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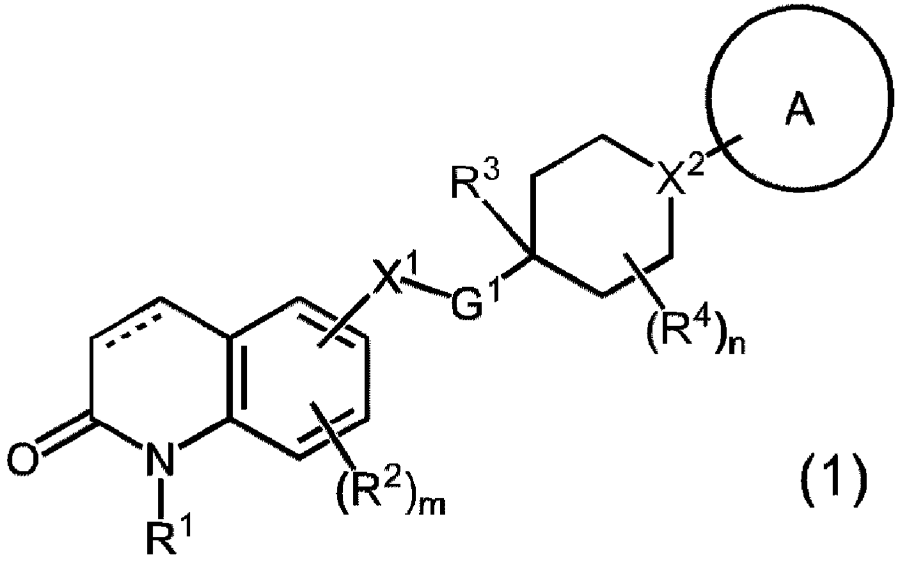
(72) Inventeurs/Inventors:
SHIMIZU, HIROSHI, JP;
KAWANO, YOSHIKAZU, JP;
ISHIKAWA, SHUNPEI, JP;
UEMATSU, YUKITAKA, JP;
SHINOHARA, TOSHIO, JP;
ITOTANI, MOTOHIRO, JP;
...

(73) Propriétaire/Owner:
OTSUKA PHARMACEUTICAL CO., LTD., JP

(74) Agent: SMART & BIGGAR LP

(54) Titre : DERIVES DE DIHYDRO- OU TETRAHYDROQUINOLIN-2-ONE ET UTILISATION DANS LE TRAITEMENT DE LA TUBERCULOSE

(54) Title: DIHYDRO- OR TETRAHYDROQUINOLIN-2-0NE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF TUBERCULOSIS



(1)

(57) Abrégé/Abstract:

It is an object of the present invention to provide a compound having an excellent antibacterial activity against tuberculosis bacteria, multidrug-resistant tuberculosis bacteria and/or non-tuberculous mycobacteria. Disclosed is a compound of the general formula

(72) **Inventeurs(suite)/Inventors(continued)**: HARAGUCHI, YOSHIKAZU, JP; TAKEMURA, ISAO, JP; KANESHIGE, ATSUNORI, JP; NAKAI, YUYA, JP; HARIGUCHI, NORIMITSU, JP; HAYASHI, YOHEI, JP; MATSUMOTO, MAKOTO, JP

(57) **Abrégé(suite)/Abstract(continued)**:

(1): wherein each symbol is defined as described in the attached specification, or a salt thereof.

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(71) Applicant: **OTSUKA PHARMACEUTICAL CO., LTD.** [JP/JP]; 2-9, Kanda Tsukasa-machi, Chiyoda-ku, Tokyo, 1018535 (JP).

(72) Inventors: **SHIMIZU, Hiroshi**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **KAWANO, Yoshikazu**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **ISHIKAWA, Shunpei**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **UEMATSU, Yukitaka**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **SHINOHARA, Toshio**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **ITOTANI, Motohiro**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **HARAGUCHI, Yoshikazu**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **TAKEMURA, Isao**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **KANESHIGE, Atsunori**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **NAKAI, Yuya**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **HARIGUCHI, Norimitsu**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **HAYASHI, Yohei**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP). **MATSUMOTO, Makoto**; c/o OTSUKA PHARMACEUTICAL CO., LTD., 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka, 5400021 (JP).

(74) Agents: **SAMEJIMA, Mutsumi** et al.; AOYAMA & PARTNERS, Umeda Hankyu Bldg. Office Tower, 8-1, Kakuda-cho, Kita-ku, Osaka-shi, Osaka, 5300017 (JP).

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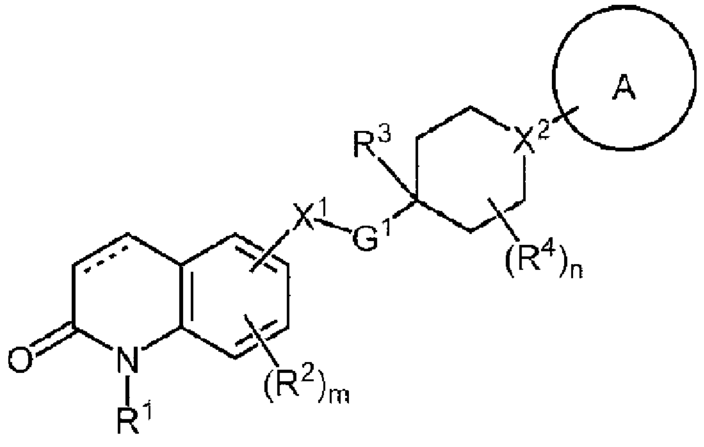
[Continued on next page]

(54) Title: HETEROBICYCLIC COMPOUNDS AND THEIR USE FOR THE TREATMENT OF TUBERCULOSIS



(1)

(57) **Abstract**: It is an object of the present invention to provide a compound having an excellent antibacterial activity against tuberculosis bacteria, multidrug-resistant tuberculosis bacteria and/or non-tuberculous mycobacteria. Disclosed is a compound of the general formula (1): wherein each symbol is defined as described in the attached specification, or a salt thereof.

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 512

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THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 512

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

[DESCRIPTION]

[Title of Invention]

DIHYDRO- OR TETRAHYDROQUINOLIN-2-ONE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF TUBERCULOSIS

[Technical Field]

[0001]

The present invention relates to a fused heterocyclic compound.

[Background Art]

[0002]

Human tuberculosis bacteria (*Mycobacterium tuberculosis*) is widely known among mycobacteria, with which third part of human beings are said to be infected. *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium caprae*, *Mycobacterium pinnipedii*, and *Mycobacterium microti* are known to belong to the tuberculosis bacteria group like human tuberculosis bacteria, and are known as mycobacteria having pathogenicity against human.

[0003]

Multidrug chemotherapy for 6 months has been recommended as a treatment for these tuberculosis bacteria. A typical therapy comprises a treatment with 4 agents of rifampicin, isoniazid, pyrazinamide, and ethambutol (or streptomycin) for the first 2 months; and a treatment with 2 agents of rifampicin and isoniazid for the remaining 4 months.

[0004]

It has been pointed out however that the medication compliance in the treatment for tuberculosis is poor due to such long-term treatment and adverse effects of the used drugs often cause the treatment to discontinue.

[0005]

The adverse effects of these drugs have been reported (Nonpatent Literatures 1 and 2), for example, rifampicin has hepatic disorder, flu syndrome, drug allergy, and contraindication to combination use with other drugs caused by P450-related enzymes; isoniazid has peripheral neuropathy and serious hepatic disorder induced with a combination use with rifampicin; ethambutol has visual loss caused by optic nerve disorder; streptomycin has hearing loss caused by eighth cranial nerve involvement; pyrazinamide has hepatic disorder, gouty attack associated with the uric acid level, and vomiting. Amongst the adverse effects of the above 5 agents used as a first-line drug, in particular, hepatotoxicity commonly-caused by rifampicin, isoniazid, and pyrazinamide is known as the most frequent adverse effect.

[0006]

It has been in fact reported that the cases where the standard chemotherapy cannot be carried out due to the adverse effects account for 70% of the cases where the drug administration is discontinued (about 23%, 52 cases) of the total (the total of 228 inpatient cases surveyed) (Nonpatent Literature 3).

[0007]

Tuberculosis bacteria resistant to antitubercular agents, multidrug-resistant tuberculosis bacteria, for example have been recently increasing, which has made the treatment of tuberculosis more difficult.

[0008]

The World Health Organization (WHO) has reported that among those who have been infected with multidrug-resistant tuberculosis (MDR-TB) resistant to potent rifampicin and isoniazid, 450,000 people have newly developed and 170,000 people have died per year, and multidrug-resistant tuberculosis patients are currently estimated as 1,500,000 in the world. An extensively-drug-resistant tuberculosis (XDR-TB) which has been resistant to many drugs has been identified, which has become a threat to public health in the world (Nonpatent Literature 4).

[0009]

Third part of those who have been infected with HIV in the world has been suspected of co-infection with tuberculosis even though not progressing to active tuberculosis (Nonpatent Literature 5). Co-infection of HIV and tuberculosis is fatal, in which one disease can accelerate the progression of the other disease and tuberculosis can easily progress to active tuberculosis. In 2012, about 320,000 people died of tuberculosis associated with HIV, which means that about 25% of the death of HIV infected people were caused by tuberculosis. It has been also reported that patients infected with both HIV and tuberculosis can develop tuberculosis in 20 to 37 times higher risk than usual (Nonpatent Literature 6).

[0010]

The American Thoracic Society and Centers for Disease Control and Prevention have recently reported the concept that carriage state itself of tuberculosis bacteria is a potential disease even though not developing to tuberculosis, and the usefulness of active treatment has been established for patients with a higher risk of developing to the disease.

[0011]

In view of the current circumstances, a desired profile for antitubercular agents includes (1) those effective for multidrug-resistant tuberculosis bacteria, (2) those which enable a short-term chemotherapy, (3) those with less adverse effects, (4) those effective for latent tuberculosis infection (LTBI).

[0012]

Mycobacterium avium and *Mycobacterium intracellulare*, which are responsible bacteria for recently increasing MAC symptom (*Mycobacterium avium-intracellulare* complex symptom), as well as other non-tuberculous mycobacteria such as *Mycobacterium kansasii*, *Mycobacterium marinum*, *Mycobacterium simiae*, *Mycobacterium scrofulaceum*, *Mycobacterium szulgai*, *Mycobacterium xenopi*, *Mycobacterium malmoense*, *Mycobacterium haemophilum*, *Mycobacterium ulcerans*, *Mycobacterium shimoidei*, *Mycobacterium fortuitum*, *Mycobacterium chelonae*, *Mycobacterium smegmatis*, and *Mycobacterium aurum* have been known as bacteria having pathogenicity in human.

[0013]

A typical chemotherapy of lung MAC symptom is polypharmacy based on three drugs of rifampicin, ethambutol, and clarithromycin, and streptomycin or kanamycin is, if needed, used in combination. Another treatment for non-tuberculous mycobacteria symptom currently includes combination use with an antitubercular agent such as rifampicin, isoniazid, ethambutol, streptomycin, kanamycin, a therapeutic agent for common bacterial infection such as a newquinolone agent, a macrolide antibacterial agent, an aminoglycoside antibacterial agent, and a tetracycline antibacterial agent.

[0014]

It has been reported however that the treatment for non-tuberculous mycobacteria needs a longer-term medication than that in common bacterial infection, the treatment tends to become refractory, and some have resulted in death. To solve the circumstances, a development of more potent drugs has been desired.

[0015]

For example, Patent Literature 1 discloses that 6-nitro-1,2,3,4-tetrahydro[2,1-b]imidazopyrane compounds have a bactericidal activity against tuberculosis bacteria (H37Rv strain) and multidrug-resistant tuberculosis bacteria *in vitro* and a therapeutic effect in oral administration for a tuberculosis-infected animal model, and thus they are useful as an antitubercular agent.

[0016]

Patent Literatures 2 and 3 disclose that 2,3-dihydroimidazo[2,1-b]oxazole compounds have a bactericidal activity against tuberculosis bacteria, multidrug-resistant tuberculosis bacteria, and atypical mycobacteria.

[0017]

Patent Literature 4 discloses that nitroimidazooxazine and nitroimidazooxazole compounds can be used as a medicament against human tuberculosis bacteria (*Mycobacterium tuberculosis*).

[0018]

Patent Literature 5 discloses that 6,7-dihydroimidazo[2,1-b][1,3]oxazine compounds have an excellent bactericidal activity against tuberculosis bacteria and multidrug-resistant tuberculosis bacteria.

[0019]

The compounds disclosed in the above references, however, structurally differ from and are not similar to the compound of the present invention.

[Citation List]

[Patent Literature]

[0020]

[PTL 1] WO 97/01562 (JP-A-11-508270)

[PTL 2] JP-A-2004-149527

[PTL 3] JP-A-2005-320316

[PTL 4] WO 2011/014776

[PTL 5] WO 2012/141338

[Non Patent Literature]

[0021]

[NPL 1] A Clinician's Guide To Tuberculosis, Michael D. Iseman 2000 by Lippincott Williams & Wilkins, printed in the USA, ISBN 0-7817-1749-3

[NPL 2] Kekkaku 2nd edition, Fumiyuki Kuze, Takahide Izumi, Igaku-shoin 1992

[NPL 3] Kekkaku Vol.74: 77-82, 1999

[NPL 4] Global tuberculosis report 2013

[NPL 5] The Internet Journal of Pulmonary Medicine 2008: Volume 10 Number 1

[NPL 6] The Global Plan To Stop TB 2011-2015

[Summary of Invention]

[Technical Problem]

[0022]

It is an object of the present invention to provide compounds having an excellent antibacterial activity against tuberculosis bacteria and multidrug-resistant tuberculosis bacteria. It is another object of the present invention to provide compounds having an excellent antibacterial activity against non-tuberculous mycobacteria.

[Solution to Problem]

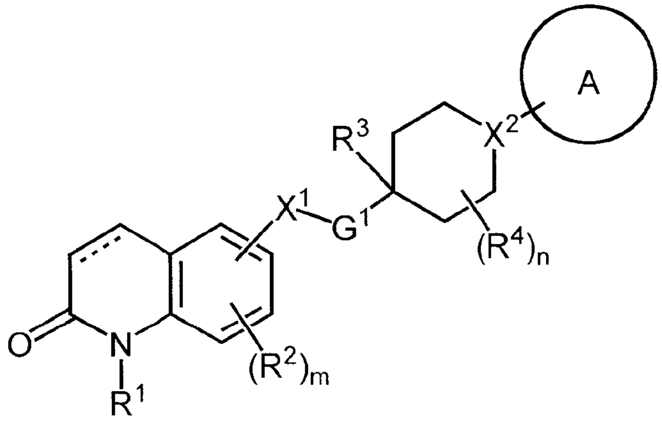
[0023]

The present inventors have achieved syntheses of novel fused heterocyclic compounds having an excellent bactericidal activity against tuberculosis bacteria, multidrug-resistant tuberculosis bacteria, and non-tuberculous mycobacteria as a result of extensive studies to solve the problem. The present invention has been accomplished on the basis of this finding.

[0024]

In one aspect, the present invention includes a compound of the general formula (1):

[Chem. 1]



(1)

or a salt thereof,

wherein R^1 is

(1) hydrogen,

(2) amino which may have one or two of the same or different lower alkyl or

(3) lower alkyl;

R^2 is

(1) halogen,

(2) amino which may have one or two of the same or different lower alkyl,

(3) lower alkyl,

(4) lower alkoxy or

(5) hydroxy;

m is an integer of 0 to 3;

provided that when m is 2 or 3, R^2 may be different from each other;

X^1 is -CH_2-, -O-, -N(R^5)-, -S-, -SO- or -SO_2-;

R^5 is

(1) hydrogen,

(2) lower alkyl or

(3) lower alkanoyl;

G^1 is lower alkylene;

R^3 is

(1) hydrogen,

(2) carboxy,

(3) halogen,

(4) lower alkyl which may have one or more hydroxy,

(5) cyano,

(6) amino which may have one or two substituents independently selected from

  (a) lower alkyl and

  (b) -C(=O)-R^6 or

(7) -O-R^7;

R^6 is

(1) lower alkoxy or

(2) lower alkyl which may have one or two of the same or different amino which may have one or two of the same or different lower alkyl;

R^7 is

(1) hydrogen,

(2) amino,

(3) lower alkanoyl or

(4) lower alkyl;

R^4 is

(1) amino which may have one or two of the same or different lower alkyl,

(2) halogen,

(3) cyano,

(4) lower alkyl,

(5) oxo,

(6) -O-R^8 or

(7) -O-C(=O)-R^9;

R^8 is

(1) hydrogen,

(2) lower alkyl,

(3) -PH(=O)OH or

(4) benzyl which may have one or more of the same or different lower alkoxy;

R^9 is

(1) lower alkyl,

(2) $-G^2$-COOH,

(3) amino which may have one or two of the same or different lower alkyl,

(4) lower alkoxy or

(5) pyrazinyl;

G^2 is lower alkylene;

n is an integer of 0 to 8;

provided that when n is 2 or more, each of R^4, R^8, R^9, and G^2 may be different from each other and may be substituted on the same carbon atom;

X^2 is N or CH;

provided that when X^2 is CH, H of the group may be substituted with R^4 which is defined as above or may be different from the other R^4;

Ring A is

(1) aryl which may have one or more substituents, or

(2) heterocyclyl which may have one or more substituents;

a moiety of formula:

[Chem. 2]

represents a single bond or a double bond; which is referred hereinafter to as Compound (1).

[Advantageous Effects of Invention]

[0025]

Compound (1) in the present invention has specific activities in particular against mycobacteria (such as tuberculosis bacterial genus and non-tuberculous mycobacterial genus), and also has excellent activities against multidrug-resistant tuberculosis bacteria.

[0026]

Compound (1) in the present invention shows not only the activities *in vitro* but also the activites *in vivo* in oral administration because the administered compound is favorably distributed in lung tissues which are the primary organ infected with the mycobacterial infectious disease.

[0027]

Compound (1) in the present invention does not induce diarrhea as seen in known antibacterial agents with a wide spectrum for common bacteria such as gram-positive bacteria and gram-negative bacteria, and thereby may become a medicinal substance which allows for a long-term administration.

[0028]

Compound (1) in the present invention is effective for intracellular parasitic bacteria such as human-origin tuberculosis bacteria which is parasitic in macrophage, and has a stronger bactericidal activity in a low concentration even in a bactericidal test than conventional antitubercular agents. It is thus expected that the relapse rate in tuberculosis will be reduced, which eventually allows for a short-term chemotherapy.

[0029]

Compound (1) in the present invention shows a low inhibitory activity against a drug-metabolizing enzyme, a low possibility for an enzyme induction of CYP3A, and a low concerns about drug interaction. Thus, the compound is expected for a combination use with conventional drugs or HIV drugs.

In addition, Compound (1) has a lower toxicity than conventional drugs, and hence the compound is also expected for long-term use in the treatment for latent tuberculosis.

[Description of Embodiments]

[0030]

The phrases and terms used herein are described in detail as below.

[0031]

Examples of "lower alkyl" include straight or branched chain alkyl groups having 1 to 6 carbon atoms, and in particular include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, and 3-methylpentyl.

[0032]

Examples of "lower alkenyl" include straight or branched chain alkenyl groups having 2 to 6 carbon atoms and 1 to 3 double bonds, and include, for example, vinyl (ethenyl), 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, and 5-hexenyl.

[0033]

Examples of "lower alkynyl" include straight or branched chain alkynyl groups having 2 to 6 carbon atoms and 1 to 3 triple bonds, and include, for example, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, and 5-hexynyl.

[0034]

Examples of "lower alkoxy" include straight or branched chain alkoxy groups having 1 to 6 carbon atoms, and include, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, isohexyloxy, and 3-methylpentyloxy.

[0035]

Examples of "lower alkenyloxy" include straight or branched chain alkenyloxy groups having 2 to 6 carbon atoms and 1 to 3 double bonds, and include, for example, vinyloxy (ethenyloxy), 1-propenyloxy, 2-propenyloxy, 2-methyl-1-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 3-methyl-2-butenyloxy, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 4-methyl-3-pentenyloxy, 1-hexenyloxy, 3-hexenyloxy, and 5-hexenyloxy.

[0036]

Examples of "lower alkynyloxy" include straight or branched chain alkynyloxy groups having 2 to 6 carbon atoms and 1 to 3 triple bonds, and include, for example, ethynyloxy, 1-propynyloxy, 2-propynyloxy, 1-butynyloxy, 2-butynyloxy, 3-butynyloxy, 1-pentynyloxy, 2-pentynyloxy, 3-pentynyloxy, 4-pentynyloxy, 1-hexynyloxy, 2-hexynyloxy, 3-hexynyloxy, 4-hexynyloxy, and 5-hexynyloxy.

[0037]

Examples of "lower alkanoyl" include straight or branched chain alkanoyl groups having 1 to 7 carbon atoms, and include, for example, formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, and hexanoyl.

[0038]

Examples of "lower alkenylcarbonyl" include straight or branched chain alkenylcarbonyl groups having 3 to 7 carbon atoms and 1 to 3 double bonds, and include, for example, vinylcarbonyl (ethenylcarbonyl), 1-propenylcarbonyl, 2-propenylcarbonyl, 2-methyl-1-propenylcarbonyl, 1-butenylcarbonyl, 2-butenylcarbonyl, 3-butenylcarbonyl, 3-methyl-2-butenylcarbonyl, 1-pentenylcarbonyl, 2-pentenylcarbonyl, 3-pentenylcarbonyl, 4-pentenylcarbonyl, 4-methyl-3-pentenylcarbonyl, 1-hexenylcarbonyl, 3-hexenylcarbonyl, and 5-hexenylcarbonyl.

[0039]

Examples of "lower alkynylcarbonyl" include straight or branched chain alkynylcarbonyl groups having 3 to 7 carbon atoms and 1 to 3 triple bonds, and include, for example, ethynylcarbonyl, 1-propynylcarbonyl, 2-propynylcarbonyl, 1-butynylcarbonyl, 2-butynylcarbonyl, 3-butynylcarbonyl, 1-pentynylcarbonyl, 2-pentynylcarbonyl, 3-pentynylcarbonyl, 4-pentynylcarbonyl, 1-hexynylcarbonyl, 2-hexynylcarbonyl, 3-hexynylcarbonyl, 4-hexynylcarbonyl, and 5-hexynylcarbonyl.

[0040]

Examples of "lower alkanoyloxy" include straight or branched chain alkanoyloxy groups having 1 to 7 carbon atoms, and include, for example, formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pentanoyloxy, tert-butylcarbonyloxy, and hexanoyloxy.

[0041]

Examples of "lower alkoxycarbonyl" include straight or branched chain alkoxycarbonyl groups having 2 to 7 carbon atoms, and include, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, and hexyloxycarbonyl.

[0042]

Examples of "lower alkylsulfanyl" include straight or branched chain alkylsulfanyl groups having 1 to 6 carbon atoms, and include, for example, methylsulfanyl, ethylsulfanyl, propylsulfanyl, isopropylsulfanyl, butylsulfanyl, tert-butylsulfanyl, pentylsulfanyl, and hexylsulfanyl.

[0043]

Examples of "lower alkylsulfinyl" include straight or branched chain alkylsulfinyl groups having 1 to 6 carbon atoms, and include, for example, methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, tert-butylsulfinyl, pentylsulfinyl, and hexylsulfinyl.

[0044]

Examples of "lower alkylsulfonyl" include straight or branched chain alkylsulfonyl groups having 1 to 6 carbon atoms, and include, for example, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, tert-butylsulfonyl, pentylsulfonyl, and hexylsulfonyl.

[0045]

Examples of "cyclo-lower-alkyl" include cycloalkyl groups having 3 to 6 carbon atoms, and include, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0046]

Examples of "cyclo-lower-alkenyl" include cycloalkenyl groups having 3 to 6 carbon atoms, and include, for example, 2-cyclopentenyl, 3-cyclopentenyl, 2-cyclohexenyl, and 3-cyclohexenyl.

[0047]

Examples of "cyclo-lower-alkoxy" include cycloalkoxy groups having 3 to 6 carbon atoms, and include, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, and cyclohexyloxy.

[0048]

Examples of "cyclo-lower-alkenyloxy" include cycloalkenyloxy groups having 3 to 6 carbon atoms, and include, for example, 2-cyclopentenyloxy, 3-cyclopentenyloxy, 2-cyclohexenyloxy, and 3-cyclohexenyloxy.

[0049]

Examples of "cyclo-lower-alkylcarbonyl" include cycloalkylcarbonyl groups having 4 to 7 carbon atoms, and include, for example, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, and cyclohexylcarbonyl.

[0050]

Examples of "cyclo-lower-alkoxycarbonyl" include cycloalkoxycarbonyl group having 4 to 7 carbon atoms, and include, for example, cyclopropyloxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, and cyclohexyloxycarbonyl.

[0051]

Examples of "aryl" include mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, phenyl, naphthyl, anthryl, and phenanthryl.

[0052]

Examples of "aryloxy" include mono-, bi-, or tri-cyclic aromatic hydrocarbon-oxy groups, and include, for example, phenyloxy, naphthyloxy, anthryloxy, and phenanthryloxy.

[0053]

Examples of "arylcarbonyl" include mono-, bi-, or tri-cyclic aromatic hydrocarbon-carbonyl groups, and include, for example, phenylcarbonyl, naphthylcarbonyl, anthrylcarbonyl, and phenanthrylcarbonyl.

[0054]

Examples of "aryloxycarbonyl" include mono-, bi-, or tri-cyclic aromatic hydrocarbon-oxycarbonyl groups, and include, for example, phenyloxycarbonyl, naphthyloxycarbonyl, anthryloxycarbonyl, and phenanthryloxycarbonyl.

[0055]

Examples of "aralkyl" include straight or branched chain alkyl groups having 1 to 3 carbon atoms which are substituted with mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, benzyl, 1-phenylethyl, 2-phenylethyl, 1-naphthylmethyl, and 2-naphthylmethyl.

[0056]

Examples of "aralkyloxy" include straight or branched chain alkoxy groups having 1 to 3 carbon atoms which are substituted with mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, benzyloxy, 1-phenylethyloxy, 2-phenylethyloxy, 1-naphthylmethyloxy, and 2-naphthylmethyloxy.

[0057]

Examples of "aralkylcarbonyl" include straight or branched chain alkylcarbonyl groups having 2 to 4 carbon atoms which are substituted with mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, benzylcarbonyl, 1-phenylethylcarbonyl, 2-phenylethylcarbonyl, 1-naphthylmethylcarbonyl, and 2-naphthylmethylcarbonyl.

[0058]

Examples of "aralkyloxycarbonyl" include straight or branched chain alkyloxycarbonyl groups having 2 to 4 carbon atoms which are substituted with mono-, bi-, or tri-cyclic aromatic hydrocarbon groups, and include, for example, benzyloxycarbonyl, 1-phenylethyloxycarbonyl, 2-phenylethyloxycarbonyl, 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, and biphenylylmethyloxycarbonyl.

[0059]

Examples of "heterocyclyl" include saturated or unsaturated monocyclic or polycyclic (e.g. bicyclic, tricyclic, spiro-form, or bicyclo-form) heterocyclyl groups comprising at least one (e.g. 1 to 5) heteroatom selected as a ring-constituent atom from oxygen atom, sulfur atom (which may form sulfoxide), and nitrogen atom (which may form amine oxide) besides carbon atoms, and for example include:

(a) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, N-oxide pyridyl, tetrahydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, dihydrotriazinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidyl, pyrazolidinyl, piperazinyl, azepanyl, 1,4-diazepanyl;

(b) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 to 5 nitrogen atoms, for example, decahydroquinolyl, indolyl, dihydroindolyl, isoindolyl, indolizinyl, benzoimidazolyl, dihydrobenzoimidazolyl, quinolyl, dihydroquinolyl, tetrahydroquinolyl, isoquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, carbostyryl, dihydrocarbostyryl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl, dihydrotriazolopyridazinyl, imidazopyridyl, naphthyridinyl, cinnolinyl, quinoxalinyl, quinazolinyl, pyrazolopyridyl, tetrahydropyridoindolyl;

(c) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 or 2 oxygen atoms, for example, furyl, tetrahydropyranyl, tetrahydrofuryl, dioxanyl;

(d) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 to 3 oxygen atoms, for example, benzofuryl, dihydrobenzofuryl, chromanyl, benzodioxanyl, benzodioxolyl;

(e) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl, morpholinyl;

(f) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzooxazolyl, benzooxadiazolyl, benzoisoxazolyl, dihydrobenzooxazinyl, furopyridyl, furopyrrolyl;

(g) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiazolinyl, thiadiazolyl, isothiazolyl, thiazolidinyl;

(h) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, benzothiazolyl, benzothiadiazolyl, thienopyridyl, imidazothiazolyl, dihydroimidazothiazolyl, thienopyrazinyl;

(i) saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic groups comprising 1 sulfur atom, for example, thienyl;

(j) saturated or unsaturated 7- to 12-membered fused heterocyclyl groups comprising 1 to 3 sulfur atoms, for example, benzothienyl;

(k) saturated or unsaturated 7- to 12-membered heterocyclic spiro groups, for example, azaspiroundecanyl; and

(l) saturated or unsaturated 7- to 12-membered bicyclo heterocyclyl groups, for example, azabicyclo-cyclooctanyl.

[0060]

"Heterocyclyloxy" refers to a group of "(heterocyclyl)-O-", and examples of heterocyclyl group include groups as illustrated above in "heterocyclyl".

[0061]

"Heterocyclylcarbonyl" refers to a group of "(heterocyclyl)-CO-", and examples of heterocyclyl group include groups as illustrated above in "heterocyclyl".

[0062]

"Heterocyclyloxycarbonyl" refers to a group of "(heterocyclyl)-O-CO-", and examples of heterocyclyl include groups as illustrated above in "heterocyclyl".

[0063]

Examples of "mono- or di-lower alkylamino" include amino groups which are mono- or di-substituted with straight or branched chain alkyl groups having 1 to 6 carbon atoms, and for example, include mono-lower alkylamino groups such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, and tert-butylamino; di-lower alkylamino groups such as dimethylamino, diethylamino, dipropylamino, dibutylamino, diisobutylamino, di-sec-butylamino, di-tert-butylamino, and N-ethyl-N-methylamino.

[0064]

Examples of "mono- or di-lower alkanoylamino" include amino groups which are mono- or di-substituted with straight or branched chain alkanoyl groups having 1 to 7 carbon atoms, for example, mono-lower alkanoylamino groups such as formylamino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, pentanoylamino, tert-butylcarbonylamino, and hexanoylamino; di-lower alkanoylamino groups such as diformylamino, diacetylamino, dipropionylamino, dibutyrylamino, diisobutyrylamino, dipentanoylamino, di-tert-butylcarbonylamino, and dihexanoylamino.

[0065]

Examples of "tri-lower alkylsilyl" include silyl groups which are tri-substituted with straight or branched chain alkyl groups having 1 to 6 carbon atoms, for example, trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl.

[0066]

Examples of "lower alkylene" include straight or branched chain alkylene groups having 1 to 6 carbon atoms, for example, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_2CH_3)-$, $-C(CH_3)(CH_2CH_3)-$, $-C(CH_2CH_3)_2-$, $-CH(CH_2CH_2CH_3)-$, $-C(CH_3)(CH_2CH_2CH_3)-$, $-C(CH_2CH_3)(CH_2CH_2CH_3)-$, $-CH(CH(CH_3)_2)-$, $-C(CH_3)(CH(CH_3)_2)-$, $-C(CH_2CH_3)(CH(CH_3)_2)-$, $-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_2CH_3)-$, $-CH(CH_2CH_3)-CH_2-$, $-(CH(CH_3))_2-$, $-CH(CH_3)-CH_2-CH_2-$, $-CH_2-CH(CH_3)-CH_2-$, $-CH_2-CH_2-CH(CH_3)-$, $-CH_2-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-CH_2-CH_2-$.

[0067]

Examples of "halogen" include fluorine, chlorine, bromine, and iodine.

[0068]

The phrase "β which may have α" means that β may be substituted with at least one (usually 1 to 10, preferably 1 to 6, more preferably 1 to 3, and 1 or 2 in the case where β is amino or carbamoyl) α, each of β being displaceable at the same or different positions.

[0069]

Examples of "substituent" in the phrase "may have one or more substituents" include groups independently selected from:

(A) halogen,

(B) cyano,

(C) nitro,

(D) hydroxy,

(E) carboxy,

(F) sulfo,

(G) sulfanyl,

(H) lower alkyl which may have one or more substituents selected from groups (Ia) and (Ib),

(I) lower alkenyl which may have one or more substituents selected from groups (Ia) and (Ib),

(J) lower alkynyl which may have one or more substituents selected from groups (Ia) and (Ib),

(K) lower alkoxy which may have one or more substituents selected from groups (Ia) and (Ib),

(L) lower alkenyloxy which may have one or more substituents selected from groups (Ia) and (Ib),

(M) lower alkynyloxy which may have one or more substituents selected from groups (Ia) and (Ib),

(N) lower alkanoyl which may have one or more substituents selected from groups (Ia) and (Ib),

(O) lower alkenylcarbonyl which may have one or more substituents selected from groups (Ia) and (Ib),

(P) lower alkynylcarbonyl which may have one or more substituents selected from groups (Ia) and (Ib),

(Q) lower alkanoyloxy which may have one or more substituents selected from groups (Ia) and (Ib),

(R) lower alkoxycarbonyl which may have one or more substituents selected from groups (Ia) and (Ib),

(S) lower alkylsulfanyl which may have one or more substituents selected from groups (Ia) and (Ib),

(T) lower alkylsulfinyl which may have one or more substituents selected from groups (Ia) and (Ib),

(U) lower alkylsulfonyl which may have one or more substituents selected from groups (Ia) and (Ib),

(V) cyclo-lower-alkyl which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(W) cyclo-lower-alkoxy which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(X) cyclo-lower-alkenyl which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(Y) cyclo-lower-alkenyloxy which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(Z) cyclo-lower-alkylcarbonylwhich may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(AA) cyclo-lower-alkoxycarbonyl group which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(BB) arylwhich may have one or more substituents selected from groups (Ia), (Ib), and (Ic),

(CC) aryloxywhich may have one or more substituents selected from groups (Ia), (Ib), and (Ic),

(DD) arylcarbonyl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic),

(EE) aryloxycarbonyl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic),

(FF) aralkylwhich may have one or more substituents selected from groups (Ia), (Ib), and (Ic),

(GG) aralkyloxy which may have one or more substituents selected from groups (Ia), (Ib), and (Ic), (HH) aralkylcarbonyl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic),

(II) aralkyloxycarbonyl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic),

(JJ) heterocyclyl which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(KK) heterocyclyloxy which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(LL) heterocyclylcarbonylwhich may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(MM) heterocyclyloxycarbonyl which may have one or more substituents selected from groups (Ia), (Ib), (Ic), and oxo,

(NN) aminowhich may have one or more substituents selected from groups (Ia) and (Ic), and

(OO) carbamoyl which may have one or more substituents selected from groups (Ia) and (Ic).

The number of any substituents in Compound (1) is not limited as long as chemically applicable, unless otherwise specified.

[0070]

The "group (Ia)" includes substituents selected from:

(a) lower alkanoyl which may have one or more substituents selected from groups (IIa) and (IIb),

(b) lower alkenylcarbonyl which may have one or more substituents selected from groups (IIa) and (IIb),

(c) lower alkynylcarbonyl which may have one or more substituents selected from groups (IIa) and (IIb),

(d) lower alkoxycarbonyl which may have one or more substituents selected from groups (IIa) and (IIb),

(e) lower alkylsulfanyl which may have one or more substituents selected from groups (IIa) and (IIb),

(f) lower alkylsulfinyl which may have one or more substituents selected from groups (IIa) and (IIb),

(g) lower alkylsulfonyl which may have one or more substituents selected from groups (IIa) and (IIb),

(h) cyclo-lower-alkyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,

(i) cyclo-lower-alkoxy which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,

(j) cyclo-lower-alkenyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,

(k) cyclo-lower-alkylcarbonyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,

(l) cyclo-lower-alkoxycarbonyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,

(m) aryl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),

(n) arylcarbonyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),

(o) aryloxycarbonyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),

(p) aralkyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),

(q) aralkylcarbonyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),

(r) aralkyloxycarbonyl which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),

(s) heterocyclyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,

(t) heterocyclylcarbonyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,

(v) heterocyclyloxycarbonyl which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo, and

(w) carbamoyl which may have one or more substituents selected from groups (IIa) and (IIc).

[0071]

The "group (Ib)" includes substituents selected from:

(a) halogen,

(b) cyano,

(c) nitro,

(d) hydroxy,

(e) carboxy,

(f) sulfo,

(g) sulfanyl,

(h) lower alkoxy which may have one or more substituents selected from groups (IIa) and (IIb),

(i) lower alkenyloxy which may have one or more substituents selected from groups (IIa) and (IIb),

(j) lower alkynyloxy which may have one or more substituents selected from groups (IIa) and (IIb),

(k) lower alkanoyloxy which may have one or more substituents selected from groups (IIa) and (IIb),

(l) cyclo-lower-alkenyloxy which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo,

(m) aryloxy which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),

(n) aralkyloxy which may have one or more substituents selected from groups (IIa), (IIb), and (IIc),

(o) heterocyclyloxy which may have one or more substituents selected from groups (IIa), (IIb), (IIc), and oxo, and

(p) amino which may have one or more substituents selected from groups (IIa) and (IIc).

[0072]

The "group (Ic)" includes substituents selected from:

(a) lower alkyl which may have one or more substituents selected from groups (IIa) and (IIb),

(b) lower alkenyl which may have one or more substituents selected from groups (IIa) and (IIb), and

(c) lower alkynyl which may have one or more substituents selected from groups (IIa) and (IIb).

[0073]

The "group (IIa)" includes substituents selected from lower alkanoyl, lower alkenylcarbonyl, lower alkynylcarbonyl, lower alkoxycarbonyl, lower alkylsulfonyl, cyclo-lower-alkyl, cyclo-lower-alkoxy, cyclo-lower-alkenyl, cyclo-lower-alkylcarbonyl, cyclo-lower-alkoxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, aralkyl, aralkylcarbonyl, aralkyloxycarbonyl, heterocyclyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, mono- or di-lower alkanoylcarbamoyl, and mono- or di-lower alkylcarbamoyl.

[0074]

The "group (IIb)" includes substituents selected from halogen, cyano, nitro, hydroxy, carboxy, sulfo, sulfanyl, amino, lower alkoxy, lower alkenyloxy, lower alkynyloxy, lower alkanoyloxy, lower alkylsulfanyl, lower alkylsulfinyl, cyclo-lower-alkenyloxy, aryloxy, aralkyloxy, heterocyclyloxy, mono- or di-lower alkylamino, and mono- or di-lower alkanoylamino.

[0075]

The "group (IIc)" includes substituents selected from lower alkyl, lower alkenyl, and lower alkynyl.

[0076]

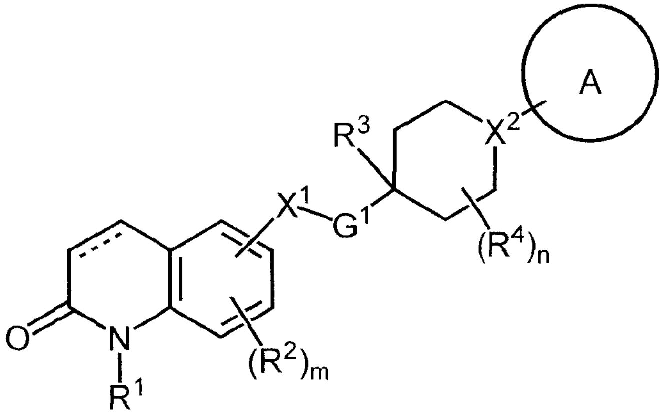
Each of symbols and structures in the general formula (1) is explained in detail as below.

[0077]

In one aspect, the present invention includes the following embodiments:

[1] A compound of the general formula (1):

[Chem. 3]



(1)

or a salt thereof,

wherein R^1 is

(1) hydrogen,

(2) amino which may have one or two of the same or different lower alkyl or

(3) lower alkyl;

R^2 is

(1) halogen,

(2) amino which may have one or two of the same or different lower alkyl,

(3) lower alkyl,

(4) lower alkoxy or

(5) hydroxy;

m is an integer of 0 to 3;

provided that when m is 2 or 3, R^2 may be different from each other;

X^1 is $-CH_2-$, -O-, $-N(R^5)-$, -S-, -SO- or $-SO_2-$;

R^5 is

(1) hydrogen,

(2) lower alkyl or

(3) lower alkanoyl;

G^1 is lower alkylene;

R^3 is

(1) hydrogen,

(2) carboxy,

(3) halogen,

(4) lower alkyl which may have one or more hydroxy,

(5) cyano,

(6) amino which may have one or two substituents independently selected from:

(a) lower alkyl and

(b) -C(=O)-R^6 or

(7) -O-R^7;

R^6 is

(1) lower alkoxy or

(2) lower alkyl which may have one or two of the same or different amino which may have one or two of the same or different lower alkyl;

R^7 is

(1) hydrogen,

(2) amino,

(3) lower alkanoyl or

(4) lower alkyl;

R^4 is

(1) amino which may have one or two of the same or different lower alkyl,

(2) halogen,

(3) cyano,

(4) lower alkyl,

(5) oxo,

(6) -O-R^8 or

(7) -O-C(=O)-R^9;

R^8 is

(1) hydrogen,

(2) lower alkyl,

(3) -PH(=O)OH or

(4) benzyl which may have one or more of the same or different lower alkoxy;

R^9 is

(1) lower alkyl,

(2) -G^2-COOH,

(3) amino which may have one or two of the same or different lower alkyl,

(4) lower alkoxy or

(5) pyrazinyl;

G^2 is lower alkylene;

n is an integer of 0 to 8;

provided that when n is 2 or more, each of R^4, R^8, R^9, and G^2 may be different from each other and may be substituted on the same carbon atom;

X^2 is N or CH;

provided that when X^2 is CH, H of the group may be substituted with R^4 which is defined as above or may be different from the other R^4;

Ring A is

(1) aryl which may have one or more substituents, or

(2) heterocyclyl which may have one or more substituents;

a moiety of formula:

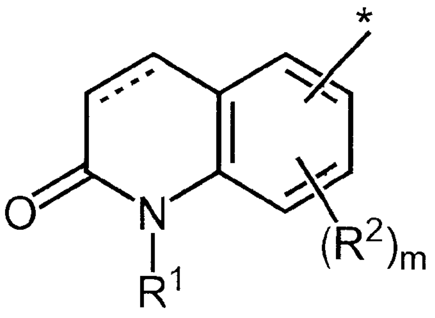
[Chem. 4]

represents a single bond or a double bond.

[0078]

[2] The compound of [1], or a salt thereof, wherein the partial structure (X):

[Chem. 5]



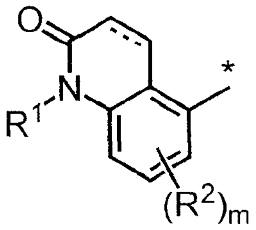
(X)

,

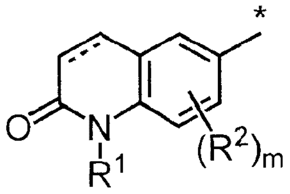
wherein * is a binding point to X^1; and other symbols are as defined in [1],

is any one of the structures selected from the group consisting of the following formulae (X1) to (X6):

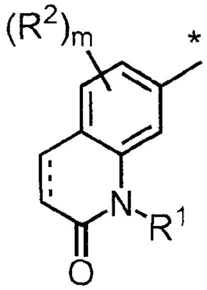
[Chem. 6]



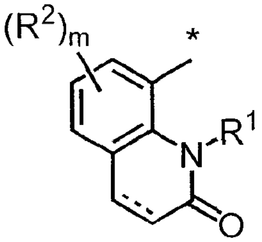
(X1)



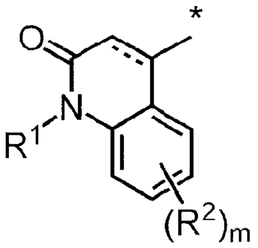
(X2)



(X3)

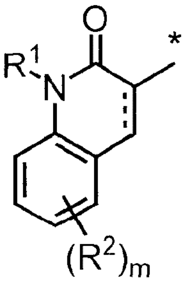


(X4)



(X5)

and



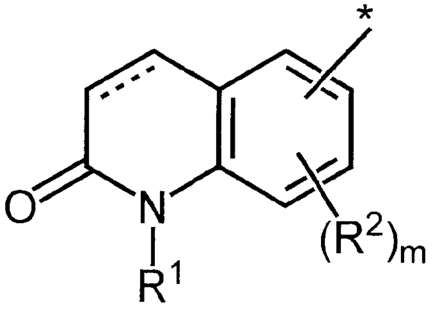
(X6)

wherein the symbols are as defined in the above and [1].

[0079]

[2A] The compound of [1], or a salt thereof, wherein the partial structure (X):

[Chem. 7]



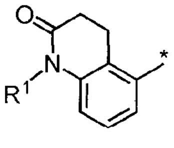
(X)

,

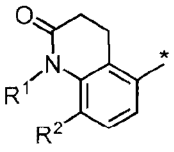
wherein * is a binding point to X^1; and other symbols are as defined in [1],

is any one of the structures selected from the group consisting of the following formulae (X1-1) to (X5-1):

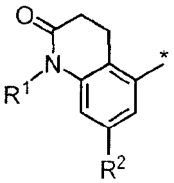
[Chem. 8]



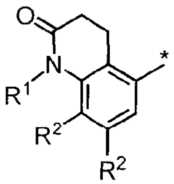
(X1-1)



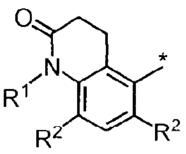
(X1-2)



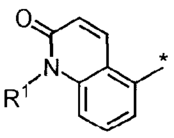
(X1-3)



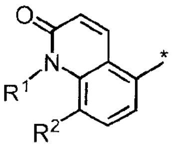
(X1-4)



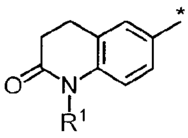
(X1-5)



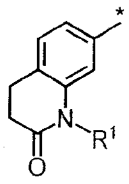
(X1-6)



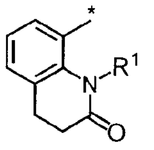
(X1-7)



(X2-1)

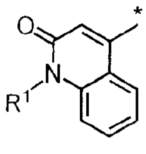


(X3-1)



(X4-1)

and



(X5-1)

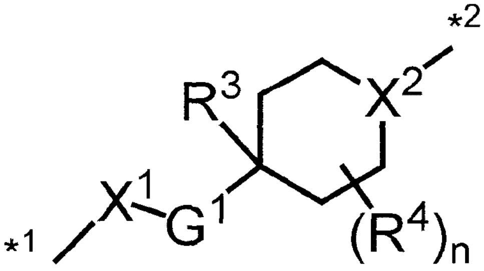
,

wherein the symbols are as defined in the above and [1].

[0080]

[3] The compound of any one of [1], [2] or [2A], or a salt thereof, wherein the partial structure (Y):

[Chem. 9]

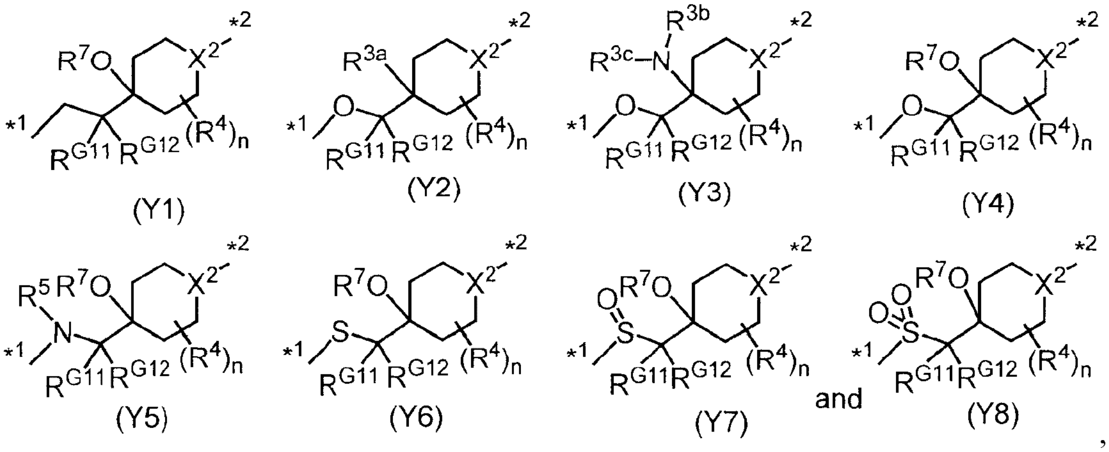


(Y)

wherein *1 is a binding point to the partial structure of Formula (X); *2 is a binding point to Ring A; and other symbols are as defined in [1],

is any one of the structures selected from the group consisting of the following formulae (Y1) to (Y8):

[Chem. 10]



,

wherein R^{3a} is (1) hydrogen, (2) carboxy, (3) halogen, (4) lower alkyl which may have one or more hydroxy, or (5) cyano;

R^{3b} and R^{3c} are each independently (1) hydrogen, (2) lower alkyl, or (3) -C(=O)-R^6;

R^{G11} and R^{G12} are each independently hydrogen or lower alkyl;

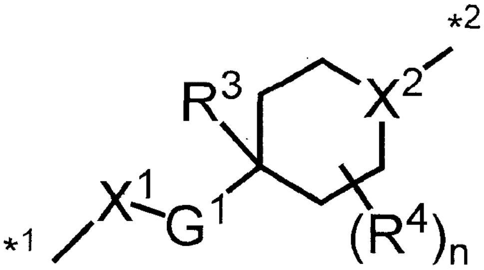
the total number of carbon atoms in R^{G11} and R^{G12} is 0 to 5; and

other symbols are as defined in [1].

[0081]

[3A] The compound of any one of [1], [2] or [2A], or a salt thereof, wherein the partial structure (Y):

[Chem. 11]

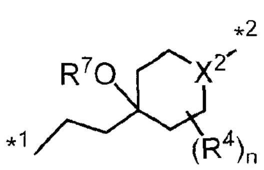


(Y)

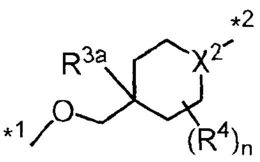
wherein *1 is a binding point to the partial structure of Formula (X); *2 is a binding point to Ring A; and other symbols are as defined in [1],

is any one of the structures selected from the group consisting of the following formulae (Y1-1) to (Y8-1):

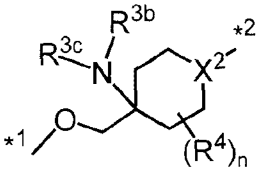
[Chem. 12]



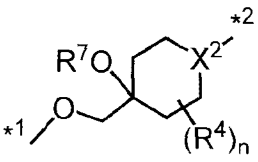
(Y1-1)



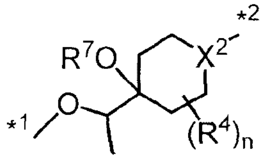
(Y2-1)



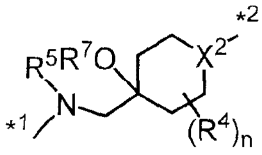
(Y3-1)



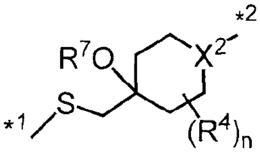
(Y4-1)



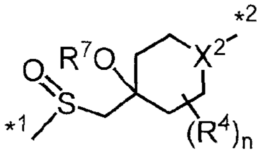
(Y4-2)



(Y5-1)

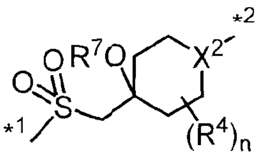


(Y6-1)



(Y7-1)

and



(Y8-1)

,

wherein R^{3a} is (1) hydrogen, (2) carboxy, (3) halogen, (4) lower alkyl which may have one or more hydroxy, or (5) cyano;

R^{3b} and R^{3c} are each independently (1) hydrogen, (2) lower alkyl, or (3) -C(=O)-R^6; and

other symbols are as defined in [1].

[0082]

[4] The compound of any one of [1], [2], [2A], [3] or [3A], or a salt thereof, wherein Ring A is aryl or heterocyclyl which may have 1 to 5 substituents independently selected from:

(a) halogen;

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl which may have one or more substituents independently selected from:

    (i) halogen,

    (ii) hydroxy,

    (iii) lower alkoxy, and

    (iv) aryloxy which may have one or more of the same or different halogen;

(f) lower alkoxy which may have one or more substituents independently selected from:

    (i) halogen,

    (ii) lower alkoxy which may have one or more of the same or different lower alkoxy,

    (iii) aryloxy which may have one or more of the same or different halogen,

    (iv) heterocyclyl which may have one or more of the same or different lower alkyl which may have one or more of the same or different halogen, and

    (v) amino which may have one or two of the same or different lower alkyl;

(g) lower alkoxycarbonyl;

(h) lower alkylsulfanyl;

(i) aryl which may have one or more of the same or different halogen;

(j) aryloxy; and

(k) aralkyloxy which may have one or more substituents independently selected from:

  (i) halogen,

  (ii) lower alkyl which may have one or more of the same or different halogen, and

  (iii) lower alkoxy which may have one or more of the same or different halogen.

[0083]

[4A] The compound of any one of [1], [2], [2A], [3] or [3A], or a salt thereof, wherein Ring A is aryl, or saturated or unsaturated mono- or bi-cyclic heterocyclyl which comprises 1 to 5 heteroatoms independently selected from oxygen, sulfur, and nitrogen, which may have 1 to 5 substituents independently selected from:

(a) halogen;

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl which may have one or more substituents independently selected from:

  (i) halogen,

  (ii) hydroxy,

  (iii) lower alkoxy, and

  (iv) aryloxy which may have one or more of the same or different halogen;

(f) lower alkoxy which may have one or more of the same or different substituents independently selected from:

(i) halogen,

(ii) lower alkoxy which may have one or more of the same or different lower alkoxy,

(iii) aryloxy which may have one or more of the same or different halogen,

(iv) heterocyclyl (e.g. pyridyl) which may have one or more of the same or different lower alkyl which may have one or more of the same or different halogen, and

(v) amino which may have one or two of the same or different lower alkyl;

(g) lower alkoxycarbonyl;

(h) lower alkylsulfanyl;

(i) aryl which may have one or more of the same or different halogen;

(j) aryloxy; and

(k) aralkyloxy which may have one or more substituents independently selected from:

(i) halogen,

(ii) lower alkyl which may have one or more of the same or different halogen, and

(iii) lower alkoxy which may have one or more of the same or different halogen.

[0084]

[4B] The compound of any one of [1], [2], [2A], [3] or [3A], or a salt thereof, wherein Ring A is:

(1) aryl;

(2) saturated or unsaturated 5- or 6-membered heteromonocyclic group comprising 1 to 4 nitrogen;

(3) saturated or unsaturated 7- to 12-membered fused heterocyclyl group comprising 1 to 5 nitrogen;

(4) saturated or unsaturated 7- to 12-membered fused heterocyclyl group comprising 1 to 3 oxygen;

(5) saturated or unsaturated 7- to 12-membered fused heterocyclyl group comprising 1 or 2 oxygen and 1 to 3 nitrogen;

(6) saturated or unsaturated 5- or 6-membered heteromonocyclic group comprising 1 sulfur; or

(7) saturated or unsaturated 7- to 12-membered fused heterocyclyl group comprising 1 to 3 sulfur,

which may have 1 to 5 substituents independently selected from:

(a) halogen;

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl which may have one or more substituents independently selected from:

    (i) halogen,

    (ii) hydroxy,

    (iii) lower alkoxy, and

(iv) aryloxy which may have one or more of the same or different halogen;

(f) lower alkoxy which may have one or more substituents independently selected from:

(i) halogen,

(ii) lower alkoxy which may have one or more of the same or different lower alkoxy,

(iii) aryloxy which may have one or more of the same or different halogens,

(iv) heterocyclyl (e.g. pyridyl) which may have one or more of the same or different lower alkyl which may have one or more of the same or different halogen, and

(v) amino which may have one or more of the same or different lower alkyl;

(g) lower alkoxycarbonyl;

(h) lower alkylsulfanyl;

(i) aryl which may have one or more of the same or different halogen;

(j) aryloxy; and

(k) aralkyloxy which may have one or more substituents independently selelcted from:

(i) halogen,

(ii) lower alkyl which may have one or more of the same or different halogen, and

(iii) lower alkoxy which may have one or more of the same or different halogen.

[0085]

[4C] The compound of any one of [1], [2], [2A], [3] or [3A], or a salt thereof, wherein Ring A is a group selelcted from:

(a1) phenyl,

(a2) pyridyl,

(a3) N-oxide pyridyl,

(a4) thienyl,

(a5) quinolyl,

(a6) isoquinolyl,

(a7) benzothienyl,

(a8) quinoxalinyl,

(a9) benzofuryl,

(a10) benzodioxolyl,

(a11) benzoxazolyl, and

(a12) benzimidazolyl,

which may have the same or different 1 to 5 substituents.

[0086]

[4D] The compound of any one of [1], [2], [2A], [3] or [3A], or a salt thereof, wherein Ring A is a group selelcted from:

(a1) phenyl,

(a2) pyridyl,

(a3) N-oxide pyridyl,

(a4) thienyl,

(a5) quinolyl,

(a6) isoquinolyl,

(a7) benzothienyl,

(a8) quinoxalinyl,

(a9) benzofuryl,

(a10) benzodioxolyl,

(a11) benzoxazolyl, and

(a12) benzimidazolyl,

which may have 1 to 5 substituents independently selected from:

(a) halogen;

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl which may have one or more substituents independently selected from:

(i) halogen,

(ii) hydroxy,

(iii) lower alkoxy, and

(iv) aryloxy which may have one or more of the same or different halogen;

(f) lower alkoxy which may have one or more substituents independently selected from:

(i) halogen,

(ii) lower alkoxy which may have one or more of the same or different lower alkoxy,

(iii) aryloxy which may have one or more of the same or different halogen,

(iv) heterocyclyl (e.g. pyridyl) which may have one or more of the same or different lower alkyls which may have one or more of the same or different halogen, and

(v) amino which may have one or more of the same or different lower alkyl;

(g) lower alkoxycarbonyl;

(h) lower alkylsulfanyl;

(i) aryl which may have one or more of the same or different halogen;

(j) aryloxy; and

(k) aralkyloxy which may have one or more substituents independently selected from:

(i) halogen,

(ii) lower alkyl which may have one or more of the same or different halogens, and

(iii) lower alkoxy which may have one or more of the same or different halogen.

[0087]

[4E] The compound of any one of [1], [2], [2A], [3] or [3A], or a salt thereof, wherein Ring A is:

(A1) phenyl which may have 1 to 5 substituents independently selected from:

(a) halogen;

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl which may have one or more substituents independently selected from:

(i) halogen,

(ii) hydroxy,

(iii) lower alkoxy, and

(iv) aryloxy which may have one or more of the same or different halogen;

(f) lower alkoxy which may have one or more substituents independently selected from:

(i) halogen,

(ii) lower alkoxy which may have one or more of the same or different lower alkoxy,

(iii) aryloxy which may have one or more of the same or different halogen,

(iv) heterocyclyl (e.g. pyridyl) which may have one or more of the same or different lower alkyls which may have one or more of the same or different halogen, and

(v) amino which may have one or two of the same or different lower alkyl;

(g) lower alkoxycarbonyl;

(h) lower alkylsulfanyl;

(i) aryl which may have one or more of the same or different halogen;

(j) aryloxy; and

(k) aralkyloxy which may have one or more substituents independently selected from:

(i) halogen,

(ii) lower alkyl which may have one or more of the same or different halogen, and

(iii) lower alkoxy which may have one or more of the same or different halogen;

(A2) pyridyl which may have 1 to 2 substituents independently selected from:

(a) halogen;

(b) cyano;

(c) lower alkyl which may have one or more of the same or different halogen; and

(d) lower alkoxy;

(A3) N-oxide pyridyl which may have 1 to 2 halogen;

(A4) thienyl;

(A5) quinolyl which may have 1 to 2 halogen;

(A6) isoquinolyl;

(A7) benzothienyl;

(A8) quinoxalinyl;

(A9) benzofuryl;

(A10) benzodioxolyl which may have 1 to 3 halogen;

(A11) benzoxazolyl which may have 1 to 2 halogen; or

(A12) benzimidazolyl which may have 1 to 3 substituents independently selected from:

  (a) halogen; and

  (b) lower alkyl which may have one or more of the same or different lower alkoxy.

[0088]

[5] The compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], or [4E], or a salt thereof, wherein R^1 is hydrogen.

[0089]

[6] The compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], [4E], or [5], or a salt thereof, wherein R^2 is halogen.

[0090]

[7] The compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], [4E], [5], or [6], wherein m is 0, 1 or 2, or a salt thereof.

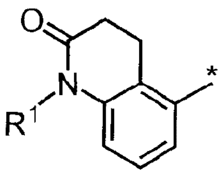
[0091]

[8] The compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], [4E], [5], [6], or [7], or a salt thereof, wherein n is 0, 1 or 2.

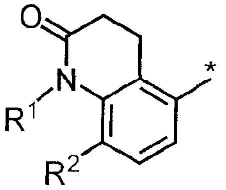
[0092]

[9] The compound of [1], or a salt thereof, wherein the partial structure (X) is a structure of a formula selected from the group consisting of the formulae (X1-1), (X1-2), (X1-3), (X1-4), (X1-6), and (X1-7):

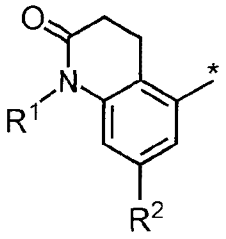
[Chem. 13]



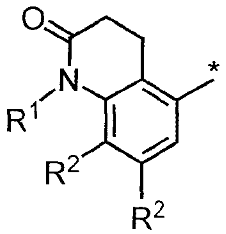
(X1-1)



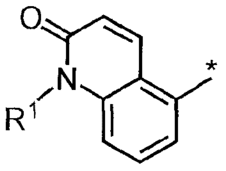
(X1-2)



(X1-3)

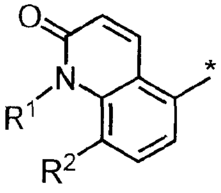


(X1-4)



(X1-6)

and



(X1-7)

wherein * is a binding point to X^1;

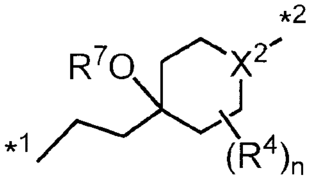
R^1 is hydrogen;

R^2 is a substituent selected from (1) halogen or (2) lower alkyl;

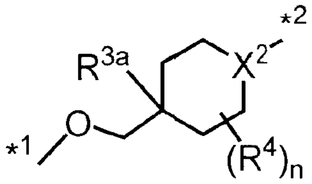
provided that when R^2 may be multiple, each of them may be different from each other;

the partial structure (Y) is a structure of a formula selected from the group consisting of the formulae (Y1-1), (Y2-1), (Y3-1), (Y4-1), (Y5-1), and (Y6-1):

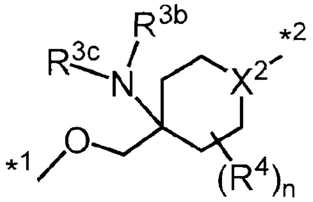
[Chem. 14]



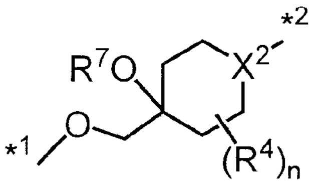
(Y1-1)



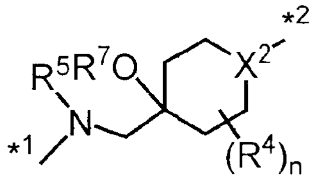
(Y2-1)



(Y3-1)

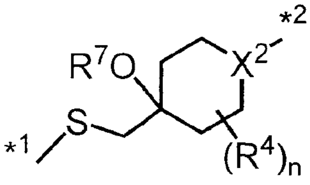


(Y4-1)



(Y5-1)

and



(Y6-1)

wherein *1 is a binding point to the partial structure of Formula (X);

*2 is a binding point to Ring A;

R^5 is hydrogen;

R^{3a} is (1) hydrogen or (2) halogen;

R^{3b} and R^{3c} are each hydrogen;

R^7 is hydrogen;

R^4 is a substituent selected from (1) halogen, (2) -O-R^8, (3) -O-C(=O)-R^9, or (4) cyano;

R^8 is (1) hydrogen or (2) lower alkyl;

R^9 is (1) lower alkyl or (2) lower alkoxy;

n is an integer of 0 to 2;

provided that when n is 2, each of R^4, R^8, and R^9 may be different from each other and may be substituted on the same carbon atom;

X^2 is N or CH;

provided that when X^2 is CH, H of the group may be substituted with R^4 which is defined as above or may be different from the other R^4; and

Ring A is phenyl or pyridyl which may have 1 to 3 substituents independently selected from:

(a) halogen;

(b) lower alkoxy which may have (i) one or more halogen and (ii) one or more lower alkoxy; or

(c) aralkyloxy which may have one or more of the same or different lower alkoxy which may have one or more of the same or different halogen; or

quinolyl which may have 1 to 2 halogen.

[0093]

[10] The compound of [1], which is selected from the group consisting of the following compounds:

5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one,

5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one,

5-{[1-(4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}quinolin-2(1H)-one,

8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one, 8-fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one,

8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(3-bromo-6-chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4S)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R*,4R*)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H)-one,

5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R*,4R*)-1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate,

(3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate,

5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{2-[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[trans-4-(4-chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[cis-4-(4-chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(1R*,2R*,4R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(1R,2R,4S)-4-(4-chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

trans-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxycyclohexanecarbonitrile, and

5-{[trans-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

[0094]

[11] The compound of [1], which is selected from the group consisting of the following compounds:

5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one,

5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one,

5-{[1-(4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}quinolin-2(1H)-one,

8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one, 8-fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one,

8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(3-bromo-6-chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4S)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R*,4R*)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H)-one,

5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R*,4R*)-1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate,

(3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate,

5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{2-[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[trans-4-(4-chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[cis-4-(4-chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(1R*,2R*,4R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(1R,2R,4S)-4-(4-chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

trans-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxycyclohexanecarbonitrile, and

5-{[trans-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one.

[0095]

[12] A pharmaceutical composition, comprising the compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], [4E], [5], [6], [7], [8], [9], [10], or [11], or a salt thereof and a pharmaceutically acceptable carrier.

[0096]

[13] An agent for diagnosing, preventing, and/or treating tuberculosis, comprising the compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], [4E], [5], [6], [7], [8], [9], [10], or [11], or a salt thereof and a pharmaceutically acceptable carrier.

[0097]

[14] The compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], [4E], [5], [6], [7], [8], [9], [10], or [11], or a salt thereof, for use of diagnosing, preventing, and/or treating tuberculosis.

[0098]

[15] Use of the compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], [4E], [5], [6], [7], [8], [9], [10], or [11], or a salt thereof, in the manufacture of a medicament for diagnosing, preventing, and/or treating tuberculosis.

[0099]

[16] Use of the compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], [4E], [5], [6], [7], [8], [9], [10], or [11], or a salt thereof, as a pharmaceutical composition.

