PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
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P.O. Box 6288
Indianapolis, IN 46206-6288
ETATS-UNIS D'AMERIQUE

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 22670	Date of mailing *(day/month/year)* 31 August 2023 (31-08-2023) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2023/021637	International filing date *(day/month/year)* 10 May 2023 (10-05-2023)
Applicant ELI LILLY AND COMPANY	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau preferably through ePCT, or on paper to:
   The International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland

   For more detailed instructions, see the *PCT Applicant's Guide,* International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	VAN DER HOEK, Anita Tel: +49 (0)30 25901-706

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 22670	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2023/021637	International filing date *(day/month/year)* 10 May 2023 (10-05-2023)	(Earliest) Priority Date *(day/month/year)* 11 May 2022 (11-05-2022)
Applicant ELI LILLY AND COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/021637

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 A61K9/48 A61K31/437 A61P3/04 A61P3/10
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	US 2019/225604 A1 (YOSHINO HITOSHI [JP] ET AL) 25 July 2019 (2019-07-25) abstract; claims 1-13; examples 67, 162-163, Test examples 1-4; tables 2-5, 1-4; compound 67 page 93 paragraph [0305]	1-3,5, 8-13 1-3,5, 8-13 4,6,7, 14-29
X Y A	JP 2019 099571 A (CHUGAI PHARMACEUTICAL CO LTD) 24 June 2019 (2019-06-24) page 105, paragraph 404; examples 162-163, test examples 1-4; compound 67 paragraph [0185]	1-3,5, 8-13 1-3,5, 8-13 4,6,7, 14-29

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2023	31/08/2023

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

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/021637

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	KAWAI TAKAHIRO ET AL: "Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 117, no. 47, 24 November 2020 (2020-11-24), pages 29959-29967, XP093070947, ISSN: 0027-8424, DOI: 10.1073/pnas.2014879117 Retrieved from the Internet: URL:http://dx.doi.org/10.1073/pnas.2014879117>	1-3,5, 8-13
A	abstract; figure 1 . page 29966, column 2, paragraph Compound Formulation - page 29967, column 1, paragraph 1	4,6,7, 14-29

Y	WO 2008/030524 A2 (MERCK & CO INC [US]; BRESLIN DAVID [US] ET AL.) 13 March 2008 (2008-03-13)	1-3,5, 8-13
A	abstract; claims 1-19; examples 1-3	4,6,7, 14-29

Y	WO 02/064132 A2 (UPJOHN CO [US]; GAO PING [US]; MOROZOWICH WALTER [US]) 22 August 2002 (2002-08-22)	1-3,5, 8-13
A	examples 1-2	4,6,7, 14-29

Y	WO 02/056878 A2 (PHARMACIA CORP [US]; GAO PING [US] ET AL.) 25 July 2002 (2002-07-25)	1-3,5, 8-13
A	examples 3-5, 7	4,6,7, 14-29

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/021637

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CL 2019000663 A1	26-07-2019
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		WO 02064132 A2	22-08-2002
		ZA 200305086 B	30-06-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/021637

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02056878 A2	25-07-2002	AR 035735 A1	07-07-2004
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		PE 20020799 A1	11-09-2002
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		US 2002156124 A1	24-10-2002
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		WO 02056878 A2	25-07-2002

Information on Search Strategy

The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number

PCT/US2023/021637

TITLE: GLP1 PHARMACEUTICAL COMPOSITIONS

APPLICANT: ELI LILLY AND COMPANY

IPC CLASSIFICATION: A61K9/14, A61K9/48, A61K31/437, A61P3/04, A61P3/10

EXAMINER: Madalinska, K

CONSULTED DATABASES: CA, REG, EMBASE, EPODOC, NPL

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61K9/146, A61K9/485, A61K31/437, A61P3/04, A61P3/10

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
a composition, capsule, spray-dried dispersion, 3-[(1 S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, GLP1RA, orforglipron, LY-3502970, OWL-833, pH modifier, calcium carbonate, magnesium carbonate, sodium bicarbonate, sodium carbonate, magnesium hydroxide, calcium hydroxide, magnesium oxide, diabetes, weight management

JP2019099571A 20190624

EPO

SUBJECT OF THE INVENTION
Pharmaceutical composition containing pyrazolopyridine derivative having GLP-1 receptor agonist activity

[0001] The present invention relates to a pharmaceutical composition comprising, as an active ingredient, a compound having the same action as GLP-1 as a GLP-1 receptor agonist or a salt thereof, or a solvate thereof. The present invention also relates to a method for preventing or treating non-insulin dependent diabetes mellitus (type 2 diabetes) or obesity using the pharmaceutical composition.

[0002] Glucagon-like peptide-1 (GLP-1: glucagon-like peptide-1) is an incretin which is secreted from L cells in the small intestine when nutrients pass through the digestive tract, and glucose is mediated via the GLP-1 receptor It is known to exhibit various actions such as dependent insulin secretion promotion, glucagon secretion suppression, gastric emptying delay, food intake suppression and the like. GLP-1 analogues have already been put into practical use as anti-diabetic agents and are considered to be one of the most effective anti-diabetic agents because they show potent HbA1c reducing action and weight-reducing action, but they are all invasive Subcutaneous administration is required. Therefore, the creation of a non-invasively administrable GLP-1 receptor agonist is expected. For example, GLP-1 analogue using absorption promoter (sodium N- (8- (2-hydroxybenzoyl) amino) caprylate: SNAC: improvement of bioavailability when orally administered Semaglutide (Patent Document 1), low molecular weight Although attempts have been made to create GLP-1 receptor agonists (patent documents 2 and 3), further improvement is required for the characteristics as a pharmaceutical including activity, metabolic stability and bioavailability.

[0003] 2-[(2,4,6,7-tetrahydro-5H-pyrazolo [4,3-c] pyridin-5-yl) carbonyl] -1H-indole (2-[(2,4,6,7-tetrahydro) The following two compounds for chemical library are known as -5H-pyrazolo [4,3-c] pyridine-5-yl) carbonyl] -1H-indol).

[0004]

[0005] Patent Document 4 discloses eukaryotes such as blastocrithidia: the following pyrazolopyridines as compounds useful for the prevention and treatment of sleeping sickness, leishmaniasis and the like caused by parasitism of Trypanosomatida. Derivatives have been described.

[0006]

[0007] WO 2012/080471 WO 2009/111700 WO 2010/114824 WO 2016/038045

[0008] The problem to be solved by the present invention is a compound having the same action as a GLP-1 receptor agonist as a GLP-1 receptor agonist, capable of non-invasive administration and capable of improving activity, metabolic stability and bioavailability. It is intended to provide a pharmaceutical composition containing the salt, or a solvate thereof, and also a method for preventing or treating non-insulin dependent diabetes mellitus (type 2 diabetes) or obesity using the pharmaceutical composition. It is to provide.

[0009] The inventors of the present invention conducted intensive studies to solve such problems, and found that the compound represented by the formula (I) in which an indole ring and a pyrazolopyridine skeleton are linked via a substituent is GLP-1 As a receptor agonist, it has been found to have the same action as GLP-1 peptide, and the present invention has been completed.

[0010] That is, in one aspect of the present invention, the following invention is provided. [1] Formula (I):

[0011]

[0012] [Wherein, X represents -N = or -CRa =; Ra is selected from a hydrogen atom, a halogen atom, and a C1-6 alkyl; Y represents -C (= O)-, -CHR-, And -S (= O) 2-; R represents a hydrogen atom or C1-6 alkyl; Q1 represents C6-10 aryl or 5- to 10-membered heteroaryl, wherein C6-10 Aryl and 5- to 10-membered heteroaryl are independently selected from halogen atoms, C1-6 alkyl (wherein C1-6 alkyl may be substituted with one or more halogen atoms), and C1-6 alkoxy. Q2 may be substituted with 1 to 5 substituents selected; Q2 represents 3-12 membered heterocyclyl or 5-10 membered heteroaryl, wherein 3-12 membered heterocyclyl and 10 Heteroaryl of is independently selected from halogen atoms, C1-6 alkyl (wherein C1-6 alkyl may be substituted with one or more halogen atoms), C1-6 alkoxy, and -NRQaRQb It may be substituted by 1 to 3 substituents, and furthermore, two C1-6 alkyl may be taken together with the carbon atom to which they are attached to form a C3-8 carbocyclic ring; RQa And RQb are independently selected from hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl; R1, R2 and R3 are each independently hydrogen atom and C1-6 alkyl (wherein C1-6, -6 alkyl is selected from halogen atoms, C1-6 alkoxy, and optionally substituted with one or more substituents independently selected from hydroxy) R4, R5 and R6 are each independently selected from a hydrogen atom, a halogen atom and C1-6 alkyl; R7 and R8 independently represent a hydrogen atom or C1-6 alkyl, wherein The -6 alkyl may be substituted with one or more substituents independently selected from a halogen atom and a C 3-15 cycloalkyl, or R 7 and R 8 together with the carbon atom to which they are attached Or C3-15 cycloalkane ring, wherein the C3-15 cycloalkane ring formed by R7 and R8

together is substituted with 1 to 3 C1-6 alkyl Well, wherein C1-6 alkyl is independent of a halogen atom, hydroxy, -NR7aR7b, C1-6 alkoxy, and 3-12 membered heterocyclyl; R7a and R7b are independently selected from a hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl; n1 is N2 represents an integer of 0 to 5; R9 represents a group represented by the formula (IIa), (IIb), (IIc), (IId):

[0013]

[0014] R9a, R9b, R9c, R9d, and R9g are each independently a hydrogen atom, C1-6 alkyl (wherein C1-6 alkyl (wherein C1-6) The alkyl is selected from a halogen atom and one or more substituents independently selected from C1-6 alkoxy), and (C1-6 alkyl) carbonyl, and R9e is a hydrogen atom, or R1 represents a C1-6 alkyl optionally substituted by one or more halogen atoms, R9 f represents a hydrogen atom or C1-6 alkyl, R9 h represents a hydrogen atom, C1-6 alkyl, (C1-6 alkyl) carbonyl , Cyano, or -S (= O) n3-R9i; n3 represents an integer of 0 to 2; R9i represents C1-6 alkyl; Z The formula (IIIa), (IIIb), (IIIc), (IIId), and (IIIe):

[0015]

[0016] Rza is selected from a hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl, and Rzb and Rzc independently represent a hydrogen atom or C1-6 alkyl, n4 represents an integer of 1 to 3; n5 and n6 independently represent an integer of 0 to 10 (* represents a binding site to a pyrazolopyridine skeleton, and ** represents a binding site to Z2 , Each represents); Z2 is selected from C1-6 alkyl, C3-15 cycloalkyl, 3-12 membered heterocyclyl, C6-10 aryl, and 5-10 membered heteroaryl, wherein Alkyl, 3- to 12-membered heterocyclyl, C 6-10 aryl, and 5- to 10-membered heteroaryl are a group A: a group A: a) oxo, b) a halogen atom, c) cyano, And Rzd and Rze are each independently selected from hydrogen atom, C1-6 alkyl and (C1-6 alkyl) carbonyl, wherein C1-6 alkyl is hydroxy, halogen atom, and C1. E) -C (= O) -NRzfRzg, which may be substituted with one or more substituents independently selected from -6alkoxy; wherein Rzf and Rzg are each independently a hydrogen atom, C1- 6 alkyl and (C1-6 alkyl) carbonyl, wherein C1-6 alkyl is substituted with one or more substituents independently selected from hydroxy, halogen atom, and C1-6 alkoxy And f)-S (= O) n 7-R zh; wherein n 7 represents an integer of 0 to 2 and R zh is a hydrogen atom or C 1 6 alkyl, g) C1-6 alkyl; wherein C1-6 alkyl is one or more independently selected from a halogen atom, hydroxy, -NRziRzj, C1-6 alkoxy, and 3- to 12-membered heterocyclyl And Rzj and Rzj independently represent a hydrogen atom or C1-6 alkyl, and a 3- to 12-membered heterocyclyl is hydroxy, C1-6 alkyl, and 3- H) C 1-6 alkoxy optionally substituted with one or more substituents independently selected from 12-membered heterocyclyl; wherein C 1-6 alkoxy is selected from hydroxy, halogen atoms, and C 1-6 alkoxy I) 3- to 12-membered heterocyclyl optionally substituted by one or more substituents selected independently; Telocyclyl is optionally substituted by one or more substituents independently selected from

C1-6 alkyl and (C1-6 alkyl) carbonyl; j) C6-10 aryl; wherein C6-10 aryl is One or more (C1-6 alkyl) carbonyl, and k) 5- to 10-membered heteroaryl; wherein 5- to 10-membered heteroaryl is C1-6 alkyl, C1-6 alkoxy, -NRzkRzl, and optionally substituted with one or more substituents independently selected from 3-12 membered heterocyclyl, wherein Rzk and Rzl are independently hydrogen atom, C1-6 alkyl, and A 3- to 12-membered heterocyclyl selected from (C1-6 alkyl) carbonyl is selected from C1-6 alkyl and (C1-6 alkyl) carbonyl Or a salt thereof, optionally substituted with one or more substituents selected from the above, or optionally substituted with one to five substituents independently selected from Or a pharmaceutical composition containing a solvate of any of them.

[0017] [2] to [1], wherein Q 1 is phenyl or pyridyl, wherein phenyl and pyridyl are substituted with 1 to 4 substituents independently selected from a halogen atom and C 1-6 alkyl Pharmaceutical composition as described.

[0018] [3] Whether R7 and R8 are both hydrogen atoms; R7 and R8 are both C1-6 alkyl; R7 is a hydrogen atom and R8 is C1-6 alkyl; or R7 and R8 are Together with the carbon atom to be bound, they form a C3-8 cycloalkane ring, wherein the C3-8 cycloalkane ring formed by R7 and R8 together is one to two C1- Optionally substituted with 6 alkyl, wherein C1-6 alkyl is optionally substituted with one or more substituents independently selected from hydroxy, C1-6 alkoxy, and 3- to 12-membered heterocyclyl The pharmaceutical composition according to [1] or [2].

[0019] [4] Z2 is selected from C1-6 alkyl, C3-15 cycloalkyl, 3-12 membered heterocyclyl, C6-10 aryl, and 5-10 membered heteroaryl, wherein C3-15 cycloalkyl, 3 -12 membered heterocyclyl, C6-10 aryl, and 5-10 membered heteroaryl are group B: group B: a) oxo, b) halogen atom, c)-NRzd1 Rze1; wherein Rzd1 and Rze1 are independently A hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl, wherein C1-6 alkyl is substituted with one or more substituents independently selected from C1-6 alkoxy And d)-S (= O) n 7-R zh1; wherein n 7 represents an integer of 0 to 2 and R zh 1 represents a C 1-6 alkyl e) 1-6 alkyl; wherein C1-6 alkyl is substituted with one or more substituents independently selected from a halogen atom, hydroxy, -NRziRzj, C1-6 alkoxy, and 3- to 12-membered heterocyclyl And Rzj and Rzj independently represent a hydrogen atom or C1-6 alkyl, and the 3-12 membered heterocyclyl is independent of hydroxy, C1-6 alkyl, and 3-12 membered heterocyclyl. C1-6 alkoxy, wherein C1-6 alkoxy is optionally substituted with one or more hydroxy, g) 3 to 12 members Wherein the 3- to 12-membered heterocyclyl may be optionally substituted by one or more (C 1-6 alkyl) carbonyls, and h) 5 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted by one or more substituents independently selected from C1-6 alkyl, and -NRzk1Rzl1, wherein Rzk1 and Rzl1 is independently selected from hydrogen atom and C1-6 alkyl, and may be substituted with 1 to 4 substituents independently selected from [1] to [3] Pharmaceutical composition as described in-.

[0020] [5] The pharmaceutical composition according to any one of [1] to [4], wherein Y is -C (= O)-. [6] The pharmaceutical composition according to any one of [1] to [5], wherein R1 is a hydrogen atom. [7] The pharmaceutical composition according to any one of [1] to [6], wherein n1 and n2 are both 0.

[0021] [8] R9 has the formula (IIb):

[0022]

[0023] R 9 b is a hydrogen atom, C 1-6 alkyl (wherein C 1-6 alkyl is substituted with one or more substituents independently selected from a halogen atom and C 1-6 alkoxy) The pharmaceutical composition according to any one of [1] to [7], which may be selected from (C1-6 alkyl) carbonyl and (C1-6 alkyl) carbonyl.

[0024] [9] The pharmaceutical composition according to any one of [1] to [8], wherein X is -N =, -CH =, or -CF =. [10] Z1 has the formula (IIIa):

[0025]

[0026] The pharmaceutical composition according to any one of [1] to [9] (* represents a binding site to a pyrazolopyridine skeleton, and ** represents a binding site to Z2). [11] 3-[(1S, 2S) -1- [5-[(4S) -2,2-dimethylan-4-yl] -2-[(4S) -2- (4-fluoro-3)] 5,5-Dimethylphenyl) -3- [3- (4-fluoro-1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, or a salt thereof, The pharmaceutical composition in any one of [1]-[10].

[0027] [12] The pharmaceutical composition according to any one of [1] to [11], which contains the compound represented by the formula (I) or a salt thereof as a hydrate. [13] non-insulin dependent diabetes (type 2 diabetes), hyperglycemia, glucose intolerance, insulin dependent diabetes (type 1 diabetes), diabetic complications, obesity, hypertension, dyslipidemia, arteriosclerosis The pharmaceutical composition according to any one of [1] to [12] for use in the prevention or treatment of coronary heart disease, cerebral infarction, nonalcoholic steatohepatitis, Parkinson's disease, or dementia . Here, examples of dementia include, for example, Alzheimer's disease.

[0028] [14] The pharmaceutical composition according to [12] for use in the prevention or treatment of non-insulin dependent diabetes mellitus (type 2 diabetes) or obesity. [15] Non-insulin dependent diabetes mellitus (type 2 diabetes), hyperglycemia, glucose intolerance disorder, insulin dependency comprising administering the pharmaceutical composition according to any of [1] to [12] to a subject Diabetes mellitus (type 1 diabetes), diabetic complications,

obesity, hypertension, dyslipidemia, arteriosclerosis, coronary heart disease, cerebral infarction, nonalcoholic steatohepatitis, Parkinson's disease, or dementia Methods of prevention or treatment. Here, examples of dementia include, for example, Alzheimer's disease.

[0029] [16] A method for preventing or treating non-insulin dependent diabetes mellitus (type 2 diabetes) or obesity, comprising administering the pharmaceutical composition according to any one of [1] to [12] to a subject.

[0030] The compound represented by the formula (I), a salt thereof or a solvate thereof contained in the pharmaceutical composition of the present invention has the same action as the GLP-1 peptide as a GLP-1 receptor agonist There is provided a preventive or therapeutic agent for non-peptide non-insulin dependent diabetes (type 2 diabetes) or obesity which is expected to have sufficient bioavailability orally.

[0031] The result of the powder X-ray-diffraction measurement of the sodium salt hydrate crystal (sample 160a) of the compound 1 obtained in Example 163 is shown. The vertical axis is the diffraction intensity, and the horizontal axis is the diffraction angle 2θ (°). The result of the powder X-ray-diffraction measurement of the sodium salt hydrate crystal (sample 160b) of the compound 1 obtained in Example 163 is shown. The vertical axis is the diffraction intensity, and the horizontal axis is the diffraction angle 2θ (°). The result of the powder X-ray-diffraction measurement of the crystal (sample 161a) of the example compound 66 obtained in Example 163 is shown. The vertical axis is the diffraction intensity, and the horizontal axis is the diffraction angle 2θ (°). The result of the powder X-ray-diffraction measurement of the crystal (sample 161b) of the example compound 66 obtained in Example 163 is shown. The vertical axis is the diffraction intensity, and the horizontal axis is the diffraction angle 2θ (°). The result of the powder X-ray diffraction measurement of the calcium salt hydrate crystal of the example compound 67 (sample 162a) obtained in Example 163 is shown. The vertical axis is the diffraction intensity, and the horizontal axis is the diffraction angle 2θ (°). The result of the powder X-ray diffraction measurement of the calcium salt hydrate crystal (sample 162b) of the example compound 67 obtained in Example 163 is shown. The vertical axis is the diffraction intensity, and the horizontal axis is the diffraction angle 2θ (°). The results of thermogravimetric measurement / differential thermal analysis of sodium salt hydrate crystals of Compound 1 obtained in Example 164 are shown. The horizontal axis is temperature (° C.), and the right vertical axis is the weight change (%) of the sample in thermogravimetry. The left vertical axis represents the heat flow observed in differential thermal analysis. The results of thermogravimetric measurement / differential thermal analysis of calcium salt hydrate crystals of Example Compound 67 obtained in Example 164 are shown. The horizontal axis is temperature (° C.), and the right vertical axis is the weight change (%) of the sample in thermogravimetry. The left vertical axis represents the heat flow observed in differential thermal analysis. Effects of example compound 67 and exenatide on insulin secretion after intravenous

administration of glucose in male cynomolgus monkeys. The area under the insulin curve is shown as mean ± standard error (n = 6). Each drug was administered by crossover method. * Indicates P <0.025 and ** indicates P <0.005, which is significant with respect to the solvent group (Williams test). Each drug concentration shows the average value of the measured plasma drug concentration. Effects of example compound 67 and exenatide on plasma glucose levels after intravenous administration of glucose in male cynomolgus monkeys. The area under the plasma glucose curve is shown as mean ± standard error (n = 6). Each drug was administered by crossover method. * Indicates P <0.025 and ** indicates P <0.005, which is significant with respect to the solvent group (Williams test). Each drug concentration shows the average value of the measured plasma drug concentration. Effects of example compound 67 and exenatide on food consumption of male cynomolgus monkeys. Food intake is shown as mean ± standard deviation (n = 6). Each drug was administered by crossover method. * Indicates P <0.025 and ** indicates P <0.005, which is significant with respect to the solvent group (Williams test). Changes in plasma drug concentrations when the substance is orally administered to cynomolgus monkeys. Both plasma concentrations and each dose display the mean value of n = 2.

[0032] Hereinafter, the present invention will be further described in a non-limiting manner. Definitions In the present invention, "halogen atom" means fluorine atom, chlorine atom, bromine atom, iodine atom and the like. In the present invention, when the halogen atom is a substituent such as aryl (for example, Ra in the case where X in Formula (I) is -CRa =), preferable halogen atoms include a fluorine atom and a chlorine atom. In the present invention, when the halogen atom is a substituent such as alkyl (eg, in the case where the C6-10 aryl of Q1 in the formula (I) or the 5- to 10-membered heteroaryl is substituted with C1-6 alkyl, Further, as the substituent), preferred halogen atoms include fluorine atom and chlorine atom. Specific examples of C1-6 alkyl having a halogen atom as a substituent include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, pentafluoroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 2 -Chloroethyl, heptafluoropropyl, 3,3,3-trifluoropropyl, 2,3-dichloropropyl, 1-fluoro-3-bromopropyl, 4-bromobutyl, 3,3,3,4,4-pentafluorobutyl 4,4-dichlorobutyl, 5-iodopentyl, 5,5-difluoropentyl, 6-chlorohexyl, 6,6,6-trifluorohexyl and the like.

[0033] In the present invention, "C1-6 alkyl" is a linear or branched alkyl group having 1 to 6 carbon atoms. For example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, 1-methylpropyl, n-pentyl, isopentyl, 2-methylbutyl, 1,1-dimethyl Propyl, 1-ethylpropyl, n-hexyl, 4-methylpentyl, 2-ethylbutyl and the like can be mentioned.

[0034] In the present invention, "C1-6 alkoxy" means a C1-6 alkyl-O- group, wherein C1-6 alkyl is as defined above. For example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy, t-butoxy, 1-methylpropoxy, n-pentyloxy, isopentyloxy, 2-methylbutoxy, 1 1-dimethylpropoxy, 1-ethylpropoxy, n-hexyloxy, 4-methyl pentyloxy, 2-ethyl butoxy and the like.

[0035] In the present invention, "(C1-6 alkyl) carbonyl" means a (C1-6 alkyl) -C (O)-group, wherein C1-6 alkyl is as defined above. For example, methylcarbonyl (acetyl), ethylcarbonyl (propionyl), n-propylcarbonyl, i-propylcarbonyl, n-butylcarbonyl, i-butylcarbonyl, sec-butylcarbonyl, t-butylcarbonyl, 1-methylpropylcarbonyl, n-Pentylcarbonyl, isopentylcarbonyl, 2-methylbutylcarbonyl, 1,1-dimethylpropylcarbonyl, 1-ethylpropylcarbonyl, n-hexylcarbonyl, 4-methylpentylcarbonyl, 2-ethylbutylcarbonyl and the like.

[0036] In the present invention, "C.sub.6-10 aryl" means an aromatic carbocyclic group, and may have a nonaromatic moiety in addition to the aromatic moiety. The ring may be monocyclic or bicyclic aryl fused to a benzene ring or a monocyclic aryl ring. For example, phenyl, 1-naphthyl, 2-naphthyl, azulenyl, isochromanyl, 2,4-dihydro-1H-isoquinoline-3-onyl, 1,3-dihydrobenzimidazole-2-onyl and the like can be mentioned, with preference given to phenyl. It can be mentioned.

[0037] In the present invention, "heteroaryl" is an aromatic 5- to 10-membered member containing one or more hetero atoms selected from nitrogen atom, oxygen atom, and sulfur atom in atoms constituting a ring. In addition to the aromatic moiety, it may have a nonaromatic moiety. The ring may be monocyclic or bicyclic heteroaryl fused to a benzene ring or a monocyclic heteroaryl ring. For example, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazolyl, pyridyl, pyrimidyl, pyridazinyl, pyridazinyl, triazinyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzothiazolyl, Benzoxazolyl, benzooxadiazolyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, benzodioxolyl, indolizinyl, imidazopyridyl, benzoisoxazolyl, benzisothiazolyl, etc. It can be mentioned.

[0038] In the present invention, "heterocyclyl" means a non-aromatic cyclic group containing one or more hetero atoms selected from nitrogen, oxygen and sulfur atoms, and is completely saturated or a moiety May be unsaturated. The ring may be 3-12 membered, preferably 3-10 membered monocyclic, or bicyclic or spirocyclic. For example, oxetanyl, azetidinyl, 3,7-dioxa-9-azabicyclo [3.3.1] nonanyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, 2-oxa-6-azaspiro [3. .3] Heptyl, 2-azaspiro [3.3] heptyl, 2,6-diazaspiro [3.3] heptyl, 2-thia-6-azaspiro [3.3] heptyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, pyrazolidinyl, thianyl , Oxanyl, thioxanyl, indolinyl, isoindolinyl, tetrahydroindolinyl, quinuclidinyl, azepinyl, tropanyl and the like.

[0039] In the present invention, the "C3-15 cycloalkyl" is a monovalent group derived by removing any one hydrogen atom from a cyclic saturated aliphatic hydrocarbon having 3 to 15 carbon atoms. Moreover, "C3-8 cycloalkyl" is a C3-C8 cycloalkyl. For example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like can be mentioned. Moreover, "C3-6 cycloalkyl" is a C3-C6 cycloalkyl. When two groups are taken together to form a C3-15 cycloalkane

ring, the group is a divalent group. For example, cyclopropane-1,1-diyl, cyclobutane-1,1-diyl, cyclopentane-1,1-diyl, cyclohexane-1,1-diyl, cycloheptane-1,1-diyl, cyclooctane-1, 1-diyl etc. are mentioned.

[0040] When groups on two carbon atoms combine to form a C3-8 carbocyclic ring, the rings form a fused ring. For example, a ring structure in which two carbon atoms are linked by -CH2-, -CH2CH2-, -CH2CH2CH2-, -CH2CH2CH2CH2-, -CH2CH2CH2CH2CH2-, -CH2CH2CH2CH2CH2CH2- and the like can be mentioned.

[0041] In addition, the cyclic hydrocarbon in the cycloalkane ring, the carbon ring and the cycloalkyl may be a bridged ring. As a bridged ring in C 3-15 cycloalkyl, for example, bicyclo [1.1.0] butane, bicyclo [3.2.1] octane, bicyclo [5.2.0] nonane, bicyclo [4.3.2 Undecane, tricyclo [2.2.1.02,6] heptane, tricyclo [4.3.1.12,5] undecane, tricyclo [3.3.1.13,7] decane (adamantane), tricyclo [3. 3.3.1.13,7] decane-2-ylidene (2-adamantylidene), pentacyclo [4.2.0.02, 5.03, 8.04, 7] octane (cuban) etc. are mentioned. As C3-15 cycloalkyl consisting of a bridged ring, for example, bicyclo [1.1.0] butyl, bicyclo [3.2.1] octyl, bicyclo [5.2.0] nonyl, bicyclo [4. 3 2] undecyl, tricyclo [2.2.1.02,6] heptyl, tricyclo [4.3.1.12,5] undecyl, adamantyl, 2-adamantylidene de sulfonyl, and the like Kyubaniru.

[0042] The present invention provides a pharmaceutical composition comprising a compound represented by formula (I), a salt thereof, or a solvate of any of them.

[0043]

[0044] X represents -N = or -CRa =; and Ra is selected from a hydrogen atom, a halogen atom, and C1-6 alkyl. X is preferably -N =, -CH = or -CF =, more preferably -CH =.

[0045] Y is selected from -C (= O)-, -CHR-, and -S (= O) 2-; R represents a hydrogen atom or C1-6 alkyl. Q1 represents C6-10 aryl or 5- to 10-membered heteroaryl, wherein C6-10 aryl and 5- to 10-membered heteroaryl are each a halogen atom, C1-6 alkyl (wherein C1-6 alkyl is , Optionally substituted with one or more halogen atoms), and may be substituted with 1 to 5 substituents independently selected from C1-6 alkoxy. Q1 is preferably phenyl or pyridyl, wherein phenyl or pyridyl is substituted with 1 to 4 substituents independently selected from a halogen atom and C1-6 alkyl. More preferably, Q1 is phenyl substituted with a halogen atom and 2 to 3 substituents independently selected from C1-6 alkyl.

[0046] Q2 represents 3 to 12 membered heterocyclyl or 5 to 10 membered heteroaryl, wherein the 3 to 12 membered heterocyclyl and 5 to 10 membered heteroaryl are halogen atoms, C1-6 alkyl (wherein C1 The -6 alkyl may be substituted with one to three substituents independently selected

from one or more halogen atoms), C1-6 alkoxy, and -NRQaRQb; , And two C1-6 alkyls together with the carbon atom to which they are attached may form a C3-8 carbocyclic ring; RQa and RQb independently represent a hydrogen atom, C1-6 alkyl, and It is selected from (C1-6 alkyl) carbonyl. Preferably, Q2 represents i) 6-membered heterocyclyl, wherein the 6-membered heterocyclyl may be substituted by one or more C1-6 alkyl, and further, two C1-6 alkyl may be substituted Together with the carbon atom to which it is attached may form a C3-8 carbon ring, or ii) represents a 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl is a halogen atom , C1-6 alkyl, C1-6 alkoxy, and -NRQcRQd may be substituted with 1 to 3 substituents independently selected from Rqc and Rqd independently represent a hydrogen atom and C1-6. It is selected from alkyl. Also preferably, Q2 represents 5-6 membered heterocyclyl or heteroaryl, wherein 5-6 membered heterocyclyl and 5-6 membered heteroaryl are 1-3 C1-6 alkyl It may be substituted.

[0047] R1, R2 and R3 each independently represent a hydrogen atom and C1-6 alkyl (wherein C1-6 alkyl is one or more substituents independently selected from a halogen atom, C1-6 alkoxy, and hydroxy) And may be substituted with Preferably, combinations of R1, R2 and R3 are all hydrogen atoms; R1 is hydrogen atom, R2 is hydrogen atom, R3 is C1-6 alkyl; and R1 is hydrogen atom, R2 is C1-6 alkyl, R3 is It is selected from C1-6 alkyl.

[0048] R4, R5, and R6 are each independently selected from a hydrogen atom, a halogen atom, and C1-6 alkyl. R4, R5 and R6 are preferably each independently a hydrogen atom or a fluorine atom. More preferably, the combinations of R4, R5 and R6 are all hydrogen atoms; or R4 is a hydrogen atom, R5 is a hydrogen atom, and R6 is a fluorine atom.

