in tetrahydrofuran (10 ml) and the mixture was heated under reflux for 14 hrs. After allowing the mixture to cool, water and ethyl acetate were added to the reaction mixture, and the mixture was stirred and partitioned. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:1.5 to 1.5:1) to give an object product as a mixture (2.71 g).

Step 5

[0272]

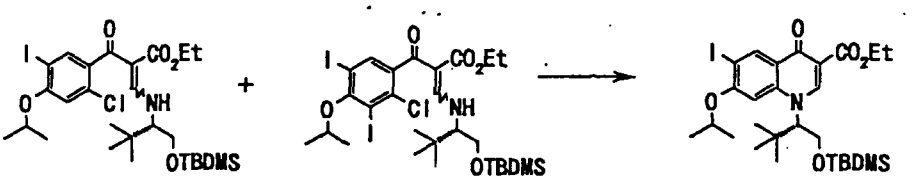


[0273] The mixture (300 mg) obtained in Step 4 was dissolved in tetrahydrofuran (2 ml), and (S)-(+)-tert leucinol (0.10 ml, 0.77 mmol) was added. The mixture was heated under reflux for 20 min. After allowing the mixture to cool, the reaction solution was concentrated under reduced pressure and the obtained residue was dissolved in dimethyl-

formamide (4 ml). Imidazole (110 mg, 1.61 mmol) and tert-butyldimethylsilyl chloride (214 mg, 1.42 mmol) were added and the mixture was stirred at room temperature for 20 min. Water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:4) to give an object product as a mixture (391 mg).

Step 6

[0274]

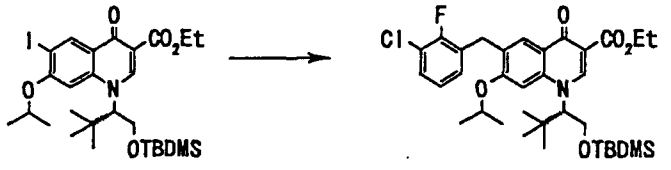


[0275] The mixture (391 mg) obtained in Step 5 was dissolved in toluene (5 ml) and sodium hydride (29 mg, 0.73 mmol) was added under ice-cooling. The mixture was stirred at room temperature for 30 min and dimethylformamide (3 ml), potassium carbonate (100 mg, 0.72 mmol) and ethyl iodide (0.058 ml, 0.73 mmol) were added to the reaction mixture. The mixture was stirred with heating at 60°C for 30 min. After allowing the mixture to cool, the reaction mixture was added to ice water. 1N Hydrochloric acid was added for neutralization and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=4:5 to 2:1) to give an object product (258 mg, yield 19%) as a pale-white yellow solid.

^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: -0.09 (3H, s), 0.00 (3H, s), 0.67 (9H, s), 1.05(9H, s), 1.40 (3H, t, J=7.1Hz), 1.46 (6H, d, J=6.0Hz), 4.09-4.20(2H, m), 4.39 (2H, q, J=7.1Hz), 4.43-4.49 (1H, m), 4.61-4.69 (1H, m), 6.87 (1H, s), 8.60 (1H, s), 8.94 (1H, s)

Step 7

[0276]

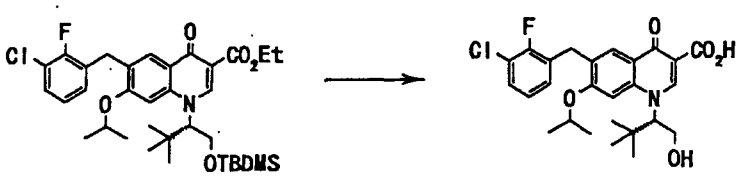


[0277] Ethyl 1,4-dihydro-1-{2,2-dimethyl-1-[(tert-butyldimethylsilyloxy)methyl]propyl}-6-iodo-7-isopropyloxy-4-oxo-3-quinolinecarboxylate (258 mg, 0.42 mmol) obtained in Step 6 was dissolved in tetrahydrofuran (5 ml). Under an argon stream, bis(dibenzylideneacetone)palladium(0) (9.7 mg, 0.017 mmol) and tri (2-furyl) phosphine (7.8 mg, 0.034 mmol) were added and a solution of 3-chloro-2-fluorobenzylzinc bromide (0.63 mmol) in tetrahydrofuran prepared as mentioned above was added dropwise at 60°C. After completion of the addition, the mixture was heated under reflux for 1 hr. After allowing the mixture to cool, saturated aqueous ammonium chloride solution was added to the reaction solution and the mixture was stirred and filtered through Celite. Water was added to the filtrate and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the obtained residue was crudely purified by silica gel chromatography (ethyl acetate:hexane=1:1 to 2:1) to give a crudely purified product (216 mg) as a pale-yellow oil.

98

Step 8

[0278]

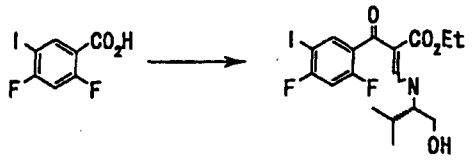


[0279] The crudely purified product (216 mg) obtained in Step 7 was dissolved in a mixture of ethanol (2 ml) and tetrahydrofuran (1 ml), and 1N aqueous sodium hydroxide solution (2.00 ml, 2.00 mmol) was added. The mixture was heated under reflux for 1 hr. After allowing the mixture to cool, 10% aqueous citric acid solution was added to the reaction solution and the mixture was stirred. The mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was treated with a mixture of diethyl ether and hexane. After filtration, the solid was vacuum-dried to give an object product (140 mg, yield 68%) as a white solid.
^{1}H NMR(DMSO-d_6 300MHz) (δ) ppm: 0.97 (9H, s), 1.18 (3H, d, J=5.9Hz), 1.26 (3H, d, J=6.0Hz), 4.04-4.09 (4H, m), 5.09-5.13 (3H, m), 7.12-7.21 (2H, m), 7.43-7.51 (2H, m), 8.19 (1H, s), 8.78 (1H, s), 15.46 (1H, s)
MS (ESI) : M+ 490

Example 4-32

Step 1

[0280]



[0281] 2,4-Difluoro-5-iodobenzoic acid (650.57 g, 2.29 mol) was dissolved in toluene (1300 ml), and thionyl chloride (184 ml, 2.52 mol) and dimethylformamide (catalytic amount) were added. The mixture was stirred at 90°C for 2 hrs. After allowing the mixture to cool, the reaction solution was concentrated under reduced pressure. The residue was dissolved in toluene (330 ml) followed by concentration under reduced pressure, and repeated again. The residue was dissolved in toluene (690 ml) and the obtained solution was added dropwise to a solution of ethyl 3,3-dimethylaminoacrylate (361.52 g, 2.525 mol) and diisopropylethylamine (480 ml, 2.75 mol) in toluene (690 ml) and the mixture was stirred with heating at 90°C for 3 hrs. After allowing the mixture to cool, (S)-(+)-valinol (260.00 g, 2.52 mol) was added to the reaction mixture and the mixture was stirred at room temperature for 1 hr. Water (2600 ml) was added to the reaction mixture and the mixture was partitioned. The aqueous layer was extracted with toluene (680 ml) . The organic layers were combined, washed twice with water (2000 ml), and dried over sodium sulfate. After filtration, concentration under reduced pressure gave a crude product (1180 g) as a brown oil.

99

Step 2

[0282]

[0283] The crude product (1180 g) obtained in Step 1 was dissolved in dimethylformamide (2500 ml) and finely ground potassium carbonate (292.00 g, 1.06 mol) was added. The mixture was stirred at room temperature for 22 hrs. The reaction mixture was added to ice water (ca. 10 L) and the mixture was stirred for 30 min. The precipitate was collected by filtration and washed with water (2000 ml). The obtained solid was vacuum-dried, and suspended in ethyl acetate (5000 ml). Filtration and vacuum-drying gave an object product (774.63 g, yield 82%) as a white yellow solid. ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.72(3H, d, J=6.6Hz), 1.10 (3H, d, J=6.6Hz), 1.28(3H, t, J=7.0Hz), 2.27 (1H, br), 3.77 (1H, br), 3.86 (1H, br), 4.23 (2H, q, J=7.0Hz), 4.56 (1H, br), 5.12 (1H, t, J=4.9Hz), 8.09 (1H, d, J=11.1Hz), 8.62 (1H, d, J=7.5Hz), 8. 68 (1H, s)
MS(ESI): M+ 448

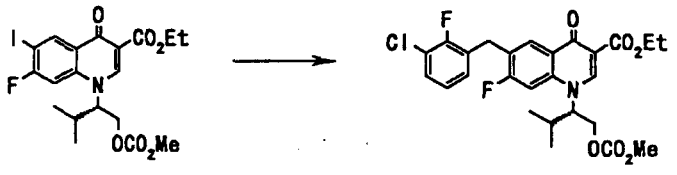
Step 3

[0284]

[0285] The compound (626.15 g, 1.40 mol) obtained in Step 2 was dissolved in chloroform (1250 ml), and pyridine (433 ml, 5.60 mol) and 4-(dimethylamino)pyridine (17.10 g, 0.14 mol) were added. A solution of methyl chloroformate (529.30 g, 5.60 mol) in chloroform (1250 ml) was added dropwise at 10°C or below. After completion of the addition, the mixture was stirred at the same temperature for 30 min. The reaction mixture was washed successively with water (1250 ml), 2N hydrochloric acid (1250 ml), water (630 ml) and saturated aqueous sodium hydrogen carbonate (630 ml), and dried over sodium sulfate. After filtration, the residue was concentrated under reduced pressure to give a crude object substance (834.02 g) as a brown oil.

Step 4

[0286]



(Preparation of 3-chloro-2-fluorobenzylzinc bromide tetrahydrofuran solution)

[0287] Under an argon stream, zinc powder (113.02 g, 1.73 mol) was suspended in tetrahydrofuran (350 ml), and 1,2-dibromoethane (1.207 ml, 14.00 mmol) and trimethylsilyl chloride (8.88 ml, 70.00 mmol) were added at 60°C. The

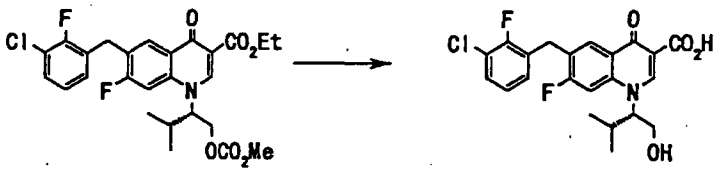
mixture was stirred with heating at 30 min. A solution of 3-chloro-2-fluorobenzyl bromide (406.73 g, 1.82 mol) in tetrahydrofuran (700 ml) was added dropwise at 60°C. The mixture was stirred with heating for 1 hr to give a solution of 3-chloro-2-fluorobenzylzinc bromide.

(Main Step)

[0288] The crude product (834.02 g) obtained in Step 3 was dissolved in tetrahydrofuran (1060 ml), and dichlorobis (triphenylphosphine) palladium (II) (19.65 g, 28.00 mmol) was added under an argon stream and a solution of 3-chloro-2-fluorobenzylzinc bromide (1.82 mol) was added dropwise at 60°C. After completion of the addition, the mixture was heated under reflux for 1.5 hrs. After allowing the mixture to cool, toluene (2120 ml) and 20% aqueous ammonium chloride solution (1410 ml) were added to the reaction solution, and the mixture was stirred and partitioned. The organic layer was washed twice with 20% aqueous ammonium chloride solution (710 ml) and twice with saturated aqueous sodium hydrogen carbonate (710 ml) and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give a crude product (849.34 g) as a brown oil.

Step 5

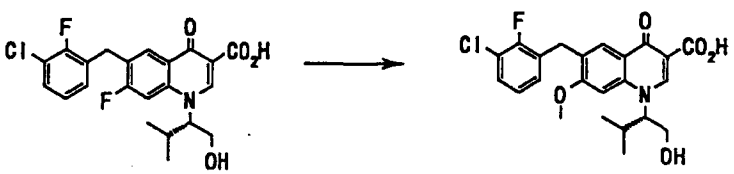
[0289]



[0290] The crude product (849.34 g) obtained in Step 4 was dissolved in isopropanol (1100 ml) and 4N aqueous sodium hydroxide solution (1050 ml, 4.20 mmol) was added. The mixture was stirred with heating at 50°C for 1.5 hrs. Activated carbon (37 g) was added to the reaction solution and the mixture was stirred at room temperature for 30 min. The mixture was filtered through Celite and 6N hydrochloric acid (740 ml) and ethyl acetate (3650 ml) were added to the filtrate. The mixture was stirred and partitioned. The organic layer was concentrated under reduced pressure and the residue was suspended in isopropanol (1070 ml). The mixture was stirred at 60°C for 1 hr. After allowing the mixture to cool, the solid was collected by filtration. The obtained solid was washed with isopropanol (740 ml) and vacuum-dried to give an object product (446.51 g, yield 73%) as a pale-yellow solid.
^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.71 (3H, d, J=6.5Hz), 1.13 (3H, d, J=6.5Hz), 2.36 (1H, br), 3.77(1H, br), 3.94 (1H, br), 4.25 (2H, s), 4.77 (1H, br), 5. 16 (1H, t, J=2.4Hz), 7.19-7.23 (1H, m), 7.32-7.35 (1H, m), 7.48-7.52 (1H, m), 8.24-8.28 (2H, m), 9.00 (1H, s), 15.00 (1H, s)
MS(ESI): M+ 436

Step 6

[0291]



[0292] The compound (443.59 g, 1.02 mol) obtained in Step 5 was dissolved in methanol (2400 ml), and a 28% sodium methoxide in methanol (2077 ml, 10.17 mol) and water (44.30 ml, 2.46 mol) were added. The mixture was heated under reflux for 17.5 hrs. Activated carbon (22 g) was added to the reaction solution and the mixture was stirred at room temperature for 1 hr. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. Water (1770 ml) was added to the residue and the mixture was stirred with ice-cooling for 1 hr. Then, 6N hydrochloric acid (1790 ml) was further added and the mixture was stirred at room temperature for 2 hrs. Ethyl acetate

(1770 ml) was added and to the mixture was stirred and partitioned. The organic layer was washed twice with 10% brine (890 ml), and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and a part of the residue was recrystallized several times (final recrystallization solvent was methanol-water) to give an object product (28.60 g, yield 67%) as a white solid.

^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.72 (3H, d, J=6.5Hz), 1.16 (3H, d, J=6.5Hz), 2.30-2.50 (1H, m), 3.70-3.90 (1H, m), 3.90-4.00 (1H, m), 4.03 (3H, s), 4.12 (2H, s), 4.80-4.90 (1H, m), 5.19 (1H, t, J=5.2Hz), 7.19-7.25 (2H, m), 7.46-7.51 (2H, m), 8.04 (1H, s), 8.88 (1H, s), 15.44 (1H, s)
MS (ESI): M+ 448

Example 4-33

Step 1

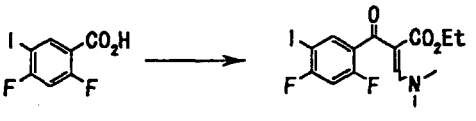
[0293]

[0294] 2,4-Difluorobenzoic acid (600.00 g, 3.80 mol) was dissolved in conc. sulfuric acid (2400 ml) and N-iodosuccinimide (854.40 g, 3.60 mol) was added by portions at 5°C or below. After completion of the addition, the mixture was stirred at the same temperature for 3 hrs. The reaction mixture was poured into ice water (ca. 10 L) and 10% aqueous sodium sulfite solution (40 ml) was added. The mixture was stirred for 30 min. The precipitate was collected by filtration. To be suspended in water (ca. 3 L) and filtration were repeated until the filtrate became not less than pH 3. The obtained wet solid (1677 g) were recrystallized from 50% aqueous ethanol (3000 ml) to give an object product (824.70 g, yield 76%) as a white solid.

^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: 6.94 (1H, dd, J=10.3, 10.3Hz), 8.46 (1H, d, J=7.5Hz)

Step 2

[0295]

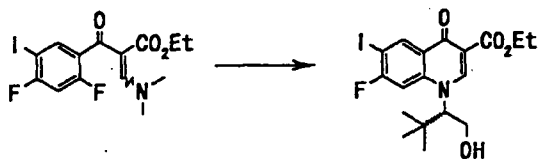


[0296] The compound (150.00 g, 0.53 mol) obtained in Step 1 was dissolved in ethyl acetate (750 ml), and oxalyl chloride (51.0 ml, 0.581 mol) and dimethylformamide (catalytic amount) were added. The mixture was stirred at room temperature for 3.5 hrs. After filtering the reaction solution, the filtrate was concentrated under reduced pressure. After the residue was dissolved in toluene (150 ml), the mixture was concentrated under reduced pressure, and repeated again. Tetrahydrofuran (300 ml) was added to dissolve the residue, and the obtained solution was added dropwise to a solution of ethyl 3,3-dimethylaminoacrylate (83.2 g, 0.581 mol) and triethylamine (96 ml, 0.686 mol) in tetrahydrofuran (450 ml). The mixture was heated under reflux for 15 hrs. After allowing the mixture to cool, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Ethyl acetate (750 ml) was added to dissolve the residue. The mixture was washed successively with aqueous ammonium chloride (400 ml), saturated aqueous sodium hydrogen carbonate (200 ml) and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give a crude object substance (206.50 g) as a brown oil.

102

Step 3

[0297]



[0298] The crude product (206.50 g) obtained in Step 2 was dissolved in tetrahydrofuran (800 ml), and (S)-(+)-tert-leucinol hydrochloride (81.10 g, 0.53 mol) and triethylamine (74 ml, 0.53 mol) were added. The mixture was stirred at room temperature for 50 min. After filtration of the reaction mixture, the filtrate was concentrated under reduced pressure and the obtained residue was dissolved in dimethylformamide (1000 ml). Potassium carbonate (146.0 g, 1.06 mol) was added and the mixture was stirred with heating at 90°C for 3 hrs. With ice-cooling, water (700 ml) was added to the reaction mixture and the precipitate was collected by filtration and washed with water. The solid collected by filtration was suspended in 30% aqueous ethanol (1000 ml) and collected by filtration. This operation was repeated with a mixture of hexane:diethyl ether=1:1. After filtration, the filtrate was vacuum-dried to give an object product (184.74 g, yield 76%) as a white solid.

^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.968 (9H, s), 1.27 (3H, t), 3.96-3.98 (2H, m), 4.18-4.27 (2H, m), 4.80 (1H, t, J=7.0Hz), 5.05 (1H, br), 8.22 (1H, d, J=11.2Hz), 8.60 (1H, s), 8.61 (1H. d, J=7.2Hz)

Step 4

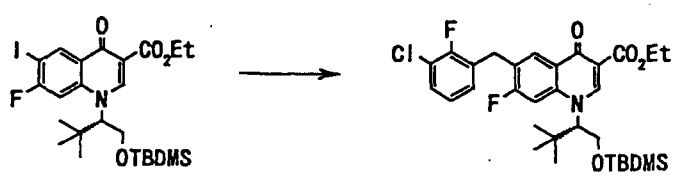
[0299]

[0300] The compound (150.00 g, 0.33 mol) obtained in Step 3 was dissolved in dimethylformamide (600 ml), and imidazole (28.80 g, 0.42 mol) and tert-butyldimethylsilyl chloride (28.80 g, 0.42 mol) were added. The mixture was stirred at room temperature for 6 hrs. Water (1200 ml) was added to the reaction mixture and the mixture was extracted with ethyl acetate (800 ml). The organic layer was washed 3 times with water, and then with saturated brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:3 to 1:2) to give an object product (164.30 g, yield 88%) as a white amorphous form.

^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: -0.08 (3H, s), 0.00 (3H, s), 0.67 (9H, s), 1.06 (9H,s), 1.41 (3H, t, J=7.1Hz), 4.05-4.18 (2H, m), 4.36-4.43 (3H, m), 7.32 (1H, d, J=10.3Hz), 8.65 (1H, s), 8.95(1H, d, J=7.4Hz)

Step 5

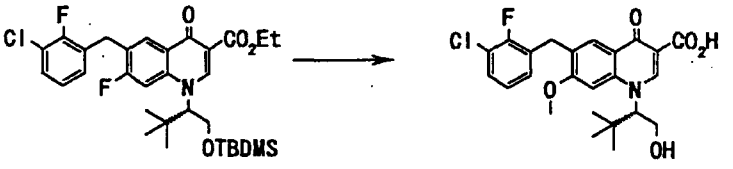
[0301]



[0302] The compound (75.0 g, 0.13 mol) obtained in Step 4 was dissolved in tetrahydrofuran (580 ml). Under an argon stream, bis(dibenzylideneacetone)palladium(0)(2.99 g, 5.20 mmol) and tri(2-furyl)phosphine (2.41 g, 10.38 mmol) were added, and a solution of 3-chloro-2-fluorobenzylzinc bromide (0.17 mol) in tetrahydrofuran was added dropwise at 60°C. After completion of the addition, the mixture was heated under reflux for 2 hrs. After allowing the mixture to cool, ethyl acetate (75 ml) and saturated aqueous ammonium chloride solution (38 ml) were added to the reaction solution. The mixture was stirred at room temperature for 30 min. and partitioned. The organic layer was washed twice with water (75 ml) and then with saturated brine (200 ml), and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:2 to 1:1) to give an object product (66.80 g, yield 73%) as a brown amorphous form.
^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: -0.10 (3H, s), -0.01(3H, s), 0.64 (9H, s), 1.06 (9H, s), 1.40 (3H, t, J=7.1Hz), 4.04-4.15 (4H, m), 4.35-4.46 (3H, m), 6.95-7.03 (2H, m), 7.24-7.31 (2H, m), 8.38 (1H, d, J=8.8Hz), 8.66 (1H, s)

Step 6

[0303]

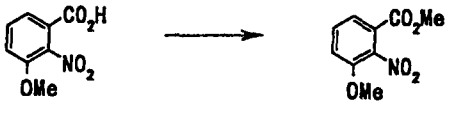


[0304] The compound (2.41 g, 4.07 mmol) obtained in Step 5 was dissolved in methanol (20 ml), and 28% sodium methoxide in methanol (8.4 ml, 40.70 mmol) and water (0.15 ml, 8.14 mmol) were added. The mixture was heated under reflux for 18 hrs. Water (1.4 ml) was added to the reaction solution and the mixture was stirred at room temperature for 1.5 hrs and filtered with Celite. The filtrate was concentrated under reduced pressure, and water (25 ml) and 2N hydrochloric acid (20 ml) were added to the residue. The mixture was stirred for 5 min and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over sodium sulfate. After the filtration, the filtrate was concentrated under reduced pressure. The residue was sonicated with hexane (20 ml) and, after standing still, hexane was removed by decantation. This was repeated three times. Diethyl ether (30 ml) was added to the residue and the mixture was sonicated. The solid was collected by filtration and the obtained solid was dissolved by heating in ethyl acetate (15 ml). Hexane (15 ml) was added and recrystallization gave an object product (1.21 g, yield 64%) as a white solid.
^{1}H NMR(DMSO-d_6 300MHz) (δ) ppm: 0.99 (9H, s), 3.99-4.11 (7H, m), 5.11-5.20 (2H, m), 7.19-7.25 (2H, m), 7.49-7.52 (2H, m), 8.03 (1H, s), 8.78(1H, s), 15.39(1H, s)
MS(ESI): M+ 462

Example 4-37

Step 1

[0305]

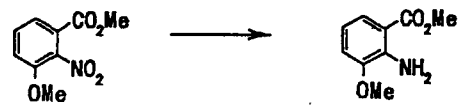


[0306] 3-Methoxy-2-nitrobenzoic acid (20.00 g, 0.10 mol) was dissolved in dimethylformamide (100 ml), and potassium carbonate (28.10 g, 0.20 mol) and methyl iodide (7.60 ml, 0.12 mol) were added. The mixture was stirred at room temperature for 1 hr. The reaction mixture was added to water (300 ml) and the mixture was stirred. The precipitate was collected by filtration, washed with water (200 ml) and vacuum-dried to give a crude object substance (23.90 g) as a white solid.

104

Step 2

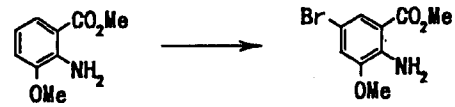
[0307]



[0308] The crude product (23.90 g) obtained in Step 1 was suspended in a mixture of tetrahydrofuran (150 ml) and methanol (50 ml), and 5% palladium-carbon (wet)(2.30 g) was added. The mixture was stirred under a hydrogen atmosphere at room temperature for 19.5 hrs. Ethyl acetate (200 ml) was added to the reaction mixture and the mixture was filtered with Celite. The filtrate was concentrated under reduced pressure and the water was removed azeotropically with toluene to give a crude product (18.80 g) as a brown oil.

Step 3

[0309]



[0310] The crude product (18.80 g) obtained in Step 2 was dissolved in dimethylformamide (200 ml), and N-bromosuccinimide (17.98 g, 0.10 mol) was added by portions at 5°C. After completion of the addition, the mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into water (500 ml) and extracted twice with ethyl acetate (300 ml). The organic layer was washed successively with water (300 ml), saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel chromatography (chloroform) to give an object product (25.11 g, yield 95%) as a yellow oil.

^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: 3.86 (6H, s), 6.02 (2H, brs), 6.90 (1H, s), 7.60 (1H, s)

Step 4

[0311]

[0312] The compound (25.11 g, 96.54 mmol) obtained in Step 3 was suspended in water (50 ml) and conc. hydrochloric acid (25 ml) was added. An aqueous solution (100 ml) of sodium nitrite (7.33 g, 106.22 mmol) was added dropwise at 5°C. After completion of the addition, the mixture was stirred at the same temperature for 5 min. This reaction solution was added dropwise to a solution of copper (I) chloride (9.55 g, 96.47 mmol) in conc. hydrochloric acid (75 ml) at room temperature. After completion of the addition, the mixture was stirred at room temperature for 13 hrs. Water (200 ml) was added to the reaction solution and the mixture was extracted with ethyl acetate (400 ml). The organic layer was washed successively with water (400 ml) and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give an object product (15.18 g, yield 56%) as an orange solid.

^{1}H NMR($CDCl_3$ 300MHz) (δ) ppm: 3.92 (3H, s), 3.93 (3H, s), 7.16 (1H, d, J=2.1Hz), 7.49 (1H, d, J=2.2Hz)

105

Step 5

[0313]

[0314] The compound (74.80 g, 0.27 mol) obtained in Step 4 was dissolved in dichloromethane (300 ml) and 1M boran tribromide/dichloromethane solution (700 ml, 0.70 mol) was added dropwise at 10°C or below. After completion of the addition, the mixture was stirred at room temperature for 1.5 hrs. The reaction mixture was added to ice water (1500 ml) and the precipitated solid was collected by filtration. The filtrate was partitioned, and the aqueous layer was extracted with ethyl acetate (200 ml). The organic layers were combined and concentrated under reduced pressure. The solid collected by filtration and the residue were dissolved in diethyl ether (1000 ml) and 1N aqueous sodium hydroxide solution (1000 ml) was added for extraction. 2N Hydrochloric acid (500 ml) was added to the aqueous layer. The mixture was stirred and extracted with ethyl acetate (800 ml). The mixture was partitioned and the organic layer was washed successively with water and saturated brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give an object product (63.83 g, yield 95%) as a beige solid.
^{1}H NMR(DMSO-d_6 300MHz) (δ) ppm: 7.23 (1H, d, J=2.4Hz), 7.28 (1H, d, J=2.4Hz), 10.99(1H, s), 13.55 (1H, brs)

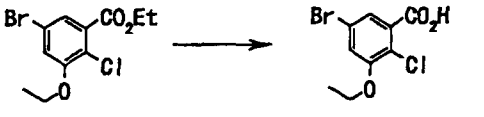
Step 6

[0315]

[0316] The compound (63.83 g, 0.25 mol) obtained in Step 5 was dissolved in dimethylformamide (400 ml), and potassium carbonate (87.70 g, 0.64 mol) and ethyl iodide (81.20 ml, 1.02 mol) were added. The mixture was stirred with heating at 50°C for 3 hrs, and saturated aqueous ammonium chloride (600 ml) and ethyl acetate (400 ml) were added to the reaction mixture. The mixture was partitioned and the aqueous layer was extracted with ethyl acetate (400 ml). The organic layers were combined and washed successively with brine (3 times) and saturated brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give an object product (76.38 g, yield 98%) as a brown solid.
^{1}H NMR($CDCl_3$ 400MHz) (δ) ppm: 1.39 (3H, t, J=7.2Hz), 1.48 (3H, t), 4.11(2H, q), 4.38 (2H, q, J=7.2Hz), 7.12 (1H, d, J=2.0Hz), 7.42 (1H, d, J=2.0Hz)

Step 7

[0317]



[0318] The compound (76.38 g, 0.25 mol) obtained in Step 6 was dissolved in ethanol (250 ml), and 8N aqueous sodium hydroxide solution (62.00 ml, 0.50 mol) was added. The mixture was stirred with heating at 50°C for 30 min. 2N Hydrochloric acid (250 ml) was added to the reaction solution with ice-cooling and the mixture was stirred, and extracted twice with ethyl acetate (350 ml). The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give an object

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product (68.79 g, yield 99%) as a pale-brown solid.
^{1}H NMR($CDCl_3$ 400MHz) (δ) ppm: 1.50 (3H, t, J=6.8Hz), 4.12 (2H, q, J=6.8Hz), 7.19 (1H, d, J=2.4Hz), 7.65(1H, d, J=2.4Hz)

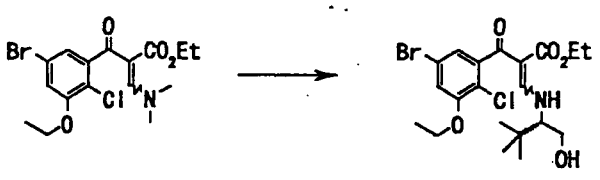
Step 8

[0319]

[0320] The compound (85.17 g, 0.31 mol) obtained in Step 7 was dissolved in toluene (450 ml), and thionyl chloride (44.40 ml, 0.61 mol) and dimethylformamide (catalytic amount) were added. The mixture was stirred at 90°C for 1 hr. After allowing the mixture to cool, the reaction solution was concentrated under reduced pressure. After the residue was dissolved in toluene, the mixture was concentrated under reduced pressure. This was repeated two more times. The residue was dissolved in tetrahydrofuran (250 ml) and the obtained solution was added dropwise to a solution of ethyl 3,3-dimethylaminoacrylate (43.60 g, 0.31 mol) and triethylamine (50.90 ml, 0.37 mol) in tetrahydrofuran (200 ml). The mixture was heated under reflux for 15 hrs. After allowing the mixture to cool, water (300 ml) and ethyl acetate (500 ml) were added to the reaction mixture. The mixture was stirred and partitioned. The organic layer was washed successively with water (300 ml) and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give a crude object substance (124.80 g) as a brown oil.

Step 9

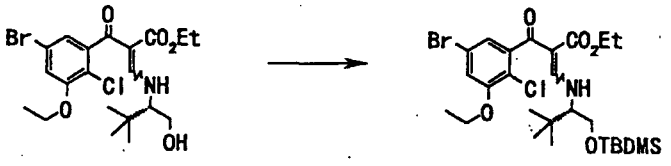
[0321]



[0322] The crude product (124.80 g) obtained in Step 8 was dissolved in tetrahydrofuran (500 ml), and (S)-(+)-tert-leucinol hydrochloride (46.80 g, 0.31 mol) and triethylamine (42.50 ml, 0.31 mol) were added. The mixture was stirred at room temperature for 40 min. After filtration of the reaction mixture, the filtrate was concentrated under reduced pressure. The obtained residue was dissolved in ethyl acetate (800 ml), washed twice with water, and then with saturated brine, and dried over sodium sulfate. After the filtration, the filtrate was concentrated under reduced pressure to give a crude object substance (131.30 g) as a brown oil.

Step 10

[0323]

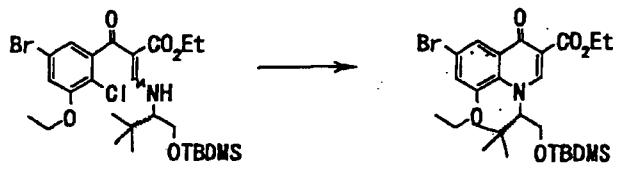


[0324] The crude product (131.30 g) obtained in Step 9 was dissolved in dimethylformamide (400 ml), and imidazole

(27.00 g, 0.40 mol) and tert-butyldimethylsilyl chloride (41.30 g, 0.27 mol) were added. The mixture was stirred at room temperature for 14 hrs. Water was added to the reaction solution and the mixture was extracted twice with ethyl acetate (500 ml) . The organic layer was washed three times with water and then with saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give a crude object substance (159.80 g) as a brown oil.

Step 11

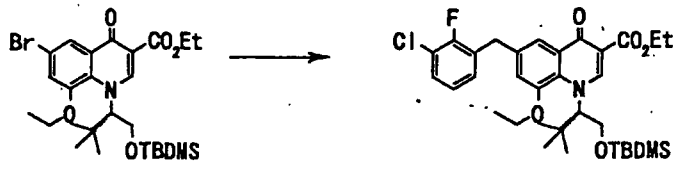
[0325]



[0326] The crude product (159.80 g) obtained in Step 10 was dissolved in toluene (1100 ml), and sodium hydride (15.80 g, 0.40 mol) was added. The mixture was stirred with heating at 100°C for 14 hrs. 1N Hydrochloric acid (400 ml) was added to the reaction solution under ice-cooling and the mixture was stirred and partitioned. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the obtained residue was dissolved in dimethylformamide (500 ml). Potassium carbonate (42.10 g, 0.31 mol) and ethyl iodide (24.40 ml, 0.31 mol) was added and the mixture was stirred with heating at 50°C for 1.5 hrs. A saturated aqueous ammonium chloride solution (400 ml) was added to the reaction solution under ice-cooling, and the mixture was stirred and extracted twice with ethyl acetate. The organic layer was washed successively with water, twice with brine and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:3 to 2:3) to give an object product (76.50 g, yield 45%) as a brown oil.
^{1}H NMR ($CDCl_3$ 400MHz) (δ) ppm: -0.05 (3H, s), 0.01 (3H, s), 0.73 (9H, s), 0.98 (9H, s), 1.40(3H, t), 1.53-1.59 (3H, m), 4.10-4.24 (4H, m), 4.34-4.44(2H,m), 6.10-6.14(1H, m), 7.22 (1H, s), 8.32 (1H, t, J=2.4Hz), 8.70 (1H, s)

Step 12

[0327]



[0328] The compound (76.50 g, 0.14 mol) obtained in Step 11 was dissolved in tetrahydrofuran (500 ml), and under an argon stream, bis(dibenzylideneacetone)palladium (0) (3.17 g, 5.51 mmol) and tri(2-furyl)phosphine (2.56 g, 11.03 mmol) were added. A solution of 3-chloro-2-fluorobenzylzinc bromide (0.28 mol) in tetrahydrofuran was added dropwise at 60°C. After completion of the addition, the mixture was heated under reflux for 2.5 hrs. After allowing the mixture to cool, saturated aqueous ammonium chloride solution (600 ml) was added to the reaction solution. The mixture was stirred at room temperature for 1 hr and filtered with Celite. After the mixture was partitioned, the aqueous layer was extracted with ethyl acetate twice. The organic layer, on the other hand, was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. All ethyl acetate layers were combined and washed successively with 1N hydrochloric acid and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The obtained residue was dissolved in dimethylformamide (400 ml) and potassium carbonate (19.00 g, 0.14 mol) and ethyl iodide (11.00 ml, 0.14 mol) were added. The mixture was stirred with heating at 50°C for 1.5 hrs. A saturated aqueous ammonium chloride solution (400 ml) was added to the reaction mixture with ice-cooling, and the mixture was stirred and extracted with ethyl acetate (500 ml). The organic layer was washed with water, brine (twice) and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced

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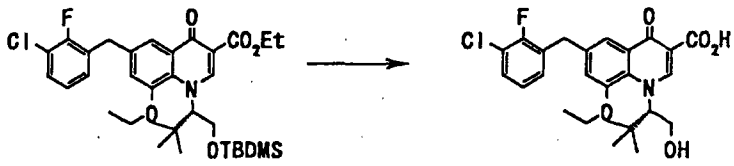
pressure and the obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=1:2 to 1:1) to give an object product (72.10 g, yield 85%) as a brown oil.
^{1}H NMR($CDCl_3$ 400MHz) (δ) ppm: -0.07 (3H, s), 0.00 (3H, s), 0.70 (9H, s), 1.24 (9H, s), 1.39 (3H, t, J=7.2Hz), 1.51-1.54 (3H, m), 4.05 (2H, s), 4.07-4.19 (4H, m), 4.33-4.45(2H, m), 6.12-6.15 (1H, m), 6.99-7.02 (2H, m), 7.04-7.09 (1H, m), 7.19-7.25 (1H, m), 8.06 (1H, d, J=2.4Hz), 8.69 (1H, s)

Step 13

[0329]



[0330] The compound (65.80 g, 0.11 mol) obtained in Step 12 was dissolved in ethanol (200 ml) and 1N aqueous sodium hydroxide solution (640 ml, 0.64 mol) was added. The mixture was heated under reflux for 2 hrs. 2N Hydrochloric acid (350 ml) was added to the reaction solution with ice-cooling and the mixture was stirred and extracted twice with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and diethyl ether (500 ml) was added the residue. The mixture was sonicated and the obtained solid was collected by filtration. The collected solid was added to ethyl acetate (250 ml) and dissolved with heating. Hexane (50 ml) was added and the precipitated solid was collected by filtration, vacuum-dried to give an object product (41.10 g, yield 81%) as a white solid.
^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.93 (9H, s), 1.49 (3H, t, J=6.9Hz), 4.00 (2H, t, J=6.4Hz), 4.20 (2H, s), 4.22-4.33 (2H, m), 5.12 (1H, t), 6.36 (1H, t, J=6.8Hz), 7.21 (1H, m), 7.39-7.48 (2H, m), 7.54 (1H, s), 7.79 (1H, s), 8.79 (1H, s), 15.04 (1H, s)
MS (ESI): M+ 476

Examples 1-3 - 1-102, 2-1 - 2-8, 3-1 - 3-86, 4-1 - 4-54

[0331] In the same manner as in Examples 1-1 and 1-2 and the above-mentioned Examples, the compounds of Examples 1-3 - 1-102, 2-1 - 2-8, 3-1 - 3-86 and 4-1 - 4-54 were obtained. The chemical structures thereof are shown in Tables 1, 2, 3 and 4.