[0100]

[17] A method of diagnosing, preventing, and/or treating tuberculosis, comprising administering to a patient an effective amount of the compound of any one of [1], [2], [2A], [3], [3A], [4], [4A], [4B], [4C], [4D], [4E], [5], [6], [7], [8], [9], [10], or [11], or a salt thereof.

[0101]

In one embodiment, m is preferably 0, 1, or 2.

[0102]

In another embodiment, G^1 is preferably $-C(R^{G11})(R^{G12})-$; more preferably $-CH_2-$ or $-CH(CH_3)-$.

[0103]

In another embodiment, R^{G11} and R^{G12} are each independently hydrogen or lower alkyl; and the total number of carbon atoms in R^{G11} and R^{G12} is 0 to 5. Preferably R^{G11} and R^{G12} are each independently hydrogen or methyl; more preferably R^{G11} is hydrogen or methyl, and R^{G12} is hydrogen.

[0104]

Examples of "$-C(R^{G11})(R^{G12})-$" in G^1 include, for example, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_2CH_3)-$, $-C(CH_3)(CH_2CH_3)-$, $-C(CH_2CH_3)_2-$, $-CH(CH_2CH_2CH_3)-$, $-C(CH_3)(CH_2CH_2CH_3)-$, $-C(CH_2CH_3)(CH_2CH_2CH_3)-$, $-CH(CH(CH_3)_2)-$, $-C(CH_3)(CH(CH_3)_2)-$, $-C(CH_2CH_3)(CH(CH_3)_2)-$.

[0105]

In another embodiment, n is preferably 0, 1, or 2.

[0106]

The "aryl" of "(1) aryl which may have one or more substituents" in Ring A is preferably (a1) phenyl.

[0107]

The "heterocyclyl" of "(2) heterocyclyl which may have one or more substituents" in Ring A is preferably selected from:

(a2) pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl),

(a3) N-oxide pyridyl (e.g. N-oxide pyridin-2-yl),

(a4) thienyl (e.g. 3-thienyl),

(a5) quinolyl (e.g. 2-quinolyl, 6-quinolyl),

(a6) isoquinolyl (e.g. 1-isoquinolyl),

(a7) benzothienyl (e.g. benzo[b]thiophen-5-yl),

(a8) quinoxalinyl (e.g. 6-quinoxalinyl),

(a9) benzofuryl (e.g. benzo[b]furan-5-yl),

(a10) benzodioxolyl (e.g. benzo[1,3]dioxol-5-yl),

(a11) benzooxazolyl (e.g. 2-benzooxazolyl), and

(a12) benzoimidazolyl (e.g. 2-benzoimidazolyl).

[0108]

Ring A is preferably aryl or heterocyclyl, which is preferably a group selected from the above (a1) to (a12), each of which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine, iodine);

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl which may have one or more substituents selected from groups (Ia) and (Ib) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);

(f) lower alkoxy which may have one or more substituents selected from groups (Ia) and (Ib) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);

(g) lower alkoxycarbonyl which may have one or more substituents selected from groups (Ia) and (Ib) (e.g. ethoxycarbonyl);

(h) lower alkylsulfanyl which may have one or more substituents selected from groups (Ia) and (Ib) (e.g. methylsulfanyl, ethylsulfanyl);

(i) aryl which may have one or more substituents selected from groups (Ia), (Ib), and (Ic) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);

(j) aryloxy which may have one or more substituents selected from groups (Ia), (Ib), and (Ic) (e.g. phenoxy); and

(k) aralkyloxy which may have one or more substituents selected from groups (Ia), (Ib), and (Ic) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy).

[0109]

Ring A is more preferably aryl or heterocyclyl, which is preferably a group selected from the above (a1) to (a12), each of which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine, iodine);

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl (e.g. methyl, ethyl, propyl, isopropyl) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) hydroxy, (iii) lower alkoxy (e.g. methoxy, ethoxy), and (iv) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);

(f) lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) lower alkoxy (e.g. methoxy, ethoxy) which may have lower alkoxy (e.g. methoxy), (iii) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine), (iv) heterocyclyl (e.g. pyridyl) which may have lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (v) amino which may have lower alkyl (e.g. methyl) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);

(g) lower alkoxycarbonyl (e.g. ethoxycarbonyl);

(h) lower alkylsulfanyl (e.g. methylsulfanyl, ethylsulfanyl);

(i) aryl (e.g. phenyl) which may have halogen (e.g. fluorine, chlorine) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);

(j) aryloxy (e.g. phenoxy); and

(k) aralkyloxy (e.g. benzyloxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine, chlorine), (ii) lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (iii) lower alkoxy (e.g. methoxy) which may have halogen (e.g. fluorine) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy).

[0110]

Ring A is further preferably

(1) aryl, which is preferably the group of the above (a1), which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine);

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl (e.g. methyl, ethyl, propyl, isopropyl) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) hydroxy, (iii) lower alkoxy (e.g. methoxy, ethoxy), and (iv) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);

(f) lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) lower alkoxy (e.g. methoxy, ethoxy) which may have lower alkoxy (e.g. methoxy), (iii) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine), (iv) heterocyclyl (e.g. pyridyl) which may have lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (v) amino which may have lower alkyl (e.g. methyl) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);

(g) lower alkoxycarbonyl (e.g. ethoxycarbonyl);

(h) lower alkylsulfanyl (e.g. methylsulfanyl, ethylsulfanyl);

(i) aryl (e.g. phenyl) which may have halogen (e.g. fluorine, chlorine) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);

(j) aryloxy (e.g. phenoxy); and

(k) aralkyloxy (e.g. benzyloxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine, chlorine), (ii) lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (iii) lower alkoxy (e.g. methoxy) which may have halogen (e.g. fluorine) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy); or

(2) heterocyclyl, which is preferably a group selected from the above (a2) to (a12), which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine, iodine);

(b) cyano;

(c) lower alkyl (e.g. methyl) which may have one or more substituents selected from (i) halogen (e.g. fluorine), and (ii) lower alkoxy (e.g. methoxy) (e.g. methyl, trifluoromethyl, methoxymethyl); and

(d) lower alkoxy (e.g. ethoxy).

[0111]

Ring A is particularly preferably

(A1) phenyl which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine);

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl (e.g. methyl, ethyl, propyl, isopropyl) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) hydroxy, (iii) lower alkoxy (e.g. methoxy, ethoxy), and (iv) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);

(f) lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine), (ii) lower alkoxy (e.g. methoxy, ethoxy) which may have lower alkoxy (e.g. methoxy), (iii) aryloxy (e.g. phenoxy) which may have halogen (e.g. fluorine), (iv) heterocyclyl (e.g. pyridyl) which may have lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (v) amino which may have lower alkyl (e.g. methyl) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);

(g) lower alkoxycarbonyl (e.g. ethoxycarbonyl);

(h) lower alkylsulfanyl (e.g. methylsulfanyl, ethylsulfanyl);

(i) aryl (e.g. phenyl) which may have halogen (e.g. fluorine, chlorine) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);

(j) aryloxy (e.g. phenoxy); and

(k) aralkyloxy (e.g. benzyloxy) which may have one or more substituents selected from (i) halogen (e.g. fluorine, chlorine), (ii) lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (iii) lower alkoxy (e.g. methoxy) which may have halogen (e.g. fluorine) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy);

(A2) pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl) which may have one or more substituents selected from:

(a) halogen (e.g. fluorine, chlorine, bromine, iodine);

(b) cyano;

(c) lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine) (e.g. methyl, trifluoromethyl); and

(d) lower alkoxy (e.g. ethoxy);

(A3) N-oxide pyridyl (e.g. N-oxide pyridin-2-yl) which may have halogen (e.g. chlorine);

(A4) thienyl (e.g. 3-thienyl);

(A5) quinolyl (e.g. 2-quinolyl, 6-quinolyl) which may have halogen (e.g. chlorine, bromine);

(A6) isoquinolyl (e.g. 1-isoquinolyl);

(A7) benzothienyl (e.g. benzo[b]thiophen-5-yl);

(A8) quinoxalinyl (e.g. 6-quinoxalinyl);

(A9) benzofuryl (e.g. benzo[b]furan-5-yl);

(A10) benzodioxolyl (e.g. benzo[1,3]dioxol-5-yl) which may have halogen (e.g. fluorine);

(A11) benzoxazolyl (e.g. 2-benzooxazolyl) which may have halogen (e.g. chlorine); or

(A12) benzimidazolyl (e.g. 2-benzoimidazolyl) which may have one or more substituents selected from:

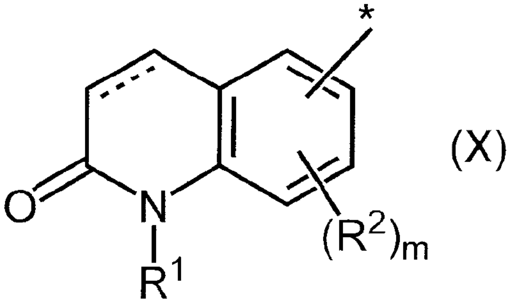
(a) halogen (e.g. fluorine); and

(b) lower alkyl (e.g. methyl) which may have lower alkoxy (e.g. methoxy) (e.g. methyl, methoxymethyl).

[0112]

In the general formula (1), the partial structure (X):

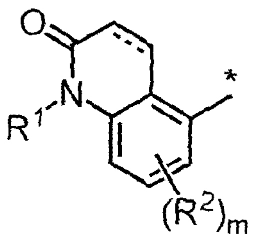
[Chem. 15]



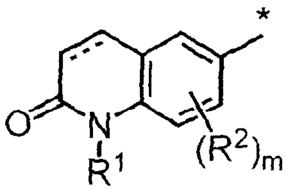
,

wherein * is the binding point to X^1 and other symbols are the same as defined above, includes a structure selected from the group consisting of the following formulae (X1) to (X6):

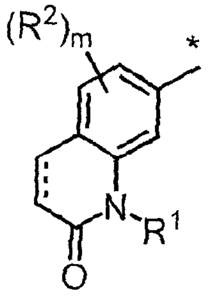
[Chem. 16]



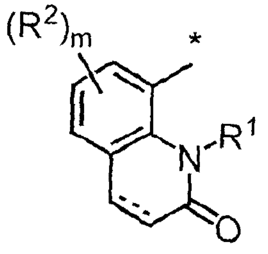
(X1)



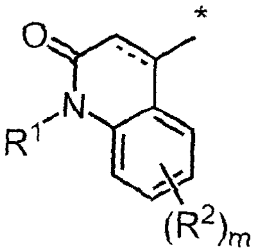
(X2)



(X3)

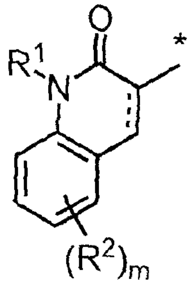


(X4)



(X5)

and



(X6)

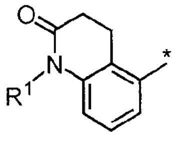
,

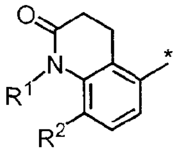
wherein each symbol is the same as defined above;

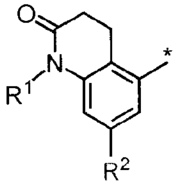
preferably a structure of Formula (X1), (X2), (X3), (X4), or (X5); and

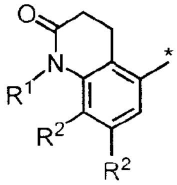
more preferably a structure selected from the group consisting of the following formulae (X1-1) to (X5-1):

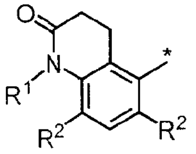
[Chem. 17]

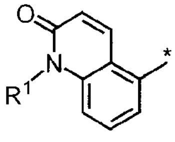

(X1-1)

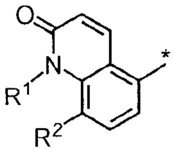

(X1-2)

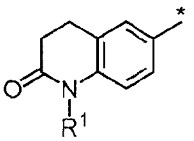

(X1-3)

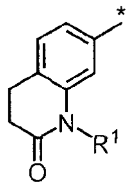

(X1-4)

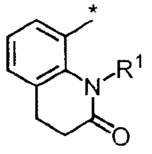

(X1-5)


(X1-6)

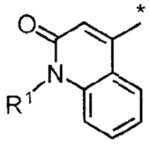

(X1-7)


(X2-1)


(X3-1)


(X4-1)

and

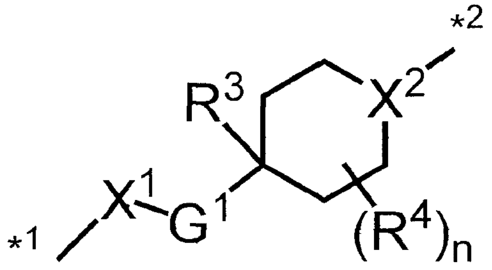

(X5-1)

wherein each symbol is the same as defined above.

[0113]

In the general formula (1), the partial structure (Y):

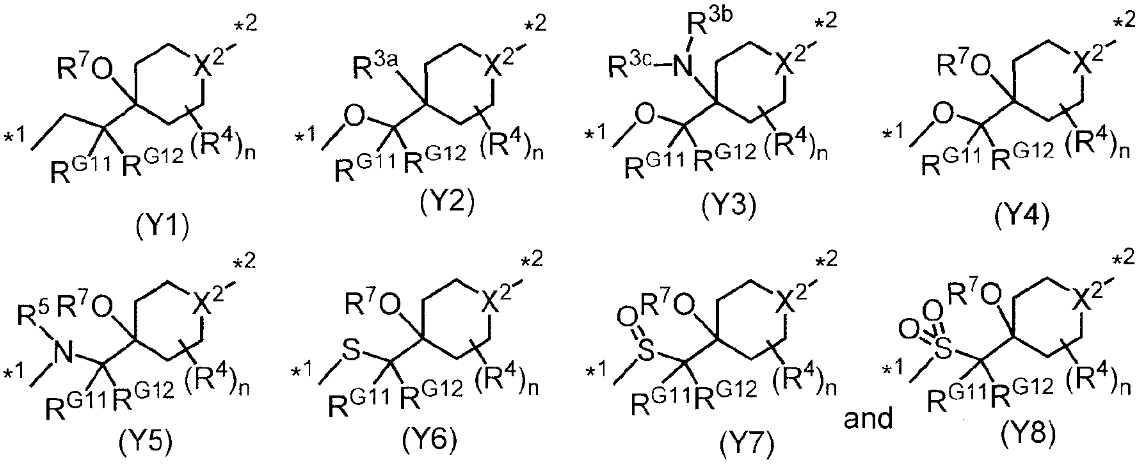
[Chem. 18]


(Y)

,

wherein *1 is the binding point to the partial structure of Formula (X); *2 represents the binding point to Ring A; and other symbols are the same as defined above, is preferably a structure selected from the group consisting of the following formulae (Y1) to (Y8):

[Chem. 19]

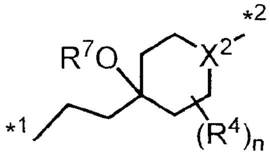


(Y1) (Y2) (Y3) (Y4) (Y5) (Y6) (Y7) (Y8)

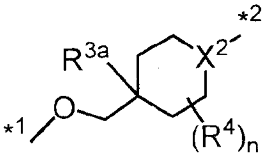
wherein R^{3a} is (1) hydrogen, (2) carboxy, (3) halogen (e.g. fluorine), (4) lower alkyl (e.g. methyl) which may have hydroxy (e.g. hydroxymethyl), or (5) cyano; R^{3b} and R^{3c} are each independently (1) hydrogen, (2) lower alkyl (e.g. methyl), or (3) -C(=O)-R^6 (e.g. methoxycarbonyl, acetyl, dimethylaminoacetyl); and other symbols are the same as defined above;

more preferably a structure selected from the group consisting of the following formulae (Y1-1) to (Y8-1):

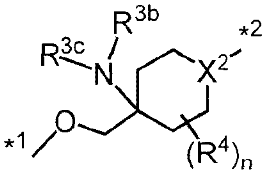
[Chem. 20]



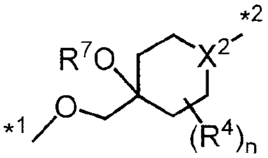
(Y1-1)



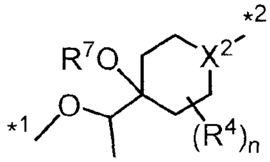
(Y2-1)



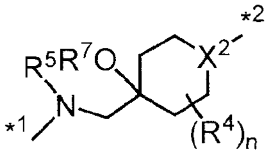
(Y3-1)



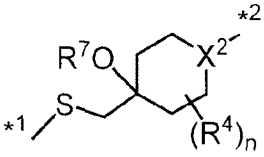
(Y4-1)



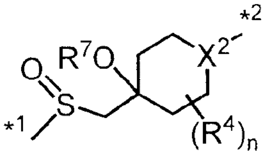
(Y4-2)



(Y5-1)

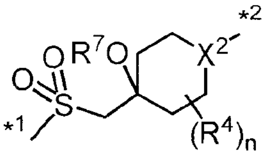


(Y6-1)



(Y7-1)

and



(Y8-1)

wherein each symbol is the same as defined above.

[0114]

In one preferable embodiment, in Formula (I),

the partial structure (X) is a structure selected from the group consisting of the formulae (X1-1), (X1-2), (X1-3), (X1-4), (X1-5), (X1-6), (X1-7), (X2-1), (X3-1), (X4-1), and (X5-1);

the partial structure (Y) is a structure selected from the group consisting of the formulae (Y1-1), (Y2-1), (Y3-1), (Y4-1), (Y4-2), (Y5-1), (Y6-1), (Y7-1), and (Y8-1);

R^1 is (1) hydrogen, (2) amino (e.g. amino) which may have one or more of the same or different lower alkyl, or (3) lower alkyl (e.g. methyl);

R^2 is a substituent selected from (1) halogen (e.g. fluorine, chlorine, bromine, iodine), (2) amino (e.g. amino) which may have one or two of the same or different lower alkyl, (3) lower alkyl (e.g. methyl, ethyl), (4) lower alkoxy (e.g. ethoxy), and (5) hydroxy;

each of R^2 may be different when it exists plurally;

R^5 is (1) hydrogen, (2) lower alkyl (e.g. methyl), or (3) lower alkanoyl (e.g. acetyl);

R^{3a} is (1) hydrogen, (2) carboxy, (3) halogen (e.g. fluorine), (4) lower alkyl (e.g. methyl) which may have one or more of hydroxy (e.g. hydroxymethyl), or (5) cyano;

R^{3b} and R^{3c} are each independently (1) hydrogen, (2) lower alkyl (e.g. methyl), or (3) -C(=O)-R^6 (e.g. methoxycarbonyl, acetyl, dimethylaminoacetyl);

R^6 is (1) lower alkoxy (e.g. methoxy), or (2) lower alkyl (e.g. methyl) which may have one or more of the same or different amino which may have one or more of the same or different lower alkyl (e.g. methyl) (e.g. methyl, dimethylaminomethyl);

R^7 is (1) hydrogen, (2) amino, (3) lower alkanoyl (e.g. acetyl), or (4) lower alkyl (e.g. methyl);

R^4 is a substituent selected from (1) amino (e.g. amino, methylamino) which may have one or two of the same or different lower alkyl (e.g. methyl), (2) halogen (e.g. fluorine), (3) cyano, (4) lower alkyl (e.g. methyl), (5) oxo, (6) -O-R^8 (e.g. hydroxy, methoxy, 4-methoxybenzyloxy, -O-PH(=O)OH), and (7) -O-C(=O)-R^9 (e.g. acetoxy, pyrazinylcarbonyloxy, ethoxycarbonyloxy, ethylaminocarbonyloxy, 3-carboxypropionyloxy);

R^8 is (1) hydrogen, (2) lower alkyl (e.g. methyl), (3) -PH(=O)OH, or (4) benzyl which may have one or more of the same or different lower alkoxy (e.g. methoxy) (e.g. 4-methoxybenzyl);

R^9 is (1) lower alkyl (e.g. methyl), (2) -G^2-COOH (e.g. 2-carboxyethyl), (3) amino which may have one or two of the same or different lower alkyl (e.g. ethyl) (e.g. ethylamino), (4) lower alkoxy (e.g. ethoxy), or (5) pyrazinyl;

G^2 is lower alkylene (e.g. -$(CH_2)_2$-);

n is 0, 1, or 2;

provided that when n is 2, each of R^4, R^8, R^9, and G^2 may be different from each other and may be substituted on the same carbon atom;

X^2 is N or CH;

provided that when X^2 is CH, H of the group may be substituted with R^4 which is defined as above or may be different from the other R^4; and

Ring A is

(1) aryl, which is preferably (a1) phenyl, which may have one or more substituents independently selected from:

(a) halogen (e.g. fluorine, chlorine, bromine);

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) lower alkyl (e.g. methyl, ethyl, propyl, isopropyl) which may have one or more substituents independently selected from (i) halogen (e.g. fluorine), (ii) hydroxy, (iii) lower alkoxy (e.g. methoxy, ethoxy), and (iv) aryloxy (e.g. phenoxy) which may have one or more of the same or different halogen (e.g. fluorine) (e.g. methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, ethoxymethyl, 2-methoxyethyl, 2-(4-fluorophenoxy)ethyl);

(f) lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy) which may have one or more substituents independently selected from (i) halogen (e.g. fluorine), (ii) lower alkoxy (e.g. methoxy, ethoxy) which may have one or more of the same or different lower alkoxy (e.g. methoxy), (iii) aryloxy (e.g. phenoxy) which may have one or more of the same or different halogen (e.g. fluorine), (iv) heterocyclyl (e.g. pyridyl) which may have one or more of the same or different lower alkyl (e.g. methyl) which may have halogen (e.g. fluorine), and (v) amino which may have one or two of the same or different lower alkyl (e.g. methyl) (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, 2-(4-fluorophenoxy)ethoxy, 5-(trifluoromethyl)pyridin-2-ylmethoxy, 2-(dimethylamino)ethoxy);

(g) lower alkoxycarbonyl (e.g. ethoxycarbonyl);

(h) lower alkylsulfanyl (e.g. methylsulfanyl, ethylsulfanyl);

(i) aryl (e.g. phenyl) which may have one or more of the same or different halogen (e.g. fluorine, chlorine) (e.g. 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl);

(j) aryloxy (e.g. phenoxy); and

(k) aralkyloxy (e.g. benzyloxy) which may have one or more substituents independently selected from (i) halogen (e.g. fluorine, chlorine), (ii) lower alkyl (e.g. methyl) which may have one or more of the same or different halogen (e.g. fluorine), and (iii) lower alkoxy (e.g. methoxy) which may have one or more of the same or different halogen (e.g. fluorine) (e.g. benzyloxy, 4-fluorobenzyloxy, 4-chlorobenzyloxy, 2,4-dichlorobenzyloxy, 4-(trifluoromethyl)benzyloxy, 4-(trifluoromethoxy)benzyloxy); or

(2) heterocyclyl, which is preferably a group selected from (a2) pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl), (a3) N-oxide pyridyl (e.g. N-oxidepyridin-2-yl), (a4) thienyl (e.g. 3-thienyl), (a5) quinolyl (e.g. 2-quinolyl, 6-quinolyl), (a6) isoquinolyl (e.g. 1-isoquinolyl), (a7) benzothienyl (e.g. benzo[b]thiophen-5-yl), (a8) quinoxalinyl (e.g. 6-quinoxalinyl), (a9)

benzofuryl (e.g. benzo[b]furan-5-yl), (a10) benzodioxolyl (e.g. benzo[1,3]dioxol-5-yl), (a11) benzoxazolyl (e.g. 2-benzoxazolyl), and (a12) benzimidazolyl (e.g. 2-benzimidazolyl), which may have one or more substituents independently selected from:

(a) halogen (e.g. fluorine, chlorine, bromine, iodine);

(b) cyano;

(c) lower alkyl (e.g. methyl) which may have one or more substituents independently selected from (i) halogen (e.g. fluorine), and (ii) lower alkoxy (e.g. methoxy) (e.g. methyl, trifluoromethyl, methoxymethyl); and

(d) lower alkoxy (e.g. ethoxy).

[0115]

A method of preparing Compound (1) in the present invention is explained as below. Compound (1) in the present invention may be for example prepared according to the preparation methods as below. The preparation methods as below are illustrative and a method of preparing Compound (1) is not limited thereto.

Examples of "hydrocarbons" as a solvent include, for example, aliphatic hydrocarbons such as hexane and pentane; alicyclic hydrocarbons such as cyclopentane and cyclohexane; aromatic hydrocarbons such as benzene and toluene.

Examples of "halogenated hydrocarbons" as a solvent include, for example, chloroform, dichloromethane.

Examples of "alcohols" as a solvent include, for example, methanol, ethanol, isopropanol, propanol, tert-butanol.

Examples of "ethers" as a solvent include, for example, chain ethers such as diethyl ether, diisopropyl ether, dibutyl ether, and diphenyl ether; circular ethers such as 1,4-dioxane and tetrahydrofurane.

Examples of "esters" as a solvent include, for example, ethyl acetate, ethyl propionate.

Examples of "ketones" as a solvent include, for example, acetone, methyl ethyl ketone, methyl isobutyl ketone.

Examples of "amides" as a solvent include, for example, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone.

Examples of "nitriles" as a solvent include, for example, acetonitrile, propionitrile.

Examples of "sulfoxides" as a solvent include, for example, dimethylsulfoxide.

[0116]

Examples of "alkali metal hydroxides" as a base include, for example, sodium hydroxide, potassium hydroxide, cesium hydroxide.

Examples of "alkali metal hydrides" as a base include, for example, sodium hydride, potassium hydride, cesium hydride.

Examples of "alkali metal carboxylates" as a base include, for example, sodium acetate, potassium acetate, sodium butyrate.

Examples of "alkali metal carbonates" as a base include, for example, sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate.

Examples of "alkali metal hydrogencarbonates" as a base include, for example, sodium hydrogencarbonate, potassium hydrogencarbonate, cesium hydrogencarbonate.

Examples of "alkali metal phosphates" as a base include, for example, sodium phosphate, potassium phosphate.

Examples of "aromatic amines" as a base include, for example, pyridine, lutidine.

Examples of "tertiary amines" as a base include, for example, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, tetramethylethylenediamine, tetramethylpropylenediamine, 1,8-diazabicyclo[5,4,0]undec-7-ene (diazabicycloundecene).

Examples of "metal amides" as a base include, for example, lithium diisopropylamide, lithium hexamethyldisilazide.

Examples of "metal alkoxides" as a base include, for example, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, sodium phenoxide.

[0117]

Examples of "protecting group of hydroxy" include, but not limited to, any protecting groups of hydroxy used in the field of synthetic organic chemistry, and include, for example, alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, hydroxymethyl, 2-hydroxyethyl, acetylmethyl); alkenyl (e.g. ethenyl, 1-propenyl, 2-propenyl, 1-methyl-2-propenyl); alkynyl (e.g. ethynyl, 1-propynyl, 2-propynyl, 1-methyl-2-propynyl); formyl; alkyl (alkenyl) carbonyls (e.g. acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, acryloyl, propioloyl, methacryloyl, crotonoyl, isocrotonoyl, (E)-2-methyl-2-butenoyl); arylcarbonyl (e.g. benzoyl, α-naphthoyl, β-naphthoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, 4-toluoyl, 4-anisoyl, 4-nitrobenzoyl, 2-nitrobenzoyl, 2-(methoxycarbonyl)benzoyl, 4-phenylbenzoyl); alkoxycarbonyl (e.g. methoxycarbonyl, tert-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, 9-fluorenylmethyloxycarbonyl); tetrahydro (thio) pyranyl (furanyl) (e.g. tetrahydropyran-2-yl, 3-bromotetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, tetrahydrothiopyran-2-yl, 4-methoxytetrahydrothiopyran-4-yl, tetrahydrofuran-2-yl, tetrahydrothiofuran-2-yl); silyl (e.g. trimethylsilyl, triethylsilyl, isopropyl dimethylsilyl, tert-butyldimethyl silyl, methyldiisopropyl silyl, methyl di-tert-butylsilyl, triisopropylsilyl, diphenylmethyl silyl, diphenylbutyl silyl, diphenylisopropyl silyl, phenyldiisopropyl silyl); alkoxymethyl (e.g. methoxymethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl, tert-butoxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl); alkoxyethyl (e.g. 1-ethoxyethyl, 1-(isopropoxy)ethyl); halogenated ethyl (e.g. 2,2,2-trichloroethyl); aralkyl (e.g. benzyl, α-naphthylmethyl, β-naphthylmethyl, diphenylmethyl, triphenylmethyl, α-naphthyldiphenylmethyl, 9-anthrylmethyl, 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenyldiphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl); alkenyloxycarbonyl (e.g. vinyloxycarbonyl, allyloxycarbonyl); aralkyloxycarbonyl (e.g. benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl).

[0118]

Examples of "protecting group of carboxy" include, but not limited to, any protecting groups of carboxy used in the field of synthetic organic chemistry, and include, for example, similar groups to the above "alkyl", "alkenyl", "alkynyl", "aralkyl", and "silyl" illustrated in the "protecting group of hydroxy".

[0119]

Examples of "protecting group of amino" include, but not limited to, any protecting groups of amino used in the field of synthetic organic chemistry, and include, for example, similar groups to the above "alkyl (alkenyl) carbonyl", "arylcarbonyl", "alkoxycarbonyl", "silyl", "aralkyl", "alkenyloxycarbonyl", and "aralkyloxycarbonyl" illustrated in the "protecting group of hydroxy".

[0120]

Examples of "protecting group of terminal acetylene" include, but not limited to, any protecting groups of terminal acetylene used in the field of synthetic organic chemistry, and include, for example, similar groups to the above "silyl" illustrated in the "protecting group of hydroxy".

[0121]

Examples of "leaving group" include, for example, halogen (e.g. chlorine, bromine, iodine), alkylsulfonyloxy (e.g. methylsulfonyloxy, ethylsulfonyloxy, trifluoromethylsulfonyloxy), arylsulfonyloxy (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, 2,4,6-trimethylbenzenesulfonyloxy, 2-nitrobenzenesulfonyloxy, 4-nitrobenzenesulfonyloxy).

[0122]

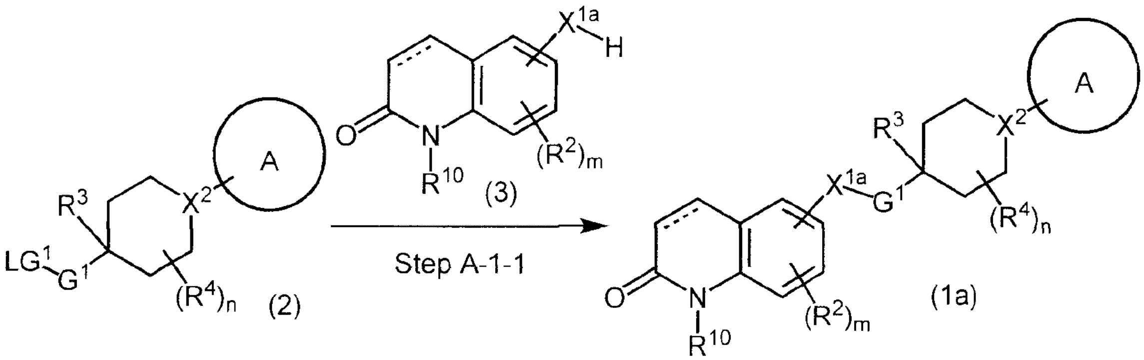
For the avoidance of doubt it is confirmed that in the general description above, in the usual way the proposal of general preferences and options in respect of different features of the compounds, methods, and compositions constitutes the proposal of general combinations of those general preferences and options for the different features, insofar as they are combinable and compatible and are put forward in the same context.

[Preparation method A: General synthetic route 1]

[0123]

Scheme A-1

[Chem. 21]

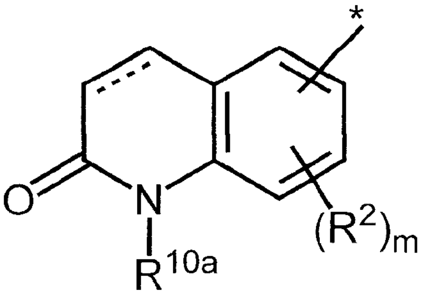


wherein X^{1a} represents -O-, -N(R^5)- or -S-; R^{10} represents hydrogen or an amino protective group; LG^1 represents a leaving group; and other symbols are as defined above.

[0124]

In the compound having R^{10}, instead of protecting the amino of the amide with R^{10}, it is possible to protect the imidic acid (hydroxyl thereof) which is a tautomer of the amide. Namely, a substructure represented by formula (aa):

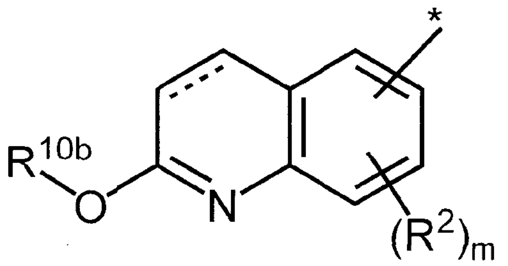
[Chem. 22]



(aa)

wherein R^{10a} represents an amino protecting group; * represents a binding point to X^{1a} (X^1); and other symbols are as defined above can be formula (aa1):

[Chem. 23]



(aa1)

wherein R^{10b} represents lower alkyl; and other symbols are as defined above.

[0125]

(Step A-1-1: (2) + (3) -> (1a))

Among the compounds represented as formula (1), compound (1a) can be obtained, for example, by reacting compound (2) and compound (3) in an inert solvent in the presence of a base.

The amount of compound (3) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (2).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (2).

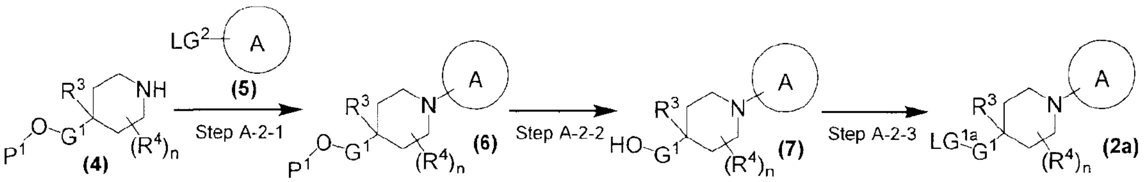
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0126]

Scheme A-2

[Chem. 24]



wherein LG^2 and LG^{1a} each independently represents a leaving group; P^1 represents a hydroxy protecting group; and other symbols are as defined above.

[0127]

(Step A-2-1: (4) + (5) -> (6))

Compound (6) can be obtained, for example, by reacting compound (4) and compound (5) in an inert solvent in the presence of a base. The amount of compound (5) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (4).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides, alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (4).

Transition metal catalyst can be used as necessary.

Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(*tert*-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro-[1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (4).

In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(*tert*-butyl)phosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (4).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0128]

(Step A-2-2: (6) -> (7))

Compound (7) can be obtained by subjecting compound (6) to a deprotection reaction.

Any of known reactions may be used as the deprotection reaction, for example, when P^1 is silyl, compound (6) can be deprotected in an inert solvent in the presence of a fluoride source or an acid to give compound (7).

Examples of the fluoride source include tetrabutylammonium fluoride, hydrofluoric acid and cesium fluoride. The amount of the fluoride source used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (6).

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (6).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0129]

(Step A-2-3: (7) -> (2a))

Among the compounds represented as formula (2), compound (2a) can be obtained by transforming hydroxy in compound (7) to a leaving group by using any known method.

For example, when the leaving group in compound (2a) is alkylsulfonyloxy or arylsulfonyloxy, compound (7) can be reacted with corresponding sulfonic anhydride (such as trifluoromethanesulfonic anhydride) or sulfonyl halide (such as benzenesulfonyl chloride, p-toluenesulfonyl chloride and methylsulfonyl chloride) etc. in an inert solvent in the presence of a base to provide compound (2a). The amount of sulfonic anhydride or sulfonyl halide used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (7).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (7).

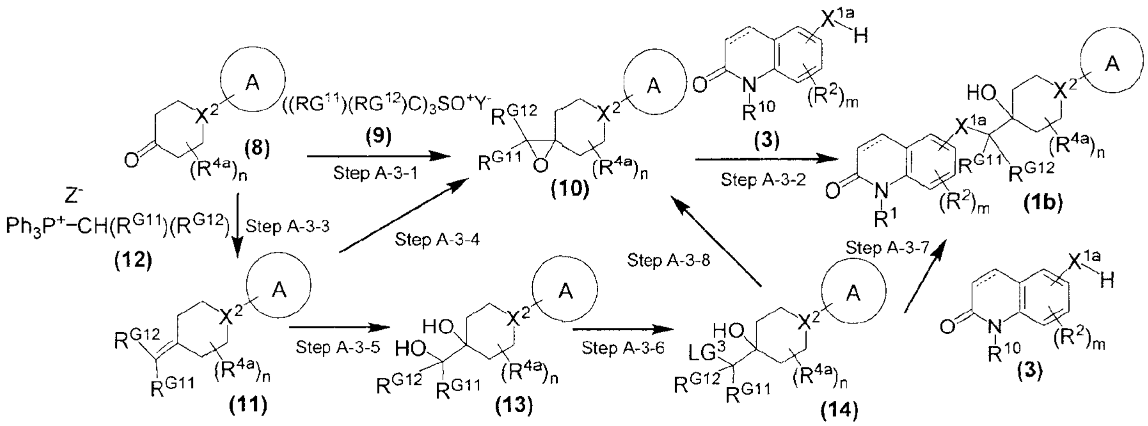
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0130]

Scheme A-3

[Chem. 25]



wherein each R^{4a} independently represents amino optionally having one or more lower alkyl, halogen, cyano, lower alkyl, -O-R^8 or -O-C(=O)-R^9; Y^- and Z^- each independently represents halide ion; LG^3 represents a leaving group; and other symbols are as defined above.

[0131]

(Step A-3-1: (8) + (9) -> (10))

Compound (10) can be obtained, for example, by reacting compound (8) with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction).

The amount of compound (9) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (8).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8).

In addition, as necessary, a salt can be added.

Examples of the salt include, for example, halogenated alkali metals such as cesium fluoride, cesium chloride, cesium bromide, cesium iodide, potassium fluoride, potassium chloride, potassium bromide, potassium iodide, sodium fluoride, sodium chloride, sodium bromide, sodium iodide, lithium fluoride, lithium chloride, lithium bromide and lithium iodide. The amount of the salt used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0132]

(Step A-3-2: (10) + (3) -> (1b))

Among the compounds represented as formula (1), compound (1b) can be obtained, for example, by reacting compound (10) with compound (3) in an inert solvent in the presence of a base or in the presence of an acid.

The amount of compound (3) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (10).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 0.01 to 10 molar equivalents, preferably 0.1 to 5 molar equivalents relative to compound (10).

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (10).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0133]

(Step A-3-3: (8) + (12) -> (11))

Compound (11) can be obtained, for example, by reacting compound (8) with compound (12) in an inert solvent in the presence of a base (Wittig reaction).

The amount of compound (12) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (8).

Examples of the base include, for example, alkali metal hydrides, metal amides, metal alkoxides and organolithium reagent, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons and ethers, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0134]

(Step A-3-4: (11) -> (10))

Compound (10) can be obtained, for example, by reacting compound (11) in an inert solvent in the presence of an oxidizing agent.

Examples of the oxidizing agent include inorganic peroxides (such as hydrogen peroxide, sodium hypochlorite and sodium periodate), organic peroxides (such as m-chloroperbenzoic acid, perbenzoic acid, peracetic acid and trifluoroperacetic acid) and dioxiranes (such as dimethyldioxirane). The amount of the oxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (11).

In addition, a base can be used, as necessary.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (11).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0135]

(Step A-3-5: (11) -> (13))

Compound (13) can be obtained, for example, by reacting compound (11) with in an inert solvent in the presence of osmium tetraoxide and a reoxidizing agent.

The amount of osmium tetraoxide used is typically 0.01 to 0.5 molar equivalents relative to compound (11). Also, potassium osmate ($K_2OsO_2(OH)_4$) may be used as an alternative to osmium tetraoxide. In addition, it is possible to use an immobilized catalyst in which osmium tetraoxide is supported on a solvent resistant polymer. Example of immobilized catalyst includes "Osmium Oxide, Immobilized Catalyst I (Os IC-I)" (trade name) (Wako Pure Chemical Industries, Ltd.).

Examples of the reoxidizing agent include, for example, N-methylmorpholine oxide, trimethylamine oxide, *tert*-butyl hydroperoxide and potassium ferricyanide ($K_3Fe(CN)_6$), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the reoxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (11).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0136]

(Step A-3-6: (13) -> (14))

Compound (14) can be obtained by transforming a specific hydroxy group in compound (13) to a leaving group. Said reaction can be performed under the conditions similar to above step A-2-3.

[0137]

(Step A-3-7: (14) + (3) -> (1b))

Among the compounds represented as formula (1), compound (1b) can be obtained, for example, by reacting compound (14) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

[0138]

(Step A-3-8: (14) -> (10))

Compound (10) can be obtained, for example, by reacting compound (14) in an inert solvent in the presence of a base.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (14).

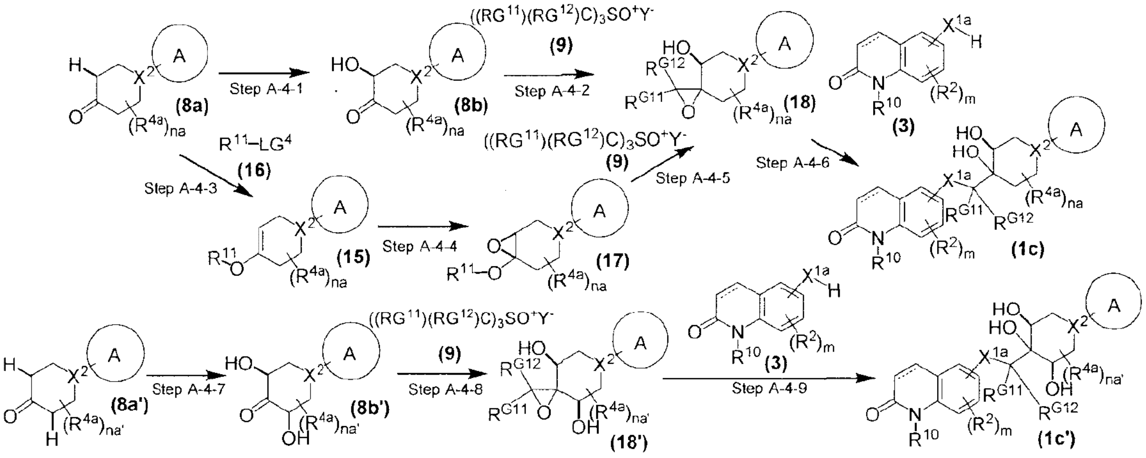
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0139]

Scheme A-4

[Chem. 26]



wherein R^{11} represents tri-lower alkyl-silyl; LG^4 represents a leaving group; na is an integer from 0 to 7; na' is an integer from 0 to 6; and other symbols are as defined above.

[0140]

(Step A-4-1: (8a) -> (8b))

Among the compounds represented as formula (8), compound (8b) can be obtained, for example, by subjecting α-aminooxylation by reacting compound (8a) with a nitroso compound in an inert solvent in the presence of a catalyst of proline or a derivative thereof, followed by hydrolysis in the presence of copper (II) sulfate catalyst.

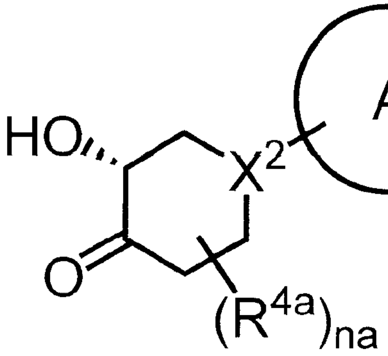
The amount of copper (II) sulfate used is typically 0.001 to 3 molar equivalents relative to compound (8a).

Example of the nitroso compound includes nitrosobenzene optionally having one or more substituents. The amount of the nitroso compound used is typically 1 to 10 molar equivalents, preferably 1 to 2 molar equivalents relative to compound (8a).

Examples of proline or a derivative thereof include LD-proline and 5-(pyrrolidin-2-yl)-1H-tetrazole. The amount of proline or a derivative thereof used is typically 0.001 to 3 molar equivalents relative to compound (8a).

In addition, by using L-proline and (S)-5-(pyrrolidin-2-yl)-1H-tetrazole etc. as proline or a derivative thereof, typically, it is possible to obtain mostly a compound represented as formula (8ba):

[Chem. 27]

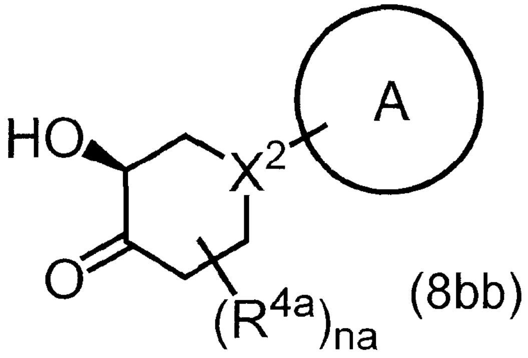


(8ba)

as compound (8b).

Alternatively, by using D-proline and (R)-5-(pyrrolidin-2-yl)-1H-tetrazole etc. as proline or a derivative thereof, typically, it is possible to obtain mostly a compound represented as formula (8bb):

[Chem. 28]



(8bb)

as compound (8b).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0141]

(Step A-4-2: (8b) + (9) -> (18))

Compound (18) can be obtained, for example, by reacting compound (8b) with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction). Said reaction can be performed under the conditions similar to above step A-3-1.

[0142]

(Step A-4-3: (8a) + (16) -> (15))

Compound (15) can be obtained, for example, by reacting compound (8a) with compound (16) in an inert solvent in the presence of a base.

The amount of compound (16) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8a).

In addition, it may possible to add sodium iodide, as necessary. The amount of sodium iodide used is typically 0.01 to 10 molar equivalents, preferably 0.1 to 5 molar equivalents relative to compound (8a).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (8a).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0143]

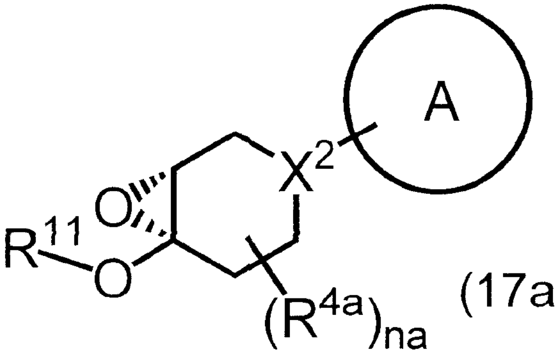
(Step A-4-4: (15) -> (17))

Compound (17) can be obtained, for example, by reacting compound (15) in an inert solvent in the presence of an oxidizing agent.

Examples of the oxidizing agent include inorganic peroxides (such as hydrogen peroxide, sodium hypochlorite and sodium periodate), organic peroxides (such as m-chloroperbenzoic acid, perbenzoic acid, peracetic acid and trifluoroperacetic acid) and dioxiranes (such as dimethyldioxirane). The amount of the oxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (15).

In addition, Shi asymmetric epoxidation is performed by using Shi epoxidizing catalyst (1-O,2-O:4-O,5-O-diisopropylidene-β-D-erythro-2,3-hexodiuro-2,6-pyranose), and it may possible to obtain, mainly, formula (17a):

[Chem. 29]



(17a)

wherein each symbol is as defined above

as compound (17). The amount of Shi epoxidizing catalyst used is typically 0.001 to 3 molar equivalents relative to compound (15).

In addition, when using a ketone compound such as Shi epoxidizing catalyst, an oxidation auxiliary can be used in place of an oxidizing agent. Example of the oxidation auxiliary includes Oxone (registered trade name). The amount of the oxidation auxiliary used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (15).

In addition, a base can be used, as necessary.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (15).

In addition, an additive agent can be added, as necessary. Example of the additive agent includes ethylenediaminetetraacetic acid disodium salt. The amount of the additive agent used is typically 0.001 to 3 molar equivalents relative to compound (15).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0144]

(Step A-4-5: (17) + (9) -> (18))

Compound (18) can be obtained, for example, by reacting compound (17) with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction). Said reaction can be performed under the conditions similar to above step A-3-1.

[0145]

(Step A-4-6: (18) + (3) -> (1c))

Among the compounds represented as formula (1), compound (1c) can be obtained, for example, by reacting compound (18) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-3-2.

[0146]

(Step A-4-7: (8a') -> (8b'))

Among the compounds represented as formula (8), compound (8b') can be obtained, for example, by subjecting α-aminohydroxylation by reacting compound (8a') with a nitroso compound in an inert solvent in the presence of a catalyst of proline or a derivative thereof, followed by hydrolysis in the presence of copper (II) sulfate catalyst. Said reaction can be performed under the conditions similar to above step A-4-1. The amount of the nitroso compound used is typically 2 to 10 molar equivalents, preferably 2 to 5 molar equivalents relative to compound (8a').

[0147]

(Step A-4-8: (8b') + (9) -> (18'))

Compound (18') can be obtained, for example, by reacting compound (8b') with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction). Said reaction can be performed under the conditions similar to above step A-3-1.

[0148]

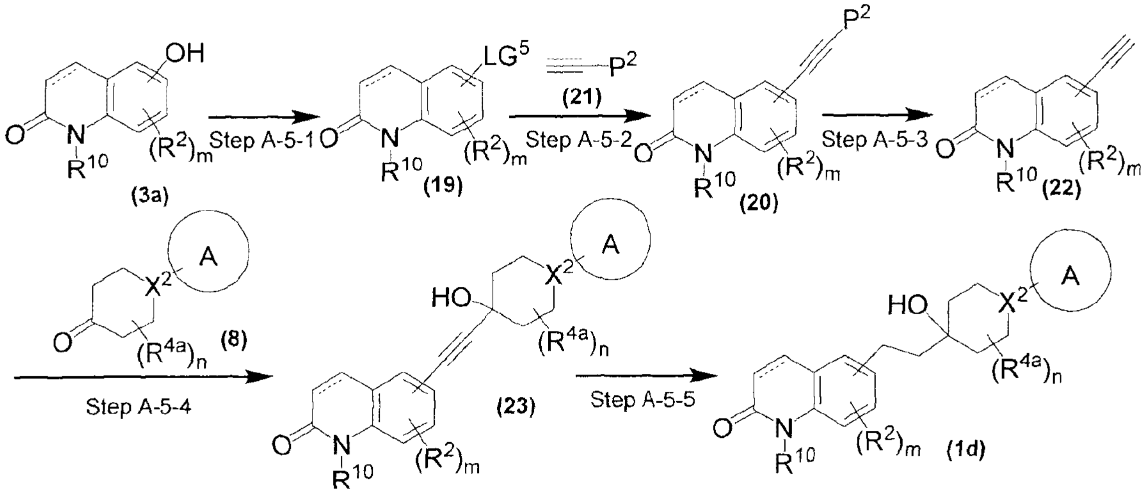
(Step A-4-9: (18') + (3) -> (1c'))

Among the compounds represented as formula (1), compound (1c') can be obtained, for example, by reacting compound (18') with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-3-2.

[0149]

Scheme A-5

[Chem. 30]



wherein LG^5 represents a leaving group; P^2 represents a protecting group on terminal acetylene; and other symbols are as defined above.

[0150]

(Step A-5-1: (3a) -> (19))

Compound (19) can be obtained by transforming hydroxy of compound (3a) to a leaving group by using any known method. For example, said reaction can be performed under the conditions similar to above step A-2-3.

[0151]

(Step A-5-2: (19) + (21) -> (20))

Compound (20) can be obtained, for example, by reacting compound (19) with compound (21) in an inert solvent, in the presence of base and transition metal catalyst. The amount of compound (21) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (19).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (19).

Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(*tert*-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro-[1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (19).

In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(*tert*-butyl)phosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (19).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0152]

(Step A-5-3: (20) -> (22))

Compound (22) can be obtained by subjecting compound (20) to a deprotection reaction.

Any of known reactions may be used as the deprotection reaction, for example, when P^2 is silyl, compound (20) can be deprotected in the presence of a fluoride source or an acid to give compound (22).

Examples of the fluoride source include tetrabutylammonium fluoride, hydrofluoric acid and cesium fluoride. The amount of the fluoride source used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (20).

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid; organic acids such as methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (20).

The acid can be used as a solvent, or an additional inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0153]

(Step A-5-4: (22) + (8) -> (23))

Compound (23) can be obtained, by treating compound (22) with a base in an inert solvent, followed by a reaction with compound (8).

The amount of compound (8) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (22).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides, organic lithium reagent and a Grignard reagent of secondary or tertiary alkyl, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (22).

Examples of the Grignard reagent of secondary or tertiary alkyl include for example, isopropylmagnesium chloride, isopropylmagnesium bromide and *tert*-butylmagnesium bromide. Examples of the organic lithium reagent include, for example, isopropyllithium, propyllithium and *tert*-butylithium.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0154]

(Step A-5-5: (23) -> (1d))

Among the compounds represented as formula (1), compound (1d) can be obtained by subjecting compound (23) in the reduction reaction in an inert solvent, in the presence of a hydrogen source and a metal catalyst.

Examples of the hydrogen source include, for example, hydrogen gas, formic acid, sodium formate, ammonium formate, cyclohexene, phosphinic acid salt and hydrazine. When using hydrogen gas as the hydrogen source, the reaction can be done under the hydrogen pressure of about 1 to 10 atm. The amount of another hydrogen source used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (23).

Examples of the metal catalyst include, for example, palladium on carbon, palladium black, palladium chloride, palladium hydroxide on carbon, platinum oxide, platinum black, platinum-palladium, platinum-carbon, Raney nickel and Raney cobalt. The amount of the metal catalyst used is typically 0.001 to 1000 molar equivalents, preferably 0.01 to 100 molar equivalents relative to compound (23).

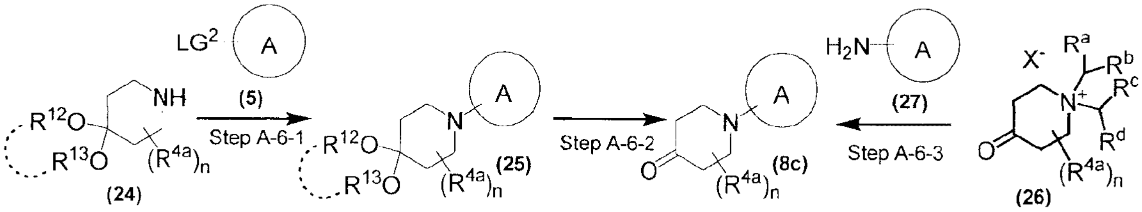
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0155]

Scheme A-6

[Chem. 31]



wherein R^{12} and R^{13} each independently represents lower alkyl, or R^{12} and R^{13} may unitedly form an acetal ring; R^a, R^b, R^c and R^d each independently represents hydrogen, lower alkyl optionally having one or more substituents, lower alkenyl optionally having one or more substituents, lower alkoxycarbonyl optionally having one or more substituents, and aryl optionally having one or more substituents or carboxy; X^- represents an inert anion such as halide ion; and other symbols are as defined above.

[0156]

(Step A-6-1: (24) + (5) -> (25))

Compound (25) can be obtained, for example, by reacting compound (24) with compound (5) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-2-1.

[0157]

(Step A-6-2: (25) -> (8c))

Among the compounds represented as formula (8), compound (8c) can be obtained, for example, by treating compound (25) with an acid.

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (25).

The acid can be used as a solvent, or an additional inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, ketones, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0158]

(Step A-6-3: (26) + (27) -> (8c))

Among the compounds represented as formula (8), compound (8c) can be obtained, for example, by reacting compound (26) with compound (27) in an inert solvent.

The amount of compound (27) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (26).

In addition, an additive agent can be added, as necessary. Examples of the additive agent include, for example, sodium acetate, sodium hydrogen carbonate, potassium carbonate, proline, thioureas, tertiary amines, acetic acid. The amount of the additive agent used is typically 0.01 to 10 molar equivalents, preferably 0.02 to 5 molar equivalents relative to compound (26).

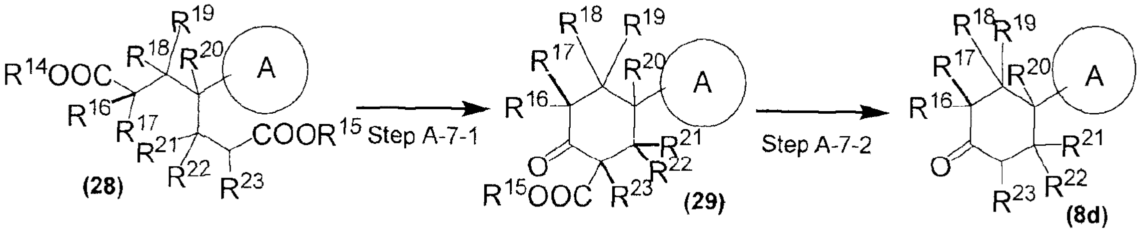
Examples of the inert solvent include, for example, water, alcohols, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0159]

Scheme A-7

[Chem. 32]



wherein R^{14} and R^{15} each independently represents lower alkyl; R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} each independently represents hydrogen, amino optionally having one or more lower alkyl, halogen, cyano, lower alkyl, -O-R^8 or -O-C(=O)-R^9; R^{23} represents hydrogen, cyano or lower alkyl; and other symbols are as defined above.

[0160]

(Step A-7-1: (28) -> (29))

Compound (29) can be obtained, for example, by subjecting compound (28) to Claisen condensation reaction in an inert solvent in the presence of a base.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (28).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0161]

(Step A-7-2: (29) -> (8d))

Compound (8d) can be obtained, for example, by subjecting compound (29) to decarbonation reaction in an inert solvent.

An acid, a base or a salt can be added, as necessary.

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio.

Examples of the salt include, for example, halogenated alkali metals such as cesium fluoride, cesium chloride, cesium bromide, cesium iodide, potassium fluoride, potassium chloride, potassium bromide, potassium iodide, sodium fluoride, sodium chloride, sodium bromide, sodium iodide, lithium fluoride, lithium chloride, lithium bromide and lithium iodide.

The amount of the acid, base or salt used is typically 1 molar equivalent to excessive amounts relative to compound (29).

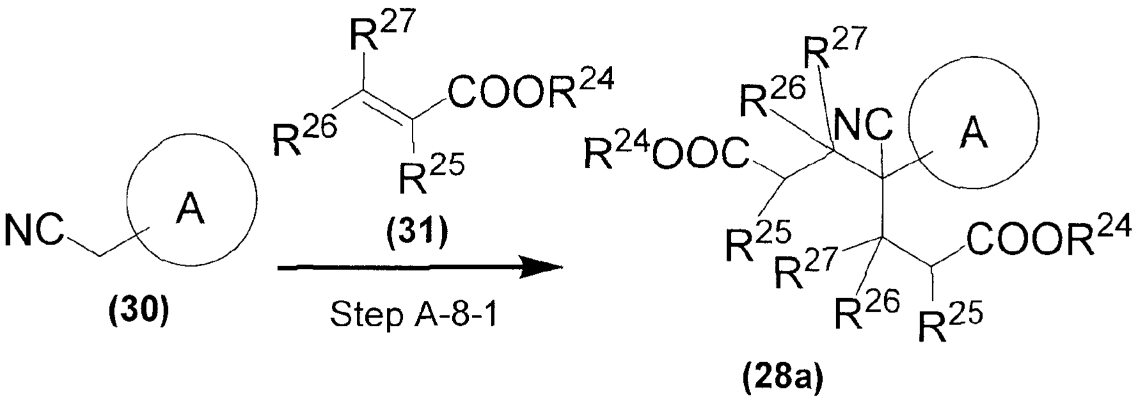
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0162]

Scheme A-8

[Chem. 33]



wherein R^{24} represents lower alkyl; R^{25} represents hydrogen, cyano or lower alkyl; R^{26} and R^{27} each independently represents hydrogen, amino optionally having one or more lower alkyl, halogen, cyano, lower alkyl, -O-R^8 or -O-C(=O)-R^9; and other symbols are as defined above.

[0163]

(Step A-8-1: (30) + (31) -> (28a))

Among the compounds represented as formula (28), compound (28a) can be obtained, for example, by reacting compound (30) with compound (31) in an inert solvent in the presence of a base (Michael addition reaction).

The amount of compound (31) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (30).

Examples of the base include, for example, basic ammonium salts, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (30).

Examples of the basic ammonium salt include tetramethylammonium hydoxide, tetraethylammonium hydoxide, tetra-n-propylammonium hydoxide, tetraisopropylammonium hydoxide, tetra-n-butylammonium hydroxide and benzyltrimethylammonium hydoxide (Triton-B).

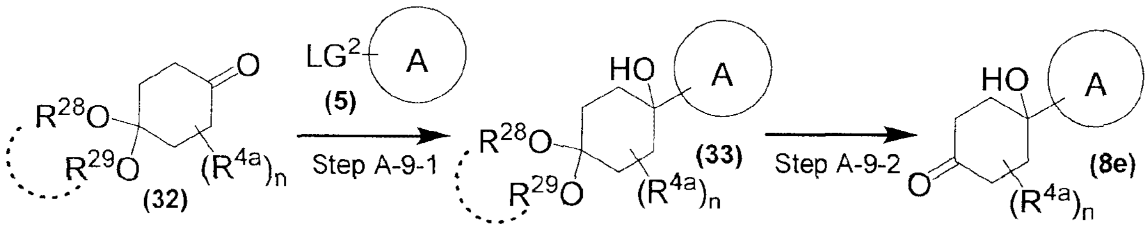
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, alcohols, ethers, amides, sulfoxides and nitriles, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0164]

Scheme A-9

[Chem. 34]



wherein R^{28} and R^{29} each independently represents a lower alkyl group, or R^{28} and R^{29} may unitedly form an acetal ring; and other symbols are as defined above.

[0165]

(Step A-9-1: (32) + (5) -> (33))

Compound (33) can be obtained, for example, by a magnesiation or lithiation of compound (5) using a method such as halogen-metal exchange method employing a Grignard reagent of secondary or tertiary alkyl or organic lithium reagent, and then reacting the obtained compound with compound (32).

The amount of compound (5) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (32).

Examples of the Grignard reagent of secondary or tertiary alkyl include for example, isopropylmagnesium chloride, isopropylmagnesium bromide and *tert*-butylmagnesium bromide. Examples of the organic lithium reagent include, for example, isopropyllithium, propyllithium and *tert*-butylithium. The amount of the Grignard reagent of secondary or tertiary alkyl or organic lithium reagent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (32).

Examples of the inert solvent include, for example, hydrocarbons, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0166]

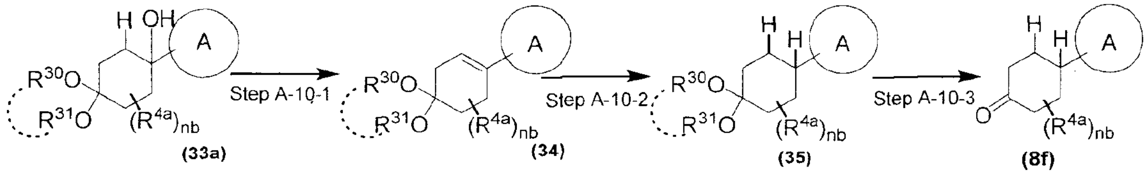
(Step A-9-2: (33) -> (8e))

Among the compounds represented as formula (8), compound (8e) can be obtained, for example, by treating compound (33) with an acid. Said reaction can be performed under the conditions similar to above step A-6-2.

[0167]

Scheme A-10

[Chem. 35]



wherein R^{30} and R^{31} each independently represents lower alkyl, or R^{30} and R^{31} may unitedly form an acetal ring; nb is an integer of 0 to 7; and other symbols are as defined above.

[0168]

(Step A-10-1: (33a) -> (34))

Compound (34) can be obtained, for example, by transforming hydroxy in compound (33a) to a leaving group by using any known method followed by olefination reaction.

For example, hydroxy of compound (33a) can be transformed to a leaving group by reacting it with sulfonic anhydride (such as trifluoromethanesulfonic anhydride) or sulfonyl halide (such as benzenesulfonyl chloride, p-toluenesulfonyl chloride and methylsulfonyl chloride) in an inert solvent in the presence of a base, followed by an elimination reaction to give compound (34). The amount of sulfonic anhydride or sulfonyl halide used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (33a).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (33a).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0169]

(Step A-10-2: (34) -> (35))

Compound (35) can be obtained by subjecting compound (34) to reduction reaction in an inert solvent, in the presence of a hydrogen source and a metal catalyst. Said reaction can be performed under the conditions similar to above step A-5-5.

[0170]

(Step A-10-3: (35) -> (8f))

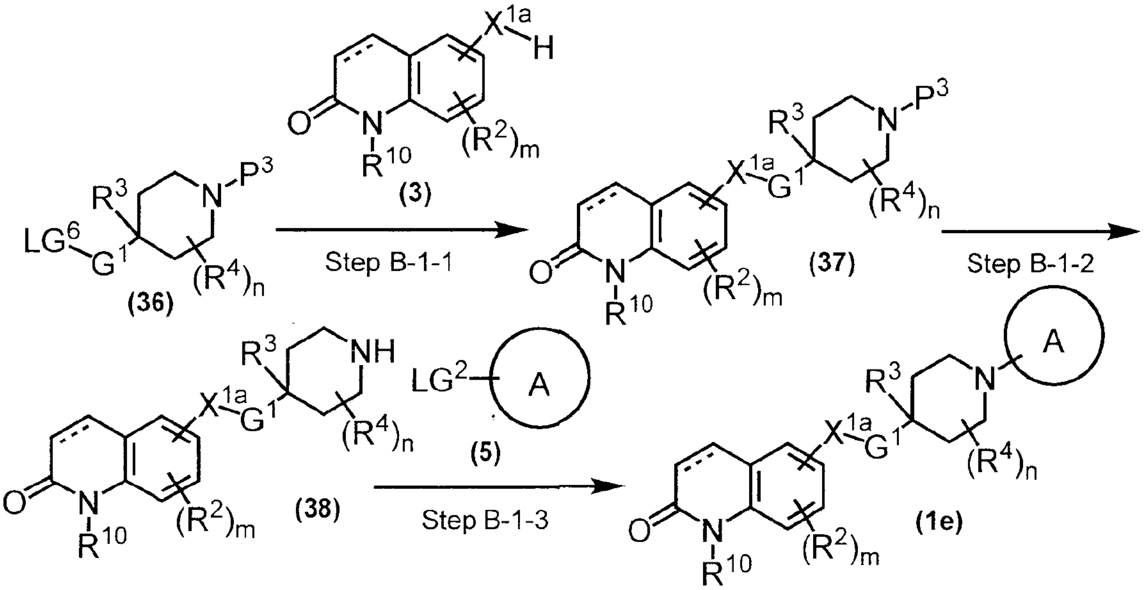
Among the compounds represented as formula (8), compound (8f) can be obtained, for example, by treating compound (35) with an acid. Said reaction can be performed under the conditions similar to above step A-6-2.

[Preparation method B: General synthetic route 2]

[0171]

Scheme B-1

[Chem. 36]



wherein LG^6 represents a leaving group; P^3 represents an amino protecting group; and other symbols are as defined above.