[0049] R7 and R8 independently represent a hydrogen atom or C1-6 alkyl, wherein C1-6 alkyl is substituted with one or more substituents independently selected from a halogen atom and C3-15 cycloalkyl And R.sup.7 and R.sup.8 may be taken together with the carbon atom to which they are attached to form a C.sub.3-15 cycloalkane ring, wherein C.sub.3 formed by R.sup.7 and R.sup.8 together The -15 cycloalkane ring may be substituted with 1 to 3 C1-6 alkyl, wherein C1-6 alkyl is a halogen atom, hydroxy, -NR7aR7b, C1-6 alkoxy, and 3 to 12 members R7a and R7b may be independently substituted with a hydrogen atom, C1-6 alkyl, optionally substituted with one or more substituents independently selected from heterocyclyl of , And is selected from (C1-6 alkyl) carbonyl. R7 and R8 are preferably taken together with the carbon atom to which they are attached to form a C3-8 cycloalkane ring, wherein C7-8 cycloalkyl formed by R7 and R8 together May be substituted with one or more C1-6 alkyl, wherein C1-6 alkyl may be substituted with one or more hydroxy. Moreover, it is preferable that C3-8 cycloalkyl is C3-6 cycloalkyl. Preferred C3-6 cycloalkyls include, for example, cyclopentyl.

[0050] n1 represents an integer of 0 to 3; n2 represents an integer of 0 to 5; Each of n1 and n2 is preferably 0-2, more preferably 0-1, and still more preferably 0. Moreover, the combination of n1

and n2 is preferably 0 and 0, 0 and 1, 0 and 2, 1 and 0, 1 and 1, 2 and 0, 0 and 0, 0 and 1, 1 and 0, 2 and 0 Is more preferred, and 0 and 0 are more preferred.

[0051] R9 is a group represented by formulas (IIa), (IIb), (IIc) and (IId):

[0052]

[0053] R9a, R9b, R9c, R9d, and R9g are each independently a hydrogen atom, C1-6 alkyl (wherein C1-6 alkyl (wherein C1-6) The alkyl is selected from a halogen atom and one or more substituents independently selected from C1-6 alkoxy), and (C1-6 alkyl) carbonyl, and R9e is a hydrogen atom, or Represents C1-6 alkyl optionally substituted by one or more substituents independently selected from a halogen atom, R9 f represents a hydrogen atom or C1-6 alkyl, and R9 h represents a hydrogen atom, C1-6 Alkyl, (C.sub.1-6 alkyl) carbonyl, cyano, or -S (.dbd.O) n3-R9i; n3 represents an integer of 0 to 2, and R9i is It represents a C1-6 alkyl.

[0054] Z1 has the formulas (IIIa), (IIIb), (IIIc), (IIId) and (IIIe):

[0055]

[0056] Rza is selected from a hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl, and Rzb and Rzc independently represent a hydrogen atom or C1-6 alkyl, n4 represents an integer of 1 to 3, and n5 and n6 independently represent an integer of 0 to 10.

[0057] * Represents a binding site to the pyrazolopyridine skeleton, and ** represents a binding site to Z2 respectively. Z2 is selected from C1-6 alkyl, C3-15 cycloalkyl, 3-12 membered heterocyclyl, C6-10 aryl, and 5-10 membered heteroaryl, wherein C3-15 cycloalkyl, 3-12 membered Heterocyclyl, C 6-10 aryl, and 5- to 10-membered heteroaryl may be optionally substituted with 1 to 5 substituents independently selected from Group A.

[0058] Group A: a) oxo, b) halogen atom, c) cyano, d) -NRzdRze; wherein Rzd and Rze are each independently selected from hydrogen atom, C1-6 alkyl and (C1-6 alkyl) carbonyl Wherein, C 1-6 alkyl is optionally substituted with one or more substituents independently selected from hydroxy, halogen atom, and C 1-6 alkoxy, e) -C (= O) -NRzfRzg Wherein Rzf and Rzg are each independently selected from hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl, wherein C1-6 alkyl is hydroxy, halogen atom, and C1-6. F) -S (= O) n7-Rzh, optionally substituted with one or more substituents independently selected from alkoxy; And Rzh represents a hydrogen atom or C1-6 alkyl; g) C1-6 alkyl; wherein C1-6 alkyl is a halogen atom, hydroxy, -NRziRzj, C1-6 alkoxy, and Optionally substituted with one or more substituents independently selected from 3- to 12-membered heterocyclyl, wherein Rzi and Rzj independently represent a hydrogen atom

or C1-6 alkyl, 3 to 12 Membered heterocyclyl may be substituted with one or more substituents independently selected from hydroxy, C1-6 alkyl, and 3-12 membered heterocyclyl; h) C1-6 alkoxy; 6 alkoxy is optionally substituted with one or more substituents independently selected from hydroxy, a halogen atom, and C 1-6 alkoxy, i 3-12 membered heterocyclyl; wherein the 3-12 membered heterocyclyl may be optionally substituted by one or more substituents independently selected from C 1-6 alkyl and (C 1-6 alkyl) carbonyl, j A) C 6-10 aryl; wherein C 6-10 aryl may be substituted with one or more (C 1-6 alkyl) carbonyl, and k) 5-10 membered heteroaryl; Heteroaryl may be optionally substituted with one or more substituents independently selected from C1-6 alkyl, C1-6 alkoxy, -NRzkRzl, and 3- to 12-membered heterocyclyl, wherein Rzk and Rzl Is independently selected from hydrogen atom, C.sub.1-6 alkyl, and (C.sub.1-6 alkyl) carbonyl, and the 3- to 12-membered heterocyclyl is C.sub.1-6. It may be substituted by one or more substituents independently selected from alkyl and (C1-6 alkyl) carbonyl.

[0059] When C1-6 alkyl in Rzd, Rze, Rzf and Rzg is substituted with hydroxy, C1-6 alkyl is preferably C2-6 alkyl, more preferably C2-4 alkyl.

[0060] Also when C1-6 alkoxy is substituted with one or more hydroxy, C1-6 alkyl is preferably C2-6 alkyl, more preferably C2-4 alkyl. Preferably, Z2 is substituted with i) 1 to 3 substituents optionally selected from C3-15 cycloalkyl optionally substituted with one or more -NRzdRze, ii) C group And C.sub.6-10 aryl, and iii) 5- to 10-membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from group D.

[0061] More preferably, Z2 is i) C6-10 aryl optionally substituted with 1 to 3 substituents independently selected from group C; and ii) 1 independently selected from group D It is selected from 5- to 10-membered heteroaryl optionally substituted by -3 substituents.

[0062] Group C: a) halogen atom, b) -NRzd2Rze2; wherein Rzd2 and Rze2 are independently selected from hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl, wherein, C1-6 alkyl Is optionally substituted with one or more C1-6 alkoxy, c) -S (= O) n7-Rzh1; wherein n7 represents an integer of 0 to 2 and Rzh1 represents C1-6 alkyl And d) C1-6 alkyl, e) C1-6 alkoxy; wherein C1-6 alkoxy is optionally substituted with one or more hydroxy groups, f) 5- to 10-membered heteroaryl; The 10-membered heteroaryl may be optionally substituted with one or more substituents independently selected from -NRzk1Rzl1, wherein Rzk1 and Rzl1 are independently hydrogen atom and It is selected from C1-6 alkyl.

[0063] Group D: a) oxo, b) halogen atom, c) C1-6 alkyl; wherein C1-6 alkyl is independently selected from halogen atoms, hydroxy, C1-6 alkoxy, and 3- to 12-membered heterocyclyl Optionally substituted

with one or more substituents, wherein the 3-12 membered heterocyclyl is optionally substituted with one or more C.sub.1-6 alkyl, and d) a 3-12 membered heterocyclyl .

[0064] In the present invention, as a compound represented by the formula (I), Z 1 is a group represented by the formula (IIIa), Y is represented by —C (= O) —, and R 9 is represented by the formula (IIb) A C3-15 cycloalkane ring which is a group represented by R 9 b is a hydrogen atom, and R 7 and R 8 taken together with the carbon atom to which they are attached is substituted by 1 to 3 C 1-6 alkyl. Preferably, the 1 to 3 C.sub.1-6 alkyl is unsubstituted, 3-[(1S, 2S) -1- [5-[(4S) -2,2-dimethyloxane-. 4-yl] -2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (4-fluoro-1-methylindazol-5-yl) -2-oxo Imidazol-1-yl] -4-methyl-6,7-dihydro-4H-pyrazolo [, 3-c] pyridine-5-carbonyl] indol-1-yl] -2-methyl cyclopropyl]-4H-1,2,4-oxadiazol-5-one (Example Compound 67) is more preferred.

[0065] Next, an example of a method for producing a compound represented by formula (I), a salt thereof or a solvate thereof is described by the following scheme group. The compound represented by the formula (I), a salt thereof, or a solvate thereof is produced via i) General Process A1 or General Process A2, ii) General Process B, and iii) General Process C. In this production method, among the compounds represented by the formula (I), Z 1 is a group represented by the formula (IIIa), Y is represented by —C (= O) —, and R 9 is represented by the formula (IIb) When R 9 b is a hydrogen atom, that is, it is an example of a preferred process for producing the compound represented by the formula (Ia).

[0066] Also, when R 7 and R 8 together with the carbon atom to which they are attached form a C 3-15 cycloalkane ring substituted with 1 to 3 C 1-6 alkyl, said 1 to 3 C 1 s The -6 alkyl is an example of a preferred process when it is unsubstituted.

[0067] In addition, when the starting material or the desired product of a certain process undergoes undesired chemical conversion under the reaction conditions of that process, for example, protection and deprotection of functional groups are performed to obtain the desired product of the relevant process. Can. For the selection of protecting groups, and the selection of methods of protection and deprotection, see, for example, T.W. W. Greene, P .; G. M. Wuts, Protective Groups in Organic Synthesis, Fourth Edition, John Wiley & Sons, Inc. , New York (2007). Some of the protection and deprotection of functional groups are also described in the following scheme.

[0068] Compound f can be synthesized by the general production method A1 shown by the following scheme.

[0069]

[0070] In the formula, P2 represents a hydrogen atom or C1-6 alkyl, P1a represents an amino protecting group, P3a and P3b independently represent C1-6 alkyl, or P3a and P3b are The bonding oxygen atom and the carbon atom to which the oxygen atom is bonded may be taken together to form a 5- to 7-membered 1,3-dioxacycloalkane ring, and Y 1 represents cyano or -CO-OP 2 , Y 2 represents = O or NHNH, and X 1 represents a leaving group.

[0071] Examples of the protecting group of amino include formyl, (C1-6 alkyl) carbonyl (acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl etc.), carbamoyl, C1-6 alkoxycarbonyl (methoxycarbonyl, ethoxycarbonyl, isopropyl Oxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl and the like, substituted silyl (trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl and the like), aralkyloxycarbonyl (benzyloxycarbonyl, 9 - Fluorenylmethyloxycarbonyl and the like), allyl and aralkyl.

[0072] As the leaving group, for example, a halogen atom, acetyloxy, trifluoroacetyloxy, methanesulfonyloxy, paratoluenesulfonyloxy and the like can be mentioned. Step A1-1a: Compound a1 can be obtained by reacting compound a with a base.

[0073] Examples of bases include metal hydrides such as sodium hydride, potassium hydride and lithium hydride; potassium t-butoxide, sodium t-butoxide, lithium t-butoxide, potassium t-pentoxide, sodium t-pentoxide, lithium t-pentoxide And metal alkoxides, etc., preferably metal alkoxides such as potassium t-butoxide.

[0074] Examples of the solvent include ether solvents such as tetrahydrofuran (THF), diethyl ether, dioxane and the like, preferably THF. The reaction temperature is generally -30 ° C to 30 ° C, preferably -10 ° C to 10 ° C.

[0075] The reaction time is generally 15 minutes to 5 hours, preferably 30 minutes to 3 hours. Compound a1 may be isolated or may be subjected to step A1-1b without isolation. Compound a can be purchased commercially from Aldlab Chemicals, LLC, Tokyo Chemical Industry, and the like. Alternatively, they can be synthesized with reference to Bioorganic Medicinal Chemistry, 1999, 7, 795-809, CN 103086955.

[0076] Compound a1 may be obtained as an alkali metal salt such as a potassium salt by contact with a base used in the reaction, but such a salt can also be added to the next step. Step A1-1b: Compound b can be obtained by reacting compound a1 with compound a2. The reaction is preferably carried out in the presence of an acid.

[0077] Examples of the acid include acids such as hydrochloric acid, acetic acid, methanesulfonic acid and p-toluenesulfonic acid, and salts of weak bases and strong acids such as pyridine

hydrochloride. Examples of the solvent include hydrocarbon solvents (hexane, heptane, benzene, toluene, xylene and the like) and alcohol solvents (methanol, ethanol and the like). Also, water may be present in the system.

[0078] The reaction temperature is generally 40 ° C to 200 ° C, preferably 60 ° C to 150 ° C. The reaction time is generally 6 minutes to 30 hours, preferably 30 minutes to 3 hours. Compound a2 can be purchased commercially from Alfa Aesar etc. as a salt to which hydrogen chloride and the like are added. With reference to Synlett, 2011, 17, 2555-2558, the compound a2 in which the hydrazine moiety is protected with t-butoxycarbonyl can also be used after being deprotected with an acid such as methanesulfonic acid. In addition, the compound: Q1-NH2 can be synthesized as a starting material with reference to Journal of Medicinal Chemistry 2003, 46, 1546-1553.

[0079] Step A1-2: Compound c can be obtained by reacting Compound b with Compound b1 or Compound b2 in the presence of a base.

[0080] As the base, tertiary amines (triethylamine, N-methylmorpholine, diisopropylethylamine, DBU, DABCO etc.), nitrogen-containing aromatic compounds (pyridine, dimethylaminopyridine, picoline, (2,6-) lutidine, pyrazine, pyridazine etc. And metal hydrides such as sodium hydride, potassium hydride and lithium hydride; potassium t-butoxide, sodium t-butoxide, lithium t-butoxide, potassium t-pentoxide, sodium t-pentoxide, lithium t-pentoxide and the like) Metal alkoxides and the like can be mentioned. When compound b2 is used, it is preferably a metal alkoxide such as potassium t-butoxide.

[0081] As the solvent, alcohol solvents such as methanol and ethanol; ether solvents such as THF and diethyl ether; ester solvents such as ethyl acetate and methyl acetate; nitrile solvents such as acetonitrile, benzonitrile and benzyl cyanide; Although amide solvents such as N-dimethylacetamide (DMA), N, N-dimethylimidazolidinone (DMI), and DMF can be used, amide solvents such as DMA are preferable.

[0082] The reaction temperature is generally -50 ° C to 70 ° C, preferably -30 ° C to 50 ° C. The reaction time is generally 15 minutes to 72 hours, preferably 1 hour to 30 hours. Compound b1 is prepared by Enamine LTD. Commercial products can be purchased from The compound can also be synthesized by reacting the compound: H2NCH2CH (OP3a) (OP3b) with phosgene or triphosgene, with reference to WO2006 / 048727. Compound b2 is prepared by UkrOrgSyntez Ltd. Commercial products can also be purchased from The compound can also be synthesized by reacting the compound: H2NCH2CH (OP3a) (OP3b) with a diisocyanate such as CDI with reference to WO 99/50262.

[0083] Step A1-3: Compound d can be obtained by reacting compound c with an acid. Examples of the acid include inorganic acids (hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid etc.), sulfonic acids (methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid etc.), carboxylic acids (formic acid FA), acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, malic acid, succinic acid, malonic acid, gluconic acid, mandelic acid, benzoic acid, salicylic acid, fluoroacetic acid, trifluoroacetic acid (TFA), tartaric acid, propionone Acid, glutaric acid, etc.).

[0084] As the solvent, ether solvents (ether, tetrahydrofuran, dioxane, dimethoxyethane, cyclopentyl methyl ether, etc.), aromatic hydrocarbon solvents (benzene, toluene, xylene, quinoline, chlorobenzene, etc.), aliphatic hydrocarbon solvents (pentane, etc.) , Hexane, heptane, octane, cyclohexane etc., amide solvents (N, N-dimethylformamide, N, N-dimethylacetamide, N-methylpyrrolidone etc.), alcohol solvents (methanol, ethanol, 2,2,2- Trifluoroethanol, n-propanol, isopropanol, n-butanol, sec-butanol, pentanol, hexanol, cyclopropanol, cyclobutanol, cyclopentanol, cyclohexanol, ethylene glucone (1, 3-propanediol, 1,4-butanediol, 1,5-pentanediol, etc.), acetic acid ester solvents (eg, methyl acetate, ethyl acetate, isopropyl acetate), acetonitrile, and their mixed solvents. Preferably, it is an ether solvent such as tetrahydrofuran.

[0085] The reaction temperature is generally 0 ° C to 100 ° C, preferably 10 ° C to 80 ° C. The reaction time is generally 10 minutes to 20 hours, preferably 30 minutes to 5 hours. Step A1-4: a) When Z2 is C1-6 alkyl, C3-15 cycloalkyl and 3-12 membered heterocyclyl, compound e is reacted with compound d1 in the presence of a base to give compound e You can get

[0086] Examples of bases include metal hydrides such as sodium hydride, potassium hydride and lithium hydride; potassium t-butoxide, sodium t-butoxide, lithium t-butoxide, potassium t-pentoxide, sodium t-pentoxide, lithium t-pentoxide And metal alkoxides, and alkyl metals such as butyllithium and ethyllithium.

[0087] As the solvent, ether solvents (ether, tetrahydrofuran, dioxane, dimethoxyethane, cyclopentyl methyl ether, etc.), aromatic hydrocarbon solvents (benzene, toluene, xylene, quinoline, chlorobenzene, etc.), aliphatic hydrocarbon solvents (pentane, etc.) , Hexane, heptane, octane, cyclohexane, etc., amide solvents (N, N-dimethylformamide, N, N-dimethylacetamide, N-methylpyrrolidone etc.), preferably amides such as N, N-dimethylacetamide It is a system solvent.

[0088] The reaction temperature is generally 0 ° C to 150 ° C, preferably 20 ° C to 120 ° C. The reaction time is generally 15 minutes to 24 hours, preferably 30 minutes to 5 hours. b) When Z2 is C6-10 aryl and 5-10 membered heteroaryl, Compound e can be obtained by reacting Compound d with Compound d1 in the presence of a base, a copper catalyst and a ligand .

[0089] Examples of the base include weak basic inorganic salts (sodium carbonate, potassium carbonate, potassium phosphate, cesium carbonate etc.) and organic bases (triethylamine, pyridine, tetrabutylammonium fluoride etc.), preferably potassium carbonate etc. It is a basic inorganic salt.

[0090] Examples of copper catalysts include copper (I) iodide, copper (I) bromide, copper (I) chloride, copper (II) acetate, copper (II) oxide, copper (I) trifluoromethanesulfonate, etc. , Preferably copper (I) iodide.

[0091] As ligands, phenanthroline, quinolin-8-ol, 2,2,6,6-tetramethylheptane-3,5-dione, N, N'-dimethylethane-1,2-diamine, trans-cyclohexane-1,2- Examples thereof include diamines and diamines such as trans-N, N'-dimethylcyclohexane-1,2-diamine and the like, with preference given to trans-N, N'-dimethylcyclohexane-1,2-diamine.

[0092] As the solvent, ether solvents (ether, tetrahydrofuran, dioxane, dimethoxyethane, cyclopentyl methyl ether, etc.), aromatic hydrocarbon solvents (benzene, toluene, xylene, quinoline, chlorobenzene, etc.), aliphatic hydrocarbon solvents (pentane, etc.) , Hexane, heptane, octane, cyclohexane etc., amide solvents (N, N-dimethylformamide, N, N-dimethylacetamide, N-methylpyrrolidone etc.), alcohol solvents (methanol, ethanol, 2,2,2- Trifluoroethanol, n-propanol, isopropanol, n-butanol, sec-butanol, pentanol, hexanol, cyclopropanol, cyclobutanol, cyclopentanol, cyclohexanol, ethylene glucone And 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol, etc., acetic acid ester solvents (eg, methyl acetate, ethyl acetate, isopropyl acetate), and acetonitrile, preferably N- Amide-based solvents such as methyl pyrrolidone.

[0093] The reaction temperature is generally 30 ° C to 200 ° C, preferably 60 ° C to 160 ° C. The reaction time is usually 1 hour to 15 hours, preferably 3 hours to 9 hours. Step A1-5: Compound f can be obtained by deprotecting compound e.

[0094] When the protecting group P1a is C1-6 alkoxycarbonyl such as t-butoxycarbonyl, it is preferable to deprotect using an acid. Examples of the acid include inorganic acids (such as hydrogen chloride, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid), sulfonic acids (such as methanesulfonic acid, benzenesulfonic acid and toluenesulfonic acid), and carboxylic acids (formic acid) Acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, malic acid, succinic acid, malonic acid, gluconic acid, mandelic acid, benzoic acid, salicylic acid, fluoroacetic acid, trifluoroacetic acid, tartaric acid, propionic acid, glutaric acid, etc. Can be mentioned.

[0095] As the solvent, ether solvents (tetrahydrofuran, methyl tetrahydrofuran, diethyl ether, t-butyl methyl ether, diisopropyl ether, cyclopentyl methyl ether, 1,2-dimethoxyethane etc.), hydrocarbon solvents (hexane, heptane, benzene, toluene, etc.) Etc.) amide solvents (N, N-dimethylformamide, N, N-dimethylacetamide, N-methyl pyrrolidone etc.), and halogen solvents (dichloromethane,

chloroform, carbon tetrachloride etc.), and preferably N-methyl Amide solvents such as pyrrolidone.

[0096] The reaction temperature is generally 0 ° C to 200 ° C, preferably 10 ° C to 120 ° C. The reaction time is generally 30 minutes to 10 hours, preferably 1 hour to 6 hours. In addition, although the compound f may be obtained as a salt with the acid used for reaction, such a salt can also be attached to the following process.

[0097] <General Production Method A2> When Z2 is a bulky group such as C3-15 cycloalkyl substituted with —NRzdRze, the compound p corresponding to the compound f is synthesized also in the general production method A2 shown in the following scheme can do.

[0098]

[0099] In the formula, Z2a represents unsubstituted C3-15 cycloalkyl or 3-12 membered heterocyclyl. P1a and P2a each represent an amino protecting group, X2, X3, X4 and X5 each independently represent a leaving group, R10a and R10b each independently represent a C1-6 alkyl, or R10a and R10b Together with the oxygen atom to which they are attached and the carbon atom to which the oxygen atom is attached may form a 5- to 7-membered 1,3-dioxacycloalkane ring.

[0100] Examples of the protecting group of amino include formyl, (C1-6 alkyl) carbonyl (acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl etc.), carbamoyl, C1-6 alkoxycarbonyl (methoxycarbonyl, ethoxycarbonyl, isopropyl Oxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl and the like, substituted silyl (trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl and the like), aralkyloxycarbonyl (benzyloxycarbonyl, 9 - Fluorenylmethyloxycarbonyl and the like), allyl, aralkyl and the like.

[0101] As the leaving group, for example, a halogen atom, acetyloxy, trifluoroacetyloxy, methanesulfonyloxy, paratoluenesulfonyloxy and the like can be mentioned. Step A2-1: Compound h can be obtained by reacting compound g with an azide in the presence of a base.

[0102] Examples of the base include tertiary amines (triethylamine, N-methylmorpholine, diisopropylethylamine, DBU, DABCO, etc.). Examples of the azide include metal azides such as sodium azide, trimethylsilyl azide and diphenylphosphoryl azide, preferably diphenylphosphoryl azide.

[0103] As the solvent, ether solvents (tetrahydrofuran, methyl tetrahydrofuran, diethyl ether, t-butyl methyl ether, diisopropyl ether, cyclopentyl methyl ether, 1,2-dimethoxyethane etc.), hydrocarbon solvents

(hexane, heptane, benzene, toluene, etc.) And amide solvents (N, N-dimethylformamide, N, N-dimethylacetamide, N-methyl pyrrolidone, etc.), preferably hydrocarbon solvents such as toluene.

[0104] The reaction temperature is generally 0 ° C to 150 ° C, preferably 10 ° C to 100 ° C. The reaction time is usually 1 hour to 10 hours, preferably 2 hours to 6 hours. The compound g is described in, for example, Journal of the American Chemical Society, 2016, 138, 1698-1708, WO2009 / 152133 and the like. Also, Enamine Ltd. Commercial products can also be purchased for example.

[0105] Step A2-2: Compound i can be obtained by reacting compound b obtained in step A1-1 b with compound h in the presence of a base.

[0106] As the base, for example, tertiary amines (triethylamine, N-methylmorpholine, diisopropylethylamine, DBU, DABCO, etc.), nitrogen-containing aromatic compounds (pyridine, dimethylaminopyridine, picoline, (2,6-) lutidine, pyrazine, And pyridazine etc.).

[0107] Examples of the solvent include ether solvents such as tetrahydrofuran (THF), diethyl ether and dioxane; and hydrocarbon solvents such as hexane, heptane, benzene and toluene. Moreover, bases, such as a pyridine, can also be used as a solvent.

[0108] The reaction temperature is generally 0 ° C to 60 ° C, preferably 5 ° C to 45 ° C. The reaction time is generally 30 minutes to 50 hours, preferably 2 hours to 10 hours. Step A2-3: Compound j can be obtained by reacting Compound i with Compound i1 or Compound i2 in the presence of a base.

[0109] Examples of the base include weakly basic inorganic salts (sodium carbonate, potassium carbonate, cesium carbonate etc.), metal hydrides (sodium hydride, potassium hydride etc.) and the like, preferably a weakly basic inorganic matter such as cesium carbonate It is salt.

[0110] As compound i1, for example, 1,2-dichloro-1-methoxyethane, 1,2-dichloro-1-ethoxyethane, 1,2-dichloro-1-i-propoxyethane, 1,2-dichloro-1-one Examples thereof include t-butoxyethane and the like, preferably 1,2-dichloro-1-ethoxyethane. Compound i1 can be purchased commercially from Tokyo Chemical Industry Co., Ltd., FCH Group, and the like.

[0111] As compound i2, for example, 2-chloro-1,1-dimethoxyethane, 2-chloro-1,1-diethoxyethane, 2-bromo-1,1-dimethoxyethane, 2-bromo-1,1-ethoxy Ethane etc. are mentioned. Compound i2 can be purchased from Tokyo Chemical Industry Co., Ltd. or the like.

[0112] As the solvent, alcohol solvents such as methanol and ethanol; ether solvents such as THF and diethyl ether; ester solvents such as ethyl acetate and methyl acetate; nitrile solvents such as acetonitrile, benzonitrile and benzyl cyanide; Amide solvents such as N-dimethylacetamide (DMA),

N, N-dimethylimidazolidinone (DMI), and DMF may be mentioned, with preference given to amide solvents such as DMA.

[0113] The reaction temperature is generally 0 ° C to 60 ° C, preferably 20 ° C to 45 ° C. The reaction time is generally 1 hour to 72 hours, preferably 12 minutes to 35 hours. Step A2-4: Compound k can be obtained by reacting Compound j with an acid.

[0114] Examples of the acid include inorganic acids (hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid etc.), sulfonic acids (methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid etc.), carboxylic acids (formic acid, Acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, malic acid, succinic acid, malonic acid, gluconic acid, mandelic acid, benzoic acid, salicylic acid, fluoroacetic acid, trifluoroacetic acid, tartaric acid, propionic acid, glutaric acid, etc.) Preferably, it is a sulfonic acid such as methanesulfonic acid.

[0115] Examples of the solvent include ether solvents such as tetrahydrofuran (THF), diethyl ether, dioxane and the like, preferably THF. The reaction temperature is generally 0 ° C to 100 ° C, preferably 20 ° C to 80 ° C.

[0116] The reaction time is generally 15 minutes to 6 hours, preferably 30 minutes to 3 hours. Step A2-5: Compound l can be obtained by reacting compound k with compound k1 in the presence of a base.

[0117] Examples of the compound k1 include halogenated C1-6 alkyl such as methyl iodide and halogenated (C1-6 alkyl) carbonyl such as acetyl chloride. When Rzd is (C1-6 alkyl) carbonyl, it is also preferable to use an acid anhydride represented by ((C1-6 alkyl) carbonyl) 2O, for example, acetic anhydride, in place of compound k1.

[0118] Examples of bases include metal hydrides such as sodium hydride, potassium hydride and lithium hydride; potassium t-butoxide, sodium t-butoxide, lithium t-butoxide, potassium t-pentoxide, sodium t-pentoxide, lithium t-pentoxide And metal alkoxides, etc., preferably metal alkoxides such as potassium pentoxide.

[0119] Examples of the solvent include ether solvents such as tetrahydrofuran (THF), diethyl ether and dioxane; hydrocarbon solvents such as hexane, heptane, benzene and toluene, preferably THF.

[0120] The reaction temperature is generally -50 ° C to 50 ° C, preferably -40 ° C to 40 ° C. The reaction time is usually 1 minute to 2 hours, preferably 3 minutes to 30 minutes. Step A2-6: Compound m can be obtained by deprotecting Compound l.

[0121] Although deprotection can select a suitable reagent and reaction conditions by the kind of protecting group, when a protecting group is t-butoxycarbonyl, it is preferable to make it react with an acid. Examples of the acid include inorganic acids (hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid etc.), sulfonic acids (methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid etc.), carboxylic acids (formic acid, Acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, malic acid, succinic acid, malonic acid, gluconic acid, mandelic acid, benzoic acid, salicylic acid, fluoroacetic acid, trifluoroacetic acid, tartaric acid, propionic acid, glutaric acid, etc.) And is preferably a carboxylic acid such as trifluoroacetic acid.

[0122] Examples of the solvent include ether solvents such as diethyl ether, THF and dimethoxyethane; halogen solvents such as dichloromethane (CH 2 Cl 2), chloroform and carbon tetrachloride; N, N-dimethylformamide; acetonitrile and the like, preferably CH 2 Cl 2 and the like Halogen solvents of

[0123] The reaction temperature is generally 0 ° C to 60 ° C, preferably 10 ° C to 40 ° C. The reaction time is usually 30 minutes to 10 hours, preferably 1 hour to 5 hours. In addition, although the compound m may be obtained as a salt with the acid used for reaction, such a salt can also be attached to process A2-7.

[0124] Step A2-7: Compound n can be obtained by protecting one of the amino in compound m. Although protection can select a suitable reagent and reaction conditions by the kind of protecting group, when a protecting group is C1-6 alkoxy carbonyl, it is preferable to make it react with a base.

[0125] As a compound used for protection, methoxycarbonyl chloride, ethoxycarbonyl chloride, 2,2,2-trichloroethoxycarbonyl chloride, benzoyl chloride (Z-Cl), 9-fluorenylmethyloxycarbonyl chloride (Fmoc-Cl), -T-butyldicarbonic acid is mentioned, preferably di-t-butyldicarbonic acid.

[0126] As the base, for example, tertiary amines (triethylamine, N-methylmorpholine, diisopropylethylamine, DBU, DABCO, etc.), nitrogen-containing aromatic compounds (pyridine, dimethylaminopyridine, picoline, (2,6-) lutidine, pyrazine, And pyridazine etc., preferably tertiary amines such as triethylamine.

[0127] Examples of the solvent include ether solvents such as diethyl ether, THF and dimethoxyethane; halogen solvents such as dichloromethane (CH 2 Cl 2), chloroform and carbon tetrachloride; N, N-dimethylformamide; acetonitrile and the like, preferably CH 2 Cl 2 and the like Halogen solvents of

[0128] The reaction temperature is generally 0 ° C to 60 ° C, preferably 15 ° C to 40 ° C. The reaction time is generally 30 minutes to 20 hours, preferably 1 hour to 5 hours. Step A2-8: Compound o can be obtained by reacting Compound n with Compound n1 in the presence of a base.

[0129] Examples of the compound n1 include halogenated C1-6 alkyl such as methyl iodide and halogenated (C1-6 alkyl) carbonyl such as acetyl chloride. When Rze is C1-6 alkyl, C1-6 alkyl is preferably unsubstituted or substituted with C1-6 alkoxy.

[0130] This step is carried out in the same manner as step A2-5, and the base, solvent, reaction temperature and reaction time used in the reaction are also the same as step A2-5. Step A2-9: Compound p can be obtained by deprotecting compound o.

[0131] Although deprotection can select a suitable reagent and reaction conditions according to the kind of protecting group, when protecting group P1a is C1-6 alkoxy carbonyl such as t-butoxycarbonyl etc., it is preferable to use acid for deprotection.

[0132] This step is carried out in the same manner as step A1-5, and the acid used for the reaction, the solvent, the reaction temperature and the reaction time are also the same as step A1-5. <General preparation method B> Compound bf can be synthesized according to the general preparation method B shown in the following scheme.