Experimental Examples

[0332] The following explains evaluation methods of the HIV integrase inhibitory activity of the compound of the present invention.

(i) Construction of recombinant integrase gene expression system

[0333] The 185th phenylalanine of HIV integrase full length gene (J. Virol., 67, 425-437 (1993)) was substituted by histidine and inserted into the restriction enzyme NdeI and XhoI sites of plasmid pET21a(+) (Novagen), whereby an integrase expression vector pET21a-IN-F185H was constructed.

(ii) Production and purification of integrase protein

[0334] Escherichia coli recombinant BL21(DE3) transformed with plasmid pET21a-IN-F185H obtained in (i) was shake cultured at 30°C in a liquid medium containing ampicillin. When the culture reached the logarithmic growth phase, isopropyl-β-D-thiogalactopyranoside was added to promote expression of integrase gene. The culture was continued for 3 hrs to promote accumulation of the integrase protein. The recombinant E. coli was collected in pellets by centrifugal separation and preserved at -80°C.
[0335] The E. coli was suspended in Lysis buffer (20 mM HEPES (pH 7.5), 5 mM DTT, 10 mM CHAPS, 10% glycerol) containing 1M sodium chloride and subjected to repeat pressurization and depressurization for rupture, and centrifugal separation at 4°C, 40,000xg, 60 min to recover a water-soluble fraction (supernatant). This was diluted 10-fold with

Lysis buffer free of sodium chloride, mixed with SP-Sepharose (Pharmacia Corporation) and stirred at 4°C for 60 min to allow adsorption of integrase protein to the resin. The resin was washed with Lysis buffer containing 100 mM sodium chloride and the integrase protein was eluted with Lysis buffer containing 1M sodium chloride.

[0336] The eluted integrase protein solution was applied to a Superdex 75 (Pharmacia Corporation) column for gel filtration. The protein was eluted with Lysis buffer containing 1M sodium chloride.

[0337] The obtained fractions of the integrase protein were collected and preserved at -80°C.

(iii) Preparation of DNA solution

[0338] The following DNA synthesized by Greiner was dissolved in TE buffer (10 mM Tris-hydrochloric acid (pH 8.0), 1 mM EDTA) and mixed with donor DNA, target DNA, each complementary strand (+ and - strands) to 1 μM. The mixture was heated at 95°C for 5 min, 80°C for 10 min, 70°C for 10 min, 60°C for 10 min, 50°C for 10 min and 40°C for 10 min and preserved at 25°C to give a double stranded DNA, which was used for the test.

Donor DNA (- strand having biotin attached to the 5' terminal) Donor + strand: 5'-Biotin-ACC CTT TTA GTC AGT GTG GAA AAT CTC TAG CA-3' (SEQ ID NO:1)
Donor - strand: 5'-ACT GCT AGA GAT TTT CCA CAC TGA CTA AAA G-3' (SEQ ID NO:2)
Target DNA (+, - strands both having digoxigenin added at 3' terminal)
Target + strand: 5'-TGA CCA AGG GCT AAT TCA CT-Dig-3' (SEQ ID NO:3)
Target - strand: 5'-AGT GAA TTA GCC CTT GGT CA-Dig-3' (SEQ ID NO:4)

(iv) Determination of enzyme (HIV integrase) inhibitory activity

[0339] The donor DNA was diluted with TE buffer to 10 nM, of which 50 μl was added to each well of streptavidin-coated microtiter plate (Roche) and allowed to adsorb at 37°C for 60 min. The DNA was washed with phosphate buffer (Dulbecco PBS, Sanko Junyaku Co., Ltd.) containing 0.1% Tween 20 and phosphate buffer. Then, a reaction mixture (70 μl) having the following composition, a test substance (10 μl) diluted with the reaction mixture and 100 μg/ml integrase protein (10 μl) were added to each well and reacted at 37°C for 60 min.

[0340] Then, 50 nM target DNA (10 μl) was added, reacted at 37°C for 10 min and washed with phosphate buffer containing 0.1% Tween 20 to stop the reaction.

[0341] Then, 100 mU/ml peroxidase labeled anti-digoxigenin antibody solution (Roche, 100 μl) was added, and the mixture was reacted at 37°C for 60 min, followed by washing with phosphate buffer containing 0.1% Tween 20.

[0342] A peroxidase color solution (Bio Rad, 100 μl) was added and allowed to react at room temperature for 4 min. The color reaction was stopped by adding 1N sulfuric acid (100 μl) . The absorbance at 450 nm was measured.

[0343] The HIV integrase inhibitory activity (IC_{50}) of the compound of the present invention was calculated from the inhibition rate according to the following formula. The results are shown in Tables 5, 6 and 7.

$$\text{inhibition rate (\%)} = [1-(\text{Object-Blank})/(\text{Control-Blank})] \times 100$$

Object; absorbance of well in the presence of test compound Control; absorbance of well in the absence of test compound Blank; absorbance of well in the absence of test compound, in the absence of integrase protein

Evaluation of antiviral activity

[0344] The effect of combined use of the compound of the present invention with known anti-HIV agents can be determined as shown below.

[0345] For example, the effect of two-drug use of an existing nucleoside reverse transcriptase inhibitor (Zidovudine, Lamivudine, Tenofovir), a non-nucleoside reverse transcriptase inhibitor (Efavirenz) or a protease inhibitor (Indinavir, Nelfinavir) and a test substance A, and the like are evaluated in an acute infection system using HIV-1 IIIB-infected CEM-SS cells by the XTT method.

[0346] In addition, the effect of three-drug use of test substance A, Zidovudine and Lamivudine, or test substance A, Tenofovir and Lamivudine and the like is evaluated.

[0347] Prior to the combined use test, IC_{50} and CC_{50} of each pharmaceutical agent alone are determined. The effect of two-drug use is evaluated based on the combination of five concentrations of pharmaceutical agent A and nine concentrations of pharmaceutical agent B, which have been determined based on the above results. For three-drug use, high concentrations of pharmaceutical agent B and pharmaceutical agent C are mixed and the obtained concentrations are combined with the concentrations of pharmaceutical agent A for evaluation.

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[0348] The experimental data of the test substance and pharmaceutical agent to be combined in the case of single use and combined use are analyzed by the programs of Prichard and Shipman MacSynergy II version 2.01 and Delta graph version 1.5d. A three dimensional plot is created at a 95% (or 68%, 99%) confidence level, from the percent inhibition at the concentration of each combined pharmaceutical agent, which is obtained from triplicate experiments, and the effect of combined use is evaluated based on the numerical values of $\mu M^2\%$ calculated therefrom. The evaluation criteria are shown in the following.

definition of interaction	$\mu M^2\%$
highly synergistic	>100
slightly synergistic	+51 to +100
additive ,	+50 to -50
slightly antagonistic	-51 to -100
highly antagonistic	<-100

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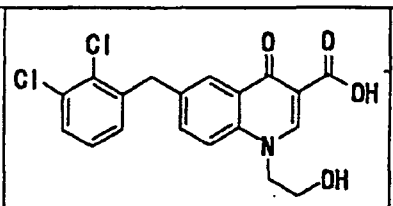
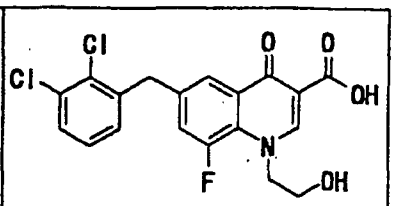
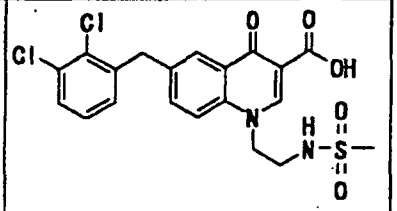
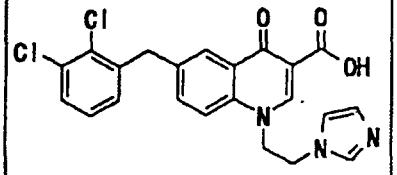
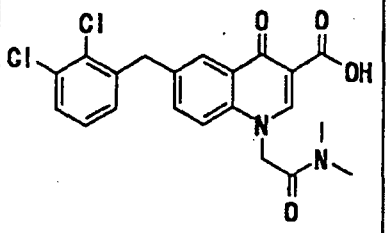
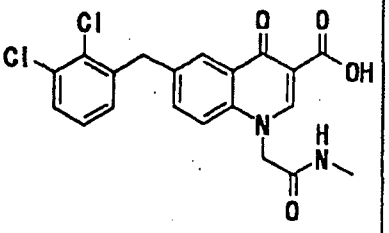
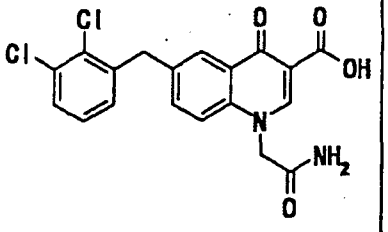
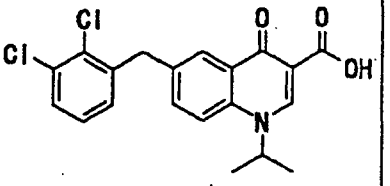
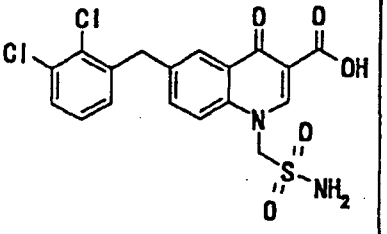
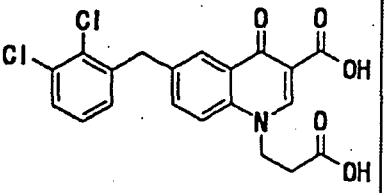
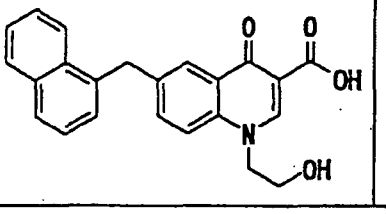
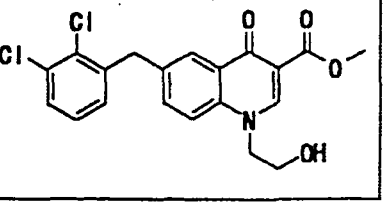
Table 1

1-1		1-2	
1-3		1-4	
1-5		1-6	
1-7		1-8	
1-9		1-10	
1-11		1-12	

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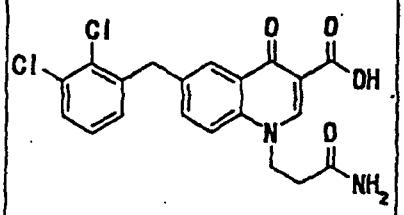
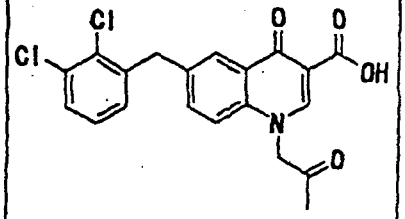
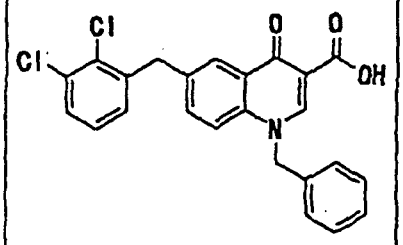
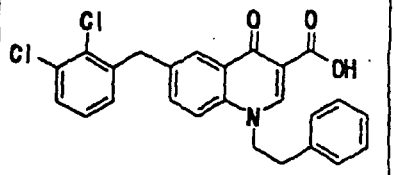
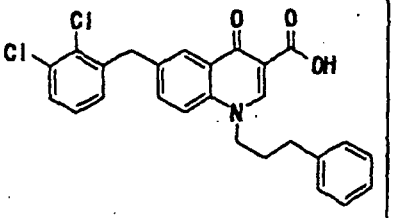
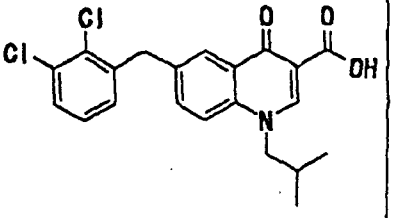
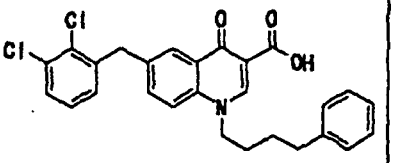
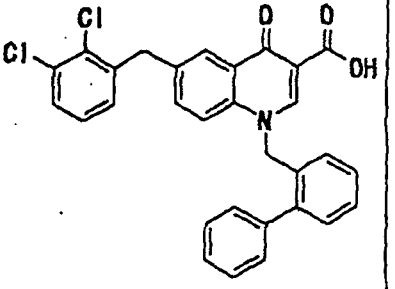
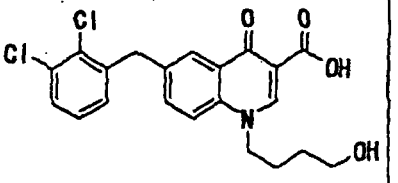
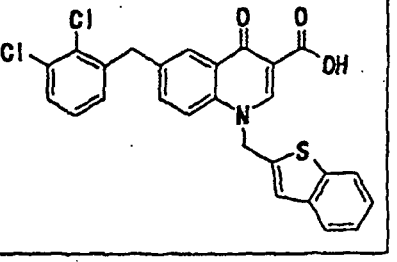
1-13		1-14	
1-15		1-16	
1-17		1-18	
1-19		1-20	
1-21		1-22	

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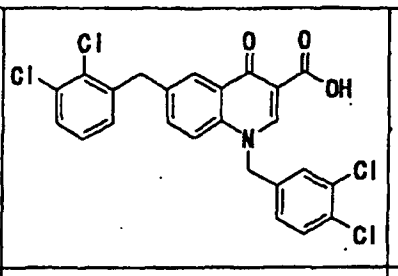
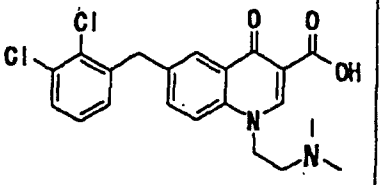
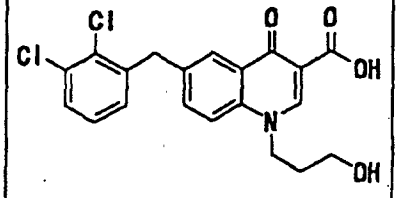
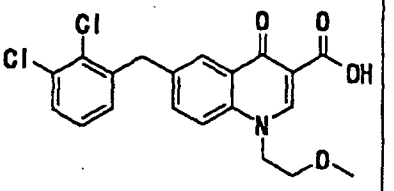
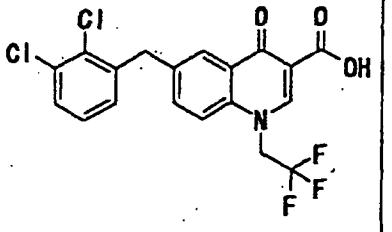
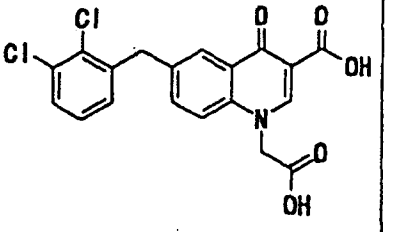
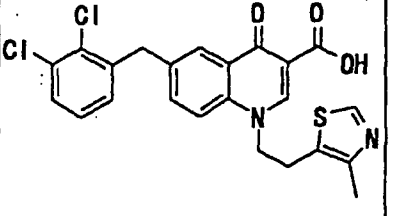
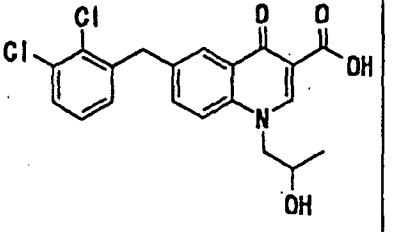
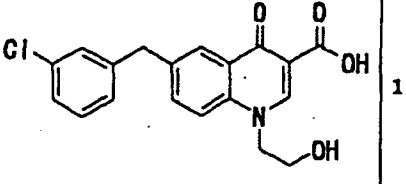
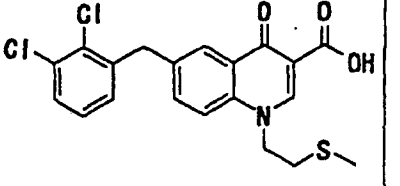
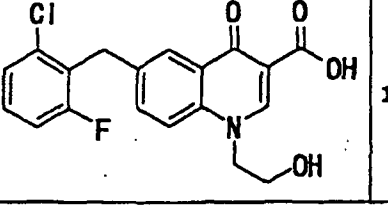
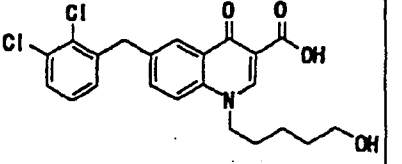
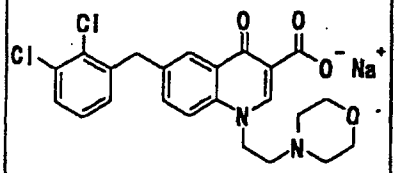
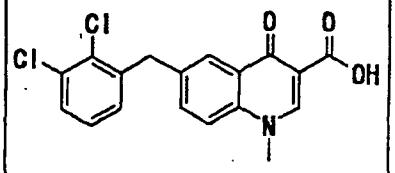
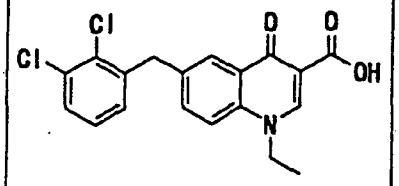
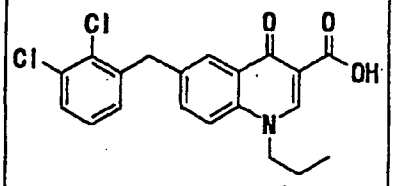
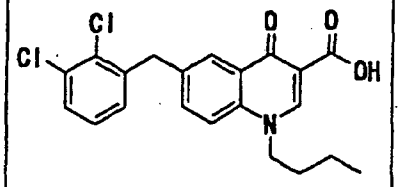
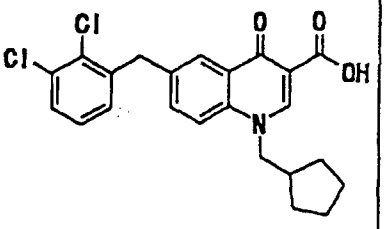
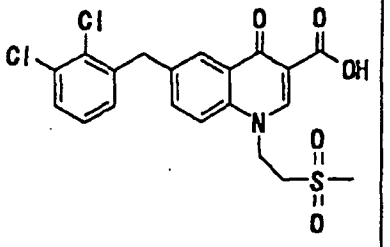
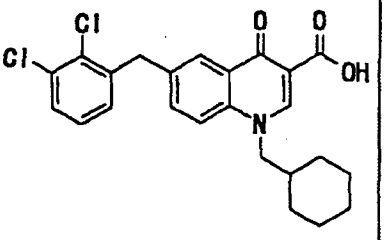
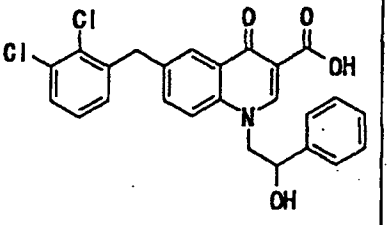
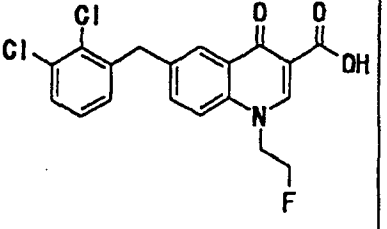
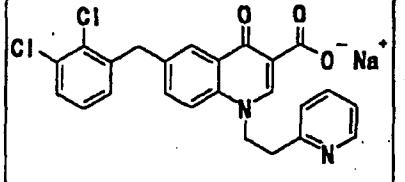
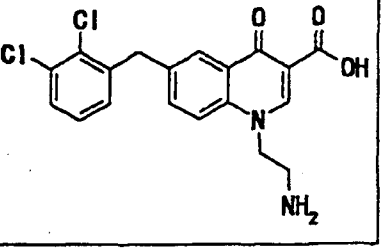
1-23		1-24	
1-25		1-26	
1-27		1-28	
1-29		1-30	
1-31		1-32	
1-33		1-34	

1-35		1-36	
1-37		1-38	
1-39		1-40	
1-41		1-42	
1-43		1-44	
1-45		1-46	

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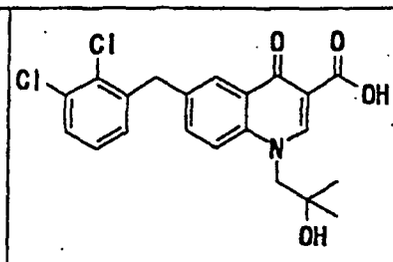
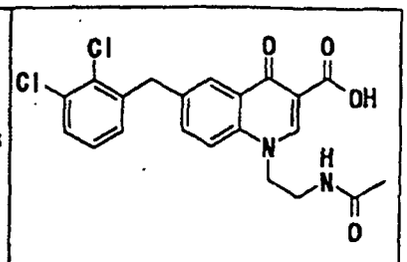
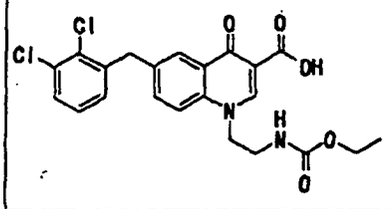
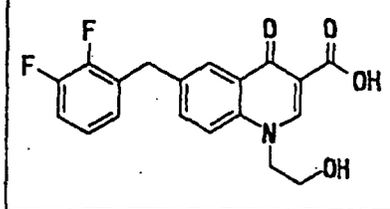
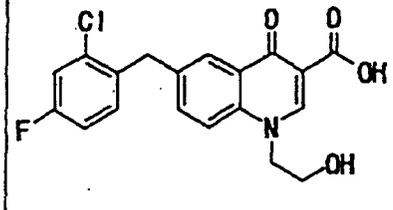
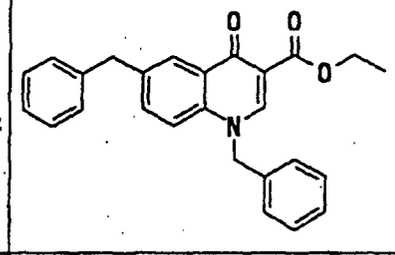
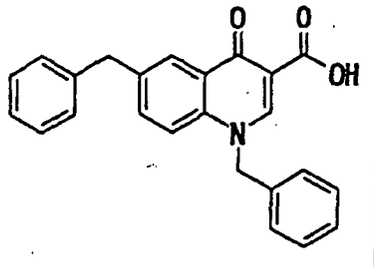
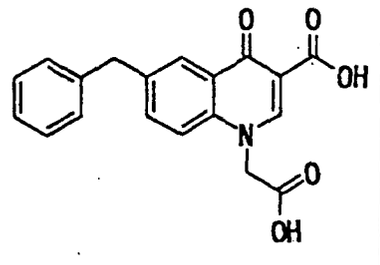
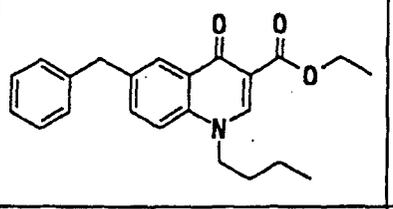
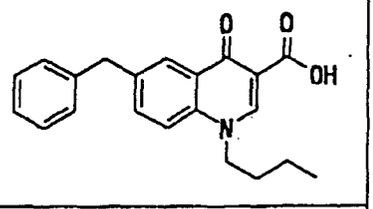
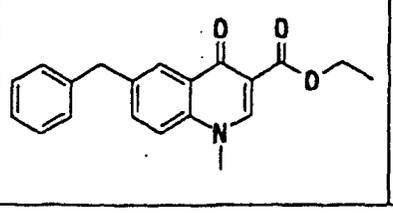
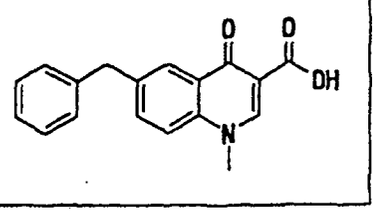
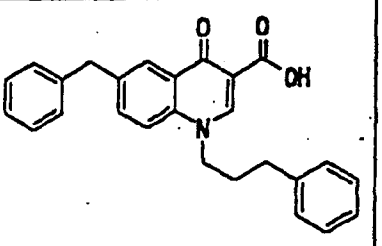
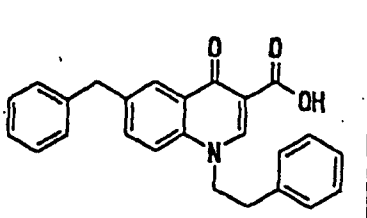
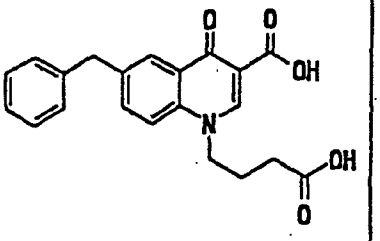
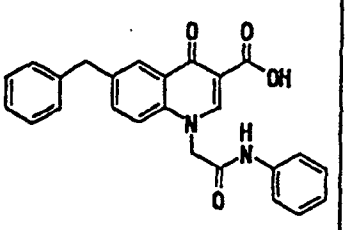
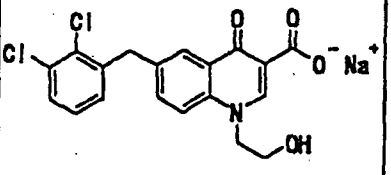
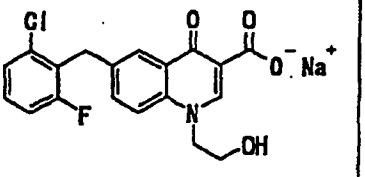
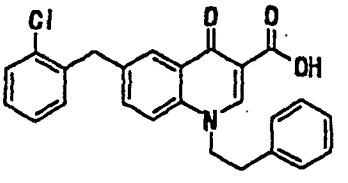
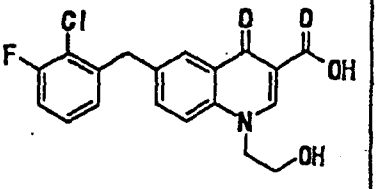
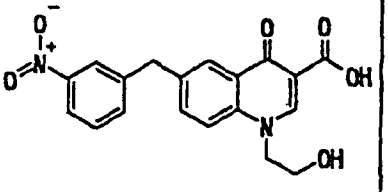
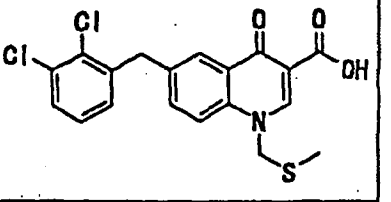
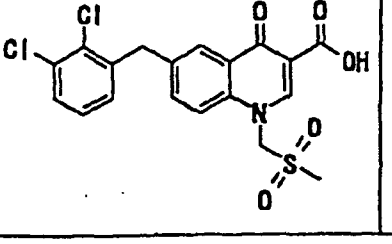
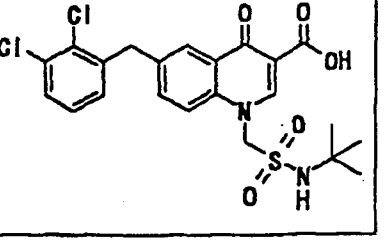
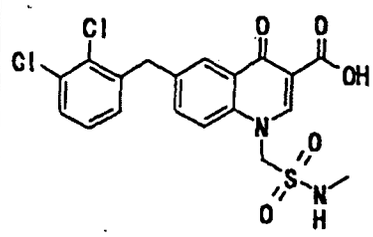
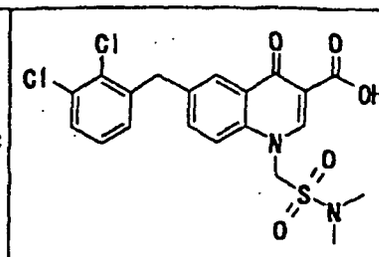
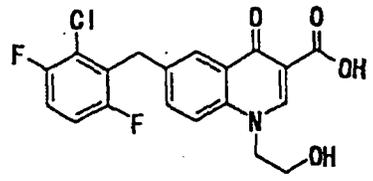
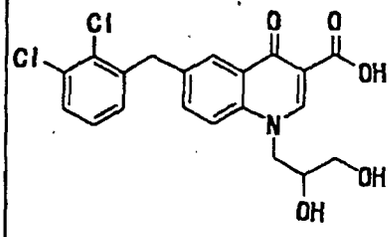
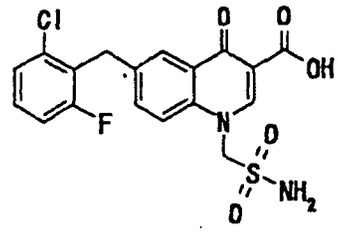
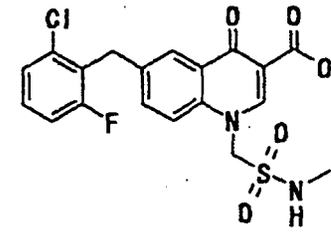
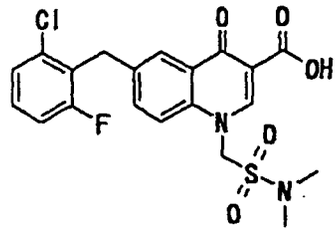
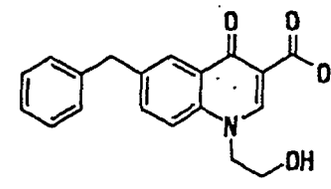
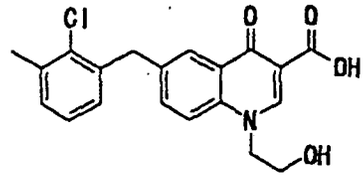
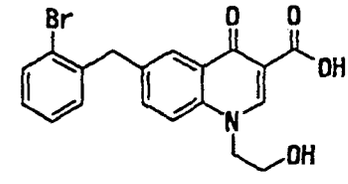
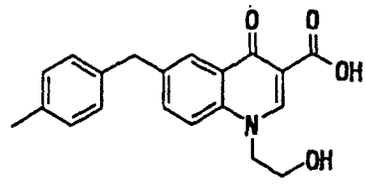
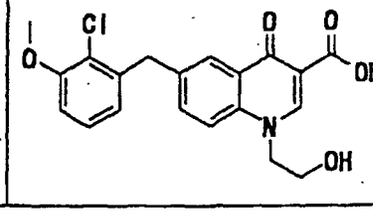
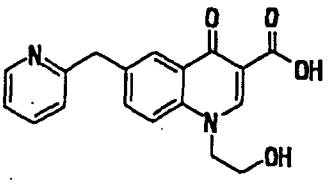
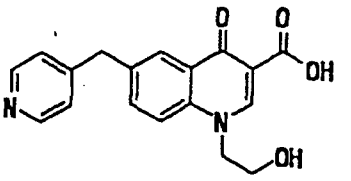
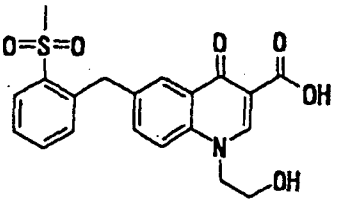
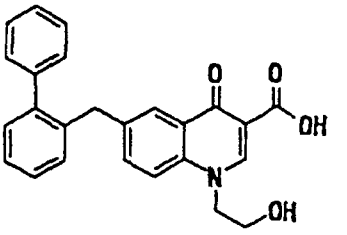
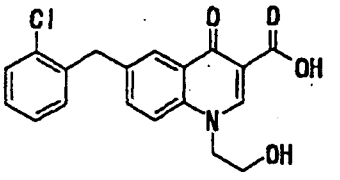
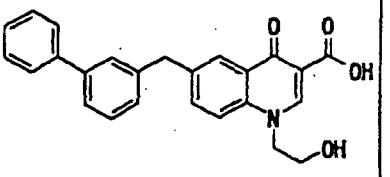
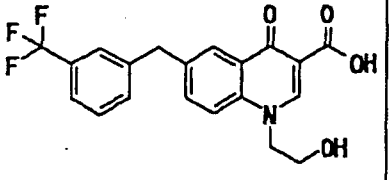
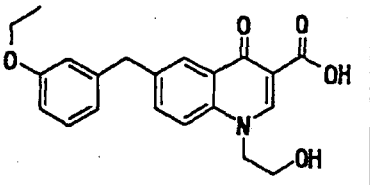
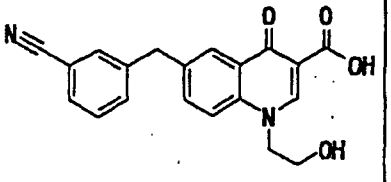
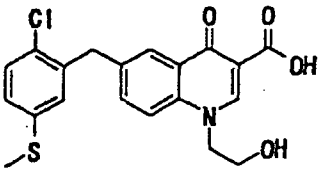
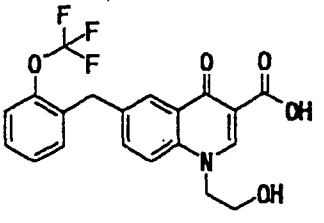
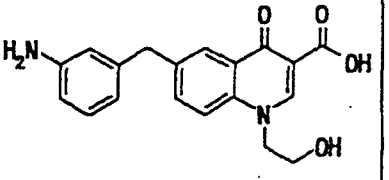
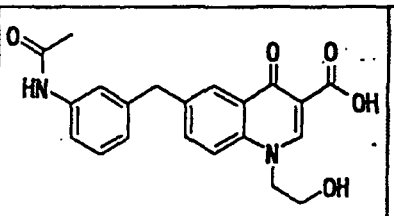
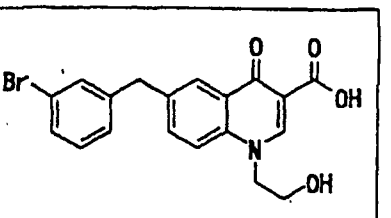
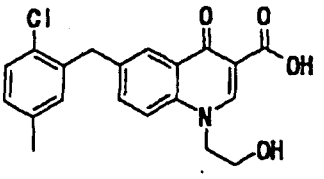
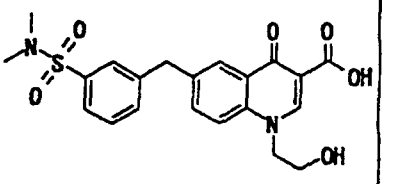
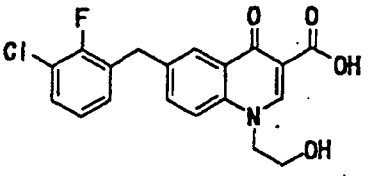
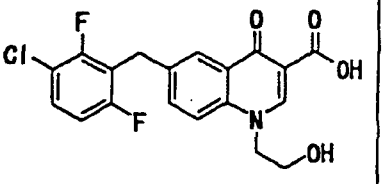
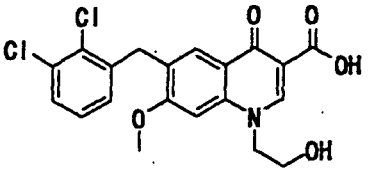
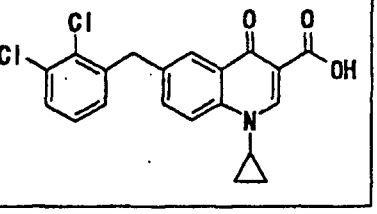
1-47		1-48	
1-49		1-50	
1-51		1-52	
1-53		1-54	
1-55		1-56	
1-57		1-58	