[0172]

(Step B-1-1: (36) + (3) -> (37))

Compound (37) can be obtained, for example, by reacting compound (36) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

[0173]

(Step B-1-2: (37) -> (38))

Compound (38) can be obtained by subjecting compound (37) to a deprotection reaction.

Any of known reactions may be used as the deprotection reaction, for example, when P^2 is *tert*-butoxycarbonyl group (Boc), compound (37) can be deprotected in an inert solvent or in the absence of solvent in the presence of an acid (such as hydrochloric acid and trifluoroacetic acid) to give compound (38).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0174]

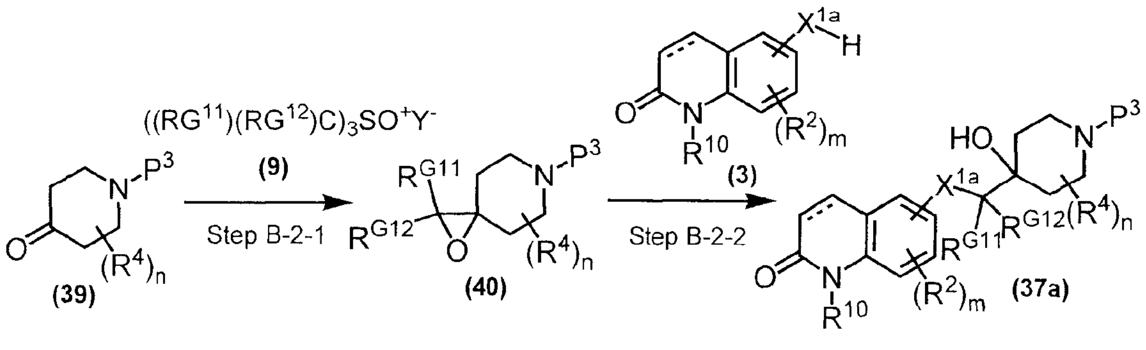
(Step B-1-3: (38) + (5) -> (1e))

Among the compounds represented as formula (1), compound (1e) can be obtained, for example, by reacting compound (38) with compound (5) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-2-1.

[0175]

Scheme B-2

[Chem. 37]



wherein each symbol is as defined above.

[0176]

(Step B-2-1: (39) + (9) -> (40))

Compound (40) can be obtained, for example, by reacting compound (39) with compound (9) in an inert solvent in the presence of a base (Corey-Chaykovsky reaction). Said reaction can be performed under the conditions similar to above step A-3-1.

[0177]

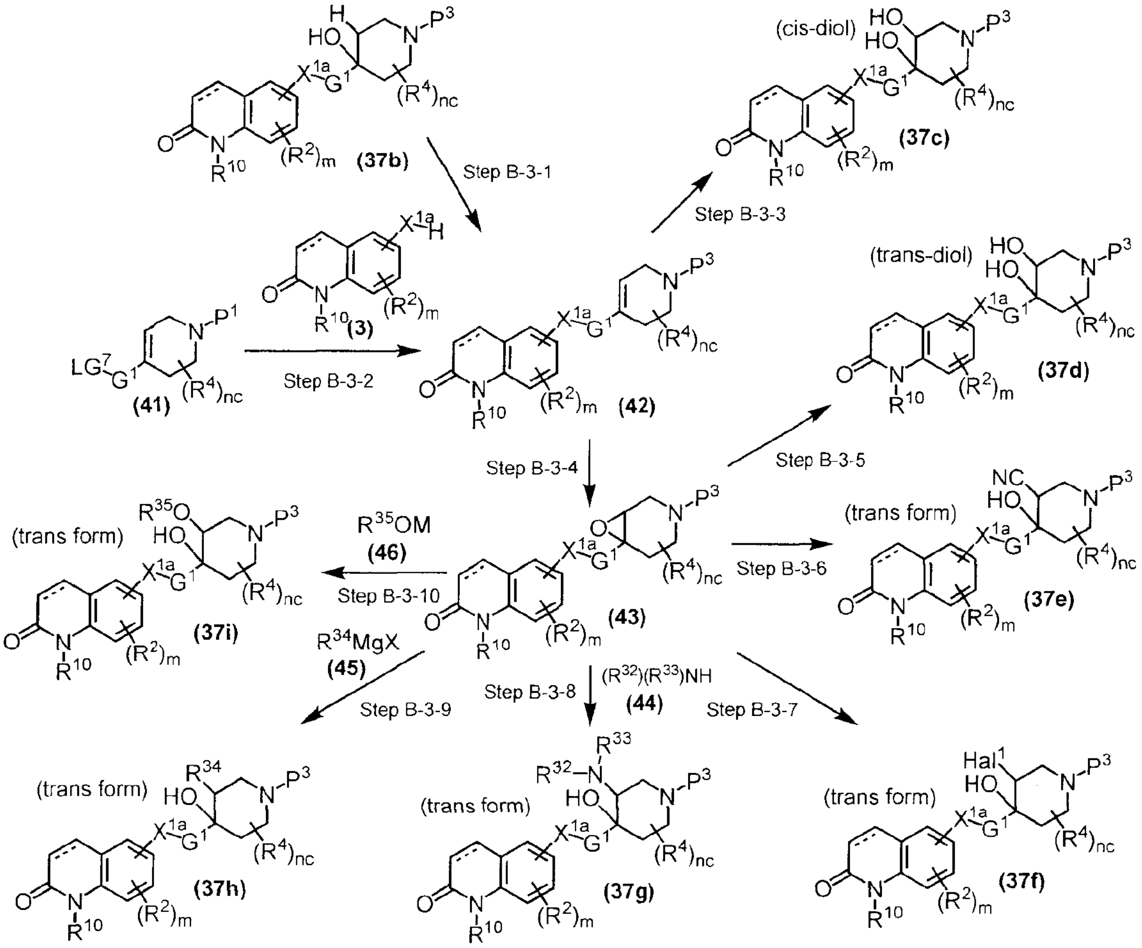
(Step B-2-2: (40) + (3) -> (37a))

Among the compounds represented as formula (37), compound (37a) can be obtained, for example, by reacting compound (40) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-3-2.

[0178]

Scheme B-3

[Chem. 38]



wherein LG^7 represents a leaving group; Hal^1 represents halogen; R^{32} and R^{33} each independently represents hydrogen or lower alkyl; R^{34} represents lower alkyl; R^{35} represents lower alkyl; M represents an alkali metal atom; X represents halogen; nc is an integer of 0 to 7; and other symbols are as defined above.

[0179]

(Step B-3-1: (37b) -> (42))

Compound (42) can be obtained, for example, by transforming hydroxy in compound (37b) to a leaving group by using any known method followed by olefination reaction. Said reaction can be performed under the conditions similar to above step A-10-1.

[0180]

(Step B-3-2: (41) + (3) -> (42))

Compound (42) can be obtained, for example, by reacting compound (41) with compound (3) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

[0181]

(Step B-3-3: (42) -> (37c))

Among the compounds represented as formula (37), compound (37c) can be obtained, for example, by reacting compound (42) in an inert solvent, in the presence of osmium tetraoxide and a reoxidizing agent.

The amount of osmium tetraoxide used is typically 0.01 to 0.5 molar equivalents relative to compound (42). Also, potassium osmate ($K_2OsO_2(OH)_4$) may be used as an alternative to osmium tetraoxide. In addition, it is possible to use an immobilized catalyst in which osmium tetraoxide is support on a solvent resistant polymer. Example of immobilized catalyst includes "Osmium Oxide, Immobilized Catalyst I (Os IC-I)" (trade name) (Wako Pure Chemical Industries, Ltd.).

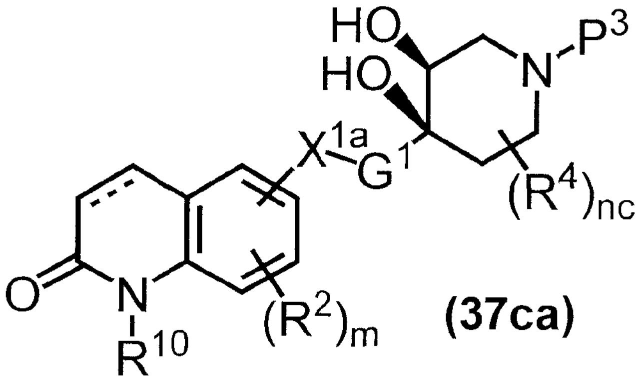
Examples of the reoxidizing agent include, for example, N-methylmorpholine oxide, trimethylamine oxide, *tert*-butyl hydroperoxide and potassium ferricyanide ($K_3Fe(CN)_6$), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the reoxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (42).

In addition, Sharpless asymmetric dihydroxylation reaction can be done by using an asymmetric amine ligand.

Examples of the asymmetric amine ligand include, for example, hydroquinine ethers such as hydroquinine anthraquinone-1,4-diyl diether [$(DHQ)_2AQN$], hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQ)_2PYR$] and hydroquinine 1,4-phthalazinediyl diether [$(DHQ)_2PHAL$] and; hydroquinidine ethers such as hydroquinidine anthraquinone-1,4-diyl diether [$(DHQD)_2AQN$], hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQD)_2PYR$] and hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$]. The amount of the asymmetric amine ligand used is typically 0.001 to 1 molar equivalent relative to compound (42).

For example, when employing a hydroquinine ether, typically, it is possible to obtain mainly, a compound represented as formula (37ca):

[Chem. 39]



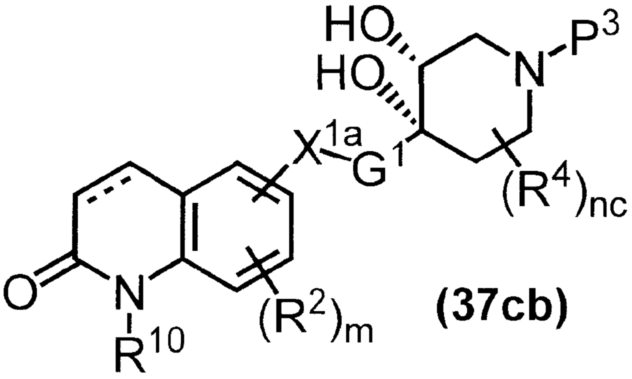
(37ca)

wherein each symbol is as defined above

as compound (37c).

For example, when using a hydroquinidine ether, typically, it is possible to obtain mainly, a compound represented as formula (37cb):

[Chem. 40]



(37cb)

wherein each symbol is as defined above

as compound (37c).

In addition, it is possible to add a base, as necessary. Examples of the base include alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydroxides, aromatic amines and tertiary amines. The amount of the base used is typically 0.001 to 3 molar equivalents relative to compound (42).

In addition, an additive agent can be added, as necessary. Example of the additive agent includes methanesulfonamide. The amount of the additive agent used is typically 0.001 to 3 molar equivalents relative to compound (42).

In addition, a commercially available reagent kit such as AD-mix-α (comprising $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$ and K_2CO_3) or AD-mix-β (comprising $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$ and K_2CO_3) can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0182]

(Step B-3-4: (42) -> (43))

Compound (43) can be obtained, for example, by reacting compound (42) in an inert solvent in the presence of an oxidizing agent. Said reaction can be performed under the conditions similar to above step A-4-4.

[0183]

(Step B-3-5: (43) -> (37d))

Among the compounds represented as formula (37), compound (37d) can be obtained, for example, by treating compound (43) with an acid.

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (43).

The acid can be used as a solvent, or an additional inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0184]

(Step B-3-6: (43) -> (37e))

Among the compounds represented as formula (37), compound (37e) can be obtained, for example, treating compound (43) with a cyane source and a base.

Examples of the cyane source include, for example, α-cyanohydrins such as α-hydroxyisobutyronitrile. The amount of the cyane source used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (43).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (43).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0185]

(Step B-3-7: (43) -> (37f))

Among the compounds represented as formula (37), compound (37f) can be obtained, by reacting for example, compound (43) with hydrogen halide in an inert solvent or in the absence of solvent.

When Hal^1 is fluorine, tetrabutylammonium dihydrogen trifluoride can be used as the hydrogen halide.

The amount of the hydrogen halide used is typically 1 molar equivalent to excessive amounts relative to compound (43).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0186]

(Step B-3-8: (43) + (44) -> (37g))

Among the compounds represented as formula (37), compound (37g) can be obtained, for example, by reacting compound (43) with compound (44).

The amount of compound (44) used is typically 1 molar equivalent to excessive amounts relative to compound (43).

Compound (44) can be used as a solvent, or an additional inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0187]

(Step B-3-9: (43) + (45) -> (37h))

Among the compounds represented as formula (37), compound (37h) can be obtained, for example, by reacting compound (43) with compound (45) in an inert solvent.

The amount of compound (45) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (43).

In addition, a copper compound can be used as a catalyst, as necessary.

Examples of the copper compound include for example, copper (I) chloride, copper (II) chloride, copper (I) bromide, copper (II) bromide, copper (I) iodide, copper (I) oxide, copper (II) oxide, copper (I) acetate, copper (II) acetate, copper (I) cyanide, copper (II) sulfate, or a dimethyl sulfide complex thereof. The amount of the copper compound used is typically 0.001 to 3 molar equivalents relative to compound (43).

Examples of the inert solvent include, for example, hydrocarbons, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0188]

(Step B-3-10: (43) + (46) -> (37i))

Among the compounds represented as formula (37), compound (37i) can be obtained, for example, by reacting compound (43) with compound (46) in an inert solvent.

The amount of compound (46) used is typically 1 molar equivalent to excessive amounts relative to compound (43).

Examples of the alkali metal represented as M include potassium, sodium and cesium.

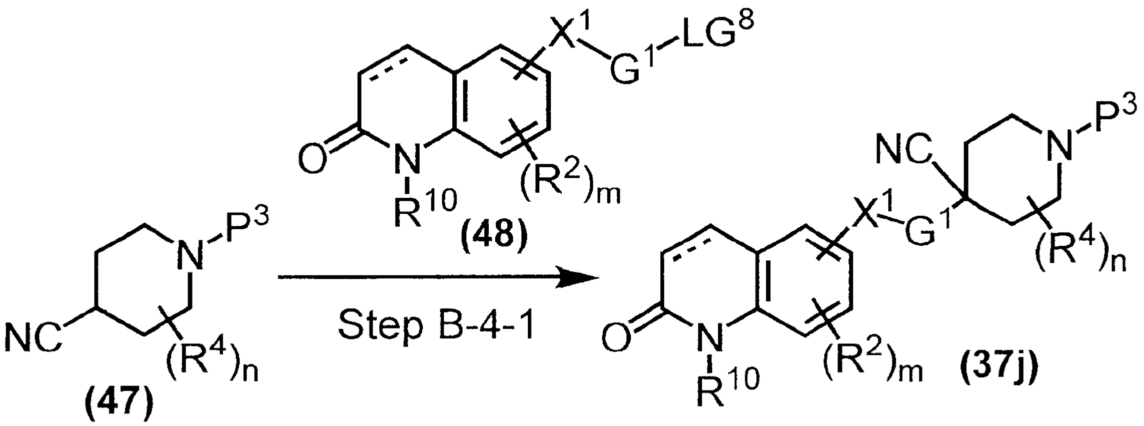
Examples of the inert solvent include, for example, alcohols corresponding to compound (46), or hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0189]

Scheme B-4

[Chem. 41]



wherein LG^8 represents a leaving group; and other symbols are as defined above.

[0190]

(Step B-4-1: (47) + (48) -> (37j))

Among the compounds represented as formula (37), compound (37j) can be obtained, for example, by reacting compound (47) with compound (48) in an inert solvent in the presence of a base.

The amount of compound (48) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (47).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (47).

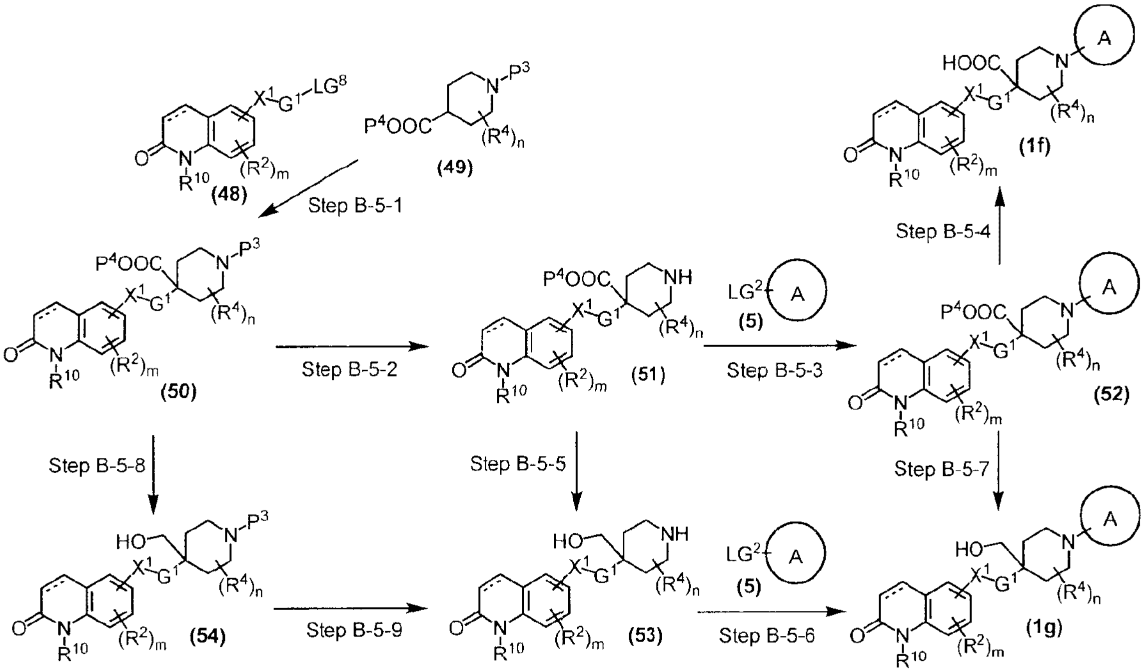
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0191]

Scheme B-5

[Chem. 42]



wherein P^4 represents a carboxy protecting group; and other symbols are as defined above.

[0192]

(Step B-5-1: (49) + (48) -> (50))

Compound (50) can be obtained, for example, by reacting compound (49) with compound (48) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step B-4-1.

[0193]

(Step B-5-2: (50) -> (51))

Compound (51) can be obtained by subjecting compound (50) to a deprotection reaction. For example, said reaction can be performed under the conditions similar to above step B-1-2.

[0194]

(Step B-5-3: (51) + (5) -> (52))

Compound (52) can be obtained, for example, by reacting compound (51) with compound (5) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-2-1.

[0195]

(Step B-5-4: (52) -> (1f))

Among the compounds represented as formula (1), compound (1f) can be obtained by subjecting compound (52) to a deprotection reaction.

Any of known reactions may be used as the deprotection reaction, for example, when P^4 is lower alkyl, said group can be deprotected by reacting the compound in an inert solvent in the presence of a base.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen phosphates and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (50).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0196]

(Step B-5-5: (51) -> (53))

Compound (53) can be obtained by subjecting P^4 of compound (51) to the deprotection reaction by using similar reaction to those of the above step B-5-4 to give carboxylic acid, and then subjecting the obtained compound to a reduction reaction in an inert solvent, in the presence of a reducing agent, alternatively, subjecting compound (51) directly to a reduction reaction in an inert solvent in the presence of a reducing agent.

Examples of the reducing agent include sodium borohydride, lithium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, sodium triethylborohydride, lithium triethylborohydride, lithium aluminum hydride, sodium dihydridobis(2-methoxyethoxy)-aluminate, borane-tetrahydrofuran complex and diisobutylaluminium hydride. The amount of the reducing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (51).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, alcohols, ethers, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0197]

(Step B-5-6: (53) + (5) -> (1g))

Compound (1g) can be obtained, for example, by reacting compound (53) with compound (5) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-2-1.

[0198]

(Step B-5-7: (52) -> (1g))

Among the compounds represented as formula (1), compound (1g) can be obtained by subjecting P^4 of compound (52) to the deprotection reaction by using similar reaction to those of the above step B-5-4 to give carboxylic acid, and then subjecting the obtained compound to a reduction reaction in an inert solvent, in the presence of a reducing agent, alternatively, subjecting compound (52) directly to a reduction reaction in an inert solvent in the presence of a reducing agent. Said reaction can be performed under the conditions similar to above step B-5-5.

[0199]

(Step B-5-8: (50) -> (54))

Compound (54) can be obtained by subjecting P^4 of compound (50)) to the deprotection reaction by using similar reaction to those of the above step B-5-4 to give carboxylic acid, and then subjecting the obtained compound to a reduction reaction in an inert solvent, in the presence of a reducing agent, alternatively, subjecting compound (50) directly to a reduction reaction in an inert solvent, in the presence of a reducing agent. Said reaction can be performed under the conditions similar to above step B-5-5.

[0200]

(Step B-5-9: (54) -> (53))

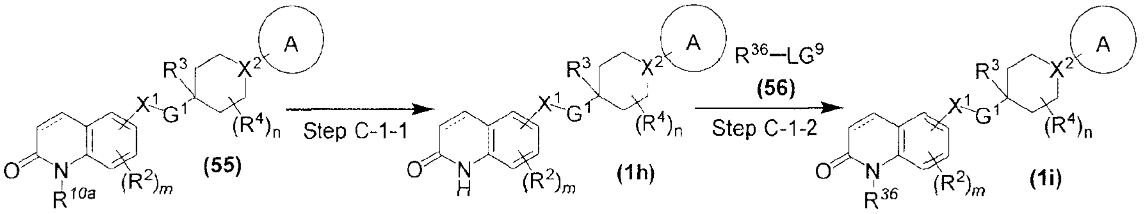
Compound (53) can be obtained by subjecting compound (54) to a deprotection reaction. For example, said reaction can be performed under the conditions similar to above step B-1-2.

[Preparation method C: Various derivatizations]

[0201]

Scheme C-1

[Chem. 43]



wherein R^{10a} represents an amino protecting group; LG^9 represents a leaving group; R^{36} represents amino optionally having one or more lower alkyl or lower alkyl; and other symbols are as defined above.

[0202]

(Step C-1-1: (55) -> (1h))

Among the compounds represented as formula (1), compound (1h) can be obtained by subjecting compound (55) to a deprotection reaction.

Any of known reactions may be used as the deprotection reaction, for example, when R^{10a} is 4-methoxybenzyl (PMB), compound (1h) can be obtained by hydrogenation in the presence of a hydrogen source and a metal catalyst, treatment with an oxidizing agent, or treatment under strong acid conditions.

When a subformula of the above formula (aa) is the formula represented as above formula (aa1), namely, compound (55) is protected as the imidic acid (lower alkyl protection), compound (1h) can be obtained by treating it under a strong acid condition.

Examples of the hydrogen source include, for example, hydrogen gas, formic acid, sodium formate, ammonium formate, cyclohexene, phosphinic acid salt and hydrazine. When using hydrogen gas as the hydrogen source, the reaction can be done under the hydrogen pressure of about 1 to 10 atm. The amount of another hydrogen source used is typically 1 molar equivalent to excessive amounts, preferably 1 to 10 molar equivalents relative to compound (55).

Examples of the metal catalyst include, for example, palladium on carbon, palladium black, palladium chloride, palladium hydroxide on carbon, platinum oxide, platinum black, platinum-palladium, platinum-carbon, Raney nickel and Raney cobalt. The amount of the metal catalyst used is typically 0.001 to 1000 molar equivalents, preferably 0.01 to 100 molar equivalents relative to compound (55).

Examples of the oxidizing agent include quinone oxidizing agents such as 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) and; metalic oxidizing agents such as ammonium hexanitratocerate (IV) (CAN). The amount of the oxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (55).

Examples of the strong acid include inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid and; organic acids such as trifluoroacetic acid and trifluoromethanesulfonic acid. The amount of the strong acid used is typically 1 molar equivalent to excessive amounts relative to compound (55).

In addition, when using the strong acid, it is possible to use a cation scavenger, as necessary. Examples of the cation scavenger include, for example, anisole, thioanisole, phenol, m-cresol, p-cresol and dimethyl sulfide. The amount of the cation scavenger used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (55).

The strong acid can be used as a solvent, or an inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, ketones, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0203]

(Step C-1-2: (1h) + (56) -> (1i))

Among the compounds represented as formula (1), compound (1i) can be obtained, for example, by reacting compound (1h) with compound (56) in an inert solvent in the presence of a base.

The amount of compound (56) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1h).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1h).

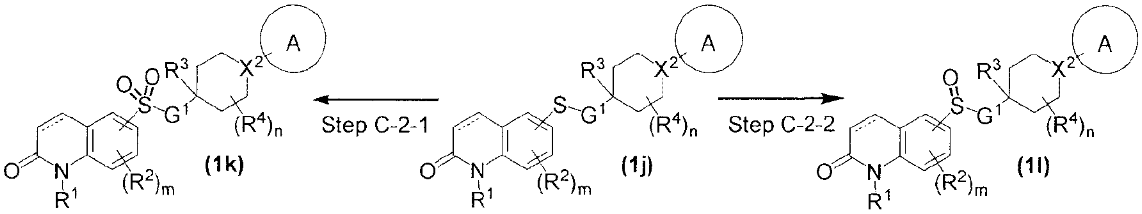
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0204]

Scheme C-2

[Chem. 44]



wherein each symbol is as defined above.

[0205]

(Step C-2-1: (1j) -> (1k))

Compound (1k) can be obtained, for example, by reacting compound (1j) in an inert solvent in the presence of an oxidizing agent.

Examples of the oxidizing agent include for example, inorganic peroxides (such as hydrogen peroxide, sodium hypochlorite and sodium periodate), organic peroxides (such as m-chloroperbenzoic acid, perbenzoic acid, peracetic acid and trifluoroperacetic acid) and dioxiranes (such as dimethyldioxirane). The amount of the oxidizing agent used is typically 2 to 10 molar equivalents, preferably 2 to 5 molar equivalents relative to compound (1j).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0206]

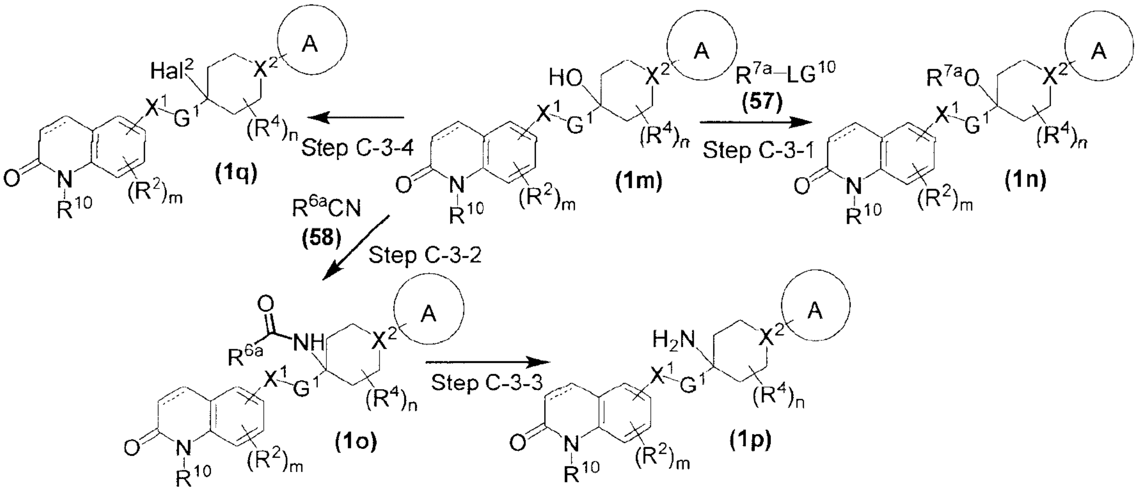
(Step C-2-2: (1j) -> (1l))

Compound (1l) can be obtained, for example, by reacting compound (1j) in an inert solvent in the presence of an oxidizing agent. Said reaction can be performed under the conditions similar to above step C-2-1. The amount of the oxidizing agent used is typically 1 to 10 molar equivalents, preferably 1 to 1.5 molar equivalents relative to compound (1j).

[0207]

Scheme C-3

[Chem. 45]



wherein R^{6a} represents lower alkyl optionally having one or more amino which optionally having one or more lower alkyl; R^{7a} represents amino, lower alkanoyl or lower alkyl; Hal^2 represents halogen; LG^{10} represents a leaving group; and other symbols are as defined above.

[0208]

(Step C-3-1: (1m) + (57) -> (1n))

Compound (1n) can be obtained, for example, by reacting compound (1m) with compound (57) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

In addition, when R^{7a} is lower alkanoyl, it is possible to use carboxylic acid anhydride such as $(R^{7a})_2O$ in place of compound (57).

[0209]

(Step C-3-2: (1m) + (58) -> (1o))

Compound (1o) can be obtained, for example, reacting compound (1m) with compound (58) in the presence of an acid.

The amount of compound (58) used is typically 1 molar equivalent to excessive amounts relative to compound (1m).

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid and; organic acids such as trifluoroacetic acid and trifluoromethanesulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (1m).

The acid or compound (58) can be used as a solvent, or an additional inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, sulfoxides and nitriles, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0210]

(Step C-3-3: (1o) -> (1p))

Compound (1p) can be obtained, for example, by treating compound (1o) with an acid.

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid and; organic acids such as trifluoroacetic acid and trifluoromethanesulfonic acid and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (1o).

The acid can be used as a solvent, or an additional inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, ketones, amides and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0211]

(Step C-3-4: (1m) -> (1q))

Compound (1q) can be obtained, for example, by reacting compound (1m) with a halogenating agent in an inert solvent.

Examples of the halogenating agent include, for example, thionyl chloride, oxalyl chloride, phosgene, phosphorus oxychloride and phosphorus pentachloride, phosphorus trichloride for chlorination; thionyl bromide and phosphorus tribromide for bromination; and bis(2-methoxyethyl)aminosulfur trifluoride and diethylaminosulfur trifluoride for fluorination.

The amount of the halogenating agent used is typically 1 to 10 molar equivalents relative to compound (1m).

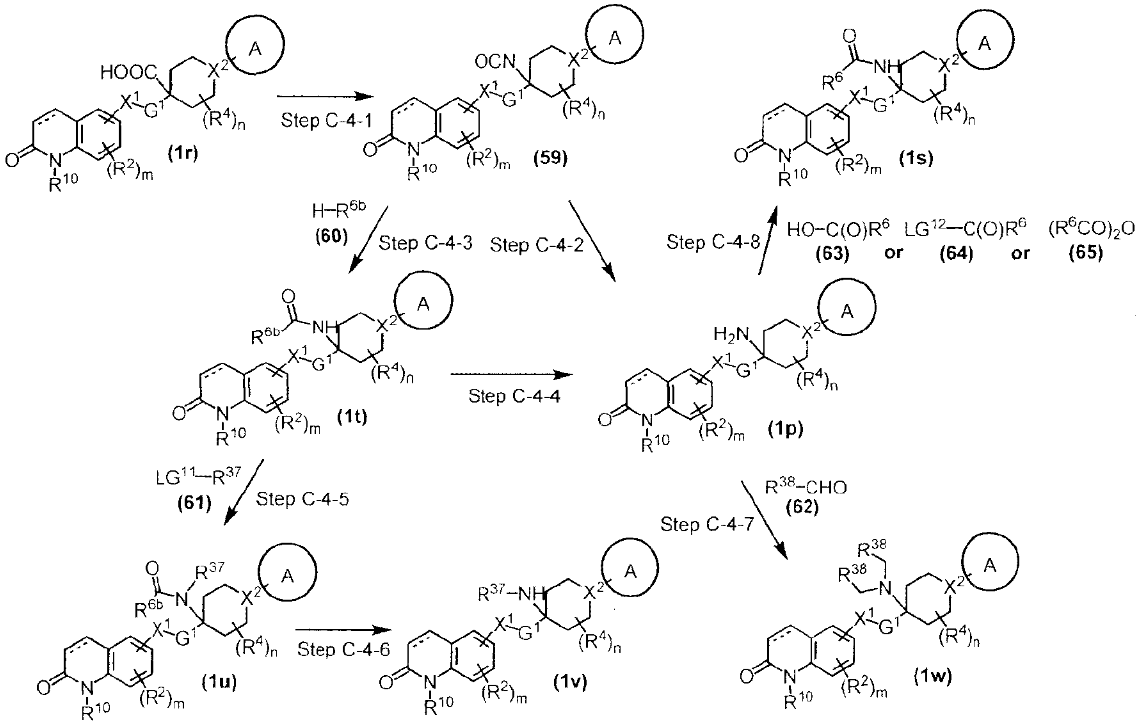
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0212]

Scheme C-4

[Chem. 46]



wherein R^{6b} represents lower alkoxy; R^{37} represents lower alkyl; R^{38} represents hydrogen or alkyl having 1 to 5 carbon atoms; LG^{11} or LG^{12} each independently represents a leaving group; and other symbols are as defined above.

[0213]

(Step C-4-1: (1r) -> (59))

Compound (59) can be obtained, for example, by reacting compound (1r) with a phosphoryl azide compound in an inert solvent in the presence of a base.

Examples of the phosphoryl azide compound include, for example, diphenylphosphoryl azide, bis(p-nitrophenyl)phosphoryl azide and diethylphosphoryl azide. The amount of the phosphoryl azide compound used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1r).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, preferably, tertiary amines, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1r).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically 40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0214]

(Step C-4-2: (59) -> (1p))

Among the compounds represented as formula (1), compound (1p) can be obtained, for example, by treating compound (59) with an acid.

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and phosphoric acid; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and 10-camphorsulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (59).

The acid can be used as a solvent, or an additional inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0215]

(Step C-4-3: (59) + (60) -> (1t))

Among the compounds represented as formula (1), compound (1t) can be obtained, for example, by reacting compound (59) with compound (60).

The amount of compound (60) used is typically 1 molar equivalent to excessive amounts relative to compound (59).

Compound (60) can be used as a solvent, or an inert solvent can be used in addition to compound (60).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0216]

(Step C-4-4: (1t) -> (1p))

Among the compounds represented as formula (1), compound (1p) can be obtained, for example, by treating compound (1t) with an acid.

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid; and organic acids such as acetic acid, trifluoroacetic acid and trifluoromethanesulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (1t).

The acid can be used as a solvent, or an additional inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, water, alcohols, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0217]

(Step C-4-5: (1t) + (61) -> (1u))

Among the compounds represented as formula (1), compound (1u) can be obtained, for example, by reacting compound (1t) with compound (61) in an inert solvent in the presence of a base.

The amount of compound (61) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1t).

Examples of the base include, for example, alkali metal hydrides and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1t).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -40 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0218]

(Step C-4-6: (1u) -> (1v))

Among the compounds represented as formula (1), compound (1v) can be obtained, for example, by treating compound (1u) with an acid. Said reaction can be performed under the conditions similar to above step C-4-4.

[0219]

(Step C-4-7: (1p) + (62) -> (1w))

Among the compounds represented as formula (1), compound (1w) can be obtained by reacting compound (1p) with compound (62) in an inert solvent, in the presence of a reducing agent (reductive amination reaction).

The amount of compound (62) used is typically 2 molar equivalents to excessive amounts relative to compound (1p).

Examples of the reducing agent include sodium borohydride, lithium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, sodium triethylborohydride, lithium triethylborohydride, lithium aluminum hydride, sodium dihydridobis(2-methoxyethoxy)-aluminate, borane-tetrahydrofuran complex, diisobutylaluminium hydride, formic acid, sodium formate and ammonium formate. The amount of the reducing agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, alcohols, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0220]

(Step C-4-8: (1p) + (63) or (64) or (65) -> (1s))

Among the compounds represented as formula (1), compound (1s) can be obtained by the condensation reaction of compound (1p) with compound (63), (64) or (65) in an inert solvent.

The respective amount of compound (63), (64) or (65) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

In addition, it is possible to add a base, as necessary. Example of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

In addition, a basic active agent can be used, as necessary. Examples of the basic active agent include N,N-dimethyl-4-aminopyridine (DMAP) and pyridine. The amount of the basic active agent used is typically 0.01 molar equivalents to excessive amounts relative to compound (1p).

In addition, especially when condensation reaction is performed with compound (63), it is preferred to use a condensation agent in the condensation. Examples of the condensation agent include, for example, carbodiimides such as 1,3-dicyclohexylcarbodiimide, 1-cyclohexyl-3-morpholinoethylcarbodiimide, 1-cyclohexyl-3-(4-diethylaminocyclohexyl)carbodiimide, 1,3-diethylcarbodiimide, 1,3-diisopropylcarbodiimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or salts thereof. The amount of the condensation agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

In addition, a condensation accelerator can be added in addition to the condensation agent. Examples of the condensation accelerator include, for example, 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), 1-hydroxy-7-azabenzotriazole (HOAt) and hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOOBt). The amount of the condensation accelerator used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1p).

In addition, tertiary amines such as pyridine can be used as a solvent, or an inert solvent can be used.

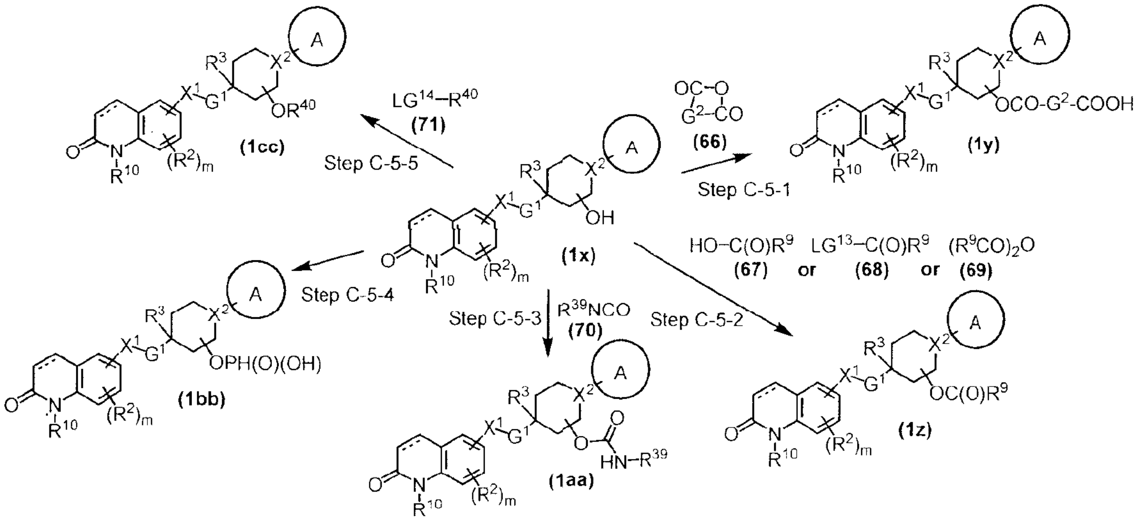
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0221]

Scheme C-5

[Chem. 47]



wherein R^{39} represents alkyl; R^{40} represents benzyl optionally having one or more lower alkoxy, or lower alkyl; LG^{13} or LG^{14} each independently represents a leaving group; and other symbols are as defined above.

[0222]

(Step C-5-1: (1x) + (66) -> (1y))

Among the compounds represented as formula (1), compound (1y) can be obtained by reacting compound (1x) with compound (66) in an inert solvent.

The amount of compound (66) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).

In addition, a basic active agent can be used, as necessary. Examples of the basic active agent include, N,N-dimethyl-4-aminopyridine (DMAP) and pyridine. The amount of the basic active agent used is typically 1 molar equivalent to excessive amounts relative to compound (1x).

In addition, pyridine etc. can be used as a solvent, or an inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0223]

(Step C-5-2: (1x) + (67) or (68) or (69) -> (1z))

Among the compounds represented as formula (1), compound (1z) can be obtained by the condensation reaction of compound (1x) with compound (67), (68) or (69) in an inert solvent.

The respective amount of compound (67), (68) or (69) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).

In addition, it is possible to add a base, as necessary. Example of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).

In addition, a basic active agent can be used, as necessary. Examples of the basic active agent include, N,N-dimethyl-4-aminopyridine (DMAP) and pyridine. The amount of the basic active agent used is typically 0.01 molar equivalents to excessive amounts relative to compound (1x).

In addition, especially when condensation reaction is performed with compound (67), it is preferred to use a condensation agent in the condensation. Examples of the condensation agent include, for example, carbodiimides such as 1,3-dicyclohexylcarbodiimide, 1-cyclohexyl-3-morpholinoethylcarbodiimide, 1-cyclohexyl-3-(4-diethylaminocyclohexyl)-carbodiimide, 1,3-diethylcarbodiimide, 1,3-diisopropylcarbodiimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or salts thereof. The amount of the condensation agent used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).

In addition, a condensation accelerator can be added in addition to the condensation agent. Examples of the condensation accelerator include, for example, 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), 1-hydroxy-7-azabenzotriazole (HOAt) and hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOOBt). The amount of the condensation accelerator used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).

In addition, tertiary amines such as pyridine can be used as a solvent, or an inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0224]

(Step C-5-3: (1x) + (70) -> (1aa))

Among the compounds represented as formula (1), compound (1aa) can be obtained, for example, by reacting compound (1x) with compound (70) in an inert solvent.

The amount of compound (70) used is typically 1 molar equivalent to excessive amounts relative to compound (1x).

In addition, a basic active agent can be used, as necessary. Examples of the basic active agent include, N,N-dimethyl-4-aminopyridine (DMAP) and pyridine. The amount of the basic active agent used is typically 1 molar equivalent to excessive amounts relative to compound (1x).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0225]

(Step C-5-4: (1x) -> (1bb))

Among the compounds represented as formula (1), compound (1bb) can be obtained, for example, reacting compound (1x) with diphenyl phosphite in an inert solvent in the presence of a base.

The amount of diphenyl phosphite used is typically 1 molar equivalent to excessive amounts relative to compound (1x).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (1x).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0226]

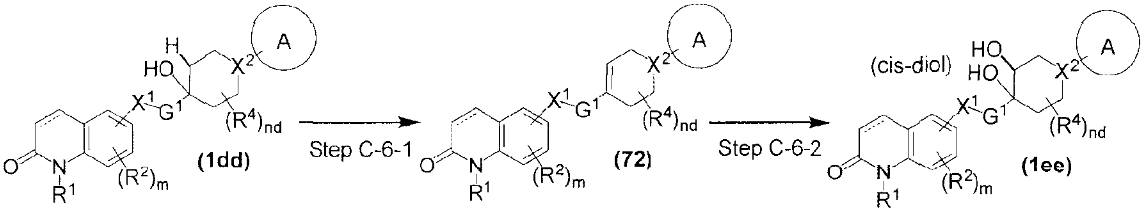
(Step C-5-5: (1x) + (71) -> (1cc))

Among the compounds represented as formula (1), compound (1cc) can be obtained, for example, by reacting compound (1x) with compound (71) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step A-1-1.

[0227]

Scheme C-6

[Chem. 48]



wherein nd is an integer of 0 to 7; and other symbols are as defined above.

[0228]

(Step C-6-1: (1dd) -> (72))

Compound (72) can be obtained, for example, by transforming hydroxy in compound (1dd) to a leaving group by using any known method followed by olefination reaction. Said reaction can be performed under the conditions similar to above step A-10-1.

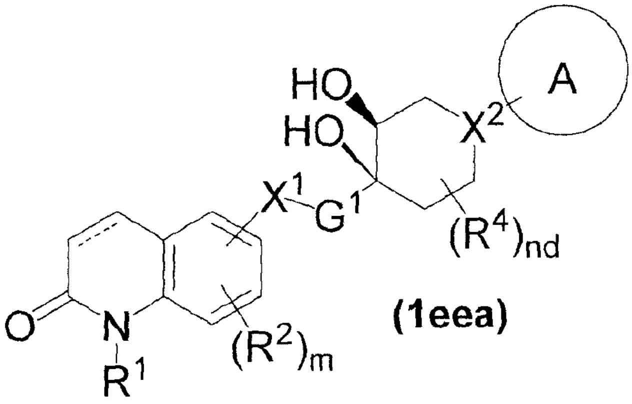
[0229]

(Step C-6-2: (72) -> (1ee))

Among the compounds represented as formula (1), compound (1ee) can be obtained, for example, reacting compound (72) in an inert solvent in the presence of osmium tetraoxide and a reoxidizing agent. Said reaction can be performed under the conditions similar to above step B-3-3.

Similar to the above step B-3-3, when, for example, a hydroquinine ether is used as a catalyst, typically, it is possible to obtain, mainly, a compound represented as formula (1eea):

[Chem. 49]

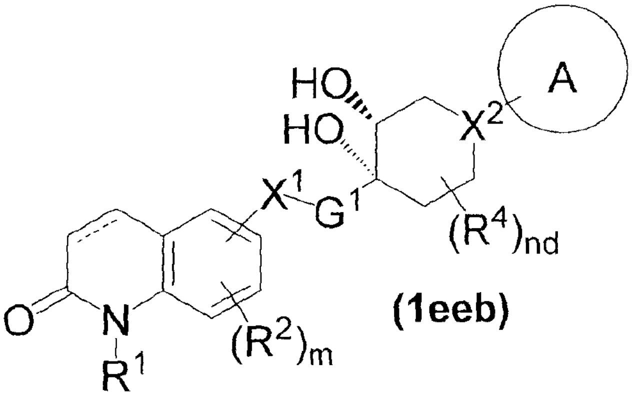

(1eea)

wherein each symbol is as defined above

as compound (1ee).

For example, when using a hydroquinidine ether, typically, it is possible to obtain, mainly, a compound represented as formula (1eeb):

[Chem. 50]


(1eeb)

wherein each symbol is as defined above

as compound (1ee).

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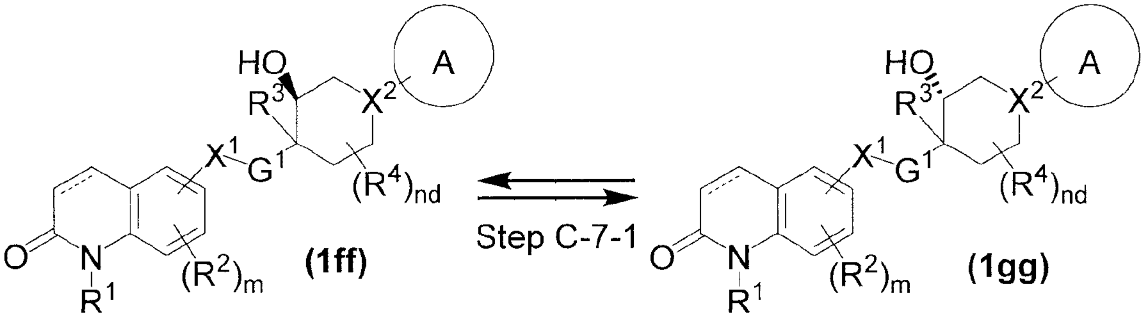
[0230]

Scheme C-7

[Chem. 51]



wherein each symbol is as defined above

[0231]

(Step C-7-1: (1ff) <--> (1gg))

Among the compounds represented as formula (1), compound (1gg) can be obtained from compound (1ff) by Mitsunobu reaction followed by a hydrolysis reaction.

Mitsunobu reaction can be performed, for example, by reacting compound (1ff) with carboxylic acid in an inert solvent, in the presence of azodicarboxylic acid ester and phosphine.

Examples of the azodicarboxylic acid ester include, for example, dimethyl azodicarboxylate, diethyl azodicarboxylate, diisopropyl azodicarboxylate, dibenzyl azodicarboxylate, di-*tert*-butyl azodicarboxylate and 1,1'-(azodicarbonyl)dipiperidine. The amount of the azodicarboxylic acid ester used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1ff).

Examples of the phosphine include, for example, triphenylphosphine, tricyclohexylphosphine and tributylphosphine. The amount of the phosphine used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1ff).

Examples of the carboxylic acid include benzoic acid, p-nitrobenzoic acid and p-methoxybenzoic acid. The amount of the carboxylic acid used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (1ff).

In addition, hydrolysis reaction after Mitsunobu reaction can be done, for example, by reacting the compound in an inert solvent in the presence of a base.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen phosphates and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 molar equivalent to excessive amounts relative to compound (1ff).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

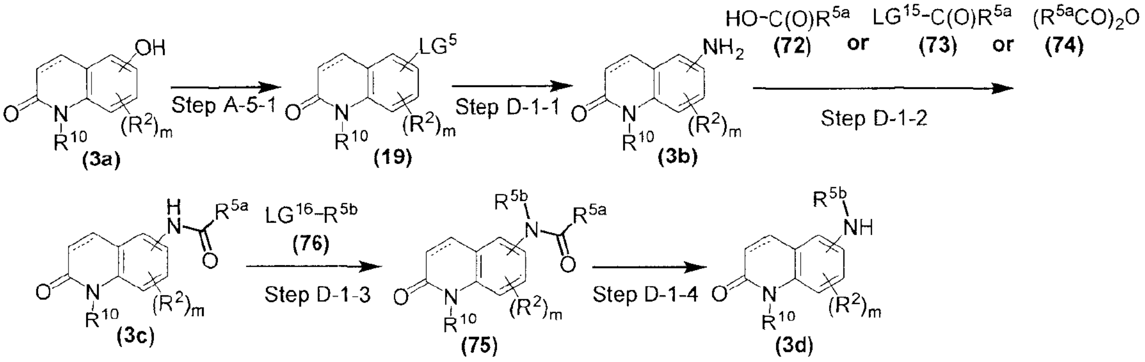
In addition, compound (1ff) can be obtained from compound (1gg) by using a similar method.

[Preparation method D: Synthesis of starting materials]

[0232]

Scheme D-1

[Chem. 52]



wherein R^{5a} represents hydrogen or lower alkyl; R^{5b} represents lower alkyl; LG^{15} and LG^{16} each independently represents a leaving group; and other symbols are as defined above.

[0233]

(Step D-1-1: (19) -> (3b))

Among the compounds represented as formula (3), compound (3b) can be obtained from compound (19) by using any known method for introducing amino, for example, by reacting compound (19) with benzophenone imine or hexamethyldisilazane in an inert solvent, in the presence of base and transition metal catalyst, followed by the hydrolysis of the obtained compound.

Examples of the benzophenone imine include, for example, benzophenone imine and 4,4'-dimethoxybenzophenone imine.

The amount of the benzophenone imine or hexamethyldisilazane used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (19).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (19).

Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(*tert*-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro-[1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (19).

In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(*tert*-butyl)phosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (19).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0234]

(Step D-1-2: (3b) + (72) or (73) or (74) -> (3c))

Among the compounds represented as formula (3), compound (3c) can be obtained by the condensation reaction of compound (3b) with compound (72), (73) or (74) in an inert solvent. Said reaction can be performed under the conditions similar to above step C-4-8.

[0235]

(Step D-1-3: (3c) + (76) -> (75))

Compound (75) can be obtained, for example, by reacting compound (3c) with compound (76) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step C-4-5.

[0236]

(Step D-1-4: (75) -> (3d))

Among the compounds represented as formula (3), compound (3d) can be obtained, for example, by treating compound (75) with an acid.

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid; and organic acids such as acetic acid, trifluoroacetic acid and trifluoromethanesulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (75).

The acid can be used as a solvent, or an additional inert solvent can be used.

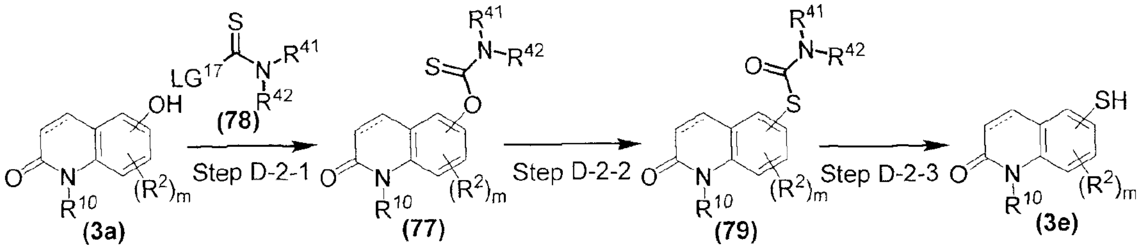
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, water, alcohols, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0237]

Scheme D-2

[Chem. 53]



wherein R^{41} and R^{42} each independently represents lower alkyl; LG^{17} represents a leaving group; and other symbols are as defined above.

[0238]

(Step D-2-1: (3a) + (78) -> (77))

Compound (77) can be obtained, for example, by reacting compound (3a) with compound (78) in an inert solvent in the presence of a base.

The amount of compound (78) used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (3a).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (3a).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0239]

(Step D-2-2: (77) -> (79))

Compound (79) can be obtained by heat treatment of compound (77) in an inert solvent.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, alcohols, water, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically 100 to 300 °C. The reaction time is typically 0.1 to 200 hours.

[0240]

(Step D-2-3: (79) -> (3e))

Among the compounds represented as formula (3), compound (3e) can be obtained, for example, by treating compound (79) with a base followed by hydrolysis.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines and metal amides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (79).

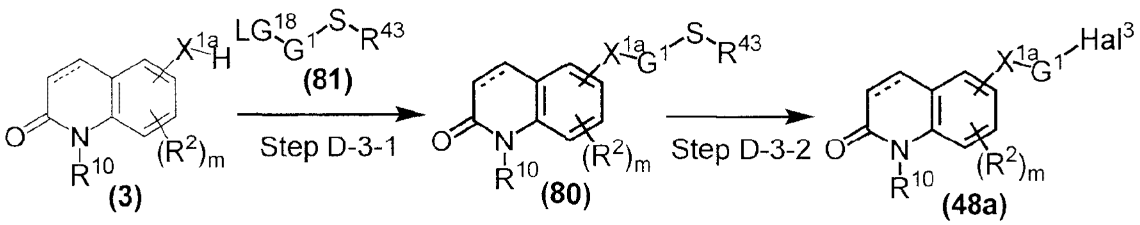
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, water, alcohols, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0241]

Scheme D-3

[Chem. 54]



wherein R^{43} represents lower alkyl; LG^{18} represents a leaving group; Hal^3 represents halogen; and other symbols are as defined above.

[0242]

(Step D-3-1: (3) + (81) -> (80))

Compound (80) can be obtained, for example, by reacting compound (3) with compound (81) in an inert solvent in the presence of a base. Said reaction can be performed similar to the above step A-1-1.

[0243]

(Step D-3-2: (80) -> (48a))

Among the compounds represented as formula (48), compound (48a) can be obtained, for example, by reacting compound (80) with a halogenating agent in an inert solvent.

Examples of the halogenating agent include, For example, sulfuryl chloride, sulfuryl fluoride. The amount of the halogenating agent used is typically 1 to 10 molar equivalents relative to compound (80).

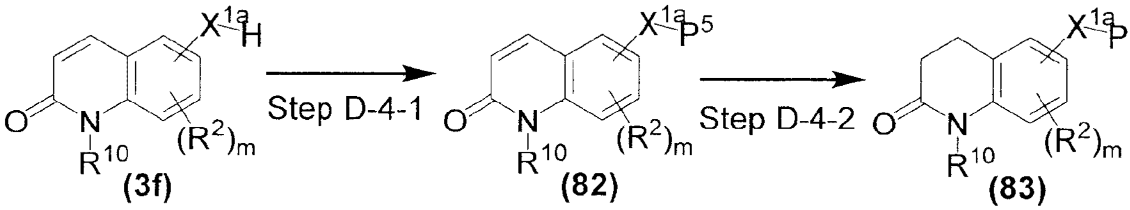
Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0244]

Scheme D-4

[Chem. 55]



wherein P^5 represents a protecting group; and other symbols are as defined above.

[0245]

(Step D-4-1: (3f) -> (82))

Compound (82) can be obtained by subjecting compound (3f) to any of known reaction for introducing a protecting group.

[0246]

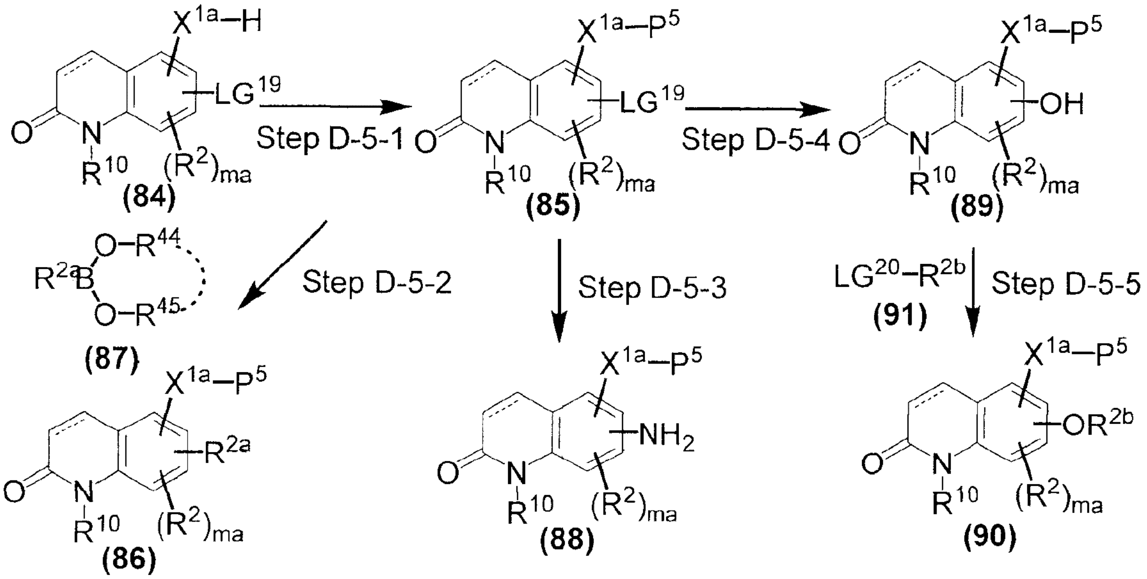
(Step D-4-2: (82) -> (83))

Compound (83) can be obtained, for example, by subjecting compound (82) to a reduction reaction in an inert solvent in the presence of a hydrogen source and a metal catalyst. Said reaction can be performed under the conditions similar to above step A-5-5.

[0247]

Scheme D-5

[Chem. 56]



wherein R^{2a} and R^{2b} each independently represents lower alkyl; R^{44} and R^{45} each independently represents hydrogen or lower alkyl, or R^{44} and R^{45} may unitedly form a ring; LG^{19} represents a leaving group; LG^{19} and LG^{20} each independently represents a leaving group; ma is an integer of 0 to 2; and other symbols are as defined above.

[0248]

(Step D-5-1: (84) -> (85))

Compound (85) can be obtained by subjecting compound (84) to known reaction for introducing a protecting group.

[0249]

(Step D-5-2: (85) + (87) -> (86))

Compound (86) can be obtained, for example, by reacting compound (85) with compound (87) in an inert solvent in the presence of a base and a transition metal catalyst.

The amount of compound (87) used is typically 0.1 to 10 molar equivalents, preferably 0.2 to 5 molar equivalents relative to compound (85).

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (85).

Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(*tert*-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro-[1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (85).

In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(*tert*-butyl)phosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (85).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0250]

(Step D-5-3: (85) -> (88))

Compound (88) can be obtained from compound (85) by using any known method for introducing amino, for example, by reacting compound (85) with benzophenone imine or hexamethyldisilazane in an inert solvent in the presence of base and transition metal catalyst followed by the hydrolysis of the obtained compound. Said reaction can be performed under the conditions similar to the above step D-1-1.

[0251]

(Step D-5-4: (85) -> (89))

Compound (89) can be obtained from compound (85) by using any known method for introducing hydroxy, for example, reacting compound (85) with a diboronic acid diester, which is $((R^{B1}O)_2B)_2$ wherein R^{B1} each independently represents lower alkyl or may unitedly form a ring (such as bis(pinacolato)diboron), or a boronic acid ester, which is $B(OR^{B2})_3$ wherein R^{B2} each independently represents hydrogen or lower alkyl, in an inert solvent, followed by the hydrolysis of the obtained compound.

The hydrolysis reaction can be done by using Oxone (registered trade name), hydroxyamine and a base.

The amount of the diboronic acid diester or boronic acid ester used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (85).

When using the diboronic acid diester, it is preferred to react in the presence of base and transition metal catalyst.

Examples of the base include, for example, alkali metal hydroxides, alkali metal hydrides, alkali metal carbonates, alkali metal carboxylates, alkali metal hydrogen carbonates, alkali metal hydrogen phosphates, aromatic amines, tertiary amines, metal amides and metal alkoxides, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the base used is typically 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents relative to compound (85).

Examples of the transition metal catalyst include, for example, palladium catalysts such as palladium (II) acetate, palladium (II) chloride, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium (0), 1,1-bis(diphenylphosphino)ferrocene dichloropalladium (II), dichlorobis(triphenylphosphine)palladium (II), bis(tri-(*tert*-butylphosphine))palladium (0), phenylallylchloro[1,3-bis(diisopropylphenyl)-2-imidazol-2-ylidene]palladium (II) and phenylallylchloro-[1,3-bis(diisopropylphenyl)-2-imidazolidinylidene]palladium (II); copper catalysts such as copper (I) iodide and copper (I) oxide; rhodium catalysts such as tris(triphenylphosphine)rhodium (III) chloride; nickel catalysts such as tetrakis(triphenylphosphine)nickel (0), and it is also possible to use any two or more of them in an appropriate ratio. The amount of the transition metal catalyst used is typically 0.001 to 3 molar equivalents relative to compound (85).

In addition, a ligand can be added as necessary. Examples of the ligand include, for example, triphenylphosphine, tri(*tert*-butyl)phosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl, 4,5'-bis(diphenylphosphino)-9,9'-dimethylxanthene. The amount of the ligand used is typically 0.001 to 3 molar equivalents relative to compound (85).

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, esters, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0252]

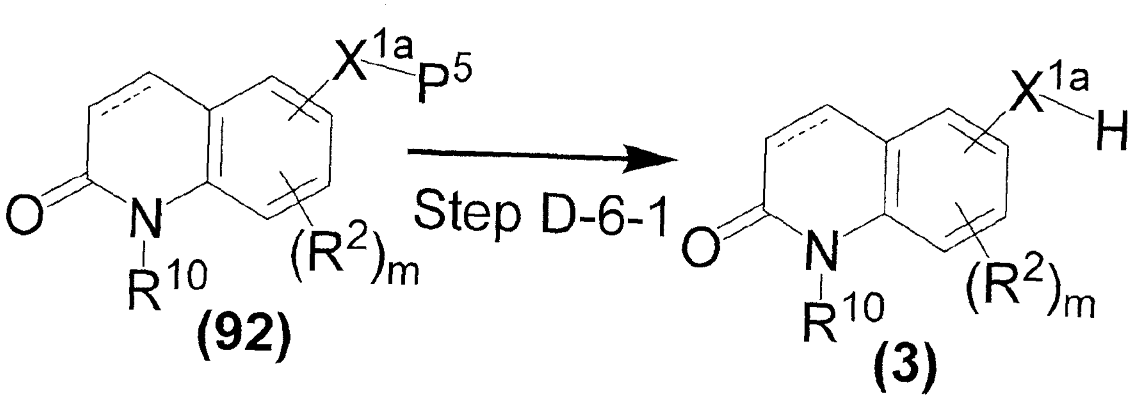
(Step D-5-5: (89) + (91) -> (90))

Compound (90) can be obtained, for example, by reacting compound (89) with compound (91) in an inert solvent in the presence of a base. Said reaction can be performed under the conditions similar to above step C-4-5.

[0253]

Scheme D-6

[Chem. 57]



wherein each symbol is as defined above.

[0254]

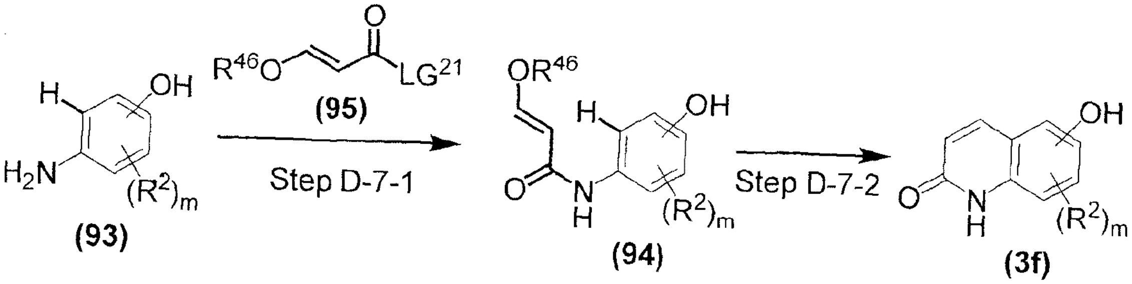
(Step D-6-1: (92) -> (3))

Compound (3) can be obtained by subjecting compound (92) to any known deprotection reaction.

[0255]

Scheme D-7

[Chem. 58]



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wherein R^{46} represents lower alkyl; LG^{21} represents a leaving group; and other symbols are as defined above.

[0256]

(Step D-7-1: (93) + (95) -> (94))

Compound (94) can be obtained by a condensation reaction of compound (93) with compound (95) in an inert solvent. Said reaction can be performed under the conditions similar to above step C-4-8.

[0257]

(Step D-7-2: (94) -> (3f))

Among the compounds represented as formula (3), compound (3f) can be obtained, for example, by treating compound (94) with an acid.

Examples of the acid include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and hydrobromic acid; and organic acids such as acetic acid, trifluoroacetic acid and trifluoromethanesulfonic acid, and it is also possible to use any two or more of them in an appropriate ratio. The amount of the acid used is typically 1 molar equivalent to excessive amounts relative to compound (94).

The acid can be used as a solvent, or an additional inert solvent can be used.

Examples of the inert solvent include, for example, hydrocarbons, halogenated hydrocarbons, ethers, water, alcohols, ketones, amides, nitriles and sulfoxides, and it is also possible to use any two or more of them in an appropriate ratio.

The reaction temperature is typically -80 to 150 °C. The reaction time is typically 0.1 to 200 hours.

[0258]

The compound (1) of the present invention can be prepared by any synthetic method including the above respective steps or a method analogous to those described above. Further, the intermediates and the starting materials in the respective steps can be prepared by considering any synthetic method including the above respective steps or a method analogous to those described above, or a method in Reference Examples and Examples disclosed herein or a method analogous to those described in Examples, and a method known or publicly known at the filing date of the present application. When an intermediate or a starting material is commercially available, such a compound may be used as it is.

[0259]

In addition, in the preparation of the compound (1), it is possible to further derivatize the obtained compound optionally by subjecting the compound to any of the known reactions such as various alkylation reaction, acylation reaction, amidation reaction, esterification reaction, etherification reaction, halogenation reaction, hydroxylation reaction, amination reaction, aryl coupling reaction, condensation reaction such as carbon extension reaction, addition reaction, substitution reaction, oxidation reaction, reduction reaction, dehydration reaction and hydrolysis reaction in addition to the above steps.

[0260]

If necessary, a functional group in the starting materials and the intermediates for the above respective steps can be protected with any protecting group by using any known method before subjecting a specific reaction, and after the completion of said specific reaction, the protecting group can be deprotected by using any known method.

[0261]

Each intermediate and the final compound in the above respective steps can be used in the next step as it is, or it is possible to isolate and purify the compound after the completion of the reaction. For example, when the compound should be isolated and purified, the reaction mixture may be cooled and subjected to a procedure for isolating the crude reaction product such as filtration, condensation or extraction, and then, the crude reaction product may be subjected to a procedure of common purification such as column chromatography or recrystallization to isolate and purify the product from the reaction mixture.