[0133]

[0134] In the formula, P21 represents hydroxy, C1-6 alkoxy or -NR21aR21b, R21a and R21b independently represent a hydrogen atom, C1-6 alkyl or C6-10 aryl, and X21 represents a hydrogen atom, halogen An atom or -Zn-X21a is represented, X21a is a bromine atom or an iodine atom, and X22 is a leaving group.

[0135] As the leaving group, for example, a halogen atom, acetyloxy, trifluoroacetyloxy, methanesulfonyloxy, paratoluenesulfonyloxy and the like can be mentioned. Step B-1: Compound bb can be obtained by reacting compound ba with compound ba1 in the presence of a palladium catalyst.

[0136] As a palladium catalyst, a complex formed separately by adding a palladium compound and a ligand can be used. Alternatively, the complex prepared separately may be used as it is. As a ligand, for example, 4,5-bis (diphenylphosphino) -9,9-dimethylxanthene, trimethylenebis (diphenylphosphine), 2- (di-t-butylphosphino) biphenyl, 2-dicyclohexylphosphino -2 ', 4', 6'-triisopropylbiphenyl, 2- (di-t-butylphosphino) -2 ', 4', 6'- triisopropyl-3, 6-dimethoxy-1, 1'-biphenyl And 2-di-t-butylphosphino-2 ', 4', 6'-triisopropylbiphenyl and the like. As a palladium compound to be combined with the ligand, for example, di-μ-chlorobis [(η -allyl) palladium (II)], tetrakis (triphenylphosphine) palladium (0) and the like can be used.

[0137] Examples of palladium catalysts usable in this step include tris (dibenzylideneacetone) dipalladium (0), 5,10,15,20-tetraphenyl-21H, 23H-porphine cobalt (II), palladium acetate (II)), Bis (di-t-butyl (4-dimethylaminophenyl) phosphine) dichloropalladium (II), [1, 1′ –bis (diphenylphosphino) ferrocene] palladium (II) dichloride dichloromethane adduct, dichlorobis (triol) Phenylphosphine) palladium (II), palladium hydroxide, tetrakis (triphenylphosphine) palladium (0), and di-μ-chlorobis [(η –allyl) palladium (II)]. In step 11, di-μ-chlorobis [(η –allyl) palladium (II)] is used as a palladium compound, and 2- (di-t-butylphosphino) -2′ , 4′ , 6′ –triisopropyl- It is preferred to use as a catalyst a complex formed with 1,1'-biphenyl as a ligand.

[0138] In addition, this step may be performed in the presence of a base. Examples of the base include weakly basic inorganic salts (sodium carbonate, potassium carbonate, cesium carbonate, sodium acetate, potassium acetate, calcium acetate etc.), metal hydrides (sodium hydride, potassium hydride etc.), metal alkoxides (potassium t (potassium t) -Butoxide, sodium t-butoxide, lithium t-butoxide, potassium t-pentoxide, sodium t-pentoxide, lithium t-pentoxide and the like) and the like.

[0139] As a reaction solvent, ether solvents such as tetrahydrofuran (THF), diethyl ether, dioxane or the like, or amide solvents such as N, N-dimethylacetamide (DMA), N, N-dimethylimidazolidinone (DMI), DMF Can be mentioned. Moreover, the mixed solvent with water may be sufficient.

[0140] The reaction temperature is generally 10 ° C to 200 ° C, preferably 40 ° C to 130 ° C. The reaction time is usually 1 minute to 20 hours, preferably 10 minutes to 10 hours. Compound ba can be purchased commercially from Aurora Fine Chemicals and the like. Synthetic Communications, 39 (14), 2506-2515, 2009 can also be used as a reference. It can also be obtained by esterification or amidification of a compound ba in which -COP21 is -COOH.

[0141] Compound ba1 in which X21 is -Zn-X21a can be purchased commercially from Focus Synthesis LLC or the like. It can also be synthesized with reference to WO 2014/201206 and the like.

[0142] Step B-2: Compound bc can be obtained by reacting compound bb with compound bb1 in the presence of a base.

[0143] Examples of the base include metal hydrides such as sodium hydride and potassium hydride, and alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and cesium hydroxide, with preference given to potassium hydroxide It is.

[0144] As the reaction solvent, amide solvents such as N, N-dimethylacetamide (DMA), N, N-dimethylimidazolidinone (DMI), DMF and the like can be mentioned, with preference given to DMI. Moreover, the mixed solvent with water may be sufficient.

[0145] The reaction temperature is generally -10 ° C to 100 ° C, preferably 0 ° C to 45 ° C. The reaction time is usually 30 minutes to 10 hours, preferably 1 hour to 5 hours. Compound bb can be purchased commercially from Aquila Pharmatech LLC and the like. It can also be synthesized with reference to WO 2013/010904, Organic Letters, 7 (18), 3965-3968, 2005, US Pat.

[0146] Step B-3: Compound bd can be obtained by reacting compound bc with hydroxyamine (H 2 NOH).

[0147] Examples of the reaction solvent include aprotic polar solvents such as dimethylsulfoxide (DMSO), dimethylformamide, dimethylacetamide and 1-methyl-2-pyrrolidinone, alcohol solvents such as methanol and ethanol, and the like. It is DMSO. Moreover, the mixed solvent with water may be sufficient.

[0148] The reaction temperature is generally -10 ° C to 100 ° C, preferably 20 ° C to 45 ° C. The reaction time is generally 2 hours to 72 hours, preferably 3 hours to 36 hours. Compound bd may be subjected to step B-4 without isolation or purification.

[0149] Step B-4: Compound bd is reacted with triphosgene, chlorocarbonic acid ester (methyl chlorocarbonate, ethyl chlorocarbonate, isopropyl chlorocarbonate etc.), carbonyldiimidazole etc., preferably carbonyldiimidazole, in the presence of a base. You can get the be.

[0150] As a base, for example, tertiary amines (triethylamine, N-methylmorpholine, diisopropylethylamine, 1,8-diazabicycloundec-7-ene (DBU), DABCO, etc.), metal hydroxides (sodium hydroxide, Potassium hydroxide), preferably tertiary amines such as DBU.

[0151] As the solvent, for example, aprotic polar solvents such as dimethylsulfoxide (DMSO), dimethylformamide, dimethylacetamide, and 1-methyl-2-pyrrolidinone, alcohol solvents such as methanol and ethanol, tetrahydrofuran (THF), diethyl ether And ether solvents such as dioxane, and the like, preferably DMSO.

[0152] The reaction temperature is generally -10 ° C to 100 ° C, preferably 20 ° C to 45 ° C. The reaction time is usually 10 minutes to 10 hours, preferably 15 minutes to 2 hours. Step B-5: Compound bf is obtained by deprotecting compound be protected with P21 using a base Can.

[0153] As the base, for example, alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and cesium hydroxide, potassium t-butoxide, sodium t-butoxide, lithium t-butoxide, potassium t-pentoxide, sodium Examples include metal alkoxides such as t-pentoxide and lithium t-pentoxide.

[0154] As the solvent, alcohol solvents such as methanol, ethanol, methoxyethanol and t-butyl alcohol; ether solvents such as THF and diethyl ether, N, N-dimethylacetamide (DMA), N, N-dimethylimidazolidinone (Amide solvents such as DMI) and DMF can be mentioned. Moreover, the mixed solvent with water may be sufficient.

[0155] The reaction temperature is generally -20 ° C to 120 ° C, preferably 20 ° C to 100 ° C. The reaction time is usually 20 minutes to 10 hours, preferably 30 minutes to 5 hours. Steps B-1, B-2, B-3, B-4 and B-5 can be switched in order. . For example, compound bc can be obtained by sequentially applying compound ba to step B-2 and step B-1. Compound bf can be obtained by sequentially applying compound ba to step B-2, step B-3, step B-4, step B-5, and step B-1. Compound bf can be obtained by sequentially applying Compound ba to Step B-2, Step B-3, Step B-4, Step B-1, and Step B-5.

[0156] Step B-Aa and Step B-Ab: When X 21 is a halogen atom, compound bb can also be obtained by subjecting compound ba to the following Step B-Aa and Step B-Ab, This may be added to step B-2.

[0157]

[0158] In the formula, RQc and RQd independently represent a hydrogen atom or C1-6 alkyl, or alternatively, RQc and RQd together with the oxygen atom to which they are attached and the boron atom to which the oxygen atom is attached, 1 And 3,2-dioxaborolanyl or 1,3,2-dioxaborinanyl may be formed.

[0159] Step B-Aa: The organic boron compound baa can be obtained by reacting the compound ba with the compound ba2 or the compound Ba3 in the presence of a palladium catalyst. This step may be performed in the presence of a base.

[0160] This step is carried out in the same manner as in step B-1, and the palladium catalyst, base, solvent, reaction temperature and reaction time used in the reaction are also the same as in step B-1. Examples of the compound ba2 include pinacol borane and 4,6,6-trimethyl-1,3,2-dioxaborinane. As compound ba3, for example, diboronic acid, pinacol diborane (4,4,4′, 4′, 5,5,5′, 5′ -octamethyl-2, 2′ -bi (1,3,2-dioxaborolane) And bis (neopentyl glycolato) diboron and bis (hexylene glycolato) diboron). These compounds can be purchased commercially from Tokyo Chemical Industry and the like. Journal of the American Chemical Society, 131 (45), 16346-16347, 2009 and Organic Synthesis, 77, 176-185, 2000, i) pinacol, ii) diborane, BH 3 · THF complex or BH 3 · dimethyl It can also be synthesized using a sulfide complex.

[0161] The organoboron compound baa may be subjected to step B-Ab without isolation. Step B-Ab: Compound bb can be obtained by reacting organic boron compound baa with compound ba1 in the presence of a base.

[0162] Examples of the base include weakly basic inorganic salts (sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like), preferably sodium carbonate.

[0163] The solvent used for the reaction, the reaction temperature, and the reaction time are the same as in step B-1. Compound bb can also be obtained by converting compound ba1 into an organic boron compound and reacting it with compound ba, similarly to the conversion of compound ba to compound baa.

[0164] Step B-B: Further, when the compound bb1 is represented by X21- (CH2) n1-CH2-CN, the compound bca corresponding to the compound bc obtained in the step B-2 is subjected to the following step B-B That is, by reacting with compound bc1 in the presence of a base, R 7 and R 8 together with the carbon atom to which they are attached form a C 3-15 cycloalkane ring, where R 7 and R 8 Can form a compound bcb corresponding to the compound bc, which may be substituted with 1 to 3 C1-6 alkyl, and the C3-15 cycloalkane ring formed by It may be attached to 3.

[0165]

[0166] In the formula, each of R7c, R7e and n8 and R7d independently represents a hydrogen atom or C1-6 alkyl, and n8 represents an integer of 0 to 3. Examples of the base include sodium hydride, potassium hydride, lithium bis (trimethylsilyl) amide (LiHMDS), and sodium bis (trimethylsilyl) amide (NaHMDS), potassium bis (trimethylsilyl) amide (KHMDS), lithium diisopropylamide (LDA) And metal hydrides such as lithium 2,2,6,6-tetramethyl pyrrolidine and the like, and preferably KHMDS.

[0167] Examples of the solvent include ether solvents such as THF, diethyl ether and dioxane, N, N-dimethylacetamide (DMA), N, N-dimethylimidazolidinone (DMI), DMF, N, N'-dimethylpropylene Amide solvents such as urea (DMPU) can be mentioned, and preferably amide solvents such as DMPU.

[0168] The reaction temperature is, for example, -20 ° C to 40 ° C, preferably -10 ° C to 10 ° C. The reaction time is, for example, 30 minutes to 8 hours, preferably 1 hour to 4 hours. The compound

bc1 is CGeneTech. Inc. Commercial products can be purchased from It can also be synthesized with reference to Organic Letters, 12 (17), 3938-3941, 2010.

[0169] <General Production Method C> Step C-1:

[0170]

[0171] Compound (Ia) can be obtained by condensing Compound f (or Compound p) and Compound bf using a condensing agent in the presence of a base. As the condensing agent, for example, benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tris (pyrrolidino) phosphonium hexafluorophosphate (PyBOP (registered trademark)), BOP condensing agent such as PyAOP, BroP, PyCloP, PyBroP (registered trademark), DEPBT, 4- (4,6-Dimethoxy-1,3,5-triazin-2-yl) -4-methylmorpholinium chloride n Hydrate (DMT-MM), 2- (1H-benzotriazol-1-yl) -1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), [dimethylamino (triazolo [4 ,. 5-b] pyridin-3-yloxy) methylide] -Dimethylazanium hexafluorophosphoric acid (HATU), ethyl (hydroxyimino) cyanoacetate (Oxyma) and the like, preferably HATU and the like.

[0172] As the base, for example, tertiary amines (triethylamine, N-methylmorpholine, diisopropylethylamine, DBU, DABCO, etc.), nitrogen-containing aromatic compounds (pyridine, dimethylaminopyridine, picoline, (2,6-) lutidine, pyrazine, And pyridazine etc., preferably tertiary amines such as diisopropylethylamine.

[0173] As the solvent, for example, ether solvents such as THF, diethyl ether, and dioxane, aprotic polar solvents such as dimethylsulfoxide (DMSO), dimethylformamide (DMF), dimethylacetamide, and 1-methyl-2-pyrrolidinone, etc. And preferably an aprotic polar solvent such as DMF.

[0174] The reaction temperature is, for example, 0 ° C to 80 ° C, preferably 20 ° C to 60 ° C. The reaction time is, for example, 1 minute to 10 hours, preferably 30 minutes to 5 hours. In addition, for example, compound d is sequentially applied to step A1-5, step C-1 and step A1-4. Compound ba is obtained in step B-2, step B-3, step B-4, step B-5, The compound (Ia) can also be obtained by switching the order of the steps, such as sequentially adding to step C-1 and step B-1. In addition, the compound represented by the formula (I) can be obtained by contacting or reacting an acid or a base that can be used for the preparation of a pharmaceutical, to obtain a salt thereof. The salt may be any pharmaceutically acceptable salt, and such salts include, for example, mineral acid salts (hydrochlorides, hydrobromides, hydroiodides, sulfates, phosphates, etc.) , Sulfonates (methane sulfonate, ethanesulfonic acid, benzene sulfonate, toluene sulfonate, etc.), carboxylates (formate, acetate, oxalate, maleate, fumarate, citric acid) Salt, malate, succinate, malonate, gluconate, mandelic acid, benzoate, salicylate, fluoroacetate, trifluoroacetate, tartrate, propionate,

glutarate, adipine Acid salts, nicotinate salts, etc., alkali metal salts (lithium salts, sodium salts, potassium salts, cesium salts, rubidium salts etc.), alkaline earth metal salts (magnesium salts, calcium salts etc.), Monium salts (ammonium salts, alkyl ammonium salts, dialkyl ammonium salts, trialkyl ammonium salts, tetraalkyl ammonium salts etc.), basic amino acid salts (lysine salts, arginine salts etc.), alkali metal salts, alkaline earth metals Salts are preferred, and sodium salts and calcium salts are more preferred. For example, a free body of a compound represented by the formula (I) is suspended or dissolved in an alcohol such as methanol or ethanol, acetonitrile, acetone, dimethyl sulfoxide or the like, and a basic aqueous solution containing sodium ions such as sodium hydroxide By adding a methanol solution containing sodium methoxide or an ethanol solution containing sodium ethoxide, the sodium salt of the compound represented by formula (I) can be obtained. The reaction temperature is, for example, 0 ° C to 80 ° C, preferably 20 ° C to 60 ° C.

[0175] The compound represented by the formula (1) or a salt thereof may be a solvate or a nonsolvate. The solvent contained in the solvate may be either water or an organic solvent. As the organic solvent, alcohols (for example, methanol, ethanol, n-propanol), dimethylformamide, acetonitrile, acetone, dimethyl sulfoxide and the like can be used. The compounds of the formula (I) and salts thereof are preferably used in the form of hydrates and also preferably in the form of non-solvates. The ratio of solvent molecules (preferably water molecules) to one molecule of the compound represented by the formula (I) or a salt thereof is, for example, 0.1 to 10, and more preferably 0.5 to 6. Also, this ratio may vary depending on the humidity, the manufacturing method, the manufacturing time, and the like.

[0176] The solvate of the compound represented by the formula (I) or a salt thereof can be obtained, for example, by a conventional method such as precipitation of the compound represented by the formula (I) or a salt thereof from a solvent. Hydrates can also be obtained by precipitating a compound represented by the formula (I) or a salt thereof from a water-containing organic solvent.

[0177] The solvate of the compound represented by the formula (I) or a salt thereof can be converted to the compound represented by the formula (I) or a salt thereof by a conventional method such as heating under reduced pressure. As a solvate of the compound represented by the formula (I) or a salt thereof, the compound represented by the formula (I) itself (free form), hydrate of free form, salt of free form, hydration of salt The free form, the free form hydrate, the free form sodium salt, the sodium salt hydrate, the free form calcium salt and the calcium salt hydrate are more preferable.

[0178] In the present invention, the compound represented by the formula (I) or a salt thereof, or a solvate thereof may be used in the form of crystals or in the form of amorphous (amorphous). .

[0179] In the present invention, all stereoisomers (eg, enantiomers, diastereomers (including cis and trans geometric isomers) of the compound represented by the formula (I)), racemates of the isomers, and others Contains a mixture. For example, compounds of formula (I) may have one or more asymmetric points, and the present invention includes racemic mixtures, diastereomeric mixtures, and enantiomers of such compounds. .

[0180] In the present invention, the atoms constituting the compound molecule represented by the formula (I) include those whose isotope is an isotope, and at least one atom has the same atomic number (proton number), and the mass number (proton and neutron) The sum of the numbers of) is substituted by different atoms. Examples of isotopes contained in the compound represented by the formula (I) include a hydrogen atom, a carbon atom, a nitrogen atom, an oxygen atom, a phosphorus atom, a sulfur atom, a fluorine atom, a chlorine atom, etc. 3H, 13C, 14C, 15N, 17O, 18O, 31P, 32P, 35S, 18F, 36Cl and the like. In particular, radioactive isotopes that decay by emitting radiation, such as 3 H and 14 C, are useful in the case of drug distribution distribution tests and the like for medicines or compounds. Stable isotopes can be used safely because they do not decay, hardly change in abundance, and have no radioactivity. Those in which the atom constituting the compound molecule represented by the formula (I) is an isotope can be converted according to a conventional method by replacing the reagent used in the synthesis with a reagent containing the corresponding isotope . The pharmaceutical composition of the present invention has GLP1 receptor agonistic action and hypoglycemic action, and by administering a pharmaceutically effective amount thereof to a patient by an appropriate administration method, non-insulin dependent diabetes mellitus (type 2 diabetes)), Hyperglycemia, glucose intolerance, insulin dependent diabetes (type 1 diabetes), diabetic complications, obesity, hypertension, dyslipidemia, arteriosclerosis, myocardial infarction, coronary heart disease, brain It can be used for the prevention or treatment of infarction, non-alcoholic steatohepatitis, Parkinson's disease or dementia.

[0181] In the present invention, "diabetes" refers to a disease or condition that causes abnormal metabolism in glucose production and utilization by failing to maintain proper blood sugar levels in the body, and insulin-dependent diabetes (type 1 diabetes)), Non-insulin dependent diabetes mellitus (type 2 diabetes).

[0182] "Hyperglycemia" refers to conditions in which plasma glucose levels during fasting and after glucose administration are higher than normal (e.g. 80-110 mg / dL on fasting in humans) and is one of the typical symptoms of diabetes It is also.

[0183] "Impaired glucose intolerance" includes insulin resistance glucose intolerance and impaired insulin secretion. By "diabetic complications" is meant complications resulting from diabetes or hyperglycemia and may be either acute or chronic complications. "Acute complications" include,

for example, ketoacidosis, infections (eg, skin infections, soft tissue infections, biliary infections, respiratory infections, urinary tract infections), and "chronic complications" include, for example, Small angiopathy (eg, nephropathy, retinopathy), neuropathy (eg, sensory neuropathy, motor neuropathy, autonomic neuropathy), foot scurvy. The major diabetic complications include diabetic retinopathy, diabetic nephropathy and diabetic neuropathy. "Coronary heart disease" includes myocardial infarction, angina pectoris and the like.

[0184] Examples of "dementia" include Alzheimer's disease, vascular dementia and diabetic dementia. The administration method of the pharmaceutical composition of the present invention includes oral administration, rectal administration, intravenous administration, intramuscular administration, subcutaneous administration, vaginal administration, intraperitoneal administration, intravesical administration, systemic administration such as inhaled administration, and ointment It may be any of topical administration by gel, cream and the like.

[0185] The pharmaceutical composition of the present invention is usually formulated into a certain formulation (dosage form) and used. Such preparations include, for example, tablets, capsules, granules, powders, fine granules, pills, aqueous or non-aqueous solutions or suspensions, and the like. The pharmaceutical composition of the present invention can also be used in the form of various controlled release formulations. Such controlled release preparations include, for example, those which are used by being implanted in the body, and those which are applied to the oral mucosa or nasal mucosa. In addition, the solution or suspension can be stored in a container suitable for dispensing into individual doses.

[0186] The various formulations described above can be manufactured by mixing the compound represented by the formula (I) or a salt thereof, or a solvate thereof with a pharmaceutically acceptable additive, by a known method. Such additives include, for example, excipients, lubricants (coating agents), binders, disintegrants, stabilizers, flavoring agents, bases, dispersants, diluents, surfactants, emulsifiers, etc. Can be mentioned.

[0187] As the excipient, for example, starch (starch, potato starch, corn starch and the like), lactose, crystalline cellulose, calcium hydrogen phosphate and the like can be mentioned. As the lubricant (coating agent), for example, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, shellac, talc, carnauba wax, paraffin and the like can be mentioned.

[0188] Examples of the binder include polyvinyl pyrrolidone, macrogol, and the same compounds as the above-mentioned excipients. Examples of the disintegrant include croscarmellose sodium, sodium carboxymethyl starch, crosslinked polyvinyl pyrrolidone and the like, chemically modified starches, and celluloses, as well as compounds similar to the above-mentioned excipients and the like.

[0189] Examples of the stabilizer include p-hydroxybenzoic acid esters such as methylparaben and propylparaben; benzalkonium chloride; phenols such as phenol and cresol; thimerosal; dehydroacetic acid; sorbic acid and the like.

[0190] As a flavoring agent, a sweetener, an acidulant, a flavoring agent etc. which are normally used are mentioned, for example. As the base, for example, fats such as pork fat; vegetable oils such as olive oil and sesame oil; higher alcohols such as stearyl alcohol and cetanol; animal oil; lanolinic acid; vaseline; paraffin; bentonite; glycerin; .

[0191] Examples of the dispersant include cellulose derivatives (eg, gum arabic, tragacanth, methyl cellulose etc.), polyester stearates, sorbitan sesquioleate, aluminum monostearate, sodium alginate, polysorbates, sorbitan fatty acid esters and the like.

[0192] Examples of the solvent or diluent in the solution include phenol, chlorocresol, purified water, distilled water and the like. As surfactant or an emulsifier, for example, polysorbate 80, polyoxyl stearate, lauromacrogol and the like can be mentioned.

[0193] The content of the compound represented by the formula (I) or a salt thereof, or a solvate thereof in a preparation varies depending on the dosage form, but is generally 0.01 to 100% by weight. The preparation may contain only one type of the compound represented by the formula (I) or a salt thereof, or a solvate thereof, or may contain two or more types.

[0194] When the pharmaceutical composition of the present invention is used as a prophylactic or therapeutic agent for non-insulin dependent diabetes mellitus (type 2 diabetes) or obesity, the dosage as the amount of the active ingredient may be: weight of symptoms, age, body weight, It can be determined as appropriate according to the relative health status, presence or absence of concomitant drug, administration method and the like. As an example, when the administration subject is a temperature-controlled animal, particularly a human, the dose as an amount of the active ingredient per day is, for example, 0.01 to 10000 mg, preferably 0.1 to 1000 mg for oral administration. Moreover, also in parenteral administration, it is 0.001 to 3000 mg, for example, preferably 0.01 to 300 mg. The above dose may be administered once per day to several weeks, or may be divided into two or more times per day.

[0195] In the present invention, “effective amount” means a therapeutically or prophylactically effective amount of the compound represented by the formula (I), a salt thereof, or a solvate of any of them, which is an active ingredient, It can be determined as appropriate according to the weight, age, weight, relative health condition, presence or absence of concomitant drug, administration method and the like.

[0196] The contents of the present invention will be further described in the following examples and reference examples. All starting materials and reagents were obtained from commercial suppliers or synthesized using known methods. Room temperature (rt) refers to 5-35 ° C. Silica gel: SHOKO Scientific Purif-Pack (registered trademark) SI 60 μm (manufactured by Shoko Scientific), Biotage (registered trademark) SNAP Ultra Silica Cartridge (manufactured by Biotage), or SNAP KP-Sil Cartridge (manufactured by Biotage); reverse phase silica gel Wakosil (registered trademark) 25C18 (Wako Pure Chemical Industries, Ltd.) or Biotage (registered trademark) SNAP Ultra C18 Cartridge (manufactured by Biotage) was used. The HPLC purification of the compound was carried out using an AutoPurification HPLC / MS System (manufactured by Waters) or a Predictive HPLC system with injection / fractionation function (manufactured by Gilson). 1 H-NMR spectra use Me 4 Si as an internal standard substance or not, ECP-400 (manufactured by JEOL), Agilent 400-MR (manufactured by Agilent Technologies), AVANCE 3 300 MHz (manufactured by Bruker) or AVANCE 3 600 MHz Cryo-TCI (S = singlet, brs = broadening red, d = doublet, t = triplet, q = quartet, dd = double doublet, dd = double double doublet, m = multiplet). Chemical shifts in NMR data are relative to Me 4 Si or deuterated solvents and are given in ppm (parts per million, δ) and coupling constants (J) are shown in Hz (Hertz). LC / MS performed retention time measurement and mass spectrometry according to the apparatus and analysis conditions of Table 1. The microwave was irradiated using InitiatorTM (manufactured by Biotage). Mass spectrometry in LC / MS was measured using a mass spectrometer: SQD (manufactured by Waters), SQD2 (manufactured by Waters), 2020 (manufactured by Shimadzu), or 2010 EV (manufactured by Shimadzu).

[0197]

[0198]

[0199] EXAMPLE 1 3-[(1S, 2S) -1- [2- [2- (3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl) -2-oxo] Imidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2-ethyl-3-methylpyridin-4-yl) indole-1-one Synthesis of [III] -2-Methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 1)

[0200]

[0201] (Step 1-1) [(5-cyano-1,2,3,6-tetrahydropyridin-4-yl) amino] potassium (compound 1b) 3- (2-cyanoethylamino) propane nitrile (compound 1a, 22. A solution of 1 M potassium tert-butoxide in THF (179 mL) was added to a solution of 0 g (179 mmol) in tetrahydrofuran (THF) (179 mL), and stirred at room temperature for 1 hour. The reaction mixture was collected by filtration, washed with THF (50 mL) and dried under reduced pressure to give the title compound 1b (23.8 g, yield 83%) as a pale brown solid.

[0202] LC / MS mass spectrometry: m / z 124 ([M + H] +). LC / MS retention time: 0.14 minutes (analysis conditions: SMD-FA05-1). 1 H-NMR (400 MHz, MeOH-d4) δ : 3.33 (2 H, t, J = 1.3 Hz), 2.90 (2 H, t, J = 5.9 Hz), 2.21 (2 H, tt, J = 5.9, 1.3 Hz).

[0203] (Step 1-2) tert-butyl 3-amino-2- (3,5-dimethylphenyl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylate (compound 1d) In a solution of 3,5-dimethylphenylhydrazine hydrochloride (Compound 1c, 5.00 g, 29.0 mmol) and Compound 1b (4.67 g, 29.0 mmol) obtained in Step 1-1 in ethanol (57.9 mL) The reaction mixture was added with 2N hydrochloric acid (23.2 mL, 46.3 mmol) and stirred at 50 ° C. for 1 hour. The reaction mixture was cooled to 0 ° C., 5 M aqueous solution of sodium hydroxide (9.27 mL, 46.3 mmol), di-tert-butyl dicarbonate (6.64 g, 30.4 mmol) were added and stirred at 0 ° C. for 1 hour . Water was added to the reaction mixture, extraction was performed with ethyl acetate, and the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the filtrate is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (ethyl acetate / hexane = 0: 1 to 1: 1) to give the title compound 1d (7.82 g, yield as pale yellow solid) 79%).

[0204] LC / MS mass spectrometry: m / z 343 ([M + H] +). LC / MS retention time: 0.99 minutes (analysis conditions: SMD-FA05-3). (Step 1-3) 3- (2,2-dimethoxyethylcarbamoylamino) -2- (3,5-dimethylphenyl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5- Carboxylic acid tert-butyl (Compound 1f) 2-isocyanato-1,1-dimethoxyethane (compound) in a solution of compound 1d (2.53 g, 7.39 mmol) obtained in step 1-2 in pyridine (7.39 mL) 1e, 1.94 g, 14.8 mmol) was added and stirred at room temperature. After 3 hours and 15 minutes, diethylamine (1.08 g, 14.8 mmol) was added and stirred for 5 minutes at room temperature, then water (50.6 mL) was added and stirred at room temperature for 20 minutes. The reaction mixture that has become a suspension is filtered, and the filtered solid is washed with water (12.7 mL) and then dried under reduced pressure to give the title compound 1f (3.20 g, yield 91%) as a pale yellow solid. The

[0205] LC / MS mass spectrometry: m / z 474 ([M + H] +). LC / MS retention time: 0.78 minutes (analysis conditions: SQD-FA05-1). (Step 1-4) 3- [2- (3,5-dimethylphenyl) -4,5,6,7-tetrahydropyrazolo [4,3-c] pyridin-3-yl] -1H-imidazole-2 -ON (Compound 1g) Formic acid (3.84 mL, 100 mmol) was added to compound 1f (158 mg, 0.334 mmol) obtained in step 1-3, and stirred at room temperature for 21 hours. The reaction mixture was concentrated under reduced pressure, toluene was added, and the solvent was evaporated under reduced pressure. The residue was dissolved by adding dichloromethane (1 mL), and then hydrogen chloride (4 M solution in dioxane, 0.835 mL, 3.34 mol) was added at room temperature. The reaction mixture was concentrated under reduced pressure, toluene was added, and the solvent was evaporated under reduced pressure to give a crude product (176 mg) of the title compound 1 g.

[0206] LC / MS mass spectrometry: m / z 310 ([M + H] +). LC / MS retention time: 0.39 minutes (analysis conditions: SQD-FA05-3). (Step 1-5) 4-bromo-2-ethyl-3-methylpyridine (compound 1i) 4-bromo-2,3-dimethylpyridine (compound 1 h, 7.05 g, 37.9 mmol) in THF (75.0 mL))) The solution was cooled to -78 ° C and 1.11 M lithium diisopropylamide n-hexane-THF solution (35.8 mL, 39.8 mmol) was added slowly. After stirring for 5 minutes at −78 ° C., iodomethane (2.84 mL, 45.5 mmol) was added. After stirring for 5 minutes at −78 ° C., the reaction solution was slowly warmed to room temperature, stirred for 30 minutes, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane / ethyl acetate) to give the title compound 1i (6.98 g, yield 92%) as an orange oil.

[0207] LC / MS mass spectrometry: m / z 200 ([M + H] +). LC / MS retention time: 0.38 minutes (analysis conditions: SQD-FA05-3). (Step 1-6) Ethyl 5-bromo-1-[(1S, 2S) -1-cyano-2-methylcyclopropyl] indole-2-carboxylate (Compound 1 1) 5-bromo-1- (cyanomethyl) indole Ethyl 2-carboxylate (Compound 1j, 3.60 g, 11.7 mmol) and (4R) -4-Methyl-1,3,2-dioxathiolane 2,2-dioxide (Compound 1 k, 4.86 g, 35.2 mmol A solution of N, N'-dimethylpropyleneurea (117 mL) in (a) was degassed under reduced pressure, purged with nitrogen, and cooled to 0 ° C. Under nitrogen atmosphere, a THF solution (46.9 mL, 46.9 mmol) of 1.0 M potassium bis (trimethylsilyl) amide was slowly added dropwise. After stirring at 0 ° C. for 2.5 hours, formic acid (5.30 mL, 141 mmol) was added, and the mixture was extracted with a mixed solution of hexane / ethyl acetate (1: 3). The organic layer was washed three times with water, twice with saturated aqueous sodium hydrogen carbonate solution and once with saturated brine, and dried over sodium sulfate. After filtration, the filtrate is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (ethyl acetate / hexane = 1: 19 to 1: 4) to give the title compound 1l (1.70 g, yield 42%) Obtained as a white solid.