1-59		1-60	
1-61		1-62	
1-63		1-64	
1-65		1-66	
1-67		1-68	
1-69		1-70	

1-71		1-72	
1-73		1-74	
1-75		1-76	
1-77		1-78	
1-79		1-80	
1-81		1-82	

1-83		1-84	
1-85		1-86	
1-87		1-88	
1-89		1-90	
1-91		1-92	
1-93		1-94	

1-95		1-96	
1-97		1-98	
1-99		1-100	
1-101		1-102	

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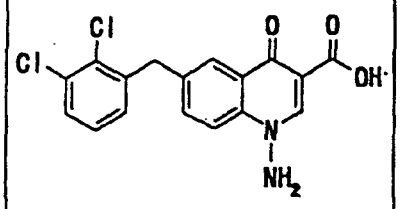
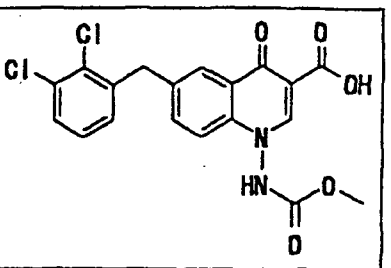
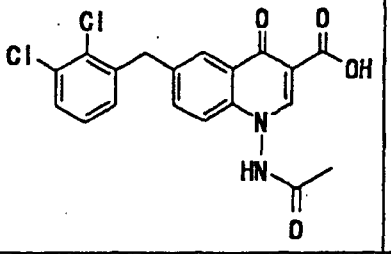
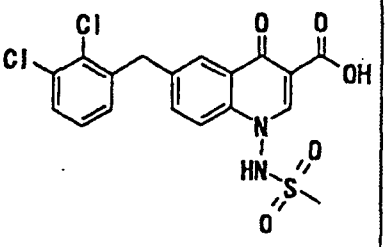
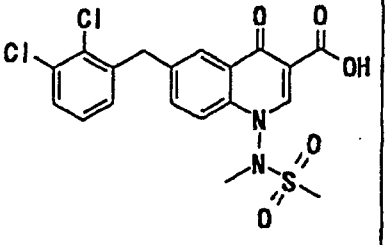
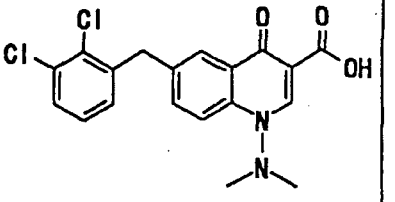
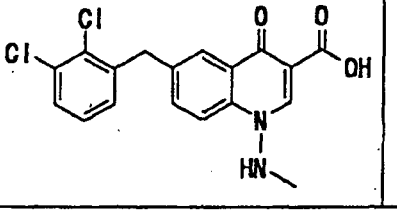
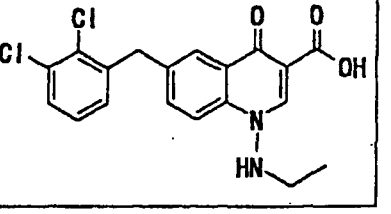
2-1		2-2	
2-3		2-4	
2-5		2-6	
2-7		2-8	

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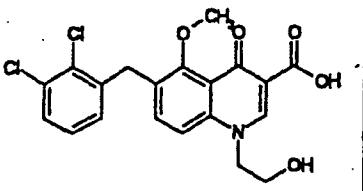
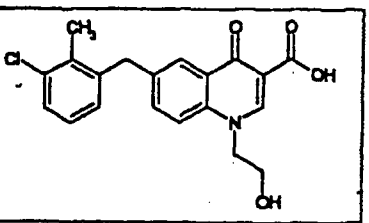
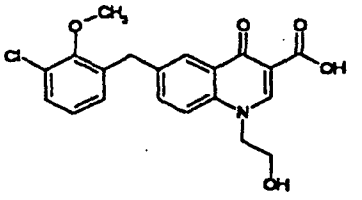
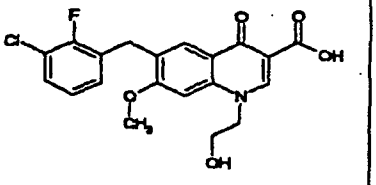
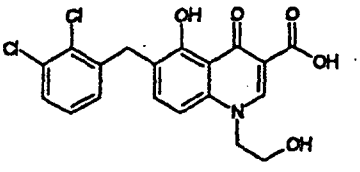
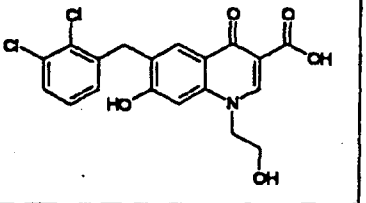
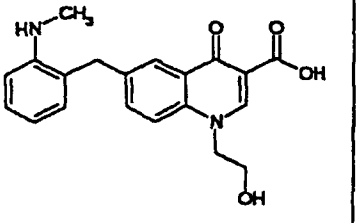
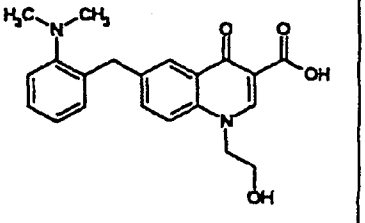
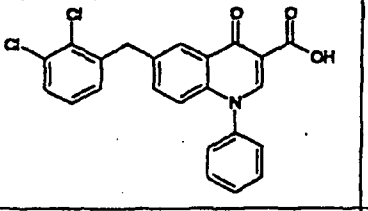
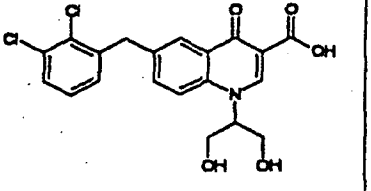
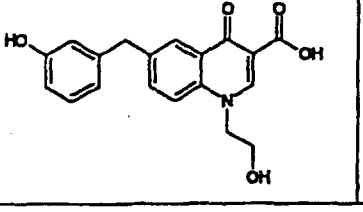
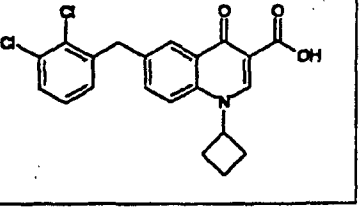
Table 3

3-1		3-2	
3-3		3-4	
3-5		3-6	
3-7		3-8	
3-9		3-10	
3-11		3-12	

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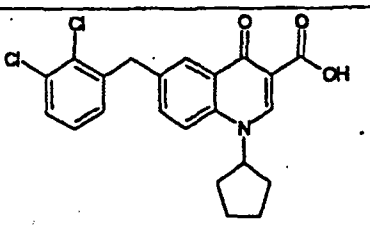
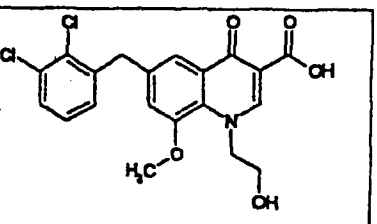
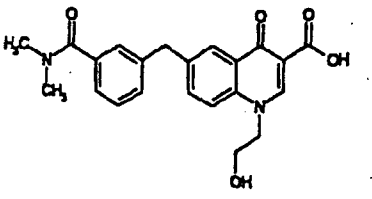
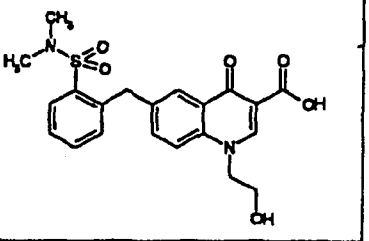
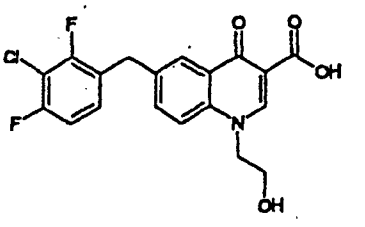
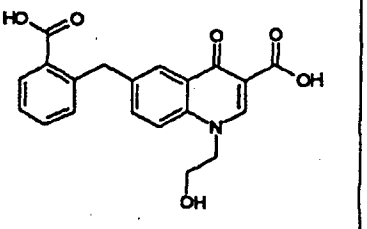
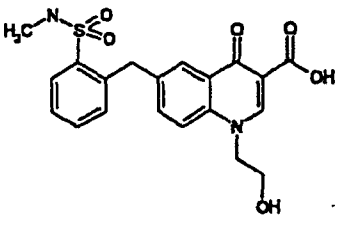
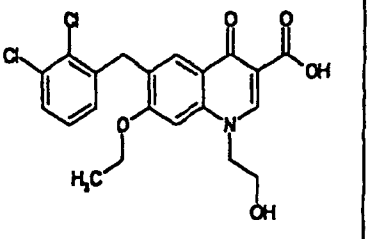
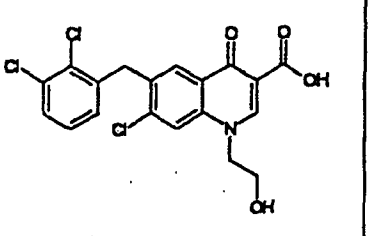
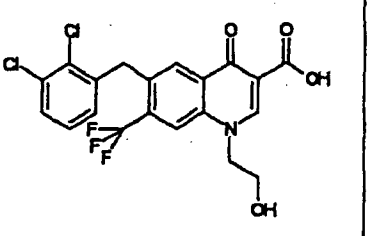
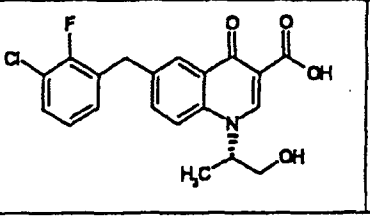
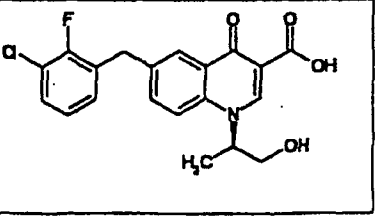
3-13		3-14	
3-15		3-16	
3-17		3-18	
3-19		3-20	
3-21		3-22	
3-23		3-24	

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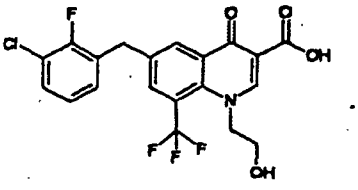
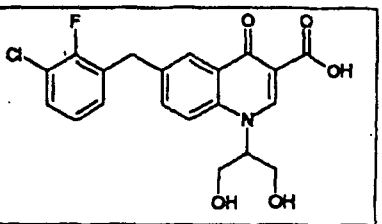
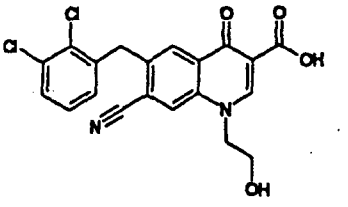
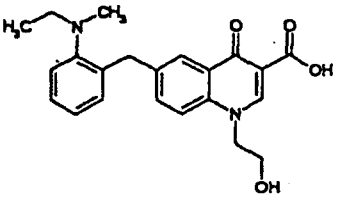
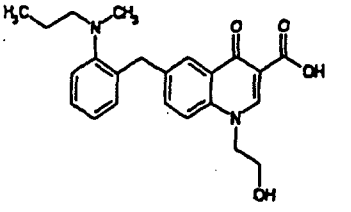
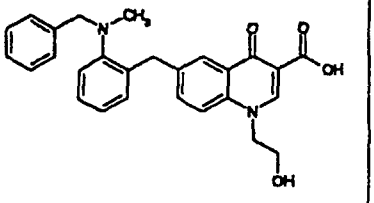
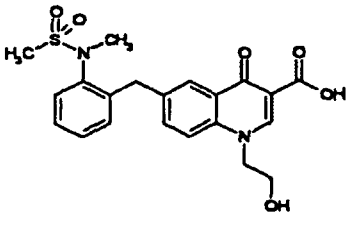
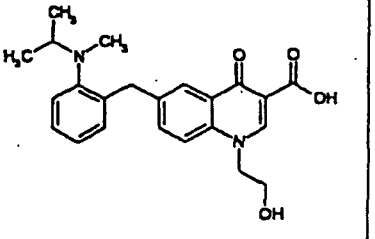
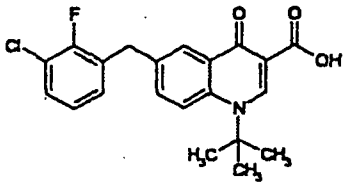
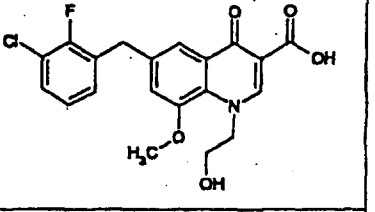
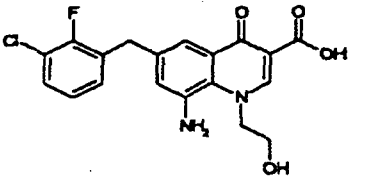
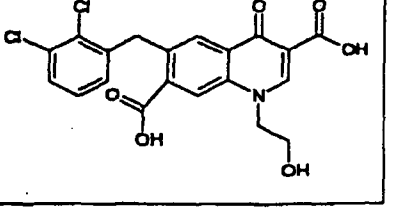
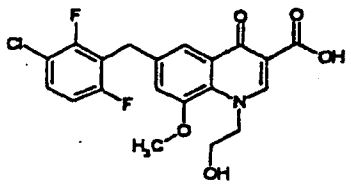
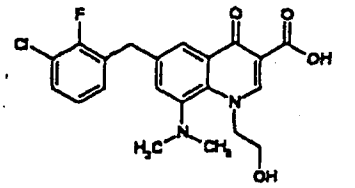
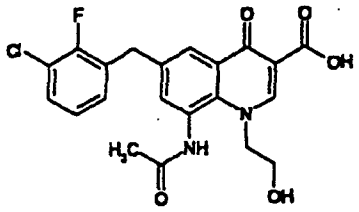
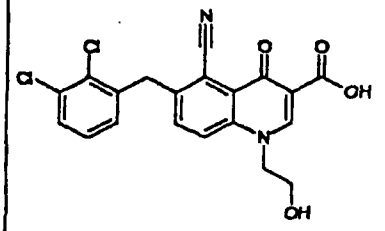
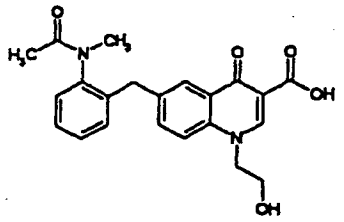
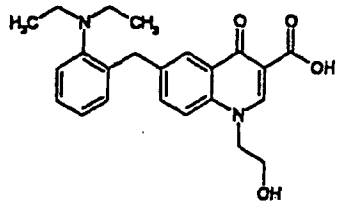
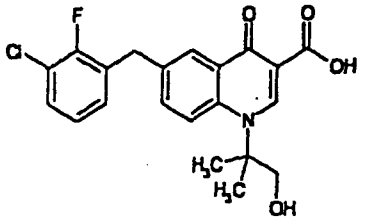
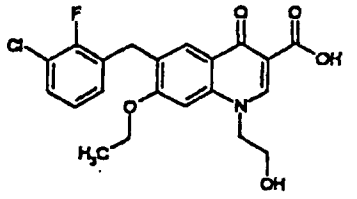
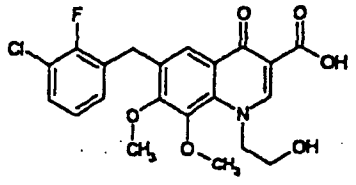
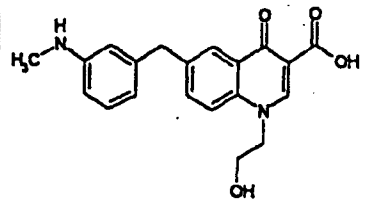
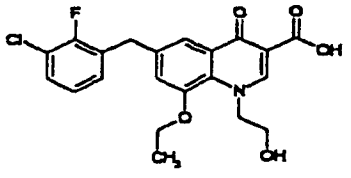
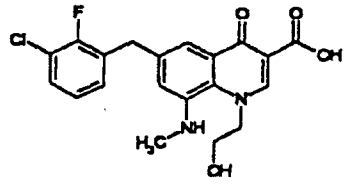
3-25		3-26	
3-27		3-28	
3-29		3-30	
3-31		3-32	
3-33		3-34	
3-35		3-36	

3-37		3-38	
3-39		3-40	
3-41		3-42	
3-43		3-44	
3-45		3-46	
3-47		3-48	

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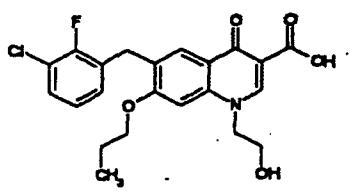
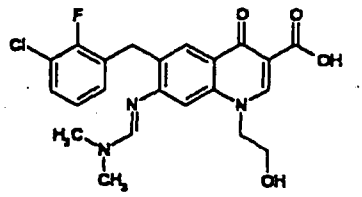
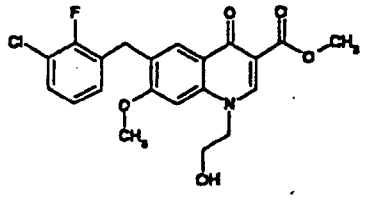
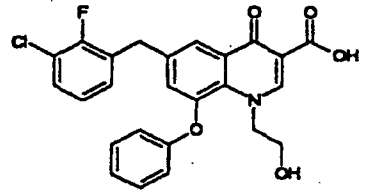
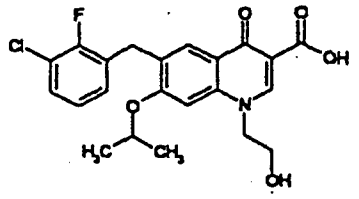
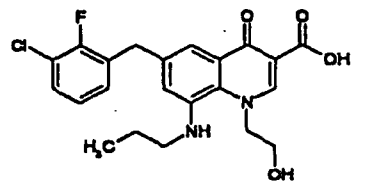
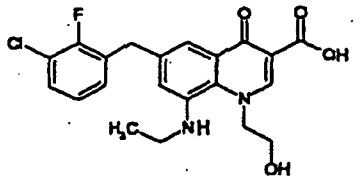
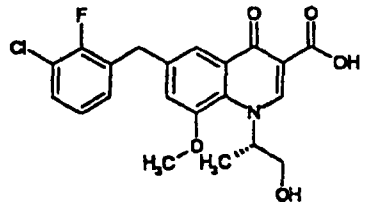
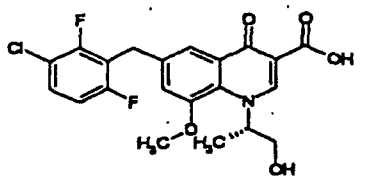
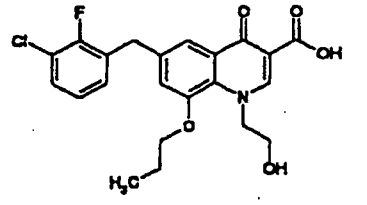
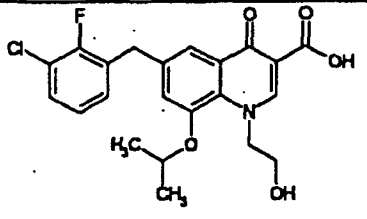
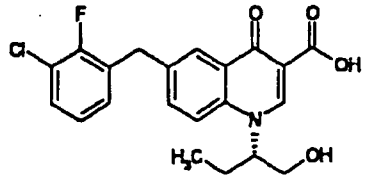
3-49		3-50	
3-51		3-52	
3-53		3-54	
3-55		3-56	
3-57		3-58	
3-59		3-60	

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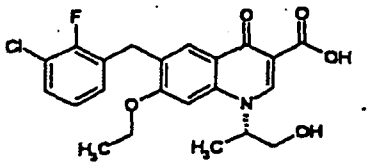
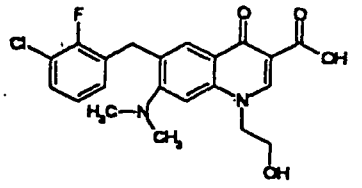
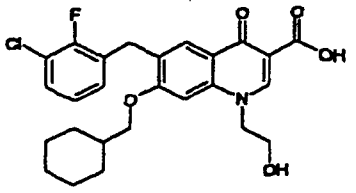
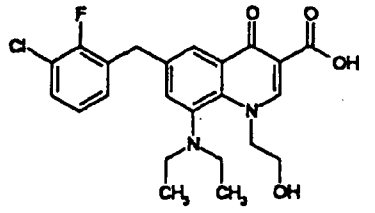
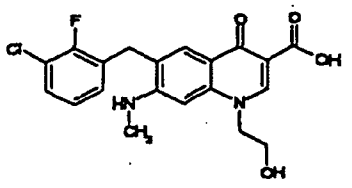
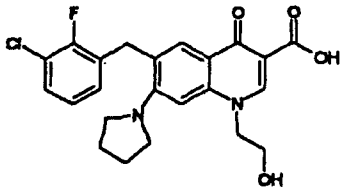
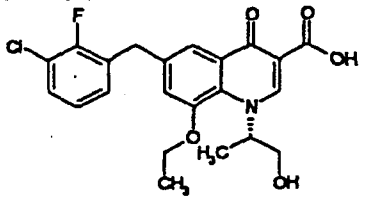
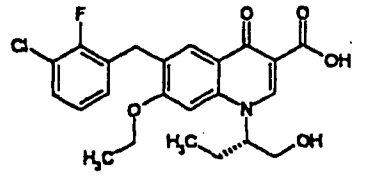
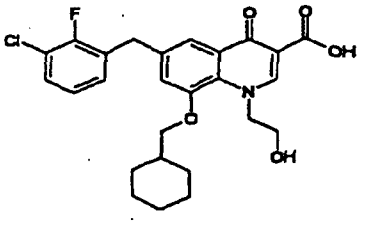
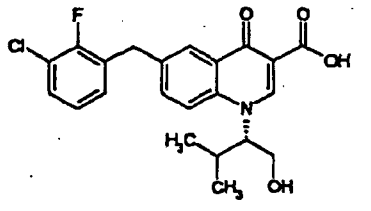
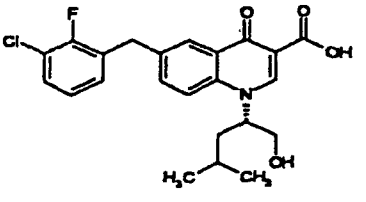
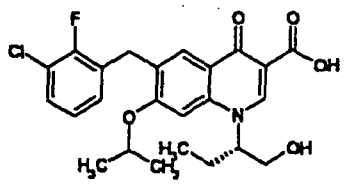
3-61		3-62	
3-63		3-64	
3-65		3-66	
3-67		3-68	
3-69		3-70	
3-71		3-72	

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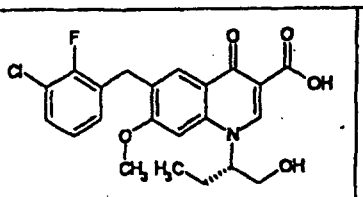
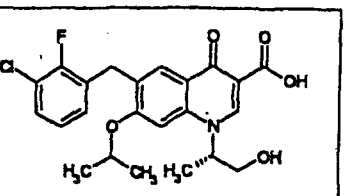
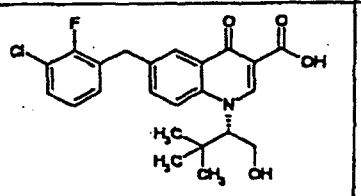
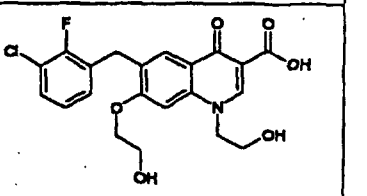
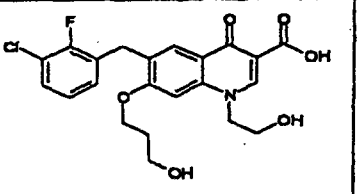
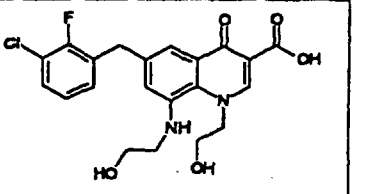
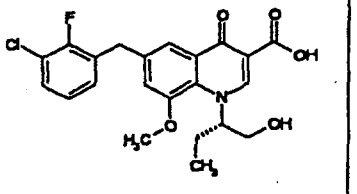
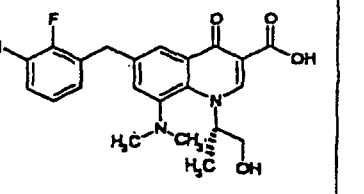
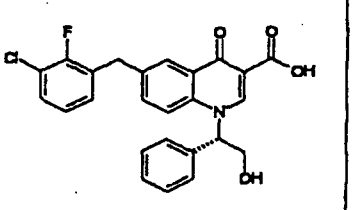
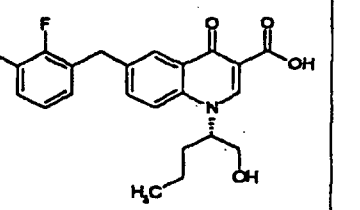
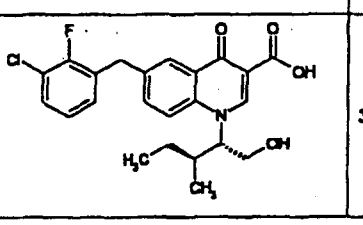
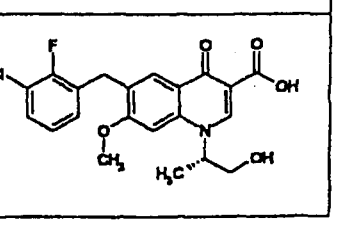
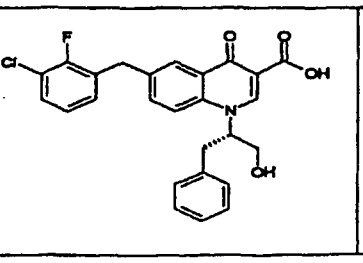
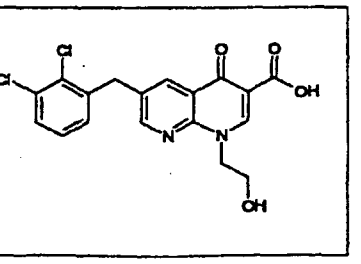
3-73		3-74	
3-75		3-76	
3-77		3-78	
3-79		3-80	
3-81		3-82	
3-83		3-84	

3-85		3-86	

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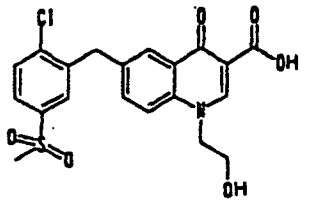
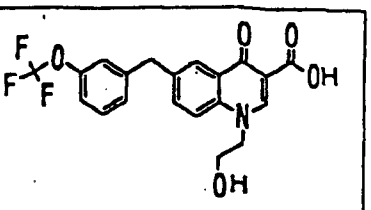
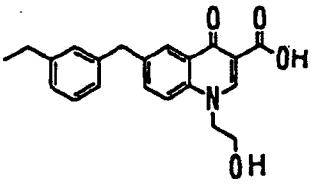
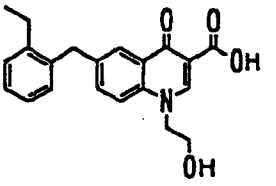
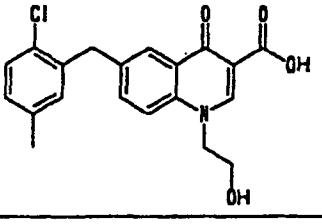
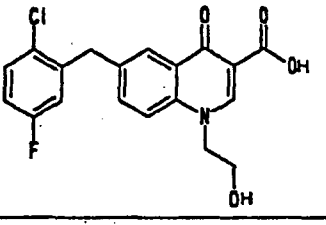
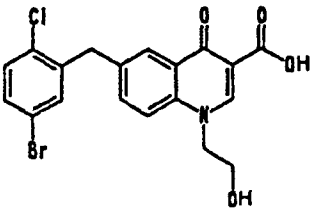
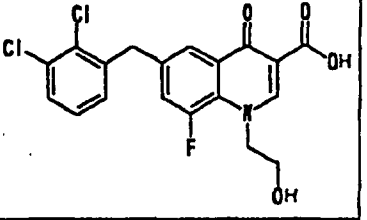
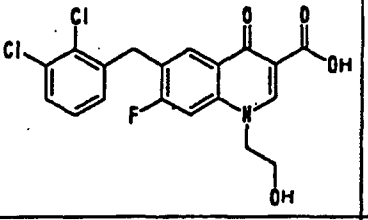
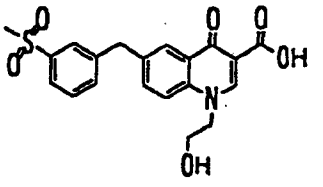
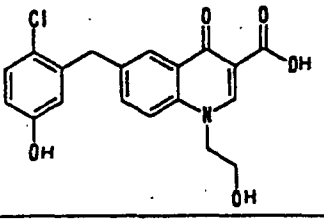
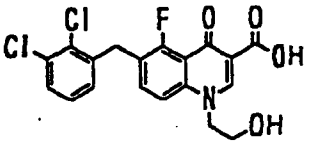
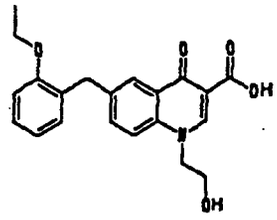
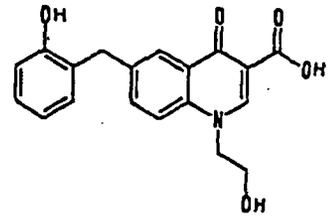
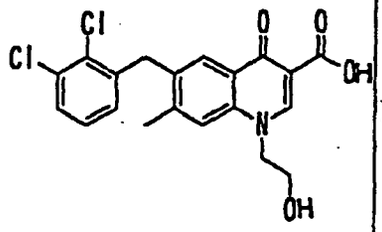
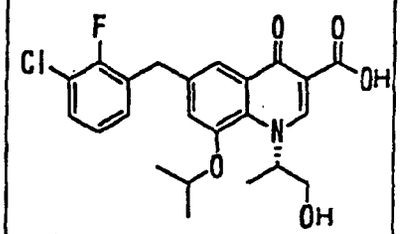
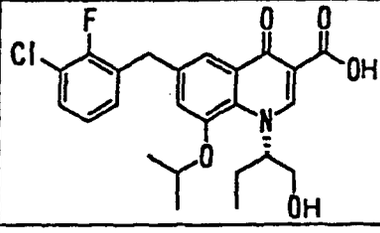
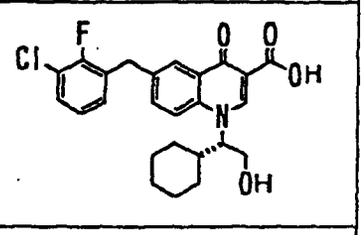
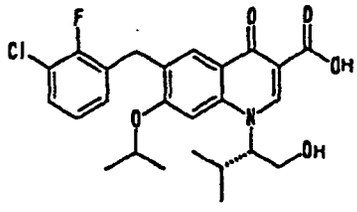
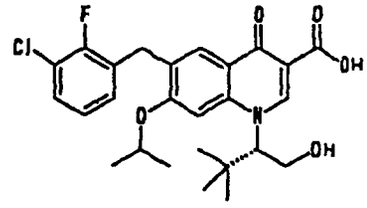
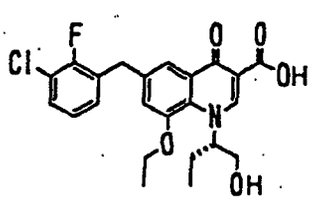
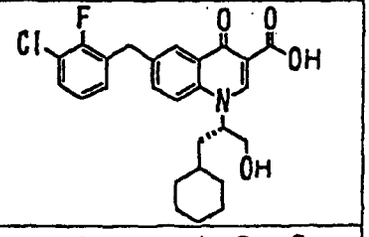
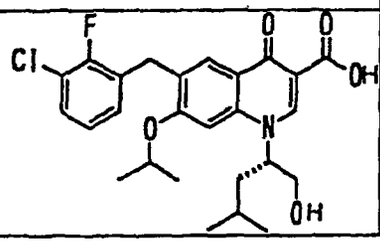
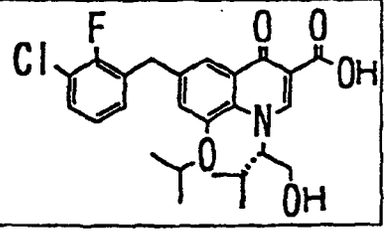
4-1		4-2	
4-3		4-4	
4-5		4-6	
4-7		4-8	
4-9		4-10	
4-11		4-12	