[0262]

The starting materials, the intermediates and the final compounds and the compound (1) of the present invention include their solvates in which a solvent is added to the compound (for example, hydrates and ethanol solvate etc.).

[0263]

The starting materials, the intermediates and the final compounds and the compound (1) of the present invention include their geometric isomers, stereoisomers and optical isomers. These isomers can be separated by any known separation method. For example, a racemic compound can be separated to a sterically pure isomer by using common method for optical resolution (for example, optical resolution by crystallization, directly resolving by a chromatography etc.). In addition, it is possible to prepare an optically active compound by using an appropriate optically active starting material.

[0264]

The starting materials and the final compounds in the above respective steps can be used in a form of an appropriate salt. Examples of such salts include those exemplified below as the salt of compound (1) of the present invention.

[0265]

When a compound obtained in the respective steps or a commercially available product is in a free form, it is possible to convert the compound to a desired salt by using a method known *per se*. Alternatively, when a compound obtained in the respective steps or a commercially available product is in a salt form, it is possible to convert the compound to a desired free form or a desired another salt form by using a method known *per se*.

[0266]

Compound (1) in the present invention includes a pharmaceutically acceptable salt form thereof.

[0267]

Among Compound (1) in the present invention, the compound with one or more basic groups may form a salt with a pharmaceutically acceptable acid. An example of the acid includes, for example, an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and phosphoric acid, and an organic acid such as methanesulfonic acid, p-toluenesulfonic acid, acetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, and lactic acid.

[0268]

Among Compound (1) in the present invention, the compound with one or more acidic groups may form a salt with a pharmaceutically acceptable base. An example of the base includes, for example, an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate, and an organic base such as methylamine, diethylamine, trimethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, guanidine, pyridine, picoline, and choline.

[0269]

Compound (1) in the present invention includes the compound wherein one or more atoms are substituted with one or more isotopic atoms. An example of the isotopic atom includes, for example, deuterium (^2H), tritium (^3H), ^{13}C, ^{14}N, and ^{18}O.

[0270]

A medical formulation/pharmaceutical composition comprising as the active ingredient Compound (1) in the present invention is illustrated as below.

[0271]

The medical formulation is what Compound (1) in the present invention is formulated into the form of the usual medical formulation, which is prepared with Compound (1) in the present invention and a pharmaceutically acceptable carrier. The carrier includes a diluent or an excipient such as a filler, a bulking agent, a binder, a humidity adding agent, a disintegrant, a surface active agent, and a lubricant as commonly used.

[0272]

Such a medical formulation may be selected from various forms depending on therapeutic purposes, and a typical example of the formulation includes, for example, a tablet, a pill, a powder, a liquid, a suspension, an emulsion, a granule, a capsule, a suppository, and an injection (such as a liquid and a suspension).

[0273]

Any known carriers may be widely used as a carrier used in preparing a tablet formulation, and include, for example, an excipient such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, and crystalline cellulose, a binder such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, and polyvinylpyrrolidone, a disintegrant such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglyceride stearate, and starch, lactose, a disintegration suppressant such as sucrose, stearin, cacao butter, and hydrogenated oil, an absorption promoter such as quaternary ammonium salt, and sodium lauryl sulfate, a humectant such as glycerin and starch, an adsorbent such as starch, lactose, kaolin, bentonite, and colloidal silica, a lubricant such as purified talc, stearate, boric acid powder, and polyethylene glycol.

[0274]

The tablet may be also formulated, if needed, as a tablet with a common coating including, for example, a sugar-coated tablet, a gelatin-encapsulated tablet, an enteric coated tablet, a film coated tablet, a double tablet or a multi-layered tablet.

[0275]

Any known carriers may be widely used as a carrier used in preparing a pill formulation, and include, for example, an excipient such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaolin, and talc, a binder such as gum arabic powder, tragacanth powder, gelatin, and ethanol, and a disintegrant such as laminaran, and agar.

[0276]

Any known carriers may be widely used as a carrier used in preparing a suppository formulation, and include, for example, polyethylene glycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin, and semisynthetic glyceride.

[0277]

It is preferable in the preparation of an injection that a liquid, an emulsion, and a suspension are sterilized and isotonic with blood. Any known diluents may be widely used as a diluent used in preparing the liquid, emulsion, and suspension, and include, for example, water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, and polyoxyethylene sorbitan fatty acid esters. In this case, the medical formulation may comprise a sufficient amount of salt, glucose or glycerin to prepare the isotonic solution, and it may also comprise a common solubilizing agent, beffering agent, soothing agent, and the like as well as a colorant, preserving agent, perfume, flavoring agent, sweetening agent, and other medicinal products, if needed.

[0278]

The amount of Compound (1) in the present invention contained in a medical formulation is not limited and may be optionally adjusted with a broad range; it is preferable that the medical formulation typically comprises 1 to 70% by weight of Compound (1) in the present invention.

[0279]

A method of administering the medical formulation in the present invention is not limited and the medical formulation may be administered depending on various dosage forms, ages and genders of patients, disease states, and other conditions. For example, a tablet, pill, liquid, suspension, emulsion, granule, and capsule may be orally administered. An injection may be intravenously administered solely or in combination with a common replacement fluid such as glucose and amino acid, and if needed, may be solely administered intramuscularly, intradermally, subcutaneously or intraperitoneally. A suppository may be rectally administered.

[0280]

A dosage amount of the medical formulation may be optionally adjusted depending on dosage regimens, ages and genders of patients, the extent of disease, and other conditions; it may be typically administered in 0.01 to 100 mg/kg, preferably 0.1 to 50 mg/kg, of body weight per day in a single dose or multiple doses.

[0281]

The dosage amount may be varied on the basis of various conditions, and a lower dosage amount than the above may be sufficient in some cases and a higher dosage amount than the above may be necessary in other cases.

[0282]

Compound (1) in the present invention has a specific efficacy in particular against tuberculosis bacteria such as mycobacteria, including tuberculosis bacteria genus, and non-tuberculous mycobacteria genus, and also has an excellent activity against multidrug-resistant tuberculosis bacteria. It not only shows an antibacterial activity *in vitro* but also expresses an antibacterial activity in oral administration *in vivo* due to its favorable distribution in lung tissues which are the primarily infected organ. Compound (1) in the present invention is thus useful as an agent for diagnosing, preventing and/or treating tuberculosis.

[0283]

Compound (1) in the present invention does not induce diarrhea as seen in known antibacterial agents with a wide spectrum for common bacteria such as gram-positive bacteria and gram-negative bacteria, and may become a medicinal substance which allows for a long-term administration.

[0284]

Compound (1) in the present invention is effective for intracellular parasitic bacteria such as human-origin tuberculosis bacteria which is parasitic in macrophage and has in a bactericidal test a stronger bactericidal activity in a low concentration than existing antitubercular agents. It can be thus expected that the relapse rate in tuberculosis will be reduced, which eventually allows for a short-term chemotherapy.

[0285]

Due to a lower toxicity than existing drugs, Compound (1) in the present invention can be also expected for long-term use in the treatment for latent tuberculosis.

[0286]

Compound (1) in the present invention shows a low inhibitory activity against a drug-metabolizing enzyme and a low possibility for an enzyme induction of CYP3A. Due to limited concerns about drug interaction, it can be expected for a combination use with other therapeutic agents. The agents capable of the combination use include, for example, a first antituberculosis drug, a secondary antituberculosis drug, a quinolone antimicrobial, a macrolide antimicrobial, an oxazolidinone antimicrobial, a sufa drug, an anti-HIV drug, delamanid, bedaquiline, or PA-824, Sutezolid currently under development.

[Examples]

[0287]

EXAMPLES

[0288]

Hereinafter, the present invention is described in more detail with reference to Reference Examples, Examples and Test Examples. These Examples are not intended to limit the present invention, and they can be modified within the scope of the present invention.

The term "room temperature" in the following Examples is usually referred to a temperature between about 10 °C to about 35 °C. A ratio of mixed solvents is referred to a volume ratio, unless otherwise specified. % is referred to a weight %, unless otherwise specified.

^{1}HNMR (proton nuclear magnetic resonance spectrum) was determined at room temperature by using a Fourier transform NMR (any one of Bruker AVANCE 300 (300 M Hz), Bruker AVANCE 500 (500 M Hz), Bruker AVANCE III 400 (400 M Hz) and Bruker AVANCE III 500 (500 M Hz)). In a silica gel column chromatography, when it is described as a basic, an aminopropylsilane-bonded silica gel was used.

[0289]

Reference Example 1

(2E)-N-(2-Chloro-5-hydroxyphenyl)-3-ethoxyprop-2-enamide

To a solution of 3-amino-4-chlorophenol (10.35 g), pyridine (6.41 mL) in N,N-dimethylacetamide (90 mL), a solution of (2E)-3-ethoxyprop-2-enoyl chloride (10.9 g) in N,N-dimethylacetamide (10 mL) was added dropwise under ice-cooling, and the reaction mixture was stirred at the same temperature for 1 h. The reaction solution was poured into water, and the precipitate was collected on a filter to provide the title compound (10.7 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.38 (3H, t, J = 7.1 Hz), 4.01 (2H, q, J = 7.1 Hz), 5.39 (1H, d, J = 12.1 Hz), 6.58 (1H, dd, J = 8.8 Hz, 2.9 Hz), 7.20 (1H, d, J = 8.9 Hz), 7.52 (1H, brs), 7.68 (1H, d, J = 12.1 Hz), 8.13 (1H, brs), 8.33 (1H, d, J = 2.9 Hz).

[0290]

Reference Example 2

(2E)-3-Ethoxy-N-(2-fluoro-5-hydroxyphenyl)prop-2-enamide

Synthesized analogous to Reference Example 1.

^{1}HNMR ($CDCl_3$) δ ppm: 1.38 (3H, t, J = 7.0 Hz), 3.99 (2H, q, J = 7.0 Hz), 5.36 (1H, d, J = 12.1 Hz), 6.49-6.55 (1H, m), 6.94 (1H, dd, J = 9.0 Hz, 8.9 Hz), 7.22 (1H, brs), 7.67 (1H, d, J = 12.1 Hz), 8.08 (1H, brs), 8.23-8.29 (1H, m).

[0291]

Reference Example 3

(2E)-N-(2,3-Difluoro-5-methoxyphenyl)-3-ethoxyprop-2-enamide

Synthesized analogous to Reference Example 1.

^{1}HNMR (CDCl$_3$) δ ppm: 1.37 (3H, t, J = 6.9 Hz), 3.78 (3H, s), 3.97 (2H, q, J = 6.9 Hz), 5.35 (1H, d, J = 12.0 Hz), 6.38-6.46 (1H, m), 7.13 (1H, s), 7.66 (1H, d, J = 12.0 Hz), 7.82-7.87 (1H, m).

[0292]

Reference Example 4

(2E)-N-(2,4-Dibromo-3-fluoro-5-methoxyphenyl)-3-ethoxyprop-2-enamide

Synthesized analogous to Reference Example 1.

^{1}HNMR (CDCl$_3$) δ ppm: 1.38 (3H, t, J = 7.2 Hz), 3.93 (3H, s), 4.00 (2H, q, J = 7.2 Hz), 5.36 (1H, d, J = 12.0 Hz), 7.47 (1H, s), 7.67 (1H, d, J = 12.0 Hz), 8.19 (1H, d, J = 2.1 Hz).

[0293]

Reference Example 5

8-Fluoro-5-hydroxyquinolin-2(1H)-one

To conc. hydrochloric acid (270 mL), a solution of (2E)-3-ethoxy-N-(2-fluoro-5-hydroxyphenyl)prop-2-enamide (27.0 g) in methanol (135 mL) was added dropwise at 65 °C, then the reaction mixture was stirred at 85 °C for 30 min. The reaction solution was poured into water, and the precipitate was collected on a filter to provide the title compound (19.2 g).

^{1}HNMR (DMSO-d6) δ ppm: 6.46 (1H, d, J = 9.8 Hz), 6.52 (1H, dd, J = 8.8 Hz, 3.7 Hz), 7.21 (1H, dd, J = 10.9 Hz, 8.8 Hz), 8.02 (1H, dd, J = 9.8 Hz, 1.6 Hz), 10.33 (1H, brs), 11.60 (1H, brs).

[0294]

Reference Example 6

8-Chloro-5-hydroxyquinolin-2(1H)-one

Synthesized analogous to Reference Example 5.

^{1}HNMR (DMSO-d6) δ ppm: 6.47 (1H, d, J = 9.7 Hz), 6.62 (1H, d, J = 8.6 Hz), 7.42 (1H, d, J = 8.6 Hz), 8.05 (1H, d, J = 9.8 Hz), 10.68 (1H, s), 10.75 (1H, brs).

[0295]

Reference Example 7

7,8-Difluoro-5-methoxyquinolin-2(1H)-one

To conc. sulfuric acid (17 mL) was added (2E)-N-(2,3-difluoro-5-methoxyphenyl)-3-ethoxyprop-2-enamide (1.66 g) at 70-80 °C, and the reaction mixture was stirred for 5 min. After the reaction solution was added to ice water, the precipitate was collected on a filter to provide the title compound (1.0 g).

^{1}HNMR (DMSO-d6) δ ppm: 3.90 (3H, s), 6.45 (1H, d, J = 9.9 Hz), 6.90 (1H, dd, J = 12.9 Hz, 6.0 Hz), 7.97 (1H, dd, J = 9.9 Hz, 1.5 Hz), 12.00 (1H, s).

[0296]

Reference Example 8

6,8-Dibromo-7-fluoro-5-methoxyquinolin-2(1H)-one

Synthesized analogous to Reference Example 7.

^{1}HNMR (DMSO-d6) δ ppm: 3.91 (3H, s), 6.61 (1H, d, J = 9.5 Hz), 8.02 (1H, d, J = 9.5 Hz), 10.96-11.10 (1H, brs).

[0297]

Reference Example 9

7-Fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

Under hydrogen atmosphere, a suspension of 7-fluoro-5-methoxyquinolin-2(1H)-one (29.0 g) and 10 % palladium on carbon (10 g) in acetic acid (600 mL) was stirred at 105 °C for 2.5 h. Insoluble materials were filtered off and the filtrate was concentrated. The residue was washed with water and dried to provide the title compound (25.7 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.62 (2H, m), 2.89 (2H, t, J = 7.5 Hz), 3.82 (3H, s), 6.15 (1H, dd, J = 9.0 Hz, 2.1 Hz), 6.32 (1H, dd, J = 10.8 Hz, 2.1 Hz), 7.92 (1H, brs).

[0298]

Reference Example 10

7,8-Difluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 9.

^{1}HNMR ($CDCl_3$) δ ppm: 2.58-2.64 (2H, m), 2.90-2.96 (2H, m), 3.79 (3H, s), 6.37 (1H, dd, J = 12.0 Hz, 6.3 Hz), 7.51 (1H, brs).

[0299]

Reference Example 11

7-Amino-8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

A mixture of 7-amino-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (0.90 g) and 48 % hydrogen bromide in water (18 mL) was heated to reflux for 20 h. The precipitate was collected on a filter, and washed with 48 % hydrogen bromide in water. The obtained solid was stirred in saturated aqueous sodium hydrogencarbonate, and the precipitated crystal was collected on a filter to provide the title compound (0.68 g).

^{1}HNMR (DMSO-d6) δ ppm: 2.30-2.36 (2H, m), 2.61-2.66 (2H, m), 4.90 (2H, brs), 5.90 (1H, d, J = 7.5 Hz), 8.90 (1H, brs), 9.60 (1H, brs).

[0300]

Reference Example 12

7-Fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 11.

^{1}HNMR (DMSO-d6) δ ppm: 2.37-2.42 (2H, m), 2.71 (2H, t, J = 7.5 Hz), 6.14 (1H, dd, J = 10.2 Hz, 2.4 Hz), 6.23 (1H, dd, J = 10.8 Hz, 2.4 Hz), 9.01-11.2 (2H, m).

[0301]

Reference Example 13

7,8-Difluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 11.

^{1}HNMR (DMSO-d6) δ ppm: 2.39-2.44 (2H, m), 2.71-2.77 (2H, m), 6.37 (1H, dd, J = 12.3 Hz, 6.6 Hz), 9.86 (1H, brs), 10.16 (1H, s).

[0302]

Reference Example 14

8-Fluoro-5-hydroxy-7-methyl-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 11.

^{1}HNMR (DMSO-d6) δ ppm: 2.11 (3H, d, J = 1.8 Hz), 2.36-2.44 (2H, m), 2.75 (2H, t, J = 7.2 Hz), 6.28 (1H, d, J = 6.3 Hz), 9.25 (1H, s), 9.77 (1H, s).

[0303]

Reference Example 15

8-Chloro-7-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 11.

^{1}HNMR (DMSO-d6) δ ppm: 2.41-2.50 (2H, m), 2.72-2.82 (2H, m), 6.47 (1H, d, J = 11.1 Hz), 9.48 (1H, brs), 10.22 (1H, brs).

[0304]

Reference Example 16

7-Fluoro-5-hydroxy-8-methyl-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 11.

^{1}HNMR (DMSO-d6) δ ppm: 1.99 (3H, d, J = 1.8 Hz), 2.34-2.40 (2H, m), 2.68-2.74 (2H, m), 6.27 (1H, d, J = 11.4 Hz), 9.45 (1H, s), 9.69 (1H, s).

[0305]

Reference Example 17

8-Ethyl-7-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-ethyl-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (150 mg) in dichloromethane (5 mL), a solution of 1 N boron tribromide in dichloromethane (2.02 mL) was added dropwise under ice-cooling, and the reaction mixture was stirred at room temperature overnight. Methanol (1 mL) was added to the reaction solution, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (ethyl acetate) to provide the title compound (100 mg).

^{1}HNMR (DMSO-d6) δ ppm: 0.96 (3H, t, J = 7.5 Hz), 2.34-2.39 (2H, m), 2.53-2.57 (2H, m), 2.67-2.73 (2H, m), 6.25 (1H, d, J = 11.7 Hz), 9.50 (1H, s), 9.71 (1H, s).

[0306]

Reference Example 18

6,8-Difluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

To a solution of 5-hydroxy-3,4-dihydroquinolin-2(1H)-one (0.50 g) in 1,2-dichloroethane (10 mL) was added fluoropyridinium triflate (2.27 g), and the reaction mixture was heated to reflux overnight. The reaction solution was concentrated, the water was added to the residue, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (38 mg).

^{1}HNMR (DMSO-d6) δ ppm: 2.44 (2H, t, J = 8.0 Hz), 2.86 (2H, t, J = 7.5 Hz), 7.10 (1H, t, J = 10.7 Hz), 9.57 (1H, brs), 9.97 (1H, brs).

[0307]

Reference Example 19

8-Chloro-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

A solution of 8-chloro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (2.00 g), 3,4-dihydro-2H-pyran (2.55 g) and pyridinium p-toluenesulfonate (0.51 g) in dichloromethane (40 mL) was stirred at room temperature overnight. The reaction solution was washed with brine, dried over sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (2.74 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.48-1.78 (3H, m), 1.79-2.08 (3H, m), 2.62 (2H, t, J = 7.7 Hz), 2.91-3.13 (2H, m), 3.56-3.67 (1H, m), 3.79-3.90 (1H, m), 5.34-5.45 (1H, m), 6.78 (1H, d, J = 9.0 Hz), 7.15 (1H, d, J = 9.0 Hz), 7.38 (1H, brs).

[0308]

Reference Example 20

8-Fluoro-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 19.

^{1}HNMR ($CDCl_3$) δ ppm: 1.57-1.75 (3H, m), 1.82-1.93 (2H, m), 1.93-2.03 (1H, m), 2.64 (2H, t, J = 7.7 Hz), 2.96-3.10 (2H, m), 3.58-3.66 (1H, m), 3.82-3.90 (1H, m), 5.35 (1H, t, J = 3.3 Hz), 6.74 (1H, dd, J = 9.1 Hz, 4.2 Hz), 6.89 (1H, t, J = 9.6 Hz), 7.90 (1H, brs).

[0309]

Reference Example 21

7-Bromo-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-fluoro-5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one (29.8 g) in methanol/water (3/1) (900 mL), copper (II) bromide (62.1 g) was added, and the reaction mixture was heated to reflux for 3 h. Water was added to the reaction solution, then which was ice-cooled to collect the precipitate on a filter. To the resultant precipitate was added ethyl acetate (1000 mL), and after refluxing for a while, insoluble materials were filtered off. The filtrate was concentrated and the precipitate was collected on a filter to provide the title compound (21.4 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.59-2.67 (2H, m), 2.90-2.95 (2H, m), 3.81 (3H, s), 6.67 (1H, d, J = 5.1 Hz), 7.71 (1H, brs).

[0310]

Reference Example 22

7-Amino-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, a solution of benzophenone imine (31.3 mL), 7-bromo-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (21.4 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (3.65 g), sodium *tert*-butoxide (19.5 g) and tris(dibenzylideneacetone)dipalladium (1.79 g) in toluene (250 mL) was heated to reflux for 2 h. The reaction solution was filtered over Celite™, water (150 mL) and 6 N hydrochloric acid (75 mL) were added to the filtrate and the reaction mixture was stirred at 80 °C for 30 min. The reaction solution was cooled to room temperature, poured into aqueous sodium hydroxide, and the precipitate was collected on a filter to provide the title compound (13.0 g).

^{1}HNMR (DMSO-d6) δ ppm: 2.36 (2H, t, J = 7.5 Hz), 2.67 (2H, t, J = 7.5 Hz), 3.66 (3H, s), 5.04 (2H, brs), 6.05 (1H, d, J = 6.9 Hz), 9.76 (1H, brs).

[0311]

Reference Example 23

8-Fluoro-5-methoxy-7-methyl-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, a solution of 7-bromo-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (50 mg), methylboronic acid (16.4 mg), 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane adduct (14.9 mg) and tripotassium phosphate (77 mg) in 1,4-dioxane (2 mL) was stirred at 100 °C for 15 h. To the reaction solution was added ethyl acetate, and insoluble materials were filtered off. The filtrate was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane -> dichloromethane/methanol) to provide the title compound (34 mg).

^{1}HNMR (CDCl$_3$) δ ppm: 2.26 (3H, d, H = 1.8 Hz), 2.55-2.65 (2H, m), 2.93 (2H, t, J = 7.7 Hz), 3.79 (3H, s), 6.32 (1H, d, J = 5.7 Hz), 8.14 (1H, brs).

[0312]

Reference Example 24

8-Fluoro-7-hydroxy-5-methoxy-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-fluoro-5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one (98 mg) in ethanol (7 mL), hydroxylamine hydrochloride (32.8 mg) and sodium hydroxide (24.4 mg) were added, and the reaction mixture was stirred at 40 °C for 72 h. After the solvent of the reaction solution was distilled off, to the residue was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (20 mg).

^{1}HNMR (DMSO-d6) δ ppm: 2.36-2.41 (2H, m), 2.68-2.73 (2H, m), 3.69 (3H, s), 6.20 (1H, d, J = 6.6 Hz), 9.72 (1H, brs), 9.90 (1H, brs).

[0313]

Reference Example 25

8-Fluoro-5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, a solution of 8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (50 g), bis(pinacolato)diboron (98 g), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (5.50 g) and di-μ-methoxobis(1,5-cyclooctadiene)diiridium (I) (6.79 g) in tetrahydrofuran (900 mL) was heated to reflux for 2.5 h. After cooling to room temperature, the reaction solution was concentrated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (44.5 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.35 (12H, s), 2.57-2.63 (2H, m), 2.94-3.00 (2H, m), 3.84 (3H, s), 6.79 (1H, d, J = 3.9 Hz), 7.50 (1H, brs).

[0314]

Reference Example 26

7-Ethoxy-8-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-fluoro-7-hydroxy-5-methoxy-3,4-dihydroquinolin-2(1H)-one (1.1 g) in N,N-dimethylformamide (20 mL) was added potassium carbonate (0.864 g) and ethyl iodide (0.505 mL), and the reaction mixture was stirred at room temperature for 3 h. The reaction solution was poured into water, and the solid was collected on a filter to provide the title compound (1.05 g).

^{1}HNMR (DMSO-d6) δ ppm: 1.33 (3H, t, J = 6.9 Hz), 2.40 (2H, t, J = 7.5 Hz), 2.75 (2H, t, J = 7.5 Hz), 3.77 (3H, s), 4.10 (2H, q, J = 6.9 Hz), 6.43 (1H, d, J = 6.9 Hz), 10.00 (1H, brs).

[0315]

Reference Example 27

7-Ethoxy-8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 17.

^{1}HNMR (DMSO-d6) δ ppm: 1.31 (3H, t, J = 6.9 Hz), 2.37-2.42 (2H, m), 2.70-2.74 (2H, m), 3.98 (2H, q, J = 6.9 Hz), 6.20 (1H, d, J = 6.9 Hz), 9.34 (1H, s), 9.82 (1H, brs).

[0316]

Reference Example 28

8-Bromo-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

To a solution of 7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (10 g) in acetic acid (600 mL), bromine (2.76 mL) was added dropwise, and then the reaction mixture was stirred at room temperature for 20 min. The reaction solution was poured into water, and the precipitate was collected on a filter to provide the title compound (8.31 g).

^{1}HNMR (DMSO-d6) δ ppm: 2.42-2.53 (2H, m), 2.76-2.86 (2H, m), 3.81 (3H, s), 6.82 (1H, d, J = 11.1 Hz), 9.17 (1H, brs).

[0317]

Reference Example 29

8-Chloro-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere, a solution of 8-bromo-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (11.3 g) and copper (I) chloride (8.56 g) in N-methyl-2-pyrrolidone (300 mL) was stirred at 130 °C for 20 h. After cooling to room temperature, the reaction mixture was poured into 5 % ammonium chloride aqueous solution, and the precipitate was collected on a filter. The obtained solid was purified by silica gel column chromatography (basic silica gel; dichloromethane) to provide the title compound (7.31 g).

^{1}HNMR (DMSO-d6) δ ppm: 2.41-2.53 (2H, m), 2.76-2.86 (2H, m), 3.80 (3H, s), 6.82 (1H, d, J = 11.7 Hz), 9.60 (1H, brs).

[0318]

Reference Example 30

7-Fluoro-5-methoxy-8-methyl-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, a solution of 8-bromo-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (1.23 g), methylboronic acid (0.81 g), potassium phosphate (2.86 g) and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane adduct (0.73 g) in 1,4-dioxane (25 mL) was stirred at 110 °C for 1 h. The reaction solution was cooled to room temperature, concentrated, and then purified by silica gel column chromatography (dichloromethane/methanol). The obtained material was treated with activated charcoal, filtrated and concentrated to provide the title compound (410 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 2.06 (3H, d, J = 1.5 Hz), 2.54-2.60 (2H, m), 2.87-2.93 (2H, m), 3.80 (3H, s), 6.34 (1H, d, J = 11.4 Hz), 7.30-7.40 (1H, brs).

[0319]

Reference Example 31

7-Fluoro-5-methoxyquinolin-2(1H)-one

Under hydrogen atmosphere, a suspension of 6,8-dibromo-7-fluoro-5-methoxyquinolin-2(1H)-one (40.6 g), sodium hydroxide (9.13 g) and 20 % palladium hydroxide on carbon (4 g) in N,N-dimethylacetamide (800 mL) was stirred at 45 °C for 2 h. Insoluble materials were filtered off by using Celite, the filtrate was poured into water and neutralized with 6 N hydrochloric acid (57.1 mL). The precipitate was collected on a filter to provide the title compound (18.2 g).

^{1}HNMR (DMSO-d6) δ ppm: 3.92 (3H, s), 6.37 (1H, d, J = 10.0 Hz), 6.63-6.72 (2H, m), 7.96 (1H, d, J = 10.0 Hz), 11.81 (1H, s).

[0320]

Reference Example 32

8-Ethenyl-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, a solution of 8-bromo-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (100 mg), 4,4,5,5-tetramethyl-2-vinyl-1,3,3-dioxaborolane (112 mg), sodium carbonate (116 mg) and tetrakis(triphenylphosphine)palladium (42.2 mg) in 1,4-dioxane/water (5/1) (2 mL) was stirred at 100 °C overnight. The reaction solution was cooled to room temperature, concentrated, and then the residue was purified by silica gel chromatography (hexane/ethyl acetate) to provide the title compound (50 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 2.55-2.61 (2H, m), 2.86-2.92 (2H, m), 3.82 (3H, s), 5.56-5.65 (2H, m), 6.36 (1H, d, J = 12.0 Hz), 6.45-6.55 (1H, m), 7.66 (1H, s).

[0321]

Reference Example 33

8-Ethyl-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, to a solution of 8-ethenyl-7-fluoro-5-methoxy-3,4-dihydroquinolin-2(1H)-one (200 mg) in acetic acid (4 mL) was added 10 % palladium on carbon (50 mg), and the reaction mixture was stirred at room temperature for 10 min under hydrogen atmosphere. The reaction solution was filtered over Celite and the solvents of the filtrate were distilled off. Water was added to the obtained residue, and the precipitate was collected on a filter to provide the title compound (150 mg).

^{1}HNMR (CDCl3) δ ppm: 1.13 (3H, t, J = 7.6 Hz), 2.51-2.60 (4H, m), 2.87-2.92 (2H, m), 3.79 (3H, s), 6.34 (1H, d, J = 11.6 Hz), 7.39 (1H, brs).

[0322]

Reference Example 34

5-(Benzyloxy)-7-fluoro-3,4-dihydroquinolin-2(1H)-one

A solution of 7-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (500 mg), potassium carbonate (496 mg) and benzyl bromide (0.39 mL) in N,N-dimethylformamide (5 mL) was stirred at room temperature for 1 h. The reaction solution was poured into cold-water, and the precipitate was collected on a filter, washed with water, ethanol and diethyl ether to provide the title compound (748 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.62 (2H, m), 2.92-2.97 (2H, m), 5.05 (2H, s), 6.17 (1H, dd, J = 9.0 Hz, 2.1 Hz), 6.39 (1H, dd, J = 10.8 Hz, 2.1 Hz), 7.30-7.45 (5H, m), 7.99 (1H, s).

[0323]

Reference Example 35

5-(Benzyloxy)-8-bromo-7-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 28.

^{1}HNMR ($CDCl_3$) δ ppm: 2.55-2.61 (2H, m), 2.95-3.00 (2H, m), 5.04 (2H, s), 6.49 (1H, d, J = 10.2 Hz), 7.30-7.45 (5H, m), 7.44 (1H, s).

[0324]

Reference Example 36

5-[(3,5-Dimethylbenzyl)oxy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 34.

^{1}HNMR (DMSO-d6) δ ppm: 2.28 (6H, s), 2.42-2.49 (2H, m), 2.85-2.91 (2H, m), 4.99 (2H, s), 6.66 (1H, dd, J = 9.0 Hz, 3.9 Hz), 6.95-7.04 (4H, m), 10.01 (1H, s).

[0325]

Reference Example 37

5-[(3,5-Dimethylbenzyl)oxy]-8-fluoro-7-hydroxy-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, a solution of 5-[(3,5-dimethylbenzyl)oxy]-8-fluoro-3,4-dihydroquinolin-2(1H)-one (1.0 g), bis(pinacolato)diboron (1.27 g), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (0.07 g) and di-μ-methoxobis(1,5-cyclooctadiene)diiridium (I) (0.09 g) in tetrahydrofuran (20 mL) was heated to reflux for 10 h. After the reaction solution was allowed to cool to room temperature, methanol (20 mL) followed by Oxone (Registered trade mark) (2.46 g) in water (20 mL) were added, and the reaction mixture was stirred at room temperature for 10 min. To the reaction solution was added water, and the precipitated crystal was collected on a filter, then washed with water, ethanol and diethyl ether to provide the title compound (500 mg).

^{1}HNMR (DMSO-d6) δ ppm: 2.28 (6H, s), 2.38-2.43 (2H, m), 2.74-2.79 (2H, m), 4.91 (2H, s), 6.28 (1H, d, J = 7.2 Hz), 6.96 (1H, s), 7.02 (2H, s), 9.72 (1H, s), 9.91 (1H, s).

[0326]

Reference Example 38

5-[(3,5-Dimethylbenzyl)oxy]-8-fluoro-7-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

A mixture of 5-[(3,5-dimethylbenzyl)oxy]-8-fluoro-7-hydroxy-3,4-dihydroquinolin-2(1H)-one (100 mg), 3,4-dihydro-2H-pyran (1 mL) and p-toluenesulfonic acid (10.9 mg) was stirred at room temperature for 30 min, and was extracted with saturated aqueous sodium hydrogencarbonate and ethyl acetate. The solvent of the organic layer was distilled off, and then the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (106 mg, 84 %).

^{1}HNMR (DMSO-d6) δ ppm: 1.50-1.90 (6H, m), 2.27 (6H, s), 2.39-2.43 (2H, m), 2.77-2.82 (2H, m), 3.31-3.54 (1H, m), 3.75-3.83 (1H, m), 4.95 (2H, s), 5.48 (1H, s),m 6.65 (1H, d, J = 6.7 Hz), 6.95 (1H, s), 7.03 (2H, s), 10.00 (1H, s).

[0327]

Reference Example 39

5-(Benzyloxy)-7-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, a solution of 5-(benzyloxy)-8-bromo-7-fluoro-3,4-dihydroquinolin-2(1H)-one (1.0 g), bis(pinacolato)diboron (1.45 g), potassium acetate (0.84 g) and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane complex (0.12 g) in DMSO (10 mL) was stirred at 110 °C for 3.5 h. The reaction solution was allowed to cool to room temperature, and was extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (850 mg).

^{1}HNMR (DMSO-d6) δ ppm: 1.31 (12H, s), 2.41-2.50 (2H, m), 2.78-2.84 (2H, m), 5.18 (2H, s), 6.65 (1H, d, J = 12.0 Hz), 7.33-7.46 (5H, m), 9.19 (1H, s).

[0328]

Reference Example 40

5-(Benzyloxy)-7-fluoro-8-hydroxy-3,4-dihydroquinolin-2(1H)-one

To a solution of 5-(benzyloxy)-7-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one (800 mg) in methanol (6 mL) was added Oxone (Registered trade mark) (1.86 g) in water (6 mL) under water-cooling and the reaction mixture was stirred at room temperature for 5min. To the reaction solution was added water, the precipitate was collected on a filter, and washed with water. The obtained crude crystal was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (300 mg).

^{1}HNMR (CD_3CN) δ ppm: 2.46-2.52 (2H, m), 2.87-2.93 (2H, m), 5.04 (2H, s), 6.49-6.56 (1H, m), 6.32 (1H, s), 7.34-7.46 (5H, m), 7.80 (1H, s).

[0329]

Reference Example 41

5-(Benzyloxy)-7-fluoro-8-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 38.

^{1}HNMR ($CDCl_3$) δ ppm: 1.5-2.0 (4H, m), 2.45-2.55 (2H, m), 2.80-2.90 (1H, m), 2.95-3.05 (1H, m), 3.45-3.55 (2H, m), 4.00-4.10 (2H, m), 4.90-4.92 (1H, m), 5.00 (2H, s), 6.39 (1H, d, J = 12.3 Hz), 7.40-7.45 (5H, m), 8.18 (1H, s).

[0330]

Reference Example 42

8-Fluoro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-fluoro-1-(4-methoxybenzyl)-5-[(4-methoxybenzyl)oxy]-3,4-dihydroquinolin-2(1H)-one (2.17 g) in ethanol/ethyl acetate (1:1) (40 mL) was added 20 % palladium hydroxide on carbon (wetted with 50 % water) (0.2 g) and stirred at room temperature for 1.5 h under hydrogen atmosphere. The reaction solution was filtered and the solvents of the filtrate were distilled off. The residue was washed with hexane to provide the title compound (1.39 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.61-2.69 (2H, m), 2.81-2.88 (2H, m), 3.74 (3H, s), 5.21 (2H, brs), 5.31 (1H, s), 6.43 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.71-6.78 (3H, m), 7.09-7.14 (2H, m).

[0331]

Reference Example 43

8-Fluoro-1-(4-methoxybenzyl)-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

To a stirred solution of 8-fluoro-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one (8.8 g) in N,N-dimethylformamide (100 mL) was added 60 % sodium hydride (1.46 g) at 0 °C and stirred at the same temperature for 20 min. 4-Methoxybenzyl chloride (5.40 mL) was added at room temperature and stirred for 5 h. To the reaction solution was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (12.7 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.56-1.72 (3H, m), 1.80-1.91 (2H, m), 1.91-2.03 (1H, m), 2.64 (2H, t, J = 7.2 Hz), 2.82-2.98 (2H, m), 3.57-3.63 (1H, m), 3.74 (3H, s), 3.80-3.88 (1H, m), 5.18 (1H, d, J = 15.3 Hz), 5.26 (1H, d, J = 15.3 Hz), 5.27-5.30 (1H, m), 6.73-6.84 (4H, m), 7.10-7.15 (2H, m).

[0332]

Reference Example 44

8-Chloro-1-(4-methoxybenzyl)-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 43.

^{1}HNMR ($CDCl_3$) δ ppm: 1.52-2.03 (6H, m), 2.50-2.60 (2H, m), 2.67-2.87 (2H, m), 3.54-3.65 (1H, m), 3.73 (3H, s), 3.75-3.88 (1H, m), 5.30-5.44 (3H, m), 6.68-6.76 (2H, m), 6.82 (1H, d, J = 9.0 Hz), 7.03-7.15 (3H, m).

[0333]

Reference Example 45

8-Chloro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-chloro-1-(4-methoxybenzyl)-5-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one (43.7 g) in ethanol (450 mL) was added p-toluenesulfonic acid pyridinium (5.47 g) and the reaction mixture was stirred at 80 °C for 1 h. The reaction solution was poured into ice water, the solution was extracted with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (33.75 g, quant.).

^{1}HNMR (DMSO-d6) δ ppm: 2.42-2.54 (2H, m), 2.62-2.72 (2H, m), 3.67 (3H, s), 5.26 (2H, brs), 6.58 (1H, d, J = 8.7 Hz), 6.76 (2H, d, J = 8.7 Hz), 6.98-7.05 (3H, m), 9.79 (1H, brs).

[0334]

Reference Example 46

5-[(3,5-Dimethylbenzyl)oxy]-8-fluoro-1-(4-methoxybenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 43.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.67 (4H, m), 1.81-1.88 (2H, m), 2.31 (6H, s), 2.56-2.61 (2H, m), 2.80-2.85 (2H, m), 3.54-3.59 (1H, m), 3.74 (3H, s), 3.84-3.92 (1H, m), 4.87 (2H, s), 5.20

(2H, s), 5.28-5.30 (1H, m), 6.60 (1H, d, J = 6.3 Hz), 6.74-6.77 (2H, m), 6.95-6.99 (3H, m), 7.12 (2H, d, J = 8.7 Hz).

[0335]

Reference Example 47

2,8-Dichloroquinolin-5-ol

To a solution of 8-chloro-5-hydroxyquinolin-2(1H)-one (13.0 g) in N,N-dimethylformamide (150 mL), thionyl chloride (14.52 mL) was added dropwise, and the reaction mixture was stirred at 80 °C for 2 h. The reaction solution was allowed to cool to room temperature, poured into ice water, the precipitate was collected on a filter and washed with water. The obtained crystal was dissolved in ethyl acetate, dried over anhydrous sodium sulfate, and then the solvent was distilled of to provide the title compound (9.8 g).

^{1}HNMR ($CDCl_3$) δ ppm: 6.97 (1H, d, J = 8.3 Hz), 7.60 (1H, d, J = 8.8 Hz), 7.79 (1H, d, J = 8.3 Hz), 8.57 (1H, d, J = 8.8 Hz), 11.03 (1H, brs).

[0336]

Reference Example 48

2-Chloro-8-fluoroquinolin-5-ol

Synthesized analogous to Reference Example 47.

^{1}HNMR (DMSO-d6) δ ppm: 6.88-6.94 (1H, m), 7.45-7.52 (1H, m), 7.56 (1H, d, J = 8.5 Hz), 8.47-8.55 (1H, m), 10.74 (1H, brs).

[0337]

Reference Example 49

2-Chloro-8-fluoro-5-(tetrahydro-2H-pyran-2-yloxy)quinoline

Synthesized analogous to Reference Example 19.

^{1}HNMR (CDCl$_3$) δ ppm: 1.60-1.83 (3H, m), 1.93-2.15 (3H, m), 3.64-3.69 (1H, m), 3.84-3.91 (1H, m), 5.57 (1H, t, J = 3.1 Hz), 7.13 (1H, dd, J = 8.7 Hz, 3.7 Hz), 7.33 (1H, dd, J = 10.2 Hz, 8.7 Hz), 7.43 (1H, d, J = 8.8 Hz), 8.53 (1H, dd, J = 8.8 Hz, 1.6 Hz).

[0338]

Reference Example 50

8-Fluoro-2-methoxyquinolin-5-ol

To a solution of 2-chloro-8-fluoro-5-(tetrahydro-2H-pyran-2-yloxy)quinoline (2.65 g) in N,N-dimethylformamide (25 mL), sodium methoxide (5M methanol solution) (5.6 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 10 h. The reaction solution was poured into water, neutralized with acetic acid, and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was dissolved into methanol (25 mL), 5 N hydrochloric acid (2 mL) was added thereto and the reaction mixture was stirred at room temperature for 5 h. To the mixture were added saturated aqueous sodium hydrogencarbonate (150 mL) and water (150 mL), the reaciton mixture was stirred at room temperature for 1 h, and the precipitate was collected on a filter to provide the title compound (1.61 g).

^{1}HNMR (CDCl$_3$) δ ppm: 4.11 (3H, s), 5.38 (1H, brs), 6.60 (1H, dd, J = 8.4 Hz, 3.5 Hz), 6.93 (1H, d, J = 9.1 Hz), 7.16 (1H, dd, J = 10.6 Hz, 8.4 Hz), 8.34 (1H, dd, J = 9.1 Hz, 1.7 Hz).

[0339]

Reference Example 51

2,8-Dichloro-5-(tetrahydro-2H-pyran-2-yloxy)quinoline

Synthesized analogous to Reference Example 19.

^{1}HNMR (CDCl$_3$) δ ppm: 1.72-1.81 (2H, m), 1.93-2.14 (4H, m), 3.63-3.68 (1H, m), 3.82-3.87 (1H, m), 5.62 (1H, t, J = 3.0 Hz), 7.15 (1H, d, J = 8.5 Hz), 7.43 (1H, d, J = 8.7 Hz), 7.72 (1H, d, J = 8.5 Hz), 8.56 (1H, d, J = 8.7 Hz).

[0340]

Reference Example 52

8-Chloro-2-methoxyquinolin-5-ol

Synthesized analogous to Reference Example 50.

^{1}HNMR (CDCl$_3$) δ ppm: 4.14 (3H, s), 5.70 (1H, brs), 6.65 (1H, d, J = 8.2 Hz), 6.93 (1H, d, J = 9.0 Hz), 7.54 (1H, d, J = 8.2 Hz), 8.37 (1H, d, J = 9.0 Hz).

[0341]

Reference Example 53

8-Fluoro-1-(4-methoxybenzyl)-5-[(4-methoxybenzyl)oxy]-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere, to a solution of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (10.0 g) in N,N-dimethylformamide (100 mL) was added sodium hydride (55 % in oil) (5.14 g) at 0 °C, the reaction mixture was stirred at the same temperature for 30 min, and 4-methoxybenzyl chloride (16.0 mL) was added thereto dropwise. The reaction mixture was stirred at the same temperature for 1.5 h, then at room temperature for 7 h. To the reaction solution was added ammonium chloride aqueous solution, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled of to provide the title compound (23.2 g, quant.).

^{1}HNMR ($CDCl_3$) δ ppm: 2.56-2.63 (2H, m), 2.82-2.89 (2H, m), 3.74 (3H, s), 3.82 (3H, s), 4.92 (2H, s), 5.22 (2H, brs), 6.59 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.78 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 6.88-6.93 (2H, m), 7.09-7.14 (2H, m), 7.27-7.32 (2H, m).

[0342]

Reference Example 54

7,8-Difluoro-1-(4-methoxybenzyl)-5-[(4-methoxybenzyl)oxy]-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 53.

^{1}HNMR ($CDCl_3$) δ ppm: 2.57-2.63 (2H, m), 2.79-2.85 (2H, m), 3.75 (3H, s), 3.82 (3H, s), 4.88 (2H, s), 5.23 (2H, brs), 6.51 (1H, dd, J = 11.7 Hz, 6.1 Hz), 6.75-6.80 (2H, m), 6.88-6.93 (2H, m), 7.09-7.15 (2H, m), 7.27-7.31 (2H, m).

[0343]

Reference Example 55

7,8-Difluoro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 42.

^{1}HNMR ($CDCl_3$) δ ppm: 2.61-2.68 (2H, m), 2.78-2.83 (2H, m), 3.75 (3H, s), 5.22 (2H, brs), 5.40-6.20 (1H, broad signal), 6.34-6.42 (1H, m), 6.74-6.80 (2H, m), 7.08-7.14 (2H, m).

[0344]

Reference Example 56

8-Fluoro-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere, to a suspension of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (5.0 g) and potassium carbonate (5.72 g) in N,N-dimethylformamide (50 mL), chloromethyl methyl sulfide (3.32 mL) was added dropwise at 0 °C, and the reaction mixture was stirred at room temperature for 36 h. To the reaction solution was added water, and the precipitate was collected on a filter to provide the title compound (4.95 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.26 (3H, s), 2.60-2.25 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 5.15 (2H, s), 6.54 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.93 (1H, dd, J = 9.7 Hz, 9.2 Hz), 7.54 (1H, brs).

[0345]

Reference Example 57

8-Fluoro-1-(4-methoxybenzyl)-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 43.

^{1}HNMR ($CDCl_3$) δ ppm: 2.22 (3H, s), 2.61-2.67 (2H, m), 2.86-2.92 (2H, m), 3.74 (3H, s), 5.10 (2H, s), 5.22 (2H, brs), 6.59 (1H, dd, J = 9.1 Hz, 3.5 Hz), 6.73-6.78 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

[0346]

Reference Example 58

5-(Chloromethoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-fluoro-1-(4-methoxybenzyl)-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one (5.48 g) in dichloromethane (100 mL), sulfuryl chloride (1.22 mL) was added dropwise under ice-cooling, and the reaction mixture was stirred at the same temperature for 1 h. The solvent was distilled off to provide the title compound (5.3 g, quant.).

^{1}HNMR ($CDCl_3$) δ ppm: 2.60-2.66 (2H, m), 2.84-2.91 (2H, m), 3.74 (3H, s), 5.22 (2H, brs), 5.84 (2H, s), 6.74-6.78 (2H, m), 6.82 (1H, dd, J = 9.2 Hz, 3.5 Hz), 6.90 (1H, dd, J = 12.4 Hz, 9.2 Hz), 7.09-7.14 (2H, m).

[0347]

Reference Example 59

1-*tert*-Butyl 4-ethyl 4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-1,4-dicarboxylate

Under argon atmosphere, to a solution of piperidine-1,4-dicarboxylic acid 4-ethyl 1-*tert*-butyl (9.75 g) in tetrahydrofuran (90 mL), lithium diisopropylamide (2 M heptane/tetrahydrofuran/ethylbenzene solution) (19.7 mL) was added dropwise at -70 °C, the reaction mixture was stirred at the same temperature for 1 h, a solution of 5-(chloromethoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (5.3 g) in tetrahydrofuran (50 mL) was added dropwise, and the reaction mixture was stirred at -40 °C for 7 h. To the reaction solution was added aqueous saturated ammonium chloride solution, the reaction was allowed to warm to room temperature, and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (6.31 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.46 (9H, s), 1.48-1.58 (2H, m), 2.17-2.24 (2H, m), 2.57-2.63 (2H, m), 2.76-2.83 (2H, m), 2.83-3.15 (2H, m), 3.74 (3H, s), 3.79-4.04 (4H, m), 4.17 (2H, q, J = 7.1 Hz), 5.21 (2H, brs), 6.45 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.77 (2H, m), 6.81 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.09-7.14 (2H, m).

[0348]

Reference Example 60

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

To a solution of 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-1,4-dicarboxylic acid 4-ethyl 1-*tert*-butyl (6.31 g) in ethyl acetate (60 mL) was added 4 N hydrochloric acid/ethyl acetate (60 mL), and the reaction mixture was stirred at room temperature for 3 h. The solvent was distilled off and to the residue was added ethyl acetate and water, the reaction mixture was made basic with aqueous sodium hydroxide, and then extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (5.37 g, quant.).

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.51-1.59 (2H, m), 1.87 (1H, brs), 2.19-2.27 (2H, m), 2.57-2.63 (2H, m), 2.74-2.84 (4H, m), 2.96-3.03 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 4.17 (2H, q, J = 7.1 Hz), 5.21 (2H, brs), 6.45 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.81 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.09-7.15 (2H, m).

[0349]

Reference Example 61

8-Chloro-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 56.

^{1}HNMR ($CDCl_3$) δ ppm: 2.26 (3H, s), 2.62 (2H, t, J = 7.7 Hz), 3.01 (2H, t, J = 7.7 Hz), 5.17 (2H, s), 6.59 (1H, d, J = 8.9 Hz), 7.19 (1H, d, J = 8.9 Hz), 7.74 (1H, brs).

[0350]

Reference Example 62

8-Chloro-1-(4-methoxybenzyl)-5-[(methylsulfanyl)methoxy]-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 43.

^{1}HNMR ($CDCl_3$) δ ppm: 2.21 (3H, s), 2.55 (2H, t, J = 6.8 Hz), 2.77 (2H, t, J = 6.8 Hz), 3.73 (3H, s), 5.12 (2H, s), 5.36 (2H, s), 6.64 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 7.05-7.08 (2H, m), 7.16 (1H, d, J = 9.0 Hz).

[0351]

Reference Example 63

8-Chloro-5-(chloromethoxy)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 58.

^{1}HNMR ($CDCl_3$) δ ppm: 2.55 (2H, t, J = 6.8 Hz), 2.76 (2H, t, J = 6.8 Hz), 3.73 (3H, s), 5.37 (2H, s), 5.85 (2H, s), 6.70-6.73 (2H, m), 6.87 (1H, d, J = 9.0 Hz), 7.04-7.07 (2H, m), 7.22 (1H, d, J = 9.0 Hz).

[0352]

Reference Example 64

4-({[8-Chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-1,4-dicarboxylic acid 4-ethyl 1-*tert*-butyl

Synthesized analogous to Reference Example 59.

^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.46 (9H, s), 1.52 (2H, br), 2.19-2.22 (2H, m), 2.52 (2H, t, J = 6.8 Hz), 2.66-2.69 (2H, m), 3.00 (2H, brs), 3.73 (3H, s), 3.92 (4H, brs), 4.16 (2H, q, J = 7.1 Hz), 5.36 (2H, s), 6.51 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 7.04-7.07 (2H, m), 7.12 (1H, d, J = 8.9 Hz).

[0353]

Reference Example 65

Ethyl 4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 60.

^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.64-1.69 (2H, m), 2.25-2.28 (2H, m), 2.52 (2H, t, J = 6.7 Hz), 2.67-2.70 (2H, m), 2.81-2.86 (2H, m), 3.07-3.12 (2H, m), 3.73 (3H, s), 3.93 (2H, s), 4.17 (2H, q, J = 7.1 Hz), 5.36 (2H, s), 6.51 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 7.04-7.07 (2H, m), 7.12 (1H, d, J = 8.8 Hz).

[0354]

Reference Example 66

Ethyl 1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

A solution of ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate (5.37 g), 2,3,5-trichloropyridine (2.50 g) and potassium carbonate (2.37 g) in N-methyl-2-pyrrolidone (50 mL) was stirred at 100 °C for 3 days. To the reaction solution was added ammonium chloride aqueous solution, and the reaction mixture was stirred and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (3.17 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.74-1.83 (2H, m), 2.32-2.39 (2H, m), 2.58-2.64 (2H, m), 2.78-2.84 (2H, m), 3.02-3.10 (2H, m), 3.60-3.68 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, brs), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.09-7.15 (2H, m), 7.59 (1H, d, J = 2.3 Hz), 8.11 (1H, d, J = 2.3 Hz).

[0355]

Reference Example 67

Ethyl 1-(3,5-difluoropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 66.

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.72-1.80 (2H, m), 2.31-2.37 (2H, m), 2.60 (2H, t, J = 7.1 Hz), 2.80 (2H, t, J = 7.1 Hz), 3.05-3.12 (2H, m), 3.69-3.77 (2H, m), 3.75 (3H, s), 3.95 (2H, s), 4.16 (2H, q, J = 7.1 Hz), 5.23 (2H, brs), 6.45 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.79 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.14 (3H, m), 7.92 (1H, d, J = 2.5 Hz).

[0356]

Reference Example 68

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(5-fluoro-3-methylpyridin-2-yl)piperidine-4-carboxylate

Under nitrogen atmosphere, a solution of ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate (2.69 g), 2-chloro-5-fluoro-3-methylpyridine (1 g), tris(dibenzylideneacetone)dipalladium (0) (0.105 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.178 g) and sodium *tert*-butoxide (1.10 g) in toluene (20 mL) was stirred at 100 °C overnight. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.36 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.2 Hz), 1.77-1.82 (2H, m), 2.28 (3H, s), 2.34-2.37 (2H, m), 2.60-2.62 (2H, m), 2.81-2.83 (2H, m), 2.93-2.99 (2H, m), 3.19-3.23 (2H, m), 3.74 (3H, s), 4.00 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.11-7.14 (2H, m), 7.18 (1H, dd, J = 8.6 Hz, 2.9 Hz), 7.99 (1H, d, J = 3.0 Hz).

[0357]

Reference Example 69

Ethyl 1-(2,4-dichlorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 68.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.80-1.85 (2H, m), 2.37-2.39 (2H, m), 2.60-2.63 (2H, m), 2.79-2.84 (4H, m), 3.20-3.24 (2H, m), 3.74 (3H, s), 3.98 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.94 (1H, d, J = 8.6 Hz), 7.11-7.13 (2H, m), 7.17 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.36 (1H, d, J = 2.5 Hz).

[0358]

Reference Example 70

Ethyl 1-(2,5-dichlorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Under nitrogen atmosphere, a solution of ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate (300 mg), 1,4-dichloro-2-iodobenzene (0.103 mL), tris(dibenzylideneacetone)dipalladium (0) (11.7 mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (19.85 mg) and cesium carbonate (415 mg) in toluene (6 mL) was stirred at 110 °C overnight. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (240 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.80-1.86 (2H, m), 2.38-2.40 (2H, m), 2.60-2.63 (2H, m), 2.81-2.85 (4H, m), 3.24-3.28 (2H, m), 3.74 (3H, s), 3.98 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.83 (1H, dd, J = 12.8 Hz, 9.1 Hz), 6.94 (1H, dd, J = 8.5 Hz, 2.4 Hz), 6.99 (1H, d, J = 2.4 Hz), 7.11-7.13 (2H, m), 7.26-7.27 (1H, m).

[0359]

Reference Example 71

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxylate

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.74-1.80 (2H, m), 2.35-2.38 (2H, m), 2.60-2.62 (2H, m), 2.80-2.82 (2H, m), 2.92-2.98 (2H, m), 3.48-3.52 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.46 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.88-6.91 (2H, m), 7.09-7.13 (4H, m).

[0360]

Reference Example 72

Ethyl 1-(2,4-dichloro-5-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.38-2.40 (2H, m), 2.60-2.63 (2H, m), 2.78-2.83 (4H, m), 3.23-3.26 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.81-6.85 (2H, m), 7.12 (2H, d, J = 8.6 Hz), 7.39 (1H, d, J = 7.6 Hz).

[0361]

Reference Example 73

Ethyl 1-(2,5-dichloro-4-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.77-2.84 (4H, m), 3.17-3.19 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.04 (1H, d, J = 7.2 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.19 (1H, d, J = 8.6 Hz).

[0362]

Reference Example 74

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2,4,5-trichlorophenyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 70.

^{1}HNMR (CDCl$_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.79-2.83 (4H, m), 3.22-3.25 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.75-6.77 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 8.9 Hz), 7.07 (1H, s), 7.12 (2H, d, J = 8.6 Hz), 7.44 (1H, s).

[0363]

Reference Example 75

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-[5-fluoro-2-(trifluoromethyl)phenyl]piperidine-4-carboxylate

Synthesized analogous to Reference Example 70.

^{1}HNMR (CDCl$_3$) δ ppm: 1.24 (3H, t, J = 7.1 Hz), 1.77-1.83 (2H, m), 2.34-2.36 (2H, m), 2.60-2.63 (2H, m), 2.81-2.85 (4H, m), 3.01-3.03 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.0 Hz), 6.87-6.91 (1H, m), 6.99 (1H, dd, J = 10.1 Hz, 2.3 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.60 (1H, dd, J = 8.7 Hz, 6.4 Hz).

[0364]

Reference Example 76

Ethyl 1-(2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 70.

^{1}HNMR (CDCl$_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.79-1.84 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.81-2.88 (4H, m), 3.32-3.35 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.19 (2H, q, J

= 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.56-6.66 (2H, m), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.92-6.97 (1H, m), 7.12 (2H, d, J = 8.6 Hz).

[0365]

Reference Example 77

Ethyl 1-(4-chloro-2,6-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 68.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.72-1.78 (2H, m), 2.30-2.32 (2H, m), 2.60-2.63 (2H, m), 2.80-2.83 (2H, m), 3.13-3.19 (4H, m), 3.74 (3H, s), 3.96 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.80-6.88 (3H, m), 7.12 (2H, d,J = 8.6 Hz).

[0366]

Reference Example 78

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2,4,6-trifluorophenyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.73-1.79 (2H, m), 2.30-2.33 (2H, m), 2.60-2.63 (2H, m), 2.80-2.83 (2H, m), 3.08-3.20 (4H, m), 3.74 (3H, s), 3.97 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.61 (2H, t, J = 8.9 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz).

[0367]

Reference Example 79

Ethyl 1-(4-chloro-2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Under nitrogen atmosphere, a solution of ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate (0.85 g), 1-bromo-4-chloro-2,5-difluorobenzene (0.616 g), tris(dibenzylideneacetone)dipalladium (0) (0.033 g), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) (0.063 g) and cesium carbonate (1.177 g) in toluene (12 mL) was stirred at 110 °C overnight. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (555 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.77-1.83 (2H, m), 2.37-2.39 (2H, m), 2.60-2.63 (2H, m), 2.80-2.87 (4H, m), 3.29-3.32 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.70-6.77 (3H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.0 Hz), 7.06 (1H, dd, J = 11.6 Hz, 6.8 Hz), 7.12 (2H, d, J = 8.6 Hz).

[0368]

Reference Example 80

Ethyl 1-(4-chloro-2-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.78-1.84 (2H, m), 2.37-2.39 (2H, m), 2.60-2.63 (2H, m), 2.80-2.87 (4H, m), 3.27-3.29 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.18 (2H, q, J

= 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.80-6.88 (2H, m), 7.02-7.06 (2H, m), 7.12 (2H, d, J = 8.6 Hz).

[0369]

Reference Example 81

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2,4,5-trifluorophenyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR (CDCl$_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.78-1.84 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.79-2.83 (4H, m), 3.23-3.25 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.74-6.93 (5H, m), 7.12 (2H, d, J = 8.6 Hz).

[0370]

Reference Example 82

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-[2-fluoro-4-(trifluoromethyl)phenyl]piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR (CDCl$_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.79-1.84 (2H, m), 2.38-2.41 (2H, m), 2.60-2.63 (2H, m), 2.81-2.83 (2H, m), 2.91-2.97 (2H, m), 3.41-3.43 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.75-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.98 (1H, t, J = 8.4 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.25-7.28 (1H, m), 7.31 (1H, d, J = 8.5 Hz).

[0371]

Reference Example 83

Ethyl 1-[2-chloro-4-(trifluoromethyl)phenyl]-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.81-1.87 (2H, m), 2.40-2.42 (2H, m), 2.60-2.63 (2H, m), 2.81-2.91 (4H, m), 3.33-3.35 (2H, m), 3.74 (3H, s), 3.99 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.74-6.77 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.07 (1H, t, J = 8.4 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.45-7.46 (1H, m), 7.61 (1H, d, J = 1.9 Hz).

[0372]

Reference Example 84

Ethyl 1-(2,4-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.37-2.40 (2H, m), 2.60-2.63 (2H, m), 2.81-2.85 (4H, m), 3.22-3.24 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.75-6.84 (6H, m), 7.12 (2H, d, J = 8.6 Hz).

[0373]

Reference Example 85

Ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2-fluoro-4-methylphenyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.28 (3H, s), 2.37-2.39 (2H, m), 2.60-2.63 (2H, m), 2.81-2.85 (4H, m), 3.26-3.28 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.80-6.86 (4H, m), 7.12 (2H, d, J = 8.5 Hz).

[0374]

Reference Example 86

Ethyl 1-[4-chloro-2-(trifluoromethyl)phenyl]-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.75-1.81 (2H, m), 2.33-2.35 (2H, m), 2.60-2.63 (2H, m), 2.81-2.86 (4H, m), 2.95-2.97 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.0 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.26-7.28 (1H, m), 7.46 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.59 (1H, d, J = 2.4 Hz).

[0375]

Reference Example 87

Ethyl 1-(4-bromo-2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.1 Hz), 1.77-1.83 (2H, m), 2.36-2.39 (2H, m), 2.60-2.63 (2H, m), 2.80-2.87 (4H, m), 3.30-3.33 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.46 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.71 (1H, dd, J = 10.2 Hz, 7.5 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz),7.12 (2H, d, J = 8.6 Hz), 7.19 (1H, dd, J = 11.4 Hz, 6.4 Hz).

[0376]

Reference Example 88

Ethyl 1-(2',4'-dichloro-2,5-difluorobiphenyl-4-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Under nitrogen atmosphere, to a solution of ethyl 1-(4-bromo-2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate (287 mg), 2,4-dichlorophenylboronic acid (108 mg) and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane adduct (17.7 mg) in 1,2-dimethoxyethane (4 mL) was added 2 M sodium carbonate aqueous solution (0.651 mL), and the reaction mixture was stirred under reflux for 20 h. The reaction solution was poured into water, and and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (213 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.80-1.86 (2H, m), 2.39-2.42 (2H, m), 2.61-2.64 (2H, m), 2.81-2.84 (2H, m), 2.90-2.95 (2H, m), 3.40-3.43 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.71 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.75-6.77 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.96 (1H, dd, J = 12.5 Hz, 6.7 Hz), 7.13 (2H, d, J = 8.5 Hz), 7.23 (1H, d, J = 8.3 Hz), 7.30 (1H, dd, J = 8.3 Hz, 2.0 Hz), 7.49 (1H, d, J = 2.1 Hz).

[0377]

Reference Example 89

Ethyl 1-(4'-chloro-2,2',5-trifluorobiphenyl-4-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 88.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J = 7.1 Hz), 1.80-1.86 (2H, m), 2.39-2.41 (2H, m), 2.60-2.63 (2H, m), 2.81-2.84 (2H, m), 2.90-2.94 (2H, m), 3.40-3.42 (2H, m), 3.74 (3H, s), 3.97 (2H, s), 4.20 (2H, q, J = 7.1 Hz), 5.22 (2H, s), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.71-6.77 (3H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.03 (1H, dd, J = 12.7 Hz, 6.7 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.17-7.21 (2H, m), 7.26-7.31 (1H, m).

[0378]

Reference Example 90

Ethyl 4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2,4-dichlorophenyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.79-1.85 (2H, m), 2.37-2.39 (2H, m), 2.51-2.54 (2H, m), 2.69-2.72 (2H, m), 2.79-2.84 (2H, m), 3.21-3.23 (2H, m), 3.73 (3H, s), 4.00 (2H, s), 4.18 (2H, q, J = 7.1 Hz), 5.37 (2H, s), 6.54 (1H, d, J = 8.9 Hz), 6.71-6.73 (2H, m), 6.95 (1H, d, J = 8.7 Hz),7.05-7.07 (2H, m), 7.14 (1H, d, J = 8.9 Hz), 7.18 (1H, dd, J = 8.7 Hz, 2.4 Hz), 7.36 (1H, d, J = 2.4 Hz).

[0379]

Reference Example 91

Ethyl 1-(4-chloro-2-fluorophenyl)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.78-1.84 (2H, m), 2.36-2.39 (2H, m), 2.51-2.54 (2H, m), 2.69-2.71 (2H, m), 2.82-2.87 (2H, m), 3.26-3.29 (2H, m), 3.73 (3H, s), 3.98 (2H, s), 4.17 (2H, q, J = 7.1 Hz), 5.37 (2H, s), 6.54 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 6.84-6.88 (1H, m),7.02-7.07 (4H, m), 7.13 (1H, d, J = 8.9 Hz).

[0380]

Reference Example 92

Ethyl 1-(4-chloro-2,6-difluorophenyl)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.72-1.79 (2H, m), 2.29-2.32 (2H, m), 2.51-2.54 (2H, m), 2.69-2.71 (2H, m), 3.13-3.21 (4H, m), 3.73 (3H, s), 3.99 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 5.37 (2H, s), 6.54 (1H, d, J = 9.0 Hz), 6.70-6.73 (2H, m), 6.84-6.89 (2H, m),7.05-7.08 (2H, m), 7.13 (1H, d, J = 8.9 Hz).

[0381]

Reference Example 93

1-(3,5-Dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

To a solution of ethyl 1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylate (3.17 g) in methanol/tetrahydrofuran (1:1) (60 mL) was added 5 N aqueous sodium hydroxide (10.3 mL), and the reaction mixture was stirred at 60 °C for 5.5 h. The solvent was distilled off and to the residue were added water and 5 N hydrochloric acid to make the reaction residue acidic, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (3.15 g, quant.).

^{1}HNMR ($CDCl_3$) δ ppm: 1.75-1.84 (2H, m), 2.34-2.43 (2H, m), 2.58-2.66 (2H, m), 2.79-2.87 (2H, m), 3.09-3.18 (2H, m), 3.61-3.69 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.22 (2H, brs), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.70-6.76 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.14 (2H, m), 7.60 (1H, d, J = 2.3 Hz), 8.11 (1H, d, J = 2.3 Hz).

[0382]

Reference Example 94

1-(3,5-Difluoropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.71-1.80 (2H, m), 2.33-2.40 (2H, m), 2.60 (2H, t, J = 7.0 Hz), 2.81 (2H, t, J = 7.0 Hz), 3.13-3.22 (2H, m), 3.71 (3H, s), 3.69-3.78 (2H, m), 3.99 (2H, s), 5.22 (2H, brs), 6.48 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.70-6.74 (2H, m), 6.81 (1H, dd, J = 13.0 Hz, 9.0 Hz), 7.08-7.14 (3H, m), 7.93 (1H, d J = 2.5 Hz), 10.77 (1H, brs).

[0383]

Reference Example 95

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(5-fluoro-3-methylpyridin-2-yl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.70-2.00 (2H, br), 2.31-2.47 (2H, m), 2.59-2.62 (2H, m), 2.82-2.85 (2H, m), 3.10-3.47 (4H, br), 3.73 (3H, s), 4.02 (2H, s), 5.22 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.74-6.76 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.31-7.37 (1H, m), 8.01 (1H, s).