[0208] LC / MS mass spectrometry: m / z 347 ([M + H] +). LC / MS retention time: 0.69 minutes (analysis conditions: SQD-AA50-1). (Step 1-7) Ethyl 1-[(1S, 2S) -1-cyano-2-methylcyclopropyl] -5- (2-ethyl-3-methylpyridin-4-yl) indole-2-carboxylate Compound 1m) Compound 1 1 (2.70 g, 7.78 mmol) obtained in Step 1-6, 4,4,4 ′ , 4 ′ , 5,5,5 ′ , 5′ -octamethyl-2, 2′ – After vacuum degassing a suspension of bi (1,3,2-dioxaborolane) (2.17 g, 8.55 mmol) and potassium acetate (1.15 g, 11.7 mmol) in dioxane (44 mL) at room temperature, It replaced with nitrogen. In a nitrogen atmosphere, 1, 1′ –bis (diphenylphosphino) ferrocene-palladium (II) dichloride dichloromethane complex (1.29 g, 1.56 mmol) was added and stirred at 100 ° C. for 3 hours. After cooling to room temperature, a solution of 4-bromo-2-ethyl-3-methylpyridine (compound 1i, 2.33 g, 11.7 mmol), sodium carbonate (2.47 g, 23.3 mmol) and water (7.4 mL) is dissolved. After degassing under reduced pressure, the solution was purged with nitrogen and stirred at 100.degree. C. for 2 hours. After cooling to room temperature, water (5.4 mL) and N-acetylcysteine (0.635 g, 3.89 mmol) were added and stirred for 0.5 hours. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed once with saturated brine and dried over sodium sulfate. After filtration, the

filtrate is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (ethyl acetate / hexane = 1: 19 to 2: 3) to give the title compound 1m (2.92 g, collection) as a pale yellow gum The rate is 97%).

[0209] LC / MS mass spectrometry: m / z 388 ([M + H] +). LC / MS retention time: 1.06 minutes (analytical conditions: SQD-AA05-2). (Step 1-8) 5- (2-ethyl-3-methylpyridin-4-yl) -1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4] -Oxadiazol-3-yl) cyclopropyl] indole-2-carboxylate (Compound 1n) Compound 1m (0.225 g, 0.581 mmol) obtained in Step 1-7 dimethyl sulfoxide (DMSO) (2 To the solution was added 50% aqueous hydroxyamine solution (0.356 mL, 5.81 mmol) and stirred at room temperature for 17 hours. Ethyl acetate (50 mL) was added, washed with water (10 mL) and saturated brine (10 mL), and dried over magnesium sulfate. After filtration, the filtrate is concentrated under reduced pressure, and the obtained residue is dissolved in DMSO (1.9 mL), carbonyldiimidazole (188 mg, 1.16 mmol) and 1,8-diazabicycloundeca-7- En (0.219 mL, 1.45 mmol) was added and stirred at room temperature for 0.5 h. Formic acid was added, and the resultant was directly purified by reverse phase chromatography (acetonitrile / water, 0.1% formic acid) to give the title compound 1n (169 mg, yield 65%) as a white powder.

[0210] LC / MS mass spectrometry: m / z 447 ([M + H] +). LC / MS retention time: 0.80 minutes (analytical conditions: SMD-FA05-3). (Step 1-9) 5- (2-ethyl-3-methylpyridin-4-yl) -1-[(1S, 2S) -2-methyl-1-(5-oxo-4H-1,2,4] -Oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (compound 1o) 2M in DMSO (40 mL) solution of compound 1n (3.61 g, 8.08 mmol) obtained in step 1-8 Aqueous sodium hydroxide solution (10.1 mL, 20.2 mmol) was added and stirred at room temperature for 1.5 hours. Formic acid was added, and the resultant was directly purified by reverse phase chromatography (acetonitrile / water, 0.1% formic acid) to give the title compound 1o (3.38 g, 100% yield) as a white powder.

[0211] LC / MS mass spectrometry: m / z 419 ([M + H] +). LC / MS retention time: 0.83 minutes (analysis conditions: SQD-AA05-2). (Step 1-10) 3-[(1S, 2S) -1- [2- [2- (3,5-dimethylphenyl) -3- (2-oxo-1H-imidazol-3-yl) -6, 7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2-ethyl-3-methylpyridin-4-yl) indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (compound 1p) 1 g (1.25 g, 3.61 mmol) of the compound obtained in step 1-4, compound 1o obtained in step 1-9 (1.59 g, 3.80 mmol), and N of [dimethylamino (triazolo [4,5-b] pyridin-3-yloxy) methylidene] -dimethylazanium hexafluorophosphate (1.51 g, 3.98 mmol) , N'-di Chill formamide (DMF) (24.1mL) solution, diisopropylethylamine (3.15 mL, 18.1 mmol) was added and stirred at room temperature for 30 minutes. The reaction mixture was directly purified by reverse phase column chromatography (acetonitrile / water, 0.1% formic acid) to give the title compound 1p (2.44 g, yield 95%) as a pale brown foam.

[0212] LC / MS mass spectrometry: m / z 710 ([M + H] +). LC / MS retention time: 0.85 minutes (analytical conditions: SMD-FA05-3). (Step 1-11) 3-[(1S, 2S) -1- [2- [2- (3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl) -2-] Oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2-ethyl-3-methylpyridin-4-yl) indole-1 -Yl] -2-Methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 1) Compound 1p (20 mg, 0.028 mmol) obtained in Step 1-10, 5- Bromo-1-methylindazole (compound 1q, 11.9 mg, 0.056 mmol), (1S, 2S) -1-N, 2-N-dimethylcyclohexane-1,2-diamine (1.6 mg, 0.011 mmol) , And carbonic acid Copper (I) iodide (1.1 mg, 0.0056 mmol) is added to a suspension of lithium (11.7 mg, 0.085 mmol) in N-methylpyrrolidone (0.188 mL) at room temperature, and the mixture is added The mixture was stirred at 130 ° C. for 3 hours under a nitrogen atmosphere. The reaction mixture was purified by reverse phase silica gel chromatography (acetonitrile / water, 0.1% formic acid) to give the title compound 1 (17.2 mg, 73% yield) as a pale brown foam.

[0213] LC / MS mass spectrometry: m / z 840 ([M + H] +). LC / MS retention time: 1.12 minutes (analytical conditions: SMD-TFA 05-3). <Examples 2 to 50> A combination of the 2-oxoimidazole compound shown in Table 2-2 below and the halogen compound shown in Table 2-3, and the same as Step 1-11 of Example 1 using an appropriate reagent The operation was carried out, and Example compounds 2 to 50 shown in Table 2-1 were obtained by the following reactions.

[0214]

[0215]

[0216]

[0217]

[0218]

[0219]

[0220]

[0221]

[0222]

[0223]

[0224]

[0225]

[0226]

[0227]

[0228]

[0229] Although rotamers exist in the compounds in Table 2-1, for example, 1 H-NMR of Example Compound 2 is as follows. Rotamer A1H-NMR (600 MHz, CDCl3) δ : 11.29 (1 H, s), 8.40 (1 H, d, J = 5.2 Hz), 7.93 (1 H, s), 7.74 (7 1H, d, J = 1.5 Hz), 7.70 (1 H, d, J = 8.6 Hz), 7.56 (1 H, s), 7.45 (1 H, dd, J = 9.0, 1 .5 Hz), 7.38 (1 H, d, J = 9.0 Hz), 7.28 (1 H, m), 7.14 (1 H, d, J = 5.2 Hz), 7.04 (2 H, d , JHF = 5.9 Hz), 6.82 (1 H, s), 6.59 (1 H, d, J = 3.0 Hz), 6.08 (1 H, d, J = 3.0 Hz), 4.96 (1H, d, J = 16.0 Hz), 4.92 (1 H, d, J = 16.0 Hz), 4.69 (1 H, ddd, J = 13.1, 4.4, 4.4 Hz), 4 06 (3H, s), 3.75 (1 H, ddd, J = 13.1, 9.5, 5.0 Hz), 3.07 (2 H, m), 2.97 (2 H, q, J = 7 .6 Hz), 2.26 (3 H, s), 2. 25 (6 H, s), 1. 88 (1 H, s), 1.51 (2 H, m), 1.37 (3 H, t, J = 7.6 Hz), 1.17 (3 H, d, J = 5.6 Hz).

[0230] Rotamer B1H-NMR (600 MHz, CDCl3) δ : 11.29 (1 H, s), 8.44 (1 H, d, J = 5.2 Hz), 8.04 (1 H, s), 7.90 (7 1H, d, J = 1.4 Hz), 7.73 (1 H, d, J = 8.8 Hz), 7.63 (1 H, dd, J = 9.0, 1.4 Hz), 7.60 (1 H) , S), 7.51 (1 H, d, J = 9.0 Hz), 7.30 (1 H, m), 7.20 (1 H, d, J = 5.2 Hz), 7.11 (2 H, d , JHF = 6.0 Hz), 6.81 (1 H, s), 6.71 (1 H, d, J = 3.0 Hz), 6.22 (1 H, d, J = 3.0 Hz), 5.24 (1H, d, J = 16.3 Hz), 4.64 (1 H, d, J = 16.3 Hz), 4.45 (1 H, ddd, J = 13.5, 4.6, 4.0 Hz), 4 12 (3H, s), 3.87 (1 H, ddd, J = 13.5, 10.2, 3.8 Hz), 3.17 (1 H, ddd, J = 15.5, 10.2, 4. 6 Hz), 3.02 (1 H, m), 3.00 (2 H, q, J = 7.6 Hz), 2.30 (3 H, s), 2.28 (6 H, s), 1.96 (1 H) , Dd, J = 6.0 Hz), 1.64 (1 H, m), 1.58 (1 H, dd, J = 9.4, 6.0 Hz), 1.39 (3 H, t, J = 7. 6 Hz), 1.19 (3 H, d, J = 6.1 Hz).

[0231]

[0232]

[0233]

[0234]

[0235]

[0236]

[0237] Example 2-oxoimidazole Compound (3-[(1S, 2S) -1- [5- (2-Ethyl-3-Methylpyridin-4-yl) -2- [2 Used in Synthesis of Compounds 2 to 5 -(4-Fluoro-3,5-dimethylphenyl) -3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5- [Carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 2g) was synthesized as follows.

[0238]

[0239] (Step 2-1) 4-Fluoro-3,5-dimethylaniline hydrochloride (compound 2b) 4-fluoro-3,5-dimethylaniline (compound 2a, 3.97 g, 28.5 mmol) in concentrated hydrochloric acid (20 mL) And water (20 mL) were added at room temperature while stirring. The mixture was stirred at the same temperature for 1 hour, and the solid in the reaction mixture was collected by filtration and dried. The obtained solid was further added with methoxycyclopentane (20 mL), stirred at 50 ° C. for 1 hour, and then stirred at room temperature for 1.5 hours. The precipitated solid was collected by filtration and washed with methoxycyclopentane (12 mL). The obtained solid was dried under reduced pressure to give the title compound 2b (4.88 g, yield 97%) as an off-white solid.

[0240] This compound was used directly in the next step (Step 2-2). (Step 2-2) (4-Fluoro-3,5-dimethylphenyl) hydrazine hydrochloride (Compound 2c) Compound 2b (1.00 g, 5.69 mmol) obtained in Step 2-1 was concentrated in hydrochloric acid (10 mL) Was added, and while vigorously stirring at 0 ° C., a solution of sodium nitrite (511 mg, 7.40 mmol) in water (2.4 mL) was added over 1 minute, and stirred at 0 ° C. for 30 minutes. Then a solution of tin (II) chloride (2.27 g, 12.0 mmol) in water (2.4 mL) was added over 2 minutes. Further water (7 mL) was added and stirred at room temperature for 1 hour. The solid in the reaction mixture was collected by filtration, washed with water (2 mL) and dried to give the title compound 2c (1.75 g, yield 77%, content 48%) as a gray solid.

[0241] LC / MS mass spectrometry: m / z 155 ([M + H] +). LC / MS retention time: 0.54 minutes (analysis conditions: SMD-FA05-1). (Step 2-3) tert-butyl 3-amino-2- (4-fluoro-3,5-dimethylphenyl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid (Compound 2d) The compound 1b obtained in Step 1-1 and the compound 2c obtained in Step 2-2 were obtained by the same procedure as Step 1-2 in Example 1, using a suitable reagent.

[0242] LC / MS mass spectrometry: m / z 361 ([M + H] +). LC / MS retention time: 1.04 minutes (analysis conditions: SMD-FA05-3). (Step 2-4) 3- (2,2-dimethoxyethylcarbamoylamino) -2- (4-fluoro-3,5-dimethylphenyl) -6,7-dihydro-4H-pyrazolo [4,3-c] It was synthesize | combined by the operation similar to the process 1-3 of Example 1 using the suitable reagent from the compound 2d obtained by the pyridine- 5-carboxylic-acid tert- butyl (compound 2e) process 2-3. LC / MS mass

spectrometry: m / z 492 ([M + H] +). LC / MS retention time: 1.07 minutes (analysis conditions: SMD-FA05-3).

[0243] (Step 2-5) 3- [2- (4-fluoro-3,5-dimethylphenyl) -4,5,6,7-tetrahydropyrazolo [4,3-c] pyridin-3-yl] -1H -Imidazol-2-one hydrochloride (Compound 2f) The compound 2e obtained in Step 2-4 was synthesized by the same procedure as in Step 1-4 of Example 1 using a suitable reagent.

[0244] LC / MS mass spectrometry: m / z 328 ([M + H] +). LC / MS retention time: 0.61 minutes (analysis conditions: SMD-FA05-3). (Step 2-6) 3-[(1S, 2S) -1- [5- (2-ethyl-3-methylpyridin-4-yl) -2- [2- (4-fluoro-3,5-dimethyl] Phenyl) -3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indol-1-yl] -2- Methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 2g) A suitable reagent from the compound 2f obtained in the step 2-5 and the compound 1o obtained in the step 1-9 The compound was synthesized by the same procedure as step 1-10 of Example 1.

[0245] Example 2-oxoimidazole Compound (3-[(1S, 2S) -1- [2- [2- (4-Fluoro-3,5-dimethylphenyl) -3- (2-) Used in the Synthesis of Compound 6 Oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2-methoxy-3-methylpyridin-4-yl) Indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 6i) was synthesized as follows.

[0246]

[0247] (Step 6-1) 5-bromo-1- (cyanomethyl) -N-methyl-N-phenylindole-2-carboxamide (compound 6c) 5-bromo-1- (cyanomethyl) indole-2-carboxylic acid (compound 6a) And N-methylaniline (compound 6b) were synthesized by the same procedure as in steps 1 to 10 of Example 1 using appropriate reagents.

[0248] LC / MS mass spectrometry: m / z 368 ([M + H] +). LC / MS retention time: 1.25 minutes (analytical conditions: SMD-FA05-3). (Step 6-2) 5-bromo-l-[(IS, 2S) -l-cyano-2-methylcyclopropyl] -N-methyl-N-phenylindole-2-carboxamide (compound 6d) step 6-1 The compound 6c obtained in the above was synthesized by the same procedure as step 1-6 in Example 1 using a suitable reagent.

[0249] LC / MS retention time: 1.37 minutes (analysis conditions: SMD-FA05-1). 1 H-NMR (400 MHz, DMSO-d6) δ : 7.69 (1 H, s), 7.65-7. 25 (7 H, m), 6.02 (1 H, brs), 3.44 (3 H, s)), 3.31 (3 H, d, J = 9.5 Hz), 2.04-1.74 (3 H, m).

[0250] (Step 6-3) 5-bromo-N-methyl-1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4-oxadiazol-3-yl) Cyclopropyl] -N-phenylindole-2-carboxamide (Compound 6e) Compound 6d obtained in Step 6-2 was synthesized by the same procedure as Step 1-8 in Example 1 using a suitable reagent.

[0251] LC / MS mass spectrometry: m / z 467 ([M + H] +). LC / MS retention time: 1.33 minutes (analysis conditions: SMD-FA 05-01). (Step 6-4) 5-bromo-1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4-oxadiazol-3-yl) cyclopropyl] indole -2-carboxylic acid (compound 6f) mixed solution of compound 6e (9.70 g, 20.8 mmol) obtained in step 6-3, potassium hydroxide (11.7 g, 208 mmol), methoxyethanol (41.5 mL) The mixture was stirred at 100 ° C. for 4 hours. Under ice-cooling, 6N hydrochloric acid (51.9 mL) was added, and the suspension was stirred at room temperature for 30 minutes. The crystals were collected by filtration and washed with water (29.1 mL), and the obtained solid was dried under reduced pressure to give the title compound 6f (7.42 g, yield 95%) as a pale brown solid.

[0252] LC / MS mass spectrometry: m / z 376 ([M-H]-). LC / MS retention time: 1.10 minutes (analysis conditions: SMD-FA05-2). (Step 6-5) 5- (2-methoxy-3-methylpyridin-4-yl) -1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4] -Oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (Compound 6h) Compound 6f (3.00 g, 7.93 mmol) obtained in Step 6-4, palladium (II) acetate (0. 1). 178 g (0.793 mmol), dicyclohexyl (2 ′ , 4 ′ , 6′ –triisopropyl- [1, 1′ –biphenyl] -2-yl) phosphane (0.756 g, 1.587 mmol), 4,4,4 ', 4', 5,5,5 ', 5'-octamethyl-2,2'-bi (1,3,2-dioxaborolane) (3.02 g, 11.9 mmol), potassium phosphate (10.1 g, 47.6 mmol) of DM O (34.7mL) suspension was degassed under reduced pressure at room temperature and purged with nitrogen. After stirring for 0.5 hours at 100 ° C. under a nitrogen atmosphere, the mixture was cooled to room temperature. Add 4-iodo-2-methoxy-3-methylpyridine (Compound 6 g, 1.98 g, 7.93 mmol), water (4.96 mL) to the solution, degass under reduced pressure, then purge with nitrogen at 100 ° C. Stir for .5 hours. After cooling to room temperature, water (12.4 mL) and formic acid (6 mL) are added and filtered, and the filtrate is directly purified by reverse phase chromatography (acetonitrile / water, 0.1% formic acid) to give the title compound 6h (1.83 g, 55% yield) was obtained.

[0253] LC / MS mass spectrometry: m / z 421 ([M + H] +). LC / MS retention time: 1.10 minutes (analysis conditions: SMD-FA05-1). (Step 6-6) 3-[(1S, 2S) -1- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- (2-oxo-1H-imidazol-3-yl]) -6,7-Dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2-methoxy-3-methylpyridin-4-yl) indol-1-yl] -2- Methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 6i) Suitable reagent from the compound 2f obtained in Step 2-5 and the compound 6h obtained in Step 6-5 The compound was synthesized by the same procedure as step 1-10 of Example 1.

[0254] The halogen compound (1- (5-bromoindazol-1-yl) -2-methylpropan-2-ol, compound 6l) used in the synthesis of the example compound 6 was synthesized as follows.

[0255] (Step 6-7) 1- (5-bromoindazol-1-yl) -2-methylpropan-2-ol (compound 6k)

[0256]

[0257] Dissolve 5-bromoindazole (compound 6j, 150 mg, 0.761 mmol) and 2,2-dimethyloxirane (compound 6k, 274 mg, 3.81 mmol) in 1-methylpyrrolidin-2-one (NMP) (1.52 mL) And potassium carbonate (526 mg, 3.81 mmol) was added. Stir at 180 ° C. for 30 minutes under microwave. Water was added to the reaction mixture and extracted with ethyl acetate. The organic layer was washed with water and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate / hexane = 1: 1) to give 6 l (115 mg, yield 56%) of the title compound.

[0258] LC / MS mass spectrometry: m / z 269 ([M + H] +). LC / MS retention time: 1.00 minutes (analysis conditions: SMD-FA05-2). Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [5- (2,2-dimethylmorpholin-4-yl) -2- [2- (4-) used in the synthesis of compound 7 Fluoro-3,5-dimethylphenyl) -3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indole- 1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 7c) was synthesized as follows.

[0259]

[0260] (Step 7-1) 5- (2,2-dimethylmorpholin-4-yl) -1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4-oxa] Diazol-3-yl) cyclopropyl] indole-2-carboxylic acid (compound 7b) 2,2-dimethylmorpholine (compound 7a, 1.98 g, 17.2 mmol), tris (dibenzylideneacetone) dipalladium (0) (0.121 g, 0.132 mmol), 2-dicyclohexylphosphino-2 ', 6'-di-i-propoxy-1,1'-biphenyl (0.123 g, 0.264 mmol), sodium tert-butoxide (5 A suspension of .08 g (529 mmol) in NMP (44 mL) was vacuum degassed at room temperature and then purged with nitrogen. Under a nitrogen atmosphere, the compound 6f (5.0 g, 13.2 mmol) obtained in Step 6-4 was added, and the mixture was stirred at 100 ° C. for 0.5 hours, and then cooled to room temperature. Formic acid was added, and the resultant was directly purified by reverse phase chromatography (acetonitrile / water, 0.1% formic acid) to give the title compound 7b (5.26 g, yield 96%).

[0261] LC / MS mass spectrometry: m / z 413 ([M + H] +). LC / MS retention time: 1.00 minutes (analysis conditions: SMD-FA05-1). (Step 7-2) 3-[(1S, 2S) -1- [5- (2,2-dimethylmorpholin-4-yl) -2- [2- (4-fluoro-3,5-dimethylphenyl)] -3- (2-Oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclo [Propyl] -4H-1,2,4-oxadiazol-5-one (Compound 7c) By using an appropriate reagent from compound 7b obtained in step 7-1 in the same manner as in step 1-10 of Example 1 Were synthesized by

[0262] Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- (2) used in the synthesis of compounds 8-10 2-Oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c]

pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl] -2-Methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 8c) was synthesized as follows.

[0263]

[0264] (Step 8-1) 1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4-oxadiazol-3-yl) cyclopropyl] -5- (oxane -4-yl) indole-2-carboxylic acid (Compound 8b) Compound 6f (0.30 g, 0.793 mmol) obtained in step 6-4, palladium (II) acetate (35.6 mg, 0.159 mmol), After vacuum degassing a suspension of 2-dicyclohexylphosphino-2 ', 6'-diisopropoxybiphenyl (0.148 g, 0.317 mmol) in N, N-dimethylacetamide (DMA) (2.64 mL), It was purged with nitrogen and stirred at room temperature for 15 minutes. Under a nitrogen atmosphere, 1 M (tetrahydro-2H-pyran-4-yl) zinc (II) iodide (compound 8a) in DMA solution (7.9 mL, 7.93 mmol) is added and stirred at 80 ° C. for 15 minutes It cooled to room temperature. Formic acid was added, and the resultant was directly purified by reverse phase chromatography (methanol / water) to give the title compound 8b (0.19 g, yield 61%).

[0265] LC / MS mass spectrometry: m / z 382 ([M-H]-). LC / MS retention time: 1.00 minutes (analysis conditions: SMD-FA05-2). (Step 8-2) 3-[(1S, 2S) -1- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- (2-oxo-1H-imidazol-3-yl]) -6,7-Dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl] -2-methylcyclopropyl] -4H- 1,2,4-Oxadiazol-5-one (Compound 8c) was synthesized from Compound 8b obtained in Step 8-1 by the same procedure as in Step 1-10 of Example 1, using an appropriate reagent .

[0266] The halogen compound (5-bromo-1-[(3R) -oxolan-3-yl] indazole, compound 8f) used in the synthesis of the example compound 8 was synthesized as follows.

[0267]

[0268] (Step 8-3) A solution of 4-methylbenzenesulfonic acid [(3S) -oxolan-3-yl] (compound 8e), (3S) -oxolan-3-ol (compound 8d, 500 mg, 5.68 mmol) in dichloromethane To 3.78 mL) at 0 ° C was added pyridine (1.28 mL, 15.9 mmol) and 4-methylbenzenesulfonyl chloride (1.51 g, 7.95 mmol). The mixture was stirred at room temperature, and after 15 hours, water and 1N hydrochloric acid were added, and the organic layer was separated. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine. The solvent was evaporated under reduced pressure to give the title compound 8e (1.36 g, yield 99%).

[0269] LC / MS retention time: 0.96 minutes (analytical conditions: SMD-FA05-1). 1 H-NMR (400 MHz, CDCl 3) δ : 7.79 (2 H, d, J = 8 Hz), 7. 35 (2 H, d, J = 8 Hz), 5.12 (1 H, m), 3.93-3 76 (4H, m), 2.46 (3H, s), 2.13-2.05 (2H, m).

[0270] (Step 8-4) 5-bromo-1-[(3R) -oxolan-3-yl] indazole (compound 8f) 5-bromo-1H-indazole (compound 6j, 300 mg, 1.52 mmol) in DMF (3. Cesium carbonate (992 mg, 3.05 mmol) and the compound 8e (369 mg, 1.52 mmol) obtained in Step 8-3 were added to the solution and the solution was stirred at 100 ° C. for 2 hours. After cooling to room temperature, water was added to the reaction solution, and extracted with ethyl acetate. The organic layer was washed with water and the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography (ethyl acetate / hexane = 1: 1) gave the title compound 8f (198 mg, yield 49%) as a colorless oil.

[0271] LC / MS mass spectrometry: m / z 267 ([M + H] +). LC / MS retention time: 1.07 minutes (analysis conditions: SMD-FA05-1). The halogen compound (N- (4-bromo-2-methoxyphenyl) -N- (3-methoxypropyl) acetamide, compound 9c) used in the synthesis of the example compound 9 was synthesized as follows.

[0272] (Step 9-1)

[0273]

[0274] Sodium hydride (50 wt% oil dispersion) (18.9 mg, 0.39 mmol) in a solution of N- (4-bromo-2-methoxyphenyl) acetamide (compound 9a, 80 mg, 0.33 mmol) in DMF (0.8 mL)) And 1-bromo-3-methoxypropane (75 mg, 0.49 mmol) were sequentially added and stirred at room temperature for 12 hours. Formic acid was added to the reaction solution, and purification was conducted by reverse phase silica gel chromatography (acetonitrile / water, 0.1% formic acid) to obtain the title compound 9c (103 mg, yield 99%) as a colorless gum.

[0275] LC / MS mass spectrometry: m / z 316 ([M + H] +). LC / MS retention time: 1.02 minutes (analysis conditions: SMD-FA05-1). The halogen compound (5-bromo-1- (2,2,2-trifluoroethyl) indazole, compound 10b) used in the synthesis of the example compound 10 was synthesized as follows.

[0276] (Step 10-1)

[0277]

[0278] Using a suitable reagent from trifluoromethanesulfonic acid 2,2,2-trifluoroethyl (compound 10a) and 5-bromo-1H-indazole (compound 6j), in the same manner as in step 8-4 of Example 8 Synthesized.

[0279] LC / MS mass spectrometry: m / z 279 ([M + H] +). LC / MS retention time: 1.17 minutes (analysis conditions: SMD-FA05-1). Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) used in the synthesis of compounds 11-13] -4-Methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2-methoxy -3-Methylpyridin-4-yl) indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 11m) is synthesized as follows did.

[0280]

[0281] (Step 11-1) tert-Butyl N- (4-fluoro-3,5-dimethylphenyl) -N-[(2-methylpropan-2-yl) oxycarbonylamino] carbamate (Compound 11b) 5-bromo 2-Fluoro-1,3-dimethylbenzene (Compound 11a, 4.66 g, 22.6 mmol) was dissolved in THF (47.6 mL) and cooled at an external temperature of -70.degree. C. 1.55 Mn-butyllithium (13.1 mL, 20.4 mmol) was added dropwise at -70.degree. C. or less and stirred for 1 hour. A toluene solution (25.0 g, 21.7 mmol) of 20 wt% azodicarboxylate di-tert-butyl is added dropwise at an internal temperature of -40 ° C. or less, and after stirring for 30 minutes, the temperature is raised to room temperature over 1 hour. 23.8 mL) and 20% aqueous ammonium chloride solution (47.6 mL) were added for extraction. The organic layer was concentrated, heptane (7.14 mL) was added, and the mixture was dissolved by heating to an external temperature of 70 ° C., and cooled over 1 hour to precipitate crystals. The crystals were collected by filtration and washed with heptane (2.38 mL). The crystals were dried to synthesize a crude product of the title compound 11b (3.53 g, yield 44%).

[0282] 1 H-NMR (400 MHz, DMSO-D6) δ : 9.64-9.51 (0.8 H, m), 9.24-9.07 (0.2 H, m), 7.09-6. 91 2H, m), 2.29-2.09 (6H, m), 1.53-1.32 (18H, m).

[0283] LC / MS retention time: 1.40 minutes (analysis conditions: SMD-FA05-3). (Steps 11-2, 3 and 4) tert-butyl (2S) -3-cyano-2-methyl-4-oxopiperidine-1-carboxylate (compound 11g) (3S) -3-aminobutane nitrile hydrochloride (Compound 11c, 10.0 g, 82.9 mmol) is dissolved in ethanol (50.0 mL) and triethylamine (13.9 mL, 99.5 mmol) and ethyl acrylate (10.8 mL, 99.5 mmol) are added at room temperature The The solution was stirred at an external temperature of 70 ° C. for 3 hours and cooled to room temperature to obtain a mixture containing ethyl 3-[[(2S) -1-cyanopropan-2-yl] amino] propanoate (Compound 11e).

[0284] To the reaction solution was added di-tert-butyl dicarbonate (21.7 mL, 99.5 mmol) at room temperature. The solution was stirred at room temperature for 14 hours, N-methylpiperazine (2.76

mL, 24.9 mmol) was added and stirred for 4 hours. 1N hydrochloric acid (50 mL) was added and extracted with toluene (50 mL). The organic layer was washed with 15% aqueous sodium chloride solution (50.0 mL). The organic layer is concentrated under reduced pressure and ethyl 3-[[(2S) -1-cyanopropan-2-yl]-[(2-methylpropan-2-yl) oxycarbonyl] amino] propanoate (compound 11f) is contained. A mixture was obtained.

[0285] To this mixture was added THF (50.0 mL), potassium tert-butoxide (10.2 g, 91.2 mmol) was added at an internal temperature of 30 ° C. or less, and the mixture was stirred at room temperature for 1 hour. The internal temperature was adjusted to 15 ° C., 2N hydrochloric acid (82.9 mL, 99.5 mmol) was added, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with 15% aqueous sodium chloride solution (50.0 mL) and concentrated to give 11 g (15.8 g, yield 80%) of the title compound.

[0286] LC / MS mass spectrometry: m / z 237 ([M-H]-). LC / MS retention time: 0.92 minutes (analysis conditions: SMD-FA05-1). (Step 11-5) (4S) -3-amino-2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine Compound 11b (2.13 g, 6.01 mmol) obtained in step 11-1 is dissolved in NMP (6.39 mL), and methanesulfonic acid (1.30 g, 13.2 mmol) was added and stirred at an external temperature of 80 ° C. for 7 hours. After cooling to room temperature, toluene (12.8 mL), potassium carbonate (0.914 g) and water (12.8 g) were added to the reaction liquid, and stirred at room temperature for 10 minutes. The aqueous layer is removed, and a solution of 11 g (1.43 g, 6.01 mmol) of the compound obtained in step 11-4 in toluene (6.3 mL), pyridine hydrochloride (71.0 mg, 0.60 mmol), and toluene (4.2 mL) was added and stirred at an external temperature of 90 ° C. for 1 hour. The reaction was cooled and washed with 1 M aqueous sodium hydroxide (12.6 mL). The organic layer was concentrated under reduced pressure to synthesize the title compound 11h (1.68 g, yield 75%).

[0287] LC / MS mass spectrometry: m / z 375 ([M + H] +). LC / MS retention time: 1.08 minutes (analysis conditions: SMD-FA05-1). (Step 11-6) (4S) -3- (2,2-dimethoxyethylcarbamoylamino) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-6,7-dihydro-4H- Pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 11j) To a solution of compound 11h (106 mg, 0.283 mmol) obtained in step 11-5 in DMA (0.53 mL), N- Add (2,2-dimethoxyethyl) imidazole-1-carboxamide (compound 11i, 62.0 mg, 0.311 mol), add potassium tert-butoxide (95.0 mg, 0.849 mol) under nitrogen atmosphere, Stir at 25 ° C. for 4 hours. Water was added to the reaction solution, and extracted with ethyl acetate. The organic layer was washed with water and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate / hexane = 3: 2) to give the title compound 11j (105 mg, yield 73%).