4-13		4-14	
4-15		4-16	
4-17		4-18	
4-19		4-20	
4-21		4-22	
4-23		4-24	

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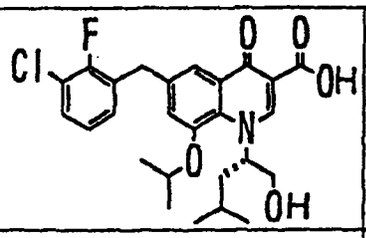
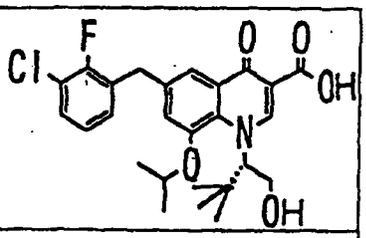
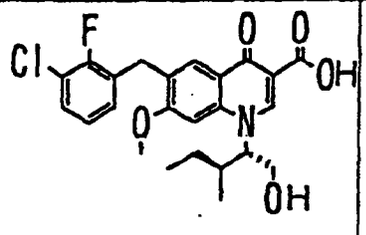
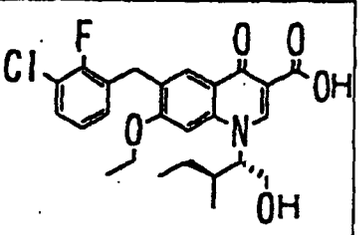
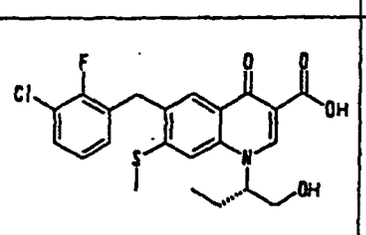
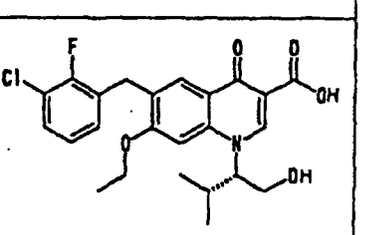
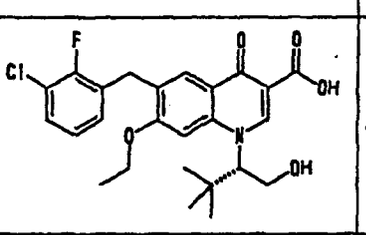
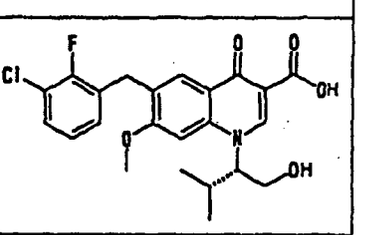
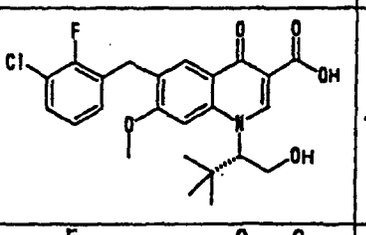
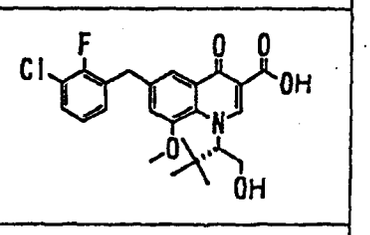
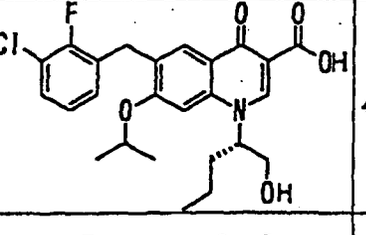
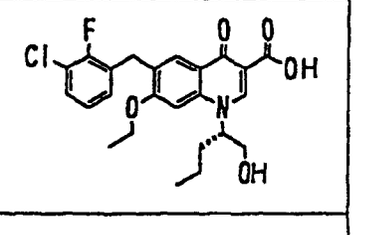
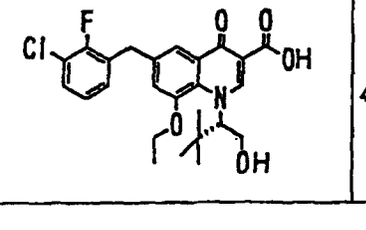
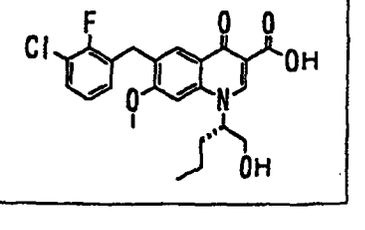
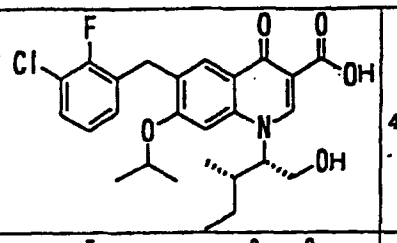
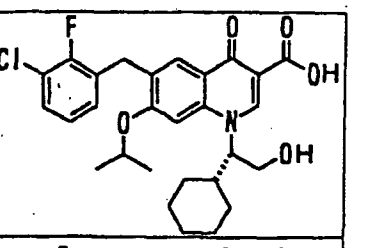
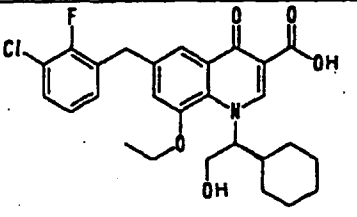
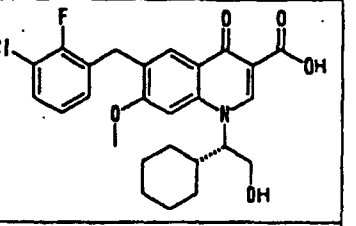
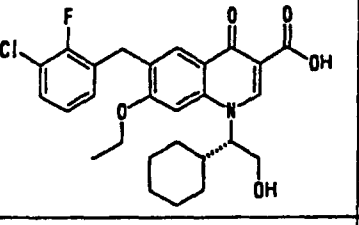
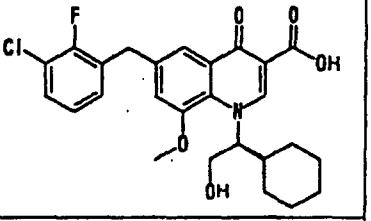
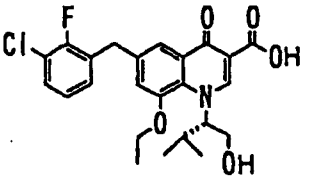
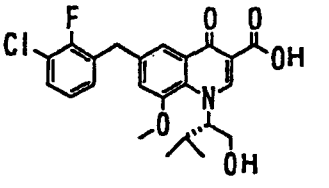
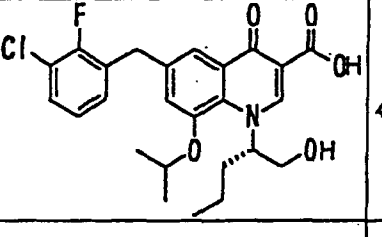
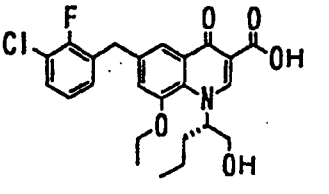
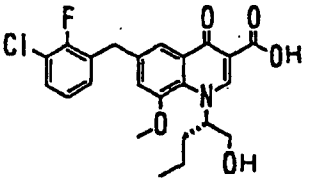
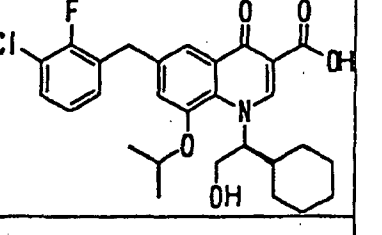
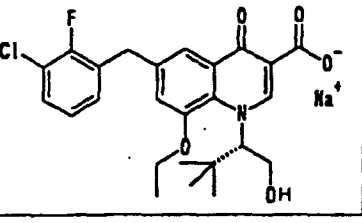
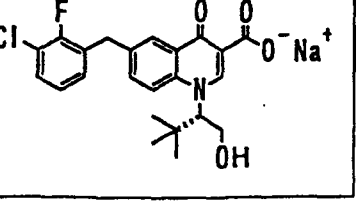
4-25		4-26	
4-27		4-28	
4-29		4-30	
4-31		4-32	
4-33		4-34	
4-35		4-36	
4-37		4-38	

4－39		4－40	
4－41		4－42	
4－43		4－44	
4－45		4－46	
4－47		4－48	
4－49		4－50	
4－51		4－52	

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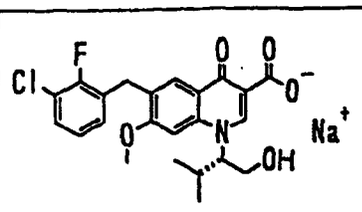
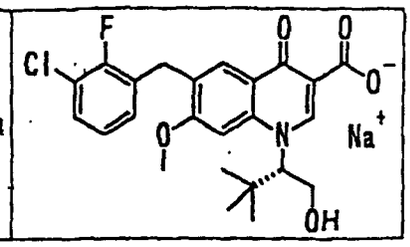
4－53		4－54	

Table 5

Ex. No.	Enzyme activity IC_{50} (μM)	Ex. No.	Enzyme activity IC_{50} (μM)
1-1	0.029	1-2	0.033
1-3	0.36	1-4	0.24
1-6	0.14	1-7	0.067
1-8	0.046	1-9	0.017
1-10	0.072	1-11	0.18
1-12	0.71	1-13	0.14
1-14	0.075	1-15	0.23
1-16	0.032	1-17	0.084
1-18	0.12	1-19	0.081
1-20	0.69	1-21	0.074
1-22	0.11	1-23	0.19
1-24	0.29	1-25	0.16
1-26	0.18	1-27	0.076
1-28	0.059	1-29	0.24
1-30	0.14	1-31	0.17
1-32	0.068	1-33	0.14
1-34	0.35	1-36	0.18
1-37	0.11	1-38	0.17
1-39	0.18	1-40	0.11
1-41	0.21	1-42	0.13
1-43	0.024	1-44	0.051
1-45	0.21	1-46	0.42
1-47	0.098	1-48	0.38
1-49	0.053	1-50	0.11
1-51	0.18	1-63	0.02
1-64	0.056	1-65	0.12
1-66	0.049	1-67	0.79
1-68	0.049	1-69	0.074
1-70	0.082	1-71	0.013

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Table 5 (continued)

Ex. No.	Enzyme activity IC_{50} (μM)	Ex. No.	Enzyme activity IC_{50} (μM)
1-72	0.025	1-73	0.031
1-74	0.098	1-75	0.016
1-76	0.028	1-77	0.063
1-78	0.59	1-79	0.077
1-80	0.35	1-86	0.15
1-87	0.14	1-88	0.45
1-92	0.28	1-93	0.37
1-96	0.23	1-97	0.13
2-1	0.17	2-2	0.18
2-3	0.11	2-4	0.018
2-5	0.30	2-6	0.092
2-7	0.079	2-8	0.085

Table 6

Ex. No.	Enzyme activity IC_{50} (μM)	Ex. No.	Enzyme activity IC_{50} (μM)
3-1	0.47	3-2	0.2
3-3	0.19	3-4	0.011
3-5	0.024	3-6	0.011
3-8	0.34	3-9	0.084
3-10	0.018	3-12	0.016
3-13	0.029	3-14	0.014
3-17	0.013	3-20	0.01
3-21	0.03	3-22	0.79
3-23	0.0072	3-24	0.039
3-25	0.069	3-26	0.011
3-27	0.075	3-33	0.0087
3-34	0.011	3-35	0.011
3-36	0.051	3-37	0.011
3-38	0.015	3-39	0.049
3-42	0.72	3-43	0.018
3-44	0.0096	3-45	0.015
3-47	0.0086	3-48	0.021
3-49	0.0079	3-50	0.018
3-52	0.012	3-53	0.0079
3-54	0.0064	3-55	0.0087
3-56	0.012	3-57	0.015
3-58	0.008	3-59	0.008
3-60	0.0055	3-61	0.0076

Table 6 (continued)

Ex. No.	Enzyme activity IC_{50} (μM)	Ex. No.	Enzyme activity IC_{50} (μM)
3-62	0.027	3-63	0.017
3-64	0.018	3-65	0.015
3-66	0.048	3-67	0.0064
3-69	0.0043	3-72	0.0038
3-73	0.0033	3-74	0.0049
3-76	0.0085	3-77	0.0089
3-78	0.016	3-79	0.0067
3-80	0.0088	3-86	0.14

Table 7

Ex. No.	Enzyme activity IC_{50} (μM)	Ex. No.	Enzyme activity IC_{50} (μM)
4-1	0.86	4-4	0.55
4-5	0.13	4-6	0.46
4-7	0.13	4-8	0.033
4-9	0.021	4-11	0.22
4-12	0.065	4-13	0.30
4-15	0.031	4-16	0.0071
4-17	0.0031	4-18	0.0020
4-19	0.0029	4-20	0.0017
4-21	0.0045	4-22	0.0029
4-23	0.0038	4-24	0.0025
4-25	0.0019	4-26	0.0015
4-27	0.0029	4-28	0.0027
4-29	0.0045	4-30	0.0029
4-31	0.0021	4-32	0.0029
4-33	0.0020	4-34	0.0039
4-35	0.0043	4-36	0.0037
4-37	0.0019	4-38	0.0033
4-39	0.0041	4-40	0.0043
4-41	0.0023	4-42	0.0023
4-43	0.0028	4-44	0.0024
4-45	0.0034	4-46	0.0050
4-47	0.0023	4-48	0.0030
4-49	0.0057	4-50	0.0031

[0349] The NMR and MS data of the Example compounds shown in the above-mentioned Table 1 to Table 4 are described in the following.

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Example 1-1

[0350] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.75(2H, t, J=4. 7Hz), 4.36(2H, s), 4.60(2H, t, J=4.8Hz), 4.98 (1H, brs), 7.37-7.39 (1H, m), 7.45 (1H, dd, J=1.4, 7.6Hz), 7.57 (1H, dd, J=1.5, 8.0Hz), 7.81 (1H, dd, J=2.1, 8.9Hz), 8.02 (1H, d, J=8.8Hz), 8.15 (1H, d, J=1.8Hz), 8.86 (1H, s), 15.18 (1H, brs)
MS (ESI): M+ 392

Example 1-2

[0351] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.78 (2H, m), 4.35 (2H, s), 4.64 (2H, m), 5.00 (1H, m), 7.39 (2H, m), 7.47 (1H, m), 7.58 (1H, m), 8.00 (1H, m), 8.81 (1H, s), 14.80 (1H, s)
MS (ESI): M+409

Example 1-3

[0352] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2. 85 (3H, s), 3. 41 (2H, m), 4.37 (2H, s), 4.63(2H, t, J=5.6Hz), 7.25-7.29 (1H, m), 7.39 (1H, dd, J=7.8, 7.8Hz), 7.47 (1H, dd, J=1.5, 7.7Hz), 7.58 (1H, dd, J=1.5, 7.8Hz), 7.84(1H, dd, J=2.0, 8.9Hz), 8.00(1H, d, J=8.9Hz), 8.15(1H, d, J=1.8Hz), 8.91 (1H, s)
MS (ESI): M+ 469

Example 1-4

[0353] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.38 (2H, s), 4.46 (2H, t, J= 5.9 Hz), 4.90 (2H, t, J= 5.9 Hz), 6.84 (1H, s), 7.14 (1H, s), 7.37-7.47 (3H, m), 7.59 (1H, m), 7.82 (1H, m), 8.01 (1H, m), 8.15 (1H, s), 8.66 (1H, s), 14.99 (1H, s)
MS (ESI): M+441

Example 1-5

[0354] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.87 (3H, s), 3.12 (3H, s), 4.35 (2H, s), 5.59 (2H, s), 7.38-7.45 (2H, m), 7.57 (1H, m), 7.71-7.76 (2H, m), 8.12 (1H, s), 8.94 (1H, s)
MS (ESI): M+432

Example 1-6

[0355] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.64 (3H, d, J= 4.4), 4.35 (2H, s), 5.24 (2H, s), 7.35-7.47 (2H, m), 7.56-7.65 (2H, m), 7.80 (1H, m), 8.13 (1H, s), 8.32 (1H, q, J= 4.4 Hz), 9.00 (1H, s)
MS (ESI): M+418

Example 1-7

[0356] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.36 (2H, s), 5.23 (2H, s), 7.35-7.45 (2H, m), 7.54-7.65 (3H, m), 7.83-7.88 (2H, m), 8.13 (1H, s), 9.01 (1H, s)
MS (ESI): M+404

Example 1-8

[0357] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.57 (6H, d, J= 6.5 Hz), 4.37 (2H, s), 5.24 (1H, m), 7.38 (1H, dd, J= 7.7, 7.7 Hz) 7.46 (1H, dd, J= 1.6, 7.7 Hz), 7.58 (1H, dd, J= 1.6, 7.7 Hz), 7.85 (1H, dd, J= 2.1, 8.9 Hz), 8.15-8.18 (2H, m), 8.86 (1H, s)
MS (ESI): M+389

Example 1-9

[0358] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.35 (2H, s), 5.98 (2H, s), 7.37-7.44 (4H, m), 7.57 (1H, m), 7.83 (1H, m), 8.10-8.12 (2H, m), 8.99 (1H, s)
MS (ESI): M+440

Example 1-10

[0359] ^{1}HNMR (DMSO-d_6 300MHz) (δ) ppm: 2.85 (2H, m), 4.36 (2H, s), 4.74 (2H, m), 7.38-7.46 (2H, m), 7.58 (1H, m), 7.85 (1H, m), 8.00 (1H, m), 8.14 (1H, s), 9.00 (1H, s)
MS (ESI): M+419

Example 1-11

[0360] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.74 (2H, dt, J= 4. 8, 5.6 Hz), 4.59 (2H, t, J= 4.9 Hz), 4.66 (2H, s), 4.98 (1H, t, J= 5.6 Hz), 7.48-7.53 (4H, m), 7.85-8.08 (5H, m), 8.18 (1H, m), 8.83 (1H, s), 15.24 (1H, brs)
MS (ESI): M+373

Example 1-12

[0361] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.70 (2H, m), 3.72 (3H, s), 4.27 (2H, s), 4.38 (2H, m), 4.96 (1H, br), 7.32-7.41 (2H, m), 7.54 (1H, dd, J= 1.8, 7.3 Hz), 7.61 (1H, dd, J= 2.2, 8.8 Hz), 7.76 (1H, d, J= 8.8 Hz), 8.00 (1H, d, J= 2.2 Hz), 8.55 (1H, s)
MS (ESI): M+405

Example 1-13

[0362] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.67 (2H, m), 4.37 (2H, s), 4.73 (2H, m), 6.97 (1H, br), 7.38-7.48 (3H, m), 7.58 (1H, m), 7.87 (1H, m), 8.01 (1H, m), 8.15 (1H, s), 8.93 (1H, s)
MS (ESI) : M+418

Example 1-14

[0363] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.30 (3H, s), 4.34 (2H, s), 5.62 (2H, s), 7.37 (1H, m), 7.44 (1H, m), 7.55 (1H, m), 7.72-7.78 (2H, m), 8. 10 (1H, s), 8.90 (1H, s)
MS (ESI): M+403

Example 1-15

[0364] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.31 (2H, s), 5.84 (2H, s), 7.26-7.41 (7H, m), 7.55 (1H, m), 7.73 (1H, m), 7.83 (1H, m), 8.13 (1H, m), 9.23 (1H, s), 15.18 (1H, brs)
MS (ESI): M+437

Example 1-16

[0365] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3. 12 (2H, t, J= 7.3 Hz), 4.38 (2H, s), 4.78 (2H, t, J= 7.3 Hz), 7.20-7.28 (5H, m), 7.37-7.47 (3H, m), 7.58 (1H, m), 7.85 (1H, m), 8.09 (1H, m), 8.15 (1H, s), 8.79 (1H, s), 15.07 (1H, brs)
MS (ESI): M+451

Example 1-17

[0366] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.13 (2H, tt, J= 7.3, 7.6 Hz), 2.70 (1H, t, J= 7.6 Hz), 4.36 (2H, s), 4.58 (2H, t, J= 7.3 Hz), 7.15-7.24 (5H, m), 7.38-7.44 (3H, m), 7.57 (1H, m), 7.82 (1H, m), 7.96 (1H, m), 8.13 (1H, s), 8.98 (1H, s), 15.14 (1H, brs)
MS (ESI): M+465

Example 1-18

[0367] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.89 (6H, d, J= 6.7 Hz), 2.16 (1H, tq, J= 6.7, 7.6 Hz), 4.37 (2H, s), 4.39 (2H, d, J= 7.6 Hz), 7.38-7.47 (2H, m), 7.58 (1H, m), 7.83 (1H, dd, J= 2.0, 8.9 Hz), 8.02 (1H, d, J= 8.9Hz), 8.14 (1H, d, J= 2.0 Hz), 8.97 (1H, s), 15.15 (1H, brs)
MS (ESI): M+403

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Example 1-19

[0368] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.61-1.64 (2H, m), 1.76-1.84 (2H, m), 2.60(2H, t, J=7.5Hz), 4.36 (2H, s), 4.56 (2H, t, J=7.2Hz), 7.15-7.17(3H, m), 7.22-7.24(2H, m), 7.38-7.40(1H, m), 7.44(1H, m), 7. 56-7.59 (1H, m), 7.82 (1H, d, J=2Hz), 7.96 (1H, d, J=8.9Hz), 8.14 (1H, d, J=1.8Hz), 9.01(1H, s), 15.15(1H, brs)
MS (ESI): M+ 514

Example 1-20

[0369] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 4.28 (2H, s), 5.73 (2H, s), 7.02(1H, d, J=7.6Hz), 7.27-7.43(11H, m), 7.55(1H, d, J=7.6Hz), 7.60-7.62(1H, m), 8.08(1H, d, J=1.6Hz), 8.92 (1H, s), 14.97 (1H, brs)
MS (ESI): M+ 502

Example 1-21

[0370] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.45-1.49 (2H, m), 1.81-1.85 (2H, m), 3.42(2H, t, J=6.3Hz), 4.36(2H, s), 4.56(2H, t, J=7.4Hz), 7.38(1H, dd, J=7.7, 7.8Hz), 7.44-7.46(1H, m), 7.57(1H, dd, J=1.4, 7.8Hz), 7.83(1H, dd, J=2.0, 8. 8Hz), 8.0 (1H, d, J=8.9Hz), 8.14(1H, d, J=1.8Hz), 9.01 (1H, s), 15.18(1H, brs)
MS (ESI): M+ 420

Example 1-22

[0371] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.32 (2H, s), 6.16(2H, s), 7.32-7.42(4H, m), 7.51-7.55(2H, m), 7.77-7.89 (3H, m), 8.06-8.12(2H, m), 9.31(1H, s), 15.02(1H, brs)
MS (ESI): M+ 494

Example 1-23

[0372] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.31(2H, s), 5.83(2H, s), 7.19-7.21 (1H, m), 7.33-7.43 (2H, m), 7.54-7. 59 (2H, m), 7.68-7.79 (3H, m), 8.12 (1H, s), 9.25 (1H, s), 15.05 (1H, brs)
MS (ESI): M+ 508

Example 1-24

[0373] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.18 (6H, s), 2.64 (2H, br), 4.36(2H, s), 4.63 (2H, br), 7.38-7.40 (1H, m), 7.45 (1H, d, J=1.3Hz), 7.56-7.58 (1H, m), 7.84 (1H, m), 8.00 (1H, d, J=8.9Hz), 8.14 (1H, d, J=1.7Hz), 8.90 (1H, s), 15.15 (1H, brs)
MS (ESI): M+ 419

Example 1-25

[0374] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.93-1.98 (2H, m), 3.45 (2H, t, J=5.6Hz), 4.36(2H, s), 4.59(2H, t, J=7.0Hz), 4.68 (1H, br), 7.37 (1H, dd, J=7.7, 7.8Hz), 7.44-7.468 (1H, m), 7.57 (1H, d, J=7.8Hz), 7.83-7.99 (1H, m), 8.00(1H, d, J=8.9Hz), 8.14 (1H, s), 8.96 (1H, s), 15.16 (1H, brs)
MS (ESI): M+ 406

Example 1-26

[0375] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.21 (3H, s), 3.70 (2H, t, J=4.8Hz), 4.36(2H, s), 4.75(2H, t, J=4.8Hz), 7.38 (1H, dd, J=7.7, 7.7Hz), 7.44-7.47 (1H, m), 7.58 (1H, dd, J=1.6, 7.8Hz), 7.83 (1H, dd, J=2.1, 8.9Hz), 8.04 (1H, d, J=8.9Hz), 8.14 (1H, d, J=2.0Hz), 8.89 (1H, s), 15.14 (1H, brs)
MS (ESI): M+ 406

Example 1-27

[0376] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.36(2H, s), 5.68 (2H, q, J=8.7Hz), 7.38 (1H, dd, J=7.7, 7.7Hz), 7.46 (1H, dd, J=1.7, 7.7Hz), 7.89 (1H, dd, J=2.1, 8.9Hz), 8.13-8.16 (2H, m), 9.11 (1H, s), 14.71 (1H, brs)
MS (ESI): M+ 430

Example 1-28

[0377] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.34 (2H, s), 4.78 (2H, s), 7.34-7.44(2H, m), 7.55-7.57 (1H, m), 7.69 (1H, d, J=8.7Hz), 7.76 (1H, d, J=9.0Hz), 8.09 (1H, s), 8.85 (1H, s), 15.37 (1H, brs)
MS (ESI) : M+ 406

Example 1-29

[0378] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.04(3H, s), 3.27-3.38(2H, m), 4.37(2H, s), 4.78(2H, t, J=6.8Hz), 7.37-7.39 (1H, m), 7.45-7.47 (1H, m), 7.58-7.61 (1H, m), 7.85-7.87 (1H, m), 8.03-8.05 (1H, m), 8.15 (1H, s), 8.73 (1H, s), 8.81 (1H, s)
MS (ESI): M+ 473

Example 1-30

[0379] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1:20 (3H, d, J=6.2Hz), 3.96 (1H, br), 4.15-4.23 (1H, m), 4.36(2H, s), 4.65-4.69 (1H, m), 5.02 (1H, br), 7.37 (1H, dd, J=7.7, 8.0Hz), 7.45 (1H, d, J=6.6Hz), 7.57 (1H, d, J=8.1Hz), 7.81 (1H, d, J=8.8Hz), 8.03 (1H, d, J=9.1Hz), 8.13 (1H, s), 8.84 (1H, s)
MS (ESI): M+ 406

Example 1-31

[0380] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.19 (2H, s), 4.61 (2H, m), 5.00 (1H, br), 7.27-7.40 (4H, m), 7.86 (1H, m), 8.02 (1H, m), 8.26 (1H, m), 8.86 (1H, s), 15.29 (1H, s)
MS (ESI): M+357

Example 1-32

[0381] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.10 (3H, s), 2.95 (2H, t, J=6.6Hz), 4.37(2H, s), 4.76(2H, t, J=6.6Hz), 7.38 (1H, dd, J=7.7, 7.8Hz), 7.45-7.47(1H, m), 7.58(1H, dd, J=1.5, 7.9Hz), 7.90(1H, dd, J=2.0, 8.9Hz), 8.00(1H, d, J=8.9Hz), 8.15(1H, d, J=1.8Hz), 9.02(1H, s), 15.12(1H, brs)
MS (ESI): M+ 422

Example 1-33

[0382] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.75 (2H, s), 4.33 (2H, s), 4.60(2H, t, J=4.8Hz), 4.98(1H, br), 7.30-7.33 (1H, m), 7.39-7.42(2H, m), 7.80(1H, dd, J=1.7, 8.9Hz), 8.02(1H, d, J=8.9Hz), 8.09(1H, s), 8. 85 (1H, s), 15,14 (1H, brs)
MS (ESI): M+ 375

Example 1-34

[0383] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.33-1.44 (4H, m), 1.75-1.81 (2H, m), 3.36-3.38 (2H, m), 4.54(2H, t, J=7.2Hz), 7.38 (1H, dd, J=7.7, 7.7Hz), 7.46 (1H, d, J=6.1Hz), 7.57 (1H, d, J=7. 8Hz), 7.83(1H, d, J=8.7Hz), 8.00 (1H, d, J=8.9Hz), 8.14 (1H, s), 9.01(1H, s), 15.19(1H, brs)
MS (ESI): M+ 434

Example 1-35

[0384] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.33-2.45 (4H, br), 2.64 (2H, t, J=6.2Hz), 3.52 (2H, t, J=4.4Hz) ; 4.27 (2H, s), 4.40 (2H, br), 7.34-7.42(2H, m), 7.55-7.60(2H, m), 7.71 (1H, d, J=8.6Hz), 8.04 (1H, s), 8.57 (1H, s)
MS (ESI): M+ 461

Example 1-36

[0385] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.08 (3H, s), 4.37 (2H, s), 7.37 (1H, dd, J=7.7, 7.7Hz), 7.44-7.46 (1H, m), 7.57 (1H, dd, J=1.7, 7. 8Hz), 7.84-7.87(1H, m), 7.92 (1H, d, J=8. 8Hz), 8.12(1H, s), 9.01(1H, s), 15.20 (1H, brs)
MS (ESI) : M+ 362

Example 1-37

[0386] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.41 (3H, t, J=7.1Hz), 4.36 (2H, s), 4.58(2H, q, J=7.1Hz), 7.38(1H, dd, J=7.8, 7.7Hz), 7.44-7.46(1H, m), 7.57(1H, dd, J=1.5, 7.9Hz), 7.83(1H, dd, J=2.1, 8.8Hz), 8.01 (1H, d, J=8.8Hz), 8.14 (1H, s), 9.02 (1H, s), 15.18 (1H, brs)
MS (ESI): M+ 376

Example 1-38

[0387] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.90 (3H, t, J=7.3Hz), 1.77-1.85(2H, m), 4.36(2H, s), 4.51(2H, t, J=7.3Hz), 7.38(1H, dd, J=7.8, 7.6Hz), 7.44-7.46(1H, m), 7.58(1H, dd, J=1.7, 7.8Hz), 7.83(1H, dd, J=2.1, 8.8Hz), 8.02 (1H, d, J=8.9Hz), 8.14(1H, d, J=2.0Hz), 9.02 (1H, s), 15.18 (1H, brs)
MS (ESI): M+ 390

Example 1-39

[0388] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.90(3H, t, J=7.3Hz), 1.30-1.37 (2H, m), 1.74-1.79 (2H, m), 4.36 (2H, s), 4.54 (2H, t, J=7.3Hz), 7.38(1H, dd, J=7.6, 7.8Hz), 7.46(1H, dd, J=1.7, 7.6Hz), 7.58 (1H, dd, J=1.7, 7.8Hz), 7.83(1H, dd, J=2.1, 8.9Hz), 8.00 (1H, d, J=8.9Hz), 8.14(1H, d, J=2.0Hz), 9.01(1H, s), 15.18 (1H, brs)
MS (ESI): M+ 404

Example 1-40

[0389] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1:27-1.29 (2H, m), 1.47-1. 50 (2H, m), 1.59-1. 66 (4H, m), 2.31-2.40 (1H, m), 4.36 (2H, s), 4.51(2H, d, J=7.6Hz), 7.38-7.47(2H, m), 7.57 (1H, dd, J=1.5, 7.8Hz), 7.82(1H, dd, J=2.0, 8.8Hz), 8.05(1H, d, J=8.9Hz), 8.14(1H, d, J=1.8Hz), 9.028 (1H, s), 15.16(1H, brs)
MS (ESI): M+ 430

Example 1-41

[0390] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.11 (3H, s), 3.77 (2H, t), 4,37(2H, s), 4.99(2H, t), 7.35-7.41 (1H, m), 7.47 (1H, d), 7.58 (1H, d, J=7.8Hz), 7.83-7.92 (2H, m), 8.16 (1H, s), 9.05 (1H, s)
MS (ESI): M+ 454

Example 1-42

[0391] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.10 (4H, br), 1.54-1.65 (4H, br), 1.83 (1H, br), 4.36(2H, s), 4.40 (2H, d, J=7.4Hz), 7.38 (1H, dd, J=7.7, 7.8Hz), 7.45-7.48(1H, m), 7.58(1H, dd, J=1.6, 7.8Hz), 7.81-7.84 (1H, m), 8.02 (1H, d, J=8.9Hz), 8.13 (1H, s), 8.93 (1H, s), 15.17(1H, brs)
MS (ESI): M+ 444

Example 1-43

[0392] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.37 (2H, s), 4.49-4.56 (1H, m), 4.77-4.82 (1H, m), 4.91-4.97 (1H, m), 5.81 (1H, d, J=4.7Hz), 7.30-760(8H, m), 7.81 (1H, d, J=11.0Hz), 8.08 (1H, d, J=8.9Hz), 8.17 (1H, d), 8.93 (1H, s), 15.19 (1H, brs)
MS (ESI): M+ 468

Example 1-44

[0393] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.37 (2H, s), 4.72-4.76 (1H, m), 4.92(2H, t, J=4.6Hz), 4.98-5.01(1H, m), 7.38 (1H, dd, J=7.8, 8.1Hz), 7.44-7.46 (1H, m), 7.58 (1H, dd, J=1.6, 7.9Hz), 7.84 (1H, dd, J=2.1, 9.0Hz), 8.03 (1H, d, J=9.3Hz), 8.15 (1H, d, J=1.8Hz), 8.78 (1H, s), 8.98 (1H, s)
MS (ESI): M+ 394

Example 1-45

[0394] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3:21 (2H, br), 4.27 (2H, s), 4.65(2H, br), 7.20-7.28(2H, m), 7.33-7.41

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(2H, m), 7.54-7.70 (5H, m), 7.77 (1H, d, J=8.7Hz), 8.05 (1H, s), 8.50 (1H, s), 8.52 (1H, s)
MS (ESI): M+ 453

Example 1-46

[0395] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.93 (2H, t), 4.35 (2H, s), 4.48(2H, s), 7.38 (1H, dd, J=7.7, 7.7Hz), 7.45(1H, d, J=6.2Hz), 7.57(1H, d, J=7.7Hz), 7.82 (1H, d), 8.02 (1H, d, J=9.1Hz), 8.13 (1H, s), 8.92 (1H, s)
MS (ESI): M+ 391

Example 1-47

[0396] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.13 (6H, s), 4. 35 (2H, s), 4.50(2H, s), 4.90 (1H, brs), 7.35-7.46 (2H, m), 7.57 (1H, d, J=7.7Hz), 7.78 (1H, d, J=7.1Hz), 8.10(1H, s), 8.19 (1H, d, J=9.0Hz), 8.88(1H, s), 15.22 (1H, brs)
MS (ESI): M+ 420

Example 1-48

[0397] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.68(3H, s), 3.46 (2H, br), 4.36(2H, s), 4.56 (2H, br), 7.38-7.60(3H, m), 7.81-8.13(4H, m), 8.80(1H, s)
MS (ESI): M+ 433

Example 1-49

[0398] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.00 (3H, t, J=7.0Hz), 3.41 (2H, br), 3.82(2H, q), 4.36(2H, s), 4.57 (2H, br), 7.24 (1H, m), 7.38 (1H, m), 7.46 (1H, m), 7.58 (1H, m), 7.83 (1H, m), 8.03 (1H, m), 8.13 (1H, s), 8.82 (1H, s)
MS (ESI): M+ 463

Example 1-50

[0399] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3. 75 (2H, m), 4. 26 (2H, s), 4.61 (2H, t, J=4.8Hz), 5.00(1H, br), 7.17-7.36 (3H, m), 7.83 (1H, dd, J=2.0, 8.8Hz), 8.03 (1H, d, J=8.9Hz), 8.21 (1H, s), 8.87 (1H, s), 15.22 (1H, brs)
MS (ESI): M+ 360

Example 1-51

[0400] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.28 (2H, s), 4.61(2H, t, J=4.8Hz), 5.00 (1H, br), 7.24-7.28 (1H, m), 7.44-7.55(2H, m), 7.80(1H, dd, J=2.1, 8.8Hz), 8.02(1H, d, J=8.9Hz), 8.13 (1H, d, J=1.9Hz), 8.86 (1H, s), 15.22 (1H, s)
MS (ESI): M+ 376

Example 1-52

[0401] ^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: 1.42(3H, t, J=7.1Hz), 4.05 (2H, s), 4.40(2H, q, J=7.1Hz), 5.35(2H, s), 7.13-7.28(8H, m), 7.33-7.35(2H, m), 8.41 (1H, d, J=2.0Hz), 8.58(1H, s)
MS (ESI): M+ 398