[0384]

Reference Example 96

1-(2,4-Dichlorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.85 (2H, m), 2.40-2.42 (2H, m), 2.61-2.64 (2H, m), 2.82-2.91 (4H, m), 3.22-3.25 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 2.9 Hz), 6.73 (2H, d, J = 8.7 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.95-6.97 (1H, m), 7.11 (2H, d, J = 8.4 Hz), 7.17-7.19 (1H, m), 7.35-7.36 (1H, m).

[0385]

Reference Example 97

1-(2,5-Dichlorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.81-1.86 (2H, m), 2.40-2.43 (2H, m), 2.61-2.64 (2H, m), 2.83-2.92 (4H, m), 3.26-3.29 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.1 Hz), 6.74 (2H, d, J = 8.6 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.94 (1H, dd, J = 8.5 Hz, 2.4 Hz), 7.01 (1H, d, J = 2.2 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.27 (1H, d, J = 8.4 Hz).

[0386]

Reference Example 98

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.70-1.85 (2H, br), 2.39-2.42 (2H, m), 2.61-2.64 (2H, m), 2.81-2.84 (2H, m), 2.98-3.09 (2H, br), 3.50-3.53 (2H, m), 3.71 (3H, s), 3.99 (2H, s), 5.22 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.1 Hz), 6.71-6.74 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.0 Hz), 6.87-6.94 (2H, m), 7.07-7.14 (4H, m).

[0387]

Reference Example 99

1-(2,4-Dichloro-5-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.80-1.86 (2H, m), 2.41-2.43 (2H, m), 2.62-2.65 (2H, m), 2.83-2.89 (4H, m), 3.25-3.27 (2H, m), 3.73 (3H, s), 4.01 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.73-6.75 (2H, m), 6.82-6.86 (2H, m), 7.12 (2H, d, J = 8.6 Hz), 7.39 (1H, d, J = 7.6 Hz).

[0388]

Reference Example 100

1-(2,5-Dichloro-4-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.79-1.85 (2H, m), 2.41-2.44 (2H, m), 2.62-2.65 (2H, m), 2.83-2.90 (4H, m), 3.19-3.21 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.2 Hz, 3.1 Hz), 6.72-6.74 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.06 (1H, d, J = 7.2 Hz), 7.11 (2H, d, J = 8.6 Hz), 7.20 (1H, d, J = 8.6 Hz).

[0389]

Reference Example 101

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2,4,5-trichlorophenyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.79-1.84 (2H, m), 2.41-2.44 (2H, m), 2.62-2.65 (2H, m), 2.83-2.92 (4H, m), 3.24-3.26 (2H, m), 3.72 (3H, s), 4.02 (2H, s), 5.23 (2H, s), 6.50-6.52 (1H, m), 6.73 (2H, d, J = 8.7 Hz), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.09-7.12 (3H, m), 7.44 (1H, s).

[0390]

Reference Example 102

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-[5-fluoro-2-(trifluoromethyl)phenyl]piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.77-1.82 (2H, m), 2.38-2.41 (2H, m), 2.63-2.66 (2H, m), 2.83-2.86 (2H, m), 2.89-2.94 (2H, m), 3.03-3.05 (2H, m), 3.72 (3H, s), 4.02 (2H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.72-6.75 (2H, m), 6.83-6.91 (2H, m), 7.03 (1H, dd, J = 10.1 Hz, 2.3 Hz), 7.11 (2H, d, J = 8.6 Hz), 7.60 (1H, dd, J = 8.8 Hz, 6.3 Hz).

[0391]

Reference Example 103

1-(2,5-Difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.85 (2H, m), 2.40-2.42 (2H, m), 2.61-2.64 (2H, m), 2.82-2.85 (2H, m), 2.91-2.96 (2H, m), 3.34-3.36 (2H, m), 3.72 (3H, s), 4.00 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.57-6.62 (1H, m), 6.64-6.70 (1H, m), 6.74 (2H, d, J = 8.5 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.92-6.98 (1H, m), 7.11 (2H, d, J = 8.5 Hz).

[0392]

Reference Example 104

1-(4-Chloro-2,6-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.74-1.80 (2H, m), 2.33-2.35 (2H, m), 2.61-2.64 (2H, m), 2.82-2.85 (2H, m), 3.15-3.18 (2H, m), 3.22-3.27 (2H, m), 3.73 (3H, s), 4.00 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.75 (2H, m), 6.81-6.89 (3H, m), 7.12 (2H, d, J = 8.6 Hz).

[0393]

Reference Example 105

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2,4,6-trifluorophenyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.75-1.80 (2H, m), 2.33-2.36 (2H, m), 2.61-2.64 (2H, m), 2.82-2.85 (2H, m), 3.10-3.13 (2H, m), 3.22-3.27 (2H, m), 3.73 (3H, s), 4.01 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.62 (2H, t, J = 8.9 Hz), 6.72-6.75 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz).

[0394]

Reference Example 106

1-(4-Chloro-2,5-difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.77-1.83 (2H, m), 2.40-2.43 (2H, m), 2.62-2.65 (2H, m), 2.82-2.85 (2H, m), 2.90-2.95 (2H, m), 3.31-3.34 (2H, m), 3.72 (3H, s), 3.99 (2H, s), 5.23 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.71-6.77 (3H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.07 (1H, dd, J = 11.6 Hz, 6.9 Hz), 7.11 (2H, d, J = 8.6 Hz).

[0395]

Reference Example 107

1-(4-Chloro-2-fluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.78-1.84 (2H, m), 2.40-2.43 (2H, m), 2.62-2.65 (2H, m), 2.82-2.85 (2H, m), 2.90-2.94 (2H, m), 3.29-3.31 (2H, m), 3.72 (3H, s), 4.00 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.71-6.73 (2H, m), 6.82-6.89 (2H, m), 7.02-7.06 (2H, m), 7.11 (2H, d, J = 8.5 Hz).

[0396]

Reference Example 108

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2,4,5-trifluorophenyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.99 (2H, br), 2.43-2.46 (2H, m), 2.62-2.65 (2H, m), 2.82-2.84 (2H, m), 2.96-3.12 (2H, br), 3.31-3.34 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.1 Hz), 6.72-6.73 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.92-7.08 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

[0397]

Reference Example 109

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-[2-fluoro-4-(trifluoromethyl)phenyl]piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.78 (2H, m), 2.19-2.21 (2H, m), 2.57-2.60 (2H, m), 2.79-2.82 (2H, m), 2.92-2.96 (2H, m), 3.38-3.41 (2H, m), 3.68 (3H, s), 4.03 (2H, s), 5.09 (2H, s), 6.73 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.79-6.82 (2H, m), 6.98 (1H, dd, J = 13.1 Hz, 9.1 Hz), 7.06 (2H, d, J = 8.7 Hz), 7.21 (1H, t, J = 8.6 Hz), 7.44-7.46 (1H, m), 7.53 (1H, dd, J = 13.2 Hz, 1.8 Hz).

[0398]

Reference Example 110

1-[2-Chloro-4-(trifluoromethyl)phenyl]-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.84-1.89 (2H, m), 2.43-2.46 (2H, m), 2.63-2.65 (2H, m), 2.83-2.86 (2H, m), 2.93-3.04 (2H, br), 3.35-3.38 (2H, m), 3.72 (3H, s), 4.03 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.75 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.11-7.12 (3H, m), 7.45-7.48 (1H, m), 7.62 (1H, d, J = 1.8 Hz).

[0399]

Reference Example 111

1-(2,4-Difluorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 2.40-2.84 (8H, m), 3.48-3.74 (7H, m), 4.08 (2H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.2 Hz, 3.21 Hz), 6.73-6.75 (2H, m), 6.84-6.99 (4H, m), 7.11 (2H, d, J = 8.5 Hz).

[0400]

Reference Example 112

4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2-fluoro-4-methylphenyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.74-1.97 (2H, br), 2.29 (3H, s), 2.40-2.44 (2H, m), 2.61-2.65 (2H, m), 2.81-3.05 (4H, m), 3.21-3.39 (2H, br), 3.71 (3H, s), 4.01 (2H, s), 5.22 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.72-6.73 (2H, m), 6.82-6.92 (4H, m), 7.11 (2H, d, J = 8.5 Hz).

[0401]

Reference Example 113

1-[4-Chloro-2-(trifluoromethyl)phenyl]-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.74-1.97 (2H, m), 2.37-2.39 (2H, m), 2.62-2.65 (2H, m), 2.83-2.86 (2H, m), 2.89-2.99 (4H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.74 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.29 (1H, d, J = 8.6 Hz), 7.47 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.60 (1H, d, J = 2.5 Hz).

[0402]

Reference Example 114

1-(2',4'-Dichloro-2,5-difluorobiphenyl-4-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.95-2.08 (2H, br), 2.45-2.48 (2H, m), 2.63-2.66 (2H, m), 2.83-2.86 (2H, m), 3.10-3.24 (2H, br), 3.48-3.50 (2H, m), 3.72 (3H, s), 4.03 (2H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.0 Hz), 6.73-6.74 (2H, m), 6.85 (1H, dd, J = 12.5 Hz, 9.1 Hz), 6.99-7.08 (2H, m), 7.12 (2H, d, J = 8.6 Hz), 7.23 (1H, d, J = 8.3 Hz), 7.31 (1H, dd, J = 8.3 Hz, 2.1 Hz), 7.50 (1H, d, J = 2.1 Hz).

[0403]

Reference Example 115

1-(4'-Chloro-2,2',5-trifluorobiphenyl-4-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.82-1.88 (2H, m), 2.42-2.45 (2H, m), 2.63-2.65 (2H, m), 2.83-2.86 (2H, m), 2.99-3.04 (2H, m), 3.42-3.45 (2H, m), 3.72 (3H, s), 4.01 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.80 (3H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.04 (1H, dd, J = 12.7 Hz, 6.7 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.17-7.21 (2H, m), 7.26-7.32 (1H, m).

[0404]

Reference Example 116

4-({[8-Chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(2,4-dichlorophenyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (CDCl$_3$) δ ppm: 1.79-1.85 (2H, m), 2.41-2.43 (2H, m), 2.51-2.54 (2H, m), 2.70-2.73 (2H, m), 2.87-2.91 (2H, m), 3.23-3.25 (2H, m), 3.70 (3H, s), 4.03 (2H, s), 5.39 (2H, s), 6.57

(1H, d, J = 9.0 Hz), 6.67-6.68 (2H m), 6.96 (1H, d, J = 8.6 Hz), 7.04-7.06 (2H, m), 7.15 (1H, d, J = 8.9 Hz), 7.18 (1H, dd, J = 8.7 Hz, 2.4 Hz), 7.36 (1H, d, J = 2.4 Hz).

[0405]

Reference Example 117

1-(4-Chloro-2-fluorophenyl)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.78-1.84 (2H, m), 2.39-2.42 (2H, m), 2.51-2.54 (2H, m), 2.70-2.72 (2H, m), 2.89-2.94 (2H, m), 3.29-3.31 (2H, m), 3.70 (3H, s), 4.01 (2H, s), 5.38 (2H, s), 6.56 (1H, d, J = 9.0 Hz), 6.67-6.69 (2H m), 6.86-6.89 (1H, m), 7.02-7.06 (4H, m), 7.15 (1H, d, J = 8.9 Hz).

[0406]

Reference Example 118

1-(4-Chloro-2,6-difluorophenyl)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.75-1.82 (2H, m), 2.32-2.35 (2H, m), 2.51-2.54 (2H, m), 2.70-2.72 (2H, m), 3.14-3.28 (4H, m), 3.72 (3H, s), 4.03 (2H, s), 5.38 (2H, s), 6.56 (1H, d, J = 8.9 Hz), 6.70 (2H, d, J = 8.6 Hz), 6.84-6.90 (2H, m), 7.06 (2H, d, J = 8.5 Hz), 7.14 (1H, d, J = 8.9 Hz).

[0407]

Reference Example 119

1-(5-Fluoro-3-methylpyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

A solution of 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-(5-fluoro-3-methylpyridin-2-yl)piperidine-4-carboxylic acid (1.33 g) and anisole (0.527 mL) in trifluoroacetic acid (10 mL) was stirred at 65 °C for 3 h. The reaction solution was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (1.00 g).

^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.75 (2H, m), 2.18-2.21 (2H, m), 2.26 (3H, s), 2.43-2.46 (2H, m), 2.80-2.89 (4H, m), 3.17-3.20 (2H, m), 4.03 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00-7.03 (1H, m), 7.05-7.52 (1H, m), 8.06-8.07 (1H, m), 10.03 (1H, s), 12.28-13.00 (1H, br).

[0408]

Reference Example 120

1-(2,4-Dichlorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.78 (2H, m), 2.20-2.23 (2H, m), 2.43-2.46 (2H, m), 2.78-2.83 (4H, m), 3.15-3.17 (2H, m), 4.05 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00-7.04 (1H, m), 7.17 (1H, d, J = 8.8 Hz), 7.34 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.53 (1H, d, J = 2.5 Hz), 10.02 (1H, s), 12.59-12.79 (1H, br).

[0409]

Reference Example 121

1-(2,5-Dichlorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.79 (2H, m), 2.19-2.22 (2H, m), 2.43-2.46 (2H, m), 2.80-2.86 (4H, m), 3.18-3.21 (2H, m), 4.07 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.00-7.04 (1H, m), 7.09 (1H, dd, J = 8.5 Hz, 2.4 Hz), 7.17 (1H, d J = 2.4 Hz), 7.43 (1H, d, J = 8.5 Hz), 10.03 (1H, s), 12.54-12.81 (1H, br).

[0410]

Reference Example 122

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR ($CDCl_3$) δ ppm: 2.34-2.41 (2H, m), 2.51-2.58 (4H, m), 2.89-2.91 (2H, m), 3.46-3.51 (2H, m), 3.72-3.75 (2H, m), 3.86 (2H, s), 6.53 (1H, dd, J = 9.2 Hz, 3.8 Hz), 6.90-6.96 (1H, m), 7.34-7.35 (2H, m), 7.57-7.59 (2H, m), 8.57-8.63 (1H, br).

[0411]

Reference Example 123

1-(2,4-Dichloro-5-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.78 (2H, m), 2.20-2.22 (2H, m), 2.43-2.46 (2H, m), 2.80-2.85 (4H, m), 3.19-3.23 (2H, m), 4.05 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00-7.04 (1H, m), 7.24 (1H, d, J = 11.2 Hz), 7.71 (1H, d, J = 7.8 Hz), 10.03 (1H, s), 12.60-12.81 (1H, br).

[0412]

Reference Example 124

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-[5-fluoro-2-(trifluoromethyl)phenyl]piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.77 (2H, m), 2.15-2.18 (2H, m), 2.43-2.46 (2H, m), 2.80-2.84 (4H, m), 2.98-3.01 (2H, m), 4.09 (2H, s), 6.64 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.03 (1H, t, J = 9.7 Hz), 7.12-7.16 (1H, m), 7.38-7.41 (1H, m), 7.73 (1H, dd, J = 8.7 Hz, 6.4 Hz), 10.03 (1H, s), 12.58-12.73 (1H, br).

[0413]

Reference Example 125

1-(2,5-Difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.77 (2H, m), 2.18-2.20 (2H, m), 2.43-2.46 (2H, m), 2.80-2.87 (4H, m), 3.27-3.29 (2H, m), 4.04 (2H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.71-6.76 (1H, m), 6.86-6.90 (1H, m), 7.02 (1H, t, J = 9.7 Hz), 7.12-7.17 (1H, m), 10.03 (1H, s), 12.71 (1H, brs).

[0414]

Reference Example 126

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-(2,4,5-trichlorophenyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.79 (2H, m), 2.18-2.22 (2H, m), 2.43-2.46 (2H, m), 2.80-2.87 (4H, m), 3.18-3.20 (2H, m), 4.06 (2H, s), 6.62 (1H, dd, J = 9.2 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.37 (1H, s), 7.76 (1H, s), 10.03 (1H, s), 12.70 (1H, brs).

[0415]

Reference Example 127

1-(4-Chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.71 (2H, m), 2.14-2.17 (2H, m), 2.43-2.46 (2H, m), 2.79-2.82 (2H, m), 3.11-3.12 (4H, m), 4.02 (2H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.01 (1H, t, J = 9.7 Hz), 7.25-7.31 (2H, m), 10.03 (1H, s), 12.70 (1H, brs).

[0416]

Reference Example 128

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-(2,4,6-trifluorophenyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.65-1.71 (2H, m), 2.14-2.17 (2H, m), 2.43-2.46 (2H, m), 2.79-2.82 (2H, m), 3.04-3.12 (4H, m), 4.02 (2H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.00-7.03 (1H, m), 7.13 (2H, t, J = 9.3 Hz), 10.03 (1H, s), 12.68 (1H, brs).

[0417]

Reference Example 129

1-(2,5-Dichloro-4-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.78 (2H, m), 2.19-2.21 (2H, m), 2.43-2.46 (2H, m), 2.79-2.83 (4H, m), 3.11-3.14 (2H, m), 4.06 (2H, s), 6.62 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.35 (1H, d, J = 7.4 Hz), 7.66 (1H, d, J = 9.1 Hz), 10.04 (1H, s), 12.69 (1H, brs).

[0418]

Reference Example 130

1-(4-Chloro-2,5-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.77 (2H, m), 2.17-2.20 (2H, m), 2.43-2.46 (2H, m), 2.80-2.88 (4H, m), 3.27-3.30 (2H, m), 4.03 (2H, s), 6.57-6.64 (1H, m), 7.02 (1H, t, J = 9.7 Hz), 7.12 (1H, dd, J = 11.3 Hz, 7.9 Hz), 7.50 (1H, dd, J = 12.0 Hz, 7.1 Hz), 10.04 (1H, s), 12.72 (1H, brs).

[0419]

Reference Example 131

1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.77 (2H, m), 2.18-2.21 (2H, m), 2.43-2.46 (2H, m), 2.80-2.84 (4H, m), 3.22-3.24 (2H, m), 4.03 (2H, s), 6.61 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00-7.03 (1H, m), 7.07 (1H, t, J = 9.1 Hz), 7.16 (1H, dd, J = 8.7 Hz, 2.0 Hz), 7.32 (1H, dd, J = 12.4 Hz, 2.4 Hz), 10.03 (1H, s), 12.70 (1H, brs).

[0420]

Reference Example 133

1-(3,5-Difluoropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 119.

^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.75 (2H, m), 2.12-1.19 (2H, m), 2.42 (2H, t, J = 7.5 Hz), 2.78 (2H, t, J = 7.5 Hz), 3.02-3.10 (2H, m), 3.62-3.69 (2H, m), 4.02 (2H, s), 6.59 (1H, dd, J = 9.0 Hz, 3.5 Hz), 6.99 (1H, t, J = 9.5 Hz), 7.75-7.81 (1H, m), 8.09 (1H, d, J = 2.5 Hz), 10.03 (1H, s), 12.72 (1H, brs).

[0421]

Reference Example 134

5-{[1-(3,5-Dichloropyridin-2-yl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

To a suspension of 1-(3,5-dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid (1.46 g) in 1,4-dioxane (15 mL) were added triethylamine (0.456 mL) and diphenylphosphoryl azide (0.705 mL), and the reaction mixture was heated to reflux for 2 h. The solvent was distilled off and to the residue was added water, and insoluble materials were filtered off to provide the title compound (1.41 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.86-2.02 (4H, m), 2.62-2.69 (2H, m), 3.06 (2H, t, J = 7.7 Hz), 3.17-3.26 (2H, m), 3.71-3.78 (2H, m), 3.95 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.54 (1H, brs), 7.62 (1H, d, J = 2.3 Hz), 8.14 (1H, d, J = 2.3 Hz).

[0422]

Reference Example 135

5-{[1-(3,5-Difluoropyridin-2-yl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.84-1.92 (2H, m), 1.92-1.98 (2H, m), 2.64 (2H, t, J = 7.5 Hz), 3.04 (2H, t, J = 7.5 Hz), 3.20-3.28 (2H, m), 3.82-3.88 (2H, m), 3.93 (2H, s), 6.42 (1H, dd, J = 9.0 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.5 Hz), 7.11-7.17 (1H, m), 7.49 (1H, brs), 7.95 (1H, d, J = 2.5 Hz).

[0423]

Reference Example 136

8-Fluoro-5-{[1-(5-fluoro-3-methylpyridin-2-yl)-4-isocyanatopiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.88-1.98 (4H, m), 2.29 (3H, s), 2.65-2.68 (2H, m), 3.05-3.08 (2H, m), 3.15-3.20 (2H, m), 3.25-3.28 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.20 (1H, dd, J = 8.5 Hz, 2.7 Hz), 7.51 (1H, brs), 8.02 (1H, d, J = 2.9 Hz).

[0424]

Reference Example 137

5-{[1-(2,4-Dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.93-2.00 (4H, m), 2.64-2.68 (2H, m), 2.99-3.08 (4H, m), 3.26-3.28 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.03 (1H, d, J = 8.7 Hz), 7.22 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.5 Hz), 7.53 (1H, brs).

[0425]

Reference Example 138

5-{[1-(2,5-Dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.88-2.00 (4H, m), 2.65-2.68 (2H, m), 3.00-3.08 (4H, m), 3.31-3.33 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.94 (1H, t, J = 9.4 Hz), 7.08 (1H, d, J = 2.3 Hz), 7.17-7.22 (1H, m), 7.28-7.30 (1H, m), 7.69 (1H, brs).

[0426]

Reference Example 139

8-Fluoro-5-({4-isocyanato-1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.98-2.08 (4H, m), 2.61-2.66 (2H, m), 2.94-2.98 (2H, m), 3.02-3.06 (2H, m), 3.54-3.57 (2H, m), 3.94 (2H, s), 6.41-6.44 (1H, m), 6.86-7.46 (5H, m), 7.56 (1H, brs).

[0427]

Reference Example 140

5-{[1-(2,4-Dichloro-5-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.92-2.01 (4H, m), 2.64-2.67 (2H, m), 2.97-3.02 (2H, m), 3.04-3.07 (2H, m), 3.29-3.31 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.89-6.96 (2H, m), 7.41 (1H, d, J = 7.6 Hz), 7.56 (1H, brs).

[0428]

Reference Example 141

8-Fluoro-5-({1-[5-fluoro-2-(trifluoromethyl)phenyl]-4-isocyanatopiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.92-1.95 (4H, m), 2.64-2.67 (2H, m), 3.05-3.08 (6H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.92-6.96 (2H, m), 7.11 (1H, dd, J = 9.9 Hz, 2.3 Hz), 7.51 (1H, brs), 7.63 (1H, dd, J = 8.8 Hz, 6.1 Hz).

[0429]

Reference Example 142

tert-Butyl (4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-1-[5-fluoro-2-(trifluoromethyl)phenyl]piperidin-4-yl)carbamate

Synthesized analogous to Reference Example 134. In place of 1,4-dioxane, *tert*-butanol was used as the solvent.

^{1}HNMR (CDCl$_3$) δ ppm: 1.42 (9H, s), 1.92-1.98 (2H, m), 2.22-2.24 (2H, m), 2.63-2.66 (2H, m), 2.93-3.06 (6H, m), 4.13 (2H, s), 4.46 (1H, brs), 6.51 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.89-6.93 (2H, m), 7.06 (1H, dd, J = 10.1 Hz, 2.4 Hz), 7.54-7.63 (2H, m).

[0430]

Reference Example 143

5-{[1-(2,5-Difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.92-2.00 (4H, m), 2.65-2.68 (2H, m), 3.02-3.07 (4H, m), 3.38-3.41 (2H, m), 3.95 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.61-6.65 (1H, m), 6.69-6.73 (1H, m), 6.92-7.00 (2H, m), 7.50 (1H, brs).

[0431]

Reference Example 144

8-Fluoro-5-{[4-isocyanato-1-(2,4,5-trichlorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.92-2.01 (4H, m), 2.63-2.68 (2H, m), 2.97-3.07 (4H, m), 3.28-3.30 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.7 Hz), 6.94 (1H, t, J = 9.5 Hz), 7.16 (1H, s), 7.47 (1H, s), 7.50 (1H, brs).

[0432]

Reference Example 145

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.93 (4H, m), 2.64-2.67 (2H, m), 3.04-3.07 (2H, m), 3.13-3.15 (2H, m), 3.40-3.45 (2H, m), 3.93 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.88-6.94 (2H, m), 7.39 (1H, t, J = 7.9 Hz), 7.54 (1H, brs).

[0433]

Reference Example 146

8-Fluoro-5-{[4-isocyanato-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.85-1.94 (4H, m), 2.64-2.67 (2H, m), 3.00-3.09 (4H, m), 3.40-3.45 (2H, m), 3.93 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.63-6.66 (2H, m), 6.93 (1H, t, J = 9.4 Hz), 7.52 (1H, brs).

[0434]

Reference Example 147

5-{[1-(2,5-Dichloro-4-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.92-2.00 (4H, m), 2.65-2.68 (2H, m), 2.98-3.03 (2H, m), 3.05-3.08 (2H, m), 3.22-3.24 (2H, m), 3.96 (2H, s), 6.45 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.94 (1H, t, J = 9.4 Hz), 7.13 (1H, d, J = 7.2 Hz), 7.22 (1H, d, J = 8.5 Hz), 7.53 (1H, brs).

[0435]

Reference Example 148

5-{[1-(4-Chloro-2,5-difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.90-2.00 (4H, m), 2.64-2.68 (2H, m), 3.02-3.07 (4H, m), 3.35-3.37 (2H, m), 3.95 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.79 (1H, dd, J = 10.5 Hz, 7.6 Hz), 6.94 (1H, d, J = 9.4 Hz), 7.09 (1H, dd, J = 11.5 Hz, 6.9 Hz), 7.58 (1H, brs).

[0436]

Reference Example 149

5-{[1-(4-Chloro-2-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.91-2.00 (4H, m), 2.64-2.68 (2H, m), 3.02-3.07 (4H, m), 3.32-3.34 (2H, m), 3.94 (2H, s), 6.44 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92-6.95 (2H, m), 7.05-7.08 (2H, m), 7.57 (1H, brs).

[0437]

Reference Example 150

8-Fluoro-5-{[4-isocyanato-1-(2,4,5-trifluorophenyl)piperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89-1.98 (4H, m), 2.65-2.68 (2H, m), 2.91-2.94 (2H, m), 2.98-3.03 (2H, m), 3.27-3.29 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.76-6.78 (2H, m), 6.81-6.87 (2H, m), 6.90-6.95 (1H, m), 7.13 (2H, d, J = 8.6 Hz).

[0438]

Reference Example 151

8-Fluoro-5-({1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-isocyanatopiperidin-4-yl}methoxy)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.90-1.99 (4H, m), 2.65-2.68 (2H, m), 2.91-2.94 (2H, m), 3.09-3.14 (2H, m), 3.45-3.48 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.76-6.78 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.04 (1H, t, J = 8.5 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.27-7.30 (1H, m), 7.35 (1H, d, J = 8.7 Hz).

[0439]

Reference Example 152

5-({1-[2-Chloro-4-(trifluoromethyl)phenyl]-4-isocyanatopiperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.92-2.01 (4H, m), 2.65-2.68 (2H, m), 2.92-2.95 (2H, m), 3.05-3.10 (2H, m), 3.37-3.40 (2H, m), 3.74 (3H, s), 3.92 (2H, s), 5.24 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.76-6.78 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.0 Hz), 7.13-7.16 (3H, m), 7.48-7.51 (1H, m), 7.63 (1H, d, J = 1.8 Hz).

[0440]

Reference Example 153

5-{[1-(2,4-Difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.90-1.95 (4H, m), 2.65-2.68 (2H, m), 2.92-2.94 (2H, m), 2.99-3.05 (2H, m), 3.26-3.28 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.75-6.78 (2H, m), 6.80-6.87 (3H, m), 6.96-7.00 (1H, m), 7.13 (2H, d, J = 8.6 Hz).

[0441]

Reference Example 154

8-Fluoro-5-{[1-(2-fluoro-4-methylphenyl)-4-isocyanatopiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.93-1.96 (4H, m), 2.65-2.68 (2H, m), 2.92-2.95 (2H, m), 2.98-3.04 (2H, m), 3.30-3.32 (2H, m), 3.74 (3H, s), 3.89 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.82-6.93 (4H, m), 7.13 (2H, d, J = 8.6 Hz).

[0442]

Reference Example 155

5-({1-[4-Chloro-2-(trifluoromethyl)phenyl]-4-isocyanatopiperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.94 (4H, m), 2.65-2.68 (2H, m), 2.91-2.97 (4H, m), 3.04-3.09 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 5.24 (2H, s), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.38 (1H, d, J = 8.6 Hz), 7.51 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.61 (1H, d, J = 2.5 Hz).

[0443]

Reference Example 156

5-{[1-(2',4'-Dichloro-2,5-difluorobiphenyl-4-yl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.91-2.00 (4H, m), 2.66-2.69 (2H, m), 2.92-2.95 (2H, m), 3.08-3.13 (2H, m), 3.45-3.48 (2H, m), 3.75 (3H, s), 3.91 (2H, s), 5.24 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.76-6.79 (3H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.98 (1H, dd, J = 12.4 Hz, 6.8 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.24 (1H, d, J = 8.3 Hz), 7.31 (1H, dd, J = 8.3 Hz, 2.2 Hz), 7.50 (1H, d, J = 2.1 Hz).

[0444]

Reference Example 157

5-{[1-(4'-Chloro-2,2',5-trifluorobiphenyl-4-yl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.91-2.00 (4H, m), 2.66-2.68 (2H, m), 2.92-2.95 (2H, m), 3.07-3.12 (2H, m), 3.45-3.47 (2H, m), 3.75 (3H, s), 3.91 (2H, s), 5.24 (2H, s), 6.50 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.76-6.87 (4H, m), 7.03-7.07 (1H, m), 7.14 (2H, d, J = 8.6 Hz), 7.18-7.22 (2H, m), 7.28-7.32 (1H, m).

[0445]

Reference Example 158

8-Chloro-5-{[1-(2,4-dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR (CDCl$_3$) δ ppm: 1.91-1.96 (4H, m), 2.57-2.59 (2H, m), 2.81-2.83 (2H, m), 2.97-3.02 (2H, m), 3.24-3.27 (2H, m), 3.73 (3H, s), 3.93 (2H, s), 5.39 (2H, s), 6.56 (1H, d, J = 8.9 Hz), 6.73 (2H, d, J = 8.6 Hz), 7.03 (1H, d, J = 8.6 Hz), 7.08 (2H, d, J = 8.6 Hz), 7.16 (1H, d, J = 8.9 Hz), 7.22 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.5 Hz).

[0446]

Reference Example 159

8-Chloro-5-{[1-(4-chloro-2-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.90-1.97 (4H, m), 2.57-2.59 (2H, m), 2.80-2.83 (2H, m), 3.00-3.05 (2H, m), 3.31-3.34 (2H, m), 3.73 (3H, s), 3.92 (2H, s), 5.39 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.72-6.74 (2H, m), 6.91-6.95 (1H, m), 7.05-7.08 (4H, m), 7.16 (1H, d, J = 8.9 Hz).

[0447]

Reference Example 160

8-Chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.83-1.91 (4H, m), 2.56-2.59 (2H, m), 2.80-2.83 (2H, m), 3.12-3.14 (2H, m), 3.39-3.44 (2H, m), 3.73 (3H, s), 3.91 (2H, s), 5.38 (2H, s), 6.55 (1H, d, J = 9.0 Hz), 6.71-6.75 (2H, m), 6.86-6.92 (2H, m), 7.06-7.09 (2H, m), 7.15 (1H, d, J = 8.9 Hz).

[0448]

Reference Example 161

5-{[4-Amino-1-(2,4,5-trifluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To 8-fluoro-5-{[4-isocyanato-1-(2,4,5-trifluorophenyl)piperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (364 mg) were added acetic acid (4 mL) and 2 N hydrochloric acid (3.2 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution, aqueous sodium hydroxide was added to make the reaction residue basic, and the solution was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by silica gel column chromatography (basic silica gel; dichloromethane/ethyl acetate) to provide the title compound (305 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.65-1.68 (2H, m), 1.90-1.95 (2H, m), 2.64-2.67 (2H, m), 2.88-2.91 (2H, m), 3.06-3.16 (4H, m), 3.71 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.80-6.94 (3H, m), 7.13 (2H, d, J = 8.6 Hz).

[0449]

Reference Example 162

5-({4-Amino-1-[2-chloro-4-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.68-1.71 (2H, m), 1.93-1.98 (2H, m), 2.65-2.67 (2H, m), 2.89-2.92 (2H, m), 3.14-3.18 (2H, m), 3.23-3.25 (2H, m), 3.73-3.75 (5H, m), 5.24 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.84 (1H, dd, 12.7 Hz, 9.1 Hz), 7.13-7.15 (3H, m), 7.45-7.48 (1H, m), 7.61 (1H, d, J = 1.8 Hz).

[0450]

Reference Example 163

5-({4-Amino-1-[2-fluoro-4-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.69 (2H, m), 1.91-1.97 (2H, m), 2.64-2.67 (2H, m), 2.88-2.91 (2H, m), 3.19-3.24 (2H, m), 3.30-3.33 (2H, m), 3.72 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.84 (1H, dd, 12.7 Hz, 9.1 Hz), 7.03 (1H, t, 8.5 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.25-7.28 (1H, m), 7.32 (1H, d, J = 8.5 Hz).

[0451]

Reference Example 164

5-{[4-Amino-1-(2,4-difluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.69 (2H, m), 1.91-1.97 (2H, m), 2.64-2.67 (2H, m), 2.88-2.91 (2H, m), 3.06-3.15 (4H, m), 3.72 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.86 (5H, m), 6.94-6.99 (1H, m), 7.13 (2H, d, J = 8.6 Hz).

[0452]

Reference Example 165

5-{[4-Amino-1-(2-fluoro-4-methylphenyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.70 (2H, m), 1.93-1.98 (2H, m), 2.28 (3H, s), 2.64-2.67 (2H, m), 2.88-2.91 (2H, m), 3.05-3.19 (4H, m), 3.73 (2H, s), 3.74 (3H, s), 5.23 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.75-6.77 (2H, m), 6.81-6.92 (4H, m), 7.13 (2H, d, J = 8.6 Hz).

[0453]

Reference Example 166

5-({4-Amino-1-[4-chloro-2-(trifluoromethyl)phenyl]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.64 (2H, m), 1.88-1.93 (2H, m), 2.64-2.67 (2H, m), 2.86-2.91 (4H, m), 3.07-3.11 (2H, m), 3.73 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.75-6.77 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.2 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.36 (1H, d, J = 8.6 Hz), 7.47-7.49 (1H, m), 7.60 (1H, d, J = 2.5 Hz).

[0454]

Reference Example 167

5-{[4-Amino-1-(2',4'-dichloro-2,5-difluorobiphenyl-4-yl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.70 (2H, m), 1.93-1.98 (2H, m), 2.65-2.68 (2H, m), 2.89-2.92 (2H, m), 3.17-3.22 (2H, m), 3.30-3.33 (2H, m), 3.73 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.78 (3H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.0 Hz), 6.96 (1H, dd, J = 12.5 Hz, 6.8 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.24 (1H, d, J = 8.3 Hz), 7.30 (1H, dd, J = 8.3 Hz, 2.1 Hz), 7.50 (1H, d, J = 2.1 Hz).

[0455]

Reference Example 168

5-{[4-Amino-1-(4'-chloro-2,2',5-trifluorobiphenyl-4-yl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.70 (2H, m), 1.92-1.98 (2H, m), 2.65-2.68 (2H, m), 2.89-2.91 (2H, m), 3.17-3.22 (2H, m), 3.30-3.32 (2H, m), 3.72 (2H, s), 3.74 (3H, s), 5.24 (2H, s), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.76-6.86 (4H, m), 7.04 (1H, dd, J = 12.5 Hz, 6.9 Hz), 7.14 (2H, d, J = 8.6 Hz), 7.18-7.22 (2H, m), 7.29-7.32 (1H, m).

[0456]

Reference Example 169

5-{[4-Amino-1-(2,4-dichlorophenyl)piperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.69 (2H, m), 1.91-1.97 (2H, m), 2.56-2.58 (2H, m), 2.77-2.79 (2H, m), 3.06-3.14 (4H, m), 3.74 (3H, s), 3.76 (2H, s), 5.38 (2H, s), 6.58 (1H, d, J = 9.0 Hz), 6.71-6.73 (2H, m), 7.01 (1H, d, J = 8.6 Hz), 7.08 (2H, d, J = 8.6 Hz), 7.15 (1H, d, J = 8.9 Hz), 7.19 (1H, dd, J = 8.7 Hz, 2.4 Hz), 7.37 (1H, d, J = 2.4 Hz).

[0457]

Reference Example 170

5-{[4-Amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.65-1.68 (2H, m), 1.90-1.96 (2H, m), 2.55-2.58 (2H, m), 2.76-2.79 (2H, m), 3.08-3.13 (2H, m), 3.16-3.20 (2H, m), 3.74 (3H, s), 3.74 (2H, s), 5.38 (2H, s), 6.58 (1H, d, J = 9.0 Hz), 6.71-6.74 (2H, m), 6.90-6.94 (1H, m), 7.03-7.09 (4H, m), 7.15 (1H, d, J = 8.9 Hz).

[0458]

Reference Example 171

5-{[4-Amino-1-(4-chloro-2,6-difluorophenyl)piperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 161.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.63 (2H, m), 1.84-1.90 (2H, m), 2.55-2.58 (2H, m), 2.76-2.79 (2H, m), 3.06-3.09 (2H, m), 3.36-3.41 (2H, m), 3.74 (3H, s), 3.75 (2H, s), 5.38 (2H, s), 6.58 (1H, d, J = 9.0 Hz), 6.72-6.74 (2H, m), 6.85-6.90 (2H, m), 7.08 (2H, d, J = 8.6 Hz), 7.15 (1H, d, J = 8.9 Hz).

[0459]

Reference Example 172

1-(*tert*-Butoxycarbonyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.42-1.47 (11H, m), 2.11-2.13 (2H, m), 2.53-2.56 (2H, m), 2.76-2.78 (2H, m), 3.02 (2H, brs), 3.69 (3H, s), 3.84 (4H, brs), 5.17 (2H, s), 6.41 (1H, dd, J = 9.2 Hz, 2.7 Hz), 6.70-6.77 (3H, m), 7.07 (2H, d, J = 8.5 Hz).

[0460]

Reference Example 173

tert-Butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-isocyanatopiperidine-1-carboxylate

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.57-1.64 (2H, m), 1.81-1.83 (2H, m), 2.64-2.67 (2H, m), 2.89-2.91 (2H, m), 2.99-3.14 (2H, br), 3.74 (3H, s), 3.84 (2H, s), 3.95-4.19 (2H, br), 5.23 (2H, s), 6.46 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.75-6.78 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.13 (2H, d, J = 8.6 Hz).

[0461]

Reference Example 174

5-[(4-Aminopiperidin-4-yl)methoxy]-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

A mixture of *tert*-butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-isocyanatopiperidine-1-carboxylate (1.18 g), acetic acid (10 mL) and 2 N hydrochloric acid (10 mL) was stirred at room temperature overnight. The reaction solution was concentrated, water was added to the residue, and the reaction mixture was made basic with aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (basic silica gel; dichloromethane/methanol) to provide the title compound (683 mg).

^{1}HNMR (CDCl$_3$) δ ppm: 1.50-1.53 (2H, m), 1.69-1.77 (2H, m), 2.63-2.66 (2H, m), 2.87-2.92 (4H, m), 2.98-3.03 (2H, br), 3.67 (2H, s), 3.74 (3H, s), 5.23 (2H, s), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.13 (2H, d, J = 8.5 Hz).

[0462]

Reference Example 175

5-{[4-Amino-1-(2-chloro-4-fluorophenyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 79.

^{1}HNMR (CDCl$_3$) δ ppm: 1.67-1.69 (2H, m), 1.92-1.98 (2H, m), 2.64-2.67 (2H, m), 2.89-2.92 (2H, m), 3.02-3.10 (4H, m), 3.74-3.74 (5H, m), 5.24 (2H, s), 6.52 (1H, dd, J = 9.0 Hz, 3.3 Hz), 6.75-6.78 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.92-6.96 (1H, m), 7.04-7.07 (1H, m), 7.12-7.14 (3H, m).

[0463]

Reference Example 176

Ethyl 1-(2,4-dichlorophenyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR (CDCl$_3$) δ ppm: 1.28 (3H, t, J = 7.1 Hz), 1.91-2.07 (4H, m), 2.04-2.46 (1H, m), 2.66-2.71 (2H, m), 3.30-3.33 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 6.94 (1H, d, J = 8.7 Hz), 7.17 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.36 (1H, d, J = 2.5 Hz).

[0464]

Reference Example 177

Ethyl 1-(4-chloro-2-fluorophenyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.28 (3H, t, J = 7.1 Hz), 1.89-2.05 (4H, m), 2.39-2.45 (1H, m), 2.69-2.75 (2H, m), 3.36-3.39 (2H, m), 4.16 (2H, q, J = 7.1 Hz), 6.84-6.88 (1H, m), 7.01-7.05 (2H, m).

[0465]

Reference Example 178

8-Fluoro-2-methoxy-5-[(methylsulfanyl)methoxy]quinoline

Synthesized analogous to Reference Example 56.

^{1}HNMR ($CDCl_3$) δ ppm: 2.29 (3H, s), 4.11 (3H, s), 5.29 (2H, s), 6.71 (1H, dd, J = 8.6 Hz, 3.4 Hz), 6.94 (1H, d, J = 9.1 Hz), 7.23-7.27 (1H, m), 8.39 (1H, dd, J = 9.1 Hz, 1.7 Hz).

[0466]

Reference Example 179

8-Chloro-2-methoxy-5-[(methylsulfanyl)methoxy]quinoline

Synthesized analogous to Reference Example 56.

^{1}HNMR ($CDCl_3$) δ ppm: 2.29 (3H, s), 4.14 (3H, s), 5.30 (2H, s), 6.74 (1H, d, J = 8.5 Hz), 6.93 (1H, d, J = 9.0 Hz), 7.64 (1H, d, J = 8.4 Hz), 8.41 (1H, d, J = 9.0 Hz).

[0467]

Reference Example 180

Ethyl 1-(2,4-dichlorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-carboxylate

Synthesized analogous to Reference Example 59.

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.1 Hz), 1.89-1.94 (2H, m), 2.48-2.50 (2H, m), 2.84-2.89 (2H, m), 3.25-3.27 (2H, m), 4.10 (3H, s), 4.16 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 6.58 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.92 (1H, d, J = 9.1 Hz), 6.97 (1H, d, J = 8.6 Hz), 7.18-7.24 (2H, m), 7.37 (1H, d, J = 2.4 Hz), 8.32 (1H, d, J = 9.1 Hz).

[0468]

Reference Example 181

Ethyl 1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-carboxylate

Synthesized analogous to Reference Example 59.

^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.87-1.93 (2H, m), 2.47-2.50 (2H, m), 2.87-2.93 (2H, m), 3.30-3.34 (2H, m), 4.10 (3H, s), 4.14 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 6.58 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.87-6.93 (2H, m), 7.03-7.07 (2H, m), 7.22 (1H, dd, J = 10.6 Hz, 8.6 Hz), 8.32 (1H, dd, J = 9.0 Hz, 1.6 Hz).

[0469]

Reference Example 182

Ethyl 4-{[(8-chloro-2-methoxyquinolin-5-yl)oxy]methyl}-1-(2,4-dichlorophenyl)piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.89-1.94 (2H, m), 2.48-2.50 (2H, m), 2.84-2.89 (2H, m), 3.25-3.27 (2H, m), 4.13 (3H, s), 4.17 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 6.64 (1H, d, J = 8.5 Hz), 6.92 (1H, d, J = 9.0 Hz), 6.97 (1H, d, J = 8.7 Hz), 7.19 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.37 (1H, d, J = 2.5 Hz), 7.61 (1H, d, J = 8.4 Hz), 8.34 (1H, d, J = 9.1 Hz).

[0470]

Reference Example 183

Ethyl 1-(4-chloro-2-fluorophenyl)-4-{[(8-chloro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-carboxylate

Synthesized analogous to Reference Example 79.

^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.1 Hz), 1.87-1.93 (2H, m), 2.47-2.50 (2H, m), 2.88-2.93 (2H, m), 3.30-3.34 (2H, m), 4.13 (3H, s), 4.16 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 6.63 (1H, d, J = 8.5 Hz), 6.87-6.93 (2H, m), 7.03-7.07 (2H, m), 7.61 (1H, d, J = 8.4 Hz), 8.34 (1H, d, J = 9.1 Hz).

[0471]

Reference Example 184

1-(2,4-Dichlorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (DMSO-d6) δ ppm: 1.80-1.86 (2H, m), 2.29-2.32 (2H, m), 2.88-2.86 (2H, m), 3.19-3.21 (2H, m), 4.00 (3H, s), 4.25 (2H, s), 6.90 (1H, dd, J = 8.7 Hz, 3.3 Hz), 7.11 (1H, d, J = 9.1 Hz), 7.19 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.44 (1H, dd, J = 10.9 Hz, 8.7 Hz), 7.54 (1H, d, J = 2.5 Hz), 8.31 (1H, dd, J = 9.1 Hz, 1.5 Hz), 12.77 (1H, brs).

[0472]

Reference Example 185

1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89-1.95 (2H, m), 2.47-2.50 (2H, m), 2.90-2.94 (2H, m), 3.31-3.33 (2H, m), 4.09 (3H, s), 4.16 (2H, s), 6.55 (1H, dd, J = 8.6 Hz, 3.2 Hz), 6.78 (1H, d, J = 9.1 Hz), 7.84-6.87 (1H, m), 7.03-7.06 (2H, m), 7.20 (1H, dd, J = 10.5 Hz, 8.7 Hz), 8.22 (1H, d, J = 9.1 Hz).

[0473]

Reference Example 186

4-{[(8-Chloro-2-methoxyquinolin-5-yl)oxy]methyl}-1-(2,4-dichlorophenyl)piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (DMSO-d6) δ ppm: 1.81-1.86 (2H, m), 2.29-2.32 (2H, m), 2.82-2.86 (2H, m), 3.19-3.21 (2H, m), 4.04 (3H, s), 4.28 (2H, s), 6.98 (1H, dd, J = 8.6 Hz), 7.12 (1H, d, J = 9.0 Hz), 7.19 (1H, d, J = 8.7 Hz), 7.35 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.54 (1H, d, J = 2.5 Hz), 7.76 (1H, d, J = 8.5 Hz), 8.34 (1H, d, J = 9.0 Hz), 12.79 (1H, brs).

[0474]

Reference Example 187

1-(4-Chloro-2-fluorophenyl)-4-{[(8-chloro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-carboxylic acid

Synthesized analogous to Reference Example 93.

^{1}HNMR (DMSO-d6) δ ppm: 1.80-1.85 (2H, m), 2.28-2.30 (2H, m), 2.84-2.88 (2H, m), 3.26-3.30 (2H, m), 4.04 (3H, s), 4.25 (2H, s), 6.97 (1H, d, J = 8.6 Hz), 7.07-7.18 (3H, m), 7.33 (1H, dd, J = 12.4 Hz, 2.4 Hz), 7.76 (1H, d, J = 8.5 Hz), 8.34 (1H, d, J = 9.0 Hz), 12.80 (1H, brs).

[0475]

Reference Example 188

5-{[1-(2,4-Dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-2-methoxyquinoline

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 2.03-2.08 (4H, m), 3.03-3.08 (2H, m), 3.29-3.31 (2H, m), 4.10 (2H, s), 4.12 (3H, s), 6.62 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.97 (1H, d, J = 9.1 Hz), 7.05 (1H, d, J = 8.6 Hz), 7.22-7.24 (2H, m), 7.39 (1H, d, J = 2.5 Hz), 8.42 (1H, dd, J = 9.1 Hz, 1.5 Hz).

[0476]

Reference Example 189

5-{[1-(4-Chloro-2-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-8-fluoro-2-methoxyquinoline

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.99-2.07 (4H, m), 3.06-3.11 (2H, m), 3.35-3.38 (2H, m), 4.09 (2H, s), 4.12 (3H, s), 6.61 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.94-6.98 (2H, m), 7.06-7.09 (2H, m), 7.22-7.26 (1H, m), 8.41 (1H, dd, J = 9.1 Hz, 1.6 Hz).

[0477]

Reference Example 190

8-Chloro-5-{[1-(2,4-dichlorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-2-methoxyquinoline

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 2.00-2.08 (4H, m), 3.03-3.08 (2H, m), 3.29-3.31 (2H, m), 4.12 (2H, s), 4.15 (3H, s), 6.67 (1H, d, J = 8.5 Hz), 6.97 (1H, d, J = 9.0 Hz), 7.05 (1H, d, J = 8.6 Hz), 7.23 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.39 (1H, d, J = 2.4 Hz), 7.64 (1H, d, J = 8.4 Hz), 8.44 (1H, d, J = 9.0 Hz).

[0478]

Reference Example 191

8-Chloro-5-{[1-(4-chloro-2-fluorophenyl)-4-isocyanatopiperidin-4-yl]methoxy}-2-methoxyquinoline

Synthesized analogous to Reference Example 134.

^{1}HNMR ($CDCl_3$) δ ppm: 1.99-2.07 (4H, m), 3.06-3.11 (2H, m), 3.35-3.38 (2H, m), 4.10 (2H, s), 4.15 (3H, s), 6.67 (1H, d, J = 8.5 Hz), 6.94-6.98 (2H, m), 7.06-7.09 (2H, m), 7.64 (1H, d, J = 8.4 Hz), 8.44 (1H, d, J = 9.0 Hz).

[0479]

Reference Example 192

4-{[(8-Chloro-2-methoxyquinolin-5-yl)oxy]methyl}-1-(2,4-dichlorophenyl)piperidine-4-amine

Synthesized analogous to Reference Example 161.

^{1}HNMR (CDCl$_3$) δ ppm: 1.41 (2H, brs), 1.76-1.78 (2H, m), 2.02-2.08 (2H, m), 3.10-3.18 (4H, m), 3.94 (2H, s), 4.15 (3H, s), 6.69 (1H, d, J = 8.5 Hz), 6.94 (1H, d, J = 9.0 Hz), 7.04 (1H, d, J = 8.7 Hz), 7.20 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.4 Hz), 7.63 (1H, d, J = 8.6 Hz), 8.42 (1H, d, J = 9.0 Hz).

[0480]

Reference Example 193

1-(4-Chloro-2-fluorophenyl)-4-{[(8-chloro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-amine

Synthesized analogous to Reference Example 161.

^{1}HNMR (CDCl$_3$) δ ppm: 1.39 (2H, brs), 1.75-1.77 (2H, m), 2.02-2.07 (2H, m), 3.14-3.25 (4H, m), 3.92 (2H, s), 4.15 (3H, s), 6.68 (1H, d, J = 8.5 Hz), 6.93-6.96 (2H, m), 7.04-7.07 (2H, m), 7.63 (1H, d, J = 8.4 Hz), 8.41 (1H, d, J = 9.0 Hz).

[0481]

Reference Example 194

1-(2,4-Dichlorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-amine

Synthesized analogous to Reference Example 161.

^{1}HNMR (CDCl$_3$) δ ppm: 1.42 (2H, brs), 1.75-1.78 (2H, m), 2.02-2.08 (2H, m), 3.09-3.18 (4H, m), 3.93 (2H, s), 4.12 (3H, s), 6.63 (1H, dd, J = 8.6 Hz, 3.3 Hz), 6.94 (1H, d, J = 9.1 Hz), 7.03 (1H, d, J = 8.6 Hz), 7.19-7.26 (2H, m), 7.38 (1H, d, J = 2.4 Hz), 8.40 (1H, dd, J = 9.0 Hz).

[0482]

Reference Example 195

1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidine-4-amine

Synthesized analogous to Reference Example 161.

^{1}HNMR (CDCl$_3$) δ ppm: 1.39 (2H, brs), 1.75-1.77 (2H, m), 2.02-2.07 (2H, m), 3.14-3.25 (4H, m), 3.91 (2H, s), 4.12 (3H, s), 6.62 (1H, dd, J = 8.6 Hz, 3.4 Hz), 6.93-6.96 (2H, m), 7.04-7.07 (2H, m), 7.23 (1H, dd, J = 10.6 Hz, 8.6 Hz), 8.39 (1H, dd, J = 9.1 Hz, 1.5 Hz).

[0483]

Reference Example 196

8-(2,5-Dichloro-4-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

To a microwave reaction tube were added 1-bromo-2,5-dichloro-4-fluorobenzene (1.00 g), sodium *tert*-butoxide (0.473 g), tris(dibenzylideneacetone)dipalladium (0.038 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.077 g), 1,4-dioxa-8-azaspiro[4.5]decane (0.590 mL) and toluene (3 mL). The tube was sealed, and then irradiated with microwave at 130 °C for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (845 mg).

^{1}HNMR (CDCl$_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.05 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 7.07 (1H, d, J = 7.5 Hz), 7.19 (1H, d, J = 8.5 Hz).

[0484]

Reference Example 197

8-(4-Chloro-2-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 196.

^{1}HNMR (CDCl$_3$) δ ppm: 1.88 (4H, t, J = 5.5 Hz), 3.14 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.88 (1H, t, J = 9.0 Hz), 7.01-7.05 (2H, m).

[0485]

Reference Example 198

8-(2,4-Dichloro-5-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 196.

^{1}HNMR (CDCl$_3$) δ ppm: 1.89 (4H, t, J = 6.0 Hz), 3.09 (4H, t, J = 6.0 Hz), 4.00 (4H, s), 6.84 (1H, d, J = 10.5 Hz), 7.38 (1H, d, J = 8.0 Hz).

[0486]

Reference Example 199

8-(4-Chloro-2,6-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 196.

^{1}HNMR (CDCl$_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 3.23 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 6.83-6.89 (2H, m).

[0487]

Reference Example 200

8-(2-Chloro-6-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 196.

^{1}HNMR ($CDCl_3$) δ ppm: 1.86 (4H, t, J = 5.5 Hz), 3.24 (4H, t, J = 5.5 Hz), 4.01 (4H, s), 6.91-6.95 (2H, m), 7.13-7.16 (1H, m).

[0488]

Reference Example 201

8-(4-Chloro-2,5-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 196.

^{1}HNMR ($CDCl_3$) δ ppm: 1.87 (4H, t, J = 6.0 Hz), 3.15 (4H, t, J = 6.0 Hz), 4.00 (4H, s), 6.73 (1H, dd, J = 10.5 Hz, 7.5 Hz), 7.06 (1H, dd, J = 11.5 Hz, 7.0 Hz).

[0489]

Reference Example 202

8-(2-Chloro-5-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Under nitrogen atmosphere, to a mixture of 3-bromo-4-chloronitrobenzene (3.05 g), sodium *tert*-butoxide (1.49 g), tris(dibenzylideneacetone)dipalladium (0.118 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.241 g), and 1,4-dioxa-8-azaspiro[4.5]decane (1.86 mL) was added toluene (24 mL), and the reaction mixture was stirred at 90-110 °C for 18 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (346 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.93 (4H, t, J = 5.5 Hz), 3.20 (4H, t, J = 5.5 Hz), 4.02 (4H, s), 7.50 (1H, d, J = 8.5 Hz), 7.82 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.91 (1H, d, J = 2.5 Hz).

[0490]

Reference Example 203

8-(2,4-Dichloro-6-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 196.

^{1}HNMR ($CDCl_3$) δ ppm: 1.78-1.86 (4H, m), 2.31 (3H, s), 2.93-2.97 (2H, m), 3.41-3.46 (2H, m), 3.99-4.02 (4H, m), 7.05 (1H, d, J = 2.5 Hz), 7.16 (1H, d, J = 2.5 Hz).

[0491]

Reference Example 204

8-[2-Chloro-5-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 196.

^{1}HNMR ($CDCl_3$) δ ppm: 1.91 (4H, t, J = 5.5 Hz), 3.13 (4H, t, J = 5.5 Hz), 4.01 (4H, s), 6.82 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.89 (1H, d, J = 2.5 Hz), 7.35 (1H, d, J = 9.0 Hz).

[0492]

Reference Example 205

8-(4-Chloro-3-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Under nitrogen atmosphere, to a mixture of 5-bromo-2-chlorotoluene (2.19 mL), sodium *tert*-butoxide (1.85 g), tris(dibenzylideneacetone)dipalladium (0.147 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.300 g) and 1,4-dioxa-8-azaspiro[4.5]decane (2.31 mL) was added toluene (24 mL), and the reaction mixture was heated to reflux for 3 h. After the reaction mixture was allowed to cool to room temperature, to the reaction solution was added water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (4.28 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 2.32 (3H, s), 3.28 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 6.70 (1H, dd, J = 8.5 Hz, 3.0 Hz), 6.80 (1H, d, J = 3.0 Hz), 7.17 (1H, d, J = 8.5 Hz).

[0493]

Reference Example 206

Ethyl 2-chloro-5-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)benzoate

Under nitrogen atmosphere, to a mixture of ethyl 5-bromo-2-chlorobenzoate (2.12 mL), cesium carbonate (12.2 g), tris(dibenzylideneacetone)dipalladium (0.114 g), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.233 g) and 1,4-dioxa-8-azaspiro[4.5]decane (1.79 mL) was added toluene (24 mL), and the reaction mixture was heated to reflux for 5 h. To the reaction solution was added aqueous saturated ammonium chloride solution, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (852 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.5 Hz), 1.83 (4H, t, J = 5.5 Hz), 3.33 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.39 (2H, q, J = 7.5 Hz), 6.95 (1H, dd, J = 8.5 Hz, 3.5 Hz), 7.27 (1H, d, J = 8.5 Hz), 7.32 (1H, d, J = 3.5 Hz).

[0494]

Reference Example 207

8-(4-Ethoxy-2-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Into an eggplant flask were added 1-bromo-4-ethoxy-2-fluorobenzene (758 mg), tris(dibenzylideneacetone)dipalladium (31.7 mg), 2',4',6'-triisopropyl-2-(dicyclohexylphosphino)-1,1'-biphenyl (X-PHOS) (39.6 mg), sodium *tert*-butoxide (499 mg) and 1,4-dioxa-8-azaspiro[4.5]decane (0.50 mL), the flask was purged with nitrogen, and then toluene (3.8 mL) was added thereto and the mixture was stirred at 100 °C for 3 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (310 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.5 Hz), 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.97 (2H, q, J = 7.5 Hz), 4.00 (4H, s), 6.59 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.63 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

[0495]

Reference Example 208

8-[2-Chloro-4-(propan-2-yl)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

To a solution of 8-[4-(propan-2-yl)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane (803 mg) in N,N-dimethylformamide (6.5 mL) was added N-chlorosuccinimide (451 mg), and the reaction mixture was stirred at room temperature for 45 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (726 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (6H, d, J = 7.0 Hz), 1.90 (4H, t, J = 5.5 Hz), 2.83 (1H, sep, J = 7.0 Hz), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.99 (1H, d, J = 8.5 Hz), 7.05 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.22 (1H, d, J = 2.0 Hz).

[0496]

Reference Example 209

8-(2-Fluoro-4-propoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 207.

^{1}HNMR ($CDCl_3$) δ ppm: 1.02 (3H, t, J = 7.0 Hz), 1.74-1.81 (2H, m), 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.85 (2H, t, J = 6.5 Hz), 3.99 (4H, s), 6.59 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.64 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

[0497]

Reference Example 210

8-(2-Chloro-4-ethylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 208.

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 1.90 (4H, t, J = 5.5 Hz), 2.57 (2H, q, J = 7.5 Hz), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.98 (1H, d, J = 8.0 Hz), 7.03 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.20 (1H, d, J = 2.0 Hz).

[0498]

Reference Example 211

8-(2-Chloro-4-propylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 208.

^{1}HNMR ($CDCl_3$) δ ppm: 0.92 (3H, t, J = 7.5 Hz), 1.60 (2H, sext, J = 7.5 Hz), 1.90 (4H, t, J = 5.5 Hz), 2.50 (2H, t, J = 7.5 Hz), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.97 (1H, d, J = 8.0 Hz), 7.00 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.18 (1H, d, J = 2.0 Hz).

[0499]

Reference Example 212

8-(2,4-Dichloro-6-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 208.

^{1}HNMR ($CDCl_3$) δ ppm: 1.84 (4H, t, J = 5.5 Hz), 3.21 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.98 (1H, dd, J = 11.0 Hz, 2.0 Hz), 7.18 (1H, dd, J = 2.0 Hz, 1.5 Hz).

[0500]

Reference Example 213

8-(4-Butoxy-2-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 207.

^{1}HNMR ($CDCl_3$) δ ppm: 0.96 (3H, t, J = 7.5 Hz), 1.43-1.51 (2H, m), 1.71-1.76 (2H, m), 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.89 (2H, t, J = 6.5 Hz), 4.00 (4H, s), 6.59 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.64 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

[0501]

Reference Example 214

8-[2-Fluoro-4-(propan-2-yloxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 207.

^{1}HNMR ($CDCl_3$) δ ppm: 1.31 (6H, d, J = 6.0 Hz), 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.43 (1H, sep, J = 6.0 Hz), 6.58 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.62 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.90 (1H, t, J = 9.0 Hz).

[0502]

Reference Example 215

8-[2-Chloro-4-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 208.

^{1}HNMR ($CDCl_3$) δ ppm: 1.90 (4H, t, J = 5.5 Hz), 3.10 (4H, t, J = 5.5 Hz), 4.01 (4H, s), 7.04 (1H, d, J = 9.0 Hz), 7.07-7.09 (1H, m), 7.26 (1H, d, J = 2.5 Hz).

[0503]

Reference Example 216

8-[2-Fluoro-4-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 207.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.16 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.92-6.97 (3H, m).

[0504]

Reference Example 217

8-(2-Fluoro-4-methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 207.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.76 (3H, s), 4.00 (4H, s), 6.60 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.65 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.93 (1H, t, J = 9.0 Hz).

[0505]

Reference Example 218

8-[2,4-Dichloro-5-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 208.

^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.92 (4H, m), 3.09-3.12 (4H, m), 4.01 (4H, s), 6.98 (1H, d, J = 1.0 Hz), 7.46 (1H, s).

[0506]

Reference Example 219

8-[2-Fluoro-5-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.19 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.75-6.80 (2H, m), 7.00 (1H, dd, J = 12.0 Hz, 9.0 Hz).

[0507]

Reference Example 220

8-[4-(Benzyloxy)-2-fluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 5.00 (2H, s), 6.60 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.72 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz), 7.31-7.34 (1H, m), 7.37-7.42 (4H, m).

[0508]

Reference Example 221

8-[2-Fluoro-4-(2-methoxyethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.44 (3H, s), 3.71-3.73 (2H, m), 3.99 (4H, s), 4.05-4.07 (2H, m), 6.63 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.91 (1H, t, J = 9.0 Hz).

[0509]

Reference Example 222

8-(2-Bromo-5-ethoxy-4-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 207.

^{1}HNMR ($CDCl_3$) δ ppm: 1.49 (3H, t, J = 7.5 Hz), 1.92 (4H, t, J = 5.5 Hz), 3.22 (4H, t, J = 5.5 Hz), 4.02 (4H, s), 4.15 (2H, q, J = 7.5 Hz), 6.61 (1H, s), 8.18 (1H, s).

[0510]

Reference Example 223

8-[4-Chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 208.

^{1}HNMR (CDCl$_3$) δ ppm: 1.85-1.89 (4H, m), 3.15-3.18 (4H, m), 4.01 (4H, s), 6.87 (1H, d, J = 9.0 Hz), 7.13 (1H, d, J = 11.5 Hz).

[0511]

Reference Example 224

8-(4-Ethoxy-2,5-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR (CDCl$_3$) δ ppm: 1.42 (3H, t, J = 7.0 Hz), 1.88 (4H, t, J = 5.5 Hz), 3.07 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.04 (2H, q, J = 7.0 Hz), 6.71 (1H, dd, J = 13.0 Hz, 7.5 Hz), 6.76 (1H, dd, J = 13.0 Hz, 8.0 Hz).

[0512]

Reference Example 225

8-[4-(Ethoxymethyl)-2-fluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR (CDCl$_3$) δ ppm: 1.24 (3H, t, J = 7.0 Hz), 1.89 (4H, t, J = 5.5 Hz), 3.16 (4H, t, J = 5.5 Hz), 3.52 (2H, q, J = 7.0 Hz), 4.00 (4H, s), 4.41 (2H, s), 6.93 (1H, t, J = 8.0 Hz), 7.00-7.05 (2H, m).

[0513]

Reference Example 226

8-(2,6-Difluoro-4-methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR (CDCl$_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 3.18 (4H, t, J = 5.5 Hz), 3.74 (3H, s), 3.99 (4H, s), 6.38-6.44 (2H, m).

[0514]

Reference Example 227

2-[4-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-2,5-difluorophenoxy]-N,N-dimethylethaneamine

Synthesized analogous to Reference Example 205.

^{1}HNMR (CDCl$_3$) δ ppm: 1.88 (4H, t, J = 5.5 Hz), 2.33 (6H, s), 2.72 (2H, t, J = 6.0 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.06 (2H, t, J = 6.0 Hz), 6.72-6.78 (2H, m).

[0515]

Reference Example 228

8-(2-Fluoro-6-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 196.

^{1}HNMR (CDCl$_3$) δ ppm: 1.82-1.84 (4H, m), 2.32 (3H, s), 3.14 (4H, brs), 4.00 (4H, s), 6.81-6.88 (1H, m), 6.93-6.98 (2H, m).

[0516]

Reference Example 229

8-(4-Ethoxy-2,3,5,6-tetrafluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR (CDCl$_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.84 (4H, t, J = 5.5 Hz), 3.26 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 4.19 (2H, q, J = 7.0 Hz).

[0517]

Reference Example 230

8-{2-Fluoro-4-[2-(2-methoxyethoxy)ethoxy]phenyl}-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR (CDCl$_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.39 (3H, s), 3.56-3.58 (2H, m), 3.70-3.72 (2H, m), 3.83 (2H, t, J = 5.0 Hz), 3.99 (4H, s), 4.08 (2H, t, J = 5.0 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.67 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.91 (1H, t, J = 9.0 Hz).

[0518]

Reference Example 231

8-(4-Chloro-2-fluoro-5-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR (CDCl$_3$) δ ppm: 1.88 (4H, t, J = 5.5 Hz), 2.29 (3H, s), 3.13 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.80 (1H, d, J = 9.0 Hz), 7.02 (1H, d, J = 12.0 Hz).

[0519]

Reference Example 232

8-(4-Ethoxy-2-fluoro-5-methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR (CDCl$_3$) δ ppm: 1.43 (3H, t, J = 7.0 Hz), 1.90 (4H, t, J = 5.5 Hz), 3.11 (4H, t, J = 5.5 Hz), 3.83 (3H, s), 4.00 (4H, s), 4.02 (2H, q, J = 7.0 Hz), 6.61 (1H, d, J = 8.5 Hz), 6.65 (1H, d, J = 13.5 Hz).

[0520]

Reference Example 233

8-(4-Ethoxy-2,6-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.38 (3H, t, J = 7.0 Hz), 1.83 (4H, t, J = 5.5 Hz), 3.17 (4H, t, J = 5.5 Hz), 3.94 (2H, q, J = 7.0 Hz), 3.99 (4H, s), 6.36-6.42 (2H, m).