[0288] LC / MS mass spectrometry: m / z 506 ([M + H] +). LC / MS retention time: 1.09 minutes (analysis conditions: SMD-FA05-1). (Step 11-7) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- (2-

oxo-1H-imidazol-3-yl) -6,7-dihydro 4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (compound 11k) in compound 11j (4.45 g, 8.79 mmol) obtained in step 11-6, THF (44.5 mL) The mixture was suspended by adding methylsulfonic acid (0.676 g, 7.03 mmol) and stirred at an external temperature of 60 ° C. for 2 hours. After cooling to room temperature, a solution of tripotassium phosphate (1.87 g, 8.79 mmol) in water (17.8 mL) is added, di-tert-butyl dicarbonate (0.768 g, 3.52 mmol) is added, and at room temperature Stir for 1 hour. Water was added to the reaction solution, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. After filtration, the organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate / hexane = 3: 7) to give the title compound 11k (3.43 g, yield 88%).

[0289] LC / MS mass spectrometry: m / z 442 ([M + H] +). LC / MS retention time: 1.09 minutes (analysis conditions: SMD-FA05-1). (Step 11-8) 3-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -1H-imidazol-2-one hydrochloride (compound 11) 4 M solution of compound 11k (1.85 g, 4.19 mmol) obtained in step 11-7 in dichloromethane (8.38 ml) Hydrogen chloride in dioxane (10.5 mL, 41.9 mmol) was added. After stirring this mixture at room temperature for 1 hour, the reaction mixture was concentrated under reduced pressure to give a crude product (1.63 g) containing 11 l of the title compound as a brown solid.

[0290] LC / MS mass spectrometry: m / z 342 ([M + H] +). LC / MS retention time: 0.63 minutes (analysis conditions: SMD-FA05-1). (Step 11-9) 3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo] -1H-Imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2-methoxy-3-methylpyridin-4-yl) indole -1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (compound 11m) obtained in step 11-5 with compound 11l obtained in step 11-8 The compound 6h was synthesized by the same procedure as in the step 1-10 of Example 1 using an appropriate reagent.

[0291] Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4] used in the synthesis of compound 14 -Methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (3-fluoro-2 -Methylpyridin-4-yl) indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 14d) was synthesized as follows.

[0292]

[0293] (Step 14-1) 5- (2-chloro-3-fluoropyridin-4-yl) -1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4] -Oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (compound 14b) from compound 6f obtained in step 6-4 and 2-chloro-3-fluoro-4-iodopyridine (compound 14a) It synthesize | combined by the operation similar to the process 6-5 of Example 6 using the suitable reagent.

[0294] LC / MS mass spectrometry: m / z 429 ([M + H] +). LC / MS retention time: 1.14 minutes (analytical conditions: SMD-TFA 05-3). (Step 14-2) 5- (3-fluoro-2-methylpyridin-4-yl) -1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4] -Oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (Compound 14c) Compound 14b (810 mg, 1.32 mmol) obtained in Step 14-1; 1,1'-bis (diphenylphosphino)) Ferrocene-palladium (II) dichloride (48 mg, 0.066 mmol), potassium carbonate (2.74 g, 19.8 mmol), methylboronic acid (792 mg, 13.2 mmol) in DMSO / water 7: 1 (13. The mixed suspension of 2 mL) was vacuum degassed at room temperature and then purged with nitrogen. After stirring for 0.5 hours at 100 ° C. under a nitrogen atmosphere, the mixture was cooled to room temperature. Formic acid was added, and the residue was directly purified by reverse phase chromatography (acetonitrile / water, 0.1% formic acid) to give the title compound 14c (124 mg, 23% yield) as a pale yellow solid.

[0295] LC / MS mass spectrometry: m / z 409 ([M + H] +). LC / MS retention time: 0.85 minutes (analytical conditions: SMD-FA05-3). (Step 14-3) 3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo] -1H-Imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (3-fluoro-2-methylpyridin-4-yl) indole -1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (compound 14d) obtained in step 11-2 and compound 11 1 obtained in step 11-8 The compound 14c was synthesized by the same procedure as step 1-10 in Example 1 using a suitable reagent.

[0296] Example 2-oxoimidazole reagent used in the synthesis of compound 15 (3-[(1S, 2S) -1- [5- [2-(dimethylamino) -3-methylpyridin-4-yl] -2- [(4S) -2- (4-Fluoro-3,5-dimethylphenyl) -4-methyl-3-(2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4 , [3-c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 15d) is as follows Synthesized.

[0297]

[0298] (Step 15-1) 4-iodo-N, N, 3-trimethylpyridin-2-amine (compound 15b) 2-chloro-4-iodo-3-methylpyridine (compound 15a, 500 mg, 1.97 mmol), N -Ethyl-N-propan-2-ylpropan-2-amine (0.515 mL, 2.96 mmol), a solution of 2 M dimethylamine in THF (2.96 mL, 5.92 mmol) in DMF (7.9 mL) 130 After stirring for 17 hours at 0 C, it was cooled to room temperature and formic acid (0.4 mL) was added. Purification by reverse phase chromatography (acetonitrile / water, 0.1% formic acid) gave the title compound 15b (258 mg, 50% yield) as a pale brown liquid.

[0299] LC / MS mass spectrometry: m / z 263 ([M + H] +). LC / MS retention time: 0.52 minutes (analysis conditions: SQD-FA05-1). (Step 15-2) 5- [2- (dimethylamino) -3-methylpyridin-4-yl] -1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1, 2,4-Oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (Compound 15c) More suitable than the compound 6f obtained in Step 6-4 and the compound 15b obtained in

Step 15-1. It synthesize | combined by the operation similar to process 6-5 of Example 6 using a reagent.

[0300] LC / MS mass spectrometry: m / z 432 ([M-H]-). LC / MS retention time: 0.51 minutes (analysis conditions: SQD-FA05-1). (Step 15-3) 3-[(1S, 2S) -1- [5- [2- (dimethylamino) -3-methylpyridin-4-yl] -2-[(4S) -2- (4- (4-S)] Fluoro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5- [Carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 15d) Compound 15c obtained in Step 15-2 and Step 11-8 The compound was synthesized by the same procedure as in step 1-10 of Example 1 using a suitable reagent from compound 11l obtained in 4.

[0301] Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) used in the synthesis of compounds 16-30] -4-Methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4) -Yl) Indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 16a) was synthesized as follows.

[0302]

[0303] (Step 16-1) 3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo] -1H-Imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl] -2 -Methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (compound 16a), which is more suitable than the compound 11l obtained in the step 11-8 and the compound 8b obtained in the step 8-1 The reagents were used for the synthesis in the same manner as in Steps 1-10 of Example 1.

[0304] The halogen compound (5-bromo-1-[(3-methyloxetan-3-yl) methyl] indazole, compound 17b) used in the synthesis of the example compound 17 was synthesized as follows. (Step 17-1)

[0305]

[0306] Using appropriate reagents from 3-methyl-3-[(4-methylphenyl) sulfonylmethyl] oxetane (compound 17a) and 5-bromo-1H-indazole (compound 6j), using step 9-1 of Example 9 and It synthesize | combined by the same operation.

[0307] LC / MS mass spectrometry: m / z 281 ([M + H] +). LC / MS retention time: 1.10 minutes (analysis conditions: SMD-FA05-2). The halogen compound (2- (4-bromo-2-methoxyphenoxy) -2-methylpropan-1-ol, compound 20b) used in the synthesis of the example compound 20 was synthesized as follows.

[0308] (Step 20-1) 2- (4-bromo-2-methoxyphenoxy) -2-methylpropan-1-ol (compound 20b)

[0309]

[0310] In a THF solution (1.38 mL) of 2- (4-bromo-2-methoxyphenoxy) -2-methylpropanecarboxylic acid (compound 20a, 400 mg, 1.38 mmol) under a nitrogen atmosphere, a THF solution of borane (0. 95M, 4.37 mL, 4.15 mmol) was added dropwise at 0 ° C. and stirred for 24 hours. After adding and stirring 1 M sodium hydroxide aqueous solution, 1N hydrochloric acid was added and it neutralized. Ethyl acetate was added and extracted. The organic layer was washed with water and the solvent was evaporated under reduced pressure to give the title compound 20b (339 mg, yield 89%).

[0311] LC / MS retention time: 1.04 minutes (analysis conditions: SMD-FA05-3). 1 H-NMR (400 MHz, CDCl 3) δ : 7.04 to 7.01 (2H, m), 6.90 to 6.86 (1H, m), 3.85 (3H, s), 3.44 (2H) , M), 3.34 (1 H, m), 1.28 (6 H, s).

[0312] The halogen compound (5-bromo-1-[(3S) -oxolan-3-yl] indazole, compound 22c) used in the synthesis of the example compound 22 was synthesized as follows.

[0313]

[0314] (Step 22-1) 4-methylbenzenesulfonic acid [(3R) -oxolan-3-yl] (compound 22b) (3R) -oxolan-3-ol and an appropriate reagent according to the process of Example 8 It synthesize | combined by the operation similar to 3.

[0315] LC / MS retention time: 0.95 minutes (analytical conditions: SMD-FA05-3). (Step 22-2) 5-bromo-1-[(3S) -oxolan-3-yl] indazole (Compound 22c) More suitable than the compound 22b obtained in Step 22-1 and 5-bromo-1H-indazole It synthesize | combined by operation similar to process 8-4 of Example 8 using a reagent.

[0316] LC / MS mass spectrometry: m / z 267 ([M + H] +). LC / MS retention time: 1.06 minutes (analysis conditions: SMD-FA05-3). The halogen compound (6-bromo-1,1-dimethyl-3,4-dihydroisochromene, compound 24d) used in the synthesis of the example compound 24 was synthesized as follows.

[0317]

[0318] (Step 24-1) Trifluoromethanesulfonic acid (1,1-dimethyl-3,4-dihydroisochromen-6-yl) (compound 24b) 1,1-dimethyl-3,4-dihydroisochromen-6-ol It was synthesized from (compound 24a) and

trifluoromethylmethane trifluoromethanesulfonate (triflate anhydride) by the same procedure as in step 8-3 of Example 8 using an appropriate reagent.

[0319] LC / MS retention time: 0.96 minutes (analysis conditions: SQD-FA05-01). (Step 24-2) 2- (1,1-dimethyl-3,4-dihydroisochromen-6-yl) -4,4,5,5-tetramethyl-1,3,2-dioxaborolane (compound 24c) Compound 24b (120 mg, 0.387 mmol) obtained in step 24-1, 4,4,5,5-tetramethyl-2- (4,4,5,5-tetramethyl-1,3,2-dioxaborolane -2-yl) -1,3,2-dioxaborolane (147 mg, 0.580 mmol), triethylamine (0.162 mL, 1.16 mmol), [1,1'-bis (diphenylphosphino) ferrocene] dichloropalladium (II) A solution of (14.2 mg, 0.019 mmol) in 1,4-dioxane (2.58 mL) was degassed under reduced pressure, purged with nitrogen, and stirred at 100 ° C. for 14 hours. After cooling to room temperature, formic acid was added and purification was conducted by reverse phase chromatography (acetonitrile / water, 0.1% formic acid) to obtain a light brown liquid mixture (134 mg) containing the title compound 24c.

[0320] LC / MS mass spectrometry: m / z 289 ([M + H] +). LC / MS retention time: 1.03 minutes (analysis conditions: SQD-FA05-1). (Step 24-3) 6-bromo-1,1-dimethyl-3,4-dihydroisochromene (compound 24d) methanol (1.9 mL) of the compound 24c (111 mg, 0.385 mmol) obtained in the step 24-2 A solution of copper bromide (II) (258 mg, 1.16 mmol) (1.9 mL) was added to the solution and stirred at 60 ° C. for 6 hours. After cooling to room temperature, a saturated aqueous ammonium chloride solution was added, extraction was performed twice with dichloromethane, and the organic layer was dried over magnesium sulfate. After filtration, the filtrate is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (ethyl acetate / hexane = 1: 4) to give the title compound 24d (47.7 mg, yield 51%) as a colorless liquid The

[0321] 1 H-NMR (400 MHz, CDCl 3) δ : 7.29 (1 H, dd, J = 2.0, 8.4 Hz), 7.24-7.22 (1 H, m), 6.97 (1 H, d, J = 8.4 Hz), 3.92 (2 H, t, J = 5.6 Hz), 2. 80 (2 H, t, J = 5.6 Hz), 1.50 (6 H, s).

[0322] LC / MS retention time: 0.96 minutes (analysis conditions: SQD-FA05-1). The halogen compound (6- (4-bromo-2-methylphenyl) -N, N-dimethylpyrimidin-4-amine, compound 25b) used in the synthesis of the example compound 25 was synthesized as follows.

[0323]

[0324] (Step 25-1) 6- (4-bromo-2-methylphenyl) -N, N-dimethylpyrimidin-4-amine (compound 25b) 4- (4-bromo-2-methylphenyl) -6-chloropyrimidine To a solution of (compound 25a, 12.9 mg, 0.045 mmol) in methanol (0.2 mL) was added 2 M dimethylamine THF solution (0.227 mL, 0.455 mmol), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was purified by reverse phase silica gel column chromatography (acetonitrile / water, 0.1% formic acid) to synthesize the title compound 25b (9.2 mg, yield 69%) as an off-white solid.

[0325] LC / MS mass spectrometry: m / z 292 ([M + H] +). LC / MS retention time: 0.67 minutes (analytical conditions: SMD-FA05-3). The halogen compound (5-bromo-4-fluoro-1- (2,2,2-trifluoroethyl) indazole, compound 28b) used in the synthesis of the example compound 28 was synthesized as follows.

[0326]

[0327] (Step 28-1) 5-bromo-4-fluoro-1- (2,2,2-trifluoroethyl) indazole (compound 28b) trifluoromethanesulfonic acid 2,2,2-trifluoroethyl (compound 10a) and It was synthesized from 5-bromo-4-fluoro-1H-indazole (Compound 28a) by the same procedure as in step 8-4 of Example 8 using a suitable reagent.

[0328] LC / MS mass spectrometry: m / z 297 ([M + H] +). LC / MS retention time: 1.20 minutes (analysis conditions: SMD-FA05-1). The halogen compound (5-bromo-4-fluoro-1-[(3-methyloxetan-3-yl) methyl] indazole, compound 29a) used in the synthesis of example compound 29 was synthesized as follows.

[0329]

[0330] (Step 29-1) 5-bromo-4-fluoro-1-[(3-methyloxetan-3-yl) methyl] indazole (compound 29a) 3-methyl-3-[(4-methylphenyl) sulfonylmethyl] The compound was synthesized from oxetane (compound 17a) and 5-bromo-4-fluoro-1H-indazole (compound 28a) by the same procedure as in step 8-4 of Example 8 using an appropriate reagent.

[0331] LC / MS mass spectrometry: m / z 299 ([M + H] +). LC / MS retention time: 1.11 minutes (analysis conditions: SMD-FA05-1). The halogen compound (1- (5-bromo-4-fluoroindazol-1-yl) -2-methylpropan-2-ol, compound 30a) used in the synthesis of the example compound 30 was synthesized as follows.

[0332]

[0333] (Step 30-1) 1- (5-bromo-4-fluoroindazol-1-yl) -2-methylpropan-2-ol (compound 30a) 5-bromo-4-fluoro-1H-indazole (compound 28a) And 2,2-dimethyloxirane (compound 6k) were synthesized by the same procedure as in step 6-7 of Example 6, using an appropriate reagent.

[0334] LC / MS mass spectrometry: m / z 287 ([M + H] +). LC / MS retention time: 1.01 minutes (analysis conditions: SMD-FA05-1). Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [5-[(4S) -2,2-dimethyloxane-4-yl] -2 used in the synthesis of compounds 31 to 40 -[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-

carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 31 1) It was synthesized as follows.

[0335]

[0336] (Step 31-1) Ethyl 5- (2,2-dimethyloxane-4-yl) -1H-indole-2-carboxylate (Compound 31c) Zinc powder (1.95 g, 29.8 mmol) in DMF (6 mL)) And nitrogen substitution was performed. Chlorotrimethylsilane (0.417 mL, 3.28 mmol), 1,2-dibromoethane (0.284 mL, 3.28 mmol) were added and stirred at room temperature for 5 minutes. A solution of 4-iodo-2,2-dimethyltetrahydropyran (5.37 g, 22.4 mmol) in DMF (9 mL) was added dropwise and stirred at room temperature for 20 minutes. In this solution, palladium (II) acetate (0.084 g, 0.373 mmol), 4-(N, N-dimethylamino) phenyl] di-tert-butylphosphine (0.198 g, 0.746 mol), 5-bromo Ethyl indole-2-carboxylate (2.0 g, 7.46 mmol) was added to carry out nitrogen substitution. After stirring for 1 hour at an external temperature of 50 ° C., the external temperature was cooled to 0 ° C. and neutralized with 5 N hydrochloric acid (6 mL). A 30% aqueous sodium chloride solution (50 mL) and ethyl acetate (100 mL) were added, and the insolubles were removed with Celite. The filtrate was extracted with ethyl acetate and washed with 30% aqueous sodium chloride solution. The extract was dried over magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate / hexane) to synthesize the title compound 31c (1.86 g, yield 83%) as a pale pink solid.

[0337] LC / MS mass spectrometry: m / z 302 ([M + H] +). LC / MS retention time: 0.90 minutes (analytical conditions: SQD-FA05-4). (Step 31-2) Ethyl 5-[(4S) -2,2-dimethyloxane-4-yl] -1H-indole-2-carboxylate (Compound 31d) Compound 31c obtained in Step 31-1 The stereoisomer contained in 900 mg was separated by supercritical fluid chromatography to obtain the title compound 31d (423 mg, yield 47%).

[0338] Preparation conditions: SFC 15 (Waters) Column: CHIRALPAK-IE / SFC, 10 × 250 mm, 5 μm (Daicel) Column temperature: 40 ° C. Solvent: supercritical carbon dioxide / methanol: ethyl acetate (1: 1) = 60/40 (Homogeneous system) flow rate: 15 mL / min, 140 bar analytical conditions instrument: Nexera (Shimadzu) column: CHIRALPAK-IE, 4.6 × 250 mm, 5 μm (Daicel) column temperature: 25 ° C. solvent: hexane / ethanol = 30/70 (Homogeneous system) Flow rate: 1 mL / min, room temperature Title compound retention time: 9.98 minutes, isomer retention time: 6.86 minutes It should be noted that the title compound is in S form by X-ray crystal structure analysis of compound 31j. Were determined.

[0339] (Step 31-3) 5-[(4S) -2,2-dimethyloxane-4-yl] -1H-indole-2-carboxylic acid (Compound 31e) Compound 31d (993 mg) obtained in Step 31-2 , 3.29 mmol) was dissolved in methanol (14.9 mL), 2 M aqueous solution of sodium hydroxide (3.62 mL, 7.25 mmol) was added dropwise, and

the mixture was stirred at an external temperature of 65 ° C. for 1 hour. The reaction solution was cooled at an external temperature of 15 ° C., and 5 N hydrochloric acid (1.52 mL, 7.58 mmol) was added dropwise. Water (7.45 mL) was added dropwise, and the precipitated solid was collected by filtration. The obtained solid was washed with water (5.0 mL) and dried under reduced pressure to give the title compound 31e (827 mg, yield 96%).

[0340] LC / MS mass spectrometry: m / z 274 ([M + H] +). LC / MS retention time: 0.65 minutes (Analytical conditions: SQD-FA05-4). (Step 31-4) 5-[(4S) -2,2-dimethyloxane-4-yl] -N-methyl-N-phenyl-1H-indole-2-carboxamide (compound 31f) in step 31-3 The obtained compound 31e (805 mg, 2.95 mmol) was dissolved in DMA (8.0 mL), and thionyl chloride (0.256 mL, 3.53 mmol) was added dropwise at an internal temperature of 10 ° C. or less. After stirring for 1 hour, N-methylaniline (0.384 mL, 3.53 mmol) and triethylamine (0.985 mL, 7.07 mmol) were added dropwise at 10 ° C. or less, and stirred at room temperature for 1 hour. Water (4.0 mL) was added dropwise, and the precipitated solid was collected by filtration. The obtained solid was washed with water (8.0 mL) and dried under reduced pressure to give the title compound 31f (995 mg, yield 93%).

[0341] LC / MS mass spectrometry: m / z 363 ([M + H] +). LC / MS retention time: 1.20 minutes (analysis conditions: SMD-FA05-1). (Step 31-5) 1- (cyanomethyl) -5-[(4S) -2,2-dimethyloxane-4-yl] -N-methyl-N-phenylindole-2-carboxamide (compound 31h) step 31 Compound 31f obtained in -4 (101 mg, 0.276 mmol) is dissolved in 1,3-dimethyl-2-imidazolidinone (DMI) (1.0 mL) at room temperature, and an aqueous 8 M potassium hydroxide solution (0.103 mL) , 0.828 mmol), water (0.10 mL) was added. To the resulting solution was added 2-chloroacetonitrile (0.026 mL, 0.414 mmol) at an external temperature of 10 ° C., and stirred for 2.5 hours. The reaction solution was extracted by adding 5N hydrochloric acid (0.193 mL), water (0.10 mL) and cyclopentyl methyl ether (1.0 mL), and the aqueous layer was extracted again with cyclopentyl methyl ether (1.0 mL). The combined organic layer is washed with a 15% aqueous sodium chloride solution (1.0 mL) and then concentrated under reduced pressure at an external temperature of 40 ° C. The title compound 31h of a pale brown oil obtained in the next step without purification It used for 31-6.

[0342] LC / MS mass spectrometry: m / z 402 ([M + H] +). LC / MS retention time: 0.93 minutes (analysis conditions: SMD-FA05-1). (Step 31-6) 1-[(1S, 2S) -1-cyano-2-methylcyclopropyl] -5-[(4S) -2,2-dimethyloxane-4-yl] -N-methyl- N-phenylindole-2-carboxamide (compound 31i): Compound 31h obtained in step 31-5 was synthesized by the same procedure as step 1-6 in Example 1 using a suitable reagent.

[0343] LC / MS mass spectrometry: m / z 442 ([M + H] +). LC / MS retention time: 0.95 minutes (analysis conditions: SQD-FA05-1). (Step 31-7) 5-[(4S) -2,2-dimethyloxane-4-yl] -N-methyl-1-[(1S, 2S) -2-methyl-1- (5-oxo-) 4H-1,2,4-oxadiazol-3-yl) cyclopropyl] -N-phenylindole-2-carboxamide

(Compound 31j) From Compound 31i obtained in Step 31-6, using a suitable reagent, It synthesize | combined by the operation similar to the process 1-6 of Example 1.

[0344] LC / MS mass spectrometry: m / z 501 ([M + H] +). LC / MS retention time: 0.99 minutes (analysis conditions: SQD-FA05-1). (Step 31-8) 5-[(4S) -2,2-dimethyloxane-4-yl] -1-[(1S, 2S) -2-methyl-1-(5-oxo-4H-1,5] 2,4-Oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (Compound 31k) from compound 31j obtained in Step 31-7, using the appropriate reagent, from Step 6- of Example 6 It synthesize | combined by the operation similar to 4.

[0345] LC / MS mass spectrometry: m / z 401 ([M-H]-). LC / MS retention time: 1.05 minutes (analysis conditions: SMD-FA05-1). (Step 31-9) 3-[(1S, 2S) -1- [5-[(4S) -2,2-dimethyl- oxane-4-yl] -2-[(4S) -2- (4-) Fluoro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5- [Carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (compound 31l) Compound 11l obtained in step 11-8 and step 31-8 The compound was synthesized by the same procedure as in step 1 to 10 of Example 1 using compound 31k obtained in and using an appropriate reagent.

[0346] The halogen compound 5-bromo-1- (2-methoxyethyl) -3-methylbenzimidazol-2-one (compound 33b) used in the synthesis of the example compound 33 was synthesized as follows.

[0347] (Step 33-1)

[0348]

[0349] It was synthesized from 5-bromo-3-methyl-1H-benzoimidazol-2-one (Compound 33a) by an operation similar to step 8-4 of Example 8 using an appropriate reagent. LC / MS mass spectrometry: m / z 285 ([M + H] +).

[0350] LC / MS retention time: 0.95 minutes (analysis conditions: SMD-FA05-1). The halogen compound (5-bromo-4-fluoro-1- (2-methoxyethyl) indazole, compound 36a) used in the synthesis of the example compound 36 was synthesized as follows.

[0351] (Step 36-1)

[0352]

[0353] It was synthesized from 5-bromo-4-fluoro-1H-indazole (Compound 28a) by the same procedure as in step 8-4 of Example 8 using a suitable reagent. LC / MS mass spectrometry: m / z 273 ([M + H] +).

[0354] LC / MS retention time: 1.10 minutes (analysis conditions: SMD-FA05-1). The halogen compound (5-bromo-4-fluoro-1-[(3S) -oxolan-3-yl] indazole, compound 40a) used in the synthesis of the example compound 40 was synthesized as follows.

[0355] (Step 40-1)

[0356]

[0357] Using the appropriate reagents from 5-bromo-4-fluoro-1H-indazole (compound 28a) and 4-methylbenzenesulfonic acid [(3R) -oxolan-3-yl] (compound 22b), the process of example 8 It synthesize | combined by the operation similar to 8-4.

[0358] LC / MS mass spectrometry: m / z 285 ([M + H] +). LC / MS retention time: 1.10 minutes (analysis conditions: SMD-FA05-1). Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4] used in the synthesis of compound 41 -Methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5-[(2S, 4S) -2-Methyloxan-4-yl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 41f) was synthesized as follows: .

[0359]

[0360] (Steps 41-1 and 2) 1-[(1S, 2S) -1-cyano-2-methylcyclopropyl] -N-methyl-5-[(2S, 4S) -2-methyloxane-4-yl] A suspension of N-phenylindole-2-carboxamide (compound 41c) zinc (29 mg, 0.44 mmol) in DMA (0.12 mL) was vacuum degassed at room temperature and then purged with nitrogen. Under nitrogen atmosphere, a 7: 5 mixed solution of chlorotrimethylsilane / 1,2-dibromoethane (0.0083 mL, 0.039 mmol of chlorotrimethylsilane) is added, and after stirring for 15 minutes, (2S) -4-iodo Add -2-Methyltetrahydro-2H-pyran (80 mg, 0.35 mmol) dropwise at room temperature, stir for 30 minutes, and mix it with iodo-[(2S) -2-methyloxane-4-yl] zinc (compound 41b) I got Palladium (II) acetate (6.4 mg, 0.028 mmol), 2-dicyclohexylphosphino-2 ', 6'-diisopropoxybiphenyl (26 mg, 0.057 mmol), 5-bromo-1-[(1S, 2S)) -L-Cyano-2-methylcyclopropyl] -N-methyl-N-phenylindole-2-carboxamide (58 mg, 0.14 mmol), DMA (0.123 mL), and after degassing under reduced pressure, nitrogen substitution And stirred at 80 ° C. for 1 hour. The reaction solution was cooled to room temperature, ethyl acetate and 1N hydrochloric acid were added, and after filtration, the filtrate was extracted with ethyl acetate. The organic layer is washed once with saturated brine and concentrated under reduced pressure, and the residue is purified by

silica gel column chromatography (ethyl acetate / hexane = 1: 1) to give the title compound 41c (31 mg, yield 51%) The

[0361] LC / MS mass spectrometry: m / z 428 ([M + H] +). LC / MS retention time: 1.01 minutes (analysis conditions: SQD-AA05-1). (Step 41-3) N-methyl-5-[(2S, 4S) -2-methyloxane-4-yl] -1-[(1S, 2S) -2-methyl-1- (5-oxo-4H— 1,2,4-Oxadiazol-3-yl) cyclopropyl] -N-phenylindole-2-carboxamide (compound 41d) Example using the appropriate reagent from compound 41c obtained in step 41-2 It synthesize | combined by the operation similar to 1 process 1-8.

[0362] LC / MS mass spectrometry: m / z 487 ([M + H] +). LC / MS retention time: 1.30 minutes (analysis conditions: SMD-FA05-1). (Step 41-4) 5-[(2S, 4S) -2-methyloxane-4-yl] -1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,5 4-Oxadiazol-3-yl) cyclopropyl] indole-2-carboxylic acid (Compound 41e) According to the process 6-4 of Example 6 with a suitable reagent from the compound 41d obtained in Process 41-3 and It synthesize | combined by the same operation.

[0363] LC / MS mass spectrometry: m / z 396 ([M-H]-). LC / MS retention time: 1.02 minutes (analysis conditions: SMD-FA05-1). (Step 41-5) 3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo] -1H-Imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5-[(2S, 4S) -2-methyloxane-4-yl] [Indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 41f) From the compound 41e obtained in step 41-4, using a suitable reagent It synthesize | combined by the operation similar to the process 1-10 of Example 1.

[0364] Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [2-[(4S) -2- (4-chloro-3,5-dimethylphenyl)] used in the synthesis of compounds 42 and 43 -4-Methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5-[(4S) -2, 2-Dimethyl oxa n-4- yl] indol -1- yl] -2- methyl cyclopropyl] -4H -1, 2, 4- oxadiazol -5-one, compound 42g), It was synthesized as follows.

[0365]

[0366] (Step 42-1, 2) (4S) -3-amino-2- (4-chloro-3,5-dimethylphenyl) -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c Analogously to Step 2-2 in Example 2 using a suitable reagent from tert-butyl pyridine-5-carboxylate (Compound 42c) 4-chloro-3,5-dimethylaniline (Compound 42a) After obtaining (4-chloro-3,5-dimethylphenyl) hydrazine hydrochloride (compound 42b), using the compound 11g obtained in step 11-4 and an appropriate reagent, Example 1, step 1-2 Compound 42c was synthesized by the same procedure as in.

[0367] LC / MS mass spectrometry: m / z 391 ([M + H] +). LC / MS retention time: 1.22 minutes (analysis conditions: SMD-FA 10-4). (Step 42-3) (4S) -2- (4-chloro-3,5-dimethylphenyl) -3- (2,2-dimethoxyethylcarbamoylamino) -4-methyl-6,7-dihydro-4H- Analogous to Step 1-3 of Example 1

using a suitable reagent from compound 42c obtained in Step 42-2 of pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 42d) Synthesized by operation.

[0368] LC / MS mass spectrometry: m / z 522 ([M + H] +). LC / MS retention time: 1.55 minutes (analytical conditions: SMD-TFA 05-5). (Step 42-4) (4S) -2- (4-chloro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro -4H-pyrazolo [4,3-c] pyridine-5-carboxylate tert-butyl (Compound 42e) According to the compound 42d obtained in Step 42-3, using a suitable reagent, Step 11-8 of Example 11 It synthesize | combined by the same operation.

[0369] LC / MS mass spectrometry: m / z 458 ([M + H] +). LC / MS retention time: 1.16 minutes (analysis conditions: SMD-FA05-1). (Step 42-5) 3-[(4S) -2- (4-chloro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridine-3-yl] -1H-imidazol-2-one hydrochloride (Compound 42f) According to the compound 42e obtained in Step 42-4, the same procedure as in Step 111-8 of Example 11 using a suitable reagent Synthesized by

[0370] LC / MS mass spectrometry: m / z 358 ([M + H] +). LC / MS retention time: 0.69 minutes (analysis conditions: SMD-FA05-1). (Step 42-6) 3-[(1S, 2S) -1- [2-[(4S) -2- (4-chloro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo] -1H-Imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5-[(4S) -2,2-dimethyloxane-4- [l] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 42g) Compound 42f obtained in Step 42-5 and Step 31-8 The compound 31k obtained in the above was synthesized by the same procedure as in the step 1-10 of Example 1 using an appropriate reagent.

[0371] Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [2-[(4S) -2- (4-chloro-3,5-dimethylphenyl)] used in the synthesis of compounds 44 and 45 -4-Methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4) -Yl) Indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 44a) was synthesized as follows.

[0372]

[0373] (Step 44-1) 3-[(1S, 2S) -1- [2-[(4S) -2- (4-chloro-3,5-dimethylphenyl) -4-methyl-3- (2-oxo] -1H-Imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl] -2 -Methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 44a), which is more suitable than the compound 42f obtained in Step 42-5 and the compound 8b obtained in Step 8-1 The reagents were used for the synthesis in the same manner as in Steps 1-10 of Example 1.