Example 1-53

[0402] ^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: 4.10 (2H, s), 5.48(2H, s), 7.13-7.50(12H, m), 8.41 (1H, d, J=1.9Hz), 8.87 (1H, s), 14.96 (1H, brs)
MS (ESI): M+ 370

Example 1-54

[0403] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.16(2H, s), 5.44(2H, s), 7.19-7.34(5H, m), 7.74 (1H, d, J=8.8Hz), 7.83 (1H, dd, J=2.0, 8.9Hz), 8.22(1H, d, J=1.9Hz), 9.08(1H, s), 13.58(1H, brs), 15.13(1H, brs)
MS (ESI): M+ 338

Example 1-55

[0404] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0. 89 (3H, t, J=7.3Hz), 1.25-1.35(5H, m), 1.66-1.76(2H, m), 4.09 (2H, s), 4.21 (2H, q, J=7.1Hz), 4.34(2H, t, J=7.2Hz), 7.20-7.33(5H, m), 7.66(1H, dd, J=2.1, 8.7Hz), 7.74(1H, d, J=8.7Hz), 8.06(1H, d, J=1.9Hz), 8.64(1H, s)
MS (ESI): M+ 364

Example 1-56

[0405] ^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: 0.99 (3H, t, J=7.3Hz), 1.43 (2H, m), 1.84-1.94 (2H, m), 4.15(2H, s), 4.28 (2H, t, J=7.4Hz), 7.20-7.34(5H, m), 7.52 (1H, d, J=8.8Hz), 7.65 (1H, dd, J=2.1, 8.8Hz), 8.42 (1H, d, J=1.9Hz), 8.72 (1H, s), 15.04 (1H, brs)
MS (ESI): M+ 336

Example 1-57

[0406] ^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: 1.41 (3H, t, J=7.2Hz), 3. 85 (3H, s), 4.11(2H, s), 4.39 (2H, q, J=7.2Hz), 7.17-7.35 (6H, m), 7.51(1H, dd, J=2.4, 8.4Hz), 8.42(1H, d, J=1.8Hz), 8.45(1H, s)
MS (ESI): M+ 322

Example 1-58

[0407] ^{1}H NMR ($CDCl_3$ 300MHz) (δ) ppm: 3.99 (3H, s), 4.16(2H, s), 7.19-7.33(5H, m), 7.52 (1H, d, J=8.7Hz), 7.68 (1H, dd, J=2.0, 8.7Hz), 8.41 (1H, s), 8.72 (1H, s)
MS (ESI): M+ 294

Example 1-59

[0408] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.08-2.15 (2H, m), 2.69 (2H, t, J=7. 8Hz), 4.16 (2H, s), 4.57(2H, t, J=7. 3Hz), 7.15-7. 31 (10H, m), 7.81(1H, dd, J=2.0, 8.8Hz), 7.92(1H, d, J=8.8Hz), 8.20(1H, d, J=1.9Hz), 8.96 (1H, s), 15.21 (1H, brs)
MS (ESI): M+ 398

Example 1-60

[0409] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.11 (2H, t, J=7.3Hz), 4.18 (2H, s), 4.77(2H, t, J=7.4Hz), 7.19-7.35 (10H, m), 7.86 (1H, d, J=8.7Hz), 8.06 (1H, d, J=8.8Hz), 8.22 (1H, s), 8.76 (1H, s), 15.14 (1H, brs)
MS (ESI) : M+ 384

Example 1-61

[0410] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.99-2.03(2H, m), 2.37(2H, t, J=7.1Hz), 4.17(2H, s), 4.54(2H, t, J=7.3Hz), 7.21-7.34 (5H, m), 7.87 (1H, dd, J=2.0, 8.8Hz), 8.05 (1H, d, J=8.8Hz), 8.21 (1H, d, J=1.9Hz), 8.98 (1H, s), 12.01 (1H, brs), 15.28 (1H, brs)
MS (ESI): M+ 366

Example 1-62

[0411] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.15 (2H, s), 5.48 (2H, s), 7.06-7.10(1H, m), 7.20-7.22(1H, m), 7.28-7.34(6H, m), 7.56-7.58(2H, m), 7.74 (1H, d, J=8.8Hz), 7.848.9Hz), 8.23 (1H, s), 9.10(1H, s), 10.63(1H, brs), 15.18 (1H, brs)
MS (ESI): M+ 413

Example 1-63

[0412] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.72 (2H, m), 4.26 (2H, s), 4.35 (2H, m), 5.23 (1H, br), 7.32-7.41 (2H, m), 7.53-7.58 (2H, m), 7.72 (1H, m), 8.05 (1H, s), 8.63 (1H, s)
MS (ESI): M+391

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Example 1-64

[0413] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.72 (2H, m), 4.23 (2H, s), 4.35 (2H, m), 5.24 (1H, br), 7.25-7.40 (3H, m), 7.57 (1H, m), 7.72 (1H, m), 8.03 (1H, s), 8.63 (1H, s)
MS (ESI): M+375

Example 1-65

[0414] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.12 (2H, t, J= 7.3 Hz), 4.31 (2H, s), 4.78 (2H, t, J= 7.3 Hz), 7.20-7.36 (7H, m), 7.46-7.48 (2H, m), 7.86 (1H, m), 8.09 (1H, m), 8.15 (1H, s), 8.78 (1H, s), 15.08 (1H, brs)
MS (ESI): M+417

Example 1-66

[0415] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.79 (2H, m), 4.39 (2H, s), 4.65 (2H, m), 5.04 (1H, m), 7.31-7.47 (3H, m), 7.88 (1H, m), 8.07 (1H, m), 8.19 (1H, m), 8.90 (1H, s), 15.25 (1H, s) MS (ESI): M+375

Example 1-67

[0416] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.74 (2H, m), 4.35 (2H, s), 4.62 (2H, m), 5.00 (1H, br), 7.62 (1H, m), 7.81 (1H, m), 7.90 (1H, m), 8.02-8.13 (2H, m), 8.23 (1H, m), 8.32 (1H, m), 8.87 (1H, s)
MS (ESI): M+368

Example 1-68

[0417] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.09 (3H, s), 4.35 (2H, s), 5. 75 (2H, s), 7.37 (1H, m), 7.44 (1H, m), 7.55 (1H, m), 7.83 (1H, m), 8.01 (1H, m), 8.12 (1H, m), 9.10 (1H, s)
MS (ESI) : M+407

Example 1-69

[0418] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.20 (3H, s), 4.36 (2H, s), 6.22 (2H, s), 7.36-7.47 (2H, m), 7.58. (1H, m), 7.86 (1H, m), 8.12-8.15 (2H, m), 9.04 (1H, s)
MS (ESI): M+439

Example 1-70

[0419] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.22 (9H, s), 4.36 (2H, s), 5.99 (2H, s), 7.35-7.46 (3H, m), 7. 58 (1H, m), 7.84 (1H, m), 8.08-8.11 (2H, m), 8.95 (1H, s), 14.75 (1H, br)
MS (ESI): M+496

Example 1-71

[0420] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.62 (3H, d, J= 4.7 Hz), 4.36 (2H, s), 6.11 (2H, s), 7.36-7.47 (2H, m), 7.54-7.60 (2H, m), 7.84 (1H, m), 8.10-8.13 (2H, m), 8.98 (1H, s), 14.79 (1H, br)
MS (ESI): M+454

Example 1-72

[0421] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.77 (6H, s), 4.37 (2H, s), 6.20 (2H, s), 7.39 (1H, dd, J= 7.8, 7.8 Hz), 7.47 (1H, dd, J= 1.7, 7.8 Hz), 7.59 (1H, dd, J= 1.7, 7.8 Hz), 7.89 (1H, m), 8.11-8.14 (2H, m), 9.04 (1H, s), 14.69 (1H, br)
MS (ESI) : M+468

Example 1-73

[0422] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, br), 4.36 (2H, s), 4.60 (2H, m), 5.00 (1H, br), 7.39-7.49 (2H, m), 7.82 (1H, m), 8.04 (1H, m), 8.11 (1H, s), 8.87 (1H, s), 15.14 (1H, brs)
MS (ESI): M+393

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Example 1-74

[0423] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.41 (1H, m), 3.51 (1H, m), 3.82 (1H, m), 4.26 (1H, m), 4.36 (2H, s), 4.79 (1H, m), 4.93 (1H, m), 5.19 (1H, m), 7.38 (1H, m), 7.46 (1H, m), 7.58 (1H, m), 7.84 (1H, m), 7.97 (1H, m), 8.15 (1H, m), 8.84 (1H, s)
MS (ESI): M+421

Example 1-75

[0424] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.32 (2H, s), 5.98 (2H, s), 7.31-7.43 (5H, m), 7.80 (1H, m), 8.06 (1H, m), 8.12 (1H, m), 8.99 (1H, m), 14.81 (1H, brs)
MS (ESI): M+424

Example 1-76

[0425] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.62 (3H, d, J= 4.4 Hz), 4.32 (2H, s), 6.11 (2H, s), 7.30-7.43 (3H, m), 7.53 (1H, q, J= 4.4 Hz), 7.84 (1H, m), 8.06 (1H, s), 8.12 (1H, m), 8.98 (1H, m), 14.74 (1H, s)
MS (ESI): M+438

Example 1-77

[0426] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.77 (6H, s), 4.33 (2H, s), 6.19 (2H, s), 7.27-7.44 (3H, m), 7.89 (1H, m), 8.06-8.14 (2H, m), 9.03 (1H, s), 14.64 (1H, s)
MS (ESI): M+452

Example 1-78

[0427] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.74 (2H, dt, J= 4.8, 5.6 Hz), 4. 17 (2H, s), 4.60 (2H, t, J= 4. 8 Hz), 4.99 (1H, t, J= 5. 6 Hz), 7.20-7.32 (5H, m), 7.82 (1H, m), 7.99 (1H, m), 8.21 (1H, m), 8.84 (1H, s), 15.27 (1H, s)
MS (ESI): M+323

Example 1-79

[0428] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.34 (3H, s), 3.75 (2H, br), 4.30 (2H, s), 4.61 (2H, t, J= 4.7 Hz), 5.00 (1H, br), 7.21-7.31 (3H, m), 7.81 (1H, dd, J= 2.0, 8.9 Hz), 8.01 (1H, d, J= 8.9 Hz), 8.15 (1H, d, J= 2.0 Hz), 8.86 (1H, s), 15.23 (1H, s)
MS (ESI): M+371

Example 1-80

[0429] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.76 (2H, m), 4.31 (2H, s), 4.61 (2H, m), 5.01 (1H, m), 7.23 1H, m), 7.36-7.47 (2H, m), 7.65 (1H, m), 7.81 (1H, m), 8.02 (1H, m), 8.14 (1H, m), 8.86 (1H, s)
MS (ESI): M+401

Example 1-81

[0430] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.26 (3H, s), 3.75 (2H, m), 4.12 (2H, s), 4.60 (2H, m), 4.99 (1H, m), 7.10-7.18 (4H, m), 7.80 (1H, m), 7.99 (1H, m), 8.20 (1H, m), 8.85 (1H, s), 15.29 (1H, s)
MS (ESI): M+337

Example 1-82

[0431] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.73 (2H, dt, J= 4.8, 5.2 Hz), 3.84 (3H, s), 4.28 (2H, s), 4.60 (2H, t, J= 4.8 Hz), 5.00 (1H, t, J= 5.2 Hz), 7.04-7.07 (2H, m), 7.30 (1H, m), 7.79 (1H, m), 8.00 (1H, m), 8.11 (1H, m), 8.84 (1H, s), 15.22 (1H, s)
MS (ESI): M+387

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Example 1-83

[0432] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.75 (2H, m), 4.50 (2H, s), 4.62 (2H, m), 7.60-8.15 (5H, m), 8.35 (1H, s), 8.68 (1H, m), 8.87 (1H, s), 15.25 (1H, br)
MS (ESI): M+324

Example 1-84

[0433] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.33 (2H, s), 4.62 (2H, m), 7.57 (2H, d, J= 6.3 Hz), 7.89 (1H, dd, J= 2.1, 8.7 Hz), 8.07 (1H, d, J= 8.7 Hz), 8.32 (1H, d, J= 2.1 Hz), 8.62 (1H, d, J= 6.3 Hz), 8.88 (2H, s)
MS (ESI): M+324

Example 1-85

[0434] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.21 (3H, s), 3.77 (2H, m), 4.61 (2H, m), 4.66 (2H, s), 5.02 (1H, m), 7.38 (1H, m), 7.55 (1H, m), 7.68 (1H, m), 7.81 (1H, m), 8.00-8.05 (2H, m), 8.19 (1H, m), 8.87 (1H, s)
MS (ESI): M+401

Example 1-86

[0435] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.73 (2H, m), 4.15 (2H, s), 4.58 (2H, m), 5.00 (1H, m), 7.23-7.50 (10H, m), 7.88-7.92 (2H, m), 8.83 (1H, s)
MS (ESI): M+399

Example 1-87

[0436] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.30 (2H, s), 4.61 (2H, m), 5.00 (1H, br), 7.26-7.38 (2H, m), 7.43-7.49 (2H, m), 7.82 (1H, m), 8.02 (1H, m), 8.14 (1H, m), 8.86 (1H, s), 15.32 (1H, s)
MS (ESI): M+357

Example 1-88

[0437] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.74 (2H, m), 4.25 (2H, s), 4.60 (2H, m), 4.98 (1H, br), 7.25-7.53 (6H, m), 7.59-7.66 (3H, m), 7.87 (1H, m), 8.10 (1H, m), 8.29 (1H, m), 8.85 (1H, s), 15.30 (1H, s)
MS (ESI): M+399

Example 1-89

[0438] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.79 (2H, m), 4.33 (2H, s), 4.64 (2H, m), 5.03 (1H, m), 7.57-7.65 (3H, m), 7.76 (1H, m), 7.91 (1H,m), 8.06 (1H, m), 8.32 (1H, m), 8.90 (1H, s), 15.31 (1H, s)
MS (ESI): M+391

Example 1-90

[0439] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.30 (3H, t, J= 6.8 Hz), 3.74 (2H, m), 3.98 (2H, q, J= 6.8 Hz), 4.12 (2H, s), 4.60 (2H, m), 5.01 (1H, m), 6.76 (1H, m), 6.82-6.84 (2H, m), 7.20 (1H, m), 7.82 (1H, m), 7.99 (1H, m), 8.22 (1H, m), 8.85 (1H, s)
MS (ESI): M+367

Example 1-91

[0440] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.25 (2H, s), 4.61 (2H, m), 7.53 (1H, m), 7.66-7.71 (2H, m), 7.83-7.89 (2H, m), 8.02 (1H, m), 8.28 (1H, m), 8.87 (1H, s)
MS (ESI): M+348

Example 1-92

[0441] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.48 (3H, m), 3.74 (2H, m), 4.26 (2H, s), 4.61 (2H, m), 5.09 (1H, br),

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7.19 (1H, m), 7.39 (2H, m), 7. 82 (1H, m), 8. 04 (1H, m), 8.13 (1H, s), 8. 85 (1H, s), 15.22 (1H, s)
MS (ESI): M+403

Example 1-93

[0442] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.24 (2H, s), 4.61 (2H, m), 5.02 (1H, br), 7.38-7.47 (4H, m), 7.80 (1H, m), 8.03 (1H, m), 8.16 (1H, m), 8.86 (1H, s), 15.23 (1H, s)
MS (ESI): M+407

Example 1-94

[0443] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.76 (2H, m), 3.99 (2H, s), 4.61 (2H, m), 5.01 (3H, m), 6.41 (3H, m), 6.93 (1H, m), 7.78 (1H, m), 8.00 (1H, m), 8.20 (1H, m), 8.86 (1H, s)
MS (ESI): M+338

Example 1-95

[0444] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.00 (3H, s), 3.76 (2H, m), 4.13 (2H, s), 4.61 (2H, m), 5.01 (1H, m), 6.98 (1H, m), 7.23 (1H, m), 7.43 (2H, m), 7.81 (1H, m), 8.01 (1H, m), 8.21 (1H, m), 8.86 (1H, s), 9.87 (1H, s)
MS (ESI): M+380

Example 1-96

[0445] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.73 (2H, m), 4.18 (2H, s), 4.59 (2H, m), 4.98 (1H, br), 7.26 (1H, s), 7.29 (1H, m), 7.39 (1H, m), 7.53 (1H, m), 7.99 (1H, s), 8.24 (1H, m), 8.85 (1H, s), 15.25 (1H, s)
MS (ESI) : M+401

Example 1-97

[0446] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.28 (3H, s), 3.75 (2H, m), 4.25 (2H, s), 4.61 (2H, m), 5.04 (1H, br), 7.13 (1H, s), 7.29-7.36 (2H, m), 7.81 (1H, m), 8.03 (1H, m), 8.13 (1H, s), 8.86 (1H, s), 15.24 (1H, s)
MS (ESI): M+371

Example 1-98

[0447] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.59 (6H, s), 3.75 (2H, m), 4.33 (2H, s), 4.61 (2H, m), 5.00 (1H, m), 7.59-7.64 (3H, m), 7.73 (1H, m), 7.87 (1H, m), 8.03 (1H, m), 8.27 (1H, s), 8.86 (1H, s), 15.27 (1H, s)
MS (ESI): M+430

Example 1-99

[0448] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.26 (2H, s), 4.61 (2H, m), 5.00 (1H, br), 7.21 (1H, m), 7.38-7.51 (2H, m), 7.83 (1H, m), 8.03 (1H, m), 8.22 (1H, s), 8.87 (1H, s)
MS (ESI): M+375

Example 1-100

[0449] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.76 (2H, m), 4.26 (2H, s), 4.61 (2H, m), 4.99 (1H, m), 7.25 (1H, m), 7.61 (1H, m), 7.81 (1H, m), 8.04 (1H, m), 8.16 (1H, m), 8.87 (1H, s), 15.16 (1H, s)
MS (ESI): M+393

Example 1-101

[0450] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.79 (2H, m), 4.01 (3H, s), 4.19(2H, s), 4.64-4.65(2H, m), 5.02 (1H, t, J=5.5Hz), 7.25 (1H, d, J=1.6Hz), 7.31-7.35(2H, m), 7.56-7.58(1H, m), 7.82(1H, s), 8.78(1H, s), 15.38(1H, brs)
MS (ESI) : M+ 422

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Example 1-102

[0451] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.19 (2H, m), 1. 30 (2H, m), 3.83 (1H, m), 4.37 (2H, s), 7.38 (1H, m), 7.46 (1H, m), 7.57 (1H, m), 7.89 (1H, m), 8.12 (1H, m), 8.24 (1H, m), 8.73 (1H, s), 15.05 (1H, s)
MS (ESI): M+387

Example 2-1

[0452] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4:37 (2H, s), 6.88 (2H, brs), 7.35-7.47 (2H, m), 7.58 (1H, m), 7.87 (1H, dd, J= 2.1, 8.9 Hz), 8.0.8 (1H, d, J= 2.1 Hz), 8.16 (1H, d, J= 8.9 Hz), 8.86 (1H, s), 15.24 (1H, brs)
MS (ESI): M+362

Example 2-2

[0453] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.75 (3H, brs), 4.36 (2H, s), 7.35 (1H, m), 7.42 (1H, m), 7.54 (1H, m), 7.72 (1H, m), 7.85 (1H, m), 8.10 (1H, s), 9.03 (1H, s), 11.61 (1H, brs)
MS (ESI): M+420

Example 2-3

[0454] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.16(3H, s), 4.36 (2H, s), 7.35-7.45(2H, m), 7.58(1H, dd, J=1.8, 7.8Hz), 7.76-7.85(2H, m), 8.10 (1H, s), 8.96 (1H, s), 12.02(1H, brs), 14.77(1H, brs)
MS (ESI): M+ 405

Example 2-4

[0455] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: -3.32 (3H, s), 4.37 (2H, s), 7.38 (1H, m), 7.46 (1H, m), 7.58 (1H, m), 7.86 (1H, m), 8.06-8.10 (2H, m), 8.82 (1H, s), 14.60 (1H, br)
MS (ESI): M+440

Example 2-5

[0456] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.46 (3H, s), 3.53 (3H, s), 4.37 (2H, s), 7.38 (1H, dd, J= 7.8, 7.8 Hz), 7.47 (1H, dd, J= 2.1, 7.8 Hz), 7.58 (1H, dd, J= 2.1, 7.8 Hz), 7.88 (1H, dd, J= 1.8, 8.7 Hz), 7.97 (1H, d, J= 8.7 Hz), 8.12 (1H, d, J= 1.8 Hz), 9.11 (1H, s), 15.54 (1H, brs)
MS (ESI): M+454

Example 2-6

[0457] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.96 (6H, s), 4.36 (2H, s), 7.38 (1H, dd, J= 7.8, 7.8 Hz), 7.46 (1H, dd, J= 2.0, 7.8 Hz), 7.57 (1H, dd, J=.2.0, 7.8 Hz), 7.86 (1H, dd, J= 2.2, 8.8 Hz), 8.12 (1H, d, J= 2.2 Hz), 8.25 (1H, d, J= 8.8 Hz), 9.25 (1H, s), 15.14 (1H, brs)
MS (ESI): M+390

Example 2-7

[0458] ^{1}H NMR (DMSO-d_6 400MHz) (5) ppm: 2.84 (3H, d), 4.35 (2H, s), 7.19 (1H, q), 7.38 (1H, m), 7.45 (1H, m), 7.55 (1H, m), 7.85 (1H, m), 8.09-8.11 (2H, m), 8.99 (1H, m)
MS (ESI): M+376

Example 2-8

[0459] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.09 (3H, t, J= 7.1 Hz), 3.13 (2H, dq, J= 6.1, 7.1 Hz), 4.36 (2H, s), 7.19 (1H, t, J= 6.1 Hz), 7.38 (1H, dd, J= 7.7, 7.7 Hz), 7.46 (1H, dd, J= 1.7, 7.7 Hz), 7.58 (1H, dd, J= 1.7, 7.8 Hz), 7.85 (1H, dd, J= 2.1, 8.8 Hz), 8.10 (1H, d, J= 2.1 Hz), 8.15 (1H, d, J= 8.8 Hz), 8.99 (1H, s), 15.14 (1H, brs)
MS (ESI): M+390

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Example 3-1

[0460] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 3.79 (3H, s), 4.28 (2H, s), 4.57 (2H, m), 5.02 (1H, m), 7.17 (1H, m), 7.32 (1H, m), 7.57 (2H, m), 7.76 (1H, m), 8.83 (1H, m), 15.75 (1H, s)
MS (ESI): M+421

Example 3-2

[0461] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.24 (3H, s), 3.77 (2H, dd, J= 5.2, 5.6Hz), 4.27 (2H, s), 4.61 (2H, t, J= 5.2Hz), 5.05 (1H, t, J= 5. 6Hz), 7.23 (2H, m), 7.34 (1H, m), 7.76 (1H, m), 8.03 (1H, m), 8.08 (1H, m), 8.86 (1H, s), 15.23 (1H, s)
MS (ESI): M+371

Example 3-3

[0462] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.73 (5H, s), 4.21 (2H, s), 4.61 (2H, t, J= 4.8Hz), 5.01 (1H, t, J= 5.2Hz), 5.02 (1H, m), 7.12 (1H, m), 7.25 (1H, m), 7.37 (1H, m), 7.81 (1H, m), 8.01 (1H, m), 8.19 (1H, m), 8.86 (1H, s), 15.26 (1H, s)
MS (ESI): M+387

Example 3-4

[0463] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.80 (2H, m), 4.01 (3H, s), 4.12 (2H, s), 4.65 (2H, m), 5.02 (1H, m), 7.17-7.50 (4H, m), 8.03 (1H, s), 8.81 (1H, s), 15.45 (1H, s)
MS (ESI): M+405

Example 3-5

[0464] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.74 (2H, t), 4.17 (2H, s), 4.56 (2H, t), 5.02 (1H, br), 7.20 (1H, m),7.31 (1H, m), 7.38 (1H, m), 7.52-7.56 (2H, m), 8.86 (1H, s), 13.63 (1H, s)
MS (ESI): M+407

Example 3-6

[0465] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.78 (2H, t), 4.18 (2H, s), 4.44-4.49 (2H, m), 5.08 (1H, t), 7.20-7.25 (2H, m), 7.34-7.40 (1H, m), 7.56 (1H, d), 7.82 (1H, s), 8.77 (1H, s), 11.10-11.30 (1H, br), 15.49 (1H, s)
MS (ESI): M+ 408

Example 3-7

[0466] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.68 (3H, d, J=4.4Hz), 3.74 (2H, t, J=4.8Hz), 4.04 (2H, s), 4.60 (2H, t, J=4.8Hz), 5.01 (1H, t), 5.27 (1H, q, J=5.2Hz), 6.51-6.56 (2H, m), 6.95 (1H, d), 7.07-7.09 (1H, m), 7.78 (1H, d, J=9.2Hz), 7.98 (1H, d, J=8.8Hz), 8.21 (1H, s), 8.84 (1H, s), 15.33 (1H, s)
MS (ESI): M+ 353

Example 3-8

[0467] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.62 (6H, s), 3.74 (2H, t), 4.24 (2H, s), 4.60 (2H, t, J=4.8Hz), 5.01 (1H, t), 6.97-7.05 (2H, m), 7.21 (2H, m), 7.77 (1H, d, J=11.2Hz), 7.97 (1H, d), 8.16 (1H, s), 8.85 (1H, s), 15.29 (1H, s)
MS (ESI): M+ 367

Example 3-9

[0468] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 4.35 (2H, s), 7.11 (1H, d, J=8. 8Hz), 7.37-7.40 (1H, m), 7.44 (1H, d), 7.56 (1H, d), 7.69-7.74 (6H, m), 8.19 (1H, s), 8.68 (1H, s), 14.99 (1H, s)
MS (ESI): M+ 424

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Example 3-10

[0469] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.84-3.95 (4H, m), 4.36 (2H, s), 5.11-5.19 (3H, m), 7.38 (1H, m), 7.45 (1H, d), 7.57 (1H, d), 7.82 (1H, d, J=9.2Hz), 8.15 (1H, d, J=8.8Hz), 8.90 (1H, s), 15.21 (1H, s)
MS (ESI): M+ 422

Example 3-11

[0470] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.76 (2H, t), 4.05 (2H, s), 4.59 (2H, t), 5.00 (1H, t), 6.61 (1H, d), 6.64 (1H, s), 6.70 (1H, d, J=8.0Hz), 7.09-7.11 (1H, m), 7.81 (1H, d, J=8.8Hz), 8.00 (1H, d, J=8.8Hz), 8.21 (1H, s), 8.86 (1H, s), 9.30 (1H, s), 15.30 (1H, s)
MS (ESI): M+ 340

Example 3-12

[0471] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1. 80-1.90 (2H, m), 2.45-2.50 (2H, m), 2.60-2.70 (2H, m), 4.36 (2H, s), 5.11-5.16 (1H, m), 7.38-7.40 (1H, m), 7.45 (1H, d), 7.57 (1H, d), 7.81 (1H, d, J=8.8Hz), 7.93 (1H, d), 8.14 (1H, s), 8.68 (1H, s), 15.16 (1H, s)
MS (ESI): M+ 402

Example 3-13

[0472] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.70-1.90 (4H, m), 1.91-2.00 (2H, m), 2.20-2.30 (2H, m), 4.37 (2H, s), 5.20-5.30 (1H, m), 7.38-7.40 (1H, m), 7.45 (1H, d), 7.57 (1H, d), 7.86 (1H, d), 8.16 (1H, d), 8.19 (1H, s), 8.75 (1H, s), 15. 16 (1H, s)
MS (ESI): M+ 416

Example 3-14

[0473] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.70-3.80 (2H, m), 3.96 (3H, s), 4.32 (2H, s), 4.81 (2H, t), 4.90 (1H, t), 7.35-7.43 (2H, m), 7.54-7.59 (2H, m), 7.69 (1H, s), 8.69 (1H, s),15.16 (1H, s)
MS (ESI): M+ 422

Example 3-15

[0474] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.88 (3H, s), 2.95 (3H, s), 3.70-3.80 (2H, m), 4.21 (2H, s), 4.61 (2H, t), 4.99 (1H, t), 7.20-7.23 (1H, m), 7.33 (1H, s), 7.37-7.38 (2H, dx2), 7. 86 (1H, d), 8.02 (1H, d, J=8. 8Hz), 8.26 (1H, s), 8.86 (1H, s), 15.30 (1H, s)
MS (ESI): M+ 395

Example 3-16

[0475] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.71 (6H, s), 3.70-3.76 (2H, m), 4.58 (2H, s), 4.60 (2H, t, J=5.2Hz), 5.02 (1H, t), 7.42 (1H, d), 7.51 (1H, m), 7.64 (1H, m), 7.80 (1H, d), 7.84 (1H, d), 8.01 (1H, d, J=8.8Hz), 8.11 (1H, s), 8.86 (1H, s), 15.25 (1H, s)
MS (ESI): M+ 431

Example 3-17

[0476] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.73-3.75 (2H, m), 4.24 (2H, s), 4.61 (2H, t), 5.00 (1H, t, J=5.6Hz), 7.31 (1H, m), 7.48-7.51 (1H, m), 7.84 (1H, d), 8.02 (1H, d), 8.21 (1H, s), 8.87 (1H, s), 15.22 (1H, s)
MS (ESI) : M+ 394

Example 3-18

[0477] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.70-3.80 (2H, m), 4.56 (2H, s), 4.60 (2H, t), 5.00 (1H, t), 7.38-7.43 (2H, m), 7.52-7.54 (1H, m), 7.78 (1H, d), 7.87 (1H, d, J=7.8Hz), 7.98 (1H, d, J=8.9Hz), 8.11 (1H, s), 8.84 (1H, s), 12.60-13.00 (1H, br), 15.29 (1H, s)

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MS (ESI): M+ 368

Example 3-19

[0478] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.74-3.77 (2H, m), 4.58 (2H, s), 4.61 (2H, t), 5.02 (1H, t, J=5.6Hz), 7.29 (1H, d), 7.46 (1H, m), 7.56 (1H, m), 7.70 (1H, m), 7.81 (1H, d), 7.87 (1H, d), 8.01 (1H, s), 8.18 (1H, s), 8.86 (1H, s), 15.27 (1H, s)
MS (ESI): M+ 417

Example 3-20

[0479] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.37 (3H, t, J=6.9Hz), 3.70-3.80 (2H, m), 4.22 (2H, s), 4.28 (2H, q, J=6.9Hz), 4.65 (2H, t), 5.00 (1H, t), 7.30-7.34 (3H, m), 7.60 (1H, d), 7.92 (1H, s), 8.80 (1H, s), 15.44 (1H, s)
MS (ESI): M+ 436

Example 3-21

[0480] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.76 (2H, m), 4.40 (2H, s), 4.63 (2H, t, J=5.1Hz), 5.02 (1H, t, J=5.6Hz), 7.20 (1H, d, J=6.3Hz), 7.35-7.39 (1H, m), 7.62 (1H, d, J=6.3Hz), 8.00 (1H, s), 8.32 (1H, s), 8.89 (1H, s), 15.87 (1H, s)
MS (ESI): M+ 426

Example 3-22

[0481] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.80 (2H, t, J=5.3Hz), 4.48 (2H, s), 4.75 (2H, t, J=4.6Hz), 5.06 (1H, t, J=5.6Hz), 7.24 (1H, d, J=6.3Hz), 7.39-7.42 (1H, m), 7.65 (1H, d, J=6.7Hz), 7.95 (1H, s), 8.40 (1H, s), 9.00 (1H, s), 14.62 (1H, s)
MS (ESI): M+ 460

Example 3-23

[0482] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.53 (3H, d, J=6.4Hz), 3.76-3.83 (2H, m), 4.26 (2H, s), 5.19-5.23 (2H, m), 7.20-7.22 (1H, m), 7.41-7.49 (2H, m), 7.86 (1H, d), 8.17 (1H, d, J=8.8Hz), 8.24 (1H, s), 8.88 (1H, s)
MS (ESI) : M+ 390

Example 3-24

[0483] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.53 (3H, d, J=6.8Hz), 3.76-3.82 (2H, m), 4.26 (2H, s), 5.19-5.23 (2H, m), 7.22-7.24 (1H, m), 7.41-7.49 (2H, m), 7.86 (1H, d), 8.17 (1H, d, J=9.2Hz), 8.24 (1H, s), 8.88 (1H, s)
MS (ESI): M+ 390

Example 3-25

[0484] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.40-3.50 (2H, m), 4.34 (2H, s), 4.57 (2H, t), 4.89 (1H, t), 7.24-7.27 (1H, m), 7.45-7.51 (2H, m), 8.35 (1H, s), 8.45 (1H, s), 9.00 (1H, s), 14.30-14.40 (1H, br)
MS (ESI): M+ 444

Example 3-26

[0485] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.84-3.96 (4H, m), 4.26 (2H, s), 5.13-5.18 (3H, m); 7.19-7.21 (1H, m), 7.40-7.48 (2H, m), 7.84 (1H, d, J=9.2Hz), 8.15 (1H, d, J=8.8Hz), 8.23 (1H, s), 8.90 (1H, s), 15.24 (1H, s)
MS (ESI): M+ 406

Example 3-27

[0486] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.77 (2H, t, J=5.2Hz), 4.53 (2H, s), 4.68 (2H, t, J=4.8Hz), 5.01 (1H, t, J=5.6Hz), 7.32 (1H, d, J=6.0Hz), 7.39-7.43 (1H, m), 7.64 (1H, d, J=6.4Hz), 8.07 (1H, s), 8.79 (1H, s), 8.96 (1H, s), 14.61 (1H, s)
MS (ESI): M+ 417

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Example 3-28

[0487] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.97 (3H, t, J=7.2Hz), 2.58 (3H, s), 2.84 (2H, q, J=7.2Hz), 3.77 (2H, t), 4.21 (2H, s), 4.60 (2H, t), 5.00 (1H, t), 7.00-7.02 (1H, m), 7.12 (1H, d), 7.20-7.24 (2H, m), 7.78 (1H, d, J=8.8Hz), 7.98 (1H, d, J=8.8Hz), 8.17 (1H, s), 8.84 (1H, s), 15.31 (1H, s)
MS (ESI) : M+381

Example 3-29

[0488] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.78 (3H, t, J=7.2Hz), 1.42 (2H, m), 2.56 (3H, s), 2.76 (2H, t, J=6.8Hz), 3.74 (2H, t), 4.23 (2H, s), 4.60 (2H, t, J=4. 8Hz), 5.02 (1H, t, J=5.6Hz), 7.00-7.03 (1H, m), 7.09 (1H, d), 7.20-7.21 (2H, m), 7.77 (1H, d, J=9.2Hz), 7.99 (1H, d, J=8.8Hz), 8.15 (1H, s), 8.85 (1H, s), 15.30 (1H, s)
MS (ESI): M+395

Example 3-30

[0489] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.52 (3H, s), 3.77 (2H, t, J=4.8Hz), 4.01 (2H, s), 4.30 (2H, s), 4.61 (2H, t), 4.90-5.10 (1H, br), 7.03-7.09 (2H, m), 7.20-7.26 (7H, m), 7.76 (1H, d), 7.98 (1H, d), 8.17 (1H, s), 8.85 (1H, s), 15.30 (1H, s)
MS (ESI): M+443

Example 3-31

[0490] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.94 (3H, s), 3.09 (3H, s), 3.75 (2H, m), 4.13-4.18 (1H, m), 4.44-4.48 (1H, m), 4.61 (2H, t), 5.02 (1H, t, J=5.6Hz), 7.33-7.37 (3H, m), 7.52 (1H, d, J=9.2Hz), 7.81 (1H, d), 8.01 (1H, d, J=8.8Hz), 8.15 (1H, s), 8.86 (1H, s), 15.27 (1H, s)
MS (ESI) : M+431