[0521]

Reference Example 234

8-[2-Fluoro-4-(2-fluoroethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 4.12-4.19 (2H, m), 4.67-4.78 (2H, m), 6.63 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

[0522]

Reference Example 235

2-[4-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-3-fluorophenoxy]-N,N-dimethylethaneamine

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 2.32 (6H, s), 2.70 (2H, t, J = 6.0 Hz), 3.08 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 4.00 (2H, t, J = 6.0 Hz), 6.62 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.67 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.91 (1H, t, J = 9.0 Hz).

[0523]

Reference Example 236

8-[2-Fluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.10 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 4.29 (2H, q, J = 8.0 Hz), 6.65 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.71 (1H, dd, J = 13.0 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

[0524]

Reference Example 237

8-(1-Benzofuran-5-yl)-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.90 (4H, t, J = 5.5 Hz), 3.27 (4H, t, J = 5.5 Hz), 4.01 (4H, s), 6.68 (1H, d, J = 2.0 Hz), 7.02 (1H, dd, J = 9.0 Hz, 2.0 Hz), 7.14 (1H, d, J = 2.0 Hz), 7.38 (1H, d, J = 9.0 Hz), 7.56 (1H, d, J = 2.0 Hz).

[0525]

Reference Example 238

6-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)quinoxaline

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.57 (4H, t, J = 5.5 Hz), 4.02 (4H, s), 7.30 (1H, d, J = 3.0 Hz), 7.55 (1H, dd, J = 9.5 Hz, 3.0 Hz), 7.92 (1H, d, J = 9.5 Hz), 8.58 (1H, d, J = 2.0 Hz), 8.68 (1H, d, J = 2.0 Hz).

[0526]

Reference Example 239

8-[4-(Difluoromethoxy)-2-fluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 206.

^{1}HNMR ($CDCl_3$) δ ppm: 1.89 (4H, t, J = 5.5 Hz), 3.13 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.43 (1H, t, J = 74.0 Hz), 6.78-6.88 (2H, m), 6.94 (1H, t, J = 9.0 Hz).

[0527]

Reference Example 240

8-[4-(Difluoromethoxy)-2,6-difluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 206.

^{1}HNMR ($CDCl_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 3.23 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.44 (1H, t, J = 73.0 Hz), 6.64-6.70 (2H, m).

[0528]

Reference Example 241

8-[2-Chloro-4-(methylsulfanyl)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 208.

^{1}HNMR ($CDCl_3$) δ ppm: 1.90 (4H, t, J = 5.5 Hz), 2.45 (3H, s), 3.09 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 6.99 (1H, d, J = 8.5 Hz), 7.12 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.20 (1H, d, J = 2.0 Hz).

[0529]

Reference Example 242

8-[4-(Ethylsulfanyl)-2,6-difluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 196.

^{1}HNMR ($CDCl_3$) δ ppm: 1.31 (3H, t, J = 7.5 Hz), 1.83 (4H, t, J = 5.5 Hz), 2.89 (2H, q, J = 7.5 Hz), 3.24 (4H, t, J = 5.5 Hz), 3.99 (4H, s), 6.77-6.83 (2H, m).

[0530]

Reference Example 243

8-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1,4-dioxa-8-azaspiro[4.5]decane

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.83 (4H, t, J = 5.5 Hz), 3.19 (4H, t, J = 5.5 Hz), 4.00 (4H, s), 4.27 (2H, q, J = 8.0 Hz), 6.45-6.50 (2H, m).

[0531]

Reference Example 244

1-(2,5-Dichloro-4-fluorophenyl)piperidin-4-one

To a solution of 8-(2,5-dichloro-4-fluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (845 mg) in acetone (20 mL) was added 5 N hydrochloric acid (10 mL), and the reaction mixture was heated to reflux for 3 h. The reaction solution was concentrated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (556 mg).

^{1}HNMR (CDCl$_3$) δ ppm: 2.64 (4H, t, J = 6.0 Hz), 3.29 (4H, t, J = 6.0 Hz), 7.08 (1H, d, J = 7.0 Hz), 7.25 (1H, d, J = 8.5 Hz).

[0532]

Reference Example 245

1-(2,4-Dichloro-5-fluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR (CDCl$_3$) δ ppm: 2.65 (4H, t, J = 6.0 Hz), 3.32 (4H, t, J = 6.0 Hz), 6.86 (1H, d, J = 10.0 Hz), 7.44 (1H, d, J = 7.5 Hz).

[0533]

Reference Example 246

1-(4-Chloro-2,6-difluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR (CDCl$_3$) δ ppm: 2.58 (4H, t, J = 6.0 Hz), 3.46 (4H, t, J = 6.0 Hz), 6.89-6.95 (2H, m).

[0534]

Reference Example 247

1-(2-Chloro-6-fluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR (CDCl$_3$) δ ppm: 2.61 (4H, t, J = 6.0 Hz), 3.46 (4H, dt, J = 1.5 Hz, 6.0 Hz), 6.92-7.04 (2H, m), 7.20-7.22 (1H, m).

[0535]

Reference Example 248

1-(4-Chloro-2,5-difluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.40 (4H, t, J = 6.0 Hz), 6.77 (1H, dd, J = 10.5 Hz, 7.5 Hz), 7.12 (1H, dd, J = 11.5 Hz, 7.0 Hz).

[0536]

Reference Example 249

1-[2-Chloro-5-(trifluoromethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.66 (4H, t, J = 6.0 Hz), 3.36 (4H, t, J = 6.0 Hz), 6.89 (1H, d, J = 1.0 Hz), 6.90 (1H, dd, J = 9.0 Hz, 1.0 Hz), 7.41 (1H, d, J = 9.0 Hz).

[0537]

Reference Example 250

1-(2-Chloro-5-nitrophenyl)piperidin-4-one

To a solution of 8-(2-chloro-5-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (346 mg) in tetrahydrofuran (4 mL) was added 5 N hydrochloric acid (2 mL), and the reaction mixture was stirred at room temperature for 13 h. The reaction solution was concentrated, neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (229 mg).

^{1}HNMR (CDCl$_3$) δ ppm: 2.69 (4H, t, J = 6.0 Hz), 3.43 (4H, t, J = 6.0 Hz), 7.57 (1H, d, J = 9.0 Hz), 7.90 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.92 (1H, d, J = 2.5 Hz).

[0538]

Reference Example 251

1-(4-Chloro-3-methylphenyl)piperidin-4-one

To a solution of 8-(4-chloro-3-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (2.26 g) in tetrahydrofuran (46 mL) was added 5 N hydrochloric acid (23 mL), and the reaction mixture was stirred at room temperature for 14 h, then at 70 °C for 3 h. The reaction solution was concentrated, neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.58 g).

^{1}HNMR (CDCl$_3$) δ ppm: 2.35 (3H, s), 2.55 (4H, t, J = 6.0 Hz), 3.56 (4H, t, J = 6.0 Hz), 6.74 (1H, dd, J = 8.5 Hz, 3.0 Hz), 6.83 (1H, d, J = 3.0 Hz), 7.23 (1H, d, J = 8.5 Hz).

[0539]

Reference Example 252

Ethyl 2-chloro-5-(4-oxopiperidin-1-yl)benzoate

Synthesized analogous to Reference Example 250.

^{1}HNMR (CDCl$_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 2.57 (4H, t, J = 6.0 Hz), 3.61 (4H, t, J = 6.0 Hz), 4.41 (2H, q, J = 7.0 Hz), 6.99 (1H, dd, J = 9.0 Hz, 3.0 Hz), 7.33 (1H, d, J = 9.0 Hz), 7.35 (1H, d, J = 3.0 Hz).

[0540]

Reference Example 253

1-[2-Chloro-4-(propan-2-yl)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (6H, d, J = 7.0 Hz), 2.64 (4H, t, J = 6.0 Hz), 2.86 (1H, sep, J = 7.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 6.99 (1H, d, J = 8.0 Hz), 7.09 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.27 (1H, d, J = 2.0 Hz).

[0541]

Reference Example 254

1-(2,4-Dichloro-6-methylphenyl)piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.37 (3H, s), 2.53-2.63 (4H, m), 3.22-3.27 (2H, m), 3.59-3.64 (2H, m), 7.10-7.12 (1H, m), 7.21 (1H, d, J = 2.5 Hz).

[0542]

Reference Example 255

1-(4-Ethoxy-2-fluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.98 (2H, q, J = 7.0 Hz), 6.62 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.67 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

[0543]

Reference Example 256

1-(2-Fluoro-4-propoxyphenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 1.03 (3H, t, J = 7.5 Hz), 1.76-1.83 (2H, m), 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.87 (2H, t, J = 6.5 Hz), 6.62 (1H, ddd, J = 8.5 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 8.5 Hz).

[0544]

Reference Example 257

1-(2-Chloro-4-ethylphenyl)piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (3H, t, J = 7.5 Hz), 2.59 (2H, q, J = 7.5 Hz), 2.64 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 6.98 (1H, d, J = 8.0 Hz), 7.06 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.25 (1H, d, J = 2.0 Hz).

[0545]

Reference Example 258

1-(2-Chloro-4-propylphenyl)piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 0.94 (3H, t, J = 7.5 Hz), 1.62 (2H, sext, J = 7.5 Hz), 2.52 (2H, t, J = 7.5 Hz), 2.64 (4H, t, J = 6.0 Hz), 3.32 (4H, t, J = 6.0 Hz), 6.97 (1H, d, J = 8.0 Hz), 7.03 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.23 (1H, d, J = 2.0 Hz).

[0546]

Reference Example 259

1-(2,4-Dichloro-6-fluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.60 (4H, t, J = 6.0 Hz), 3.43 (4H, dt, J = 1.0 Hz, 6.0 Hz), 7.02 (1H, dd, J = 11.0 Hz, 2.0 Hz), 7.24 (1H, t, J = 2.0 Hz).

[0547]

Reference Example 260

1-(4-Butoxy-2-fluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 0.97 (3H, t, J = 7.5 Hz), 1.44-1.52 (2H, m), 1.72-1.78 (2H, m), 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.90 (2H, t, J = 6.5 Hz), 6.62 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.67 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.93 (1H, t, J = 9.0 Hz).

[0548]

Reference Example 261

1-[2-Fluoro-4-(propan-2-yloxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 1.32 (6H, d, J = 6.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 4.45 (1H, sep, J = 6.0 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.66 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

[0549]

Reference Example 262

1-[2-Chloro-4-(trifluoromethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.65 (4H, t, J = 6.0 Hz), 3.33 (4H, t, J = 6.0 Hz), 7.06 (1H, d, J = 9.0 Hz), 7.12 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.32 (1H, d, J = 2.5 Hz).

[0550]

Reference Example 263

1-[2,4-Dichloro-5-(trifluoromethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.65 (4H, t, J = 6.0 Hz), 3.34 (4H, t, J = 6.0 Hz), 6.98 (1H, d, J = 1.0 Hz), 7.53 (1H, s).

[0551]

Reference Example 264

1-[2-Fluoro-4-(trifluoromethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.40 (4H, t, J = 6.0 Hz), 6.96-7.02 (3H, m).

[0552]

Reference Example 265

1-(2-Fluoro-4-methoxyphenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.77 (3H, s), 6.63 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.95 (1H, t, J = 9.0 Hz).

[0553]

Reference Example 266

1-[4-(Benzyloxy)-2-fluorophenyl]piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 5.02 (2H, s), 6.70 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.76 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz), 7.32-7.36 (1H, m), 7.37-7.43 (4H, m).

[0554]

Reference Example 267

1-[2-Fluoro-4-(2-methoxyethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.61 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.45 (3H, s), 3.73-3.74 (2H, m), 4.06-4.08 (2H, m), 6.66 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.72 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.93 (1H, t, J = 9.0 Hz).

[0555]

Reference Example 268

1-[4-Chloro-2-fluoro-5-(trifluoromethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.42 (4H, t, J = 6.0 Hz), 6.91 (1H, dd, J = 8.0 Hz, 1.0 Hz), 7.20 (1H, d, J = 11.5 Hz).

[0556]

Reference Example 269

1-(2-Bromo-5-ethoxy-4-nitrophenyl)piperidin-4-one

To a solution of 8-(2-bromo-5-ethoxy-4-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (2.70 g) in tetrahydrofuran (54 mL) was added 2 N hydrochloric acid (54 mL), and the reaction mixture was stirred at room temperature for 64 h, then at 70 °C for 6 h. To the reaction mixture were added acetone (80 mL) and 5 N hydrochloric acid (40 mL), and the reaction mixture was heated to reflux for 5 h. The reaction solution was concentrated, neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (662 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.50 (3H, t, J = 7.0 Hz), 2.69 (4H, t, J = 6.0 Hz), 3.44 (4H, t, J = 6.0 Hz), 4.17 (2H, q, J = 7.0 Hz), 6.63 (1H, s), 8.21 (1H, s).

[0557]

Reference Example 270

1-(4-Ethoxy-2,5-difluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 1.43 (3H, t, J = 7.0 Hz), 2.61 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 4.06 (2H, q, J = 7.0 Hz), 6.75 (1H, dd, J = 13.0 Hz, 8.0 Hz), 6.76 (1H, dd, J = 12.5 Hz, 8.0 Hz).

[0558]

Reference Example 271

1-[4-(Ethoxymethyl)-2-fluorophenyl]piperidin-4-one

To a solution of 8-[4-(ethoxymethyl)-2-fluorophenyl]-1,4-dioxa-8-azaspiro[4.5]decane (1.19 g) in ethanol/water (12-1.2 mL) was added oxalic acid (1.81 g), and the reaction mixture was heated to reflux for 6 h. To the reaction solution was added water, the mixture was neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (756 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.25 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.40 (4H, t, J = 6.0 Hz), 3.54 (2H, q, J = 7.0 Hz), 4.43 (2H, s), 6.95 (1H, t, J = 8.5 Hz), 7.05 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.09 (1H, dd, J = 13.0 Hz, 2.0 Hz).

[0559]

Reference Example 272

1-(2,6-Difluoro-4-methoxyphenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.57 (4H, t, J = 6.0 Hz), 3.40 (4H, t, J = 6.0 Hz), 3.76 (3H, s), 6.42-6.48 (2H, m).

[0560]

Reference Example 273

1-{4-[2-(Dimethylamino)ethoxy]-2,5-difluorophenyl}piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.34 (6H, s), 2.61 (4H, t, J = 6.0 Hz), 2.74 (2H, t, J = 5.5 Hz), 3.31 (4H, t, J = 6.0 Hz), 4.08 (2H, t, J = 5.5 Hz), 6.74-6.81 (2H, m).

[0561]

Reference Example 274

1-(4-Ethoxy-2,3,5,6-tetrafluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 2.59 (4H, t, J = 6.0 Hz), 3.48 (4H, t, J = 6.0 Hz), 4.23 (2H, q, J = 7.0 Hz).

[0562]

Reference Example 275

1-(4-Chloro-2-fluoro-6-methylphenyl)piperidin-4-one

To a solution of 8-(2-fluoro-6-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (3.46 g) in N,N-dimethylformamide (28 mL) was added N-chlorosuccinimide (2.57 g), and the reaction mixture was stirred at room temperature for 77 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give a mixture of 8-(2-fluoro-6-methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane and the title compound (1.9 g). To the mixture were added tetrahydrofuran (40 mL) and 2 N hydrochloric acid (20L), and the reaction mixture was stirred at room temperature for 13 h, then at 70 °C for 6 h. The reaction solution was concentrated and neutralized with 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (307 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 2.38 (3H, s), 2.53-2.59 (4H, m), 3.32-3.37 (4H, m), 6.92 (1H, dd, J = 11.5 Hz, 2.0 Hz), 7.00-7.02 (1H, m).

[0563]

Reference Example 276

1-{2-Fluoro-4-[2-(2-methoxyethoxy)ethoxy]phenyl}piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.61 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.0 Hz), 3.40 (3H, s), 3.57-3.59 (2H, m), 3.71-3.72 (2H, m), 3.84 (2H, t, J = 5.0 Hz), 4.10 (2H, t, J = 5.0 Hz), 6.64 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.71 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.92 (1H, t, J = 9.0 Hz).

[0564]

Reference Example 277

1-(4-Chloro-2-fluoro-5-methylphenyl)piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.31 (3H, s), 2.62 (4H, t, J = 6.0 Hz), 3.37 (4H, t, J = 6.0 Hz), 6.82 (1H, d, J = 9.0 Hz), 7.08 (1H, d, J = 12.0 Hz).

[0565]

Reference Example 278

1-(4-Ethoxy-2-fluoro-5-methoxyphenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 1.45 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.34 (4H, t, J = 6.0 Hz), 3.85 (3H, s), 4.04 (2H, q, J = 7.0 Hz), 6.60 (1H, d, J = 8.5 Hz), 6.69 (1H, d, J = 13.0 Hz).

[0566]

Reference Example 279

1-(4-Ethoxy-2,6-difluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J = 7.0 Hz), 2.57 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 3.96 (2H, q, J = 7.0 Hz), 6.40-6.46 (2H, m).

[0567]

Reference Example 280

1-[2-Fluoro-4-(2-fluoroethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.32 (4H, t, J = 6.0 Hz), 4.14-4.21 (2H, m), 4.68-4.79 (2H, m), 6.66 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.72 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

[0568]

Reference Example 281

1-{4-[2-(Dimethylamino)ethoxy]-2-fluorophenyl}piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.33 (6H, s), 2.62 (4H, t, J = 6.0 Hz), 2.71 (2H, t, J = 5.5 Hz), 3.31 (4H, t, J = 6.0 Hz), 4.01 (2H, t, J = 5.5 Hz), 6.65 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.71 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

[0569]

Reference Example 282

1-[2-Fluoro-4-(2,2,2-trifluoroethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.33 (4H, t, J = 6.0 Hz), 4.31 (2H, q, J = 8.0 Hz), 6.68 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.75 (1H, dd, J = 13.0 Hz, 3.0 Hz), 6.96 (1H, t, J = 9.0 Hz).

[0570]

Reference Example 283

1-(Quinoxalin-6-yl)piperidin-4-one

Synthesized analogous to Reference Example 271.

^{1}HNMR ($CDCl_3$) δ ppm: 2.64 (4H, t, J = 6.0 Hz), 3.84 (4H, t, J = 6.0 Hz), 7.36 (1H, d, J = 3.0 Hz), 7.57 (1H, dd, J = 9.5 Hz, 3.0 Hz), 8.00 (1H, d, J = 9.5 Hz), 8.63 (1H, d, J = 2.0 Hz), 8.72 (1H, d, J = 2.0 Hz).

[0571]

Reference Example 284

1-(1-Benzofuran-5-yl)piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.54 (4H, t, J = 6.0 Hz), 6.70 (1H, dd, J = 2.5 Hz, 0.5 Hz), 7.05 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.17 (1H, dd, J = 2.5 Hz, 0.5 Hz), 7.43 (1H, d, J = 9.0 Hz), 7.60 (1H, d, J = 2.5 Hz).

[0572]

Reference Example 285

1-[4-(Difluoromethoxy)-2-fluorophenyl]piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.37 (4H, t, J = 6.0 Hz), 6.46 (1H, t, J = 73.5 Hz), 6.88 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.92 (1H, dd, J = 12.5 Hz, 2.5 Hz), 6.97 (1H, t, J = 9.0 Hz).

[0573]

Reference Example 286

1-[4-(Difluoromethoxy)-2,6-difluorophenyl]piperidin-4-one

Synthesized analogous to Reference Example 244.

^{1}HNMR ($CDCl_3$) δ ppm: 2.59 (4H, t, J = 6.0 Hz), 3.45 (4H, t, J = 6.0 Hz), 6.47 (1H, t, J = 72.5 Hz), 6.70-6.76 (2H, m).

[0574]

Reference Example 287

1-[2-Chloro-4-(methylsulfanyl)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 271.

^{1}HNMR ($CDCl_3$) δ ppm: 2.47 (3H, s), 2.64 (4H, t, J = 6.0 Hz), 3.31 (4H, t, J = 6.00 Hz), 6.99 (1H, d, J = 8.5 Hz), 7.15 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.32 (1H, d, J = 2.0 Hz).

[0575]

Reference Example 288

1-[4-(Ethylsulfanyl)-2,6-difluorophenyl]piperidin-4-one

Synthesized analogous to Reference Example 271.

^{1}HNMR ($CDCl_3$) δ ppm: 1.33 (3H, t, J = 7.5 Hz), 2.58 (4H, t, J = 6.0 Hz), 2.92 (2H, q, J = 7.5 Hz), 3.45 (4H, t, J = 6.0 Hz), 6.80-6.86 (2H, m).

[0576]

Reference Example 289

1-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR ($CDCl_3$) δ ppm: 2.58 (4H, t, J = 6.0 Hz), 3.41 (4H, t, J = 6.0 Hz), 4.30 (2H, q, J = 8.0 Hz), 6.49-6.55 (2H, m).

[0577]

Reference Example 290

1-Bromo-4-ethoxy-2-fluoro-5-nitrobenzene

To a suspension of 4-bromo-5-fluoro-2-nitrophenol (5.14 g) and potassium carbonate (6.02 g) in acetonitrile (100 mL) was added ethyl iodide (2.29 mL), and the reaction mixture was heated to reflux for 4 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (4.73 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.50 (3H, t, J = 7.0 Hz), 4.16 (2H, q, J = 7.0 Hz), 6.86 (1H, d, J = 10.0 Hz), 8.14 (1H, d, J = 7.0 Hz).

[0578]

Reference Example 291

4-Bromo-2,5-difluorophenyl ethyl ether

Synthesized analogous to Reference Example 290.

^{1}HNMR (CDCl$_3$) δ ppm: 1.46 (3H, t, J = 7.0 Hz), 4.07 (2H, q, J = 7.0 Hz), 6.76 (1H, dd, J = 9.5 Hz, 7.0 Hz), 7.25 (1H, dd, J = 10.5 Hz, 7.0 Hz).

[0579]

Reference Example 292

1-Bromo-4-(ethoxymethyl)-2-fluorobenzene

To a solution of (4-bromo-3-fluorophenyl)methanol (2.19 g) in N,N-dimethylformamide (22 mL) was added sodium hydride (55 % in oil) (0.282 g), and the reaction mixture was stirred at room temperature for 1.5 h. Then ethyl iodide (1.12 mL) was added thereto and the mixture was stirred at 60 °C for 5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with 5 N aqueous sodium hydroxide and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.28 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.25 (3H, t, J = 7.0 Hz), 3.54 (2H, q, J = 7.0 Hz), 4.45 (2H, s), 7.00 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.13 (1H, dd, J = 9.5 Hz, 1.5 Hz), 7.50 (1H, dd, J = 8.0 Hz, 7.0 Hz).

[0580]

Reference Example 293

2-(4-Bromo-2,5-difluorophenoxy)-N,N-dimethylethaneamine

To a suspension of 4-bromo-2,5-difluorophenol (4.44 g) and potassium carbonate (9.69 g) in acetonitrile (90 mL) were added sodium iodide (4.14 g) and 2-chloro-N,N-dimethylethylamine hydrochloride (3.98 g), and the reaction mixture was heated to reflux for 5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with 5 N aqueous sodium hydroxide and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to provide the title compound (2.11 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.39 (6H, s), 2.83 (2H, t, J = 5.5 Hz), 4.13 (2H, t, J = 5.5 Hz), 6.75-6.80 (1H, m), 7.21-7.27 (1H, m).

[0581]

Reference Example 294

1-Bromo-4-ethoxy-2-fluoro-5-methoxybenzene

Synthesized analogous to Reference Example 290.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (3H, t, J = 7.0 Hz), 3.84 (3H, s), 4.05 (2H, q, J = 7.0 Hz), 6.70 (1H, d, J = 10.0 Hz), 6.96 (1H, d, J = 6.5 Hz).

[0582]

Reference Example 295

4-Bromo-3,5-difluorophenyl ethyl ether

Synthesized analogous to Reference Example 290.

^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 3.99 (2H, q, J = 7.0 Hz), 6.50-6.54 (2H, m).

[0583]

Reference Example 296

4-Bromo-3,5-difluorophenyl ethyl sulfide

Synthesized analogous to Reference Example 290.

^{1}HNMR ($CDCl_3$) δ ppm: 1.35 (3H, t, J = 7.5 Hz), 2.96 (2H, q, J = 7.5 Hz), 6.84-6.87 (2H, m).

[0584]

Reference Example 297

4-Bromo-3,5-difluorophenyl 2,2,2-trifluoroethyl ether

Synthesized analogous to Reference Example 290.

^{1}HNMR ($CDCl_3$) δ ppm: 4.33 (2H, q, J = 8.0 Hz), 6.59-6.62 (2H, m).

[0585]

Reference Example 298

4-Chloro-2-fluoro-5-(2-fluoroethoxy)aniline

Synthesized analogous to Reference Example 292.

^{1}HNMR ($CDCl_3$) δ ppm: 3.73 (2H, brs), 4.15-4.23 (2H, m), 4.69-4.81 (2H, m), 6.41 (1H, d, J = 8.0 Hz), 7.02 (1H, d, J = 10.5 Hz).

[0586]

Reference Example 299

4-Chloro-2-fluoro-5-(2,2,2-trifluoroethoxy)aniline

Synthesized analogous to Reference Example 290.

^{1}HNMR ($CDCl_3$) δ ppm: 3.78 (2H, brs), 4.32 (2H, q, J = 8.0 Hz), 6.46 (1H, d, J = 8.0 Hz), 7.04 (1H, d, J = 10.5 Hz).

[0587]

Reference Example 300

4-Chloro-5-[2-(dimethylamino)ethoxy]-2-fluoroaniline

Synthesized analogous to Reference Example 292.

^{1}HNMR ($CDCl_3$) δ ppm: 2.36 (6H, s), 2.76 (2H, t, J = 6.0 Hz), 3.72 (2H, brs), 4.03 (2H, t, J = 6.0 Hz), 6.39 (1H, d, J = 8.0 Hz), 7.01 (1H, d, J = 10.5 Hz).

[0588]

Reference Example 301

4-Chloro-5-[(4-chlorobenzyl)oxy]-2-fluoroaniline

Synthesized analogous to Reference Example 292.

^{1}HNMR ($CDCl_3$) δ ppm: 3.70 (2H, brs), 5.02 (2H, s), 6.37 (1H, d, J = 8.0 Hz), 7.04 (1H, d, J = 10.5 Hz), 7.34-7.39 (4H, m).

[0589]

Reference Example 302

4-Chloro-2-fluoro-5-(2-methoxyethoxy)aniline

Synthesized analogous to Reference Example 292.

^{1}HNMR ($CDCl_3$) δ ppm: 3.47 (3H, s), 3.72 (2H, brs), 3.76 (2H, t, J = 5.0 Hz), 4.09 (2H, t, J = 5.0 Hz), 6.42 (1H, d, J = 8.0 Hz), 7.01 (1H, d, J = 10.0 Hz).

[0590]

Reference Example 303

4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethoxy]aniline

Synthesized analogous to Reference Example 292.

^{1}HNMR ($CDCl_3$) δ ppm: 3.73 (2H, brs), 4.26-4.31 (4H, m), 6.45 (1H, d, J = 8.0 Hz), 6.90-6.92 (2H, m), 6.96-7.01 (2H, m), 7.02 (1H, d, J = 10.0 Hz).

[0591]

Reference Example 304

4-Chloro-2-fluoro-5-propylaniline

Under nitrogen atmosphere, a solution of 1-bromo-2-chloro-4-fluoro-5-nitrobenzene (1.40 g), tetrakis(triphenylphosphine)palladium (0) (0.318 g), sodium carbonate (1.75 g) and trans-propenylboronic acid (0.945 g) in 1,4-dioxane-water (30-6 mL) was stirred at 100 °C for 5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give (E)-4-chloro-2-fluoro-5-(1-propenyl)aniline. Under nitrogen atmosphere, to platinum on carbon (wetted with 56 % water) (140 mg) was added a solution of the obtained compound in ethanol (14 mL) and the reaction mixture was stirred at room temperature for 5 h under hydrogen atmosphere. The reaction solution was filtrated with Celite, the filter was washed with ethanol, and the solvent of the filtrate was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (405 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 0.95 (3H, t, J = 7.0 Hz), 1.55-1.63 (2H, m), 2.56 (2H, t, J = 7.5 Hz), 3.64 (2H, brs), 6.61 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 11.0 Hz).

[0592]

Reference Example 305

1-Chloro-2-ethenyl-5-fluoro-4-nitrobenzene

Under nitrogen atmosphere, a solution of 1-bromo-2-chloro-4-fluoro-5-nitrobenzene (4.14 g), tetrakis(triphenylphosphine)palladium (0) (0.941 g), sodium carbonate (5.18 g) and vinylboronic acid pinacol ester (5.95 mL) in 1,4-dioxane-water (80-16 mL) was stirred at 100 °C for 3 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (3.20 g).

^{1}HNMR ($CDCl_3$) δ ppm: 5.57 (1H, d, J = 11.0 Hz), 5.85 (1H, d, J = 17.0 Hz), 7.00 (1H, J = 17.0 Hz, 11.0 Hz), 7.35 (1H, dd, J = 10.0 Hz), 8.28 (1H, d, J = 8.0 Hz).

[0593]

Reference Example 306

4-Chloro-5-ethyl-2-fluoroaniline

Under nitrogen atmosphere, to a suspension of platinum on carbon (wetted with 56 % water) (150 mg) in ethanol was added a solution of 1-chloro-2-ethenyl-5-fluoro-4-nitrobenzene (1.49 g) in ethanol, and the reaction mixture was stirred at room temperature for 5 h under hydrogen atmosphere. The reaction solution was filtered with Celite, the filtrate was washed with ethanol, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (929 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.17 (3H, t, J = 7.5 Hz), 2.62 (2H, q, J = 7.5 Hz), 3.65 (2H, brs), 6.63 (1H, d, J = 9.5 Hz), 6.98 (1H, d, J = 10.5 Hz).

[0594]

Reference Example 307

2-(2-Chloro-4-fluoro-5-nitrophenyl)ethanol

Under nitrogen atmosphere, to a solution of 1-chloro-2-ethenyl-5-fluoro-4-nitrobenzene (3.69 g) in tetrahydrofuran (70 mL) was added a solution of 1 M borane-tetrahydrofuran complex solution (18.3 mL), and the reaction mixture was stirred at room temperature for 10 h. To the reaction solution were added 10 % aqueous sodium hydroxide (0.925 g) and 30 % hydrogen peroxide water (2.26 mL), and the reaction mixture was stirred at room temperature for 14 h. To the reaction solution was added aqueous saturated ammonium chloride solution, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.08 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.51 (1H, t, J = 5.0 Hz), 3.05 (2H, t, J = 6.5 Hz), 3.93-3.96 (2H, m), 7.36 (1H, J = 10.0 Hz), 8.08 (1H, d, J = 8.0 Hz).

[0595]

Reference Example 308

5-Ethoxy-2,4-difluoroaniline

Synthesized analogous to Reference Example 292.

^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 3.54 (2H, brs), 4.02 (2H, q, J = 7.0 Hz), 6.41 (1H, t, J = 8.5 Hz), 6.80 (1H, t, J = 10.5 Hz).

[0596]

Reference Example 309

4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethyl]aniline

Synthesized analogous to Reference Example 306.

^{1}HNMR ($CDCl_3$) δ ppm: 3.08 (2H, t, J = 7.0 Hz), 3.70 (2H, brs), 4.10 (2H, t, J = 7.0 Hz), 6.73 (1H, d, J = 9.0 Hz), 6.83 (2H, dd, J = 9.5 Hz, 4.0 Hz), 6.96 (2H, t, J = 9.5 Hz), 7.03 (1H, d, J = 10.5 Hz).

[0597]

Reference Example 310

4-Chloro-2-fluoro-5-(2-methoxyethyl)aniline

Synthesized analogous to Reference Example 292.

^{1}HNMR ($CDCl_3$) δ ppm: 2.88 (2H, t, J = 7.0 Hz), 3.36 (3H, s), 3.56 (2H, t, J = 7.0 Hz), 3.67 (2H, brs), 6.68 (1H, d, J = 9.5 Hz), 7.00 (1H, d, J = 10.5 Hz).

[0598]

Reference Example 311

1-Chloro-5-fluoro-2-[2-(4-fluorophenoxy) ethyl]-4-nitrobenzene

Under nitrogen atmosphere, to a solution of 2-(2-chloro-4-fluoro-5-nitrophenyl)ethanol (507 mg), 4-fluorophenol (259 mg) and triphenylphosphine (666 mg) in dichloromethane (10 mL) was added a solution of 2.2 M diethyl azodicarboxylate in toluene (1.26 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. To the reaction solution was added 1 N hydrochloric acid, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (260 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 3.25 (2H, t, J = 6.5 Hz), 4.18 (2H, t, J = 6.5 Hz), 6.82 (2H, dd, J = 9.0 Hz, 4.5 Hz), 6.97 (2H, dd, J = 9.0 Hz, 8.5 Hz), 7.37 (1H, J = 10.0 Hz), 8.13 (1H, d, J = 7.5 Hz).

[0599]

Reference Example 312

5-Ethenyl-2,4-difluoroaniline

Under nitrogen atmosphere, a solution of 5-bromo-2,4-difluoroaniline (2.04 g), vinylboronic acid pinacol ester (3.44 mL), potassium fluoride (1.81 g), tri-*tert*-butylphosphine-tetrafluoroborate (0.137 g) and tris(dibenzylideneacetone)dipalladium (0.172 g) in tetrahydrofuran/water (4: 1) (25 mL) was heated to reflux for 9 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off.

The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.09 g).

^{1}HNMR ($CDCl_3$) δ ppm: 3.58 (2H, brs), 5.29 (1H, d, J = 11.5 Hz), 5.67 (1H, d, J = 17.5 Hz), 6.72-6.78 (2H, m), 6.87 (1H, dd, J = 9.5 Hz, 7.5 Hz).

[0600]

Reference Example 313

2,4-Difluoro-5-[(1E)-prop-1-en-1-yl]aniline

Synthesized analogous to Reference Example 312.

^{1}HNMR ($CDCl_3$) δ ppm: 1.87 (3H, dd, J = 6.5 Hz, 1.0 Hz), 3.54 (2H, brs), 6.15 (1H, dq, J = 16.0 Hz, 6.5 Hz), 6.42 (1H, dd, J = 16.0 Hz, 1.0 Hz), 6.72 (1H, t, J = 10.5 Hz), 6.79 (1H, dd, J = 9.5 Hz, 7.5 Hz).

[0601]

Reference Example 314

5-Ethyl-2,4-difluoroaniline

Under nitrogen atmosphere, to 10 % palladium on carbon (wetted with 50 % water) (110 mg) was added a solution of 5-ethenyl-2,4-difluoroaniline (1.09 g) in ethanol (11 mL), and the reaction mixture was stirred at room temperature for 5 h under hydrogen atmosphere. The reaction solution was filtrated with Celite, the filter was washed with ethanol, and the solvent of the filtrate was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (692 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.17 (3H, t, J = 7.5 Hz), 2.55 (2H, q, J = 7.5 Hz), 3.51 (2H, brs), 6.59 (1H, dd, J = 9.5 Hz, 7.5 Hz), 6.71 (1H, dd, J = 11.0 Hz, 10.0 Hz).

[0602]

Reference Example 315

2,4-Difluoro-5-propylaniline

Synthesized analogous to Reference Example 314.

^{1}HNMR (CDCl$_3$) δ ppm: 0.93 (3H, t, J = 7.5 Hz), 1.58 (2H, sext, J = 7.5 Hz), 2.49 (2H, t, J = 7.5 Hz), 3.49 (2H, brs) 6.57 (1H, dd, J = 10.0 Hz, 7.5 Hz), 6.71 (1H, dd, J = 11.0 Hz, 9.5 Hz).

[0603]

Reference Example 316

2-(5-Amino-2-chloro-4-fluorophenyl)ethanol

Synthesized analogous to Reference Example 306.

^{1}HNMR (CDCl$_3$) δ ppm: 1.43 (1H, brs), 2.88 (2H, t, J = 6.5 Hz), 3.70 (2H, brs), 3.84 (2H, t, J = 6.5 Hz), 6.69 (1H, d, J = 9.5 Hz), 7.02 (1H, d, J = 10.5 Hz).

[0604]

Reference Example 317

1-Methyl-1-(2-nitrobenzyl)-4-oxopiperidinium bromide

To a solution of 1-methyl-4-piperidone (29.1 mL) in acetone (300 mL) was added 2-nitrobenzyl bromide (48.8 g), and the reaction mixture was stirred at room temperature. After 2 h, the precipitate was collected on a filter, and washed with acetone and ethanol to provide the title compound (63.2 g).

^{1}HNMR (DMSO-d6) δ ppm: 2.52-2.60 (2H, m), 2.81-2.96 (2H, m), 3.22 (3H, s), 3.63-3.72 (2H, m), 3.73-3.89 (2H, m), 5.11 (2H, s), 7.80-7.95 (3H, m), 8.18 (1H, d, J = 7.2 Hz).

[0605]

Reference Example 318

1-(4-Chloro-5-ethoxy-2-fluorophenyl)piperidin-4-one

To a solution of 4-chloro-5-ethoxy-2-fluoroaniline (2.60 g) in ethanol-water (27-18 mL) was added 1-benzyl-1-methyl-4-oxopiperidinium bromide (3.90 g), and the reaction mixture was stirred at 100 °C for 14 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (2.42 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.45 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 4.06 (2H, q, J = 7.0 Hz), 6.56 (1H, d, J = 8.0 Hz), 7.11 (1H, d, J = 11.5 Hz).

[0606]

Reference Example 319

1-[4-Chloro-2-fluoro-5-(2-fluoroethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 4.25 (2H, dt, J = 28.0 Hz, 4.0 Hz), 4.77 (2H, dt, J = 47.5 Hz, 4.0 Hz), 6.64 (1H, d, J = 8.0 Hz), 7.12 (1H, d, J = 11.5 Hz).

[0607]

Reference Example 320

1-[4-Chloro-2-fluoro-5-(propan-2-yloxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 1.35 (6H, d, J = 6.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.38 (4H, t, J = 6.0 Hz), 4.43 (1H, sep, J = 6.0 Hz), 6.59 (1H, d, J = 8.0 Hz), 7.10 (1H, d, J = 11.5 Hz).

[0608]

Reference Example 321

1-[4-Chloro-2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 4.37 (2H, q, J = 8.0 Hz), 6.66 (1H, d, J = 7.5 Hz), 7.14 (1H, d, J = 11.5 Hz).

[0609]

Reference Example 322

1-{4-Chloro-5-[(4-chlorobenzyl)oxy]-2-fluorophenyl}piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 2.60 (4H, t, J = 6.0 Hz), 3.35 (4H, t, J = 6.0 Hz), 5.06 (2H, s), 6.55 (1H, d, J = 7.5 Hz), 7.13 (1H, d, J = 11.5 Hz), 7.36-7.40 (4H, m).

[0610]

Reference Example 323

1-[4-Chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 3.47 (3H, s), 3.76-3.78 (2H, m), 4.14-4.16 (2H, m), 6.66 (1H, d, J = 7.5 Hz), 7.10 (1H, d, J = 11.5 Hz).

[0611]

Reference Example 324

1-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethoxy]phenyl}piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 3.37 (4H, t, J = 6.0 Hz), 4.30-4.35 (4H, m), 6.66 (1H, d, J = 7.5 Hz), 6.88-6.92 (2H, m), 6.97-7.01 (2H, m), 7.12 (1H, d, J = 11.5 Hz).

[0612]

Reference Example 325

1-(4-Chloro-2-fluoro-5-propoxyphenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 1.07 (3H, t, J = 7.5 Hz), 1.81-1.88 (2H, m), 2.62 (4H, t, J = 6.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 3.94 (2H, t, J = 6.5 Hz), 6.55 (1H, d, J = 7.5 Hz), 7.10 (1H, d, J = 11.5 Hz).

[0613]

Reference Example 326

1-(5,6-Dimethylpyridin-2-yl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 2.17 (3H, s), 2.38 (3H, s), 2.48 (4H, t, J = 6.0 Hz), 3.87 (4H, t, J = 6.0 Hz), 6.52 (1H, d, J = 8.5 Hz), 7.26 (1H, d, J = 8.5 Hz).

[0614]

Reference Example 327

1-(4-Chloro-2-fluoro-5-propylphenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 0.97 (3H, t, J = 7.5 Hz), 1.57-1.65 (2H, m), 2.61-2.64 (2H, m), 2.62 (4H, t, J = 6.0 Hz), 3.38 (4H, t, J = 6.0 Hz), 6.79 (1H, d, J = 9.0 Hz), 7.08 (1H, d, J = 12.0 Hz).

[0615]

Reference Example 328

1-[4-Chloro-2-fluoro-5-(propan-2-yl)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 1.22 (6H, d, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.33 (1H, sep, J = 7.0 Hz), 3.39 (4H, t, J = 6.0 Hz), 6.86 (1H, d, J = 9.5 Hz), 7.07 (1H, d, J = 12.0 Hz).

[0616]

Reference Example 329

1-(2,4-Difluoro-5-methylphenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 2.22 (3H, s), 2.62 (4H, t, J = 6.0 Hz), 3.33 (4H, t, J = 6.0 Hz), 6.77-6.81 (2H, m).

[0617]

Reference Example 330

1-(4-Chloro-5-ethyl-2-fluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 2.62 (4H, t, J = 6.0 Hz), 2.68 (2H, q, J = 7.5 Hz), 3.38 (4H, t, J = 6.0 Hz), 6.82 (1H, d, J = 9.0 Hz), 7.08 (1H, d, J = 11.5 Hz).

[0618]

Reference Example 331

1-(4-Chloro-2-fluoro-5-methoxyphenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.41 (4H, t, J = 6.0 Hz), 3.88 (3H, s), 6.55 (1H, d, J = 8.0 Hz), 7.12 (1H, d, J = 11.5 Hz).

[0619]

Reference Example 332

1-(2,2,6-Trifluoro-1,3-benzodioxol-5-yl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.32 (4H, t, J = 6.0 Hz), 6.80 (1H, d, J = 7.0 Hz), 6.90 (1H, d, J = 10.5 Hz).

[0620]

Reference Example 333

1-(5-Ethoxy-2,4-difluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (3H, t, J = 7.0 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.34 (4H, t, J = 6.0 Hz), 4.08 (2H, q, J = 7.0 Hz), 6.63 (1H, t, J = 8.0 Hz), 6.88 (1H, t, J = 11.0 Hz).

[0621]

Reference Example 334

1-(2,4-Difluoro-5-methoxyphenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 2.63 (4H, t, J = 6.0 Hz), 3.35 (4H, t, J = 6.0 Hz), 3.87 (3H, s), 6.63 (1H, t, J = 8.0 Hz), 6.89 (1H, t, J = 11.5 Hz).

[0622]

Reference Example 335

1-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethyl]phenyl}piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 2.61 (4H, t, J = 6.0 Hz), 3.14 (2H, t, J = 6.5 Hz), 3.38 (4H, t, J = 6.0 Hz), 4.12 (2H, t, J = 6.5 Hz), 6.79-6.84 (1H, m), 6.91-6.98 (4H, m), 7.11 (1H, d, J = 11.5 Hz).

[0623]

Reference Example 336

1-(5-Ethyl-2,4-difluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 2.62 (2H, q, J = 7.5 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.34 (4H, t, J = 6.0 Hz), 6.79 (1H, dd, J = 11.5 Hz, 9.5 Hz), 6.81 (1H, dd, J = 9.5 Hz, 8.0 Hz).

[0624]

Reference Example 337

1-(2,4-Difluoro-5-propylphenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 0.94 (3H, t, J = 7.5 Hz), 1.60 (2H, sext, J = 7.5 Hz), 2.55 (2H, t, J = 7.5 Hz), 2.62 (4H, t, J = 6.0 Hz), 3.33 (4H, t, J = 6.0 Hz), 6.76-6.82 (2H, m).

[0625]

Reference Example 338

1-[4-Chloro-2-fluoro-5-(2-methoxyethyl)phenyl]piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR (CDCl$_3$) δ ppm: 2.62 (4H, t, J = 6.0 Hz), 2.94 (2H, t, J = 7.0 Hz), 3.36 (3H, s), 3.39 (4H, t, J = 6.0 Hz), 3.58 (2H, t, J = 7.0 Hz), 6.88 (1H, d, J = 9.0 Hz), 7.09 (1H, d, J = 12.0 Hz).

[0626]

Reference Example 339

1-(2-Bromo-4-chloro-6-fluorophenyl)piperidin-4-one

Synthesized analogous to Reference Example 318.

^{1}HNMR ($CDCl_3$) δ ppm: 2.61 (4H, brs), 3.34-3.51 (4H, m), 7.07 (1H, dd, J = 11.2 Hz, 2.4 Hz), 7.43 (1H, t, 2.0 Hz).

[0627]

Reference Example 340

6-(3,5-Dichloropyridin-2-yl)-1-oxa-6-azaspiro[2.5]octane

A solution of 1-(3,5-dichloropyridin-2-yl)piperidin-4-one (3.0 g), trimethylsulfoxonium iodide (2.69 g) and potassium *tert*-butoxide (1.37 g) in 1,2-dimethoxyethane (60 mL) was refluxed for 21 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.01 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.69 (2H, m), 1.96-2.04 (2H, m), 2.73 (2H, s), 3.38-3.46 (2H, m), 3.50-3.58 (2H, m), 7.60 (1H, d, J = 2.2 Hz), 8.12 (1H, d, J = 2.2 Hz).

[0628]

Reference Example 341

6-(2,4-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

To a solution of trimethylsulfoxonium iodide (550 mg) in dimethyl sulfoxide (6.8 mL) was added sodium hydride (55 % in oil) (109 mg), and the reaction mixture was stirred at room temperature for 30 min. To the reaction mixture was added a solution of 1-(2,4-dichlorophenyl)piperidin-4-one (555 mg) in dimethyl sulfoxide (3 mL), and the reaction mixture was stirred at room temperature for 2.5 h. Under ice-cooling, to the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed sequentially with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (442 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.06-2.11 (2H, m), 2.73 (2H, s), 3.08-3.13 (2H, m), 3.15-3.20 (2H, m), 7.00 (1H, d, J = 8.5 Hz), 7.19 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.38 (1H, d, J = 2.5 Hz).

[0629]

Reference Example 342

6-(2,5-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.67 (2H, m), 2.04-2.10 (2H, m), 2.73 (2H, s), 3.10-3.16 (2H, m), 3.18-3.22 (2H, m), 6.95 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.03 (1H, d, J = 2.5 Hz), 7.28 (1H, d, J = 8.5 Hz).

[0630]

Reference Example 343

6-(2,5-Dichloro-4-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 2.05-2.11 (2H, m), 2.73 (2H, s), 3.06-3.16 (4H, m), 7.09 (1H, d, J = 7.0 Hz), 7.21 (1H, d, J = 8.5 Hz).

[0631]

Reference Example 344

6-(2-Chloro-4-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 2.06-2.11 (2H, m), 2.73 (2H, s), 3.05-3.16 (4H, m), 6.94 (1H, ddd, J = 8.5 Hz, 8.0 Hz, 3.0 Hz), 7.04 (1H, dd, J = 8.5 Hz, 5.5 Hz), 7.14 (1H, dd, J = 8.0 Hz, 3.0 Hz).

[0632]

Reference Example 345

6-Phenyl-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 1.95-2.00 (2H, m), 2.72 (2H, s), 3.32-3.37 (2H, m), 3.40-3.44 (2H, m), 6.86 (1H, t, J = 7.0 Hz), 6.97 (2H, d, J = 8.0 Hz), 7.27 (2H, dd, J = 8.0 Hz, 7.0 Hz).

[0633]

Reference Example 346

N,N-Dimethyl-4-(1-oxa-6-azaspiro[2.5]oct-6-yl)aniline

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.68 (2H, m), 1.95-2.00 (2H, m), 2.70 (2H, s), 2.87 (6H, s), 3.16-3.24 (4H, m), 6.74 (2H, d, J = 9.5 Hz), 6.95 (2H, d, J = 9.5 Hz).

[0634]

Reference Example 347

6-(3-Chlorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.58-1.62 (2H, m), 1.94-1.99 (2H, m), 2.72 (2H, s), 3.32-3.37 (2H, m), 3.42-3.47 (2H, m), 6.79-6.83 (2H, m), 6.91 (1H, t, J = 2.0 Hz), 7.16 (1H, t, J = 8.5 Hz).

[0635]

Reference Example 348

6-(Pyridin-3-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 1.98-2.04 (2H, m), 2.74 (2H, s), 3.35-3.40 (2H, m), 3.45-3.50 (2H, m), 7.17 (1H, dd, J = 8.5 Hz, 4.5 Hz), 7.23 (1H, ddd, J = 8.5 Hz, 3.0 Hz, 1.5 Hz), 8.10 (1H, dd, J = 4.5 Hz, 1.5 Hz), 8.35 (1H, d, J = 3.0 Hz).

[0636]

Reference Example 349

6-(Thiophen-3-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.62-1.67 (2H, m), 1.95-2.00 (2H, m), 2.72 (2H, s), 3.23-3.33 (4H, m), 6.22-6.24 (1H, m), 6.88-6.90 (1H, m), 7.23-7.26 (1H, m).

[0637]

Reference Example 350

6-(4-Chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.61-1.65 (2H, m), 2.03-2.09 (2H, m), 2.73 (2H, s), 3.14-3.18 (2H, m), 3.21-3.25 (2H, m), 6.89-6.23 (1H, m), 7.03-7.07 (2H, m).

[0638]

Reference Example 351

6-(2,4-Dichloro-5-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.59-1.64 (2H, m), 2.07-2.12 (2H, m), 2.74 (2H, s), 3.08-3.13 (2H, m), 3.17-3.21 (2H, m), 6.86 (1H, d, J = 10.5 Hz), 7.40 (1H, d, J = 7.5 Hz).

[0639]

Reference Example 352

6-(2,3-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.61-1.65 (2H, m), 2.08-2.13 (2H, m), 2.74 (2H, s), 3.11-3.16 (2H, m), 3.18-3.22 (2H, m), 6.99 (1H, dd, J = 7.0 Hz, 2.5 Hz), 7.13-7.17 (2H, m).

[0640]

Reference Example 353

6-(4-Chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 1.92-1.97 (2H, m), 2.71 (2H, s), 3.19-3.23 (2H, m), 3.34-3.39 (2H, m), 6.85-6.91 (2H, m).

[0641]

Reference Example 354

6-[4-Chloro-2-(trifluoromethyl)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.53-1.57 (2H, m), 2.05-2.10 (2H, m), 2.72 (2H, s), 2.96-3.01 (2H, m), 3.05-3.09 (2H, m), 7.33 (1H, d, J = 8.5 Hz), 7.48 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.61 (1H, d, J = 2.5 Hz).

[0642]

Reference Example 355

6-(3,4-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.57-1.61 (2H, m), 1.95-2.00 (2H, m), 2.73 (2H, s), 3.30-3.35 (2H, m), 3.40-3.45 (2H, m), 6.78 (1H, dd, J = 9.0 Hz, 3.0 Hz), 7.00 (1H, d, J = 3.0 Hz), 7.27 (1H, d, J = 9.0 Hz).

[0643]

Reference Example 356

6-(4-Chloro-2-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.68 (2H, m), 1.96-2.01 (2H, m), 2.30 (3H, s), 2.72 (2H, s), 2.94-2.99 (2H, m), 3.01-3.06 (2H, m), 6.97 (1H, d, J = 8.0 Hz), 7.12 (1H, dd, J = 8.0 Hz, 2.5 Hz), 7.16 (1H, d, J = 2.5 Hz).

[0644]

Reference Example 357

6-[2-(Trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.14-3.24 (4H, m), 6.99 (1H, ddd, J = 8.0 Hz, 7.5 Hz, 1.5 Hz), 7.06 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.19-7.26 (2H, m).

[0645]

Reference Example 358

6-(2-Chloro-6-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.67 (2H, brs), 1.94 (2H, brs), 2.71 (2H, s), 3.19-3.26 (2H, m), 3.36-3.41 (2H, m), 6.92-6.99 (2H, m), 7.14-7.19 (1H, m).

[0646]

Reference Example 359

6-(4-Chloro-2,5-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.03-2.09 (2H, m), 2.74 (2H, s), 3.14-3.19 (2H, m), 3.23-3.27 (2H, m), 6.76 (1H, dd, J = 11.0 Hz, 8.0 Hz), 7.08 (1H, dd, J = 11.5 Hz, 7.0 Hz).

[0647]

Reference Example 360

6-(2-Bromo-4-chlorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.07-2.12 (2H, m), 2.73 (2H, s), 3.07-3.12 (2H, m), 3.14-3.18 (2H, m), 7.00 (1H, d, J = 8.5 Hz), 7.24 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.57 (1H, d, J = 2.5 Hz).

[0648]

Reference Example 361

6-(2,4,6-Trichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.68 (2H, m), 1.92-1.97 (2H, m), 2.71 (2H, s), 3.16-3.20 (2H, m), 3.41-3.46 (2H, m), 7.27-7.30 (2H, m).

[0649]

Reference Example 362

6-(2,6-Dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.71 (2H, m), 1.92-1.97 (2H, m), 2.71 (2H, s), 3.20-3.25 (2H, m), 3.43-3.48 (2H, m), 6.97 (1H, t, J = 8.0 Hz), 7.25-7.29 (2H, m).

[0650]

Reference Example 363

6-(4-Chloro-3-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 1.97-2.02 (2H, m), 2.73 (2H, s), 3.29-3.34 (2H, m), 3.38-3.43 (2H, m), 3.89 (3H, s), 6.50 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.54 (1H, d, J = 3.0 Hz), 7.21 (1H, d, J = 9.0 Hz).

[0651]

Reference Example 364

6-(3-Ethoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 1.59-1.64 (2H, m), 1.93-1.99 (2H, m), 2.71 (2H, s), 3.32-3.37 (2H, m), 3.40-3.45 (2H, m), 4.02 (2H, q, J = 7.0 Hz), 6.41 (1H, dd, J = 8.0 Hz, 2.5 Hz), 6.51 (1H, t, J = 2.5 Hz), 6.57 (1H, dd, J = 8.0 Hz, 2.5 Hz), 7.16 (1H, t, J = 8.0 Hz).

[0652]

Reference Example 365

6-(4-Ethoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.64-1.68 (2H, m), 1.96-2.02 (2H, m), 2.72 (2H, s), 3.17-3.29 (4H, m), 3.99 (2H, q, J = 7.0 Hz), 6.84 (2H, d, J = 9.0 Hz), 6.94 (2H, d, J = 9.0 Hz).

[0653]

Reference Example 366

6-[3-(Propan-2-yl)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.25 (6H, d, J = 7.0 Hz), 1.63-1.68 (2H, m), 1.95-2.01 (2H, m), 2.72 (2H, s), 2.86 (1H, sep, J = 7.0 Hz), 3.30-3.34 (2H, m), 3.35-3.43 (2H, m), 6.76 (1H, dd, J = 7.5 Hz, 1.0 Hz), 6.79 (1H, dd, J = 7.5 Hz, 2.5 Hz), 6.85 (1H, dd, J = 2.5 Hz, 1.0 Hz), 7.20 (1H, t, J = 7.5 Hz).

[0654]

Reference Example 367

6-[4-(Propan-2-yl)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (6H, d, J = 7.0 Hz), 1.62-1.67 (2H, m), 1.94-2.00 (2H, m), 2.71 (2H, s), 2.84 (1H, sep, J = 7.0 Hz), 3.26-3.38 (4H, m), 6.92 (2H, d, J = 8.5 Hz), 7.13 (2H, d, J = 8.5 Hz).

[0655]

Reference Example 368

6-(3,5-Dichloropyridin-4-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 2.00-2.06 (2H, m), 2.74 (2H, s), 3.35-3.40 (2H, m), 3.54-3.59 (2H, m), 8.35 (2H, s).

[0656]

Reference Example 369

4-(1-Oxa-6-azaspiro[2.5]oct-6-yl)benzonitrile

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.54-1.59 (2H, m), 1.95-2.01 (2H, m), 2.74 (2H, s), 3.46-3.51 (2H, m), 3.63-3.68 (2H, m), 6.89 (2H, d, J = 9.0 Hz), 7.50 (2H, d, J = 9.0 Hz).

[0657]

Reference Example 370

3-(1-Oxa-6-azaspiro[2.5]oct-6-yl)benzonitrile

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.58-1.63 (2H, m), 1.97-2.02 (2H, m), 2.74 (2H, s), 3.35-3.40 (2H, m), 3.48-3.52 (2H, m), 7.09 (1H, dd, J = 7.5 Hz, 1.0 Hz), 7.14-7.16 (2H, m), 7.32 (1H, dd, J = 9.0 Hz, 7.5 Hz).

[0658]

Reference Example 371

6-(4-Phenoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.64-1.68 (2H, m), 1.98-2.03 (2H, m), 2.73 (2H, s), 3.26-3.31 (2H, m), 3.34-3.38 (2H, m), 6.94-6.97 (6H, m), 7.04 (1H, t, J = 7.5 Hz), 7.28-7.31 (2H, m).

[0659]

Reference Example 372

6-(Biphenyl-2-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.39-1.44 (2H, m), 1.67-1.73 (2H, m), 2.61 (2H, s), 2.90-3.02 (4H, m), 7.08 (2H, t, J = 7.5 Hz), 7.25-7.31 (3H, m), 7.40 (2H, t, J = 7.5 Hz), 7.64-7.66 (2H, m).

[0660]

Reference Example 373

6-[2-Chloro-5-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 2.07-2.12 (2H, m), 2.74 (2H, s), 3.12-3.17 (2H, m), 3.21-3.25 (2H, m), 6.85 (1H, ddd, J = 8.5 Hz, 2.5 Hz, 1.0 Hz), 6.90 (1H, d, J = 2.5 Hz), 7.37 (1H, d, J = 8.5 Hz).

[0661]

Reference Example 374

6-[2-(Propan-2-yl)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23 (6H, d, J = 7.0 Hz), 1.68 (2H, brs), 1.98 (2H, brs), 2.72 (2H, s), 2.93-2.98 (2H, m), 3.04-3.09 (2H, m), 3.52 (1H, sep J = 7.0 Hz), 7.08-7.18 (3H, m), 7.24-7.28 (1H, m).

[0662]

Reference Example 375

6-(2-Chloro-5-nitrophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.70 (2H, m), 2.09-2.14 (2H, m), 2.76 (2H, s), 3.18-3.31 (4H, m), 7.52 (1H, d, J = 8.5 Hz), 7.84 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.92 (1H, d, J = 2.5 Hz).

[0663]

Reference Example 376

6-(2-Ethylphenyl)-1-oxa-6-azaspiro[2.5]octane

To a solution of trimethylsulfoxonium iodide (1.48 g) in dimethyl sulfoxide (10 mL) was added sodium *tert*-butoxide (0.65 g), and the reaction mixture was stirred at room temperature for 30 min. To the reaction solution was added a solution of 1-(2-ethylphenyl)-piperidin-4-one (1.24 g) in dimethyl sulfoxide (4 mL), and the reaction mixture was stirred at room temperature for 8.5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (880 mg) as a colorless oil.

^{1}HNMR ($CDCl_3$) δ ppm: 1.26 (3H, t, J = 7.5 Hz), 1.65-1.69 (2H, m), 1.96-1.99 (2H, m), 2.72 (2H, s), 2.73 (2H, q, J = 7.5 Hz), 2.96-3.00 (2H, m), 3.05-3.10 (2H, m), 7.02-7.19 (3H, m), 7.21-7.28 (1H, m).

[0664]

Reference Example 377

6-[3-(Trifluoromethyl)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 1.97-2.02 (2H, m), 2.74 (2H, s), 3.36-3.41 (2H, m), 3.47-3.52 (2H, m), 7.08 (1H, d, J = 8.0 Hz), 7.10 (1H, dd, J = 8.0 Hz, 2.5 Hz), 7.15 (1H, d, J = 2.5 Hz), 7.35 (1H, t, J = 8.0 Hz).

[0665]

Reference Example 378

6-(4-Chloro-3-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.59-1.64 (2H, m), 1.94-2.00 (2H, m), 2.33 (3H, s), 2.72 (2H, s), 3.27-3.32 (2H, m), 3.36-3.40 (2H, m), 6.73 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.82 (1H, d, J = 3.0 Hz), 7.19 (1H, d, J = 9.0 Hz).

[0666]

Reference Example 379

Ethyl 4-(1-oxa-6-azaspiro[2.5]oct-6-yl)benzoate

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.37 (3H, t, J = 7.0 Hz), 1.56-1.60 (2H, m), 1.95-2.00 (2H, m), 2.74 (2H, s), 3.46-3.51 (2H, m), 3.62-3.66 (2H, m), 4.33 (2H, q, J = 7.0 Hz), 6.90 (2H, d, J = 9.0 Hz), 6.93 (2H, d, J = 9.0 Hz).

[0667]

Reference Example 380

Ethyl 2-chloro-5-(1-oxa-6-azaspiro[2.5]oct-6-yl)benzoate

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.41 (3H, t, J = 7.0 Hz), 1.59-1.63 (2H, m), 1.96-2.01 (2H, m), 2.73 (2H, s), 3.32-3.37 (2H, m), 3.43-3.47 (2H, m), 4.40 (2H, q, J = 7.0 Hz), 6.98 (1H, dd, J = 9.0 Hz, 3.0 Hz), 7.29 (1H, d, J = 9.0 Hz), 7.34 (1H, d, J = 3.0 Hz).

[0668]

Reference Example 381

6-(2-Chloro-4-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.05-2.10 (2H, m), 2.28 (3H, s), 2.72 (2H, s), 3.07-3.17 (4H, m), 6.98 (1H, d, J = 8.5 Hz), 7.02 (1H, dd, J = 8.5 Hz, 1.5 Hz), 7.20 (1H, d, J = 1.5 Hz).

[0669]

Reference Example 382

6-(4-Methylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 1.95-2.00 (2H, m), 2.28 (3H, s), 2.72 (2H, s), 3.26-3.31 (2H, m), 3.33-3.37 (2H, m), 6.89 (2H, d, J = 8.5 Hz), 7.08 (2H, d, J = 8.5 Hz).

[0670]

Reference Example 383

6-(4-Chloro-2-nitrophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.53-1.57 (2H, m), 2.10-2.15 (2H, m), 2.74 (2H, s), 3.17-3.23 (4H, m), 7.14 (1H, d, J = 8.5 Hz), 7.45 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.80 (1H, d, J = 2.5 Hz).

[0671]

Reference Example 384

6-[2-Chloro-4-(propan-2-yl)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.22 (6H, d, J = 7.0 Hz), 1.62-1.65 (2H, m), 2.05-2.10 (2H, m), 2.72 (2H, s), 2.84 (1H, sep, J = 7.0 Hz), 3.09-3.16 (4H, m), 7.00 (1H, d, J = 8.5 Hz), 7.07 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.24 (1H, d, J = 2.0 Hz).

[0672]

Reference Example 385

6-(4-Bromo-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.14-3.19 (2H, m), 3.21-3.25 (2H, m), 6.86 (1H, t, J = 9.0 Hz), 7.17-7.21 (2H, m).

[0673]

Reference Example 386

6-(4-Ethoxy-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.63-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.08-3.17 (4H, m), 3.97 (2H, q, J = 7.0 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.65 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

[0674]

Reference Example 387

6-(2-Fluoro-4-propoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.02 (3H, t, J = 7.5 Hz), 1.63-1.67 (2H, m), 1.75-1.82 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.09-3.17 (4H, m), 3.86 (2H, t, J = 6.5 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.65 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.94 (1H, t, J = 9.0 Hz).

[0675]

Reference Example 388

6-(2,4-Dichloro-6-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.43-1.46 (1H, m), 1.67-1.71 (1H, m), 1.85-1.90 (1H, m), 2.05-2.11 (1H, m), 2.33 (1.5H, s), 2.34 (1.5H, s), 2.70 (1H, s), 2.72 (1H, s), 2.90-2.94 (1H, m), 3.10-3.15 (1H, m), 3.34-3.39 (1H, m), 3.58-3.63 (1H, m), 7.06-7.09 (1H, m), 7.17-7.19 (1H, m).

[0676]

Reference Example 389

6-(2-Chloro-4-ethylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.5 Hz), 1.62-1.66 (2H, m), 2.05-2.10 (2H, m), 2.58 (2H, q, J = 7.5 Hz), 2.72 (2H, s), 3.09-3.17 (4H, m), 7.00 (1H, d, J = 8.5 Hz), 7.05 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.22 (1H, d, J = 2.0 Hz).

[0677]

Reference Example 390

6-(2-Chloro-4-propylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 0.93 (3H, t, J = 7.5 Hz), 1.57-1.65 (4H, m), 2.05-2.10 (2H, m), 2.51 (2H, t, J = 7.5 Hz), 2.72 (2H, s), 3.09-3.20 (4H, m), 6.99 (1H, d, J = 8.0 Hz), 7.02 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.20 (1H, d, J = 2.0 Hz).

[0678]

Reference Example 391

6-(2,4-Dichloro-6-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.65 (2H, brs), 1.95 (2H, brs), 2.71 (2H, s), 3.15-3.22 (2H, m), 3.33-3.38 (2H, m), 6.99 (1H, dd, J = 11.5 Hz, 2.5 Hz), 7.20 (1H, dd, J = 2.5 Hz, 2.0 Hz).

[0679]

Reference Example 392

6-(2-Chloro-4,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.64 (2H, brs), 1.95 (2H, brs), 2.71 (2H, s), 3.12-3.18 (2H, m), 3.30-3.38 (2H, m), 6.74 (1H, ddd, J = 11.5 Hz, 8.5 Hz, 3.0 Hz), 6.96 (1H, ddd, J = 8.0 Hz, 3.0 Hz, 2.0 Hz).

[0680]

Reference Example 393

6-(4-Butoxy-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 0.97 (3H, t, J = 7.5 Hz), 1.44-1.51 (2H, m), 1.63-1.67 (2H, m), 1.71-1.77 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.16 (4H, m), 3.90 (2H, t, J = 6.5 Hz), 6.61 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.65 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

[0681]

Reference Example 394

6-[2-Fluoro-4-(propan-2-yloxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.31 (6H, d, J = 6.0 Hz), 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.18 (4H, m), 4.44 (1H, sep, J = 6.0 Hz), 6.61 (1H, ddd, J = 8.5 Hz, 3.0 Hz, 1.0 Hz), 6.64 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, dd, J = 9.5 Hz, 8.5 Hz).

[0682]

Reference Example 395

6-[2-Chloro-4-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.08-2.13 (2H, m), 2.74 (2H, s), 3.10-3.15 (2H, m), 3.18-3.22 (2H, m), 7.07 (1H, d, J = 8.5 Hz), 7.11 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.28 (1H, d, J = 2.5 Hz).

[0683]

Reference Example 396

6-[2,4-Dichloro-5-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.61-1.65 (2H, m), 2.07-2.12 (2H, m), 2.74 (2H, s), 3.10-3.15 (2H, m), 3.18-3.23 (2H, m), 7.00 (1H, d, J = 1.0 Hz), 7.48 (1H, s).

[0684]

Reference Example 397

6-(2-Fluoro-4-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.63-1.67 (2H, m), 2.03-2.08 (2H, m), 2.72 (2H, s), 3.07-3.17 (4H, m), 3.77 (3H, s), 6.62 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.66 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.96 (1H, t, J = 9.0 Hz).