[0374] Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3-methylphenyl) -4] used in the synthesis of compounds 46 and 47 -Methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-

pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxan-4-yl)) Indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 46f) was synthesized as follows.

[0375]

[0376] (Step 46-1) (4S) -3-amino-2- (4-fluoro-3-methylphenyl) -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5 Using a suitable reagent from tert-butyl carboxylate (compound 46b) (4-fluoro-3-methylphenyl) hydrazine hydrochloride (compound 46a) and 11 g of the compound obtained in step 11-4, using an appropriate reagent It synthesize | combined by the operation similar to process 1-2.

[0377] LC / MS mass spectrometry: m / z 361 ([M + H] +). LC / MS retention time: 1.02 minutes (analysis conditions: SMD-FA05-1). (Step 46-2) (4S) -3- (2,2-dimethoxyethylcarbamoylamino) -2- (4-fluoro-3-methylphenyl) -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] tert-butyl pyridine-5-carboxylate (Compound 46c) By a procedure similar to the step 1-3 in Example 1 using a suitable reagent from the compound 46b obtained in the step 46-1 Synthesized.

[0378] LC / MS mass spectrometry: m / z 492 ([M + H] +). LC / MS retention time: 1.03 minutes (analysis conditions: SMD-FA05-1). (Step 46-3) (4S) -2- (4-fluoro-3-methylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H -Pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 46d), similar to step 11-7 in Example 11 using a suitable reagent from compound 46c obtained in Step 46-2 Were synthesized by

[0379] LC / MS mass spectrometry: m / z 428 ([M + H] +). LC / MS retention time: 2.11 minutes (analysis conditions: SMD-FA05-long). (Step 46-4) 3-[(4S) -2- (4-fluoro-3-methylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] pyridine- 3-yl] -1H-imidazol-2-one hydrochloride (Compound 46e): Compound 46d obtained in Step 46-3 was synthesized by the same procedure as in Step 11-8 of Example 11, using an appropriate reagent. did.

[0380] LC / MS mass spectrometry: m / z 328 ([M + H] +). LC / MS retention time: 0.59 minutes (analytical conditions: SMD-FA05-3). (Step 46-5) 3-[(1S, 2S) -1- [2-[(4S) -2- (4-fluoro-3-methylphenyl) -4-methyl-3- (2-oxo-1H] -Imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl] -2-methyl Cyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 46f) According to the compound 46e obtained in the step 46-4 and the compound 8b obtained in the step 8-1, a suitable reagent is prepared It synthesize | combined by operation similar to the process 1-10 of Example 1 using.

[0381] Example 2-oxoimidazole reagent (3-[(1S, 2S) -1- [5-[(4S) -2,2-dimethyl- oxane-4-yl] -2 used in the synthesis of compounds 48 to 50 -[(4S) -2- (4-Fluoro-3-methylphenyl) -4-methyl-3- (2-

oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4 , [3-c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, compound 48a) is Synthesized.

[0382]

[0383] (Step 48-1) 3-[(1S, 2S) -1- [5-[(4S) -2,2-dimethyloxane-4-yl] -2-[(4S) -2- (4-) Fluoro-3-methylphenyl) -4-methyl-3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] Indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 48a) Compound 46e obtained in step 46-5 and obtained in step 31-8 The compound was synthesized by the same procedure as in Steps 1 to 10 of Example 1 using an appropriate reagent from Compound 31k.

[0384] Examples 51 to 53 3-[(1S, 2S) -1- [5-bromo-2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methyl) Indazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclo The same procedure as in step 7-1 of Example 7 is performed using [propyl] -4H-1,2,4-oxadiazol-5-one (Compound 51d) and substituted morpholine, and a suitable reagent, and Reaction of to give Example compounds 51 to 53 shown in Table 2-4.

[0385]

[0386]

[0387] Compound 51d was synthesized as follows.

[0388]

[0389] (Step 51-1) 2- (4-fluoro-3,5-dimethylphenyl) -3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3] -C] tert-Butyl pyridine-5-carboxylate (Compound 51a) A solution of compound 2f (0.611 g, 1.68 mmol) obtained in step 2-5 in a suspension of dichloromethane (16.8 mL) in triethylamine (0. 8). 936 mL (6.72 mmol) and di-t-butyl dicarbonate (0.425 mL, 1.85 mmol) were added, and the mixture was stirred at room temperature for 2 hours. Water (20.0 mL) and 5% aqueous potassium hydrogen sulfate solution (20.0 mL) were added to the reaction mixture, and the mixture was extracted with dichloromethane and dried over magnesium sulfate. After filtration, the filtrate is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (ethyl acetate / hexane = 0: 1 to 1: 0) to give the title compound 51a (0.360 g, yield 50%) Obtained.

[0390] LC / MS mass spectrometry: m / z 428 ([M + H] +). LC / MS retention time: 1.06 minutes (analysis conditions: SMD-FA05-3). (Step 51-2) 2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7 -Dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl

(Compound 51b) A more suitable reagent than compound 51a obtained in step 51-1 and 5-bromo-1-methylindazole The compound was synthesized by the same operation as step 1-11 of Example 1.

[0391] LC / MS mass spectrometry: m / z 558 ([M + H] +). LC / MS retention time: 1.25 minutes (analysis conditions: SMD-FA05-1). (Step 51-3) 1- [2- (4-fluoro-3,5-dimethylphenyl) -4,5,6,7-tetrahydropyrazolo [4,3-c] pyridin-3-yl] -3 -(1-Methylindazol-5-yl) imidazol-2-one hydrochloride (Compound 51c) By using an appropriate reagent from compound 51b obtained in step 51-2 in a manner similar to step 11-9 of Example 11. Were synthesized by

[0392] LC / MS mass spectrometry: m / z 458 ([M + H] +). LC / MS retention time: 0.78 minutes (analysis conditions: SMD-FA05-1). (Step 51-4) 3-[(1S, 2S) -1- [5-bromo-2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazole) -5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 51d) With the use of a suitable reagent from the compound 51c obtained in Step 51-3 and the compound 6f obtained in Step 6-4 It synthesize | combined by the operation similar to the process 1-10 of Example 1.

[0393] LC / MS mass spectrometry: m / z 817 ([M + H] +). LC / MS retention time: 1.41 minutes (analysis conditions: SMD-FA05-1). <Examples 54 to 73> The amine derivative and the carboxylic acid derivative are treated in the same manner as in Step 1-10 of Example 1, and the following reactions are taken to obtain Example compounds 54 to 72 shown in Table 2-5, and Example Compound 73 was obtained.

[0394]

[0395]

[0396]

[0397]

[0398]

[0399]

[0400]

[0401]

[0402] In addition, although a rotamer exists in the compound in Table 2-5, 1H-NMR of Example compound 66 and 67 is as follows, for example. <Example compound 66> Major rotational isomer 1 H-NMR (600 MHz, CDCl 3) δ : 11.32. (1 H, s), 8.04 (1 H, d, J = 0.4 Hz), 7.86 (1 H, 1 H, d, J = 1.4 Hz), 7.61 (1 H, m), 7.59 (1 H, m), 7.52 (1 H, s), 7. 50 (H, d, J = 9.0 Hz) , 7.27 (1H, m), 7.15 (2H, d, JHF = 6.0 Hz), 6.74 (1 H, d, J = 3.1 Hz), 6.70 (1 H, s), 6 4. 32 (1 H, d, J = 3.1 Hz), 5.79 (1 H, q, J = 6.6 Hz), 4.47 (1 H, dd, J = 13.6, 5.0 Hz), 4. 12 (3 H, s), 3.89-3. 81 (2 H, m), 3. 60 (1 H, ddd, J = 13.6, 13.1, 3.6 Hz), 3.15 (1 H, ddd J = 16.0, 13.1, 5.0 Hz), 3.09-2.98 (2 H, m), 2. 27 (6 H, d, JHF = 1.4 Hz), 1.91 (1 H, dd) , J = 6.0 Hz), 1.82 to 1.60 (4 H, m), 1.60 to 1.50 (2 H, m), 1.55 (3 H, d, J = 6.6 Hz), 1 .34 (3H, s), 1.28 (3H, s), 1.19 (3H, d, J = 5.9 Hz).

[0403] The minor rotomer 1H-NMR (600 MHz, CDCl3) δ : 11.26 (1 H, s), 7.93 (1 H, s), 7.65 (1 H, s), 7.57 (1 H, d, J 6.46 (1 H, m), 7.34 (2 H, s), 7. 25 (1 H, m), 7.05 (2 H, d, JHF = 6.0 Hz), 6. 69 (1 H, s), 6.59 (1 H, d, J = 3.1 Hz), 6.09 (1 H, d, J = 3.1 Hz), 5.26 (1 H, q, J = 6.6 Hz), 4.87 (1 H, dd, J = 12.8, 5.1 Hz), 4.07 (3 H, s), 3.90-3. 78 (2 H, m), 3. 40 (1 H, ddd) , J = 12.8, 12.6, 4.5 Hz), 3.10-2.98 (3 H, m), 2.23 (6 H, s), 1.82-1. 37 (10 H, m) , 1.3 (3H, s), 1.25 (3H, s), 1.06 (3H, d, J = 6.2Hz).

[0404] <Example compound 67> Major rotational isomer 1 H-NMR (600 MHz, CDCl 3) δ : 11.32. (1 H, s), 8.13 (1 H, d, JHF = 0.7 Hz), 7.59 (1 H, d, J = 8.6 Hz), 7.52 (1 H, s), 7. 48 (1 H, dd, J = 8.9 Hz, JHF = 6.9 Hz), 7.28 (1 H, d, J = 8 .9 Hz), 7.26 (1 H, dd, J = 8.6, 1.7 Hz), 7.16 (2 H, d, JHF = 6.1 Hz), 6.70 (1 H, s), 6.61 (1H, dd, J = 3.0 Hz, JHF = 1.1 Hz), 6.31 (1 H, d, J = 3.0 Hz), 5.79 (1 H, q, J = 6.7 Hz), 4. 47 (1 H, dd, J = 13.5, 5.2 Hz), 4.12 (3 H, s), 3.88 (1 H, m), 3. 83 (1 H, m), 3 60 (1H, ddd, J = 13.5, 12.9, 3.6 Hz), 3.15 (1H, ddd, J = 15.8, 12.9, 5.2 Hz), 3.04 (1H, 1H, m), 3.00 (1 H, m), 2.29 (6 H, d, JHF = 1.1 Hz), 1.91 (1 H, dd, J = 6.1, 5.8 Hz), 1.79- 1.76 (2H, m), 1.74 (1H, m), 1.65 (1H, m), 1.57 (3H, d, J = 6.7 Hz), 1.60-1.55 (1 H, m), 1.52 (1 H, dd, J = 9.5, 5.8 Hz), 1.34 (3 H, s), 1.28 (3 H, s), 1.20 (3 H, d, J = 6.0 Hz).

[0405] Side rotation isomer 1 H-NMR (600 MHz, CDCl 3) δ : 11.27 (1 H, s), 8.04 (1 H, s), 7.55 (1 H, d, J = 8.7 Hz), 7.52 (1H, s), 7.25-7.22 (2H, m), 7.12 (1H, d, J = 8.8 Hz), 7.06 (2 H, d, JHF = 6.0 Hz), 6 .71 (1 H, s), 6.47 (1 H, m), 6.08 (1 H, d, J = 3.0 Hz), 5.26 (1 H, q, J = 6.6 Hz), 4.87 (1H, dd, J = 13.1, 4.8 Hz), 4.07 (3H, s), 3.90-3.80 (2H, m), 3.39 (1H, ddd, J = 13. 1, 12.2, 4.6 Hz), 3.08-2.97 (3 H, m), 2. 25 (6 H, s), 1.79-1.73 (3 H, m), 1.67 (1. 3H, d, = 1.6 Hz), 1.64 (1 H, m), 1.45 to 1.37 (2 H, m), 1.34 (3 H, s), 1.28 (3 H, s), 1.06 (1. 3H, d, J = 6.0 Hz).

[0406] The compound 55e used in the synthesis of the example compound 55 was synthesized as follows.

[0407]

[0408] (Step 55-1) tert-butyl 3-amino-2- (4-chloro-3,5-dimethylphenyl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid (Compound 55a) The compound 42a obtained in Step 42-1 and the compound 1b obtained in Step 1-1 were synthesized by the same procedure as in Step 1-2 of Example 1, using an appropriate reagent.

[0409] LC / MS mass spectrometry: m / z 377 ([M + H] +). LC / MS retention time: 0.87 minutes (analysis conditions: SQD-FA05-1). (Step 55-2) 2- (4-chloro-3,5-dimethylphenyl) -3- (2,2-dimethoxyethylcarbamoylamino) -6,7-dihydro-4H-pyrazolo [4,3-c] It was synthesize | combined by operation similar to the process 1-3 of Example 1 from the compound 55a obtained at the pyridine-5-carboxylic-acid tert- butyl (compound 55b) process 55-1 using the suitable reagent.

[0410] LC / MS mass spectrometry: m / z 508 ([M + H] +). LC / MS retention time: 0.83 minutes (analysis conditions: SQD-FA05-1). (Step 55-3) 2- (4-chloro-3,5-dimethylphenyl) -3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3 -C] tert-butyl pyridine-5-carboxylate (Compound 55c) Compound 55b (903 mg, 1.78 mmol) obtained in Step 55-2, p-toluenesulfonic acid monohydrate (338 mg, 1.78 mmol) A suspension of DMF (7.11 mL) was stirred at 80 ° C. for 1 hour. After cooling to room temperature, potassium phosphate (377 mg, 1.78 mmol), water (3.5 mL) and di-tert-butyl dicarbonate (388 mg, 1.78 mmol) were added and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture, extraction was performed with ethyl acetate, and the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate / hexane = 1: 4 to 1: 0) to give the title compound 55c as a pale yellow foam (799 mg, yield) 100%).

[0411] LC / MS mass spectrometry: m / z 444 ([M + H] +). LC / MS retention time: 0.82 minutes (analysis conditions: SQD-FA05-1). (Step 55-4) 2- (4-chloro-3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7 -Dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylate tert-Butyl (compound 55d) from compound 55c obtained in step 55-3 and 5-bromo-1-methylindazole (compound 1q) The compound was synthesized by the same procedure as step 1-11 of Example 1 using an appropriate reagent.

[0412] LC / MS mass spectrometry: m / z 574 ([M + H] +). LC / MS retention time: 1.34 minutes (analysis conditions: SMD-FA05-1). (Step 55-5) 1- [2- (4-chloro-3,5-dimethylphenyl) -4,5,6,7-tetrahydropyrazolo [4,3-c] pyridin-3-yl] -3 -(1-Methylindazol-5-yl) imidazol-2-one hydrochloride (Compound 55e) By using an appropriate reagent from compound 55d obtained in Step 55-4 in a manner similar to Step 11-8 of Example 11. Were synthesized by

[0413] LC / MS mass spectrometry: m / z 474 ([M + H] +). LC / MS retention time: 0.81 minutes (analysis conditions: SMD-FA05-1). The compound 56c used in the synthesis of the example compound 56 was synthesized as follows.

[0414]

[0415] (Step 56-1) 2- (4-fluoro-3,5-dimethylphenyl) -3- [3- [1- (2-methoxyethyl) indazol-5-yl] -2-oxoimidazol-1-yl Tert-Butyl -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid (Compound 56b) Compound 51a obtained in step 51-1 and 5-bromo-1- (2) It synthesize | combined by the operation similar to the process 1-11 of Example 1 using a suitable reagent from-methoxyethyl) indazole (compound 56a).

[0416] LC / MS mass spectrometry: m / z 602 ([M + H] +). LC / MS retention time: 1.30 minutes (analysis conditions: SMD-FA05-2). (Step 56-2) 1- [2- (4-fluoro-3,5-dimethylphenyl) -4,5,6,7-tetrahydropyrazolo [4,3-c] pyridin-3-yl] -3 -[1- (2-Methoxyethyl) indazol-5-yl] imidazol-2-one hydrochloride (Compound 56c) According to the procedure of Example 11 using a suitable reagent from compound 56b obtained in Step 56-1 It synthesize | combined by the operation similar to 11-8.

[0417] LC / MS mass spectrometry: m / z 502 ([M + H] +). LC / MS retention time: 0.54 minutes (analysis conditions: SQD-FA05-1). The amine derivative (compound 57j) used in the synthesis of the example compound 57 was synthesized as follows.

[0418]

[0419] (Step 57-1) tert-Butyl N- (4-isocyanatocuban-1-yl) carbamate (Compound 57b) 4-[(2-methylpropan-2-yl) oxycarbonylamino] cuban-1-carboxylic acid To a solution of the acid (compound 57a, 111 mg, 0.423 mmol) in toluene (2.1 mL) is added triethylamine (0.0676 mL, 0.487 mmol) and diphenylphosphoryl azide (0.10 mL, 0.465 mmol) at room temperature, The mixture was stirred at room temperature for 100 minutes and then at 85 ° C. for 3.5 hours. The reaction mixture was evaporated under reduced pressure to give the title compound 57b as a crude product.

[0420] 1 H-NMR (400 MHz, CDCl 3) δ : 12.3 (1 H, brs), 3.95 (6 H, brs), 1.45 (9 H, s). (Step 57-2) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3-[[4-[(2-methylpropan-2-yl) oxycarbonylamino] [Cuban-1-yl] carbamoylamino] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (compound 57c) with compound 57b obtained in step 57-1 The compound 11h obtained in Step 11-5 was synthesized by the same procedure as Step 1-3 in Example 1 using a suitable reagent.

[0421] LC / MS mass spectrometry: m / z 636 ([M + H] +). LC / MS retention time: 0.93 minutes (analysis conditions: SQD-FA05-1). (Step 57-3) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -3- [5-hydroxy-3- [4-[(2-methylpropan-2-yl) oxycarbonyl] Amino] cuban-1-yl] -2-oxoimidazolidin-1-yl] -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 57d) 1,2-dichloromethane in a suspension of compound 57c (31.6 mg, 0.050 mmol) obtained in step 57-2 and cesium carbonate (82.8 mg, 0.254 mmol) in DMA (0.25 mL) 1-Ethoxyethane (0.0155 mL, 0.127 mmol) was added at room temperature and stirred at room temperature for 170 minutes. Cesium carbonate (104 mg, 0.32 mmol) and then 1,2-dichloro-1-ethoxyethane (0.0184 mL, 0.162 mmol) were added to the reaction mixture at room temperature and stirred at room temperature for 16 hours. The reaction mixture was adjusted to pH 7 with ethyl acetate and water and adjusted to pH 7 with 1N hydrochloric acid (0.54 mL), and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. Toluene was added and the solvent was evaporated under reduced pressure to give the title compound 57d as a crude product.

[0422] LC / MS mass spectrometry: m / z 678 ([M + H] +). LC / MS retention time: 0.98 minutes (analytical conditions: SQD-FA05-1). (Step 57-4) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- [3- [4-[(2-methylpropan-2-yl) oxycarbonyl] Amino] cuban-1-yl] -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (compound 57e) step 57 After adding methylsulfonic acid (0.011 mL, 0.17 mmol) to a solution of compound 57d (115 mg, 0.17 mmol) obtained in -3 in THF (1.1 mL) at room temperature, the mixture is stirred at 60 ° C. for 90 minutes did. To the reaction mixture was added potassium phosphate (36.5 mg, 0.172 mmol), water (0.45 mL) and (2-methylpropan-2-yl) oxycarbonyl tert-butyl carbonate (0.012 mL, 0.052 mmol) Stir for 1 hour. The reaction mixture was diluted with dichloromethane and then washed with water. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate / hexane = 1: 2 to 1: 1) to give the title compound 57e (48.5 mg, yield 43%).

[0423] LC / MS mass spectrometry: m / z 660 ([M + H] +). LC / MS retention time: 1.04 minutes (analysis conditions: SQD-FA05-1). (Step 57-5) (4S) -3- [3- [4- [acetyl-[(2-methylpropan-2-yl) oxycarbonyl] amino] cuban-1-yl] -2-oxoimidazole-1 -Yl] -2- (4-Fluoro-3,5-dimethylphenyl) -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (compound 57f) A solution of compound 57e (16.1 mg, 0.024 mmol) obtained in Step 57-4 in THF (0.22 mL) at –26 ° C. in 1.7 M potassium pentoxide toluene solution (0.024 mL) 0.041 mmol) was added and it stirred at -30 degreeC for 3 minutes. Acetic anhydride (8 μL, 0.085 mmol) was added to the reaction mixture at -30 ° C and stirred for 5 minutes at -30 ° C to -25 ° C and for 3 minutes at -25 ° C to room temperature. Water (0.5 mL) was added to the reaction mixture and then diluted with ethyl acetate, water was further added, and the mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, evaporated under reduced pressure, and purified by silica gel

column chromatography (ethyl acetate / hexane = 1: 3 to 2: 3) to give the title compound 57f (9.2 mg, yield 54%) I got

[0424] LC / MS mass spectrometry: m / z 701 ([M + H] +). LC / MS retention time: 1.12 minutes (analysis conditions: SQD-FA05-1). (Step 57-6) N- [4- [3-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -2-oxoimidazol-1-yl] cuban-1-yl] acetamide 2,2,2-trifluoroacetic acid salt (compound 57 g) obtained in step 57-5 To a solution of compound 57f (8.5 mg, 0.012 mmol) in dichloromethane (0.097 mL) was added TFA (0.019 mL) at room temperature, and stirred at room temperature for 3 hours. The reaction mixture was evaporated under reduced pressure, toluene was added and the solvent was evaporated, hexane-dichloromethane was added, and the solvent was evaporated to obtain 57 g (9.4 mg) of the title compound as a crude product.

[0425] LC / MS mass spectrometry: m / z 501 ([M + H] +). LC / MS retention time: 0.49 minutes (analysis conditions: SQD-FA05-1). (Step 57-7) (4S) -3- [3- (4-acetamidocuban-1-yl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3,5-dimethylphenyl) -4-Methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 57h) 57 g of the compound obtained in step 57-6, Using and it synthesize | combined by the operation similar to the process 51-1 of Example 51.

[0426] LC / MS mass spectrometry: m / z 602 ([M + H] +). LC / MS retention time: 0.85 minutes (analytical conditions: SQD-FA05-1). (Step 57-8) (4S) -3- [3- [4- [acetyl (2-methoxyethyl) amino] cuban-1-yl] -2-oxoimidazol-1-yl] -2- (4- (4-S) Fluoro-3,5-dimethylphenyl) -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (compound 57i) obtained in step 57-7 It synthesize | combined by operation similar to process 57-5 of Example 57 from the compound 57h using a suitable reagent.

[0427] LC / MS mass spectrometry: m / z 660 ([M + H] +). LC / MS retention time: 0.93 minutes (analysis conditions: SQD-FA05-1). (Step 57-9) N- [4- [3-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -2-oxoimidazol-1-yl] cuban-1-yl] -N- (2-methoxyethyl) acetamide hydrochloride (Compound 57j) obtained in step 57-8 The resulting compound was synthesized by the same procedure as in step 11-8 of Example 11 using a suitable reagent from Compound 57i.

[0428] LC / MS mass spectrometry: m / z 560 ([M + H] +). LC / MS retention time: 0.53 minutes (analysis conditions: SQD-FA05-1). The compound 58e used in the synthesis of the example compound 58 was synthesized as follows.

[0429]

[0430] (Step 58-1) tert-Butyl 3-amino-2- (4-fluoro-3-methylphenyl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylate (compound 58a) A compound of the compound 1b obtained in Step 1-1 and the compound 46a obtained in Step 46-1 were synthesized by the same procedure as in Step 1-2 of Example 1, using an appropriate reagent.

[0431] LC / MS mass spectrometry: m / z 347 ([M + H] +). LC / MS retention time: 0.98 minutes (analysis conditions: SMD-FA05-3). (Step 58-2) 3- (2,2-dimethoxyethylcarbamoylamino) -2- (4-fluoro-3-methylphenyl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine- It was synthesize | combined by operation similar to the process 1-3 of Example 1 from the compound 58a obtained at the 5-carboxylic acid tert- butyl (compound 58b) process 58-1 using an appropriate reagent.

[0432] LC / MS mass spectrometry: m / z 478 ([M + H] +). LC / MS retention time: 1.03 minutes (analysis conditions: SMD-FA05-3). (Step 58-3) 2- (4-fluoro-3-methylphenyl) -3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c The compound was synthesized by the same procedure as in step 11-7 of Example 11, using a suitable reagent from compound 58b obtained in tert-butyl pyridine-5-carboxylate (Compound 58c) in step 58-2.

[0433] LC / MS mass spectrometry: m / z 414 ([M + H] +). LC / MS retention time: 0.72 minutes (analysis conditions: SQD-FA05-1). (Step 58-4) 2- (4-fluoro-3-methylphenyl) -3- [3- [1- (2-methoxyethyl) indazol-5-yl] -2-oxoimidazol-1-yl]- 6,7-Dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 58d) Compound 58c obtained in Step 58-3 and 5-bromo-1- (2-methoxy) The compound was synthesized from ethyl) indazole (compound 56a) by an operation similar to steps 1-11 of Example 1 using a suitable reagent.

[0434] LC / MS mass spectrometry: m / z 588 ([M + H] +). LC / MS retention time: 0.88 minutes (Analytical conditions: SQD-FA05-1). (Step 58-5) 1- [2- (4-fluoro-3-methylphenyl) -4,5,6,7-tetrahydropyrazolo [4,3-c] pyridin-3-yl] -3- [1- (2-Methoxyethyl) indazol-5-yl] imidazol-2-one hydrochloride (Compound 58e) The compound 58d obtained in Step 58-4 was treated with an appropriate reagent according to Example 11-11- It synthesize | combined by the operation similar to 9.

[0435] LC / MS mass spectrometry: m / z 488 ([M + H] +). LC / MS retention time: 0.50 minutes (analytical conditions: SQD-FA05-1). The compound 60c used in the synthesis of the example compound 60 was synthesized as follows.

[0436]

[0437] (Step 60-1) 2- (3,5-dimethylphenyl) -3- (2-oxo-1H-imidazol-3-yl) -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine It was synthesize | combined by the operation similar to the process 51-1 of Example

51 using the suitable reagent from the compound 1g obtained by 5-5-carboxylic acid tert- butyl (compound 60a) process 1-4.

[0438] LC / MS mass spectrometry: m / z 410 ([M + H] +). LC / MS retention time: 0.77 minutes (analysis conditions: SQD-FA05-1). (Step 60-2) 2- (3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H -Pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 60b) Reagent suitable from Compound 60a obtained in Step 60-1 and 5-bromo-1-methylindazole (Compound 1q) The compound was synthesized by the same operation as step 1-11 of Example 1.

[0439] LC / MS mass spectrometry: m / z 540 ([M + H] +). LC / MS retention time: 1.24 minutes (analysis conditions: SMD-FA05-3). (Step 60-3) 1- [2- (3,5-dimethylphenyl) -4,5,6,7-tetrahydropyrazolo [4,3-c] pyridin-3-yl] -3- (1-) Synthesis by the same procedure as step 11-8 of Example 11, using a suitable reagent, from compound 60b obtained in step 60-2 from methyl indazol-5-yl) imidazol-2-one hydrochloride (Compound 60c) did.

[0440] LC / MS mass spectrometry: m / z 440 ([M + H] +). LC / MS retention time: 0.74 minutes (analytical conditions: SMD-FA05-2). The compound 61b used in the synthesis of the example compound 61 was synthesized as follows.

[0441]

[0442] (Step 61-1) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- [3- (1-methylindazol-5-yl) -2-oxoimidazole- 1-yl] tert-Butyl 1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylate (Compound 61a) Compound 11k obtained in step 11-7 and 5-bromo-1 -It synthesize | combined by operation similar to the process 1-11 of Example 1 using a suitable reagent from methyl indazole (compound 1q).

[0443] LC / MS mass spectrometry: m / z 572 ([M + H] +). LC / MS retention time: 1.30 minutes (analysis conditions: SMD-FA05-1). (Step 61-2) 1-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -3- (1-methylindazol-5-yl) imidazol-2-one hydrochloride (Compound 61b) Example using the appropriate reagent from compound 61a obtained in step 61-1 It synthesize | combined by the operation similar to 11 process 11-8.

[0444] LC / MS mass spectrometry: m / z 472 ([M + H] +). LC / MS retention time: 0.79 minutes (analysis conditions: SMD-FA05-1). The compound 62b used in the synthesis of the example compound 62 was synthesized as follows.

[0445]

[0446] (Step 62-1) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -3- [3- [1- (2-methoxyethyl) indazol-5-yl] -2-oxoimidazole 1-yl] -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 62a) with compound 11k obtained in step 11-7 It was synthesized from 5-bromo-1-(2-methoxyethyl) indazole (Compound 56a) by the same procedure as in step 1-11 of Example 1 using an appropriate reagent.

[0447] LC / MS mass spectrometry: m / z 616 ([M + H] +). LC / MS retention time: 1.29 minutes (analysis conditions: SMD-FA05-1). (Step 62-2) 1-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -3- [1- (2-methoxyethyl) indazol-5-yl] imidazol-2-one hydrochloride (Compound 62b) Suitable reagent from compound 62a obtained in step 62-1 The compound was synthesized by the same procedure as step 11-8 of Example 11.

[0448] LC / MS mass spectrometry: m / z 516 ([M + H] +). LC / MS retention time: 0.76 minutes (analysis conditions: SMD-FA05-1). The compound 63g used in the synthesis of the example compound 63 was synthesized as follows.

[0449]

[0450] (Step 63-1) 5-bromo-7-fluoro-N-methyl-N-phenyl-1H-indole-2-carboxamide (compound 63b) 5-bromo-7-fluoro-1H-indole-2-carboxylic acid Compound 63a) was synthesized by the same procedure as in Steps 1 to 10 of Example 1 using a suitable reagent.

[0451] (Step 63-2) 5-bromo-1- (cyanomethyl) -7-fluoro-N-methyl-N-phenylindole-2-carboxamide (Compound 63c) More suitable than the compound 63b obtained in Step 63-1. It synthesize | combined by the operation similar to process 9-1 of Example 9 using a reagent.

[0452] LC / MS mass spectrometry: m / z 386 ([M + H] +). LC / MS retention time: 3.17 minutes (analysis conditions: SMD-FA 10-long). (Step 63-3) 5-bromo-1-[(1S, 2S) -1-cyano-2-methylcyclopropyl] -7-fluoro-N-methyl-N-phenylindole-2-carboxamide (compound 63d) The compound 63c obtained in Step 63-2 was synthesized by the same procedure as Step 1-6 in Example 1 using a suitable reagent.

[0453] LC / MS mass spectrometry: m / z 426 ([M + H] +). LC / MS retention time: 1.36 minutes (analysis conditions: SMD-FA05-1). 1 H-NMR (300 MHz, CDCl 3) δ : 7.75 (1 H, s), 7.43-7.30 (6 H, m), 6.08 (1 H, brs), 3.44 (3 H, s), 2.11-1.69 (3H, m), 1.40-1.35 (3H, m).

[0454] (Step 63-4) 1-[(1S, 2S) -1-cyano-2-methylcyclopropyl] -7-fluoro-N-methyl-5- (oxane-4-yl) -N-phenylindole-2 -Carboxamide (compound 63e) Compound 63d obtained in step 63-3 and (tetrahydro-2H-pyran-4-yl) zinc (II) iodide (compound 8a) using a suitable reagent from Example 8; It synthesize | combined by the operation similar to process 8-1.

[0455] LC / MS mass spectrometry: m / z 432 ([M + H] +). LC / MS retention time: 1.22 minutes (analysis conditions: SMD-FA05-1). (Step 63-5) 7-fluoro-N-methyl-1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4-oxadiazol-3-yl) Cyclopropyl] -5- (Oxan-4-yl) -N-phenylindole-2-carboxamide (Compound 63f) From compound 63e obtained in Step 63-4, using the appropriate reagent, step 1 of Example 1 It synthesize | combined by the operation similar to -8.

[0456] LC / MS mass spectrometry: m / z 491 ([M + H] +). LC / MS retention time: 1.21 minutes (analytical conditions: SQD-FA05-01). (Step 63-6) 7-fluoro-1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4-oxadiazol-3-yl) cyclopropyl]- 5- (Oxan-4-yl) indole-2-carboxylic acid (Compound 63g) By a procedure similar to the step 6-4 of Example 6 using a suitable reagent from the compound 63f obtained in Step 63-5 Synthesized.