Example 3-32

[0491] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.01 (6H, d), 2.52 (3H, s), 3.12-3.19 (1H, m), 3.73-3.75 (2H, m), 4.20 (2H, s), 4.60 (2H, t), 5.02 (1H, t), 7.00-7.02 (1H, m), 7.11 (1H, d), 7.19-7.22 (2H, m), 7.77 (1H, d, J=8.8Hz), 7.98 (1H, d, J=9.2Hz), 8.18 (1H, s), 8.84 (1H, s), 15.31 (1H, s)
MS (ESI): M+395

Example 3-33

[0492] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.86 (9H, s), 4.26 (2H, s), 7.22-7.24 (1H, m), 7.42-7.49 (2H, m), 7.79 (1H, d, J=9.2Hz), 8.28 (1H, s), 8.39 (1H, d, J=8. 8Hz), 8.98 (1H, s), 15.16 (1H, s)
MS (ESI): M+388

Example 3-34

[0493] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.71 (2H, m), 3.96 (3H, s), 4.21 (2H, s), 4.81 (2H, t), 4.89 (1H, t), 7.19-7.24 (1H, m), 7.40-7.52 (3H, m), 7.77 (1H, s), 8.68 (1H, s), 15.17 (1H, s)
MS (ESI): M+406

Example 3-35

[0494] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.09 (2H, s), 4.83 (2H, t), 5.33 (1H, t), 5.81 (2H, s), 7.15 (1H, s), 7.15-7.24 (1H, m), 7.36 (1H, m), 7.48 (1H, m), 7.57 (1H, s), 8.77 (1H, s), 15.37 (1H, s)
MS (ESI) : M+391

Example 3-36

[0495] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3:79 (2H, t), 4.60 (2H, s), 4.68 (2H, t), 5.05 (1H, t), 7.11 (1H, d, J=6.0Hz), 7.30-7.34 (1H, m), 7.57 (1H, d, J=6.8Hz), 8.02 (1H, s), 8.38 (1H, s), 8.95 (1H, s), 13.60-14.00 (1H, br), 14.88 (1H, s)
MS (ESI): M+436

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Example 3-37

[0496] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.70-3.72 (2H, m), 4.98 (3H, s), 4.23 (2H, s), 4.81 (2H, t), 4.89 (1H, t), 7.20-7.26 (1H, m), 7.50 (1H, s), 7.62-7.67 (2H, m), 8.68 (1H, s), 15.10 (1H, s)
MS (ESI): M+424

Example 3-38

[0497] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.67 (6H, s), 3.39 (2H, m), 4.21 (2H, s), 4.72 (1H, t), 4.97 (2H, t), 7.20-7.22 (1H, m), 7.40-7.50 (2H, m), 7.65 (1H, s), 7.84 (1H, s), 15.10 (1H, s)
MS (ESI): M+419

Example 3-39

[0498] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.10 (3H, s), 4.50-4.60 (2H, m), 4.23 (2H, s), 4.65 (2H, t), 5.00 (1H, t), 7.20-7.30 (1H, m), 7.40-7.50 (2H, m), 7.65 (1H, s), 8.20 (1H, s), 8.83 (1H, s), 10.20 (1H, s), 15.00 (1H, s)
MS (ESI): M+433

Example 3-40

[0499] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.74-3.75 (2H, m), 4.55 (2H, s), 4.65 (2H, t), 5.00 (1H, t), 7.17 (1H, d, J=6.3Hz), 7.34-7.39 (1H, m), 7.62 (1H, d, J=6.6Hz), 7.73 (1H, d, J=9.3Hz), 8.34 (1H, d, J=9.3Hz), 8.97 (1H, s), 14.62 (1H, s)
MS (ESI): M+417

Example 3-41

[0500] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.45 (3H, s), 2.97 (3H, s), 3.74-3.76 (2H, m), 4.12 (2H, s), 4.61 (2H, m), 5.03 (1H, t, J=5.6Hz), 7.24-7.30 (1H, m), 7.3.0-7.39 (3H, m), 7.76 (1H, d), 8.01 (1H, d, J=8.8Hz), 8.13 (1H, s), 8.87 (1H, s), 15.23 (1H, s)
MS (ESI): M+ 395

Example 3-42

[0501] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.88 (6H, t, J=7.2Hz), 2.91 (4H, q, J=6.8Hz), 3.75 (2H, m), 4.23 (2H, s), 4.60 (2H, t), 5.02 (1H, t, J=5.6Hz), 7.00-7.06 (1H, m), 7.14-7.25 (3H, m), 7.77 (1H, d), 7.98 (1H, d, J=8.8Hz), 8.16 (1H, s), 8.84 (1H, s), 15.32 (1H, s)
MS (ESI): M+ 395

Example 3-43

[0502] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.78 (6H, s), 3.99 (2H, s), 4.25 (2H, s), 4.23 (2H, s), 5.52 (1H, br), 7.20-7.22 (1H, m), 7.42-7.49 (2H, m), 7.76 (1H, d, J=9.2Hz), 8.27 (1H, s), 8.34 (1H, d, J=9.2Hz), 9.05 (1H, s)
MS (ESI): M+ 404

Example 3-44

[0503] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.36 (3H, t, J=6.9Hz), 3.70-3.80 (2H, m), 4.12 (2H, s), 4.24 (2H, q, J=7.0Hz), 4.62 (2H, t), 5.00 (1H, t), 7.16-7.27 (3H, m), 7.40-7.50 (1H, m), 8.12 (1H, s), 8.80 (1H, s), 15.50 (1H, s)
MS (ESI): M+ 420

Example 3-45

[0504] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.70-3.80 (2H, m), 3.84 (3H, s), 3.85 (3H,s), 4.19 (2H, s), 4.75 (2H, t), 4.92 (1H, t, J=5.6Hz), 7.21-7.28 (2H, m), 7.45-7.50 (1H, m), 7.95 (1H, s), 8.75 (1H, s), 15.09 (1H, s)
MS (ESI) : M+ 436

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Example 3-46

[0505] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.62 (3H, s), 3.74 (2H, m), 4.02 (2H, s), 4.61 (2H, t), 5.01 (1H, t), 5.50-5.60 (1H, m), 6.30-6.43 (3H, m), 6.95-7.01 (1H, m), 7.82 (1H, d), 7.99 (1H, d, J=8.8Hz), 8.21 (1H, s), 8.85 (1H, s), 15.33 (1H, s)
MS (ESI): M+ 353

Example 3-47

[0506] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.42 (3H, t, J=6. 8Hz), 3.70-3.80 (2H, m), 4.20-4.23 (4H, m), 4.84-5.00 (3H, m), 7.20-7.30 (1H, m), 7.40-7.49 (3H, m), 7.77 (1H, s), 8.67 (1H, s)
MS (ESI): M+ 420

Example 3-48

[0507] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.78 (3H, s), 3.60-3.70 (2H, m), 4.16 (2H, s), 4.75-4.79 (2H, m), 5.38 (1H, t), 6.20-6.27 (1H, m), 7.07 (1H, s), 7.20-7.23 (1H, m), 7.39-7.49 (3H, m), 8.80 (1H, s), 15.32 (1H, s)
MS (ESI): M+ 405

Example 3-49

[0508] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.94 (3H, t, J=7.2Hz), 1.72-1.78 (2H, m), 3.77 (2H, m), 4.13-4.14 (4H, m), 4.62 (2H, t), 5.00 (1H, br), 7.12-7.18 (2H, m), 7.26 (1H, s), 7.44-7.46 (1H, m), 8.13 (1H, s), 8.79 (1H, s), 15.49 (1H, s)
MS (ESI): M+ 434

Example 3-50

[0509] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.00 (3H, s), 3.08 (3H, s), 3.75-3.77 (2H, m), 4.16 (2H, s), 4.57 (2H, t), 5.00 (1H, t, J=5.6Hz), 7.09-7.18 (2H, m), 7.24 (1H, s), 7.40-7.41 (1H, m), 7.85 (1H, s), 8.01 (1H, s), 8.72 (1H, s), 15.67 (1H, s)
MS (ESI): M+ 446

Example 3-51

[0510] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.72 (3H, s), 3.72-3.80 (2H, m), 3.95 (3H, s), 4.06 (2H, s), 4.40-4.50 (2H, m), 5.00 (1H, t), 7.12 (1H, s), 7.15-7.19 (2H, m), 7.40-7.45 (1H, m), 7.88 (1H, s), 8.51 (1H, s)
MS (ESI): M+ 420

Example 3-52

[0511] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.77 (2H, m), 4.17 (2H, s), 4.72 (2H, t, J=4.8Hz), 4.97 (1H, t, J=5.6Hz), 7.08 (2H, d, J=7.6Hz), 7.09-7.25 (2H, m), 7.31-7.36 (2H, m), 7.43-7.49 (3H, m), 8.04 (1H, s), 7.76 (1H, s), 15.02 (1H, s)
MS (ESI): M+ 468

Example 3-53

[0512] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.24 (6H, d, J=7.2Hz), 3.75 (2H, t), 4.08 (2H, s), 4.61 (2H, t), 4.99-5.04 (2H, m), 7.11-7.20 (2H, m), 7.28 (1H, s), 7.43-7.45 (1H, m), 8.17 (1H, s), 8.79 (1H, s), 15.52 (1H, s)
MS (ESI): M+ 434

Example 3-54

[0513] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.99 (3H, t, J=7.3Hz), 1.60-1.70 (2H, m), 3.00-3.10 (2H, m), 3.70-3.80 (2H, m), 4.15 (2H, s), 4.82 (2H, t), 5.50 (1H, t), 6.20 (1H, t), 7.08 (1H, s), 7.10-7.20 (1H, m), 7.40-7.51 (3H, m), 8.78 (1H, s), 15.30-15.40 (1H, br)
MS (ESI): M+ 433

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Example 3-55

[0514] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.24 (3H, t, J=6.9Hz), 3.08 (2H, m), 3.71-3.80 (2H, m), 4.15 (2H, s), 4.83 (2H, t), 5.43 (1H, t), 6.21 (1H, t), 7.10 (1H, s), 7.17-7.23 (1H, m), 7.36-7.52 (3H, m), 8.78 (1H, s).
MS (ESI): M+ 419.

Example 3-56

[0515] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1. 53 (3H, d, J=6.8Hz), 3. 72 (2H, m), 3.99 (3H, s), 4.21 (2H, s), 5.12 (1H, t), 5.70-5.90 (1H, m), 7.20-7.21 (1H, m), 7.40-7.55 (3H, m), 7.76 (1H, s), 8.85 (1H, s), 15.00-15.20 (1H, br)
MS (ESI): M+ 420

Example 3-57

[0516] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.52 (3H, d, J=6.8Hz), 3.71 (2H, t), 4.00 (3H, s), 4.23 (2H, s), 5.10 (1H, t), 5.80-5.90 (1H, m), 7.20-7.30 (1H, m), 7.51 (1H, s), 7.60-7.67 (2H, m), 8.85 (1H, s), 14.90-15.10 (1H, br)
MS (ESI): M+ 438

Example 3-58

[0517] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.03 (3H, d, J=8.4Hz), 1. 78-1.87 (2H, m), 3.73-3.75 (2H, m), 4.12 (2H, t), 4.20 (2H, s), 4.85 (2H, t), 4.92 (1H, t), 7.20 (1H, m), 7.39-7.51 (3H, m), 7.76 (1H, s), 8.68 (1H, s), 15.17 (1H, s)
MS (ESI): M+ 434

Example 3-59

[0518] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.35 (6H, s), 3.72-3.75 (2H, m), 4.20 (2H, s), 4.83-4.91 (4H, m), 7.20 (1H, m), 7.39-7.49 (3H, m), 7.74 (1H, s), 8.66 (1H, s), 15.18 (1H, s)
MS (ESI): M+ 434

Example 3-60

[0519] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.86 (3H, t, J=7.3Hz), 1. 80-2.10 (2H, m), 3.70-3.90 (2H, m), 4.26 (2H, s), 5.00-5.10 (1H, m), 5.17 (1H, t, J=5.4Hz), 7.19-7.24 (1H, m), 7.39-7.51 (2H, m), 7.84 (1H, d, J=8.8Hz), 8.20 (1H, d, J=8.8Hz), 8.23 (1H, s), 8.86 (1H, s), 15.24 (1H, s)
MS (ESI): M+ 404

Example 3-61

[0520] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.36 (3H, t, J=6.9Hz), 1.52 (3H, d, J=6.6Hz), 3.78-3.80 (2H,m), 4.12 (2H, s), 4.26 (2H, q, J=7.0Hz), 5.21-5.30 (2H, m), 7.16-7.24 (2H, m), 7.40-7.46 (2H, m), 8.14 (1H, s), 8.81 (1H, s), 15.40-15.60 (1H, br)
MS (ESI) : M+ 434

Example 3-62

[0521] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.88 (6H, s), 3.70-3.80 (2H, m), 4.22 (2H, s), 4.60-4.70 (2H, m), 5.05 (1H, t), 7.20-7.31 (3H, m), 7.50-7.60 (1H, m), 7.80 (1H, s), 8.78 (1H, s), 15.30-15.40 (1H, br)
MS (ESI) : M+ 419

Example 3-63

[0522] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.90-1.29 (5H, m), 1.62-1.80 (6H, m), 3.75-3.78 (2H, m), 3.96 (2H, d, J=10.8Hz), 4.13 (2H, s), 4.60-4.62 (2H, m), 5.02 (1H, t), 7.06-7.24 (2H, m), 7.14 (1H, s), 7.42-7.44 (1H, m), 8.16 (1H, s), 8.79 (1H, s)
MS (ESI) : M+ 488

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Example 3-64

[0523] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.85-0.89 (6H, m), 2.96-3.00 (2H, m), 3.10-3.20 (2H, m), 3.33-3.40 (2H, m), 4.22 (2H, s), 4.74 (1H, t), 5.09-5.10(2H, m), 7.20 (1H, m), 7.38-7.47 (2H, m), 7.59 (1H, s), 7.89 (1H, s), 8.72 (1H, s), 15.08 (1H, s)
MS (ESI): M+ 447

Example 3-65

[0524] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.91 (3H, d, J=4. 7Hz), 3. 75-3.81 (2H, m), 4.01 (2H, s), 4.50-4.55 (2H, m), 5.04 (1H, t, J=5.5Hz), 6.59 (1H, s), 6.60-6.68 (1H, m), 7.15-7.24 (2H, m), 7.51-7.55 (1H, m), 7.63 (1H, s), 8.65 (1H, s), 15.90 (1H, s)
MS (ESI) : M+ 405

Example 3-66

[0525] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.91-2.00 (4H, m), 3.40-3.50 (4H, m), 3.70-3.81, (2H, m), 4.30 (2H, s), 4.50-4.55 (2H, m), 5.05 (1H, t), 6.87 (1H, s), 7.10-7.12 (1H, m), 7.18-7.21 (1H, m), 7.49-7.52 (1H, m), 7.72 (1H, s), 8.69 (1H, s), 15.65 (1H, s)
MS (ESI): M+ 445

Example 3-67

[0526] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.44 (3H, t), 1.55 (3H, d), 3.70-3.77, (2H, m), 4.19 (2H, s), 4.28 (2H, q, J=8.8Hz), 5.14(1H, t), 5.83-5.90 (1H, m), 7.20 (1H, m), 7.39-7.40 (1H, m), 7.48-7.50 (2H, m), 7.75 (1H, s), 8.86 (1H, s),15. 13 (1H, s)
MS (ESI): M+ 434

Example 3-68

[0527] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.86 (3H, t, J=7.3Hz), 1.37 (3H, t, J=6.9Hz), 1.80-2.00, (2H, m), 3.70-3.90 (2H, m), 4.12 (2H, s), 4.20-4.28 (2H, m), 5.00-5:17 (2H, m), 7.14-7.30 (2H, m), 7.42-7.49 (2H, m), 8.14 (1H, s), 8.78 (1H, s),15.50 (1H, s)
MS (ESI): M+ 448

Example 3-69

[0528] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.09-1.27 (5H, m), 1.68-1.82 (6H, m), 3.71-3.73 (2H, m), 3.99 (2H, d, J=5.6Hz), 4.20 (2H, s), 4.80-4.85 (2H, m), 4.92 (1H, t, J=5.6Hz), 7.20 (1H, m), 7.38-7.40 (1H, m), 7.40-7.53 (2H, m), 7.75 (1H, s), 8.68 (1H, s),15.16 (1H, s)
MS (ESI): M+ 488

Example 3-70

[0529] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.70 (3H, d, J=6.4Hz), 1.12 (3H, d, J=6.4Hz), 2.30-2.40 (1H, m), 3.75-3.78 (1H, m), 3.95-4.00 (1H, m), 4.25 (2H, s), 4.80-4.85 (1H, m), 5.18 (1H, t), 7.20-7.21 (1H, m), 7.41-7.48 (2H, m), 7.84 (1H, d), 8.21 (1H, s), 8.25 (1H, d, J=9.2Hz), 8.92 (1H, s),15.21 (1H, s)
MS (ESI): M+ 418

Example 3-71

[0530] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.85 (3H, d), 0.90 (3H, d), 1.40-1.50 (1H, m), 1.80-1.91 (2H, m), 3.71-3.80 (2H, m), 4.25 (2H, s), 5.15-5.20 (2H, m), 7.20-7.21 (1H, m), 7.41-7.48 (2H, m), 7.84 (1H, d, J=8.8Hz), 8.22 (1H, s), 8.24 (1H, d, J=8. 8Hz), 8.83 (1H, s),15.20 (1H, s)
MS (ESI): M+ 432

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Example 3-72

[0531] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.86 (3H, t, J=7.3Hz), 1.23 (6H, m), 1.80-2.00 (2H, m), 3.70-3.90 (2H, m), 4.09 (2H, s), 5.00-5.18 (3H, m), 7.12-7.21 (2H, m), 7.44-7.47 (2H, m), 8.20 (1H, s), 8.79 (1H, s),15.54 (1H, s)
MS (ESI): M+ 462

Example 3-73

[0532] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.87 (3H, t, J=7.3Hz), 1.80-2.10 (2H, m), 3.70-3.90 (2H, m), 4.02 (3H, s), 4.11 (2H, s), 5.00-5.19 (2H, m), 7.16-7.24 (2H, m), 7.44-7.48 (2H, m), 8.04 (1H, s), 8.78 (1H, s),15.44 (1H, s)
MS (ESI): M+ 434

Example 3-74

[0533] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.23 (6H, dx2), 1.51 (3H, d, J=6.6Hz), 3.77 (2H, t), 4.09 (2H, s), 4.90-5.10 (1H, m), 5.19-5.30 (2H, m), 7.12-7.21 (2H, m), 7.41-7.47 (2H, m), 8.20 (1H, s), 8.81 (1H, s), 15.55 (1H, s)
MS (ESI): M+ 448

Example 3-75

[0534] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.00 (9H, s), 4.07-4.12 (2H, m), 4.30 (2H, s), 5.12-5.14 (2H, m), 7.20-7.25 (1H, m), 7.40-7.45 (1H, m), 7.51-7.53 (1H, m), 7.87 (1H, d), 8.25 (1H, s), 8.41 (1H, d, J=9.2Hz), 8.85 (1H, s), 15.20-15.21 (1H, br)
MS (ESI): M+ 432

Example 3-76

[0535] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.70-3.81 (4H, m), 4.15 (2H, s), 4.24 (2H, t, J=5.0Hz), 4.60-4.62 (2H, m), 5.00-5.02 (2H, m), 7.15-7.20 (1H, m), 7.32-7.34 (2H, m), 7.44-7.49 (1H, m), 8.06 (1H, s), 8.79 (1H, s), 15.48 (1H, s)
MS (ESI): M+ 436

Example 3-77

[0536] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.90-1.92 (2H, m), 3.53-3.54 (2H, m), 3.70-3.80 (2H, m), 4.12 (2H, s), 4.20-4.30 (2H, m), 4.60-4.70 (3H, m), 5.02 (1H, t), 7.16-7.22 (2H, m), 7.30 (1H, s), 7.40-7.50 (1H, m), 8.11 (1H, s), 8.80 (1H, s)
MS (ESI): M+ 450

Example 3-78

[0537] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.10-3.20 (2H, m), 3.60-3.80 (4H, m), 4.15 (2H, s), 4.78-4.85 (3H, m), 5.30-5.40 (1H, m), 6.10-6.20 (1H, m), 7.15-7.20 (2H, m), 7.30-7.52 (3H, m), 8.77 (1H, s), 15.33 (1H, s)
MS (ESI): M+ 435

Example 3-79

[0538] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.89 (3H, t, J=7.4Hz), 1.90-2.00 (2H, m), 3.70-3.80 (2H, m), 3.99 (3H, s), 4.22 (2H, s), 5.15 (1H, t, J=5.4Hz), 5.70-5.80 (1H, m), 7.19-7.24 (1H, m), 7.38-7.52 (2H, m), 7.55 (1H, s), 7.77 (1H, s), 8.86 (1H, s), 15.12 (1H, s)
MS (ESI): M+ 434

Example 3-80

[0539] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.59 (3H, d, J=7.2Hz), 2.61 (3H, s), 2.80 (3H, s), 4.20 (2H, s), 4.96 (1H, t, J=5. 6Hz), 6. 50-6.60 (1H, m), 7.19-7.23 (1H, m), 7.40-7.49 (2H, m), 7.60 (1H, s), 7.80 (1H, s), 8.81 (1H, s), 15.06 (1H, s)
MS (ESI): M+ 433

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Example 3-81

[0540] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 4.10-4.40 (4H, m), 5.50-5.60 (1H, m), 6.20-6.30 (1H, m), 7. 19-7.22 (1H, m), 7.30-7.40 (6H, m), 7.40-7.50 (1H, m), 7.77 (1H, d), 8.00 (1H, d), 8.21 (1H, s), 9.03 (1H, s), 15.11 (1H, s)
MS (ESI): M+ 452

Example 3-82

[0541] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.86 (3H, t), 1.18-1.34 (2H, m), 1.87-1.98 (2H, m), 3.73-3.84 (2H, m), 4.25 (2H, s), 5.13-5.17 (2H, m), 7.21 (1H, m), 7.41-7.48 (2H, m), 7.83 (1H, d, J=8.0Hz), 8.19 (1H, d), 8.22 (1H, s), 8.85 (1H, s), 15.22 (1H, s)
MS (ESI): M+ 418

Example 3-83

[0542] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.72 (3H, t, J=7.3Hz), 0.90-1.20 (5H, m), 2.10-2.30 (1H, m), 3.70-3.80 (1H, m), 3.90-4.10 (1H, m), 4.26 (2H, s), 4.90-5.00 (1H, m), 5.10-5.20 (1H, m), 7.20-7.25 (1H, m), 7.40-7.52 (2H, m), 7.84 (1H, d, J=7.8Hz), 8.23 (1H, s), 8.26 (1H, d), 8.92 (1H, s), 15.22 (1H, s)
MS (ESI): M+ 432

Example 3-84

[0543] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.54 (3H, d, J=6.6Hz), 3.81-3.82 (2H, m), 4.02 (3H, s), 4.12 (2H, s), 5.22 (1H, t, J=5.4Hz), 5.23-5.40 (1H, m), 7.15-7.26 (2H, m), 7.44-7.50 (2H, m), 8.05 (1H, s), 8.82 (1H, s), 15.46 (1H, s)
MS (ESI): M- 418

Example 3-85

[0544] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.25-3.38 (2H, m), 3.82-3.89 (2H, m), 4.21 (2H, s), 5.27 (1H, t), 5.40-5.50 (1H, m), 7.10-7.21 (6H, m), 7.30-7.40 (1H, m), 7.40-7.50 (1H, m), 7.77 (1H, d), 8.14 (1H, d), 8.14 (1H, s), 8.96 (1H, s), 15.15 (1H, s)
MS (ESI): M+ 466

Example 3-86

[0545] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.70-3.80 (2H, m), 4.42 (2H, s), 4.69 (2H, t), 4.95 (1H, t), 7.37-7.42 (1H, m), 7.51 (1H, d, J=6.2Hz), 7.59 (1H, d, J=7.9Hz), 8.48 (1H, s), 8.99 (1H, s), 9.04 (1H, s), 14.68 (1H, s)
MS (ESI): M+ 393

Example 4-1

[0546] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.26 (3H, s), 3.74 (2H, m), 4.42 (2H, s), 4.61 (2H, m), 5.09 (1H, br), 7.78 (1H, m), 7.84 (2H, m), 8.04-8.07 (2H, m), 8.18 (1H, m), 8.86 (1H, s), 15.19 (1H, s)
MS (ESI) : M+435

Example 4-2

[0547] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.73 (2H, m), 4.23 (2H, s), 4.59 (2H, m), 4.99 (1H, br), 7.20 (1H, m), 7.31-7.34 (2H, m), 7.44 (1H, m), 7.85 (1H, m), 8.01 (1H, s), 8.26 (1H, m), 8.85 (1H, s), 15.27 (1H, s)
MS (ESI): M+407

Example 4-3

[0548] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.15 (3H, t, J= 7.6 Hz), 2.57 (2H, q, J= 7.6 Hz), 3.73 (2H, m), 4.13 (2H, s), 4.59 (2H, m), 4.99 (1H, m), 7.05 (2H, m), 7:13 (1H, m), 7.20 (1H, m), 7.81 (1H, m), 7.98 (1H, m), 8.21 (1H, s), 8.84 (1H, s), 15.28 (1H, s)
MS (ESI): M+351

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Example 4-4

[0549] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 1.07 (3H, t, J= 7.53 Hz), 2.58 (2H, q, J= 7.53 Hz), 3.76 (2H, m), 4.22 (2H, s), 4.61 (2H, m), 5.02 (1H, m), 7.19-7.23 (4H, m), 7.76 (1H, m), 8.01 (1H, m), 8.09 (1H, s), 8.86 (1H, s), 15.26 (1H, s)
MS (ESI): M+351

Example 4-5

[0550] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 2.28 (3H, s), 3. 75 (2H, m), 4.24(2H, s), 4.61 (2H, m), 5.04(1H, br), 7.13 (1H, d, J=8.1Hz), 7.28-7.36 (2H, m), 7.81(1H, d, J=6.7Hz), 8.03 (1H, d, J=8.9Hz), 8.13 (1H, s), 8.86 (1H, s), 15.24 (1H, brs)
MS (ESI): M+ 372

Example 4-6

[0551] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.29 (2H, s), 4.62 (2H, m), 5.07 (1H, m), 7.19 (1H, m), 7.40 (1H, m), 7.52 (1H, m), 7.84 (1H, m), 8.05 (1H, m), 8.19 (1H, s), 8.87 (1H, s), 15.20 (1H, s)
MS (ESI): M+375

Example 4-7

[0552] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3. 75 (2H, m), 4.29 (2H, s), 4.61(2H, t, J=5.0Hz), 5.01(2H, t, J=5.4Hz), 7.45 (1H, d), 7.51 (1H, d, J=11.2Hz), 7.74 (1H, d), 7.84 (1H, dd), 8.01 (1H, d), 8.15 (1H, s), 8.86 (1H, s), 15.21 (1H, brs)
MS (ESI): M+ 436

Example 4-8

Example 4-9

[0553] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.76 (2H, m), 4.34 (2H, s), 4.59 (2H, m), 5.01 (1H, m), 7.37 (2H, m), 7.62 (1H, m), 8.07 (2H, m), 8.88 (1H, s), 14.99 (1H, s)
MS (ESI): M+409

Example 4-10

[0554] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.20 (3H, s), 3.74 (2H, m), 4.31 (2H, s), 4.61(2H, t), 5.00 (1H, t), 7.55-7.66(2H, m), 7.78(1H, d), 7.84-7.89(2H, m), 8.03 (1H, d, J=8.9Hz), 8.30 (1H, s), 8.86 (1H, s), 15.27 (1H, brs)
MS (ESI): M+ 402

Example 4-11

[0555] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.75 (2H, m), 4.18 (2H, s), 4.61 (2H, m), 5.02 (1H, m), 6.69 (1H, m), 6.77 (1H, m), 7.23 (1H, m), 7.80 (1H, m), 8.02 (1H, m), 8.15 (1H, s), 8.86 (1H, s), 9.66 (1H, s), 15.24 (1H, s)
MS (ESI): M+373

Example 4-12

[0556] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 3.75 (2H, m), 4.29 (2H, s), 4.58 (2H, m), 5.00 (1H, s), 7.31 (1H, m), 7.35 (1H, m), 7.58 (1H, m), 7.71 (1H, m), 7.82 (1H, m), 8.86 (1H, s)
MS (ESI): M+409

Example 4-13

[0557] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.34 (3H, t, J=6. 8Hz), 3.73 (2H, m), 4.00 (2H, q, J=6.8Hz), 4.09 (2H, s), 4.59 (2H, m), 5.00 (1H, m), 6.89 (1H, m), 6.95 (1H, m), 7.19 (1H, m), 7.27 (1H, m), 7.83 (1H, m), 7.97 (1H, m), 8.24 (1H, s), 8.84 (1H, s), 15.33 (1H, s)
MS (ESI) : M+367

Example 4-14

[0558] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 3.73 (2H, m), 4.06 (2H, s), 4.60 (2H, m), 5.05 (1H, m), 6.74 (1H, m), 6.85 (1H, m), 7.05 (1H, m), 7.14 (1H, m), 7.82 (1H, m), 7.99 (1H, m), 8.19 (1H, s), 8.84 (1H, s), 9.55 (1H, s), 15.34 (1H, s)
MS (ESI): M+339

Example 4-15

[0559] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 2.49 (3H, s), 3.77 (2H, m), 4.27 (2H, s), 4.60 (2H, m), .01 (1H, s), 7.17 (1H, m), 7.35 (1H, m), 7.59 (1H, m), 7.78 (1H, s), 7.95 (1H, s), 8.81 (1H, s), 15.22 (1H, s)
MS (ESI): M+406

Example 4-16

[0560] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 1.35 (3H, d), 1.40 (3H, d), 1.54 (3H, d, J=6.8Hz), 3.72 (2H, m), 4.20 (2H, s), 4.86-4.92 (1H, m), 5.12 (1H, t, J=5.2Hz), 5.80-5.90 (1H, m), 7.20 (1H, m), 7.39-7.52 (3H, m), 7.74 (1H, s), 8.84 (1H, s), 15.13 (1H, s)
MS (ESI): M+ 448

Example 4-17

[0561] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.89 (3H, t, J=7.2Hz), 1.35-1.37 (6H, d), 1. 88-2.06 (2H, m), 3.73-3.79 (2H, m), 4.20 (2H, s), 4.80-5.00 (1H, m), 5.16 (1H, t), 5.81-5.84 (1H, m), 7.20 (1H, m), 7.40-7.53 (3H, m), 7.75 (1H, s), 8.83 (1H, s), 15.09 (1H, s)
MS (ESI): M+ 462

Example 4-18

[0562] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.80-1.40 (6H, m), 1.40-1.60 (2H, m), 1.70-1.80 (1H, m), 1.80-2.10 (2H, m), 3.70-3.80 (1H, m), 3.90-4.00 (1H, m), 4.26 (2H, s), 4.80-5.00 (1H, m), 5.19 (1H, t), 7.22-7.25 (1H, m), 7.42-7.49 (2H, m), 7.85 (1H, d), 8.22 (1H, s), 8.26 (1H, d, J=9.1Hz), 8.95 (1H, s)
MS (ESI): M+ 458

Example 4-19

[0563] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.70 (3H, d, J=6.6Hz), 1.14 (3H, d, J=6.4Hz), 1.21-1.24 (6H, m), 2.20-2.40 (1H, m), 3.70-3.80 (1H, m), 3.90-4.00 (1H, m), 4.09 (2H, s), 4.80-4.90 (1H, m), 5.00-5.20 (2H, m), 7.12-7.22 (2H, m), 7.43-7.47 (2H, m), 8.19 (1H, s), 8.87 (1H, s), 15.51 (1H, s)
MS (ESI): M+ 476

Example 4-20

[0564] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.97 (9H, s), 1.18 (3H, d, J=5.9Hz), 1.26 (3H, d, J=6.0Hz), 4.04-4.09 (4H, m), 5.09-5.13 (3H, m), 7.12-7.21 (2H, m), 7.43-7.51 (2H, m), 8.19 (1H, s), 8.78 (1H, s), 15.46 (1H, s)
MS (ESI): M+ 490

Example 4-21

[0565] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.89 (3H, t, J=7.6Hz), 1.44 (3H, t), 1.92-2.06 (2H, m), 3.78 (2H, m), 4.19 (2H, s), 4.25 (2H, q), 5.17 (1H, t, 5.6Hz), 5.78-5.83 (1H, m), 7.20 (1H, m), 7.39-7.51 (3H, m), 7.76 (1H, s), 8.85 (1H, s), 15.11 (1H, s)
MS (ESI): M+ 448

Example 4-22

[0566] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.80-1.30 (6H, m), 1.50-1.80 (5H, m), 1.80-1.90 (2H, m), 3.60-3.80 (2H, m), 4.26 (2H, s), 5.10-5.20 (2H, m), 7.22 (1H, m), 7.30-7.50 (2H, m), 7.85 (1H, d), 8.23 (1H, d), 8.23 (1H, s), 8.84 (1H, s), 15.20 (1H, s)

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MS (ESI): M+ 472

Example 4-23

[0567] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.85 (3H, d), 0.91 (3H, d), 1.24-1.27 (6H, m), 1.35-1.43 (1H, m), 1.70-1.80 (1H, m), 1.91-1.95 (1H, m), 3.75-3.80 (2H, m), 4.08 (2H, s), 5.00-5.10 (1H, m), 5.16-5.19 (2H, m), 7.14-7.21 (2H, *m*), 7.43-7.44 (2H, *m*), 8.18 (1H, s), 8.79 (1H, *s*)
MS (ESI): M+ 490

Example 4-24

[0568] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.72 (3H, d), 1.09 (3H, d), 1.37-1.40 (6H, m), 2.35-2.38 (1H, *m*), 3.77-3.79 (1H, m), 3.91-3.94 (1H, m), 4.20 (2H, s), 4.92-4.96 (1H, m), 5.23 (1H, t), 5.74-5.76 (1H, m), 7.21 (1H, m), 7.40-7.53 (3H, m), 7.75 (1H,s), 8.88 (1H, s), 15.08 (1H, s)
MS (ESI): M+ 476

Example 4-25

[0569] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.84 (3H, d, J=6.8Hz), 0.87 (3H, d, J=6.4Hz), 1.37 (3H, d, J=11.2Hz), 1.42 (3H, d, J=10.8Hz), 1.83-1.87 (2H, *m*), 3.79-3.80 (2H, *m*), 4.20 (2H, s), 4.90-4.96 (1H, *m*), 5.20 (1H, t), 6.08-6.10 (1H, m), 7.21 (1H, m), 7.39-7.55 (3H, m), 7.75 (1H,s), 8.78 (1H, s), 15.08 (1H, s)
MS (ESI): M+ 490

Example 4-26

[0570] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.91 (9H, s), 1.35 (3H, d), 1.44 (3H, d), 4.02-4.03 (2H, m), 4.20 (2H, s), 4.92-4.95 (1H, m), 5.15 (1H, t), 6.43 (1H, t), 7.19-7.21 (1H, m), 7.39-7.48 (2H, m), 7.55 (1H, s), 7.79 (1H, s), 8.80 (1H, s), 15.05 (1H, s)
MS (ESI): M+ 490

Example 4-27

[0571] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.76 (3H, t), 0.97-1.03 (2H, *m*), 1.12 (3H, d), 2.10-2.20 (1H, *m*), 3.75-3.80 (1H, m), 3.98-4.02 (1H, m), 4.02 (3H, s), 4.11 (2H, s), 4.92-4.95 (1H, m), 5.19 (1H, t), 7.16-7.25 (2H, m), 7.44-7.50 (2H, m), 8.02 (1H, s), 8.87 (1H, s), 15.40 (1H, s)
MS (ESI): M+ 462