[0685]

Reference Example 398

6-(2,4,6-Trifluorophenyl)-1-oxa-6-azaspiro[2.5]octane

To a solution of trimethylsulfoxonium iodide (4.89 g) in dimethyl sulfoxide (50 mL) was added sodium *tert*-butoxide (1.93 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. To the reaction mixture was added a solution of 1-(2,4,6-trifluorophenyl)piperidin-4-one (4.85 g) in dimethyl sulfoxide (10 mL) dropwise, and the reaction mixture was stirred at room temperature for 2 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (4.3 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.60-1.68 (2H, m), 1.89-1.99 (2H, m), 2.71 (2H, s), 3.13-3.23 (2H, m), 3.30-3.38 (2H, m), 6.58-6.68 (2H, m).

[0686]

Reference Example 399

6-[2-Fluoro-4-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.61-1.66 (2H, m), 2.05-2.10 (2H, m), 2.74 (2H, s), 3.15-3.20 (2H, m), 3.23-3.27 (2H, m), 6.94-7.00 (3H, m).

[0687]

Reference Example 400

6-[4-(Benzyloxy)-2-fluorophenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.17 (4H, m), 5.01 (2H, s), 6.69 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.73 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz), 7.31-7.35 (1H, m), 7.36-7.43 (4H, m).

[0688]

Reference Example 401

6-[2-Fluoro-4-(2-methoxyethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.18 (4H, m), 3.45 (3H, s), 3.72-3.74 (2H, m), 4.05-4.07 (2H, m), 6.65 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.69 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

[0689]

Reference Example 402

6-[4-Chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.03-2.09 (2H, m), 2.74 (2H, s), 3.16-3.21 (2H, m), 3.24-3.28 (2H, m), 6.90 (1H, dd, J = 8.0 Hz, 1.0 Hz), 7.15 (1H, d, J = 11.5 Hz).

[0690]

Reference Example 403

6-(2-Bromo-5-ethoxy-4-nitrophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.50 (3H, t, J = 7.0 Hz), 1.58-1.63 (2H, m), 2.14-2.20 (2H, m), 2.76 (2H, s), 3.17-3.22 (2H, m), 3.34-3.38 (2H, m), 4.17 (2H, q, J = 7.0 Hz), 6.63 (1H, s), 8.19 (1H, s).

[0691]

Reference Example 404

6-(4-Ethoxy-2,5-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (3H, t, J = 7.0 Hz), 1.62-1.66 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.06-3.17 (4H, m), 4.04 (2H, q, J = 7.0 Hz), 6.73 (1H, dd, J = 13.0 Hz, 7.5 Hz), 6.79 (1H, dd, J = 13.0 Hz, 8.0 Hz).

[0692]

Reference Example 405

6-[4-(Ethoxymethyl)-2-fluorophenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.24 (3H, t, J = 7.0 Hz), 1.63-1.67 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.15-3.20 (2H, m), 3.22-3.26 (2H, m), 3.53 (2H, q, J = 7.0 Hz),4.42 (2H, s), 6.93-6.98 (1H, m), 7.02-7.07 (2H, m).

[0693]

Reference Example 406

6-(2,6-Difluoro-4-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.68 (2H, m), 1.89-1.94 (2H, m), 2.70 (2H, s), 3.12-3.19 (2H, m), 3.29-3.34 (2H, m), 3.75 (3H, s), 6.39-6.45 (2H, m).

[0694]

Reference Example 407

2-[2,5-Difluoro-4-(1-oxa-6-azaspiro[2.5]oct-6-yl)phenoxy]-N,N-dimethylethaneamine

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.61-1.66 (2H, m), 2.01-2.07 (2H, m), 2.34 (6H, s), 2.72 (2H, s), 2.73 (2H, t, J = 6.0 Hz), 3.06-3.18 (4H, m), 4.07 (2H, t, J = 6.0 Hz), 6.75 (1H, dd, J = 13.0 Hz, 8.0 Hz), 6.78 (1H, dd, J = 12.5 Hz, 8.0 Hz).

[0695]

Reference Example 408

6-(4-Ethoxy-2,3,5,6-tetrafluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.40 (3H, t, J = 7.0 Hz), 1.60-1.65 (2H, m), 1.94-1.99 (2H, m), 2.72 (2H, s), 3.21-3.26 (2H, m), 3.37-3.42 (2H, m), 4.21 (2H, q, J = 7.0 Hz), 6.73 (1H, dd, J = 13.0 Hz, 7.5 Hz), 6.79 (1H, dd, J = 13.0 Hz, 8.0 Hz).

[0696]

Reference Example 409

6-(4-Chloro-5-ethoxy-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.45 (3H, t, J = 7.0 Hz), 1.60-1.64 (2H, m), 2.05-2.10 (2H, m), 2.73 (2H, s), 3.14-3.18 (2H, m), 3.22-3.26 (2H, m), 4.06 (2H, q, J = 7.0 Hz), 6.57 (1H, d, J = 8.0 Hz), 7.07 (1H, d, J = 11.5 Hz).

[0697]

Reference Example 410

6-{2-Fluoro-4-[2-(2-methoxyethoxy)ethoxy]phenyl}-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.72 (2H, s), 3.07-3.17 (4H, m), 3.39 (3H, s), 3.57-3.59 (2H, m), 3.70-3.72 (2H, m), 3.83-3.85 (2H, m), 4.08-4.10 (2H, m), 6.63 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.93 (1H, t, J = 9.0 Hz).

[0698]

Reference Example 411

6-(4-Chloro-2-fluoro-6-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.80 (4H, brs), 2.32 (3H, s), 2.71 (2H, s), 3.08 (2H, brs), 3.24 (2H, brs), 6.89 (1H, dd, J = 11.5 Hz, 2.0 Hz), 6.96-6.98 (1H, m).

[0699]

Reference Example 412

6-(4-Chloro-2-fluoro-5-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.60-1.65 (2H, m), 2.02-2.08 (2H, m), 2.30 (3H, s), 2.73 (2H, s), 3.13-3.17 (2H, m), 3.20-3.24 (2H, m), 6.82 (1H, d, J = 9.5 Hz), 7.04 (1H, d, J = 12.0 Hz).

[0700]

Reference Example 413

6-(4-Ethoxy-2-fluoro-5-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.44 (3H, t, J = 7.0 Hz), 1.62-1.67 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.09-3.20 (4H, m), 3.85 (3H, s), 4.03 (2H, q, J = 7.0 Hz), 6.62 (1H, d, J = 8.0 Hz), 6.67 (1H, d, J = 13.0 Hz).

[0701]

Reference Example 414

6-[2-Fluoro-4-(2-fluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.62-1.67 (2H, m), 2.03-2.08 (2H, m), 2.72 (2H, s), 3.08-3.18 (4H, m), 4.16 (2H, dt, J = 28.0 Hz, 4.0 Hz), 4.73 (2H, dt, J = 47.5 Hz, 4.0 Hz), 6.65 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.70 (1H, dd, J = 13.5 Hz, 2.5 Hz), 6.95 (1H, t, J = 9.0 Hz).

[0702]

Reference Example 415

6-(4-Ethoxy-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.39 (3H, t, J = 7.0 Hz), 1.63-1.68 (2H, m), 1.88-1.94 (2H, m), 2.70 (2H, s), 3.12-3.18 (2H, m), 3.28-3.33 (2H, m), 3.95 (2H, q, J = 7.0 Hz), 6.38-6.43 (2H, m).

[0703]

Reference Example 416

2-[3-Fluoro-4-(1-oxa-6-azaspiro[2.5]oct-6-yl)phenoxy]-N,N-dimethylethaneamine

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.62-1.67 (2H, m), 2.02-2.07 (2H, m), 2.33 (6H, s), 2.68-2.72 (2H, m), 2.72 (2H, s), 3.07-3.17 (4H, m), 3.99-4.02 (2H, m), 6.64 (1H, ddd, J = 9.0 Hz, 3.0 Hz, 1.0 Hz), 6.68 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.94 (1H, t, J = 9.0 Hz).

[0704]

Reference Example 417

6-(1-Benzothiophen-5-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.67-1.71 (2H, m), 2.01-2.07 (2H, m), 2.74 (2H, s), 3.33-3.38 (2H, m), 3.42-3.46 (2H, m), 7.12 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.23 (1H, d, J = 5.0 Hz), 7.35 (1H, d, J = 2.5 Hz), 7.41 (1H, d, J = 5.0 Hz), 7.74 (1H, d, J = 9.0 Hz).

[0705]

Reference Example 418

6-[2-Fluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.63-1.66 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.10-3.20 (4H, m), 4.30 (2H, q, J = 8.0 Hz), 6.67 (1H, ddd, J = 9.0 Hz, 2.5 Hz, 1.0 Hz), 6.72 (1H, dd, J = 13.0 Hz, 2.5 Hz), 6.96 (1H, t, J = 9.0 Hz).

[0706]

Reference Example 419

6-(1-Oxa-6-azaspiro[2.5]oct-6-yl)quinoxaline

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.68 (2H, m), 2.03-2.08 (2H, m), 2.77 (2H, s), 3.54-3.59 (2H, m), 3.69-3.74 (2H, m), 7.33 (1H, d, J = 2.5 Hz), 7.56 (1H, dd, J = 9.5 Hz, 2.5 Hz), 7.94 (1H, d, J = 9.5 Hz), 8.60 (1H, d, J = 2.0 Hz), 8.69 (1H, d, J = 2.0 Hz).

[0707]

Reference Example 420

6-(1-Benzofuran-5-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.71 (2H, m), 2.00-2.06 (2H, m), 2.73 (2H, s), 3.26-3.36 (4H, m), 6.69 (1H, d, J = 2.0 Hz), 7.03 (1H, dd, J = 9.0 Hz, 2.5 Hz), 7.16 (1H, d, J = 2.5 Hz), 7.40 (1H, d, J = 9.0 Hz), 7.57 (1H, d, J = 2.0 Hz).

[0708]

Reference Example 421

6-[4-(Difluoromethoxy)-2-fluorophenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.66 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.13-3.18 (2H, m), 3.20-3.24 (2H, m), 6.44 (1H, t, J = 73.5 Hz), 6.86 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.89 (1H, dd, J = 13.5 Hz, 3.0 Hz), 6.97 (1H, t, J = 9.0 Hz).

[0709]

Reference Example 422

6-(1-Oxa-6-azaspiro[2.5]oct-6-yl)quinoline

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.71 (2H, m), 2.03-2.08 (2H, m), 2.76 (2H, s), 3.43-3.48 (2H, m), 3.57-3.61 (2H, m), 7.07-7.09 (1H, m), 7.30-7.32 (1H, m), 7.51-7.53 (1H, m), 7.94-8.00 (2H, m), 8.69-8.73 (1H, m).

[0710]

Reference Example 423

6-(5-Chloro-3-fluoropyridin-2-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 398.

^{1}HNMR ($CDCl_3$) δ ppm: 1.56-1.65 (2H, m), 1.91-2.01 (2H, m), 2.73 (2H, s), 3.52-3.59 (2H, m), 3.70-3.77 (2H, m), 7.27 (1H, dd, J = 12.2 Hz, 2.2 Hz), 7.95-7.99 (1H, m).

[0711]

Reference Example 424

6-(2,4-Difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.11-3.21 (4H, m), 6.78-6.84 (2H, m), 6.93-6.98 (1H, m).

[0712]

Reference Example 425

6-[4-Chloro-2-fluoro-5-(2-fluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.60-1.64 (2H, m), 2.04-2.10 (2H, m), 2.73 (2H, s), 3.14-3.19 (2H, m), 3.22-3.27 (2H, m), 4.25 (2H, dt, J = 28.0 Hz, 4.5 Hz), 4.76 (2H, dt, J = 47.5 Hz, 4.5 Hz), 6.64 (1H, d, J = 8.0 Hz), 7.08 (1H, d, J = 11.5 Hz).

[0713]

Reference Example 426

6-[4-Chloro-2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.60-1.64 (2H, m), 2.04-2.09 (2H, m), 2.74 (2H, s), 3.14-3.19 (2H, m), 3.22-3.27 (2H, m), 4.36 (2H, q, J = 8.5 Hz), 6.67 (1H, d, J = 8.0 Hz), 7.09 (1H, d, J = 11.5 Hz).

[0714]

Reference Example 427

6-[4-Chloro-2-fluoro-5-(propan-2-yloxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.35 (6H, d, J = 6.5 Hz), 1.60-1.64 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.13-3.18 (2H, m), 3.21-3.25 (2H, m), 4.43 (1H, sep, J = 6.5 Hz), 6.61 (1H, d, J = 8.0 Hz), 7.06 (1H, d, J = 12.0 Hz).

[0715]

Reference Example 428

6-{4-Chloro-5-[(4-chlorobenzyl)oxy]-2-fluorophenyl}-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.57-1.62 (2H, m), 2.03-2.09 (2H, m), 2.73 (2H, s), 3.09-3.14 (2H, m), 3.18-3.22 (2H, m), 5.06 (2H, s), 6.57 (1H, d, J = 7.5 Hz), 7.09 (1H, d, J = 11.5 Hz), 7.36 (2H, d, J = 8.5 Hz), 7.39 (2H, d, J = 8.5 Hz).

[0716]

Reference Example 429

6-[4-Chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.61-1.64 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.13-3.18 (2H, m), 3.22-3.26 (2H, m), 3.47 (3H, s), 3.77 (2H, t, J = 5.0 Hz), 4.14 (2H, t, J = 5.0 Hz), 6.66 (1H, d, J = 8.0 Hz), 7.06 (1H, d, J = 11.5 Hz).

[0717]

Reference Example 430

2-[2-Chloro-4-fluoro-5-(1-oxa-6-azaspiro[2.5]oct-6-yl)phenoxy]-N,N-dimethylethaneamine

To a solution of 4-chloro-5-[2-(dimethylamino)ethoxy]-2-fluoroaniline (4.46 g) in ethanol-water (45-30 mL) was added 1-benzyl-1-methyl-4-oxopiperidinium bromide (5.45 g), and the reaction mixture was stirred at 100 °C for 23 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off to give 1-(4-chloro-5-(2-(dimethylamino)ethoxy)-2-fluorophenyl)piperidin-4-one (ketone compound). To a solution of trimethylsulfoxonium iodide (4.22 g) in dimethyl sulfoxide (55 mL) was added sodium hydride (55 % in oil) (0.84 g), and the reaction mixture was stirred at room temperature for 30 min. The solution of the obtained ketone compound in dimethyl sulfoxide (8 mL) was added thereto, and the reaction mixture was stirred at room temperature for 2.5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate.

The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (NH silica gel; hexane/ethyl acetate) to provide the title compound (2.10 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.04-2.09 (2H, m), 2.36 (6H, s), 2.73 (2H, s), 2.77 (2H, t, J = 6.0 Hz), 3.13-3.18 (2H, m), 3.22-3.26 (2H, m), 4.08 (2H, t, J = 6.0 Hz), 6.61 (1H, d, J = 8.0 Hz), 7.06 (1H, d, J = 11.5 Hz).

[0718]

Reference Example 431

6-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethoxy]phenyl}-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.59-1.63 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.13-3.17 (2H, m), 3.21-3.25 (2H, m), 4.29-4.31 (2H, m), 4.33-4.35 (2H, m), 6.67 (1H, d, J = 7.5 Hz), 6.90 (2H, dd, J = 9.0 Hz, 2.5 Hz), 6.99 (2H, t, J = 9.0 Hz), 7.08 (1H, d, J = 11.5 Hz).

[0719]

Reference Example 432

6-(4-Chloro-2-fluoro-5-propoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.06 (3H, t, J = 7.5 Hz), 1.60-1.64 (2H, m), 1.81-1.88 (2H, m), 2.05-2.10 (2H, m), 2.73 (2H, s), 3.14-3.19 (2H, m), 3.22-3.26 (2H, m), 3.94 (2H, t, J = 6.5 Hz), 6.57 (1H, d, J = 7.5 Hz), 7.07 (1H, d, J = 11.5 Hz).

[0720]

Reference Example 433

6-[4-Chloro-2-fluoro-5-(propan-2-yl)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.22 (6H, d, J = 6.5 Hz), 1.62-1.66 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.16-3.26 (4H, m), 3.32 (1H, sep, J = 6.5 Hz), 6.88 (1H, d, J = 9.5 Hz), 7.04 (1H, d, J = 11.5 Hz).

[0721]

Reference Example 434

6-(4-Chloro-2-fluoro-5-propylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 0.96 (3H, t, J = 7.5 Hz), 1.56-1.65 (4H, m), 2.03-2.08 (2H, m), 2.62 (2H, t, J = 7.5 Hz), 2.73 (2H, s), 3.13-3.18 (2H, m), 3.20-3.25 (2H, m), 6.80 (1H, d, J = 9.5 Hz), 7.04 (1H, d, J = 12.0 Hz).

[0722]

Reference Example 435

6-[4-(Difluoromethoxy)-2,6-difluorophenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR (CDCl$_3$) δ ppm: 1.61-1.66 (2H, m), 1.92-1.97 (2H, m), 2.71 (2H, s), 3.17-3.24 (2H, m), 3.34-3.39 (2H, m), 6.45 (1H, t, J = 73.5 Hz), 6.66-6.72 (2H, m).

[0723]

Reference Example 436

6-(5,6-Dimethylpyridin-2-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.54-1.92 (2H, m), 1.85-1.93 (2H, m), 2.15 (3H, s), 2.37 (3H, s), 2.72 (2H, s), 3.55-3.62 (2H, m), 3.76-3.84 (2H, m), 6.45 (1H, d, J = 8.5 Hz), 7.21 (1H, d, J = 8.5 Hz).

[0724]

Reference Example 437

6-(2,4-Difluoro-5-methylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.66 (2H, m), 2.03-2.08 (2H, m), 2.21 (3H, s), 2.72 (2H, s), 3.10-3.19 (4H, m), 6.76 (1H, dd, J = 12.0 Hz, 9.5 Hz), 6.80 (1H, t, J = 8.5 Hz).

[0725]

Reference Example 438

6-(4-Chloro-2-fluoro-5-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 2.05-2.11 (2H, m), 2.74 (2H, s), 3.15-3.20 (2H, m), 3.24-3.28 (2H, m), 3.87 (3H, s), 6.57 (1H, d, J = 8.0 Hz), 7.08 (1H, d, J = 11.5 Hz).

[0726]

Reference Example 439

6-(4-Chloro-5-ethyl-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.5 Hz), 1.61-1.66 (2H, m), 2.03-2.08 (2H, m), 2.68 (2H, q, J = 7.5 Hz), 2.73 (2H, s), 3.14-3.19 (2H, m), 3.21-3.25 (2H, m), 6.83 (1H, d, J = 9.0 Hz), 7.04 (1H, d, J = 12.0 Hz).

[0727]

Reference Example 440

6-(2,2,6-Trifluoro-1,3-benzodioxol-5-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.05-2.10 (2H, m), 2.73 (2H, s), 3.09-3.18 (4H, m), 6.80 (1H, d, J = 7.0 Hz), 6.86 (1H, d, J = 10.0 Hz).

[0728]

Reference Example 441

6-[2-Chloro-4-(methylsulfanyl)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.59-1.64 (2H, m), 2.04-2.10 (2H, m), 2.46 (3H, s), 2.73 (2H, s), 3.09-3.18 (4H, m), 6.99-7.01 (1H, m), 7.12-7.15 (1H, m), 7.26-7.30 (1H, m).

[0729]

Reference Example 442

6-(5-Ethoxy-2,4-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.42 (3H, t, J = 7.0 Hz), 1.60-1.64 (2H, m), 2.04-2.09 (2H, m), 2.73 (2H, s), 3.10-3.15 (2H, m), 3.16-3.21 (2H, m), 4.07 (2H, q, J = 7.0 Hz), 6.65 (1H, t, J = 9.0 Hz), 6.85 (1H, t, J = 11.5 Hz).

[0730]

Reference Example 443

6-(2,4-Difluoro-5-methoxyphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.05-2.10 (2H, m), 2.73 (2H, s), 3.12-3.16 (2H, m), 3.18-3.22 (2H, m), 3.87 (3H, s), 6.65 (1H, t, J = 8.5 Hz), 6.86 (1H, t, J = 11.5 Hz).

[0731]

Reference Example 444

6-(4-Bromo-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 398.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.65 (2H, m), 1.91-1.97 (2H, m), 2.71 (2H, s), 3.19-3.23 (2H, m), 3.35-3.39 (2H, m), 7.00-7.05 (2H, m).

[0732]

Reference Example 445

6-(5-Ethyl-2,4-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.20 (3H, t, J = 7.5 Hz), 1.62-1.66 (2H, m), 2.03-2.08 (2H, m), 2.60 (2H, q, J = 7.5 Hz), 2.73 (2H, s), 3.11-3.20 (4H, m), 6.76 (1H, dd, J = 12.0 Hz, 10.0 Hz), 6.82 (1H, t, J = 9.0 Hz).

[0733]

Reference Example 446

6-{4-Chloro-2-fluoro-5-[2-(4-fluorophenoxy) ethyl]phenyl}-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.64 (2H, m), 2.03-2.08 (2H, m), 2.73 (2H, s), 3.11-3.18 (2H, m), 3.13 (2H, t, J = 7.0 Hz), 3.21-3.25 (2H, m), 4.12 (2H, t, J = 7.0 Hz), 6.80-6.84 (2H, m), 6.92 (1H, d, J = 9.0 Hz), 6.96 (2H, t, J = 8.5 Hz), 7.07 (1H, d, J = 12.0 Hz).

[0734]

Reference Example 447

6-(2,4-Difluoro-5-propylphenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 0.94 (3H, t, J = 7.5 Hz), 1.55-1.66 (4H, m), 2.03-2.08 (2H, m), 2.55 (2H, t, J = 7.5 Hz), 2.73 (2H, s), 3.11-3.19 (4H, m), 6.76 (1H, dd, J = 11.5 Hz, 9.5 Hz), 6.79 (1H, dd, J = 9.0 Hz, 8.0 Hz).

[0735]

Reference Example 448

6-[4-(Ethylsulfanyl)-2,6-difluorophenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.31 (3H, t, J = 7.5 Hz), 1.62-1.66 (2H, m), 1.90-1.96 (2H, m), 2.70 (2H, s), 2.90 (2H, q, J = 7.5 Hz), 3.19-3.25 (2H, m), 3.34-3.38 (2H, m), 6.78-6.84 (2H, m).

[0736]

Reference Example 449

6-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 398.

^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.66 (2H, m), 1.91-1.96 (2H, m), 2.71 (2H, s), 3.14-3.18 (2H, m), 3.31-3.35 (2H, m), 4.28 (2H, q, J = 8.0 Hz), 6.46-6.52 (2H, m).

[0737]

Reference Example 450

6-[4-Chloro-2-fluoro-5-(2-methoxyethyl)phenyl]-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 341.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.65 (2H, m), 2.02-2.08 (2H, m), 2.73 (2H, s), 2.94 (2H, t, J = 7.0 Hz), 3.14-3.19 (2H, m), 3.21-3.25 (2H, m), 3.36 (3H, s), 3.58 (2H, t, J = 7.0 Hz), 6.88 (1H, d, J = 9.5 Hz), 7.05 (1H, d, J = 12.0 Hz).

[0738]

Reference Example 451

6-(2,2-Difluoro-1,3-benzodioxol-5-yl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 398.

^{1}HNMR (CDCl$_3$) δ ppm: 1.60-1.65 (2H, m), 1.98-2.03 (2H, m), 2.73 (2H, s), 3.22-3.27 (2H, m), 3.29-3.34 (2H, m), 6.62 (1H, dd, J = 8.5 Hz, 2.0 Hz), 6.74 (1H, d, J = 2.0 Hz), 6.93 (1H, d, J = 8.5 Hz).

[0739]

Reference Example 452

6-(2-Bromo-4-chloro-6-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane

Synthesized analogous to Reference Example 398.

^{1}HNMR (DMSO-d6) δ ppm: 0.86-2.41 (4H, m), 2.71 (2H, s), 3.03 (2H, m), 3.27-3.44 (2H, m), 7.04 (1H, dd, J = 11.3 Hz, 2.4 Hz), 7.39 (1H, t, J = 2.0 Hz).

[0740]

Reference Example 453

tert-Butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidine-1-carboxylate

Under argon atmosphere, a solution of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (1.0 g), *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (1.30 g) and tripotassium phosphate (0.234 g) in N,N-dimethylformamide/2-propanol (1:1) (10 mL) was stirred at 70 °C for 48 h. To the reaction solution was added water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was washed with diethyl ether to provide the title compound (1.15 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.56-1.78 (4H, m), 1.99-2.08 (1H, m), 2.64 (2H, t, J = 7.7 Hz), 2.99 (2H, t, J = 7.7 Hz), 3.12-3.30 (2H, m), 3.79 (2H, s), 3.82-4.10 (2H, m), 6.46 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.56 (1H, brs).

[0741]

Reference Example 454

8-Fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 60.

^{1}HNMR ($CDCl_3$) δ ppm: 1.44-1.73 (5H, m), 2.02 (1H, brs), 2.61-2.68 (2H, m), 2.87-2.94 (2H, m), 2.97-3.09 (4H, m), 3.79 (2H, s), 6.47 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.4 Hz), 7.59 (1H, brs).

[0742]

Reference Example 455

tert-Butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 453.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.58-1.67 (2H, m), 1.67-1.74 (2H, m), 1.99 (1H, brs), 2.61-2.67 (2H, m), 2.83-2.89 (2H, m), 3.11-3.30 (2H, m), 3.74 (3H, s), 3.75 (2H, s), 3.79-4.05 (2H, m), 5.23 (2H, brs), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.78 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

[0743]

Reference Example 456

8-Fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

To a solution of *tert*-butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate (6.35 g) in ethyl acetate (60 mL) was added 4 N hydrochloric acid/ethyl acetate (60 mL), and the reaction mixture was stirred at room temperature for 4 h. The solvent was distilled off, and the residue was crystallized from ethyl acetate/ethanol to provide the title compound (5.15 g).

^{1}HNMR (DMSO-d6) δ ppm: 1.64-1.73 (2H, m), 1.85-1.94 (2H, m), 2.57-2.66 (2H, m), 2.86-2.94 (2H, m), 3.04-3.13 (2H, m), 3.13-3.21 (2H, m), 3.68 (3H, s), 3.75 (2H, s), 5.10 (2H, brs), 5.14 (1H, s), 6.69 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.78-6.83 (2H, m), 6.98 (1H, dd, J = 13.1 Hz, 9.2 Hz), 7.04-7.09 (2H, m), 8.45-8.71 (2H, m).

[0744]

Reference Example 457

8-Fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a suspension of 8-fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride (1.10 g) in ethyl acetate were added water and 5 N aqueous sodium hydroxide to make the reaction residue weakly basic, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was distilled of to provide the title compound (1.03 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.64-1.74 (4H, m), 1.95 (2H, brs), 2.62-2.67 (2H, m), 2.84-2.93 (4H, m), 3.00-3.07 (2H, m), 3.74 (3H, s), 3.75 (2H, s), 5.23 (2H, s), 6.51 (1H, dd, J = 9.0 Hz, 2.5 Hz), 6.76 (2H, d, J = 8.0 Hz), 6.83 (1H, dd, J = 12.5 Hz, 9.0 Hz), 7.12 (2H, d, J = 8.0 Hz).

[0745]

Reference Example 458

tert-Butyl 4-{[(8-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 453.

^{1}HNMR (CDCl$_3$) δ ppm: 1.47 (9H, s), 1.58-1.70 (2H, m), 1.70-1.76 (2H, m), 1.97 (1H, brs), 2.59-2.67 (2H, m), 2.99 (2H, t, J = 7.7 Hz), 3.12-3.30 (2H, m), 3.81 (2H, s), 3.82-4.10 (2H, m), 6.52 (1H, d, J = 8.9 Hz), 7.18 (1H, d, J = 8.9 Hz), 7.74 (1H, brs).

[0746]

Reference Example 459

8-Chloro-5-[(4-hydroxypiperidin-4-yl)methoxy]-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 60.

^{1}HNMR (CDCl$_3$) δ ppm: 1.55-2.20 (6H, m), 2.62 (2H, t, J = 7.7 Hz), 2.84-2.96 (2H, m), 2.96-3.11 (4H, m), 3.81 (2H, s), 6.53 (1H, d, J = 8.9 Hz), 7.18 (1H, d, J = 8.9 Hz), 7.78 (1H, brs).

[0747]

Reference Example 460

8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate

To a suspension of 8-fluoro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (10 g) in dichloromethane (100 mL) was added pyridine (4.03 mL), and to the mixture trifluoromethanesulfonic anhydride (6.70 mL) was added dropwise under ice-cooling and then the reaction mixture was stirred at the same temperature for 4 h. To the reaction solution was added water, and the solution was extracted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (12.8 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.68-2.73 (2H, m), 2.93-2.98 (2H, m), 3.75 (3H, s), 5.23 (2H, brs), 6.75-6.79 (2H, m), 6.92-7.00 (2H, m), 7.07-7.12 (2H, m).

[0748]

Reference Example 461

5-Amino-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere, a solution of 8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate (17.5 g), benzophenone imine (9.44 mL), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.89 g), palladium (II) acetate (0.453 g) and cesium carbonate (13.16 g) in toluene (170 mL) was heated to reflux for 12 h. After the reaction mixture was allowed to cool to room temperature, to the reaction solution was added basic silica gel (80 g), and the reaction mixture was filtered. The filtrate was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was dissolved in tetrahydrofuran (170 mL), and 1 N hydrochloric acid (80 mL) was added thereto. The mixture was stirred at room temperature for 1 h, 1 N aqueous sodium hydroxide (80 mL) and water was added thereto, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (basic silica gel; dichloromethane/ethyl acetate) to provide the title compound (9.74 g).

^{1}HNMR (CDCl$_3$) δ ppm: 2.60-2.70 (4H, m), 3.44 (2H, brs), 3.74 (3H, s), 5.20 (2H, brs), 6.36 (1H, dd, J = 8.8 Hz, 3.8 Hz), 6.70-6.78 (3H, m), 7.10-7.14 (2H, m).

[0749]

Reference Example 462

N-[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide

To acetic anhydride (7 mL) was added 5-amino-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (782 mg), and the reactoin mixture was stirred at room temperature for 15 min. To the reaction solution was added diethyl ether, and the precipitate was collected on a filter to provide the title compound (760 mg).

^{1}HNMR (DMSO-d6) δ ppm: 2.02 (3H, s), 2.47-2.62 (2H, m), 2.66-2.78 (2H, m), 3.68 (3H, s), 5.08 (2H, brs), 6.73-6.85 (2H, m), 6.95-7.13 (4H, m), 9.55 (1H, brs).

[0750]

Reference Example 463

8-Chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate

Synthesized analogous to Reference Example 460.

^{1}HNMR (DMSO-d6) δ ppm: 2.58-2.68 (2H, m), 2.81-2.89 (2H, m), 3.66 (3H, s), 5.27 (2H, brs), 6.70-6.79 (2H, m), 6.98-7.08 (2H, m), 7.22 (1H, d, J = 9.0 Hz), 7.46 (1H, d, J = 9.0 Hz).

[0751]

Reference Example 464

5-Amino-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 461.

^{1}HNMR (CDCl$_3$) δ ppm: 2.47-2.63 (4H, m), 3.58 (2H, brs), 3.73 (3H, s), 5.34 (2H, brs), 6.41 (1H, d, J = 8.7 Hz), 6.67-6.76 (2H, m), 7.01 (1H, d, J = 8.7 Hz), 7.03-7.10 (2H, m).

[0752]

Reference Example 465

N-[8-Chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide

Synthesized analogous to Reference Example 462.

^{1}HNMR (DMSO-d6) δ ppm: 2.02 (3H, brs), 2.42-2.54 (2H, m), 2.58-2.67 (2H, m), 3.67 (3H, s), 5.25 (2H, s), 6.71-6.79 (2H, m), 6.96-7.04 (2H, m), 7.15 (1H, d, J = 8.9 Hz), 7.23 (1H, d, J = 8.9 Hz), 9.58 (1H, brs).

[0753]

Reference Example 466

7,8-Difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate

Synthesized analogous to Reference Example 460.

^{1}HNMR (CDCl$_3$) δ ppm: 2.68-2.73 (2H, m), 2.89-2.97 (2H, m), 3.76 (3H, s), 5.24 (2H, brs), 6.76-6.81 (2H, m), 6.86 (1H, dd, J = 9.3 Hz, 6.1 Hz), 7.07-7.12 (2H, m).

[0754]

Reference Example 467

5-Amino-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 461.

^{1}HNMR (CDCl$_3$) δ ppm: 2.55-2.63 (2H, m), 2.63-2.71 (2H, m), 3.51 (2H, brs), 3.75 (3H, s), 5.21 (2H, brs), 6.24 (1H, dd, J = 11.3 Hz, 6.4 Hz), 6.71-6.81 (2H, m), 7.07-7.16 (2H, m).

[0755]

Reference Example 468

N-[7,8-Difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide

Synthesized analogous to Reference Example 462.

^{1}HNMR (CDCl$_3$) δ ppm: 2.18 (3H, s), 2.58-2.68 (2H, m), 2.68-2.76 (2H, m), 3.74 (3H, s), 5.22 (2H, s), 6.71-6.80 (2H, m), 6.90 (1H, brs), 7.07-7.14 (2H, m), 7.17 (1H, dd, J = 11.0 Hz, 6.9 Hz).

[0756]

Reference Example 469

2,2,2-Trifluoro-N-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide

To a solution of 5-amino-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (0.7 g) in dichloromethane (7 mL), trifluoroacetic anhydride (0.389 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 1.5 h. The solvent was distilled off, and the residue was washed with diisopropyl ether to provide the title compound (0.87 g).

^{1}HNMR (CDCl$_3$) δ ppm: 2.63-2.70 (2H, m), 2.70-2.76 (2H, m), 3.73 (3H, s), 5.23 (2H, brs), 6.73-6.78 (2H, m), 6.97 (1H, dd, J = 12.3 Hz, 8.9 Hz), 7.08-7.12 (2H, m), 7.15 (1H, dd, J = 8.9 Hz, 4.1 Hz), 7.69 (1H, brs).

[0757]

Reference Example 470

8-Fluoro-1-(4-methoxybenzyl)-5-(methylamino)-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere, to a solution of 2,2,2-trifluoro-N-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide (0.87 g) in N-methyl-2-pyrrolidone (8 mL) was added sodium hydride (55 % in oil) (0.105 g) under ice-cooling. The reaction mixture was stirred at the same temperature for 15 min, and methyl iodide (0.273 mL) was added dropwise thereto. The reaction mixture was stirred at room temperature for 15 h. To the reaction solution was added aqueous saturated ammonium chloride solution, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was dissolved in methanol/tetrahydrofuran (1:1) (16 mL), 5 N aqueous sodium hydroxide (1.32 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 2 h. The solvent was distilled off, and to the residue was added aqueous saturated ammonium chloride solution, and then the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.60 g).

^{1}HNMR (CDCl$_3$) δ ppm: 2.58-2.63 (2H, m), 2.63-2.68 (2H, m), 2.82 (3H, brs), 3.33 (1H, brs), 3.73 (3H, s), 5.21 (2H, brs), 6.32 (1H, dd, J = 9.0 Hz, 3.4 Hz), 6.72-6.77 (2H, m), 6.83 (1H, dd, J = 12.9 Hz, 9.0 Hz), 7.09-7.14 (2H, m).

[0758]

Reference Example 471

5-[{[1-(2,4-Dichlorophenyl)-4-hydroxypiperidin-4-yl]methyl} (methyl)amino]-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-fluoro-1-(4-methoxybenzyl)-5-(methylamino)-3,4-dihydroquinolin-2(1H)-one (0.61 g) in acetic acid (3 mL) was added a solution of 6-(2,4-dichlorophenyl)-1-oxa-6-azaspiro[2.5]octane (3.00 g) in acetic acid (3 mL), and the reaction mixture was stirred at 60 °C for 13 h. The solvent was distilled off and to the residue was added saturated aqueous sodium hydrogencarbonate, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.53 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.42-1.50 (2H, m), 1.60-1.69 (2H, m), 2.51 (1H, s), 2.60-2.67 (2H, m), 2.69 (3H, s), 2.87-2.95 (2H, m), 2.95-3.00 (2H, m), 3.00-3.06 (2H, m), 3.07 (2H, s), 3.69 (3H, s), 5.21 (2H, brs), 6.71-6.76 (2H, m), 6.84-6.95 (2H, m), 6.97 (1H, d, J = 8.6 Hz), 7.03-7.13 (2H, m), 7.17 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.34 (1H, d, J = 2.5 Hz).

[0759]

Reference Example 472

5-({[1-(2,4-Dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR (DMSO-d6) δ ppm: 1.71 (4H, brs), 2.58-2.61 (2H, m), 2.69-2.72 (2H, m), 2.90-3.10 (6H, m), 3.68 (3H, s), 4.50-4.60 (1H, m), 4.69 (1H, s), 5.08 (2H, brs), 6.41 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.78-6.89 (3H, m), 7.06 (2H, d, J = 8.7 Hz), 7.25 (1H, d, J = 11.1 Hz), 7.70 (1H, d, J = 7.8 Hz).

[0760]

Reference Example 473

5-({[1-(4-Chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR ($CDCl_3$) δ ppm: 1.68 (1H, s), 1.75-2.00 (4H, m), 2.68 (4H, s), 2.95-3.15 (4H, m), 3.15-3.30 (2H, m), 3.55-3.70 (1H, brs), 3.74 (3H, s), 5.22 (2H, brs), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.71-6.87 (4H, m), 7.03-7.18 (3H, m).

[0761]

Reference Example 474

5-({[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR ($CDCl_3$) δ ppm: 1.65-1.95 (5H, m), 2.68 (4H, s), 3.00-3.15 (4H, m), 3.28-3.44 (2H, m), 3.60-3.71 (1H, brs), 3.74 (3H, s), 5.21 (2H, brs), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.71-6.94 (5H, m), 7.13 (2H, d, J = 8.4 Hz).

[0762]

Reference Example 475

5-({[1-(2,4-Dichloro-6-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR (CDCl$_3$) δ ppm: 1.68-1.94 (5H, m), 2.68 (4H, s), 2.95-3.15 (4H, m), 3.30-3.45 (2H, m), 3.60-3.70 (1H, brs), 3.74 (3H, s), 5.21 (2H, brs), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.72-6.88 (3H, m), 6.96-7.02 (1H, m), 7.10-7.21 (3H, m).

[0763]

Reference Example 476

5-({[1-(2-Chloro-4,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.94 (5H, m), 2.68 (4H, m), 2.93-3.04 (2H, m), 3.11 (2H, brs), 3.29-3.43 (2H, m), 3.60-3.72 (1H, brs), 3.74 (3H, s), 5.21 (2H, brs), 6.41 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.69-6.88 (4H, m), 6.91-7.00 (1H, m), 7.08-7.17 (2H, m).

[0764]

Reference Example 477

5-[({1-[2-Chloro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}methyl)amino]-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR (CDCl$_3$) δ ppm: 1.80-1.96 (4H, m), 2.68 (4H, s), 2.98-3.19 (7H, m), 3.73 (3H, s), 5.21 (2H, s), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.73-6.86 (3H, m), 7.04-7.11 (5H, m).

[0765]

Reference Example 478

5-({[1-(4-Ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 6.9 Hz), 1.75-1.99 (5H, m), 2.60-2.75 (4H, m), 2.92-3.20 (6H, m), 3.60-3.80 (4H, m), 3.97 (2H, q, J = 6.9 Hz), 5.21 (2H, brs), 6.36-6.43 (1H, m), 6.57-6.68 (2H, m), 6.70-6.87 (3H, m), 6.89-6.99 (1H, m), 7.08-7.17 (2H, m).

[0766]

Reference Example 479

5-({[1-(2-Chloro-4-ethylphenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J = 7.8 Hz), 1.68-2.00 (5H, m), 2.58 (2H, q, H = 7.8 Hz), 2.68 (4H, brs), 2.94-3.07 (2H, m), 3.08-3.12 (4H, m), 3.62-3.89 (4H, m), 5.21 (2H, brs), 6.41 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.70-6.88 (3H, m), 6.96-7.25 (5H, m).

[0767]

Reference Example 480

8-Fluoro-5-[({1-[2-fluoro-4-(propan-2-yloxy)phenyl]-4-hydroxypiperidin-4-yl}methyl)amino]-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR (CDCl$_3$) δ ppm: 1.30 (6H, d, J = 6 Hz), 1.75-1.98 (4H, m), 2.25-2.50 (1H, brs), 2.55-2.75 (4H, m), 2.90-3.18 (6H, m), 3.50-3.80 (4H, m), 4.36-4.50 (1H, m), 5.19 (2H, brs), 6.37 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.54-6.98 (6H, m), 7.04-7.16 (2H, m).

[0768]

Reference Example 481

5-({[1-(2-Chloro-4-propylphenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR (CDCl$_3$) δ ppm: 0.92 (3H, t, J = 7.4 Hz), 1.60 (2H, sex, J = 7.4 Hz), 1.77-1.99 (4H, m), 2.22 (1H, brs), 2.50 (2H, t, J = 7.4 Hz), 2.58-2.73 (4H, m), 2.92-3.20 (6H, m), 3.60-3.80 (4H, m), 5.20 (2H, brs), 6.39 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.67-6.88 (3H, m), 6.94-7.05 (2H, m), 7.06-7.15 (2H, m), 7.16-7.20 (1H, m).

[0769]

Reference Example 482

8-Fluoro-5-({[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 471.

^{1}HNMR (CDCl$_3$) δ ppm: 1.74-1.92 (4H, m), 2.60-2.76 (4H, m), 2.98-3.05 (4H, m), 3.31-3.42 (2H, m), 3.65-3.80 (1H, m), 3.73 (3H, s), 5.16-5.28 (2H, m), 6.40 (1H, dd, J = 9.0 Hz, 3.6 Hz), 6.58-6.67 (2H, m), 6.72-6.78 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.0 Hz), 7.10-7.16 (2H, m).

[0770]

Reference Example 483

8-Chloro-5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of N-[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide (200 mg) and 6-(4-chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane (202 mg) in N,N-dimethylformamide/2-propanol (1:1) (2 mL) was added tripotassium phosphate (59.2 mg), and the mixture was stirred at 90 °C for 18 h. To the mixture was added sodium hydroxide (11.2 mg), and the mixture was stirred at 90 °C for 18 h. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (279 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.93 (4H, m), 2.33 (1H, brs), 2.53 (4H, brs), 2.97-3.25 (6H, m), 3.68 (3H, s), 3.92 (1H, brs), 5.31 (2H, brs), 6.43 (1H, d, J = 8.7 Hz), 6.63-6.72 (2H, m), 6.83-6.93 (1H, m), 6.98-7.11 (5H, m).

[0771]

Reference Example 484

8-Chloro-5-({[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 483.

^{1}HNMR ($CDCl_3$) δ ppm: 1.70-1.89 (4H, m), 2.32 (1H, brs), 2.54 (4H, m), 3.00-3.16 (4H, m), 3.30-3.44 (2H, m), 3.69 (3H, s), 3.96 (1H, brs), 5.32 (2H, brs), 6.43 (1H, d, J = 8.7 Hz), 6.65-6.72 (2H, m), 6.81-6.93 (2H, m), 7.01-7.13 (3H, m).

[0772]

Reference Example 485

8-Chloro-5-({[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of N-[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]acetamide (200 mg) and 6-(2,4-dichloro-5-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane (200 mg) in N,N-dimethylformamide/2-propanol (1:1) (2 mL) was added tripotassium phosphate (59.2 mg), and the reaction mixture was stirred at 90 °C for 16 h. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (324 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.76-1.94 (4H, m), 2.30 (1H, brs), 2.53 (4H, brs), 2.92-3.20 (6H, m), 3.68 (3H, s), 3.92 (1H, brs), 5.32 (2H, s), 6.44 (1H, d, J = 9.0 Hz), 6.66-6.70 (2H, m), 6.85 (1H, d, J = 10.5 Hz), 7.00-7.13 (3H, m), 7.37 (1H, d, J = 7.8 Hz).

[0773]

Reference Example 486

8-Chloro-5-({[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 483.

^{1}HNMR (DMSO-d6) δ ppm: 1.29 (3H, t, J = 6.9 Hz), 1.60-1.78 (4H, m), 2.55-2.65 (2H, m), 2.89-2.98 (4H, m), 3.04 (2H, d, J = 5.7 Hz), 3.17-3.23 (2H, m), 3.67 (3H, s), 3.96 (2H,q, J = 6.9 Hz), 4.50 (1H, brs), 4.72-4.75 (1H, m), 5.23 (2H, brs), 6.50 (1H, d, J = 8.7 Hz), 6.62-6.71 (2H, m), 6.72-6.79 (2H, m), 6.94-7.08 (4H, m).

[0774]

Reference Example 487

8-Chloro-5-({[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 483.

^{1}HNMR ($CDCl_3$) δ ppm: 1.71-1.89 (4H, m), 2.38 (1H, brs), 2.54 (4H, brs), 2.93-3.06 (2H, m), 3.11 (2H, brs), 3.30-3.44 (2H, m), 3.69 (3H, s), 3.97 (1H, brs), 5.32 (2H, s), 6.43 (1H, d, J = 9.0 Hz), 6.55-6.72 (4H, m), 7.01-7.12 (3H, m).

[0775]

Reference Example 488

8-Chloro-5-({[1-(4-chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 485.

^{1}HNMR ($CDCl_3$) δ ppm: 1.72-1.92 (4H, m), 2.10 (1H, brs), 2.54 (4H, brs), 2.98-3.28 (6H, m), 3.70 (3H, s), 3.90 (1H, brs), 5.32 (2H, brs), 6.44 (1H, d, J = 8.7 Hz), 6.66-6.80 (3H, m), 7.01-7.12 (4H, m).

[0776]

Reference Example 489

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 485.

^{1}HNMR (CDCl$_3$) δ ppm: 1.77-1.86 (2H, m), 1.86-1.97 (2H, m), 2.56-2.72 (4H, m), 2.98-3.10 (2H, m), 3.15-3.26 (2H, m), 3.75 (3H, s), 3.77-3.83 (1H, m), 5.22 (1H, brs), 6.27 (1H, dd, J = 12.4 Hz, 6.3 Hz), 6.71-6.81 (2H, m), 6.87-6.95 (1H, m), 7.01-7.08 (2H, m), 7.09-7.17 (2H, m).

[0777]

Reference Example 490

5-({[1-(4-Bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}amino)-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 485.

^{1}HNMR (CDCl$_3$) δ ppm: 1.74-1.95 (4H, m), 2.57-2.74 (4H, m), 2.97-3.09 (4H, m), 3.16-3.26 (2H, m), 3.75 (3H, s), 3.77-3.83 (1H, m), 5.22 (2H, brs), 6.27 (1H, dd, J = 12.4 Hz, 6.3 Hz), 6.73-6.79 (2H, m), 6.86 (1H, t, J = 8.6 Hz), 7.09-7.16 (2H, m), 7.17-7.22 (2H, m).

[0778]

Reference Example 491

5-{[1-(2-Chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: 1.85-1.88 (2H, m), 1.93-1.99 (2H, m), 2.06 (1H, brs), 2.65-2.68 (2H, m), 2.89-2.92 (2H, m), 3.07-3.12 (2H, m), 3.21-3.23 (2H, m), 3.74 (3H, s), 3.83 (2H, s), 5.24 (2H, brs), 6.54 (1H, dd, J = 9.0, 3.0 Hz), 6.76 (2H, d, J = 8.5 Hz), 6.85 (1H, dd, J = 12.5H, 9.0 Hz), 6.97 (1H, dt, J = 1.5 Hz, 8.0 Hz), 7.10 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.13 (2H, d, J = 8.5 Hz), 7.23 (1H, dt, J = 1.5 Hz, 8.0 Hz), 7.37 (1H, dd, J = 8.0 Hz, 1.5 Hz).

[0779]

Reference Example 492

5-{[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one

A solution of 5-[(3,5-dimethylbenzyl)oxy]-8-fluoro-1-(4-methoxybenzyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,4-dihydroquinolin-2(1H)-one (630 mg), potassium carbonate (335 mg) and 10 % palladium on carbon (300 mg) in 2-propanol (15ml) was stirred at room temperature for 1 h under hydrogen atmosphere. The reaction solution was filtrated and to the filtrate were added sodium hydroxide (445 mg), N,N-dimethylformamide (15 mL) and 6-(4-chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octane (740 mg), then the solution was stirred at 70 °C for 19.5 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (370 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.70 (4H, m), 1.80-2.00 (6H), 2.60-2.65 (2H, m), 2.79-2.84 (2H, m), 3.04-3.13 (2H, m), 3.20-3.24 (3H, m), 3.52-3.62 (1H, m), 3.70-3.90 (6H,m), 5.21 (2H, s), 5.33 (1H, s), 6.51 (1H, d, J = 6.0 Hz), 6.74-6.79 (2H, m), 6.88-6.95 (1H, m), 7.01-7.07 (2H, m), 7.11-7.15 (2H, m).

[0780]

Reference Example 493

1-(4-Chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidin-4-ol

Synthesized analogous to Reference Example 453.

^{1}HNMR ($CDCl_3$) δ ppm: 1.86-1.93 (2H, m), 1.93-2.02 (2H, m), 2.10 (1H, s), 3.07-3.15 (2H, m), 3.47-3.56 (2H, m), 4.00 (2H, s), 4.12 (3H, s), 6.65 (1H, dd, J = 8.7 Hz, 3.4 Hz), 6.85-6.93 (2H, m), 6.95 (1H, d, J = 9.1 Hz), 7.24 (1H, dd, J = 10.6 Hz, 8.7 Hz), 8.37 (1H, dd, J = 9.1 Hz, 1.6 Hz).

[0781]

Reference Example 494

1-(4-Chloro-2-fluorophenyl)-4-{[(8-fluoro-2-methoxyquinolin-5-yl)oxy]methyl}piperidin-4-ol

Synthesized analogous to Reference Example 453.

^{1}HNMR ($CDCl_3$) δ ppm: 1.92-1.98 (2H, m), 1.98-2.06 (2H, m), 2.08 (1H, s), 3.11-3.19 (2H, m), 3.23-3.31 (2H, m), 4.00 (2H, s), 4.12 (3H, s), 6.65 (1H, dd, J = 8.6 Hz, 3.4 Hz), 6.92-6.98 (2H, m), 7.03-7.09 (2H, m), 7.24 (1H, dd, J = 10.5 Hz, 8.6 Hz), 8.37 (1H, dd, J = 9.1 Hz, 1.6 Hz).

[0782]

Reference Example 495

tert-Butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate

A solution of 8-fluoro-5-hydroxy-3,4-dihydroquinolin-2(1H)-one (4.66 g), *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2H)-carboxylate (5.95 g) and potassium carbonate (3.55 g) in N-methyl-2-pyrrolidone (100 mL) was stirred at 80 °C for 4 h. To the reaction solution were added water (400 mL) and ethyl acetate (100 mL) and the solution was stirred at room temperature for 20 min. The precipitated crystal was collected on a filter and washed with ethyl acetate to provide the title compound (8.48 g).

^{1}HNMR (DMSO-d6) δ ppm: 1.41 (9H, s), 2.08-2.15 (2H, m), 2.42-2.48 (2H, m), 2.82-2.89 (2H, m), 3.40-3.48 (2H, m), 3.81-3.91 (2H), 4.41-4.47 (2H, m), 5.65-5.82 (1H, m), 6.60 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.2 Hz), 10.01 (1H, brs).

[0783]

Reference Example 496

tert-Butyl 4-{[(8-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate

To a solution of *tert*-butyl 4-{[(8-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidine-1-carboxylate (13.7 g) in acetonitrile (180 mL) were added N,N,N',N'-tetramethyl-1,3-diaminopropane (31.8 mL) and methanesulfonyl chloride (7.74 mL), and the solution was stirred at room temperature overnight. The reaction solution was poured into water, and the precipitate was collected on a filter. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (10.7 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.48 (9H, s), 2.14-2.24 (2H, m), 2.59-2.64 (2H, m), 2.97-3.02 (2H, m), 3.52-3.59 (2H, m), 3.92-3.98 (2H), 4.42-4.48 (2H, m), 5.76-5.84 (1H, m), 6.51 (1H, d, J = 9.0 Hz), 7.16 (1H, d, J = 9.0 Hz), 7.75 (1H, brs).

[0784]

Reference Example 497

tert-Butyl 4-{[(8-chloro-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate

Synthesized analogous to Reference Example 495.

^{1}HNMR (CDCl$_3$) δ ppm: 1.48 (9H, s), 2.15-2.22 (2H, m), 2.60-2.63 (2H, m), 2.93-2.97 (2H, m), 3.55-3.57 (2H, m), 3.93-3.99 (2H, m), 4.40 (2H, brs), 5.72-5.84 (1H, m), 6.43 (1H, d, J = 10.9 Hz), 7.75 (1H, brs).

[0785]

Reference Example 498

tert-Butyl 4-{[(7,8-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate

Synthesized analogous to Reference Example 495.

^{1}HNMR (CDCl$_3$) δ ppm: 1.48 (9H, s), 2.13-2.24 (2H, m), 2.60-2.64 (2H, m), 2.93-2.96 (2H, m), 3.52-3.60 (2H, m), 3.92-3.99 (2H, m), 4.37 (2H, brs), 5.71-5.87 (1H, m), 6.37 (1H, dd, J = 12.0 Hz, 6.3 Hz), 7.58 (1H, brs).

[0786]

Reference Example 499

tert-Butyl (3S*,4S*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

To a solution of *tert*-butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate (0.38 g) in acetone (3 mL)-water (1 mL) were added aqueous solution of 4.8 M N-methylmorpholine-N-oxide (0.42 mL) and aqueous solution of 4 % osmium tetraoxide (0.01 mL) and the reaction mixture was stirred at room temperature for 6 days. The solvent was distilled off, and the obtained crude crystal was washed with ethyl acetate to provide the title compound (0.36 g).

^{1}HNMR (DMSO-d6) δ ppm: 1.40 (9H, s), 1.54-1.73 (2H, m), 2.44 (2H, t, J = 7.6 Hz), 2.74-3.09 (4H, m), 3.46-3.55 (1H, m), 3.62 (1H, d, J = 8.8 Hz), 3.66-3.85 (2H, m), 3.98 (1H, d, J = 8.8 Hz), 4.58 (1H, brs), 4.92-5.01 (1H, m), 6.54 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.01 (1H, t, J = 9.4 Hz), 10.01 (1H, brs).

[0787]

Reference Example 500

tert-Butyl (3R,4R)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

To a suspension of *tert*-butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate (0.753 g) and AD-Mix-beta (2.8 g) in acetone (25 mL) was added water (15 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added aqueous saturated sodium sulfite under ice-cooling, and the solution was stirred for 10 min. Then the solution was extracted with ethyl acetate, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate), and recrystallized from ethanol to provide the title compound (347 mg, over 99 % ee).

^{1}HNMR (CDCl$_3$) δ ppm: 1.47 (9H, s), 1.69-1.75 (1H, m), 1.83-1.86 (1H, m), 2.36-2.37 (1H, m), 2.51-2.60 (1H, m), 2.64 (2H, t, J = 7.7 Hz), 2.91-3.00 (3H, m), 3.01-3.20 (1H, m), 3.68-4.17 (5H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.51 (1H, brs).

[0788]

Reference Example 501

tert-Butyl (3S,4S)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

A solution of *tert*-butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate (200 mg) and AD-Mix-alpha (743 mg) in acetone/water = (2: 1) (10 mL) was stirred at room temperature overnight, and the reaction solution was treated in a manner analogous to Reference Example 500 to provide the title compound (131 mg, 90 % ee).

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.69-1.75 (1H, m), 1.83-1.86 (1H, m), 2.26-2.39 (1H, m), 2.52-2.60 (1H, m), 2.64 (2H, t, J = 7.6 Hz), 2.91-3.20 (4H, m), 3.71-4.19 (5H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.93 (1H, t, J = 9.4 Hz), 7.50 (1H, brs).

[0789]

Reference Example 502

tert-Butyl (3R,4R)-4-{[(8-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 500.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.71-1.77 (1H, m), 1.83-1.86 (1H, m), 2.37-2.69 (4H, m), 2.87-3.02 (3H, m), 3.03-3.20 (1H, m), 3.69-4.17 (5H, m), 6.55 (1H, d, J = 8.9 Hz), 7.19 (1H, t, J = 8.9 Hz), 7.76 (1H, brs).

[0790]

Reference Example 503

tert-Butyl (3S,4S)-4-{[(8-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 501.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.71-1.77 (1H, m), 1.83-1.86 (1H, m), 2.36-2.68 (4H, m), 2.86-3.02 (3H, m), 3.03-3.20 (1H, m), 3.67-4.19 (5H, m), 6.55 (1H, d, J = 9.0 Hz), 7.18 (1H, t, J = 8.9 Hz), 7.74 (1H, brs).

[0791]

Reference Example 504

tert-Butyl (3R*,4R*)-4-{[(8-chloro-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

To a solution of *tert*-butyl 4-{[(8-chloro-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate (250 mg) in tetrahydrofuran/water (3: 1) (4 mL) were added Osmium Oxide, Immobilized Catalyst I (content: 7 %) (110 mg) and N-methylmorpholine N-oxide (0.254 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added aqueous saturated sodium sulfite under ice-cooling, insoluble materials were filtered off, and the filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (249 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.71-1.77 (1H, m), 1.83-1.85 (1H, m), 2.20-2.57 (2H, m), 2.62 (2H, t, J = 7.7 Hz), 2.88-3.01 (3H, m), 3.02-3.19 (1H, m), 3.69-4.17 (5H, m), 6.47 (1H, d, J = 10.6 Hz), 7.75 (1H, brs).

[0792]

Reference Example 505

tert-Butyl (3R,4R)-4-{[(8-chloro-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 500.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.71-1.77 (1H, m), 1.83-1.85 (1H, m), 2.20-2.57 (2H, m), 2.60-2.63 (2H, m), 2.88-3.01 (3H, m), 3.02-3.19 (1H, m), 3.69-4.17 (5H, m), 6.47 (1H, d, J = 10.6 Hz), 7.75 (1H, brs).

[0793]

Reference Example 506

tert-Butyl (3R,4R)-4-{[(7,8-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 500.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.70-1.76 (1H, m), 1.82-1.85 (1H, m), 2.28-2.69 (4H, m), 2.85-3.21 (4H, m), 3.68-4.20 (5H, m), 6.41 (1H, dd, J = 11.8 Hz, 6.3 Hz), 7.61 (1H, brs).

[0794]

Reference Example 507

tert-Butyl (3R*,4R*)-4-{[(7,8-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 504.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.70-1.77 (1H, m), 1.82-1.85 (1H, m), 2.28-2.79 (4H, m), 2.83-3.21 (4H, m), 3.68-4.20 (5H, m), 6.41 (1H, dd, J = 11.8 Hz, 6.3 Hz), 7.71 (1H, brs).

[0795]

Reference Example 508

5-{[(3S*,4S*)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one hydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.80 (1H, m), 1.95-2.07 (1H, m), 2.47 (2H, t, J = 8.0 Hz), 2.83-3.16 (6H, m), 3.66 (1H, d, J = 8.8 Hz), 3.85-3.95 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 5.07 (1H, brs), 5.34-5.44 (1H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.5 Hz), 8.63-8.83 (2H, m), 10.04 (1H, brs).

[0796]

Reference Example 509

5-{[(3R,4R)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one hydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.77 (1H, m), 1.99-2.05 (1H, m), 2.45-2.48 (2H, m), 2.85-3.12 (6H, m), 3.66 (1H, d, J = 8.8 Hz), 3.90-3.93 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 4.97-5.22 (1H, m), 5.28-5.51 (1H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.7 Hz), 7.03 (1H, t, J = 9.7 Hz), 8.73-8.96 (2H, m), 10.06 (1H, brs).

[0797]

Reference Example 510

5-{[(3R,4R)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 60.

^{1}HNMR (DMSO-d6) δ ppm: 1.49-1.55 (1H, m), 1.62-1.72 (1H, m), 1.80-2.10 (1H, broad signal), 2.43-2.49 (2H, m), 2.54-2.62 (2H, m), 2.62-2.75 (2H, m), 2.82-2.95 (2H, m), 3.47-3.54 (1H, m), 3.54 (1H, d, J = 8.7 Hz), 3.96 (1H, d, J = 8.7 Hz), 4.20 (1H, s), 4.50 (1H, d, J = 6.5 Hz), 6.54 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.00 (1H, t, J = 9.7 Hz), 10.02 (1H, brs).

[0798]

Reference Example 511

5-{[(3S,4S)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one hydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.74-1.77 (1H, m), 1.99-2.05 (1H, m), 2.45-2.48 (2H, m), 2.85-3.12 (6H, m), 3.66 (1H, d, J = 8.8 Hz), 3.90-3.93 (1H, m), 4.04 (1H, d, J = 8.8 Hz), 4.41-5.77 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.6 Hz), 7.02 (1H, t, J = 9.7 Hz), 8.76-9.00 (2H, m), 10.05 (1H, brs).

[0799]

Reference Example 512

tert-Butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,6-dihydropyridine-1(2H)-carboxylate

Synthesized analogous to Reference Example 495.

^{1}HNMR (CDCl$_3$) δ ppm: 1.47 (9H, s), 2.13-2.23 (2H, m), 2.59-2.67 (2H, m), 2.83-2.92 (2H, m), 3.49-3.60 (2H, m), 3.74 (3H, s), 3.89-3.99 (2H, m), 4.32-4.39 (2H, m), 5.22 (2H, brs), 5.70-5.80 (1H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.71-6.78 (2H, m), 6.81 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

[0800]

Reference Example 513

tert-Butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 499.

^{1}HNMR (CDCl$_3$) δ ppm: 1.47 (9H, s), 1.64-1.75 (1H, m), 1.78-1.87 (1H, m), 2.26-2.35 (1H, m), 2.48-2.56 (1H, m), 2.61-2.68 (2H, m), 2.76-3.00 (3H, m), 3.01-3.18 (1H, m), 3.74 (3H, s), 3.75-3.83 (1H, m), 3.84-3.98 (3H, m), 3.99-4.16 (1H, m), 5.16-5.30 (2H, m), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.72-6.79 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.2 Hz), 7.09-7.16 (2H, m).

[0801]

Reference Example 514

tert-Butyl (3R,4R)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 500.

^{1}HNMR (CDCl$_3$) δ ppm: 1.47 (9H, s), 1.67-1.73 (1H, m), 1.81-1.84 (1H, m), 2.38-2.39 (1H, m), 2.51-2.68 (3H, m), 2.78-3.18 (4H, m), 3.71-3.82 (4H, m), 3.85-4.18 (4H, m), 5.18-5.27 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz).

[0802]

Reference Example 515

tert-Butyl (3S,4S)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 501.

^{1}HNMR (CDCl$_3$) δ ppm: 1.46 (9H, s), 1.67-1.74 (1H, m), 1.81-1.84 (1H, m), 2.35-2.68 (4H, m), 2.78-3.19 (4H, m), 3.71-4.18 (8H, m), 5.18-5.27 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.6 Hz).

[0803]

Reference Example 516

tert-Butyl (3R,4R)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 43.

^{1}HNMR (CDCl$_3$) δ ppm: 1.46 (9H, s), 1.68-1.74 (1H, m), 1.81-1.84 (1H, m), 2.29 (1H, d, J = 6.2 Hz), 2.46-2.78 (5H, m), 2.84-3.19 (2H, m), 3.65-4.17 (8H, m), 5.34-5.41 (2H, m), 6.59 (1H, d, J = 9.0 Hz), 6.71-6.74 (2H, m), 7.07 (2H, d, J = 8.6 Hz), 7.15 (1H, d, J = 8.9 Hz).

[0804]

Reference Example 517

tert-Butyl (3S,4S)-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 43.

^{1}HNMR (CDCl$_3$) δ ppm: 1.46 (9H, s), 1.67-1.74 (1H, m), 1.81-1.84 (1H, m), 2.27 (1H, d, J = 6.2 Hz), 2.46-2.78 (5H, m), 2.84-3.19 (2H, m), 3.65-4.17 (8H, m), 5.34-5.41 (2H, m), 6.59 (1H, d, J = 9.0 Hz), 6.71-6.74 (2H, m), 7.05-7.08 (2H, m), 7.15 (1H, d, J = 8.9 Hz).

[0805]

Reference Example 518

tert-Butyl (3R,4R)-4-({[8-chloro-7-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 43.

^{1}HNMR (CDCl$_3$) δ ppm: 1.46 (9H, s), 1.69-1.75 (1H, m), 1.81-1.84 (1H, m), 2.19-2.74 (6H, m), 2.84-3.21 (2H, m), 3.63-4.19 (8H, m), 5.35-5.42 (2H, m), 6.53 (1H, d, J = 10.5 Hz), 6.72-6.75 (2H, m), 7.06 (2H, d, J = 8.6 Hz).

[0806]

Reference Example 519

tert-Butyl (3R*,4R*)-4-({[8-chloro-7-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 43.

^{1}HNMR (CDCl$_3$) δ ppm: 1.46 (9H, s), 1.68-1.75 (1H, m), 1.81-1.83 (1H, m), 2.18-2.24 (1H, m), 2.40-2.73 (5H, m), 2.84-3.21 (2H, m), 3.63-4.19 (8H, m), 5.35-5.42 (2H, m), 6.53 (1H, d, J = 10.5 Hz), 6.72-6.75 (2H, m), 7.05-7.07 (2H, m).

[0807]

Reference Example 520

tert-Butyl (3R,4R)-4-({[7,8-difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 43.

^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.68-1.74 (1H, m), 1.80-1.83 (1H, m), 2.21-2.70 (4H, m), 2.73-2.86 (2H, m), 2.86-3.22 (2H, m), 3.63-4.19 (8H, m), 5.19-5.27 (2H, m), 6.46 (1H, dd, J = 11.4 Hz, 5.9 Hz), 6.76-6.79 (2H, m), 7.12 (2H, d, J = 8.6 Hz).

[0808]

Reference Example 521

tert-Butyl (3R*,4R*)-4-({[7,8-difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 43.

^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.68-1.74 (1H, m), 1.80-1.83 (1H, m), 2.21-2.70 (4H, m), 2.73-2.86 (2H, m), 2.86-3.22 (2H, m), 3.63-4.19 (8H, m), 5.19-5.27 (2H, m), 6.46 (1H, dd, J = 11.5 Hz, 5.9 Hz), 6.76-6.79 (2H, m), 7.12 (2H, d, J = 8.6 Hz).

[0809]

Reference Example 522

5-{[(3S*,4S*)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.70-1.80 (1H, m), 1.95-2.07 (1H, m), 2.56-2.65 (2H, m), 2.81-3.16 (6H, m), 3.65 (1H, d, J = 8.8 Hz), 3.68 (3H, s), 3.86-3.95 (1H, m), 4.02 (1H, d, J = 8.8 Hz), 5.00-5.20 (3H, m), 5.40 (1H, brs), 6.67 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.77-6.84 (2H, m), 6.99 (1H, dd, J = 13.1 Hz, 9.1 Hz), 7.04-7.11 (2H, m), 8.91 (2H, brs).

[0810]

Reference Example 523

5-{[(3S*,4S*)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 457.