[0457] LC / MS mass spectrometry: m / z 402 ([M + H] +). LC / MS retention time: 0.97 minutes (analysis conditions: SMD-FA05-1). The compound 64b used in the synthesis of the example compound 64 was synthesized as follows.

[0458]

[0459] (Step 64-1) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- [2-oxo-3- [1-[(3R) -oxolane-3-] [l] indazol-5-yl] imidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylate tert-butyl (compound 64a) obtained in step 11-7 Using the appropriate compound from the compound 11k obtained and the compound 8f obtained in Step 8-4, the compound was synthesized by the same procedure as Step 1-11 of Example 1.

[0460] LC / MS mass spectrometry: m / z 628 ([M + H] +). LC / MS retention time: 1.32 minutes (analysis conditions: SMD-FA05-1). (Step 64-2) 1-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -3- [1-[(3R) -oxolan-3-yl] indazol-5-yl] imidazol-2-one hydrochloride (Compound 64b) Compound 64a obtained in step 64-1 More, it synthesize | combined by the operation similar to process 11-8 of Example 11 using a suitable reagent.

[0461] LC / MS mass spectrometry: m / z 528 ([M + H] +). LC / MS retention time: 0.78 minutes (analysis conditions: SMD-FA05-1). The compound 65c used in the synthesis of the example compound 65 was synthesized as follows.

[0462]

[0463] (Step 65-1) (4S) -2- (4-chloro-3,5-dimethylphenyl) -3- [3- (4-fluoro-1-methylindazol-5-yl) -2-oxoimidazole- 1-yl] tert-butyl 1-yl] -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylate (compound 65b) compounds 42e and 5 obtained in step 42-4 -It synthesize | combined by the operation similar to the process 1-11 of Example 1 using a suitable reagent from the bromo-4-fluoro- 1-methyl indazole (compound 65a).

[0464] LC / MS mass spectrometry: m / z 606 ([M + H] +). LC / MS retention time: 1.38 minutes (analysis conditions: SMD-FA05-1). (Step 65-2) 1-[(4S) -2- (4-chloro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -3- (4-fluoro-1-methylindazol-5-yl) imidazol-2-one hydrochloride (Compound 65c) Suitable reagent from the compound Compound 65b obtained in Step 65-1 The compound was synthesized by the same procedure as step 11-8 of Example 11.

[0465] LC / MS mass spectrometry: m / z 506 ([M + H] +). LC / MS retention time: 0.86 minutes (analysis conditions: SMD-FA05-1). The compound 67b used in the synthesis of the example compound 67 was synthesized as follows.

[0466]

[0467] (Step 67-1) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (4-fluoro-1-methylindazol-5-yl) -2-oxoimidazole- 1-yl] tert-butyl 1-yl] -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylate (compound 67a) compounds 11k and 5 obtained in step 11-7 -It synthesize | combined by the operation similar to the process 1-11 of Example 1 using a suitable reagent from the bromo-4-fluoro- 1-methyl indazole (compound 65a).

[0468] LC / MS mass spectrometry: m / z 590 ([M + H] +). LC / MS retention time: 1.31 minutes (analysis conditions: SMD-FA05-1). (Step 67-2) 1-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -3- (4-fluoro-1-methylindazol-5-yl) imidazol-2-one hydrochloride (Compound 67b) Suitable reagent from the compound Compound 67a obtained in Step 67-1 The compound was synthesized by the same procedure as step 11-8 of Example 11.

[0469] LC / MS mass spectrometry: m / z 490 ([M + H] +). LC / MS retention time: 0.80 minutes (analysis conditions: SMD-FA05-1). The compound 68c used in the synthesis of the example compound 68 was synthesized as follows.

[0470]

[0471] (Step 68-1) (4S) -3- [3- (4-chloro-1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3,5 -Dimethylphenyl) -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 68b) Compounds 11k and 5 obtained in step 11-7 -It synthesize | combined by the operation similar to the process 1-11 of Example 1 using a suitable reagent from the bromo 4-chloro 1 -methyl indazole (compound 68a).

[0472] LC / MS mass spectrometry: m / z 606 ([M + H] +). LC / MS retention time: 1.34 minutes (analysis conditions: SMD-FA05-1). (Step 68-2) 1- (4-chloro-1-methylindazol-5-yl) -3-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4 5,6,7-Tetrahydropyrazolo [4,3-c] pyridin-3-yl] imidazol-2-one hydrochloride (Compound 68c) From Compound 68b obtained in Step 68-1, a more suitable It synthesize | combined by operation similar to process 11-8 of Example 11 using.

[0473] LC / MS mass spectrometry: m / z 506 ([M + H] +). LC / MS retention time: 0.83 minutes (analysis conditions: SMD-FA05-1). The compound 69b used in the synthesis of the example compound 69 was synthesized as follows.

[0474]

[0475] (Step 69-1) (4S) -3- [3- (4-Fluoro-1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -2- (4-fluoro-3-methyl) Phenyl) -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 69a) Compound 46d obtained in step 46-3 and 5-bromo It synthesize | combined by the operation similar to the process 1-11 of Example 1 from 4-fluoro- 1-methyl indazole (compound 65a) using a suitable reagent.

[0476] LC / MS mass spectrometry: m / z 576 ([M + H] +). LC / MS retention time: 1.25 minutes (analysis conditions: SMD-FA05-1). (Step 69-2) 1- (4-Fluoro-1-methylindazol-5-yl) -3-[(4S) -2- (4-fluoro-3-methylphenyl) -4-methyl-4,5 6,7-Tetrahydropyrazolo [4,3-c] pyridin-3-yl] imidazol-2-one hydrochloride (Compound 69b) From Compound 69a obtained in Step 69-1, using an appropriate reagent, It synthesize | combined by the operation similar to the process 11-8 of Example 11.

[0477] LC / MS mass spectrometry: m / z 476 ([M + H] +). LC / MS retention time: 0.77 minutes (analysis conditions: SMD-FA05-1). The compound 70c used in the synthesis of the example compound 70 was synthesized as follows.

[0478]

[0479] (Step 70-1) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (6-fluoro-1-methylindazol-5-yl) -2-oxoimidazole- 1-yl] tert-butyl 1-yl] -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylate (compound 70b) compounds 11k and 5 obtained in step 11-7 -It synthesize | combined by

operation similar to the process 1-11 of Example 1 from the bromo-6-fluoro- 1-methyl indazole (compound 70a) using a suitable reagent.

[0480] LC / MS mass spectrometry: m / z 590 ([M + H] +). LC / MS retention time: 1.28 minutes (analysis conditions: SMD-FA05-1). (Step 70-2) 1-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -3- (6-fluoro-1-methylindazol-5-yl) imidazol-2-one hydrochloride (Compound 70c) From Compound 70b obtained in Step 70-1, appropriate reagents It synthesize | combined by operation similar to process 11-8 of Example 11 using.

[0481] LC / MS mass spectrometry: m / z 490 ([M + H] +). LC / MS retention time: 0.81 minutes (analysis conditions: SMD-FA05-1). The compound 71b used in the synthesis of the example compound 71 was synthesized as follows.

[0482]

[0483] (Step 71-1) 5-bromo-6-fluoro-1- (2-methoxyethyl) indazole (compound 71b) From 5-bromo-6-fluoro-1H-indazole (compound 71a) using a suitable reagent, It synthesize | combined by the operation similar to the process 8-4 of Example 8.

[0484] LC / MS mass spectrometry: m / z 273 ([M + H] +). LC / MS retention time: 1.06 minutes (analysis conditions: SMD-FA05-1). (Step 71-2) (4S) -2- (4-fluoro-3,5-dimethylphenyl) -3- [3- [6-fluoro-1-(2-methoxyethyl) indazol-5-yl]- 2-oxoimidazol-1-yl] -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carboxylic acid tert-butyl (Compound 71c) obtained in step 11-7 Using the appropriate reagent from the compound 11k obtained and the compound 71b obtained in Step 71-1, synthesis was performed by the same procedure as Step 1-11 of Example 1.

[0485] LC / MS mass spectrometry: m / z 634 ([M + H] +). LC / MS retention time: 1.30 minutes (analysis conditions: SMD-FA05-1). (Step 71-3) 1-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-4,5,6,7-tetrahydropyrazolo [4,3-c] Pyridin-3-yl] -3- [6-fluoro-1- (2-methoxyethyl) indazol-5-yl] imidazol-2-one hydrochloride (Compound 71d) from compound 71c obtained in step 71-2 The compound was synthesized by the same procedure as step 11-8 of Example 11 using an appropriate reagent.

[0486] LC / MS mass spectrometry: m / z 534 ([M + H] +). LC / MS retention time: 0.83 minutes (analysis conditions: SMD-FA05-1). Example 73 3-[(1S, 2S) -1- [5- (2-ethyl-3-methylpyridin-4-yl) -2-[(4S) -2- (4-fluoro-3, 5-dimethylphenyl) -4-methyl-3- [3- (1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3- Synthesis of c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 73) (Step 73-1)

[0487]

[0488] Racemic compound (Compound 73a, 29.6 mg, 0.058 mmol) synthesized in the same manner as the compound obtained in Step 61-2 and Compound 1o obtained in Step 1-9 (26.8 mg, 0.064 mmol) HATU (26.6 mg, 0.070 mmol) and N, N-diisopropylethylamine (18.1 mg, 0.14 mmol) were added to a solution of (1.5 mL) in DMF, and the mixture was stirred at room temperature for 1 hour. The reaction solution was diluted with ethyl acetate and washed with distilled water. The organic layer was concentrated under reduced pressure to give a residue which is a mixture of stereoisomers. The stereoisomers were separated by reverse phase HPLC to obtain Entity A (14.5 mg, 29% yield) and Entity B (15.5 mg, 31% yield) which is the title compound 73 as a white solid.

[0489] Preparation conditions Column: YMC Actus ODS-A, 20 × 100 mm, 5 μm Solvent: 0.1% formic acid aqueous solution / 0.1% formic acid acetonitrile solution = 40/60 (homogeneous system) Flow rate: 20 mL / min, room temperature Entity ALC / MS mass spectrometry: m / z 872 ([M + H] +).

[0490] LC / MS retention time: 0.99 minutes (analysis conditions: SMD-FA05-3). Entity B (compound 73) LC / MS mass spectrometry: m / z 872 ([M + H] +).

[0491] LC / MS retention time: 1.01 minutes (analysis conditions: SMD-FA05-3). EXAMPLE 74 3-[(1S, 2S) -1- [6-Fluoro-2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- [3 3- (1-Methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2 Synthesis of -Methoxy-3-methylpyridin-4-yl) indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 74)

[0492]

[0493] (Step 74-1) 5-bromo-6-fluoro-N-methyl-N-phenyl-1H-indole-2-carboxamide (compound 74b) 5-bromo-6-fluoro-1H-indole-2-carboxylic acid (compound 74b) Compound 74a) was synthesized by the same procedure as in Steps 1 to 10 of Example 1 using an appropriate reagent.

[0494] LC / MS mass spectrometry: m / z 347 ([M + H] +). LC / MS retention time: 1.06 minutes (analytical conditions: SMD-TFA 05-4). (Step 74-2) 5-bromo-1- (cyanomethyl) -6-fluoro-N-methyl-N-phenylindole-2-carboxamide (compound 74c) More suitable than the compound 74b obtained in the step 74-1. It synthesize | combined by the operation similar to process 9-1 of Example 9 using a reagent.

[0495] LC / MS mass spectrometry: m / z 386 ([M + H] +). LC / MS retention time: 1.06 minutes (analytical conditions: SMD-TFA 50-4). (Step 74-3) 5-bromo-1-[(1S, 2S) -1-cyano-2-methylcyclopropyl] -6-fluoro-N-methyl-N-phenylindole-2-carboxamide (compound 74d) Using the appropriate reagent

from compound 74c obtained in step 74-2 and (4R) -4-methyl-1,3,2-dioxathiolane 2,2-dioxide (compound 1k), step 1- of Example 1 It synthesize | combined by the operation similar to 6.

[0496] LC / MS mass spectrometry: m / z 426 ([M + H] +). LC / MS retention time: 1.04 minutes (analysis conditions: SMD-FA 10-5). (Step 74-4) 5-bromo-6-fluoro-N-methyl-1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4-oxadiazole- 3-yl) cyclopropyl] -N-phenylindole-2-carboxamide (Compound 74e) The same procedure as in Step 1-8 in Example 1 using a suitable reagent from compound 74d obtained in Step 74-3 Synthesized by

[0497] LC / MS mass spectrometry: m / z 485 ([M + H] +). LC / MS retention time: 1.33 minutes (analysis conditions: SMD-FA05-1). (Step 74-5) 5-bromo-6-fluoro-1-[(1S, 2S) -2-methyl-1- (5-oxo-4H-1,2,4-oxadiazol-3-yl) It was synthesize | combined by operation similar to the process 6-4 of Example 6 from the compound 74e obtained by the cyclopropyl] indole 2-carboxylic acid (compound 74f) process 74-4 using the suitable reagent.

[0498] LC / MS mass spectrometry: m / z 396 ([M + H] +). LC / MS retention time: 0.80 minutes (analytical conditions: SQD-FA05-1). (Step 74-6) 3-[(1S, 2S) -1- [5-bromo-6-fluoro-2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-] Methyl-3- [3- (1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] Indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 74g) Compound 74f obtained in step 74-5 and obtained in step 61-2 The compound 61b was synthesized by the same procedure as in the step 1-10 of Example 1 using an appropriate reagent.

[0499] LC / MS mass spectrometry: m / z 849 ([M + H] +). LC / MS retention time: 1.42 minutes (analysis conditions: SMD-FA05-1). (Step 74-7) 3-[(1S, 2S) -1- [6-fluoro-2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3-] [3- (1-Methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2-Methoxy-3-methylpyridin-4-yl) indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 74) Step 74-6 The compound was synthesized by the same procedure as in step 6-5 of Example 6 using 74 g of the compound obtained above and 4-iodo-2-methoxy-3-methylpyridine (Compound 6 g), and appropriate reagents.

[0500] LC / MS mass spectrometry: m / z 892 ([M + H] +). LC / MS retention time: 1.48 minutes (analytical conditions: SMD-TFA 05-1). <Examples 75 to 77> The same procedures as in step 8-1 of Example 8 are carried out using an indole bromide compound and an iodo (oxane-4-yl) zinc derivative, and an appropriate reagent, and the following reaction gives a table Example compounds 75 to 77 shown in 2-6 were obtained.

[0501]

[0502]

[0503] The compound 75b used in the synthesis of the example compound 75 was synthesized as follows. (Step 75-1) Iodo (6-oxaspiro [4.5] decan-9-yl) zinc (Compound 75b)

[0504]

[0505] Using 9-iodo-6-oxaspiro [4.5] decane (Compound 75a), and using an appropriate reagent, it was synthesized by the same procedure as step 41-1 of Example 41. This compound was used directly in the next step.

[0506] The compound 76a used in the synthesis of the example compound 76 was synthesized as follows.

[0507]

[0508] (Step 76-1) 3-[(1S, 2S) -1- [5-bromo-2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- [1- (2) -Methoxyethyl) indazol-5-yl] -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indol-1-yl]- 2-Methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 76a) More suitable than the compound 56b obtained in Step 56-1 and the compound 6f obtained in Step 6-4 The synthesis was carried out in the same manner as in steps 1 to 10 of Example 1 using the above reagents.

[0509] LC / MS mass spectrometry: m / z 861 ([M + H] +). LC / MS retention time: 1.45 minutes (analysis conditions: SMD-FA05-2). <Example 77>

[0510]

[0511] (Step 77-1) A solution of 2-ethyl-4-iodooxane (Compound 77b) but-3-en-1-ol (0.588 mL, 6.93 mmol) in acetic acid (2.48 mL) was added with propionaldehyde (0. 650 mL (9.01 mmol) and lithium iodide (2.78 g, 20.8 mmol) were sequentially added, and stirred at 60 ° C. for 1 hour. To the reaction mixture was added water and extracted with dichloromethane. The organic layer was washed with 10% aqueous sodium thiosulfate solution, saturated aqueous sodium hydrogen carbonate solution, and dried over magnesium sulfate. After filtration, the filtrate is concentrated under reduced pressure (150 hpa as the lower limit), and the residue is purified by silica gel

chromatography (ethyl acetate / hexane = 0: 1 to 1: 9) to give the title compound 77b as a pale yellow oil. Were obtained as a diastereomer mixture (1.12 g, yield 67%, syn: anti = 1.00: 0.45).

[0512] 1 H-NMR (400 MHz, CDCl 3): syn δ : 4.31 to 4.23 (1 H, m), 3.90 to 3.82 (1 H, m), 3.44 to 3.37 (1 H, m) , 3.21-3.15 (1 H, m), 2.37-1.38 (6 H, m), 0.92 (3 H, t, J = 7.4 Hz).

[0513] anti δ : 4.87 to 4.84 (1 H, m), 3.90 to 3.82 (2 H, m), 3.70 to 3.64 (1 H, m), 2.37 to 1. 38 (6H, m), 0.94 (3H, t, J = 7.6 Hz).

[0514] (Step 77-2) A solution of (2-ethyloxane-4-yl) -iodozinc (compound 77c) zinc (102 mg, 1.56 mmol) in DMA (0.25 mL) under a nitrogen atmosphere with chloro (trimethyl) silane (A mixture of 0.017 mL, 0.137 mmol) and 1,2-dibromoethane (0.012 mL, 0.137 mmol) was slowly added dropwise to keep the temperature at 65 ° C. or lower, and stirred at room temperature for 15 minutes. Subsequently, a solution of compound 77b (300 mg, 1.25 mmol) obtained in Step 77-1 in DMA (0.625 mL) is slowly added dropwise so as to keep the temperature at 65 ° C. or lower. The mixture was stirred for 30 minutes to obtain a DMA solution (0.86 M) of a diastereomeric mixture of the title compound 77c.

[0515] (Step 77-3) 3-[(1S, 2S) -1- [5- (2-ethyloxane-4-yl) -2- [2- (4-fluoro-3,5-dimethylphenyl) -3-] [3- (1-Methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indole-1 [L, 2-Methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 77) DMA of Compound 51d (40.0 mg, 0.049 mmol) obtained in Step 51-4 (0.163 mL) solution, palladium (II) acetate (2.20 mg, 0.00978 mmol), 2- (2-dicyclohexylphosphanylphenyl) -1-N, 1-N, 3-N, 3-N- Tetramethyl bee Zen-1,3-diamine (8.54mg, 0.020mmol) and the mixture was degassed under reduced pressure, purged with nitrogen, and stirred for 5 minutes at room temperature. Subsequently, a solution of compound 77c obtained in Step 77-2 in DMA (0.86 M, 0.398 mL, 0.342 mmol) was added, and stirred at room temperature for 1.5 hours. Formic acid was added to the reaction mixture and purification was conducted by reverse phase silica gel chromatography (acetonitrile / water, 0.1% formic acid) to obtain a syn isomer diastereomer mixture. The syn isomer diastereomer mixture is separated into stereoisomers by reverse phase HPLC, and the white amorphous Entity A (17.4 mg, yield 41%) and the white amorphous title compound 77, Entity B (14.9 mg (yield 37%) was obtained.

[0516] Preparation conditions Column: CHIRALCEL OD-RH 5 μm, 4.6 mm × 150 mm (Daicel) Solvent: 0.1% aqueous formic acid solution / 0.1% formic acid acetonitrile solution = 20/80 (homogeneous system) Flow rate: 1.0 mL / min , Room temperature Entity ALC / MS mass spectrometry: m / z 851 ([M + H] +).

[0517] HPLC retention time: 4.99 minutes (preparation conditions). LC / MS retention time: 1.46 minutes (analysis conditions: SMD-FA05-1). Entity B (compound 77) LC / MS mass spectrometry: m / z 851 ([M + H] +).

[0518] HPLC retention time: 6.64 minutes (preparation conditions). LC / MS retention time: 1.46 minutes (analysis conditions: SMD-FA05-1). EXAMPLE 78 3-[(1S, 2S) -2-ethyl-1- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazole-) 5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indole-1 Synthesis of [-yl] cyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 78)

[0519]

[0520] (Step 78-1) 2- [5-bromo-2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl) -2-oxo Imidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indol-1-yl] acetonitrile (compound 78a) Compound 51c obtained in step 51-3 And 5-bromo-1- (cyanomethyl) indole-2-carboxylic acid (Compound 6a) were synthesized by the same procedure as step 1-10 in Example 1 using a suitable reagent.

[0521] LC / MS mass spectrometry: m / z 718 ([M + H] +). LC / MS retention time: 1.30 minutes (analysis conditions: SMD-FA05-1). (Step 78-2) 2- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl) -2-oxoimidazole-1-] [Yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl] acetonitrile (compound 78b) step 78-1 Were prepared from Compound 78a obtained in the above and (tetrahydro-2H-pyran-4-yl) zinc (II) iodide (compound 8a) using the appropriate reagent and in the same manner as in step 8-1 of Example 8 did.

[0522] LC / MS mass spectrometry: m / z 724 ([M + H] +). LC / MS retention time: 1.21 minutes (analysis conditions: SMD-FA05-1). (Step 78-3) (1S, 2S) -2-ethyl-1- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazole-5-) Yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl The compound 78b obtained in Step 78-2 of cyclopropane-1-carbonitrile (Compound 78d) was synthesized by the same procedure as in Step 1-6 of Example 1, using an appropriate reagent.

[0523] LC / MS mass spectrometry: m / z 778 ([M + H] +). LC / MS retention time: 1.27 minutes (analysis conditions: SMD-FA05-RP). (Step 78-4) 3-[(1S, 2S) -2-ethyl-1- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazole) -5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indole- 1-yl] cyclopropyl] -4H-1,2,4-oxadiazol-5-one (compound 78) according to the procedure of Example 1 using a suitable reagent from compound 78d obtained in Step 78-2 It synthesize | combined by the operation similar to 1-8.

[0524] LC / MS mass spectrometry: m / z 837 ([M + H] +). LC / MS retention time: 1.39 minutes (analytical conditions: SMD-TFA 05-2). Example 79 3-[(1S, 2S) -1- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl)] -2-Oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl]- Synthesis of 2- (hydroxymethyl) cyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 79)

[0525]

[0526] (Step 79-1) 5-bromo-1-[(1S, 2S) -1-cyano-2- (phenylmethoxymethyl) cyclopropyl] -N-methyl-N-phenylindole-2-carboxamide (compound 79b) Example 6 using a suitable reagent from compound 6c obtained in step 6-1 and (4R) -4- (phenylmethoxymethyl) -1,3,2-dioxathiolane 2,2-dioxide (compound 79a) It synthesize | combined by the operation similar to the process 1-6 of.

[0527] LC / MS mass spectrometry: m / z 514 ([M + H] +). LC / MS retention time: 1.48 minutes (analysis conditions: SMD-FA05-1). (Step 79-2) 1-[(1S, 2S) -1-cyano-2- (phenylmethoxymethyl) cyclopropyl] -N-methyl-5- (oxane-4-yl) -N-phenylindole-2 Carboxamide (compound 79c) Compound 79b obtained in Step 79-1 and (tetrahydro-2H-pyran-4-yl) zinc (II) iodide (compound 8a) using a suitable reagent from Example 8; It synthesize | combined by the operation similar to process 8-1.

[0528] LC / MS mass spectrometry: m / z 520 ([M + H] +). LC / MS retention time: 1.37 minutes (analysis conditions: SMD-FA05-1). (Step 79-3) N-methyl-5- (oxan-4-yl) -1-[(1S, 2S) -1- (5-oxo-4H-1,2,4-oxadiazole-3-) Step 1 of Example 1 using an appropriate reagent from compound 79c obtained in step 79-2 from step 79-2; It synthesize | combined by the operation similar to 8.

[0529] LC / MS mass spectrometry: m / z 579 ([M + H] +). LC / MS retention time: 1.37 minutes (analysis conditions: SMD-FA05-1). (Step 79-4) 5- (Oxan-4-yl) -1-[(1S, 2S) -1- (5-oxo-4H-1,2,4-oxadiazol-3-yl) -2 -(Phenylmethoxymethyl) cyclopropyl] indole-2-carboxylic acid (79e) Compound 79d obtained in Step 79-3 was synthesized by the same procedure as in Step 6-4 of Example 6, using an appropriate reagent. did.

[0530] LC / MS mass spectrometry: m / z 490 ([M + H] +). LC / MS retention time: 1.12 minutes (analysis conditions: SMD-FA05-1). (Step 79-5) 3-[(1S, 2S) -1- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl]) -2-Oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl] -2- (phenylmethoxymethyl) cyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 79f) Compound 79e obtained in step 79-4 and obtained in step 51-3 The compound was synthesized from Compound 51c by using a suitable reagent and in the same manner as in Steps 1 to 10 of Example 1.

[0531] LC / MS mass spectrometry: m / z 929 ([M + H] +). LC / MS retention time: 1.41 minutes (analysis conditions: SMD-FA05-1). (Step 79-6) 3-[(1S, 2S) -1- [2- [2- (4-fluoro-3,5-dimethylphenyl) -3- [3- (1-methylindazol-5-yl]) -2-Oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane-4-yl) indol-1-yl] -2- (Hydroxymethyl) cyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 79) of the compound 79f (35.4 mg, 0.0381 mmol) obtained in the step 79-5 The dichloromethane (0.762 mL) solution was cooled to 0 ° C., and 1 M boron trichloride solution in hexane (0.191 mL, 0.191 mmol) was slowly added. The reaction solution was warmed to room temperature and stirred for 105 minutes, then a saturated aqueous sodium hydrogen carbonate solution was added to the reaction solution, and the aqueous layer was extracted with dichloromethane. The organic layer was washed with brine and dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by reverse phase column chromatography (acetonitrile / water, 0.1% formic acid) to give the title compound (18.5 mg, yield 50%) .

[0532] LC / MS mass spectrometry: m / z 839 ([M + H] +). LC / MS retention time: 1.20 minutes (analytical conditions: SMD-TFA 05-1). Example 80 3-[(1S, 2S) -1- [2-[(4S, 6R) -2- (4-fluoro-3,5-dimethylphenyl) -4,6-dimethyl-3- [3- (1-Methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (oxane Synthesis of 4-yl) indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 80)

[0533]

[0534] (Step 80-1) Ethyl (E) -3-[[(2S) -1-cyanopropan-2-yl] amino] but-2-enoate (Compound 80c) (3S) -3-aminobutanenitrile Ethyl 3-oxobutanoate (Compound 80a, 13 g, 99.9 mmol) is added to a solution of compound 80b (7.0 g, 83.2 mmol) and iodine (2.12 g, 8.35 mmol) in acetonitrile (50 mL) Stir for 4 hours. The reaction mixture is concentrated under reduced pressure, the solvent is evaporated, and the residue is purified by silica gel column chromatography (petroleum ether / ethyl acetate = 1: 0 to 3: 2) to give the title compound 80c (9.5 g, yield 58%) as a yellow oil.

[0535] LC / MS mass spectrometry: m / z 197 ([M + H] +). LC / MS retention time: 0.86 minutes (analysis conditions: SMD-FA10-1). (Step 80-2) Ethyl 3-[[(2S) -1-cyanopropan-2-yl] amino] butanoate (Compound 80d) Compound 80c (10 g, 51.0 mmol) obtained in Step 80-1 and Acetic acid (3 mL) was added to a solution of sodium triacetoxyborohydride (43.3 g, 204 mmol) in dichloromethane (200 mL) and stirred at room temperature for 16 hours. Water and acetic acid were added to the reaction solution to adjust to pH 5, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration, the filtrate is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (petroleum ether / ethyl acetate = 1: 0 to 1: 4) to give the title compound 80d (5.5 g, yield 54%) Was obtained as a yellow oil.

[0536] LC / MS retention time: 0.83 minutes (analysis conditions: SMD-FA 10-4). (Step 80-3) (6S) -1-formyl-4-hydroxy-2,6-dimethyl-3,6-dihydro-2H-pyridine-5-carbonitrile (compound 80e) potassium tert butoxide (680 mg, 6. A solution of compound 80d (1.0 g, 5.04 mmol) obtained in Step 80-2 in toluene (5 mL) was slowly added dropwise to a solution of 06 mmol) in toluene (10 mL) at 80 ° C. After stirring for 1 hour at 80 ° C., the solution was cooled to room temperature to obtain a toluene solution of (6S) -4-hydroxy-2,6-dimethyl-1,2,3,6-tetrahydropyridine-5-carbonitrile .

[0537] A solution of acetic anhydride (12.1 g, 118 mmol) in toluene (5 mL) was slowly added dropwise to formic acid (7.26 g) at 0 ° C., and stirred for 30 minutes at 0 ° C. to prepare (6S) -4-hydroxy A toluene solution of 2,6-dimethyl-1,2,3,6-tetrahydropyridine-5-carbonitrile was slowly added dropwise. After stirring at 110 ° C. for 16 hours, the reaction mixture was cooled to room temperature, the reaction mixture was concentrated under reduced pressure, the solvent was evaporated, and a mixture (1.3 g) containing the title compound 80e was obtained as an oil.

[0538] (Step 80-4) (4S) -3-amino-2- (4-fluoro-3,5-dimethylphenyl) -4,6-dimethyl-6,7-dihydro-4H-pyrazolo [4,3-c Compound 80e (1.30 g, 7.21 mmol) obtained in Step 80-3 and hydrochloride salt of (4-fluoro-3,5-dimethylphenyl) hydrazine (Compound 2c) A solution of 690 mg (3.62 mmol) in ethanol (30 mL) was heated to 75 ° C. and stirred for 16 hours. Cool to room temperature and concentrate the reaction under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane / methanol = 1: 0 to 9: 1) to give the title compound 80f (two steps from step 80-3, 800 mg, yield 35%) as a yellow solid.

[0539] LC / MS mass spectrometry: m / z 317 ([M + H] +). LC / MS retention time: 0.79 minutes (analysis conditions: SMD-FA 10-3). (Step 80-5) 1- (2,2-dimethoxyethyl) -3-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -5-formyl-4,6-dimethyl-6 , 7-dihydro-4H-pyrazolo [4,3-c] pyridin-3-yl] urea (compound 80 g) in N, N'-carbodiimidazole (1.63 g, 10.1 mmol) in DMA (50 mL) solution At 0 ° C., 2,2-dimethoxyethane-1-amine (1.14 g, 10.8 mmol) was added and stirred for 30 minutes. To the solution was sequentially added potassium tert-butoxide (5.62 g, 50.1 mmol) and compound 80f (2.64 g, 8.34 mmol) obtained in Step 80-4. After stirring at room temperature for 6 hours, water was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give 80 g (2.80 g, yield 75%) of the title compound as a brown oil.

[0540] LC / MS mass spectrometry: m / z 448 ([M + H] +). LC / MS retention time: 0.84 minutes (analysis conditions: SMD-FA10-2). (Step 80-6) (4S, 6R) -2- (4-fluoro-3,5-dimethylphenyl) -4,6-dimethyl-3-(2-oxo-1H-imidazol-3-yl) -6 , 7-Dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbaldehyde (Compound 80h) 80 g (2.50 g, 5.59 mmol) of the compound obtained in step 80-5 and 4-methylbenzenesulfone A solution of acid (1.06 g, 6.16 mmol) in DMF (30 mL) was warmed to 80 ° C. and stirred for 2 hours. After cooling to room temperature, water was added and the aqueous layer was extracted

with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether / ethyl acetate = 1: 0 to 3: 1) to give a diastereomeric mixture (480 mg) containing the title compound (compound 80h) as a white solid.

[0541] LC / MS mass spectrometry: m / z 384 ([M + H] +). LC / MS retention time: 1.64 minutes (analytical conditions: SMD-TFA 05-6). Title compound (Compound 80h: (4S, 6R) -2- (4-fluoro-3,5-dimethylphenyl) -4,6-dimethyl-3- (2-oxo-1H-imidazol-3-yl) -6 A diastereomeric mixture (480 mg, 5.59 mmol) containing 1,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbaldehyde) is separated into stereoisomers by SFC to give the title compound 80h. Entity A (155 mg, 7.0% yield) and Entity B (270 mg, 12% yield) were obtained.

[0542] SFC preparation conditions Column: CHIRALPAK AD-H, 50 × 500 mm, 3 μm (Daicel) solvent: supercritical carbon dioxide / ethanol = 70: 30 (homogeneous system) flow rate: 150 mL / min, 35 ° C. Detection wavelength: 254 nm Entity A (compound 80 h) SFC retention time: 4.07 minutes.