Example 4-28

[0572] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.74 (3H, t, J=7.6Hz), 0.99-1.03 (2H, m), 1.11 (3H, d), 1.37 (3H, t, J=6.8Hz), 2.10-2.20 (1H, *m*), 3.70-3.80 (1H, m), 3.96-4.00 (1H, m), 4.11 (2H, s), 4.26 (2H, q, J=7.2Hz), 4.92-5.00 (1H, m), 5.18 (1H, t), 7.14-7.18 (1H, m), 7.24-7.25 (1H, m), 7.40 (1H, s), 7.44-7.46 (1H, m), 8.12 (1H, s), 8.86 (1H, s), 15.46 (1H, s)
MS (ESI): M+ 476

Example 4-29

[0573] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.89 (3H, t, J=7.3Hz), 1.98-2. 01 (2H, m), 2.70 (3H, s), 3.80-3.90 (2H, m), 4.21 (2H, s), 5.10-5.21 (2H, m), 7.15-7.22 (2H, m), 7.49-7.51 (1H, m),7.65 (1H, s), 8.04 (1H, s), 8.84 (1H, s), 15.25 (1H, s)
MS (ESI): M+ 450

Example 4-30

[0574] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.70 (3H, d, J=6.5Hz), 1.15 (3H, d, J=6.5Hz), 1.37 (3H, t, J=6.9Hz), 2.30-2.40 (1H, m), 3.70-3.80 (1H, m), 3.90-4.00 (1H, m), 4.11 (2H, s), 4.20-4.30 (2H, m), 4.80-4.90 (1H, m), 5.18 (1H, t), 7.14-7.20 (1H, m), 7.24-7.26 (1H, m), 7.43-7.49 (2H, m), 8.13 (1H, s), 8.87 (1H, s), 15.49 (1H, s)
MS (ESI): M+ 462

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Example 4-31

[0575] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.97 (9H, s), 1.37 (3H, t, J=6.9Hz), 4.02-4.11 (4H, m), 4.25-4.31 (2H, m), 5.10-5.20 (2H, m), 7.14-7.26 (2H, m), 7.44-7.49 (2H, m), 8.12 (1H, s), 8.78 (1H, s), 15.43 (1H, s)
MS (ESI): M+ 476

Example 4-32

[0576] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.72 (3H, d, J=6.5Hz), 1.16 (3H, d, J=6.5Hz), 2.30-2.50 (1H, m), 3.70-3.90 (1H, m),3.90-4.00 (1H, m), 4.03 (3H, s), 4.12 (2H, s), 4.80-4.90 (1H, m), 5.19 (1H, t), 7.19-7.25 (2H, m), 7.46-7.51 (2H, m), 8.04 (1H, s), 8.88 (1H, s), 15.44 (1H, s)
MS (ESI): M+ 448

Example 4-33

[0577] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.99 (9H, s), 3.99-4.11 (7H, m), 5.11-5.20 (2H, m), 7.19-7.25 (2H, m), 7.49-7.52 (2H, m), 8.03 (1H, s), 8.78 (1H, s), 15.39 (1H, s)
MS (ESI): M+ 462

Example 4-34

[0578] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.93 (9H, s), 3.90-4. 03 (5H, m), 4.22 (2H, s), 5.10 (1H, t), 6.20 (1H, t), 7.20-7.30 (1H, m), 7.40-7.57 (2H, m), 7.60 (1H, s), 7.79 (1H, s), 8.78 (1H, s), 15.05 (1H, s)
MS (ESI): M+ 462

Example 4-35

[0579] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.86 (3H, t, J=7.2Hz), 1.19-1.29 (8H, m), 1.90-1.93 (2H, m), 3.72-3.80 (2H, m), 4.08 (2H, s), 5.02-5.04 (1H, m), 5.10-5.20 (2H, m), 7.11-7.22 (2H, m), 7.43-7.46 (2H, m), 8.18 (1H, s), 8.78 (1H, s), 15.51 (1H, s)
MS (ESI): M+ 476

Example 4-36

[0580] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.88 (3H, t, J=7.2Hz), 1.20-1.35 (2H, m), 1.36 (3H, t, J=6.8Hz), 1.80-2.00 (2H, m), 3.70-3.80 (2H, m), 4.11 (2H, s), 4.25 (2H, q, J=7.2Hz), 5.17 (1H, t, J=5.6Hz), 7.14-7.18 (1H, m), 7.24-7.26 (1H, m), 7.41 (1H, s), 7.41-7.45 (1H, m), 8.13 (1H, s), 8.78 (1H, s), 15.48 (1H, s)
MS (ESI): M+ 462

Example 4-37

[0581] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.93 (9H, s), 1.49 (3H, t), 4.00 (2H, t, J=6.4Hz), 4.20 (2H, s), 4.22-4.33 (2H, m), 5.12 (1H, t), 6.36 (1H, t, J=6.8Hz), 7.21 (1H, m), 7.39-7.48 (2H, m), 7.54 (1H, s), 7.79 (1H, s), 8.79 (1H, s), 15.04 (1H, s)
MS (ESI): M+ 476

Example 4-38

[0582] ^{1}H NMR (DMSO-d_6 40OMHz) (δ) ppm: 0.89 (3H, t, J=8.0Hz), 1.23-1.40 (2H, m), 1.80-2.00 (2H, m), 3.75-3.90 (2H, m), 4.02 (3H, s), 4.11 (2H, s), 5.10-5.21 (2H, m), 7.16-7.24 (2H, m), 7.44-7.49 (2H, m), 8.03 (1H, s), 8.80 (1H, s), 15.44 (1H, br)
MS (ESI): M+ 448

Example 4-39

[0583] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.74 (3H, t, J=7.1Hz), 0.84-1.24 (11H, m), 2.10-2.30 (1H, m), 3.70-3.80 (1H, m), 3.90-4.00 (1H, m), 4.09 (2H, s), 4.80-5.17 (3H, m), 7.15-7.22 (2H, m), 7.40-7.50 (2H, m), 8.19 (1H, s), 8.87 (1H, s), 15.51 (1H, s)

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MS (ESI): M+ 490

Example 4-40

[0584] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.80-0.89 (1H, m), 1.04-1.30 (11H, m), 1.50-1.60 (2H, m), I.70-1.80 (1H, m), 1.93-2.01 (2H, m), 3.73-3.76 (1H, m), 3.96-4.00 (1H, m), 4.07 (2H, s), 4.80-4.89 (1H, m), 5.00-5.17 (2H, m), 7.12-7.21 (2H, m), 7.40-7.42 (2H, m), 8.17 (1H, s), 8.87 (1H, s)
MS (ESI): M+ 516

Example 4-41

[0585] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0. 80-1.30 (6H, m), 1.46 (3H, t, J=6.9Hz), 1.50-1.70 (2H, m), 1.70-1.80 (1H, m), 1.90-2.10 (2H, m), 3.70-3.81 (1H, m), 3.92-4.00 (1H, m), 4.20 (3H, s), 4.23 (2H, q, J=6.6Hz), 5.20 (1H, t, J=4.8Hz), 5.70-5.81 (1H, m), 7.19-7.24 (1H, m), 7.38-7.51 (3H, m), 7.77 (1H, s), 8.91 (1H, s), 15.11 (1H, s)
MS (ESI): M+ 502

Example 4-42

[0586] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.84-1.30 (6H, m), 1.50-1.70 (2H, m), 1.70-1.90 (1H, m), 1.94-2.10 (2H, m), 3.70-3.79 (1H, m), 3.90-4.00 (1H, m), 4.03 (3H, s), 4.10 (2H, s), 4.80-5.00 (1H, m), 5.19 (1H, m), 7.19-7.30 (2H, m), 7.43-7.48 (2H, m), 8.02 (1H, s), 8.87 (1H, s), 15.45 (1H, s)
MS (ESI): M+ 488

Example 4-43

[0587] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.80-1.00 (1H, m), 1.14-1.28 (5H, m), 1.37 (3H, t, J=6.9Hz), 1.50-1.70 (2H, m), 1.70-1.80 (1H, m), 1.90-2.10 (2H, m), 3.70-3.80 (1H, m), 3.90-4.00 (1H, m), 4.11 (2H, s), 4.25 (2H, q), 4.80-5.00 (1H, m), 5.18 (1H, m), 7.17-7.26 (2H, m), 7.41-7.47 (2H, m), 8.13 (1H, s), 8.89 (1H, s)
MS (ESI): M+ 502

Example 4-44

[0588] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.80-1.00 (1H, m), 1.00-1.40 (5H, m), 1.50-1.70 (2H, m), 1.70-1. 80 (1H, m), 1.90-2.10 (2H, m), 3.70-3.80 (1H, m), 3.90-4.00 (1H, m), 3.98 (3H, s), 4.21(2H, s), 5.20 (1H, m), 5.60-5.70 (1H, m), 7.19-7.25 (1H, m), 7.39-7.54 (3H, m), 7.77 (1H, s), 8.92 (1H, s)
MS (ESI): M+ 488

Example 4-45

[0589] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.74 (3H, d, J=4.0Hz), 1.08 (3H, d, J=8.0Hz), 1.45 (3H, t, J=8.0Hz), 2.36-2.40 (2H, m), 3.70-3.80 (1H, m), 3.89-3.93 (1H, m), 4.19 (2H, s), 4.26(2H, q, J=8.0Hz), 5.20 (1H, t, J=8.0Hz), 5.69-5.73(1H, m), 7.17-7.20 (1H, m), 7.39 (1H, m), 7.48-7.51 (2H, m), 7.76 (1H, s), 8.89 (1H, s)
MS (ESI): M+ 462

Example 4-46

[0590] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.73 (3H, d, J=6.8Hz), 1.08 (3H, d, J=6.8Hz), 2.20-2.40 (2H, m), 3.81-3.91 (1H, m), 3.91-3.99 (1H, m), 3.99 (3H, s), 4.22 (2H, s), 5.20 (1H, m), 5.55-5.58 (1H, m), 7.10-7.22 (1H, m), 7.41-7.55 (3H, m), 7.77 (1H, s), 8.91 (1H, s), 15.09 (1H, s)
MS (ESI): M+ 448

Example 4-47

[0591] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0. 85 (3H, d, J=7.3Hz), 1.10-1.34 (2H, m), 1.33 (6H, d, J=6.0Hz), 1.70-2.00 (2H, m), 3.75 (2H, m), 4.17 (2H, s), 4.80-4.90 (1H, m), 5.14 (1H, m), 5.80-6.00 (1H, m), 7.10-7.20 (1H, m), 7.30-7.50 (3H, m), 7.72 (1H, s), 8.80 (1H, s)
MS (ESI): M+ 476

Example 4-48

[0592] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.89 (3H, t), 1.20-1.40 (2H, m), 1.44 (3H, t), 1.80-2.00 (2H, m), 3.78 (2H, m), 4.20 (2H, s), 4.23 (2H, q, J=6.8Hz), 5.16 (1H, t, J=5.6Hz), 5.90-5.92(1H, m), 7.15-7.21 (1H, m), 7.39-7.52 (3H, m), 7.76 (1H, s), 8.84 (1H, s), 15.10 (1H, s)
MS (ESI): M+ 462

Example 4-49

[0593] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.89 (3H, t), 1.23-1.35 (2H, m), 1.87-1.96 (2H, m), 3.72-3.79 (2H, m), 3.98 (3H, s), 4.21 (2H, s), 5.15 (1H, t, J=5.2Hz), 5.85-5.88 (1H, m), 7.15-7.21 (1H, m), 7.39-7.48 (2H, m), 7.54 (1H, s), 7.76 (1H, s), 8.85 (1H, s), 15.10 (1H, s)
MS (ESI): M+ 448

Example 4-50

[0594] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.80-1.00 (1H, m), 1.11-1.20 (4H, m), 1.20-1.30 (1H, m), 1.35 (3H,d), 1.40 (3H, d), 1.55-1.70 (2H, m), 1.72-1.80 (1H, m), 1.95-2.10 (2H, m), 3.77-3.79 (1H, m), 3.95-3.98 (1H, m), 4.20 (2H, s), 4.91-4.94 (1H, m), 5.24 (1H, t), 5.81-5.83 (1H, m), 7.15-7.21 (1H, m), 7.39-7.50 (2H, m), 7.53 (1H, s), 7.74 (1H, s), 8.89 (1H, s), 15.09 (1H, s)
MS (ESI): M+ 516

Example 4-51

[0595] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.91 (9H, s), 1.48 (3H, t, J=6.9Hz), 3.90-4.00 (2H, m), 4.13 (2H, s), 4.22 (2H, q, J=7.0Hz), 4.90-5.00 (1H, m), 6.10-6.20 (1H, m), 7.17-7.22 (1H, m), 7.34-7.36 (2H, m), 7.45-7.50 (1H, m), 7.77 (1H, s), 8.75 (1H, s)
MS (ESI): M+ 476

Example 4-52

[0596] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.93 (9H, s), 3.90-4.02 (2H, m), 4.15 (2H, s), 4.80-4.81 (1H, m), 5.05 (1H, m), 7.19-7.21 (1H, m), 7.35-7.40 (1H, m), 7.43-7.45 (1H, m), 7.57 (1H, d), 8.01-8.03 (1H, d, J=8.8Hz), 8.12 (1H, s), 8.76 (1H, s)
MS (ESI): M+ 432

Example 4-53

[0597] ^{1}H NMR (DMSO-d_6 400MHz) (δ) ppm: 0.81 (3H, d), 1.20 (3H, d), 2.28-2.41 (1H, m), 3.98 (3H, s), 4.00-4.05 (2H, m), 4.08 (2H, s), 4.51-4.60 (1H, m), 7.02-7.08 (2H, m), 7.19 (1H, s), 7.28-7.30 (1H, m), 8.15 (1H, s), 8.60 (1H, s)
MS (ESI): M+ 448

Example 4-54

[0598] ^{1}H NMR (DMSO-d_6 300MHz) (δ) ppm: 0.95 (9H, s), 3.96 (3H, s), 3.96-4.03 (4H, m), 4.83 (1H, m), 5.17 (1H, m), 7.13-7.23 (2H, m), 7.28 (1H, s), 7.42-7.47 (1H, m), 7.80 (1H, s), 8.73 (1H, s)
MS (ESI): M+ 462

Sequence Listing Free Text

[0599]

SEQ ID NO:1: Donor + chain for HIV integrase activity determination
SEQ ID NO:2: Donor - chain for HIV integrase activity determination
SEQ ID NO:3: Target + chain for HIV integrase activity determination
SEQ ID NO:4: Target - chain for HIV integrase activity determination

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Industrial Field of Utilization

[0600] As is clear from the above results, the compounds of the present invention has high HIV integrase inhibitory activity.

[0601] Therefore, the compounds can be useful pharmaceutical agents for the prophylaxis or therapy of AIDS, as anti-HIV agents having HIV integrase inhibitory activity. Moreover, by a combined use with other anti-HIV agents such as protease inhibitors, reverse transcriptase inhibitors and the like, the compounds can become more effective anti-HIV agents. Since the compounds have high inhibitory activity specific for integrases, they can provide safe pharmaceutical agents for human with a fewer side effects.

[0602] This application is based on patent application Nos. 2002-336843, 2003-65807 and 2003-139616 filed in Japan, the contents of which are all hereby incorporated by reference.

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SEQUENCE LISTING

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166

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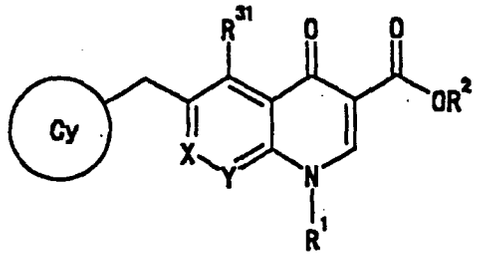
Claims

1. An anti-HIV agent comprising a 4-oxoquinoline compound represented by the following formula [I] or a pharmaceutically acceptable salt thereof as an active ingredient:



[I]

wherein

ring Cy is a C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the following group A or a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group A

wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom (s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom; group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group and R^{a3} is C_{1-4} alkyl group;

R^1 is a substituent selected from the following group B or a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B

wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A;

R^2 is a hydrogen atom or a C_{1-4} alkyl group;

R^{31} is a hydrogen atom, a cyano group, a hydroxy group, an amino group, a nitro group, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a C_{1-4} alkylsulfanyl group, a halo C_{1-4} alkyl group or a halo C_{1-4} alkyloxy group;

X is a C-R^{32} or a nitrogen atom; and

Y is a C-R^{33} or a nitrogen atom

wherein R^{32} and R^{33} are the same or different and each is hydrogen atom, cyano group, nitro group, halogen atom, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or, C_{1-10} alkyl group optionally substituted by

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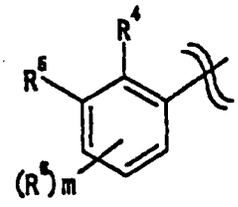
1 to 3 substituents selected from halogen atom and the above-mentioned group B, $-OR^{a7}$, $-SR^{a7}$, $-NR^{a7}R^{a8}$, $-NR^{a7}COR^{a9}$, $-COOR^{a10}$ or $-N=CH-NR^{a10}R^{a11}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, R^{a9} is C_{1-4} alkyl group, and R^{a10} and R^{a11} are the same or different and each is hydrogen atom or C_{1-4} alkyl group.

2. The anti-HIV agent of claim 1, wherein X is C-R^{32} and Y is C-R^{33}.

3. The anti-HIV agent of claim 1, wherein ring Cy is



wherein

R^4 and R^6 are the same or different and each is a substituent selected from the following group A

wherein group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$

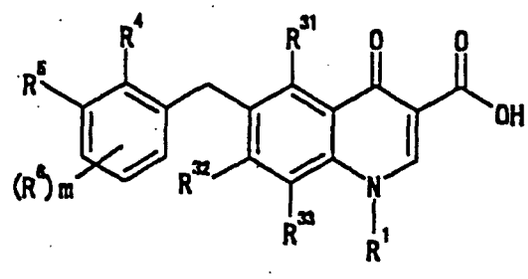
wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group and R^{a3} is C_{1-4} alkyl group;

R^5 is a substituent selected from hydrogen atom and group A, and R^4 and R^5 may form a fused ring together with a benzene ring they substitute; and

m is 0 or an integer of 1 to 3, and when m is 2 or 3, then R^6 of each m may be the same or different.

4. The anti-HIV agent of claim 1, wherein R^2 is a hydrogen atom.

5. A 4-oxoquinoline compound represented by the following formula [II] or a pharmaceutically acceptable salt thereof:



[II]

wherein

R^4 and R^6 are the same or different and each is a substituent selected from the following group A

wherein group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group and R^{a3} is C_{1-4} alkyl group;

R^5 is a substituent selected from hydrogen atom and the above-mentioned group A, and R^4 and R^5 may form a fused ring together with a benzene ring they substitute;

m is 0 or an integer of 1 to 3, and when m is 2 or 3, then R^6 of each m may be the same or different;

R^1 is a substituent selected from the following group B or a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B

wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A;

R^{31} is a hydrogen atom, a cyano group, a hydroxy group, an amino group, a nitro group, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a C_{1-4} alkylsulfanyl group, a halo C_{1-4} alkyl group or a halo C_{1-4} alkyloxy group; and

R^{32} and R^{33} are the same or different and each is a hydrogen atom, a cyano group, a nitro group, a halogen atom, a C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, a heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, OR^{a7}, $-SR^{a7}$, $-NR^{a7}R^{a8}$, $-NR^{a7}COR^{a9}$, $-COOR^{a10}$ or $-N=CH-NR^{a10}R^{a11}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, R^{a9} is C_{1-4} alkyl group, and R^{a10} and R^{a11} are the same or different and each is hydrogen atom or C_{1-4} alkyl group.

6. The 4-oxoquinoline compound of claim 5, wherein R^{31} is a hydrogen atom, a cyano group, a hydroxy group or a C_{1-4} alkoxy group, or a pharmaceutically acceptable salt thereof.

7. The 4-oxoquinoline compound of claim 6, wherein R^{31} is a hydrogen atom, or a pharmaceutically acceptable salt thereof.

8. The 4-oxoquinoline compound of claim 5, wherein

R^{32} and R^{33} are the same or different and each is a hydrogen atom, a cyano group, a halogen atom, a heterocyclic group optionally substituted by 1 to 5 substituents selected from the following group A

wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group and R^{a3} is C_{1-4} alkyl group,

a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B

wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl

group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A,
$-OR^{a7}$, $-SR^{a7}$, $-NR^{a7}R^{a8}$, $-NR^{a7}COR^{a9}$, $-COOR^{a10}$ or $-N=CH-NR^{a10}R^{a11}$
wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, R^{a9} is C_{1-4} alkyl group, and R^{a10} and R^{a11} are the same or different and each is hydrogen atom or C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

9. The 4-oxoquinoline compound of claim 5, wherein

R^{32} is a hydrogen atom, a cyano group, a halogen atom, a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B
wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$
wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A,
$-OR^{a7}$, $-SR^{a7}$, $-NR^{a7}R^{a8}$, $-NR^{a7}COR^{a9}$ or $-COOR^{a10}$
wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, R^{a9} is C_{1-4} alkyl group, and R^{a10} is hydrogen atom or C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

10. The 4-oxoquinoline compound of claim 9, wherein R^{32} is a hydrogen atom, $-OR^{a7}$ or $-NR^{a7}R^{a8}$ wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B, or a pharmaceutically acceptable salt thereof.

11. The 4-oxoquinoline compound of claim 8, wherein

R^{33} is a hydrogen atom, a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B
wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$
wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A,

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$-OR^{a7}$ or $-NR^{a7}R^{a8}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group, optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B,

or a pharmaceutically acceptable salt thereof.

12. The 4-oxoquinoline compound of claim 11, wherein

R^{33} is a hydrogen atom, $-OR^{a7}$ or $-NR^{a7}R^{a8}$

wherein R^{a7} and R^{a8} are the same or different and each is hydrogen atom, group B or C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the above-mentioned group B,

or a pharmaceutically acceptable salt thereof.

13. The 4-oxoquinoline compound of any of claims 8 to 12, wherein

R^{a7} and R^{a8} are the same or different and each is a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and the following group B wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$

wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A,

or a pharmaceutically acceptable salt thereof.

14. The 4-oxoquinoline compound of claim 5, wherein

R^4 and R^5 are the same or different and each is a substituent selected from cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a2}COOR^{a3}$ and $-COOR^{a1}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group, and R^{a3} is C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

15. The 4-oxoquinoline compound of claim 14, wherein

R^4 is a phenyl group, a halogen atom, a C_{1-4} alkyl group, a halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$ or $-COOR^{a1}$

wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group, and R^{a3} is C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

16. The 4-oxoquinoline compound of claim 15, wherein R^4 is a halogen atom, or a pharmaceutically acceptable salt thereof.

17. The 4-oxoquinoline compound of claim 5, wherein

R^5 is a hydrogen atom, a cyano group, a phenyl group, a nitro group, a halogen atom, a C_{1-4} alkyl group, a halo C_{1-4} alkyl group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$ or $-NR^{a1}COR^{a3}$
wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group, and R^{a3} is C_{1-4} alkyl group,

or a pharmaceutically acceptable salt thereof.

18. The 4-oxoquinoline compound of claim 5, wherein R^6 is a halogen atom,
or a pharmaceutically acceptable salt thereof.

19. The 4-oxoquinoline compound of claim 5, wherein m is 0 or 1,
or a pharmaceutically acceptable salt thereof.

20. The 4-oxoquinoline compound of claim 5, wherein

R^1 is a C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the following group A
wherein group A is a group consisting of cyano group, phenyl group, nitro group, halogen atom, C_{1-4} alkyl group, halo C_{1-4} alkyl group, halo C_{1-4} alkyloxy group, $-OR^{a1}$, $-SR^{a1}$, $-NR^{a1}R^{a2}$, $-CONR^{a1}R^{a2}$, $-SO_2NR^{a1}R^{a2}$, $-COR^{a3}$, $-NR^{a1}COR^{a3}$, $-SO_2R^{a3}$, $-NR^{a1}SO_2R^{a3}$, $-COOR^{a1}$ and $-NR^{a2}COOR^{a3}$
wherein R^{a1} and R^{a2} are the same or different and each is hydrogen atom, C_{1-4} alkyl group or benzyl group and R^{a3} is C_{1-4} alkyl group,
a substituent selected from $-NR^{a4}R^{a5}$, $-NR^{a4}COR^{a6}$, $-NR^{a4}SO_2R^{a6}$ and $-NR^{a5}COOR^{a6}$
wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (wherein the heterocyclic group is a saturated or unsaturated ring containing, besides carbon atom(s), at least one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, or
a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B
wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$ (wherein R^{a4}, R^{a5}, R^{a6} and group A are as defined above),

or a pharmaceutically acceptable salt thereof.

21. The 4-oxoquinoline compound of claim 20, wherein

R^1 is a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from halogen atom and group B
wherein group B is a group consisting of C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, $-OR^{a4}$, $-SR^{a4}$, $-NR^{a4}R^{a5}$, $-CONR^{a4}R^{a5}$, $-SO_2NR^{a4}R^{a5}$, $-COR^{a6}$, $-NR^{a4}COR^{a6}$, $-SO_2R^{a6}$, $-NR^{a4}SO_2R^{a6}$, $-COOR^{a4}$ and $-NR^{a5}COOR^{a6}$
wherein R^{a4} and R^{a5} are the same or different and each is hydrogen atom, C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A, and R^{a6} is C_{1-4} alkyl group, C_{3-10} carbon ring group optionally substituted by 1 to 5 substituents selected from the above-mentioned group A or heterocyclic group (as defined above) optionally substituted by 1 to 5 substituents selected from the above-mentioned group A,

or a pharmaceutically acceptable salt thereof.

22. The 4-oxoquinoline compound of claim 5, which is selected from the group consisting of the following compounds:

6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-1),
6-(2,3-Dichlorobenzyl)-8-fluoro-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-2),
6-(2,3-Dichlorobenzyl)-1-(2-methanesulfonylaminoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-3),
6-(2,3-Dichlorobenzyl)-1-(2-imidazol-1-ylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-4),
6-(2,3-Dichlorobenzyl)-1-dimethylcarbamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic-acid (Example 1-5),
6-(2,3-Dichlorobenzyl)-1-methylcarbamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-6),
1-Carbamoylmethyl-6-(2,3-Dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-7),
6-(2,3-Dichlorobenzyl)-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-8),
6-(2,3-Dichlorobenzyl)-4-oxo-1-sulfamoylmethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 1-9),
1-(2-Carboxyethyl)-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-10),
1-(2-Hydroxyethyl)-6-naphthalen-1-ylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-11),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methyl ester (Example 1-12),
1-(2-Carbamoylethyl)-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-13),
6-(2,3-Dichlorobenzyl)-4-oxo-1-(2-oxopropyl)-1,4-dihydroquinoline-3-carboxylic acid (Example 1-14),
1-Benzyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-15),
6-(2,3-Dichlorobenzyl)-4-oxo-1-phenethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 1-16),
6-(2,3-Dichlorobenzyl)-1-(3-phenylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-17),
6-(2,3-Dichlorobenzyl)-1-isobutyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-18),
6-(2,3-Dichlorobenzyl)-1-(4-phenylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-19),
1-Biphenyl-2-ylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-20),
6-(2,3-Dichlorobenzyl)-1-(4-hydroxybutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-21),
1-Benzo[b]thiophen-2-ylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-22),
6-(2,3-dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-23),
6-(2,3-Dichlorobenzyl)-1-(2-dimethylaminoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-24),
6-(2,3-Dichlorobenzyl)-1-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-25),
6-(2,3-Dichlorobenzyl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-26),
6-(2,3-Dichlorobenzyl)-1-(2,2,2-trifluoroethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-27),
1-Carboxymethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-28),
6-(2,3-Dichlorobenzyl)-1-[2-(4-methylthiazol-5-yl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-29),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-30),
6-(2,3-Dichlorobenzyl)-1-(2-methylsulfanylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-32),
6-(2-Chloro-6-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-33),
6-(2,3-Dichlorobenzyl)-1-(5-hydroxypentyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-34),
6-(2,3-dichlorobenzyl)-1-(2-morpholin-4-ylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-35),
6-(2,3-Dichlorobenzyl)-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-36),
6-(2,3-Dichlorobenzyl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-37),
6-(2,3-Dichlorobenzyl)-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylic acid (Example 1-38),
1-Butyl-6-(2,3-Dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-39),
1-Cyclopentylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-40),
6-(2,3-Dichlorobenzyl)-1-(2-methanesulfonylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-41),
1-Cyclohexylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-42),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxy-2-phenylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-43),
6-(2,3-Dichlorobenzyl)-1-(2-fluoroethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-44),
6-(2,3-Dichlorobenzyl)-4-oxo-1-(2-pyridin-2-ylethyl)-1,4-dihydroquinoline-3-carboxylic acid (Example 1-45),
1-(2-Aminoethyl)-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-46),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxy-2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example

1-47),
1-(2-Acetylaminoethyl)-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-48),
6-(2,3-Dichlorobenzyl)-1-(2-ethoxycarbonylaminoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-49),
6-(2,3-Difluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-50),
6-(2-Chloro-4-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-51),
6-(2-Chlorobenzyl)-4-oxo-1-phenethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 1-65),
6-(2-Chloro-3-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-66),
6-(2,3-Dichlorobenzyl)-1-methylsulfanylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-68),
6-(2,3-Dichlorobenzyl)-1-methanesulfonylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-69),
1-tert-Butylsulfamoylmethyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-70),
6-(2,3-Dichlorobenzyl)-1-methylsulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-71),
6-(2,3-Dichlorobenzyl)-1-dimethylsulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-72),
6-(2-Chloro-3,6-difluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-73),
6-(2,3-Dichlorobenzyl)-1-(2,3-Dihydroxypropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-74),
6-(2-Chloro-6-fluorobenzyl)-1-sulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-75),
6-(2-Chloro-6-fluorobenzyl)-1-methylsulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-76),
6-(2-Chloro-6-fluorobenzyl)-1-dimethylsulfamoylmethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-77),
6-(2-Chloro-3-methylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-79),
6-(2-Bromobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-80),
6-(2-Chloro-3-methoxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-82),
1-(2-Hydroxyethyl)-6-(2-methanesulfonylbenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-85),
6-Biphenyl-2-ylmethyl-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-86),
6-(2-Chlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-87),
6-(2-Chloro-5-methylsulfanylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-92),
1-(2-Hydroxyethyl)-4-oxo-6-(2-trifluoromethyloxybenzyl)-1,4-dihydroquinoline-3-carboxylic acid (Example 1-93),
6-(2-Chloro-5-methylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-97),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-99),
6-(3-Chloro-2,6-difluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-100),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-101),
1-Cyclopropyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 1-102),
1-Amino-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-1),
6-(2,3-Dichlorobenzyl)-1-methoxycarbonylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-2),
1-Acetylamino-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-3),
6-(2,3-Dichlorobenzyl)-1-methanesulfonylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-4),
6-(2,3-Dichlorobenzyl)-1-(N-methanesulfonyl-N-methylamino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-5),
6-(2,3-Dichlorobenzyl)-1-dimethylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-6),
6-(2,3-Dichlorobenzyl)-1-methylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-7),
6-(2,3-Dichlorobenzyl)-1-ethylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 2-8),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-5-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-1),

6-(3-Chloro-2-methylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-2),
6-(3-Chloro-2-methoxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-3),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-4),
6-(2,3-Dichlorobenzyl)-5-hydroxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-5),
6-(2,3-Dichlorobenzyl)-7-hydroxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-6),
1-(2-Hydroxyethyl)-6-(2-methylaminobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-7),
6-(2-Dimethylaminobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-8),
6-(2,3-Dichlorobenzyl)-4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylic acid (Example 3-9),
6-(2,3-Dichlorobenzyl)-1-[2-hydroxy-1-(hydroxymethyl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-10),
1-Cyclobutyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-12),
1-Cyclopentyl-6-(2,3-dichlorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-13),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-14),
6-(2-Dimethylsulfamoylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-16),
6-(3-Chloro-2,4-difluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-17),
6-(2-Carboxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-18),
1-(2-Hydroxyethyl)-6-(2-methylsulfamoylbenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-19),
6-(2,3-Dichlorobenzyl)-7-ethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-20),
7-Chloro-6-(2,3-dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-21),
6-(2,3-Dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-7-trifluoromethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 3-22),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-23),
(R)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-24),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-8-trifluoromethyl-1,4-dihydroquinoline-3-carboxylic acid (Example 3-25),
6-(3-Chloro-2-fluorobenzyl)-1-[2-hydroxy-1-(hydroxymethyl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-26),
7-Cyano-6-(2,3-dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-27),
6-(2-Ethylmethylaminobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-28),
6-[2-(N-Methyl-N-propylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-29),
6-[2-(N-Benzyl-N-methylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-30),
6-[2-(N-Methanesulfonyl-N-methylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-31),
6-[2-(N-Isopropyl-N-methylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-32),
1-tert-Butyl-6-(3-Chloro-2-fluorobenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-33),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-34),
8-Amino-6-(3-chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-35),
7-Carboxy-6-(2,3-dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-36),

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6-(3-Chloro-2,6-difluorobenzyl)-1-(2-hydroxyethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-37),
6-(3-Chloro-2-fluorobenzyl)-8-dimethylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-38),
8-Acetylamino-6-(3-chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-39),
5-Cyano-6-(2,3-dichlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-40),
6-[2-(N-Acetyl-N-methylamino)benzyl]-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-41),
6-(2-Diethylaminobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-42),
6-(3-Chloro-2-fluorobenzyl)-1-(1,1-dimethyl-2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-43),
6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-44),
6-(3-Chloro-2-fluorobenzyl)-7,8-dimethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-45),
6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-47),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-8-methylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-48),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-7-propyloxy-1,4-dihydroquinoline-3-carboxylic acid (Example 3-49),
6-(3-Chloro-2-fluorobenzyl)-7-(dimethylaminomethyleneamino)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-50),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methyl ester (Example 3-51),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-8-phenoxy-1,4-dihydroquinoline-3-carboxylic acid (Example 3-52),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-darboxylic acid (Example 3-53),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-8-propylamino-1,4-dihydroquinoline-3-carboxylic acid (Example 3-54),
6-(3-Chloro-2-fluorobenzyl)-8-ethylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-55),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-56),
(S)-6-(3-Chloro-2,6-difluorobenzyl)-1-(2-hydroxy-1-methylethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-57),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-8-propyloxy-1,4-dihydroquinoline-3-carboxylic acid (Example 3-58),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-59),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-60),
(S)-6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-61),
6-(3-Chloro-2-fluorobenzyl)-7-dimethylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-62),
6-(3-Chloro-2-fluorobenzyl)-7-cyclohexylmethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-63),
6-(3-Chloro-2-fluorobenzyl)-8-diethylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-64),
6-(3-Chloro-2-fluorobenzyl)-7-methylamino-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-65),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-7-pyrrolidin-1-yl-1,4-dihydroquinoline-3-carboxylic acid (Example 3-66),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxy-

lic acid (Example 3-67),
(S)-6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-[1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-68),
6-(3-Chloro-2-fluorobenzyl)-8-cyclohexylmethoxy-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-69),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-70),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-3-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-71),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-72),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example , 3-73),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-7-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-74),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-75),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-(2-hydroxyethyloxy)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-76),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-7-(3-hydroxypropyloxy)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-77),
6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxyethyl)-8-(2-hydroxyethylamino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-78),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-79),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-dimethylamino-1-(2-hydroxy-1-methylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-80),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-phenylethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-81),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-82),
6-(3-Chloro-2-fluorobenzyl)-1-((1S,2S)-1-hydroxymethyl-2-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-83),
(S) -6- (3-Chloro-2-fluorobenzyl) -1- (2-hydroxy-1-methylethyl) -7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-84),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-benzyl-2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 3-85),
6-(2-Chloro-5-methanesulfonylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-1),
6-(2-Ethylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-4),
6-(2-Chloro-5-methylbenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-5),
6-(2-Chloro-5-fluorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-6),
6-(5-Bromo-2-chlorobenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-7),
6-(2,3-Dichlorobenzyl)-7-fluoro-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-9),
6-(2-Chloro-5-hydroxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-11),
6-(2,3-Dichlorobenzyl)-5-fluoro-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-12),
6-(2-Ethoxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-13),
6-(2-Hydroxybenzyl)-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-14),
6-(2,3-Dichlorobenzyl)-7-methyl-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-15),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(2-hydroxy-1-methylethyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-16),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-17),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic ac-

id (Example 4-18),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-19),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-20),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-[1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-21),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2-cyclohexyl-1-(hydroxymethyl)ethyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-22),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-3-methylbutyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-23),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-24),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-3-methylbutyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-25),
(S)-6-(3-Chloro-2-fluorobenzyl)-[2,2-dimethyl-1-(hydroxymethyl)propyl]-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-26),
6-(3-Chloro-2-fluorobenzyl)-1-((1S,2S)-1-hydroxymethyl-2-methylbutyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-27),
6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-((1S,2S)-1-hydroxymethyl-2-methylbutyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-28),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)propyl]-7-methylsulfanyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-29),
(S)-6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-(1-hydroxymethyl-2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-30),
(S)-6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-31),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-32),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-33),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-34),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-35),
(S)-6-(3-Chloro-2-fluorobenzyl)-7-ethoxy-1-[1-(hydroxymethyl)butyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-36),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-37),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-38),
6-(3-Chloro-2-fluorobenzyl)-1-((1S,2S)-1-hydroxymethyl-2-methylbutyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-39),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-7-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-40),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-8-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-41),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-42),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-7-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-43),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-44),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-(1-hydroxymethyl-2-methylpropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-45),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-hydroxymethyl-2-methylpropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-46),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-car-

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boxylic acid (Example 4-47),
(S)-6-(3-Chloro-2-fluorobenzyl)-8-ethoxy-1-[1-(hydroxymethyl)butyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-48),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[1-(hydroxymethyl)butyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-49),
(S)-6-(3-Chloro-2-fluorobenzyl)-1-(1-cyclohexyl-2-hydroxyethyl)-8-isopropyloxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-50) and
(S)-6-(3-Chloro-2-fluorobenzyl)-1-[2,2-dimethyl-1-(hydroxymethyl)propyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Example 4-52),

or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising a 4-oxoquinoline compound of any of claims 5 to 22, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

24. An integrase inhibitor comprising a 4-oxoquinoline compound of any of claims 1 to 22, or a pharmaceutically acceptable salt thereof, as an active ingredient.

25. An antiviral agent comprising a 4-oxoquinoline compound of any of claims 5 to 22, or a pharmaceutically acceptable salt thereof, as an active ingredient.

26. An anti-HIV agent comprising a 4-oxoquinoline compound of any of claims 5 to 22, or a pharmaceutically acceptable salt thereof, as an active ingredient.

27. An anti-HIV composition comprising a 4-oxoquinoline compound of any of claims 1 to 22, or a pharmaceutically acceptable salt thereof, and other one or more kinds of anti-HIV active substance as an active ingredient.

28. An anti-HIV agent comprising a 4-oxoquinoline compound of any of claims 1 to 22, or a pharmaceutically acceptable salt thereof, as an active ingredient, for multiple drug combination therapy with other anti-HIV agent(s).

29. Use of a 4-oxoquinoline compound of any of claims 5 to 22 or a pharmaceutically acceptable salt thereof, for the production of an anti-HIV agent.

30. Use of a 4-oxoquinoline compound of any of claims 5 to 22 or a pharmaceutically acceptable salt thereof, for the production of an integrase inhibitor.

31. Use of a 4-oxoquinoline compound of any of claims 5 to 22 or a pharmaceutically acceptable salt thereof, for the production of an antiviral agent.

32. A method for the prophylaxis or treatment of an HIV infectious disease, which comprises administering an effective amount of a 4-oxoquinoline compound of any of claims 5 to 22 or a pharmaceutically acceptable salt thereof to a mammal.

33. The method for the prophylaxis or treatment of an HIV infectious disease according to claim 32, which further comprises administering an effective amount of at least one different anti-HIV active substance to said mammal.

34. A method for inhibiting integrase, which comprises administering an effective amount of a 4-oxoquinoline compound of any of claims 5 to 22 or a pharmaceutically acceptable salt thereof to a mammal.

35. A method for the prophylaxis or treatment of a virus infectious disease, which comprises administering an effective amount of a 4-oxoquinoline compound of any of claims 5 to 22 or a pharmaceutically acceptable salt thereof to a mammal.

36. An anti-HIV composition comprising a 4-oxoquinoline compound of any of claims 5 to 22 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

37. A pharmaceutical composition for inhibiting integrase, which comprises a 4-oxoquinoline compound of any of claims 5 to 22 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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38. An antiviral composition comprising a 4-oxoquinoline compound of any of claims 5 to 22 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

39. A commercial package comprising the composition of claim 36 and a written matter associated therewith, the written matter stating that the composition can or should be used for the prophylaxis or treatment of an HIV infectious disease.

40. A commercial package comprising the composition of claim 37 and a written matter associated therewith, the written matter stating that the composition can or should be used for inhibiting integrase.

41. A commercial package comprising the composition of claim 38 and a written matter associated therewith, the written matter stating that the composition can or should be used for the prophylaxis or treatment of a viral infectious disease.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/14773

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D215/56, 401/06, 409/06, 417/06, 471/04, A61K31/47, 31/4709, 31/5377, 31/4375, A61P31/12, 31/18, 43/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D215/56, 401/06, 409/06, 417/06, 471/04, A61K31/47, 31/4709, 31/5377, 31/4375, A61P31/12, 31/18, 43/00

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/CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/45269 A1 (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE), 15 October, 1998 (15.10.98), & FR 2761687 A & EP 975597 A & JP 2001-518890 A	1-31,36-41
A	WO 97/38999 A1 (THE GOVERNMENT OF THE UNITED STATES OF AMERICA), 23 October, 1997 (23.10.97), & CA 2250863 A & AU 2815797 A & EP 892801 A & JP 2000-508662 A & US 6187775 B1 & US 2001/9914 A1	1-31,36-41
A	WO 02/004444 A2 (PHARMACIA & UPJOHN CO.), 17 January, 2002 (17.01.02), & US 2002/025960 A1 & US 6559145 B2 & US 2003/207880 A1	1-31,36-41

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January, 2004 (22.01.04)	10 February, 2004 (10.02.04)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/14773

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/001714 A1 (MICROCIDE PHARMACEUTICALS, INC.), 13 January, 2000 (13.01.00), Compounds of RN:254883-06-2 & US 6399629 B1 & AU 9952073 A1	5-31,36-41
A	ABDUL-AHAD, P.G. et al., "Trends in dehydrogenase inhibitory potencies of some quinolones, using quantum chemical indices", Compound 11, European Journal of Medicinal Chemistry 17(4), pp.301-6 (1982)	5-31,36-41
A	YOSHIMOTO, M. et al., "Correlation Analysis of Baker's Studies on Enzyme Inhibition. 2. Chymotrypsin, Trypsin, Thymidine Phosphorylase, Uridine Phosphorylase, Thymidilate Synthetase, Cytosine Nucleoside Deaminase, Dihydrofolate Reductase, Malate, Glutamate, Lactate, and Glyceraldehyde-phosphate Dehydrogenase", table XXIV, compound 33, Journal of Medicinal Chemistry 19(1), pages 71 to 98 (1976)	5-31,36-41
A	BAKER, B.R. et al., "Irreversible Enzyme Inhibitors. 191. Hydrophobic Bonding to Some Dehydrogenases by 6-, 7-, or 8-, compound 25, Journal of Medicinal Chemistry 15(3), pp.235-7 (1972)	5-31,36-41
X A	US 3472859 A (Sterling Drug Inc.), 14 October, 1969 (14.10.69), & NL 6714679 A	5-23,25,31, 38,41 24,26-30, 36-37,39-40
A	WO 01/098275 A2 (PHARMACIA & UPJOHN CO.), 27 December, 2001 (27.12.01), & US 2002/103220 A1 & US 6653307 B2 & EP 1292575 A2 & BR 2001011729 A & JP 2004-501138 A	1-31,36-41
A	WO 00/040563 A1 (PHARMACIA & UPJOHN CO.), 13 July, 2000 (13.07.00), & US 6248736 B1 & EP 1140851 A1 & BR 9916781 A & JP 2002-534417 A & NZ 512823 A & ZA 2001004710 A & NO 2001003379 A	1-31,36-41
A	WO 00/040561 A1 (PHARMACIA & UPJOHN CO.), 13 July, 2000 (13.07.00), & US 6248739 B1 & EP 1140850 A1 & AU 760207 A & JP 2002-534416 A & NZ 512824 A & ZA 2001004711 A & NO 2001003383 A	1-31,36-41

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/14773

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WALTON, L. et al., "In Vitro Cleavable-Complex Assay to Monitor Antimicrobial Potency of Quinolones", Antimicrobial Agents and Chemotherapy 32(7), pp.1086-9 (1988)	1-31,36-41
A	STEFANCICH, G. et al., "Antibacterial and antifungal agents. VII. Synthesis of (1-pyrryl) methylquinolonecarboxylic acids", Farmaco, Edizione Scientifica 42(1), pages 3 to 16 (1987)	1-31,36-41

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/14773

Box I ***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. [X] Claims Nos.: 32 to 35
because they relate to subject matter not required to be searched by this Authority, namely:
The inventions as set forth in claims 32 to 35 are relevant to methods for treatment of the human body by therapy.

2. [ ] Claims Nos.:
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:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II ***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 an additional fee, this Authority did not invite payment of any additional fee.

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.
[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

August 13, 2001

Exhibit-B

Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents

Table of Contents

August 13, 2001

Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents

These Guidelines were developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. Leadership of the Panel consists of Anthony S. Fauci, National Institutes of Health, Bethesda, MD (co-chair); John G. Bartlett, Johns Hopkins University, Baltimore, MD (co-chair); Eric P. Goosby, DHHS, Washington, DC, (co-convener); and Jennifer Kates, Henry J. Kaiser Foundation, San Francisco, CA, (co-convener).

Current members of the Panel include: Jean Anderson (Johns Hopkins University, Baltimore, MD), Rodney Armstead (UHP Healthcare, Inc., Inglewood, CA), A. Cornelius Baker (Whitman-Walker Clinic, Washington, DC), David Barr (Forum for Collaborative HIV Research, Washington, DC), Samuel A. Bozzette (SDVA Medical Center, San Diego, CA), Charles Carpenter (Brown University School of Medicine, Providence, RI), Martin Delaney (Project *Inform*, San Francisco, CA), Lawrence Deyton, (Dept. of Veterans Affairs, Washington, DC), Wafaa El-Sadr (Harlem Hospital, New York, NY), Courtney Fletcher (University of Minnesota, MN), Fred Gordin, (Veterans Administration Medical Center, Washington, DC), Mark Harrington (Treatment Action Group, New York, NY), Martin S. Hirsch (Massachusetts General Hospital, Boston, MA), John W. Mellors (University of Pittsburgh, Pittsburgh, PA), James Neaton (University of Minnesota, Minneapolis, MN), Sallie Perryman (New York State Department of Health, New York, NY), John Phair (Northwestern University, Chicago, IL), Robert T. Schooley (University of Colorado, Denver, CO), Renslow Sherer (The CORE Center, Cook County Hospital, Chicago, IL), Stephen A. Spector (University of California San Diego, La Jolla, CA), Sharilyn K. Stanley (Texas Department Of Health, Austin, TX), Paul Volberding (University of California, San Francisco, CA), Suzanne Willard (MCP Hahnemann University, Philadelphia, PA) ; *participants from the Department of Health and Human Services*: Victoria Cargill (National Institutes of Health), Oren Cohen (National Institutes of Health), Mark Dybul (National Institutes of Health), T. Randolph Graydon (Health Care Financing Administration), Heidi Jolson (Food and Drug Administration), Jonathan Kaplan (Centers for Disease Control and Prevention), Abe Macher (Health Resources and Services Administration), Henry Masur (National Institutes of Health), Lynne Mofenson (National Institutes of Health), Jeffrey Murray (Food and Drug Administration), Joseph O'Neill (Health Resources and Services Administration), Alice Pau (National Institutes of Health), Lucille C. Perez (Substance Abuse and Mental Health Services Administration). *Non-voting observers include*: Gerry Bally (Health Canada, Ottawa, Ontario), Douglas Brust (National Institutes of Health), Sophia Chang (Center for Quality HIV Care, V.A., Palo Alto, CA), Washington, DC), Richard Marlink (Harvard AIDS Institute, Cambridge, MA), Celia Maxwell (AIDS Education and Training Center, Washington, DC), Howard Minkoff (Maimonides Medical Center, Brooklyn, NY), James Oleske (UMDNJ, Newark, NJ), Daniel Simpson (Indian Health Service, Rockville, MD).

Summary

The availability of an increasing number of antiretroviral agents and the rapid evolution of new information has introduced extraordinary complexity into the treatment of HIV-infected persons. In 1996, the Department of Health and Human Services and the Henry J. Kaiser Family Foundation convened the Panel on Clinical Practices for the Treatment of HIV to develop guidelines for the clinical management of HIV-infected adults and adolescents.

This report recommends that care should be supervised by an expert, and makes recommendations for laboratory monitoring including plasma HIV RNA, CD4 cell counts and HIV drug resistance testing. The report also provides guidelines for antiretroviral therapy, including when to start treatment, what drugs to initiate, when to change therapy, and therapeutic options when changing therapy. Special considerations are provided for adolescents and pregnant women. As with treatment of other chronic conditions, therapeutic decisions require a mutual understanding between the patient and the health care provider regarding the benefits and risks of treatment. Antiretroviral regimens are complex, have major side effects, pose difficulty with adherence, and carry serious potential consequences from the development of viral resistance due to non-adherence to the drug regimen or suboptimal levels of antiretroviral agents. Patient education and involvement in therapeutic decisions is important for all medical conditions, but is considered especially critical for HIV infection and its treatment.

With regard to specific recommendations, treatment should be offered to all patients with the acute HIV syndrome, those within six months of HIV seroconversion, and all patients with symptoms ascribed to HIV infection. Recommendations for offering antiretroviral therapy in asymptomatic patients require analysis of many real and potential risks and benefits. In general, treatment should be offered to individuals with fewer than 350 $CD4^+$ T cells/mm^3 or plasma HIV RNA levels exceeding 30,000 copies/mL (bDNA assay) or 55,000 copies/mL (RT-PCR assay). The strength of the recommendation to treat asymptomatic patients should be based on the willingness and readiness of the individual to begin therapy; the degree of existing immunodeficiency as determined by the $CD4^+$ T cell count; the risk of disease progression as determined by the $CD4^+$ T cell count and level of plasma HIV RNA; the potential benefits and risks of initiating therapy in asymptomatic individuals; and the likelihood, after counseling and education, of adherence to the prescribed treatment regimen. Once the decision has been made to initiate antiretroviral therapy, the goals should be maximal and durable suppression of viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Results of therapy are evaluated primarily with plasma HIV RNA levels; these are expected to show a one-$\log_{10}$ decrease at eight weeks and no detectable virus (<50 copies/mL) at 4-6 months after initiation of treatment. Failure of therapy at 4-6 months may be ascribed to non-adherence, inadequate potency of drugs or suboptimal levels of antiretroviral agents, viral resistance, and other factors that are poorly understood. Patients whose therapy fails in spite of a high level of adherence to the regimen should have their regimen changed; this change should be guided by a thorough drug treatment history and the results of drug resistance testing. Optimal changes in therapy may be especially difficult to achieve for patients in whom the preferred regimen has failed, due to limitations in the available alternative antiretroviral regimens that have documented efficacy; these decisions are further confounded by problems with adherence, toxicity, and resistance. In some settings it

may be preferable to participate in a clinical trial with or without access to new drugs or to use a regimen that may not achieve complete suppression of viral replication.

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the **HIV/AIDS Treatment Information Service website** (http://www.hivatis.org).

1887 August 13, 2001

Guidelines for the Use of Antiretroviral Agents In HIV-Infected Adults and Adolescents

Introduction

This document was developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. The document contains recommendations for the clinical use of antiretroviral agents in the treatment of HIV-infected adults and adolescents (defined here as late puberty or Tanner V). Guidance for the use of antiretroviral treatment in pediatric HIV infection is not contained in this document. While the pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected individuals, there are unique therapeutic and management considerations in HIV-infected children. In recognition of these differences, a separate document addresses pediatric-specific issues related to antiretroviral therapy, and is available at (**http://www.hivatis.org**).

These guidelines are intended for use by clinicians and other health care providers who use antiretroviral therapy to treat HIV-infected adults and adolescents and serve as a companion to the therapeutic principles formulated by the National Institutes of Health (NIH) Panel to Define Principles of Therapy of HIV Infection *(1)*. Together the documents should provide the pathogenesis-based rationale for therapeutic strategies as well as practical guidelines for implementing these strategies. While the guidelines represent the current state of knowledge regarding the use of antiretroviral agents, this is a rapidly evolving field of science, and the availability of new agents or new clinical data regarding the use of existing agents will result in changes in therapeutic options and preferences. Thus, in recognition of the need for frequent updates to this document, a subgroup of the Panel, the Antiretroviral Working Group, meets monthly to review new data; recommendations for changes in this document are then submitted to the Panel and incorporated as appropriate. Copies of this document and all updates are available from the HIV/AIDS Treatment Information Service-ATIS (1–800–448–0440; TTY 1–888–480–3739; Fax 301–519–6616) and on the ATIS Web site (**http://www.hivatis.org**). They are also available from the National Prevention Information Network (NPIN) Web site (**http://www.cdcnpin.org**). These recommendations are not intended to substitute for the judgment of a clinician who is an expert in the care of HIV-infected individuals. It is important to note that the Panel felt that, where possible, the treatment of HIV-infected patients should be directed by a clinician with extensive experience in the care of these patients. When this is not possible, it is important to have access to such expertise through consultations.

Each recommendation is accompanied by a rating that includes a letter and a Roman numeral (Table 1); and is similar to the rating schemes used in previous guidelines on the prophylaxis of opportunistic infections (OIs) issued by the U.S. Public Health Service and the Infectious Diseases Society of America *(2)*. The letter indicates the strength of the recommendation, based on the opinion of the Panel, while the Roman numeral rating reflects the nature of the evidence supporting the recommendation (Table 1). Thus, recommendations based on data from clinical trials with clinical endpoints are differentiated from those with laboratory endpoints such as

$CD4^+$ T lymphocyte count or plasma HIV RNA levels; where no clinical trial data are available, recommendations are based on the opinions of experts familiar with the relevant scientific literature.

This document addresses the following issues: the use of testing for plasma HIV RNA levels (viral load) and $CD4^+$ T cell count; the use of testing for antiretroviral drug resistance; considerations for when to initiate therapy in established HIV infection; adherence to antiretroviral therapy; special considerations for therapy in patients with advanced stage disease; therapy-related adverse events; interruption of therapy; considerations for changing therapy and available therapeutic options; the treatment of acute HIV infection; considerations for antiretroviral therapy in adolescents; and considerations for antiretroviral therapy in the pregnant woman.

Use of Testing for Plasma HIV RNA Levels and $CD4^+$ T Cell Count in Guiding Decisions for Therapy

Decisions regarding initiation or changes in antiretroviral therapy should be guided by monitoring the laboratory parameters of plasma HIV RNA (viral load) and $CD4^+$ T cell count, as well as the clinical condition of the patient. Results of these two laboratory tests give the physician important information about the virologic and immunologic status of the patient and the risk of disease progression to AIDS *(3, 4)*. It should be noted that HIV viral load testing has been approved by the FDA for determining prognosis and for monitoring the response to therapy only for the RT- PCR assay (Roche). Multiple analyses in over 5000 patients who participated in approximately 18 trials with viral load monitoring showed a statistically significant dose-response type association between decreases in plasma viremia and improved clinical outcome based on standard endpoints of new AIDS-defining diagnoses and survival. This relationship was observed over a range of patient baseline characteristics including: pretreatment plasma RNA level, $CD4^+$ T cell count, and prior drug experience. Thus, it is the consensus of the Panel that viral load testing is an essential parameter in decisions to initiate or change antiretroviral therapies. Measurement of plasma HIV RNA levels (viral load), using quantitative methods, should be performed at the time of diagnosis and every 3–4 months thereafter in the untreated patient (AIII) (Table 2). $CD4^+$ T cell counts should be measured at the time of diagnosis and generally every 3-6 months thereafter (AIII). These intervals between tests are merely recommendations and flexibility should be exercised according to the circumstances of the individual case. Plasma HIV RNA levels should also be measured immediately prior to and again at 2-8 weeks after initiation of antiretroviral therapy (AIII). This second time point allows the clinician to evaluate the initial effectiveness of therapy, since in most patients adherence to a regimen of potent antiretroviral agents should result in a large decrease (~ 1.0 $\log_{10}$) in viral load by 2-8 weeks. The viral load should continue to decline over the following weeks and in most individuals becomes below detectable levels (currently defined as <50 RNA copies/mL) by 16-20 weeks. The rate of viral load decline towards undetectable is affected by the baseline $CD4^+$ T cell count, the initial viral load, potency of the regimen, adherence to the regimen, prior exposure to antiretroviral agents, and the presence of any OIs. These individual differences must be considered when monitoring the effect of therapy. However, the absence of a virologic response of the magnitude discussed above should prompt the physician to reassess patient adherence, rule out malabsorption, consider repeat RNA testing to document lack of response, and/or consider a

change in drug regimen. Once the patient is on therapy, HIV RNA testing should be repeated every 3–4 months to evaluate the continuing effectiveness of therapy (AII). With optimal therapy viral, levels in plasma at 6 months should be undetectable, that is, below 50 copies of HIV RNA per mL of plasma *(5)*. Data from clinical trials strongly suggest that lowering plasma HIV RNA to below 50 copies/mL is associated with a more complete and durable viral suppression, compared with reducing HIV RNA to levels between 50-500 copies/mL *(6)*. If HIV RNA remains detectable in plasma after 16-20 weeks of therapy, the plasma HIV RNA test should be repeated to confirm the result and a change in therapy should be considered, according to the guidelines in the section "Considerations for Changing a Failing Regimen" (see p. 23) (BIII).

When making decisions regarding the initiation of therapy, the $CD4^+$ T lymphocyte count and plasma HIV RNA measurement should ideally be performed on two occasions to ensure accuracy and consistency of measurement (BIII). However, in patients who present with advanced HIV disease, antiretroviral therapy should generally be initiated after the first viral load measurement is obtained in order to prevent a potentially deleterious delay in treatment. It is recognized that the requirement for two measurements of viral load may place a significant financial burden on patients or payers. Nonetheless, the Panel feels that two measurements of viral load will provide the clinician with the best information for subsequent follow-up of the patient. Plasma HIV RNA levels should not be measured during or within four weeks after successful treatment of any intercurrent infection, resolution of symptomatic illness, or immunization. Because there are differences among commercially available tests, confirmatory plasma HIV RNA levels should be measured by the same laboratory using the same technique in order to ensure consistent results.

A minimally significant change in plasma viremia is considered to be a 3-fold or 0.5 $\log_{10}$ increase or decrease. A significant decrease in $CD4^+$ T lymphocyte count is a decrease of >30% from baseline for absolute cell numbers and a decrease of >3% from baseline in percentages of cells *(7)*. Discordance between trends in $CD4^+$ T cell numbers and plasma HIV RNA levels can occur and was found in 20% of patients in one cohort studied *(8)*. Such discordance can complicate decisions regarding antiretroviral therapy and may be due to a number of factors that affect plasma HIV RNA testing. In general, viral load and trends in viral load are felt to be more informative for guiding decisions regarding antiretroviral therapy than are $CD4^+$ T cell counts; exceptions to this rule do occur, however. For further discussion refer to "Considerations for Changing a Failing Regimen", p. 23. In many such cases, expert consultation should be considered.

Testing for Drug Resistance

Background

Testing for HIV resistance to antiretroviral drugs is a rational adjunct to guide antiretroviral therapy. When combined with a detailed drug history and efforts aimed at maximizing drug adherence, these assays may help to maximize the benefits of antiretroviral therapy. Many studies in treatment experienced patients have shown strong associations between the presence of drug resistance (identified by either genotyping or phenotyping resistance assays) and failure of the antiretroviral treatment regimen to suppress HIV replication. Genotyping assays detect drug

resistance mutations that are present in the relevant viral genes (i.e., RT and protease). Some genotyping assays involve sequencing of the entire RT and protease genes, while others utilize probes to detect selected mutations that are known to confer drug resistance. Genotyping assays can be performed relatively rapidly, such that results can be reported within 1-2 weeks of sample collection. Interpretation of test results requires an appreciation of the range of mutations that are selected for by various antiretroviral drugs, as well as the potential for cross-resistance to other drugs conferred by some of these mutations (see the **http://hiv-web.lanl.gov** Web site). Consultation with an expert in HIV drug resistance is encouraged to facilitate interpretation of genotypic test results.

Phenotyping assays measure the ability of viruses to grow in various concentrations of antiretroviral drugs. Automated, recombinant phenotyping assays are commercially available with turn-around times of 2-3 weeks; however, phenotyping assays are generally more costly to perform compared with genotypic assays. Recombinant phenotyping assays involve insertion of the RT and protease gene sequences derived from patient plasma HIV RNA into the backbone of a laboratory clone of HIV either by cloning or *in vitro* recombination. Replication of the recombinant virus at various drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference strain of HIV. The concentrations of drugs that inhibit 50% and 90% of viral replication (i.e., the IC50 and IC90) are calculated, and the ratio of the IC50s of the test and reference viruses is reported as the fold increase in IC50, or fold resistance. Interpretation of phenotyping assay results is complicated by the paucity of data on the specific level of resistance (fold increase in IC50) that is associated with failure of different drugs; again, consultation with an expert may be helpful for interpretation of test results.

Further limitations of both genotyping and phenotyping assays include the lack of uniform quality assurance for all assays that are currently available, relatively high cost, and insensitivity for minor viral species; if drug-resistant viruses are present but constitute less than 10-20% of the circulating virus population, they will likely not be detected by current assays. This limitation is of particular importance when interpreting data about susceptibility to drugs that the patient has taken in the past but are not part of the current antiretroviral regimen. If drug resistance had developed to a drug that was subsequently discontinued, the drug-resistant virus can become a minor species because its growth advantage is lost *(9)*. Consequently, resistance assays should be performed while the patient is taking his/her antiretroviral regimen, and data suggesting the absence of resistance should be interpreted carefully in relation to the prior treatment history.

Use of resistance assays in clinical practice

Resistance assays may be useful in the setting of virologic failure on antiretroviral therapy and in acute HIV infection (Table 3). Recent prospective data supporting the use of resistance testing in clinical practice come from trials in which the utility of resistance tests were assessed in the setting of virologic failure. The VIRADAPT *(10)* and GART *(11)* studies compared virologic responses to antiretroviral treatment regimens when genotyping resistance tests were available to help guide therapy with those observed when changes in therapy were guided solely by clinical judgment. The results of both studies indicated that the short-term virologic response to therapy was significantly greater when results of resistance testing were available. Similarly, a recent prospective, randomized, multicenter trial has shown that therapy selected on the basis of

phenotypic resistance testing significantly improves the virological response to antiretroviral therapy, compared with therapy selected without the aid of phenotypic testing *(12)*. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in the setting of virologic failure (BII). Similar rationale applies to the potential use of resistance testing in the setting of suboptimal viral load reduction, as detailed in "Criteria for Changing Therapy", p.24 (BIII). It should be noted that virologic failure in the setting of HAART (Highly Active Antiretroviral Therapy) is in some instances associated with resistance only to one component of the regimen *(13)*; in this situation, it may be possible to substitute individual drugs in a failing regimen, although this concept requires clinical validation ("Considerations for Changing a Failing Regimen", p. 23). There are currently no prospective data to support the use of one type of resistance assay over the other (i.e., genotyping vs. phenotyping) in different clinical situations. Therefore, one type of assay is generally recommended per sample; however, in the setting of a complex prior treatment history, both assays may provide important and complementary information.

Transmission of drug-resistant strains of HIV has been documented, and may be associated with a suboptimal virologic response to initial antiretroviral therapy *(14-17)*. Treatment of acute HIV infection is associated with improved immunological outcome *(18, 19)*, and optimization of the initial antiretroviral regimen through the use of resistance testing is a reasonable, albeit untested, strategy (CIII). Because of its more rapid turnaround time, the use of a genotypic assay may be preferred in this setting; however, therapy should not be withheld while awaiting the results of resistance testing. The use of resistance testing prior to initiation of antiretroviral therapy in chronic HIV infection is not generally recommended (DIII) because of uncertainty about the prevalence of resistance in treatment-naive individuals and the fact that currently available resistance assays may fail to detect drug resistant species that were transmitted at the time of primary infection but became a minor species in the absence of selective drug pressure. The currently favored approach would be to reserve resistance testing for cases in which viral load suppression was suboptimal after initiation of therapy (see above), although this may change as more information becomes available on the prevalence of resistant virus in antiretroviral-naïve individuals.

In general, recommendations for resistance testing in pregnancy should be the same as for non-pregnant patients: acute HIV infection, virologic failure on an antiretroviral regimen, or suboptimal viral load suppression after initiation of antiretroviral therapy are all appropriate indications for resistance testing. If an HIV^+ pregnant woman is taking an antiretroviral regimen that does not include zidovudine, or if zidovudine was discontinued because of maternal drug resistance, intrapartum and neonatal zidovudine prophylaxis should still be administered to prevent mother-to-infant HIV transmission ("Considerations for Antiretroviral Therapy in the HIV-Infected Pregnant Woman", see p. 29 and Table 24). It is important to note that not all of zidovudine's activity in preventing mother-to-infant transmission of HIV can be accounted for by its effect on maternal viral load *(20)*; furthermore, preliminary data indicate that the rate of perinatal transmission following zidovudine prophylaxis may not differ between those with and without zidovudine resistance mutations *(21, 22)*. Further studies are needed to determine the best strategy to prevent mother-to-infant HIV transmission in the presence of zidovudine resistance.

Considerations for Patients with Established HIV Infection

Patients with established HIV infection are discussed in two arbitrarily defined clinical categories: 1) asymptomatic infection or 2) symptomatic disease (wasting, thrush or unexplained fever for > 2 weeks) including AIDS, defined according to the 1993 CDC classification system *(23)*. All patients in the second category should be offered antiretroviral therapy. Considerations for initiating antiretroviral therapy in the first category of patients are complex and are discussed separately below. Before initiating therapy in any patient, however, the following evaluation should be performed:

- Complete history and physical (AII)
- Complete blood count, chemistry profile (including serum transaminases and lipid profile (AII)
- $CD4^+$ T lymphocyte count (AI)
- Plasma HIV RNA Measurement (AI)

Additional evaluation should include routine tests pertinent to the prevention of OIs, if not already performed (RPR or VDRL, tuberculin skin test, toxoplasma IgG serology, and gynecologic exam with Pap smear), and other tests as clinically indicated (e.g., chest X-ray, hepatitis C virus (HCV) serology, ophthalmologic exam) (AII). Hepatitis B virus (HBV) serology is indicated in a patient who is a candidate for the hepatitis B vaccine or has abnormal liver function tests (AII), and CMV serology may be useful in certain individuals, as discussed in the "USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with the Human Immunodeficiency Virus" *(2)* (BIII).

Considerations for Initiating Therapy in the Patient with Asymptomatic HIV Infection

Initial placebo-controlled trials of zidovudine clearly established that antiretroviral treatment was associated with clinical benefit in HIV-infected individuals with advanced HIV disease and immunosuppression *(24)*. Later studies of immediate versus delayed zidovudine therapy in HIV-infected patients without AIDS demonstrated only a modest and transient advantage in favor of immediate therapy when probabilities of AIDS-free survival were compared *(25)*. As more nucleoside analogue reverse transcriptase inhibitors became available, it was shown that combinations of these drugs provided additional, more durable clinical benefit compared with monotherapy *(25)*. When protease inhibitors became available, studies in patients with advanced HIV disease demonstrated substantial additional clinical benefit when protease inhibitor plus dual nucleoside regimens were compared with dual nucleoside therapy alone *(26-28)*. These clinical trials data as well as observational data indicating that the risk of opportunistic diseases increases markedly when the $CD4^+$ T cell count declines to <200 cells/mm^3 strongly support the recommendation that all patients with a $CD4^+$ T cell count <200 cells/mm^3 or clinically-defined AIDS should be offered antiretroviral therapy.

Although there is theoretical benefit to antiretroviral therapy for patients with $CD4^+$ T cell counts greater than 200 cells/mm^3, no studies have been conducted comparing immediate versus delayed potent combination antiretroviral therapy in these patients. A major dilemma confronting patients and practitioners is that the antiretroviral regimens currently available that have the greatest potency in terms of viral suppression and $CD4^+$ T cell preservation are medically complex, are associated with a number of specific side effects and drug interactions, and pose a substantial challenge for adherence. Furthermore, the development of mutations associated with drug resistance can render therapy less effective or ineffective. Thus, decisions regarding treatment of asymptomatic, chronically infected individuals with $CD4^+$ T cell counts >200 cells/mm^3 must balance a number of competing factors that influence risk and benefit.

The optimal time to initiate antiretroviral therapy is not known. Table 4 summarizes the potential benefits and risks of early and of delayed initiation of therapy in the asymptomatic patient that the clinician and the patient must consider in deciding when to initiate therapy. Potential benefits of early therapy include earlier suppression of viral replication; preservation of immune function; prolongation of disease-free survival; and decrease in the risk of viral transmission. Risks include i) the adverse effects of the drugs on quality of life; ii) the inconvenience of most of the suppressive regimens currently available leading to reduced adherence; iii) development of drug resistance over time because of early initiation of therapy; iv) limitation of future treatment options due to premature cycling of the patient through the available drugs; v) the risk of transmission of virus resistant to antiretroviral drugs; vi) serious and unknown toxicities associated with some antiretroviral drugs (e.g., elevations in serum levels of cholesterol and triglycerides, alterations in the distribution of body fat, insulin resistance and even frank diabetes mellitus); and vii) the unknown durability of effect of the currently available therapies. The benefits of delayed therapy include minimization of treatment-related negative effects on quality of life and drug-related toxicities; preservation of treatment options; and delay in the development of drug resistance. Risks of delayed therapy include the theoretical possibility that some damage to the immune system that might otherwise be salvaged by earlier therapy is irreversible; the possibility that suppression of viral replication may be more difficult at a later stage of disease; and the increased risk of HIV transmission to others during a longer untreated period.

The strength of the recommendation for therapy must balance the readiness of the patient for treatment; consideration of the prognosis for disease-free survival in the absence of treatment as determined by baseline $CD4^+$ T cell count, viral load, (Table 5 and Figure 1), and the slope of the $CD4^+$ T cell count decline; and assessment of the risks and potential benefits associated with initiating antiretroviral therapy. [Note that the HIV RNA values shown in Table 5 and Figure 1 (first line or column) were obtained with the bDNA assay from the Multicenter AIDS Cohort Study (MACS). Expected values of HIV RNA obtained with the RT-PCR assay are also shown in Table 5 and Figure 1; comparison of the results obtained from the RT-PCR and bDNA assays using the manufacturer's controls consistently indicate that the HIV-1 RNA values obtained by RT-PCR are approximately two times higher than those obtained by the bDNA assay *(4)*. Thus, the MACS HIV RNA values have been multiplied by approximately 2 to be consistent with current RT-PCR values. A third test for HIV RNA, the Nucleic-Acid Sequence Based Amplification (NASBA), is currently used in some clinical settings. However, formulas for converting values obtained from either bDNA or RT-PCR assays to NASBA-equivalent values