[0543] LC / MS mass spectrometry: m / z 384 ([M + H] +). LC / MS retention time: 2.15 minutes (analysis conditions: SMD-FA1060-1). 1 H-NMR (300 MHz, DMSO-D6) δ : 10.35 (1 H, s), 8.24 (1 H, s), 7.11 (2 H, d, J = 6.3 Hz), 6.60-6 .58 (2H, m), 5.21-5.14 (1 H, m), 4.46-4.21 (1 H, m), 2.96-2.89 (1 H, m), 2.74 -2.68 (1 H, m), 2.20 (6 H, s), 1. 27-1. 13 (6 H, m).

[0544] In addition, it was determined from 2D-NOESY that the compound 80h is a 6R isomer from the fact that the configuration is cis. Entity BSFC retention time: 5.60 minutes.

[0545] LC / MS mass spectrometry: m / z 384 ([M + H] +). LC / MS retention time: 2.16 minutes (analysis conditions: SMD-FA1060-1). 1 H-NMR (300 MHz, DMSO-D6) δ : 10.35 (1 H, s), 8.31 (1 H, s), 7.08 (2 H, d, J = 6.3 Hz), 6.61-6 .54 (2H, m), 5.39 (1 H, q, J = 6.9 Hz), 3.89-3.84 (1 H, m), 2.90 (1 H, dd, J = 3.3, 15.6 Hz), 2.59-2.51 (1 H, m), 2.20 (6 H, d, J = 2.1 Hz), 1.55 (3 H, d, J = 6.6 Hz), 1. 18 (3H, d, J = 6.6 Hz).

[0546] (Step 80-7) 3-[(4S, 6R) -2- (4-fluoro-3,5-dimethylphenyl) -4,6-dimethyl-4,5,6,7-tetrahydropyrazolo [4, 3-C] Pyridin-3-yl] -1H-imidazol-2-one (Compound 80i) 5 M water in a solution of compound 80h (100 mg, 0.261 mmol) obtained in Step 80-6 in ethanol (1.0 mL) Aqueous sodium oxide solution (0.261 mL) was added and stirred at 80 ° C. for 10 hours. The reaction solution was cooled to room temperature and stirred for 60 hours, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate to synthesize the title compound 80i (79%, 73 mg) as a white solid.

[0547] LC / MS mass spectrometry: m / z 356 ([M + H] +). LC / MS retention time: 0.44 minutes (analysis conditions: SQD-FA05-2). (Step 80-8) 1-[(4S, 6R) -2- (4-fluoro-3,5-dimethylphenyl) -4,6-dimethyl-4,5,6,7-tetrahydropyrazolo [4, 3-c] Pyridin-3-yl] -3- (1-methylindazol-5-yl) imidazol-2-one (Compound 80j) Compound 80i (15 mg, 0.042 mmol) obtained in step 80-7, 5-bromo-1-methylindazole (Compound 1q, 10.7 mg, 0.051 mmol), (1S, 2S) -1-N, 2-N-dimethylcyclohexane-1,2-diamine (6.00 mg, 0. 1). Copper (I) iodide (4.02 mg, 0.021 mmol) in a suspension of 042 mmol) and potassium carbonate (17.5 mg, 0.127 mmol) in N-methyl piperazine (0.188 mL)) Was added at room temperature, and the mixture was stirred at 130 ° C. for 90 minutes under a nitrogen atmosphere. The reaction mixture was purified by reverse phase silica gel chromatography (acetonitrile / water, 0.1% formic acid) and concentrated in vacuo. To the residue was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound 80j (17.4 mg, yield 85%).

[0548] LC / MS mass spectrometry: m / z 486 ([M + H] +). LC / MS retention time: 0.51 minutes (analysis conditions: SQD-FA05-2). (Step 80-9) 5- (Oxan-4-yl) -1-[(1S, 2S) -2- [5-oxo-4- (2-trimethylsilylethoxymethyl) -1,2,4-oxadi] 2-Aryl-3-yl] -2-methylcyclopropyl] indole-2-carboxylic acid 2-trimethylsilylethoxymethyl (Compound 80k) DMF of compound 8b (100 mg, 0.261 mmol) obtained in step 8-1 (2. 55 wt% sodium hydride (34.1 mg, 0.782 mmol) and 2- (trimethylsilyl) ethoxymethyl chloride (0.116 mL, 0.652 mmol) were added to the solution and the solution was stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride solution is added, and the mixture is extracted with ethyl acetate, concentrated, and the obtained residue is purified by normal phase column chromatography (ethyl acetate / hexane) to give the title compound 80k (147 mg, yield 88) as a yellow gum. %) Got. LC / MS retention time: 1.21 minutes (Analytical conditions: SQD-FA05-2) (Step 80-10) 5- (Oxan-4-yl) -1-[(1S, 2S) -1- [5-] Oxo-4- (2-trimethylsilylethoxymethyl) -1,2,4-oxadiazol-3-yl] -2-methylcyclopropyl] indole-2-carboxylic acid (80 l) obtained in step 80-9 Magnesium bromide-diethyl ether complex (295 mg, 1.14 mmol) was added to a solution of compound 80k (147 mg, 0.228 mmol) in dichloromethane (2.3 mL), and the mixture was stirred at 0 ° C. for 6.5 hours. The mixture is warmed to room temperature and stirred for 30 minutes, saturated aqueous ammonium chloride solution is added, extraction is performed with ethyl acetate, and after concentration, the residue is diluted with DMSO and water, and reverse phase chromatography (acetonitrile / water, 0.1% formic acid) The title compound 801 (60 mg, 51% yield) was synthesized.

[0549] LC / MS mass spectrometry: m / z 512 ([M-H]-). LC / MS retention time: 1.03 minutes (analysis conditions: SQD-FA05-2). (Step 80-11) 5- (Oxan-4-yl) -1-[(1S, 2S) -2- [5-oxo-4- (2-trimethylsilylethoxymethyl) -1,2,4-oxadi] [Azole-3-yl] -2-methylcyclopropyl] indole-2-carbonyl chloride (Compound 80m) to a solution of compound 80l (18 mg, 0.036 mmol) obtained in step 80-10 in acetonitrile (0.36 mL), Add 1-chloro-N, N, 2-trimethylprop-1-en-1-amine (0.0057 mL, 0.043

mmol), stir at room temperature for 2 hours and concentrate to give the title compound 80m as a crude product I got This compound was used directly in the next step.

[0550] (Step 80-12) 3-[(1S, 2S) -2- [2-[(4S, 6R) -2- (4-fluoro-3,5-dimethylphenyl) -4,6-dimethyl-3-] [3- (1-Methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5-(Oxan-4-yl) indol-1-yl] -2-methylcyclopropyl] -4- (2-trimethylsilylethoxymethyl) -1,2,4-oxadiazol-5-one (compound 80n) step 80- Compound 80m obtained in 11 is dissolved in THF (0.717 mL), and compound 80j (19.1 mg, 0.036 mmol) obtained in Step 80-8 and N, N-diisopropylethylamine (0.0188 mL, .108Mmol) was added, at room temperature, after stirring for 22 hours, methanol was added and formic acid. After concentration, the residue was diluted with DMSO and water and purified by reverse phase column chromatography (acetonitrile / water, 0.1% formic acid) to synthesize the title compound 80n (32 mg, yield 91%).

[0551] LC / MS mass spectrometry: m / z 982 ([M + H] +). LC / MS retention time: 1.12 minutes (analysis conditions: SQD-FA 50-1). (Step 80-13) 3-[(1S, 2S) -1- [2-[(4S, 6R) -2- (4-fluoro-3,5-dimethylphenyl) -4,6-dimethyl-3-] [3- (1-Methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- ((Oxn-4-yl) indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 80) Compound 80 n (obtained from step 80-12) Acetic acid (0.0019 mL, 0.033 mmol) and 1 M solution of tetrabutylammonium fluoride in THF (0.065 mL, 0.065 mmol) in a solution of 32 mg, 0.033 mmol) in THF (0.326 mL) It was stirred 66 h at Ete 80 ° C.. Acetic acid (0.0019 mL, 0.033 mmol) and 1 M tetrabutylammonium fluoride in THF (0.065 mL, 0.065 mmol) are added and stirred for 23.5 hours, and a solution of 1 M tetrabutylammonium fluoride in THF (0.065 mL, 0.065 mmol) was added, and after stirring for 7 hours, formic acid was added. After concentration, it was diluted with DMSO and water, and purified by reverse phase column chromatography (acetonitrile / water, 0.1% formic acid) to synthesize the title compound 80 (18 mg, yield 65%).

[0552] LC / MS mass spectrometry: m / z 851 ([M + H] +). LC / MS retention time: 1.42 minutes (analytical conditions: SMD-TFA 05-1). Moreover, similarly to Examples 1 to 80, Example compounds 101 to 159 shown in the following Table 2-7 were obtained.

[0553]

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[0571]

[0572] <Example 160> Preparation of monosodium salt hydrate crystal of compound 1 3-[(1S, 2S) -1- [2-[2- (3,5-dimethylphenyl) -3 obtained in Example 1] -[3- (1-Methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] -5- (2-Ethyl-3-methylpyridin-4-yl) indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Compound 1, 1005.5 mg Acetonitrile (3.02 mL) was added to) and dissolved at room temperature. To this solution were added 5 M aqueous sodium hydroxide solution (0.495 mL) and seed crystals of Compound 1 sodium hydrate, and the mixture was stirred at room temperature for 2 hours. Further, after adding tert-butyl methyl ether (3.02 mL) and stirring at room temperature for 1 hour, tert-butyl methyl ether (9.05 mL) is added,

and stirring is carried out at room temperature for 2 hours. Crystals (1007.0 mg) were obtained as powdery crystals (Sample 160a). The seed crystals were obtained by the following method.

[0573] Compound 1 (26.9 mg) was added with DMSO (0.244 mL) and 2 M aqueous solution of sodium hydroxide (0.032 mL). The lysate (0.030 mL) was lyophilized at -20.degree. C. for 2 days. Acetonitrile (0.015 mL) is added to the obtained lyophilizate, and after shaking and stirring at room temperature for 2 days, tert-butyl methyl ether (0.015 mL) is added, and shaking is performed at room temperature for 12 days. Sodium salt hydrate crystals of Compound 1 were obtained as powdery crystals (Sample 160b).

[0574] <Example 161> Crystal Preparation of Example Compound 66 3-[(1S, 2S) -1- [5-[(4S) -2,2-dimethylan-4-yl] -2-[(4S) -2- (4-fluoro-3,5-dimethylphenyl) -4-methyl-3- [3- (1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -6,7- Dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one (Example Compound 66 (400.3 mg) was suspended in ethanol (8.00 mL), seed crystals of Example Compound 66 were added, and the mixture was stirred at 70 ° C. for 5 minutes. The suspension was stirred at 50 ° C. for 1 hour, and then stirred at room temperature for 17 hours to obtain crystals of Example Compound 66 (381.1 mg) as powdery crystals (Sample 161a). The seed crystals were obtained by the following method.

[0575] Example Compound 66 (31.8 mg) was suspended in ethanol (0.636 mL) and stirred at 80.degree. The suspension was stirred at 40 ° C. for 1 hour, and then stirred at room temperature for 22 hours to obtain crystals of Example Compound 66 (24.2 mg) as powdery crystals (Sample 161b).

[0576] Example 162 Preparation of 1/2 Calcium Salt Hydrate Crystal of Example Compound 67 3-[(1S, 2S) -1- [5-[(4S) -2,2-dimethylan -4-yl] -2-[(4S) -2- (4-Fluoro-3,5-dimethylphenyl) -3- [3- (4-fluoro-1-methylindazol-5-yl) -2-oxoimidazole-1 -Yl] -4-methyl-6,7-dihydro-4H-pyrazolo [4,3-c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2, Ethanol (5.60 mL) and 2 M aqueous solution of sodium hydroxide (0.75 mL) were added to 4-oxadiazol-5-one (Example compound 67, 1120 mg), and dissolved at room temperature. To this solution were added 1.26 M calcium acetate aqueous solution (0.68 mL), a seed crystal of calcium hydrate of Example Compound 67, and water (0.68 mL), and the mixture was stirred at room temperature for 3 hours. Further, water (1.2 mL) was added, and after stirring for 1 hour at room temperature, water (2.3 mL) was added, and calcium salt hydrate crystals of Example Compound 67 (973.0 mg) by stirring for 1 hour at room temperature Were obtained as powdery crystals (Sample 162a). The seed crystals were obtained by the following method.

[0577] Example Compound 67 (69.0 mg) was dissolved in DMSO (0.229 mL) and 1.06 M calcium methoxyethoxide (0.147 mL) was added. The lysate (0.015 mL) was lyophilized at -20.degree. C. for 2 days. A water-acetonitrile mixed solution (3: 1, 0.015 mL) is added to the obtained

lyophilizate, and calcium salt hydrate crystals of Example Compound 67 are converted to powdery crystals by shaking at room temperature for 7 days. Sample (Sample 162b).

[0578] Example 163 Powder X-Ray Diffraction Measurement The sodium salt hydrate crystals of Compound 1 (Samples 160a and 160b) obtained in Example 160, the crystals of Example Compound 66 obtained in Example 161 (Samples 161a and 161b) The calcium salt hydrate crystals (Samples 162a and 162b) of Example Compound 67 obtained in Example 162 were subjected to powder X-ray diffraction measurement by the following measurement methods. The results are shown in FIGS.

[0579] Measuring apparatus: D8 Discover with GADDS CS diffractometer (made by Bruker AXS) vs. cathode: Cu tube voltage: 40 kV tube current: 40 mA scanning range: 5 to 25.3 ° sampling width: 0.02 ° <Example 164> thermal weight Measurement / differential thermal analysis Sodium salt hydrate crystal of Compound 1 (Sample 160a) and calcium salt hydrate crystal of Example Compound 67 (Sample 162a) were subjected to thermogravimetric / differential thermal analysis by the following measurement method. . The results are shown in FIG. 7 and FIG. Sample 160a was dehydrated to about 110 ° C., and did not show a clear melting point. In addition, sample 162a was dehydrated to around 240 ° C. and did not show a clear melting point.

[0580] Measuring device: EXSTAR TG / DTA 6200 R (Seiko Instruments (current company name: Hitachi High-Tech Science) product) measurement range: 30-350 ° C. temperature rising rate: 10 ° C./ minute atmosphere: nitrogen <Example 165> Karl Fischer moisture measuring compound 1 The percentage of water contained in sodium salt hydrate crystals (Sample 160a) and calcium salt hydrate crystals of Example Compound 67 (Sample 162a) was measured with a coulometric Karl Fischer moisture meter (756 KF Coulomer manufactured by Metrome). The results were 7.4% for sample 160a and 6.2% for sample 162a.

[0581] From the results of Example 164 and Example 165, it was confirmed that the water contained in the sodium salt hydrate crystal of Compound 1 and the calcium salt hydrate of Example Compound 67 was mainly water of crystallization.

[0582] <Test Example 1> In vitro cAMP signal activation measurement of a compound in human GLP1R (peptide) Human GLP-1 (7-37) is purchased from Peptide Institute, dissolved in phosphate buffered saline to 200 μM, It stored at 80 degreeC freezer.

[0583] (Cell culture) Human GLP1R stable expression cell line (hGLP1R-HEK293) was used for experiment. Cells were prepared in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (Sigma-Aldrich), 100 units / mL penicillin G and 100 μg / mL

streptomycin sulfate (Gibco), 500 μg / mL geneticin (Gibco). The cells were cultured at 37 ° C. in a humidified atmosphere containing% CO 2.

[0584] (CAMP assay) hGLP1R-HEK293 cells were seeded at 2.0 × 10 4 cells / well in a 96-well plate and cultured overnight. The medium for cell culture was replaced with 50 μL of medium A (DMEM, 20 mM HEPES, 0.05% BSA, 0.5 mM 3-isobutyl-1-methylxanthine) and incubated for 30 minutes at 37 ° C. the next day. Subsequently, 50 μL of medium B (DMEM, 20 mM HEPES, 0.05% BSA, 0.5 mM 3-isobutyl-1-methylxanthine) containing GLP-1 or a compound was added and further incubated at 37 ° C. for 30 minutes. Thereafter, 100 μL of Assaylysis buffer (Applied Bioscience) was added and incubated at 37 ° C. for 30 minutes. cAMP concentrations were quantified using the cAMP HiRange kit (Cisbio Bioassays).

[0585] (Calculation of EC50) The cAMP concentration in each well was converted to the reaction rate (%), with the cAMP concentration as 100% when human GLP-1 (7-37) was allowed to act at a concentration of 1 nM. Dose response curves for each example compound were generated using 4-parameter logistic regression analysis with XLfit (ver 5.4.0.8), and the 50% effect concentration (EC50) was calculated. The results are shown in Table 3.

[0586]

[0587] <Test Example 2> Insulin Secretion Promoting Action and Hypoglycemic Action Under anesthesia with a male cynomolgus monkey, Example Compound 67 solution (solvent: PEG 400 (10 vol%): propylene glycol (10 vol%): 100 mM Glycine-NaOH buffer solution, A pH of 9.0 (80 vol%) was continuously administered intravenously for 40 minutes to achieve a steady state plasma drug concentration of 0.94, 1.6, or 4.8 nmol / L. A control drug, exenatide solution (solvent: Tween 0.05% / PBS (-)), was similarly administered to bring the drug concentration in plasma to a steady state of 9.2 or 23.9 pmol / L. The solvent of the Example Compound 67 solution was administered to the solvent group. Next, a 50% glucose solution was intravenously administered at a glucose level of 0.5 g / kg, blood was collected at intervals of 5 minutes or 10 minutes, and plasma insulin concentration and glucose concentration were measured. The area under the curve was calculated from the time transition after drug administration time of each parameter, and insulin secretion promoting action and hypoglycemic action were evaluated.

[0588] In the Example compound 67 administration group, a drug concentration-dependent increase in area under the insulin curve (FIG. 9) and a decrease in area under the plasma glucose curve were observed at steady-state plasma concentration of 0.94 to 4.8 nmol / L. Figure 10). A similar increase in the area under the insulin curve (Fig. 9) and a decrease in the area under the plasma

glucose curve were also observed at steady-state plasma concentrations of 9.2 to 23.9 pmol / L after continuous intravenous administration of the control drug sexenatide It was done (Figure 10).

[0589] In addition, 9.2 pmol / L (38.5 pg / mL) of exenatide is the therapeutic concentration range (50-350 pg / mL) of exenatide concentration in human diabetic patients (Pharmaceutical interview form, byetta subcutaneous injection 5μg pen 300, byetta subcutaneous injection 10μg It was a value close to the lower limit value of Pen 300, September 2016 (revised 9th edition). From the above, Example Compound 67 was shown to exhibit an insulin secretion promoting action and a hypoglycemic action equivalent to exenatide at a plasma concentration of 1.6 nmol / L or more.

[0590] Test Example 3 Feeding Inhibitory Action The compound Example 67 was orally administered to male cynomolgus monkeys for 5 consecutive days, and the influence on the food intake for 90 minutes from 3 hours after each day was examined. In addition, exenatide, which is a control drug, was administered subcutaneously for 5 consecutive days, and the influence on food intake from 30 minutes to 90 minutes after administration was examined. As the solvent group, solvents for oral administration of Example Compound 67 (DMSO (10 vol%): Cremophor EL (10 vol%): PEG 400 (15 vol%): 100 mM Glycine-NaOH buffer pH 10 (65 vol%), 1 mL / kg) Both solvents for subcutaneous administration of exenatide (0.05 w / v% Tween / PBS (-), 0.1 mL / kg) were administered. In combination with this, the Example Compound 67 administration group (administration drug concentration, 0.05 or 0.1 mg / mL), a solvent for subcutaneous administration, exenatide administration group (administration drug concentration, 3 or 6 μg / mL) For oral administration, a solvent for oral administration was additionally administered.

[0591] Example Compound 67 dose-dependently suppressed food intake (FIG. 11A). The degree of inhibition was nearly equivalent to the control drug exenatide (FIG. 11B). The plasma drug concentration (mean value ± standard error) immediately after food intake measurement in each group is 8.0 ± 1.0 nM (0.05 mg / kg group) and 16.3 ± 2 in the Example Compound 67 administration group .3 nM (0.1 mg / kg group), 91 ± 8.5 pM (0.3 μg / kg group) and 199 ± 13.1 pM (0.6 μg / kg group) in the exenatide administration group.

[0592] Test Example 4 Pharmacokinetics of the Compound Example Suspension of calcium salt hydrate crystal of Example Compound 67 (Sample 162a) obtained in Example 162 (dose: 0.05, 0.15, 0.45 and After oral administration (gavage with a gastric catheter) of 1.35 mg / kg) to male cynomolgus monkeys (n = 2 for each dose), blood was collected from the vein over time to separate plasma. The drug concentration in plasma was quantified by liquid chromatography tandem mass spectrometry. The lower limit of quantification was 0.3 ng / mL. Changes in plasma drug concentration are shown in Figure 12; maximum plasma drug concentration arrival time (Tmax), maximum plasma drug concentration (Cmax) and area under the plasma drug

concentration-time curve (AUC0-24h) up to 24 hours after administration are shown in Table 4 Shown in.

[0593] Plasma drug concentrations after oral administration decreased with a similar transition pattern after reaching Cmax at 2 hours after administration at all doses. The increase in plasma drug exposure at doses of 0.05, 0.15, 0.45 and 1.35 mg / kg (dose ratio: 1: 3: 9: 27) was approximately proportional to the dose increase (Cmax ratio: 1. 0: 4.3: 6.7: 31, AUC 0-24 h ratio: 1.0: 5.7: 8.8: 44). The substance was shown to be absorbed in the digestive tract in a dose-dependent manner and to disappear.

[0594]

Formula (I): [wherein, X represents -N = or -CRa =; Ra is selected from a hydrogen atom, a halogen atom, and a C1-6 alkyl; Y represents -C (= O)- R is a hydrogen atom or C1-6 alkyl; Q1 is a C6-10 aryl or a 5- to 10-membered heteroaryl; Wherein C 6-10 aryl and 5- to 10-membered heteroaryl are halogen atoms, C 1-6 alkyl (wherein C 1-6 alkyl may be substituted with one or more halogen atoms), and C 1-6 Optionally substituted with 1 to 5 substituents independently selected from alkoxy; Q 2 represents 3 to 12 membered heterocyclyl or 5 to 10 membered heteroaryl, wherein 3 to 12 membered Heterocyclyl and The 5- to 10-membered heteroaryl is independently from a halogen atom, C1-6 alkyl (wherein C1-6 alkyl may be substituted with one or more halogen atoms), C1-6 alkoxy, and -NRQaRQb And the two C1-6 alkyls are taken together with the carbon atom to which they are attached to form a C3-8 carbocyclic ring. RQa and RQb are independently selected from hydrogen atom, C1-6 alkyl and (C1-6 alkyl) carbonyl; R1, R2 and R3 are each independently hydrogen atom and C1-6 alkyl (Wherein C 1-6 alkyl may be substituted with one or more substituents independently selected from halogen atom, C 1-6 alkoxy, and hydroxy) R4, R5 and R6 are each independently selected from hydrogen atom, halogen atom and C1-6 alkyl; R7 and R8 independently represent hydrogen atom or C1-6 alkyl, Wherein C 1-6 alkyl may be substituted with one or more substituents independently selected from halogen atoms and C 3-15 cycloalkyl, or R 7 and R 8 together with the carbon atom to which they are attached And form a C 3-15 cycloalkane ring, wherein the C 3-15 cycloalkane ring formed by R 7 and R 8 together is substituted with 1 to 3 C 1-6 alkyl And C1-6 alkyl is a halogen atom, hydroxy, -NR7aR7b, C1-6 alkoxy, and 3- to 12-membered heterocyclyl. And R7a and R7b are independently selected from a hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl; n1 is optionally substituted with one or more substituents independently selected from , N represents an integer of 0 to 5; R9 represents a group represented by the formula (IIa), (IIb), (IIc), (IId): -CO2R9f, and -C (= O); R9a, R9b, R9c, R9d, and R9g are each independently a hydrogen atom, C1-6 alkyl (wherein C1-6 alkyl is a halogen atom and C1-6 alkoxy; And R 9 e is a hydrogen atom, or one or more halo, optionally selected from one or more substituents independently selected from R9f represents a hydrogen atom or a C1-6 alkyl, R9h represents a hydrogen atom, a C1-6 alkyl, (C1-6 alkyl) carbonyl, cyano, Or -S (= O) n3-R9i; n3

represents an integer of 0 to 2; R9i represents C1-6 alkyl; Z1 represents a group represented by the formula (IIIa), (IIIb), (IIIc), (IIId), and (IIIe): selected from the group represented by: Rza is selected from a hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl; Rzb and Rzc are independently hydrogen Atom or C1-6 alkyl, n4 represents an integer of 1 to 3, n5 and n6 each independently represent an integer of 0 to 10 (* represents a binding site to a pyrazolopyridine skeleton , ** each represent a binding site to Z 2); Z 2 is C 1-6 alkyl, C 3-15 cycloalkyl, 3-12 membered heterocyclyl, C 6-10 aryl, and 5-10 membered heteroaryl And C3-15 cycloalkyl, 3-12 membered heterocyclyl, C6-10 aryl, and 5-10 membered heteroaryl are selected from the group A: a group A) oxo, b) a halogen atom, c) cyano, d) -NRzdRze; wherein Rzd and Rze are each independently selected from hydrogen atom, C1-6 alkyl and (C1-6 alkyl) carbonyl, wherein C1-6 alkyl is hydroxy, E) -C (= O) -NR, which may be substituted with a halogen atom, and one or more substituents independently selected from C1-6 alkoxy; wherein Rzf and Rzg are each independently selected from hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl, wherein C1-6 alkyl is hydroxy, halogen atom, and C1- F) -S (= O) n7-Rzh, which may be substituted with one or more substituents independently selected from 6 alkoxy; wherein n7 represents an integer of 0 to 2 and Rzh is A hydrogen atom or C1-6 alkyl, g) C1-6 alkyl; wherein C1-6 alkyl is independently from a halogen atom, hydroxy, -NRziRzj, C1-6 alkoxy, and 3- to 12-membered heterocyclyl It may be substituted by one or more substituents selected, wherein Rzi and Rzj independently represent a hydrogen atom or C1-6 alkyl, -12 membered heterocyclyl is optionally substituted with one or more substituents independently selected from hydroxy, C1-6 alkyl, and 3-12 membered heterocyclyl; h) C1-6 alkoxy; C1-6 alkoxy is optionally substituted by one or more substituents independently selected from hydroxy, halogen atom, and C1-6 alkoxy, i) 3- to 12-membered heterocyclyl; Membered heterocyclyl is optionally substituted by one or more substituents independently selected from C1-6 alkyl and (C1-6 alkyl) carbonyl; j) C6-10 aryl; wherein C6-10 aryl Is optionally substituted with one or more (C.sub.1-6 alkyl) carbonyl, and k) a 5- to 10-membered heteroaryl; The aryl may be substituted with one or more substituents independently selected from C1-6 alkyl, C1-6 alkoxy, -NRzkRzl, and 3-12 membered heterocyclyl, wherein Rzk and Rzl are , Independently selected from hydrogen atom, C1-6 alkyl, and (C1-6 alkyl) carbonyl; 3- to 12-membered heterocyclyl is independently selected from C1-6 alkyl and (C1-6 alkyl) carbonyl Or a substituent thereof, or a salt thereof, or any one of them, which may be substituted by one or more substituents, or may be substituted by 1 to 5 substituents independently selected from Pharmaceutical composition containing the solvate of <1>.

The medicament according to claim 1, wherein Q1 is phenyl or pyridyl, wherein phenyl and pyridyl are substituted with a halogen atom and 1 to 4 substituents independently selected from C1-6 alkyl. Composition.

R7 and R8 are both hydrogen atoms; R7 and R8 are both C1-6 alkyl; R7 is a hydrogen atom and R8 is C1-6 alkyl; or the carbon to which R7 and R8 are attached Taken together with the atoms to form a C3-8 cycloalkane ring, wherein the C3-8 cycloalkane ring formed by R7 and R8 together is 1-2 C1-6 alkyl Optionally substituted, wherein C 1-6 alkyl is optionally substituted with one or more

substituents independently selected from hydroxy, C 1-6 alkoxy, and 3- to 12-membered heterocyclyl The pharmaceutical composition according to item 1 or 2.

Z2 is selected from C1-6 alkyl, C3-15 cycloalkyl, 3-12 membered heterocyclyl, C6-10 aryl, and 5-10 membered heteroaryl, wherein C3-15 cycloalkyl, 3-12 membered Heterocyclyl, C6-10 aryl, and 5- to 10-membered heteroaryl are group B: group B: a) oxo, b) halogen atom, c) -NRzd1 Rze1; wherein Rzd1 and Rze1 are independently hydrogen atoms , C1-6 alkyl, and (C1-6 alkyl) carbonyl, wherein C1-6 alkyl is optionally substituted with one or more C1-6 alkoxy, d) -S (= O) n7-Rzh1; wherein n7 represents an integer of 0 to 2 and Rzh1 represents C1-6 alkyl; e) C1-6 alkyl; wherein C1-6 The alkyl may be optionally substituted by one or more substituents independently selected from a halogen atom, hydroxy, -NRziRzj, C1-6 alkoxy, and 3-12 membered heterocyclyl, wherein Rzi and Rzj are And independently represent a hydrogen atom or C.sub.1-6 alkyl, and the 3-12 membered heterocyclyl is substituted with one or more substituents independently selected from hydroxy, C.sub.1-6 alkyl, and 3-12 membered heterocyclyl. Optionally substituted, f) C1-6 alkoxy; wherein C1-6 alkoxy is optionally substituted with one or more hydroxy groups g) 3-12 membered heterocyclyl; wherein here 3-12 membered heterocyclyl Are optionally substituted with one or more (C.sub.1-6 alkyl) carbonyl, and h) 5- to 10-membered heteroaryl; The 10-membered heteroaryl may be substituted by one or more substituents independently selected from C1-6 alkyl, and -NRzk1Rzl1, wherein Rzk1 and Rzl1 independently represent a hydrogen atom and C1. The pharmaceutical composition according to any one of claims 1 to 3, which is optionally substituted with 1 to 4 substituents independently selected from -6 alkyl.

The pharmaceutical composition according to any one of claims 1 to 4, wherein Y is -C (= O)-.

The pharmaceutical composition according to any one of claims 1 to 5, wherein R1 is a hydrogen atom.

The pharmaceutical composition according to any one of claims 1 to 6, wherein n1 and n2 are both zero.

R 9 is a group represented by formula (IIb): R 9 b is a hydrogen atom, C 1-6 alkyl (wherein C 1-6 alkyl is independently selected from a halogen atom and C 1-6 alkoxy) The pharmaceutical composition according to any one of claims 1 to 7, which is selected from the above substituents (which may be substituted) and (C1-6 alkyl) carbonyl.

The pharmaceutical composition according to any one of claims 1 to 8, wherein X is -N =, -CH = or -CF =.

The pharmaceutical composition according to any one of claims 1 to 9, wherein Z1 is represented by the formula (IIIa): (* indicates a binding site to a pyrazolopyridine skeleton, ** indicates a Z2 with Z2 The binding sites are each represented).

3-[(1S, 2S) -1- [5-[(4S) -2,2-dimethyl- oxane-4-yl] -2-[(4S) -2- (4-fluoro-3,5-) Dimethylphenyl) -3- [3- (4-fluoro-1-methylindazol-5-yl) -2-oxoimidazol-1-yl] -4-methyl-6,7-dihydro-4H-pyrazolo [4 ,. The compound of the present invention contains 3-c] pyridine-5-carbonyl] indol-1-yl] -2-methylcyclopropyl] -4H-1,2,4-oxadiazol-5-one, or a salt thereof. The pharmaceutical composition as described in any one of -10.

The pharmaceutical composition according to any one of claims 1 to 11, which contains the compound represented by the formula (I) or a salt thereof as a hydrate.

Non-insulin dependent diabetes (type 2 diabetes), hyperglycemia, glucose intolerance, insulin dependent diabetes (type 1 diabetes), diabetic complications, obesity, hypertension, dyslipidemia, arteriosclerosis, coronary The pharmaceutical composition according to any one of claims 1 to 12 for use in the prevention or treatment of arterial heart disease, cerebral infarction, non-alcoholic steatohepatitis, Parkinson's disease or dementia.

Pharmaceutical composition according to claim 13, for use in the prevention or treatment of non-insulin dependent diabetes mellitus (type 2 diabetes) or obesity.