^{1}HNMR ($CDCl_3$) δ ppm: 1.66-1.76 (1H, m), 1.78-1.87 (1H, m), 1.96-2.44 (2H, br), 2.59-2.68 (2H, m), 2.75-3.02 (6H, m), 3.73 (3H, s), 3.74-3.80 (1H, m), 3.85-3.93 (2H, m), 5.15-5.30 (2H, m), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.72-6.78 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.16 (2H, m).

[0811]

Reference Example 524

5-{[(3R,4R)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of *tert*-butyl (3R,4R)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate (2.89 g) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL), and the reaction mixture was stirred at room temperature for 3 h. To the reaction solution was added 5 N aqueous sodium hydroxide, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off to provide the title compound (1.84 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.69-1.78 (1H, m), 1.82-1.86 (1H, m), 2.62-2.65 (2H, m), 2.80-3.02 (6H, m), 3.71-3.95 (6H, m), 5.17-5.26 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.74-6.76 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.12 (2H, d, J = 8.5 Hz).

[0812]

Reference Example 525

5-{[(3S,4S)-3,4-Dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 524.

^{1}HNMR ($CDCl_3$) δ ppm: 1.73-1.78 (1H, m), 1.82-1.86 (1H, m), 2.56-2.66 (2H, m), 2.79-3.06 (6H, m), 3.71-3.92 (6H, m), 5.17-5.26 (2H, m), 6.52 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.74-6.76 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.11 (2H, d, J = 8.5 Hz).

[0813]

Reference Example 526

5-{[(3S*,4S*)-1-(2,4-Dichlorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere, to a solution of 5-{[(3S*,4S*)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride (0.37 g), 1-bromo-2,4-dichlorobenzene (0.20 g), triethylamine (0.27 mL) and sodium *tert*-butoxide (0.18 g) in toluene (3 mL) were added 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (15 mg) and tris(dibenzylideneacetone)dipalladium (0) (7 mg), and the reaction mixture was stirred while heating at 100 °C overnight. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (40 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.94-2.00 (2H, m), 2.44-2.51 (1H, m), 2.61-2.71 (3H, m), 2.80-2.96 (3H, m), 2.97-3.14 (2H, m), 3.24-3.33 (1H, m), 3.74 (3H, s), 3.94 (1H, d, J = 9.2 Hz), 4.00-4.08 (2H, m), 5.15-5.34 (2H, m), 6.56 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.67-6.80 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.00 (1H, d, J = 8.6 Hz), 7.09-7.16 (2H, m), 7.20 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.4 Hz).

[0814]

Reference Example 527

5-{[(3S*,4S*)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: 1.93-2.00 (2H, m), 2.42-2.50 (1H, m), 2.58-2.70 (3H, m), 2.79-2.97 (3H, m), 3.00-3.10 (1H, m), 3.12-3.22 (1H, m), 3.30-3.39 (1H, m), 3.74 (3H, s), 3.94 (1H, d, J = 9.1 Hz), 3.97-4.07 (2H, m), 5.14-5.32 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.81-6.95 (2H, m), 7.02-7.09 (2H, m), 7.10-7.16 (2H, m).

[0815]

Reference Example 528

2-[(3R,4R)-4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidin-1-yl]-5-iodopyridine-3-carbonitrile

A solution of 2-chloro-5-iodopyridine-3-carbonitrile (0.675 g), 5-{[(3R,4R)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (1 g) and potassium carbonate (0.642 g) in N-methyl-2-pyrrolidone (20 mL) was stirred at

100 °C overnight. The reaction solution was poured into water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (678 mg).

^{1}HNMR (CDCl$_3$) δ ppm: 1.85-1.92 (1H, m), 1.96-2.00 (1H, m), 2.62-2.65 (2H, m), 2.77-2.87 (2H, m), 2.89-3.04 (2H, m), 3.26-3.30 (1H, m), 3.43-3.48 (1H, m), 3.74 (3H, s), 3.90-4.00 (3H, m), 4.15-4.20 (1H, m), 4.25-4.29 (1H, m), 5.18-5.27 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.98 (1H, d, J = 2.4 Hz), 8.46 (1H, d, J = 2.3 Hz).

[0816]

Reference Example 529

2-[(3S,4S)-4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidin-1-yl]-5-iodopyridine-3-carbonitrile

Synthesized analogous to Reference Example 528.

^{1}HNMR (CDCl$_3$) δ ppm: 1.85-1.91 (1H, m), 1.95-1.99 (1H, m), 2.62-2.65 (2H, m), 2.77-2.87 (2H, m), 2.89-3.04 (2H, m), 3.26-3.30 (1H, m), 3.42-3.48 (1H, m), 3.74 (3H, s), 3.90-4.00 (3H, m), 4.15-4.20 (1H, m), 4.25-4.29 (1H, m), 5.18-5.27 (2H, m), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.77 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.98 (1H, d, J = 2.3 Hz), 8.46 (1H, d, J = 2.3 Hz).

[0817]

Reference Example 530

tert-Butyl (3S*,4S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

To a solution of *tert*-butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate (5.31 g) in N,N-dimethylformamide (10 mL) were added imidazole (2.72 g) and *tert*-butyl dimethylchlorosilane (3.01 g) at 0 °C, and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water, 2 M citric acid solution and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (5.5 g).

^{1}HNMR (CDCl$_3$) δ ppm: -0.15 (3H, s), 0.08 (3H, s), 0.83 (9H, s), 1.48 (9H, s), 1.67-1.75 (1H, m), 1.82-1.99 (1H, m), 2.42-2.68 (3H, m), 2.70-3.18 (4H, m), 3.55 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.77-4.15 (4H, m), 5.14-5.32 (2H, m), 6.45 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.0 Hz), 7.08-7.15 (2H, m).

[0818]

Reference Example 531

tert-Butyl (3R,4R)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 530.

^{1}HNMR (CDCl$_3$) δ ppm: -0.14 (3H, s), 0.08 (3H, s), 0.83 (9H, s), 1.48 (9H, s), 1.67-1.76 (1H, m), 1.82-2.00 (1H, m), 2.42-2.68 (3H, m), 2.70-3.18 (4H, m), 3.55 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.78-4.16 (4H, m), 5.16-5.29 (2H, m), 6.45 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.07-7.15 (2H, m).

[0819]

Reference Example 532

tert-Butyl (3S,4S)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 530.

^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.08 (3H, s), 0.83 (9H, s), 1.48 (9H, s), 1.67-1.76 (1H, m), 1.81-1.99 (1H, m), 2.42-2.69 (3H, m), 2.70-3.18 (4H, m), 3.55 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.77-4.16 (4H, m), 5.14-5.31 (2H, m), 6.45 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.07-7.16 (2H, m).

[0820]

Reference Example 533

tert-Butyl (3R,4R)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 530.

^{1}HNMR ($CDCl_3$) δ ppm: -0.18 (3H, s), 0.07 (3H, brs), 0.83 (9H, s), 1.47 (9H, s), 1.69-1.72 (1H, m), 1.80-1.98 (1H, m), 2.42-3.15 (7H, m), 3.56 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.77-4.17 (4H, m), 5.32 (1H, d, J = 15.3 Hz), 5.43 (1H, d, J = 15.2 Hz), 6.52 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 7.05 (2H, d, J = 8.6 Hz), 7.14 (1H, d, J = 8.9 Hz).

[0821]

Reference Example 534

tert-Butyl (3S,4S)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[8-chloro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 530.

^{1}HNMR (CDCl$_3$) δ ppm: -0.18 (3H, s), 0.07 (3H, brs), 0.83 (9H, s), 1.47 (9H, s), 1.69-1.72 (1H, m), 1.80-1.98 (1H, m), 2.42-3.15 (7H, m), 3.56 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.77-4.17 (4H, m), 5.32 (1H, d, J = 14.7 Hz), 5.43 (1H, d, J = 15.2 Hz), 6.52 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 7.05 (2H, d, J = 8.7 Hz), 7.14 (1H, d, J = 8.9 Hz).

[0822]

Reference Example 535

tert-Butyl (3R,4R)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[8-chloro-7-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 530.

^{1}HNMR (CDCl$_3$) δ ppm: -0.17 (3H, s), 0.07 (3H, brs), 0.84 (9H, s), 1.47 (9H, s), 1.70-1.73 (1H, m), 1.78-1.97 (1H, m), 2.42-3.18 (7H, m), 3.54 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.76-4.16 (4H, m), 5.32 (1H, d, J = 15.1 Hz), 5.44 (1H, d, J = 15.2 Hz), 6.45 (1H, d, J = 10.5 Hz), 6.71 (2H, d, J = 8.6 Hz), 7.04 (2H, d, J = 8.6 Hz).

[0823]

Reference Example 536

tert-Butyl (3R*,4R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[8-chloro-7-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 530.

^{1}HNMR (CDCl$_3$) δ ppm: -0.17 (3H, s), 0.07 (3H, brs), 0.84 (9H, s), 1.47 (9H, s), 1.70-1.73 (1H, m), 1.77-1.95 (1H, m), 2.42-3.18 (7H, m), 3.54 (1H, d, J = 8.4 Hz), 3.73 (3H, s), 3.76-

4.16 (4H, m), 5.32 (1H, d, J = 15.8 Hz), 5.44 (1H, d, J = 15.1 Hz), 6.45 (1H, d, J = 10.4 Hz), 6.71 (2H, d, J = 8.7 Hz), 7.04 (2H, d, J = 8.6 Hz).

[0824]

Reference Example 537

tert-Butyl (3R,4R)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[7,8-difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 530.

^{1}HNMR (CDCl$_3$) δ ppm: -0.13 (3H, s), 0.09 (3H, brs), 0.84 (9H, s), 1.48 (9H, s), 1.70-1.73 (1H, m), 1.77-1.97 (1H, m), 2.38-3.20 (7H, m), 3.51 (1H, d, J = 8.4 Hz), 3.71-4.16 (7H, m), 5.23 (2H, brs), 6.38 (1H, dd, J = 11.5 Hz, 5.8 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

[0825]

Reference Example 538

tert-Butyl (3R,4R)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[7,8-difluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 530.

^{1}HNMR (CDCl$_3$) δ ppm: -0.13 (3H, s), 0.09 (3H, brs), 0.84 (9H, s), 1.48 (9H, s), 1.70-1.73 (1H, m), 1.77-1.97 (1H, m), 2.41-3.18 (7H, m), 3.51 (1H, d, J = 8.4 Hz), 3.71-4.16 (7H, m), 5.23 (2H, brs), 6.38 (1H, dd, J = 11.5 Hz, 5.9 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

[0826]

Reference Example 539

5-({(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of *tert*-butyl (3S*,4S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate (1.82 g) and 2,6-lutidine (1.31 mL) in dichloromethane (1 mL), trimethylsilyl trifluoromethanesulfonate (2.04 mL) was added dropwise under cooling with water-bath, and the reaction mixture was stirred at room temperature for 4 h. To the reaction solution was added saturated aqueous sodium hydrogencarbonate, and the solution was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound. The compound was used for the next step without further purification.

^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.03 (3H, s), 0.14 (9H, s), 0.83 (9H, s), 1.68-1.88 (2H, m), 2.58-2.66 (2H, m), 2.77-3.04 (6H, m), 3.70 (1H, d, J = 8.2 Hz), 3.73 (3H, s), 3.77-3.83 (1H, m), 3.97 (1H, d, J = 8.2 Hz), 5.16-5.30 (2H, m), 6.40 (1H, d, J = 9.0 Hz, 3.2 Hz), 6.71-6.78 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.08-7.15 (2H, m).

[0827]

Reference Example 540

5-({(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 539.

^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.02 (3H, s), 0.13 (9H, s), 0.83 (9H, s), 1.68-1.88 (2H, m), 2.58-2.66 (2H, m), 2.77-3.02 (6H, m), 3.69 (1H, d, J = 8.2 Hz), 3.73 (3H, s), 3.74-3.80

(1H, m), 3.97 (1H, d, J = 8.2 Hz), 5.16-5.29 (2H, m), 6.41 (1H, d, J = 9.0 Hz, 3.2 Hz), 6.71-6.78 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.08-7.15 (2H, m).

[0828]

Reference Example 541

5-({(3S,4S)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 539.

^{1}HNMR (CDCl$_3$) δ ppm: -0.12 (3H, s), 0.02 (3H, s), 0.13 (9H, s), 0.82 (9H, s), 1.68-1.86 (2H, m), 2.59-2.66 (2H, m), 2.76-3.01 (6H, m), 3.69 (1H, d, J = 8.2 Hz), 3.73 (3H, s), 3.74-3.80 (1H, m), 3.97 (1H, d, J = 8.2 Hz), 5.16-5.29 (2H, m), 6.41 (1H, d, J = 9.0 Hz, 3.2 Hz), 6.71-6.78 (2H, m), 6.83 (1H, dd, J = 12.6 Hz, 9.0 Hz), 7.08-7.16 (2H, m).

[0829]

Reference Example 542

5-({(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 539.

^{1}HNMR (CDCl$_3$) δ ppm: -0.14 (3H, s), 0.00 (3H, s), 0.12 (9H, s), 0.83 (9H, s), 1.69-1.78 (2H, m), 2.54 (2H, t, J = 6.7 Hz), 2.69-2.97 (6H, m), 3.69-3.71 (5H, m), 3.98 (1H, d, J = 8.2 Hz), 5.34 (1H, d, J = 15.3 Hz), 5.41 (1H, d, J = 15.2 Hz), 6.48 (1H, d, J = 8.9 Hz), 6.68-6.71 (2H, m), 7.04-7.07 (2H, m), 7.15 (1H, d, J = 8.9 Hz).

[0830]

Reference Example 543

5-({(3S,4S)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 539.

^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.02 (3H, s), 0.13 (9H, s), 0.83 (9H, s), 1.75-1.78 (1H, m), 1.86-1.94 (1H, m), 2.52-2.55 (2H, m), 2.67-3.04 (6H, m), 3.54-3.56 (1H, m),3.72 (3H, s), 3.83-3.85 (1H, m), 3.90-3.99 (2H, m), 5.34-5.41 (2H, m), 6.46 (1H, d, J = 9.0 Hz), 6.68-6.70 (2H, m), 7.04-7.07 (2H, m), 7.13-7.15 (1H, m).

[0831]

Reference Example 544

5-({(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 539.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.03 (3H, s), 0.15 (9H, s), 0.84 (9H, s), 1.77-1.80 (1H, m), 1.92-1.98 (1H, m), 2.52-2.56 (2H, m), 2.65-2.78 (2H, m), 2.97-3.09 (4H m), 3.15-3.56 (1H, m), 3.69-3.72 (4H, m), 3.87-3.90 (1H, m), 3.97 (1H, d, J = 8.1 Hz), 5.35 (1H, d, J = 15.1 Hz), 5.42 (1H, d, J = 15.1 Hz), 6.37 (1H, d, J = 10.4 Hz), 6.70 (2H, d, J = 8.6 Hz), 7.04 (2H, d, J = 8.6 Hz).

[0832]

Reference Example 545

5-({(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 539.

^{1}HNMR (CDCl$_3$) δ ppm: -0.13 (3H, s), 0.01 (3H, s), 0.13 (9H, s), 0.84 (9H, s), 1.67-1.77 (1H, m), 2.52-2.55 (2H, m), 2.64-2.81 (4H, m), 2.86-2.96 (2H, m), 3.66-3.72 (5H, m), 3.95 (1H, d, J = 8.1 Hz), 5.34 (1H, d, J = 15.2 Hz), 5.42 (1H, d, J = 15.2 Hz), 6.40 (1H, d, J = 10.6 Hz), 6.69-6.72 (2H, m), 7.03-7.06 (2H, m).

[0833]

Reference Example 546

5-({(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 539.

^{1}HNMR (CDCl$_3$) δ ppm: -0.11 (3H, s), 0.06 (3H, s), 0.17 (9H, s), 0.84 (9H, s), 1.83-1.86 (1H, m), 2.08-2.15 (2H, m), 2.58-2.68 (2H, m), 2.82-2.84 (2H, m), 3.05-3.25 (4H, m), 3.69 (1H, d, J = 8.1 Hz), 3.75 (3H, s), 3.97 (1H, d, J = 8.1 Hz), 4.04 (1H, dd, J = 10.7 Hz, 4.8 Hz), 5.23 (2H, s), 6.29 (1H, dd, J = 11.4 Hz, 5.8 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

[0834]

Reference Example 547

5-({(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 539.

^{1}HNMR (CDCl$_3$) δ ppm: -0.11 (3H, s), 0.03 (3H, s), 0.14 (9H, s), 0.83 (9H, s), 1.81-1.87 (2H, m), 2.58-2.67 (2H, m), 2.82-3.02 (6H, m), 3.65 (1H, d, J = 8.0 Hz), 3.74 (3H, s), 3.77-3.80 (1H, m), 3.94 (1H, d, J = 8.0 Hz), 5.23 (2H, s), 6.32 (1H, dd, J = 11.6 Hz, 5.7 Hz), 6.75-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

[0835]

Reference Example 548

5-{[(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

A solution of 5-({(3R*,4R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (1.74 g) and potassium carbonate (1.95 g) in methanol (45 mL) was stirred at 50 °C for 18 h. To the reaction solution was added water and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.17 g).

^{1}HNMR (CDCl$_3$) δ ppm: -0.16 (3H, s), 0.03 (3H, s), 0.82 (9H, s), 1.71-1.79 (1H, m), 1.84-1.95 (1H, m), 2.46-2.70 (3H, m), 2.74-3.02 (6H, m), 3.54 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.82 (1H, d, J = 8.5 Hz), 3.87-3.94 (1H, m), 5.22 (2H, brs), 6.47 (1H, d, J = 9.0 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.15 (2H, m).

[0836]

Reference Example 549

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 548.

^{1}HNMR (CDCl$_3$) δ ppm: -0.16 (3H, s), 0.03 (3H, s), 0.82 (9H, s), 1.71-1.79 (1H, m), 1.84-1.95 (1H, m), 2.44-2.70 (3H, m), 2.74-3.02 (6H, m), 3.54 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 3.87-3.95 (1H, m), 5.22 (2H, brs), 6.47 (1H, d, J = 9.1 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.15 (2H, m).

[0837]

Reference Example 550

5-{[(3S,4S)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 548.

^{1}HNMR (CDCl$_3$) δ ppm: -0.16 (3H, s), 0.03 (3H, s), 0.82 (9H, s), 1.71-1.79 (1H, m), 1.85-1.95 (1H, m), 2.42-2.70 (3H, m), 2.74-3.02 (6H, m), 3.54 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 3.88-3.95 (1H, m), 5.22 (2H, brs), 6.47 (1H, d, J = 9.1 Hz, 3.3 Hz), 6.72-6.79 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.16 (2H, m).

[0838]

Reference Example 551

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 548.

^{1}HNMR (CDCl$_3$) δ ppm: -0.19 (3H, s), 0.02 (3H, s), 0.82 (9H, s), 1.73-1.76 (1H, m), 1.85-1.90 (1H, m), 2.52-2.55 (3H, m), 2.63-2.85 (4H, m), 2.91-2.98 (2H, m), 3.55 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.84 (1H, d, J = 8.5 Hz), 3.88 (1H, dd, J = 10.3 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.1 Hz), 5.43 (1H, d, J = 15.1 Hz), 6.54 (1H, d, J = 8.9 Hz), 6.68-6.71 (2H, m), 7.06 (2H, d, J = 8.6 Hz), 7.14 (1H, d, J = 8.9 Hz).

[0839]

Reference Example 552

5-{[(3S,4S)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 548.

^{1}HNMR (CDCl$_3$) δ ppm: -0.19 (3H, s), 0.02 (3H, s), 0.82 (9H, s), 1.72-1.76 (1H, m), 1.85-1.92 (1H, m), 2.52-2.55 (3H, m), 2.63-2.85 (4H, m), 2.91-2.98 (2H, m), 3.55 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.84 (1H, d, J = 8.5 Hz), 3.88 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.33 (1H, d, J = 15.1 Hz), 5.43 (1H, d, J = 15.1 Hz), 6.54 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 7.04-7.07 (2H, m), 7.14 (1H, d, J = 8.9 Hz).

[0840]

Reference Example 553

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 548.

^{1}HNMR (CDCl$_3$) δ ppm: -0.18 (3H, s), 0.03 (3H, s), 0.83 (9H, s), 1.74-1.77 (1H, m), 1.83-1.89 (1H, m), 2.53-2.55 (3H, m), 2.63-2.69 (1H, m), 2.76-2.82 (3H, m), 2.92-2.98 (2H, m), 3.53 (1H, d, J = 8.4 Hz), 3.72 (3H, s), 3.81 (1H, d, J = 8.4 Hz), 3.87 (1H, dd, J = 10.3 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.2 Hz), 5.44 (1H, d, J = 15.2 Hz), 6.47 (1H, d, J = 10.6 Hz), 6.69-6.72 (2H, m), 7.03-7.06 (2H, m).

[0841]

Reference Example 554

5-{[(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 548.

^{1}HNMR (CDCl$_3$) δ ppm: -0.18 (3H, s), 0.03 (3H, s), 0.83 (9H, s), 1.74-1.77 (1H, m), 1.83-1.89 (1H, m), 2.52-2.55 (3H, m), 2.63-2.69 (1H, m), 2.76-2.82 (3H, m), 2.92-2.98 (2H, m), 3.53 (1H, d, J = 8.4 Hz), 3.72 (3H, s), 3.80 (1H, d, J = 8.4 Hz), 3.86 (1H, dd, J = 10.3 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.3 Hz), 5.44 (1H, d, J = 15.4 Hz), 6.47 (1H, d, J = 10.6 Hz), 6.69-6.72 (2H, m), 7.03-7.06 (2H, m).

[0842]

Reference Example 555

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 548.

^{1}HNMR (CDCl$_3$) δ ppm: -0.15 (3H, s), 0.04 (3H, s), 0.83 (9H, s), 1.73-1.76 (1H, m), 1.83-1.89 (1H, m), 2.53-2.67 (3H, m), 2.76-2.98 (6H, m), 3.50 (1H, d, J = 8.4 Hz), 3.74 (3H, s), 3.78 (1H, d, J = 8.5 Hz), 3.88 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.23 (2H, s), 6.40 (1H, dd, J = 11.6 Hz, 5.9 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

[0843]

Reference Example 556

5-{[(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 548.

^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.04 (3H, s), 0.83 (9H, s), 1.73-1.77 (1H, m), 1.83-1.89 (1H, m), 2.53-2.67 (3H, m), 2.76-2.98 (6H, m), 3.50 (1H, d, J = 8.5 Hz), 3.74 (3H, s), 3.78 (1H, d, J = 8.4 Hz), 3.88 (1H, dd, J = 10.3 Hz, 5.2 Hz), 5.23 (2H, s), 6.40 (1H, dd, J = 11.6 Hz, 5.9 Hz), 6.74-6.77 (2H, m), 7.11 (2H, d, J = 8.6 Hz).

[0844]

Reference Example 557

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.83-1.91 (1H, m), 2.10-2.22 (1H, m), 2.50-2.54 (1H, m), 2.57-2.70 (2H, m), 2.80-2.96 (3H, m), 3.02-3.19 (2H, m), 3.26-3.34 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.5 Hz), 4.12-4.18 (1H, m), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.72-6.78 (2H, m), 6.79-6.94 (2H, m), 7.03-7.09 (2H, m), 7.10-7.16 (2H, m).

[0845]

Reference Example 558

5-{[(3S,4S)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.82-1.91 (1H, m), 2.10-2.22 (1H, m), 2.50-2.56 (1H, m), 2.57-2.71 (2H, m), 2.79-2.96 (3H, m), 3.02-3.19 (2H, m), 3.26-3.34 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.5 Hz), 4.12-4.18 (1H, m), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.78 (2H, m), 6.79-6.94 (2H, m), 7.02-7.09 (2H, m), 7.10-7.16 (2H, m).

[0846]

Reference Example 559

5-{[(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxy-1-(2,2,6-trifluoro-1,3-benzodioxol-5-yl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.13-2.20 (1H, m), 2.52 (1H, d, J = 2.5 Hz), 2.59-2.69 (2H, m), 2.80-2.96 (3H, m), 3.03-3.06 (2H, m), 3.17-3.20 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.5 Hz), 4.12-4.16 (1H, m), 5.23 (2H, s), 6.48 (1H, dd, J = 9.0 Hz, 3.0 Hz), 6.74 (2H, d, J = 8.5 Hz), 6.79 (1H, d, J = 7.0 Hz), 6.83 (1H, dd, J = 12.5 Hz, 9.0 Hz), 6.87 (1H, d, J = 10.0 Hz), 7.11 (2H, d, J = 8.5 Hz).

[0847]

Reference Example 560

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxy-1-(2,2,6-trifluoro-1,3-benzodioxol-5-yl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.85-1.89 (1H, m), 2.13-2.20 (1H, m), 2.51 (1H, d, J = 2.3 Hz), 2.59-2.69 (2H, m), 2.81-2.95 (3H, m), 3.03-3.06 (2H, m), 3.18 (1H, dd, J = 10.8 Hz, 5.2 Hz), 3.63 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.12-4.16 (1H, m), 5.23 (2H, m), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.79 (1H, d, J = 7.0 Hz), 6.82-6.88 (2H, m), 7.12 (2H, d, J = 8.6 Hz).

[0848]

Reference Example 561

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.13-2.19 (1H, m), 2.55-2.59 (3H, m), 2.68-2.89 (3H, m), 2.99-3.22 (3H, m), 3.66 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.5 Hz), 4.17 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.33 (1H, d, J = 15.1 Hz), 5.44 (1H, d, J = 15.1 Hz), 6.56 (1H, d, J = 9.0 Hz), 6.70 (2H, d, J = 8.6 Hz), 6.93-6.97 (1H, m), 7.02-708 (3H, m), 7.13-7.16 (2H, m).

[0849]

Reference Example 562

5-{[(3S,4S)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.14-2.20 (1H, m), 2.55-2.59 (3H, m), 2.68-2.89 (3H, m), 2.99-3.22 (3H, m), 3.66 (1H, d, J = 8.6 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.17 (1H, dd, J = 10.2 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.0 Hz), 5.44 (1H, d, J = 15.0 Hz), 6.56 (1H, d, J = 9.0 Hz), 6.70 (2H, d, J = 8.6 Hz), 6.93-6.97 (1H, m), 7.02-7.08 (3H, m), 7.13-7.16 (2H, m).

[0850]

Reference Example 563

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.86-1.88 (1H, m), 2.11-2.17 (1H, m), 2.55-2.59 (3H, m), 2.63-2.85 (3H, m), 2.99-3.22 (3H, m), 3.63 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 4.14 (1H, dd, J = 10.2 Hz, 5.2 Hz), 5.33 (1H, d, J = 15.2 Hz), 5.45 (1H, d, J = 15.2 Hz), 6.49 (1H, d, J = 10.5 Hz), 6.70-6.72 (2H, m), 6.93-6.97 (1H, m), 7.02-7.07 (3H, m), 7.15 (1H, dd, J = 8.3 Hz, 2.9 Hz).

[0851]

Reference Example 564

5-{[(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.86-1.88 (1H, m), 2.11-2.18 (1H, m), 2.55-2.84 (6H, m), 2.99-3.22 (3H, m), 3.63 (1H, d, J = 8.4 Hz), 3.72 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 4.14 (1H, dd, J = 10.2 Hz, 5.3 Hz), 5.33 (1H, d, J = 14.9 Hz), 5.45 (1H, d, J = 14.6 Hz), 6.49 (1H, d, J = 10.5 Hz), 6.70-6.72 (2H, m), 6.93-6.97 (1H, m), 7.02-7.07 (3H, m), 7.15 (1H, dd, J = 8.3 Hz, 2.9 Hz).

[0852]

Reference Example 565

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.12-2.18 (1H, m), 2.51 (1H, d, J = 2.3 Hz), 2.59-2.69 (2H, m), 2.81-2.93 (3H, m), 3.03-3.33 (3H, m), 3.62 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.13 (1H, dd, J = 10.4 Hz, 5.2 Hz), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.73-6.77 (3H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.07-7.12 (3H, m).

[0853]

Reference Example 566

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.86-1.89 (1H, m), 2.14-2.20 (1H, m), 2.58 (1H, d, J = 2.4 Hz), 2.61-2.70 (2H, m), 2.76 (1H, t, J = 10.7 Hz), 2.84-2.97 (2H, m), 3.05-3.12 (2H, m), 3.25-3.28 (1H, m), 3.64 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.17 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.17-5.28 (2H, m), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.99 (1H, d, J = 8.7 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.20 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.39 (1H, d, J = 2.5 Hz).

[0854]

Reference Example 567

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.86-1.90 (1H, m), 2.14-2.20 (1H, m), 2.57 (1H, d, J = 2.4 Hz), 2.63-2.66 (2H, m), 2.75 (1H, t, J = 10.7 Hz), 2.83-2.96 (2H, m), 3.06-3.08 (2H, m), 3.28 (1H, dd, J = 11.1 Hz, 5.2 Hz), 3.64 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.17 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.19-5.27 (2H, m), 6.48 (1H, dd, J = 9.1 Hz, 3.1 Hz), 6.73-6.76 (2H, m), 6.82-6.87 (2H, m), 7.12 (2H, d, J = 8.5 Hz), 7.42 (1H, d, J = 7.6 Hz).

[0855]

Reference Example 568

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2,5-dichloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.86-1.89 (1H, m), 2.14-2.20 (1H, m), 2.56 (1H, d, J = 2.3 Hz), 2.62-2.66 (2H, m), 2.75 (1H, t, J = 10.6 Hz),2.83-3.11 (4H, m), 3.18-3.21 (1H, m), 3.64 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.16 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.19-5.27 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.73-6.76 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08 (1H, d, J = 7.1 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.21 (1H, d, J = 4.4 Hz).

[0856]

Reference Example 569

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 1.40 (3H, t, J = 7.0 Hz), 1.84-1.88 (1H, m), 2.12-2.21 (1H, m), 2.53-3.23 (9H, m), 3.63 (1H, d, J = 8.8 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.3 Hz), 3.98 (2H, q, J = 7.1 Hz), 4.16 (1H, dd, J = 10.0 Hz, 5.2 Hz), 5.23 (2H, brs), 6.47-6.50 (1H, m), 6.61-6.67 (2H, m), 6.74-6.76 (2H, m), 6.81-6.94 (2H, m), 7.11-7.13 (2H, m).

[0857]

Reference Example 570

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.11 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.12-2.17 (1H, m), 2.58-2.93 (6H, m), 2.99-3.23 (3H, m), 3.60 (1H, d, J = 8.5 Hz), 3.74 (3H, s), 3.81 (1H, d, J = 8.5 Hz), 4.15 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.24 (2H, brs), 6.41 (1H, dd, J = 11.5 Hz, 5.9 Hz), 6.75-6.78 (2H, m), 6.94-6.97 (1H, m), 7.03 (1H, dd, J = 8.9 Hz, 5.5 Hz), 7.11-7.16 (3H, m).

[0858]

Reference Example 571

5-{[(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.11 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.11-2.18 (1H, m), 2.58-2.92 (6H, m), 2.99-3.23 (3H, m), 3.60 (1H, d, J = 8.5 Hz), 3.74 (3H, s), 3.81 (1H, d, J = 8.5 Hz), 4.15 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.24 (2H, brs), 6.41 (1H, dd, J = 11.6 Hz, 5.9 Hz), 6.75-6.78 (2H, m), 6.94-6.97 (1H, m), 7.03 (1H, dd, J = 9.0 Hz, 5.5 Hz), 7.11-7.16 (3H, m).

[0859]

Reference Example 572

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.13-2.19 (1H, m), 2.54-2.58 (3H, m), 2.69-2.86 (3H, m), 3.02-3.12 (2H, m), 3.24-3.27 (1H, m), 3.65 (1H, d, J = 8.6 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.5 Hz), 4.14-4.18 (1H, m), 5.33 (1H, d, J = 15.1 Hz), 5.44 (1H, d, J = 14.8 Hz), 6.55 (1H, d, J = 8.9 Hz), 6.68-6.71 (2H, m), 6.99 (1H, d, J = 8.7 Hz), 7.07 (2H, d, J = 8.6 Hz), 7.15 (1H, d, J = 9.0 Hz), 7.20 (1H, dd, J = 8.7 Hz, 2.4 Hz), 7.38 (1H, d, J = 2.4 Hz).

[0860]

Reference Example 573

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2,5-dichloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.85-1.88 (1H, m), 2.12-2.19 (1H, m), 2.55-2.57 (3H, m), 2.67-2.86 (3H, m), 2.98-3.20 (3H, m), 3.65 (1H, d, J = 8.6 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.14-4.17 (1H, m), 5.33 (1H, d, J = 15.2 Hz), 5.44 (1H, d, J = 15.2 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 7.06-7.09 (3H, m), 7.16 (1H, d, J = 8.9 Hz), 7.22 (1H, d, J = 8.5 Hz).

[0861]

Reference Example 574

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 1.86-1.89 (1H, m), 2.13-2.17 (1H, m), 2.54-2.57 (3H, m), 2.67-2.86 (3H, m), 3.05-3.07 (2H, m), 3.26-3.29 (1H, m), 3.65 (1H, d, J = 8.6 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.14-4.17 (1H, m), 5.33 (1H, d, J = 15.1 Hz), 5.44 (1H, d, J = 15.1 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.68-6.71 (2H, m), 6.86 (1H, d, J = 10.5 Hz), 7.05-7.08 (2H, m), 7.16 (1H, d, J = 8.9 Hz), 7.41 (1H, d, J = 7.6 Hz).

[0862]

Reference Example 575

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2-chloro-4-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.86-1.89 (1H, m), 2.14-2.21 (1H, m), 2.58 (1H, d, J = 2.2 Hz), 2.59-2.69 (2H, m), 2.76 (1H, t, J = 10.6 Hz), 2.84-3.13 (4H, m), 3.18-3.25 (1H, m), 3.65 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.18 (1H, dd, J = 10.3 Hz, 5.3 Hz),5.19-5.27 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.73-6.76 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.0 Hz), 6.93-6.97 (1H, m), 7.04 (1H, dd, J = 8.8 Hz, 5.4 Hz), 7.11-7.16 (3H, m).

[0863]

Reference Example 576

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.17 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.85-1.87 (1H, m), 2.12-2.17 (1H, m), 2.51-2.85 (6H, m), 3.03-3.17 (2H, m), 3.29-3.32 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.10-4.13 (1H, m), 5.33 (1H, d, J = 15.2 Hz), 5.44 (1H, d, J = 14.8 Hz), 6.55 (1H, d, J = 9.0 Hz), 6.54-6.56 (2H, m), 6.74 (1H, dd, J = 10.5 Hz, 7.6 Hz), 7.05-7.10 (3H, m), 7.15 (1H, d, J = 8.7 Hz).

[0864]

Reference Example 577

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.08-2.15 (1H, m). 2.51 (1H, d, J = 2.3 Hz), 2.58-2.69 (2H, m), 2.78-2.89 (3H, m), 3.03-3.33 (3H, m), 3.58 (1H. d, J = 8.5 Hz), 3.74 (3H, s), 3.81 (1H, d, J = 8.5 Hz), 4.10-4.14 (1H, m), 5.23 (2H, brs), 6.41 (1H, dd, J = 11.5 Hz, 6.0 Hz), 6.73-6.77 (3H, m). 7.07-7.12 (3H, m).

[0865]

Reference Example 578

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.10 (3H, s), 0.85 (9H, s), 1.81-1.85 (1H, m), 2.09-2.15 (1H, m), 2.53-2.64 (3H, m), 2.72-2.83 (2H, m), 2.89-2.93 (1H, m), 3.07-3.13 (1H, m), 3.39-3.48 (2H, m), 3.60 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.83 (1H, d, J = 8.6 Hz), 4.07-4.10 (1H, m), 5.22 (2H, brs), 6.46 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.75 (2H, m), 6.81-6.87 (3H, m), 7.11 (2H, d, J = 8.5 Hz), 7.20-7.24 (2H, m).

[0866]

Reference Example 579

5-({(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[2-fluoro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.86-1.89 (1H, m), 2.13-2.19 (1H, m), 2.53 (1H, d, J = 2.3 Hz), 2.61-2.66 (2H, m), 2.84-2.91 (3H, m), 3.06-3.32 (3H, m), 3.63 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.15 (1H, dd, J = 10.4 Hz, 5.3 Hz), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.1 Hz, 3.2 Hz), 6.75 (2H, d, J = 8.6 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 6.96-7.00 (3H, m), 7.12 (2H, d, J = 8.6 Hz).

[0867]

Reference Example 580

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR (CDCl$_3$) δ ppm: -0.12 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 1.86-1.89 (1H, m), 2.15-2.20 (1H, m), 2.55 (1H, d, J = 2.3 Hz), 2.59-2.69 (2H, m), 2.83-2.95 (3H, m), 3.06-3.38 (3H, m), 3.63 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.5 Hz), 4.17 (1H, dd, J = 10.4 Hz, 5.3 Hz), 5.23 (2H, brs), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.93-7.09 (4H, m), 7.12 (2H, d, J = 8.6 Hz).

[0868]

Reference Example 581

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR (CDCl$_3$) δ ppm: -0.12 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.87-1.90 (1H, m), 2.16-2.22 (1H, m), 2.60 (1H, d, J = 2.4 Hz), 2.63-2.67 (2H, m), 2.79 (1H, t, J = 10.7 Hz), 2.85-2.98 (2H, m), 3.10-3.13 (2H, m), 3.32-3.35 (1H, m), 3.65 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.6 Hz), 4.20 (1H, dd, J = 10.3 Hz, 5.3 Hz), 5.19-5.27 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.99 (1H, dt, J = 1.4 Hz, 7.6 Hz), 7.08 (1H, dd, J = 8.0 Hz, 1.4 Hz), 7.12 (2H, d, J = 8.7 Hz), 7.22-7.25 (1H, m), 7.38 (1H, dd, J = 7.9 Hz, 1.5 Hz).

[0869]

Reference Example 582

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2,4-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.13-2.20 (1H, m), 2.53 (1H, d, J = 2.3 Hz), 2.59-3.25 (8H, m), 3.63 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.14-4.17 (1H, m), 5.23 (2H, brs), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.79-6.86 (3H, m), 6.94-6.97 (1H, m), 7.12 (2H, d, J = 8.6 Hz).

[0870]

Reference Example 583

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.14 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.78-1.81 (1H, m), 2.08-2.15 (1H, m), 2.58 (1H, d, J = 2.3 Hz), 2.59-2.70 (2H, m), 2.84-3.05 (3H, m), 3.14 (1H, dd, 11.7 Hz, 5.3 Hz), 3.25-3.29 (1H, m), 3.46-3.50 (1H, m), 3.62 (1H, d, J = 8.5 Hz), 3.73 (3H, s), 3.86 (1H, d, J = 8.5 Hz), 4.10 (1H, dd, J = 10.3 Hz, 5.5 Hz), 5.23 (2H, brs), 6.49 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.76 (2H, m), 6.81-6.94 (4H, m), 7.12 (2H, d, J = 8.6 Hz).

[0871]

Reference Example 584

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxy-1-phenylpiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR (DMSO-d6) δ ppm: -0.17 (3H, s), 0.05 (3H, s), 0.80 (9H, s), 1.67-1.70 (1H, m), 1.93-1.99 (1H, m), 2.50-3.00 (6H, m), 3.40-3.50 (2H, m), 3.61 (1H, d, J = 8.7 Hz), 3.67 (3H, s), 3.91-3.95 (2H, m), 4.43 (1H, s), 5.02-5.16 (2H, m), 6.60 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.76-6.79 (3H, m), 6.92-704 (5H, m), 7.22-7.25 (2H, m).

[0872]

Reference Example 585

5-({(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-hydroxy-1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR (DMSO-d6) δ ppm: -0.17 (3H, s), 0.06 (3H, s), 0.80 (9H, s), 1.68-1.70 (1H, m), 1.93-1.99 (1H, m), 2.45-3.03 (6H, m), 3.40-3.51 (2H, m), 3.61 (1H, d, J = 8.7 Hz), 3.67 (3H, s), 3.91-3.94 (2H, m), 4.48 (1H, s), 5.02-5.16 (2H, m), 6.60 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.76-6.78 (2H, m), 6.92-7.04 (5H, m), 7.21 (2H, d, J = 8.9 Hz).

[0873]

Reference Example 586

5-({(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[4-(difluoromethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR (DMSO-d6) δ ppm: -0.17 (3H, s), 0.05 (3H, s), 0.80 (9H, s), 1.67-1.70 (1H, m), 1.93-1.98 (1H, m), 2.50-3.00 (6H, m), 3.41-3.51 (2H, m), 3.61 (1H, d, J = 8.7 Hz), 3.67 (3H, s), 3.91-3.95 (2H, m), 4.44 (1H, s), 5.01-5.17 (2H, m), 6.60 (1H, dd, J = 9.4 Hz, 3.1 Hz), 6.78 (2H, d, J = 8.7 Hz), 6.91-7.07 (7H, m).

[0874]

Reference Example 587

5-{[(3R*,4R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR (CDCl$_3$) δ ppm: -0.12 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 1.82-1.89 (1H, m), 2.08-2.18 (1H, m), 2.53 (1H, d, J = 2.5 Hz), 2.58-2.69 (2H, m), 2.78-2.91 (3H, m), 3.02-3.10 (1H, m), 3.11-3.17 (1H, m), 3.26-3.32 (1H, m), 3.58 (1H, d, J = 8.5 Hz), 3.74 (3H, s), 3.80 (1H, d, J = 8.5 Hz), 4.09-4.15 (1H, m), 5.24 (2H, brs), 6.39 (1H, dd, J = 12.0 Hz, 6.0 Hz), 6.74-6.79 (2H, m), 6.87-6.92 (1H, m), 7.04-7.09 (2H, m), 7.09-7.14 (2H, m).

[0875]

Reference Example 588

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-7-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.16 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.85-1.88 (1H, m), 2.09-2.16 (1H, m), 2.53-2.57 (3H, m), 2.63-2.86 (3H, m), 3.03-3.30 (3H, m), 3.61 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.83 (1H, d, J = 8.5 Hz), 4.09-4.13 (1H, m), 5.33 (1H, d, J = 15.2 Hz), 5.45 (1H, d, J = 15.2 Hz), 6.48 (1H, d, J = 10.5 Hz), 6.69-6.72 (2H, m), 6.87-6.91 (1H, m), 7.04-7.08 (4H, m).

[0876]

Reference Example 589

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-chloro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

HNMR ($CDCl_3$) δ ppm: -0.17 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 1.82-1.89 (1H, m), 2.10-2.20 (1H, m), 2.51-2.58 (3H, m), 2.65-2.64 (1H, m), 2.78-2.87 (2H, m), 3.03-3.09 (1H, m), 3.11-3.18 (1H, m), 3.25-3.31 (1H, m), 3.63 (1H, d, J = 8.5 Hz), 3.72 (3H, s), 3.85 (1H, d, J = 8.5 Hz), 4.10-4.16 (1H, m), 5.32 (1H, d, J = 15.0 Hz), 5.43 (1H, d, J = 15.0 Hz), 6.54 (1H, d, J = 9.0 Hz), 6.68-6.72 (2H, m), 6.88 (1H, t, J = 9.0 Hz), 7.03-7.09 (4H, m), 7.14 (1H, d, J = 9.0 Hz).

[0877]

Reference Example 590

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluoro-5-methoxyphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.12 (3H, s), 0.072 (3H, s), 0.84 (9H, s), 1.86-1.90 (1H, m), 2.12-2.20 (1H, m), 2.52 (1H, d, J = 2.3 Hz), 2.58-2.70 (2H, m), 2.82-2.96 (3H, m), 3.07-3.19 (2H, m), 3.31-3.36 (1H, m), 3.63 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 3.87 (3H, s), 4.12-4.17 (1H, m), 5.23 (2H, s), 6.48 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.55 (1H, d, J = 7.7 Hz), 6.74 (2H, d, J = 8.6 Hz), 6.84 (1H, dd, J = 12.6 Hz, 9.2 Hz), 7.08 (1H, d, J = 11.6 Hz), 7.12 (2H, d, J = 8.6 Hz).

[0878]

Reference Example 591

5-{[(3R,4R)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluoro-5-methylphenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.13 (3H, s), 0.072 (3H, s), 0.84 (9H, s), 1.84-1.88 (1H, m), 2.11-2.20 (1H, m), 2.30 (3H, s), 2.53 (1H, d, J = 2.4 Hz), 2.59-2.70 (2H, m), 2.80-2.96 (3H, m), 3.03-3.09 (1H, m), 3.12-3.17 (1H, m), 3.27-3.32 (1H, m), 3.62 (1H, d, J = 8.6 Hz), 3.73 (3H, s), 3.85 (1H, d, J = 8.6 Hz), 4.12-4.17 (1H, m), 5.23 (2H, s), 6.48 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.74 (2H, d, J = 8.8 Hz), 6.81 (1H, d, J = 8.8 Hz), 6.83 (1H, dd, J = 12.8 Hz, 9.2 Hz), 7.05 (1H, d, J = 11.8 Hz), 7.12 (2H, d, J = 8.8 Hz).

[0879]

Reference Example 592

5-{[1-(4-Chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, to a solution of 5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one (441 mg) in tetrahydrofuran (8 mL), Burgess reagent (597 mg) was added under ice-cooling, and the reaction mixture was stirred at room temperature for 16.5 h, then at 60 °C for 2 h. To the reaction solution was added water, and the precipitate was collected on a filter to provide the title compound (380 mg). The compound was used for the next step without further purification.

^{1}HNMR ($CDCl_3$) δ ppm: 2.29-2.34 (2H, m), 2.63 (2H, t, J = 8.0 Hz), 3.02 (2H, t, J = 8.0 Hz), 3.32-3.35 (2H, m), 3.72 (2H, brs), 4.43 (2H, s), 5.85 (1H, brs), 6.48 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.87-6.93 (3H, m), 7.49 (1H, brs).

[0880]

Reference Example 593

8-Chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 592.

^{1}HNMR ($CDCl_3$) δ ppm: 2.23-2.32 (2H, m), 2.60-2.66 (2H, m), 3.02 (2H, t, J = 8.1 Hz), 3.32-3.35 (2H, m), 3.72 (2H, brs), 4.46 (2H, s), 5.85 (1H, brs), 6.54 (1H, d, J = 8.9 Hz), 6.87-6.92 (2H, m), 7.16-7.19 (1H, m), 7.74 (1H, brs).

[0881]

Reference Example 594

5-{[1-(4-Chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 592.

^{1}HNMR ($CDCl_3$) δ ppm: 2.28-2.32 (2H, m), 2.60-2.65 (2H, m), 2.95-2.99 (2H, m), 3.33-3.35 (2H, m), 3.73 (2H, brs), 4.41 (2H, s), 5.86 (1H, brs), 6.40 (1H, dd, J = 12.1 Hz, 6.3 Hz), 6.86-6.93 (2H, m), 7.67 (1H, brs).

[0882]

Reference Example 595

5-{[1-(4-Bromo-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

To a solution of 5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one (8 g) in N-methyl-2-pyrrolidone (60 mL) was added N,N,N',N'-tetramethyl-1,3-diaminopropane (13.59 mL), then methanesulfonyl chloride (5.30 mL) was added dropwise under ice-cooling. The reaction mixture was stirred at room temperature for 16 h. To the reaction solution were added water and *tert*-butyl methyl ether, and the precipitate was collected on a filter. The obtained solid was washed with water and diisopropyl ether to provide the title compound (7.27 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.33-2.37 (2H, m), 2.61-2.65 (2H, m), 3.00-3.05 (2H, m), 3.29 (2H, t, J = 5.6 Hz), 3.65 (2H, brs), 4.44 (2H, s), 5.88 (1H, brs), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.83 (1H, t, J = 9.1 Hz), 6.90 (1H, t, J = 9.4 Hz), 7.16-7.22 (2H, m), 7.49 (1H, brs).

[0883]

Reference Example 596

5-{[1-(4-Bromo-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 592.

^{1}HNMR (DMSO-d6) δ ppm: 2.25 (2H, brs), 2.44-2.48 (2H, m), 2.86-2.90 (2H, m), 3.20-3.22 (2H, m), 3.57-3.60 (2H, m), 4.52 (2H, s), 5.91 (1H, brs), 6.72 (1H, d, J = 9.0 Hz), 6.98-7.02 (1H, m), 7.23-7.30 (2H, m), 7.42-7.45 (1H, m), 9.37 (1H, brs).

[0884]

Reference Example 597

5-{[1-(4-Bromo-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 592.

^{1}HNMR (DMSO-d6) δ ppm: 2.25 (2H, brs), 2.42-2.47 (2H, m), 2.81-2.85 (2H, m), 3.21 (2H, t, J = 5.6 Hz), 3.59 (2H, brs), 4.49 (2H, s), 5.92 (1H, brs), 6.79 (1H, dd, J = 12.8 Hz, 6.3 Hz), 7.00 (1H, t, J = 9.1 Hz), 7.27-7.30 (1H, m), 7.43 (1H, dd, J = 12.2 Hz, 2.3 Hz), 10.31 (1H, brs).

[0885]

Reference Example 598

8-Chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR (DMSO-d6) δ ppm: 2.23 (2H, brs), 2.45-2.49 (2H, m), 2.83-2.87 (2H, m), 3.25-3.29 (2H, m), 3.64 (2H, brs), 4.53 (2H, s), 5.89 (1H, brs), 6.87 (1H, d, J = 11.6 Hz), 7.23-7.33 (2H, m), 9.70 (1H, brs).

[0886]

Reference Example 599

5-{[1-(4-Bromo-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-chloro-7-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR (DMSO-d6) δ ppm: 2.25 (2H, brs), 2.45-2.49 (2H, m), 2.82-2.86 (2H, m), 3.21 (2H, t, J = 5.6 Hz), 3.59 (2H, brs), 4.54 (2H, s), 5.93 (1H, brs), 6.87 (1H, d, J = 11.6 Hz), 7.00 (1H, t, J = 9.1 Hz), 7.27-7.30 (1H, m), 7.43 (1H, dd, J = 12.3 Hz, 2.3 Hz), 9.69 (1H, brs).

[0887]

Reference Example 600

5-{[1-(2-Chloro-4,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR ($CDCl_3$) δ ppm: 2.32 (2H, brs), 2.62-2.66 (2H, m), 3.03 (2H, t, J = 8.1 Hz), 3.27-3.29 (2H, m), 3.66 (2H, brs), 4.45 (2H, s), 5.86 (1H, brs), 6.49 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.73-6.78 (1H, m), 6.89-6.98 (2H, m), 7.52 (1H, brs).

[0888]

Reference Example 601

5-{[1-(4-Bromo-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR ($CDCl_3$) δ ppm: 2.31 (2H, brs), 2.61-2.65 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.32-3.35 (2H, m), 3.72 (2H, brs), 4.43 (2H, s), 5.85 (1H, brs), 6.48 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.3 Hz), 7.01-7.06 (2H, m), 7.51 (1H, brs).

[0889]

Reference Example 602

8-Fluoro-5-{[1-(2,4,6-trifluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR ($CDCl_3$) δ ppm: 2.28-2.35 (2H, m), 2.60-2.66 (2H, m), 3.03 (2H, t, J = 7.7 Hz), 3.31 (2H, t, J = 5.5 Hz), 3.65-3.3.70 (2H, m), 4.44 (2H, brs), 5.83-5.88 (1H, m), 6.49 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.60-6.69 (2H, m), 6.90 (1H, t, J = 9.5 Hz), 7.49 (1H, brs).

[0890]

Reference Example 603

5-{[1-(2,4-Dichloro-6-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR ($CDCl_3$) δ ppm: 2.32 (2H, brs), 2.62-2.65 (2H, m), 3.03 (2H, t, J = 7.7 Hz), 3.29-3.32 (2H, m), 3.69 (2H, brs), 4.44 (2H, s), 5.86 (1H, brs), 6.49 (1H, dd, J = 9.3 Hz, 3.9 Hz), 6.91 (1H, t, J = 9.3 Hz), 7.00 (1H, dd, J = 11.3 Hz, 2.4 Hz), 7.20-7.21 (1H, m), 7.52 (1H, brs).

[0891]

Reference Example 604

5-({1-[2,6-Difluoro-4-(2,2,2-trifluoroethoxy)phenyl]-1,2,3,6-tetrahydropyridin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR ($CDCl_3$) δ ppm: 2.30-2.34 (2H, m), 2.62-2.65 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.28-3.31 (2H, m), 3.66 (2H, brs), 4.29 (2H, q, J = 8.0 Hz), 4.43 (2H, s), 5.85 (1H, brs), 6.47-6.54 (3H, m), 6.91 (1H, t, J = 9.5 Hz), 7.52 (1H, brs).

[0892]

Reference Example 605

5-({1-[4-(Difluoromethoxy)-2,6-difluorophenyl]-1,2,3,6-tetrahydropyridin-4-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR ($CDCl_3$) δ ppm: 2.30-2.35 (2H, m), 2.62-2.65 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.31-3.34 (2H, m), 3.71 (2H, brs), 4.44 (2H, s), 5.86 (1H, brs), 6.46 (1H, t, J = 73.2 Hz), 6.48 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.68-6.73 (2H, m), 6.91 (1H, t, J = 9.5 Hz), 7.57 (1H, brs).

[0893]

Reference Example 606

5-{[1-(4-Ethoxy-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR ($CDCl_3$) δ ppm: 1.39 (3H, t, J = 6.8 Hz), 2.30-2.34 (2H, m), 2.60-2.65 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.26-3.29 (2H, m), 3.64 (2H, brs), 3.96 (2H, q, J = 6.8 Hz), 4.43 (2H, s), 5.85 (1H, brs), 6.39-6.46 (2H, m), 6.49 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.56 (1H, brs).

[0894]

Reference Example 607

5-{[1-(4-Chloro-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR ($CDCl_3$) δ ppm: 2.31-2.38 (2H, m), 2.61 (2H, t, J = 7.6 Hz), 2.95 (2H, t, J = 7.6 Hz), 3.28 (2H, t, J = 5.6 Hz), 3.63-3.68 (2H, m), 4.45 (2H, s), 5.90 (1H, brs), 6.38 (1H, dd, J = 11.7 Hz, 6.3 Hz), 6.87 (1H, t, J = 8.9 Hz), 7.02-7.09 (2H, m), 7.57 (1H, brs).

[0895]

Reference Example 608

8-Chloro-5-{[1-(4-chloro-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR (CDCl$_3$) δ ppm: 2.32-2.39 (2H, m), 2.58 (2H, t, J = 7.5 Hz), 3.00 (2H, t, J = 7.5 Hz), 3.28 (2H, t, J = 5.5 Hz), 3.66 (2H, s), 4.47 (2H, s), 5.90 (1H, s), 6.54 (1H, d, J = 9.0 Hz), 6.86-6.91 (1H, m), 7.02-7.10 (2H, m), 7.16 (1H, d, J = 9.0 Hz), 7.79 (1H, s).

[0896]

Reference Example 609

5-{[1-(4-Bromo-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR (CDCl$_3$) δ ppm: 2.31 (2H, brs), 2.60-2.64 (2H, m), 3.02 (2H, t, J = 7.7 Hz), 3.32-3.35 (2H, m), 3.72 (2H, brs), 4.46 (2H, s), 5.85 (1H, brs), 6.54 (1H, d, J = 8.9 Hz), 7.01-7.06 (2H, m), 7.17 (1H, d, J = 8.9 Hz), 7.73 (1H, brs).

[0897]

Reference Example 610

5-{[1-(2-Bromo-4-chloro-6-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR (DMSO-d6) δ ppm: 2.15-2.37 (2H, m), 2.42-2.49 (2H, m), 2.88 (2H, t, J = 7,6 Hz), 3.17-3.29 (2H, m), 3.59 (2H, brs), 4.48 (2H, s), 5.89 (1H, brs), 6.63 (1H, dd, J = 9.1 Hz, 3.8 Hz), 7.02 (1H, t, J = 9.7 Hz), 7.52 (1H, dd, J = 11.8 Hz, 2.4 Hz), 7.62-7.69 (1H, m), 10.03 (1H, brs).

[0898]

Reference Example 611

5-{[1-(4-Chloro-2,5-difluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 592.

^{1}HNMR ($CDCl_3$) δ ppm: 2.29-2.40 (2H, m), 2.46-2.72 (2H, m), 3.01 (2H, t, J = 7.6 Hz), 3.30 (2H, t, J = 5.7 Hz), 3.60-3.72 (2H, m), 4.44 (2H, brs), 5.82-5.92 (1H, m), 6.47 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.67-6.76 (1H, m), 6.91 (1H, t, J = 9.4 Hz), 7.08 (1H, dd, J = 11.7 Hz, 6.9 Hz), 7.52 (1H, brs).

[0899]

Reference Example 612

5-{[1-(4-Chloro-2-fluorophenyl)-1,2,3,6-tetrahydropyridin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 592.

^{1}HNMR ($CDCl_3$) δ ppm: 2.32-2.38 (2H, m), 2.61-2.67 (2H, m), 3.00-3.05 (2H, m), 3.28-3.30 (2H, m), 3.65 (2H, brs), 4.44 (2H, s), 5.89 (1H, brs), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.86-6.93 (2H, m), 7.03-7.09 (2H, m), 7.52 (1H, brs).

[0900]

Reference Example 613

4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridine

Under nitrogen atmosphere, to a solution of potassium hexamethyldisilazide (2.05 g) in tetrahydrofuran (10 mL) was added a solution of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (2.00 g) in tetrahydrofuran (10 mL) at -78 °C, and the reaction mixture was stirred for 30 min. Then *tert*-butyldimethylsilyl chloride (1.35 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1.5 h. To the reaction solution were added hexane and water to extract the product. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled of to provide the title compound (2.89 g).

^{1}HNMR (CDCl$_3$) δ ppm: 0.17 (6H, s), 0.93 (9H, s), 2.20-2.24 (2H, m), 3.29-3.32 (2H, m), 3.64-3.66 (2H, m), 4.87-4.89 (1H, m), 6.84-6.89 (2H, m).

[0901]

Reference Example 614

1-(4-Bromo-2-fluorophenyl)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1,2,3,6-tetrahydropyridine

To a solution of 1-(4-bromo-2-fluorophenyl)piperidin-4-one (20 g) in acetonitrile (60 mL) , triethylamine (12.81 mL), *tert*-butyl dimethylchlorosilane (12.74 g) and sodium iodide (12.67 g) were addedunder ice-cooling. Under nitrogen atmosphere, the reaction mixture was stirred at reflux for 1 h. The reaction solution was allowed to cool to room temperature, and hexane was added thereto, filtered with Celite, and the filtrate was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to provide the title compound (28.8 g).

^{1}HNMR (CDCl$_3$) δ ppm: 0.16 (6H, s), 0.93 (9H, s), 2.03-2.09 (2H, m), 3.11 (2H, t, J = 5.7 Hz), 3.43 (2H, dd, J = 5.7 Hz, 2.5 Hz), 4.73-4.76 (1H, m), 6.65 (1H, t, J = 8.9 Hz), 6.97-7.05 (2H, m).

[0902]

Reference Example 615

4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-1,2,3,6-tetrahydropyridine

Synthesized analogous to Reference Example 614.

^{1}HNMR (CDCl$_3$) δ ppm: 0.16 (6H, s), 0.93 (9H, s), 2.19-2.26 (2H, m), 3.28 (2H, t, J = 5.7 Hz), 3.60 (2H, dd, J = 5.7 Hz, 2.5 Hz), 4.89-4.92 (1H, m), 6.88 (1H, t, J = 8.9 Hz), 6.99-7.06 (2H, m).

[0903]

Reference Example 616

1-(4-Bromo-2,6-difluorophenyl)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1,2,3,6-tetrahydropyridine

Synthesized analogous to Reference Example 614.

^{1}HNMR (CDCl$_3$) δ ppm: 0.17 (6H, s), 0.93 (9H, s), 2.18-2.24 (2H, m), 3.27-3.33 (2H, m), 3.62-3.68 (2H, m), 4.86-4.89 (1H, m), 6.98-7.04 (2H, m).

[0904]

Reference Example 617

(1R,6R)-3-(4-Bromo-2-fluorophenyl)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-7-oxa-3-azabicyclo[4.1.0]heptane

To a solution of potassium carbonate (9.44 g) in 32 mL of 4 x 10^{-4} M aqueous ethylenediamine tetraacetic acid disodium salt was added a solution of 1-(4-bromo-2-fluorophenyl)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1,2,3,6-tetrahydropyridine (8.8 g) in acetonitrile/1-propanol/toluene (1:1:2) (95 mL). After the addition of Shi epoxidizing catalyst

(1.765 g) under ice-cooling, 30 % hydrogen peroxide aqueous solution (9.31 mL) was added dropwise thereto at an internal temperature of 2 °C, and the reaction mixture was stirred at the same temperature for 12 h. To the reaction solution were added hexane and water to extract the product. The organic layer was washed with water, brine and sodium sulfite, dried over anhydrous sodium sulfate, and the solvent was distilled off to provide the title compound (8.79 g).

^{1}HNMR (CDCl$_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.19-2.25 (1H, m), 2.29-2.36 (1H, m), 2.81-2.89 (1H, m), 3.08-3.14 (1H, m), 3.17 (1H, d, J = 13.7 Hz), 3.37 (1H, d, J = 4.5 Hz), 3.56-3.63 (1H, m), 6.72 (1H, t, J = 9.0 Hz), 7.13-7.19 (2H, m).

[0905]

Reference Example 618

(1R,6R)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-(4-chloro-2,6-difluorophenyl)-7-oxa-3-azabicyclo[4.1.0]heptane

Synthesized analogous to Reference Example 617.

^{1}HNMR (CDCl$_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.13-2.19 (1H, m), 2.23-2.31 (1H, m), 2.91-2.97 (1H, m), 3.07-3.14 (1H, m), 3.33-3.40 (2H, m), 3.51 (1H, dd, 13.7 Hz, 4.0 Hz), 6.83-6.90 (2H, m).

[0906]

Reference Example 619

(1R*,6R*)-3-(4-Bromo-2,6-difluorophenyl)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-7-oxa-3-azabicyclo[4.1.0]heptane

To a solution of 1-(4-bromo-2,6-difluorophenyl)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1,2,3,6-tetrahydropyridine (7.0 g) and 1,1,1-trifluoroacetone (0.93 mL) in acetonitrile/toluene/1-propanol (1: 2: 1) (84 mL) was added a solution of potassium carbonate (7.18 g) and ethylenediamine tetraacetic acid disodium salt (3.9 mg) in water (26 mL) at 0 °C. To the reaction mixture, 30 % hydrogen peroxide aqueous solution (7.07 mL) was added dropwise at an internal temperature of 3-5 °C, and the mixture was stirred at the same temperature for 9.5 h. To the reaction solution were added toluene and aqueous 1 M sodium thiosulfate to extract the product. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (6.58 g).

^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.17 (3H, s), 0.90 (9H, s), 2.12-2.19 (1H, m), 2.22-2.30 (1H, m), 2.91-2.98 (1H, m), 3.06-3.14 (1H, m), 3.34 (1H, d, J = 4.1 Hz), 3.37 (1H, d, J = 14.1 Hz), 3.53 (1H, dd, J = 14.1 Hz, 4.1 Hz), 6.97-7.03 (2H, m).

[0907]

Reference Example 620

(1R,6R)-3-(4-Bromo-2,6-difluorophenyl)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-7-oxa-3-azabicyclo[4.1.0]heptane

Synthesized analogous to Reference Example 617.

^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.14-2.18 (1H, m), 2.23-2.29 (1H, m), 2.92-2.97 (1H, m), 3.07-3.13 (1H, m), 3.35 (1H, d, J = 4.0 Hz), 3.37 (1H, d, J = 14.0 Hz), 3.53 (1H, dd, J = 14.0 Hz, 4.0 Hz), 6.98-7.03 (2H, m).

[0908]

Reference Example 621

(1R,6R)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-(4-chloro-2-fluorophenyl)-7-oxa-3-azabicyclo[4.1.0]heptane

Synthesized analogous to Reference Example 617.

^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.20-2.24 (1H, m), 2.29-2.34 (1H, m), 2.82-2.88 (1H, m), 3.07-3.11 (1H, m), 3.17 (1H, d, J = 14.0 Hz), 3.37 (1H, d, J = 4.3), 3.57-3.62 (1H, m), 6.79 (1H, t, J = 9.2 Hz), 6.99-7.04 (2H, m).

[0909]

Reference Example 622

($1R^*$,$6R^*$)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-(4-chloro-2,6-difluorophenyl)-7-oxa-3-azabicyclo[4.1.0]heptane

Synthesized analogous to Reference Example 619.

^{1}HNMR ($CDCl_3$) δ ppm: 0.14 (3H, s), 0.18 (3H, s), 0.90 (9H, s), 2.12-2.19 (1H, m), 2.22-2.31 (1H, m), 2.90-2.97 (1H, m), 3.06-3.15 (1H, m), 3.33-3.40 (2H, m), 3.53 (1H, dd, J = 14.0 Hz, 3.2 Hz), 6.83-6.90 (2H, m).

[0910]

Reference Example 623

(3R,4R)-6-(4-Chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

To a suspension of trimethylsulfoxonium iodide (3.44 g) in dimethyl sulfoxide (37 mL) was added sodium *tert*-butoxide (1.50 g), and the reaction mixture was stirred at room temperature for 30 min. Then a solution of (3R)-1-(4-chloro-2,6-difluorophenyl)-3-hydroxypiperidin-4-one (3.72 g, 81.7 % ee) in dimethyl sulfoxide (37 mL) was added to the mixture, and the reaction mixture was stirred at room temperature for 10 min. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off.

The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and recrystallization from ethanol to provide the title compound (1.49 g, 98 % ee).

^{1}HNMR ($CDCl_3$) δ ppm: 1.76 (1H, dt, J = 14.0 Hz, 4.0 Hz), 2.05 (1H, d, J = 11.0 Hz), 2.09 (1H, ddd, J = 14.0 Hz, 9.5 Hz, 4.5 Hz), 2.69 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.06-3.10 (1H, m), 3.13-3.18 (1H, m), 3.26-3.32 (1H, m), 3.39-3.44 (1H, m), 3.85 (1H, ddd, J = 11.0 Hz, 8.5 Hz, 4.5 Hz), 6.87-6.92 (2H, m).

[0911]

Reference Example 624

(3R*,4R*)-6-(4-Chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

Synthesized analogous to Reference Example 623.

^{1}HNMR ($CDCl_3$) δ ppm: 1.76 (1H, dt, J = 14.0 Hz, 4.0 Hz), 2.05 (1H, d, J = 11.0 Hz), 2.09 (1H, ddd, J = 14.0 Hz, 9.5 Hz, 4.5 Hz), 2.69 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.06-3.10 (1H, m), 3.13-3.18 (1H, m), 3.26-3.32 (1H, m), 3.39-3.44 (1H, m), 3.85 (1H, ddd, J = 11.0 Hz, 8.5 Hz, 4.5 Hz), 6.87-6.92 (2H, m).

[0912]

Reference Example 625

(3R*,4R*)-6-(4-Chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

To a suspension of 1-(4-chloro-2-fluorophenyl)piperidin-4-one (3.00 g) and DL-proline (0.455 g) in N,N-dimethylformamide (20 mL) was added a solution of nitrosobenzene (1.41 g) in N,N-dimethylformamide (40 mL) at 0 °C over 6 h, and the reaction mixture was stirred at the same temperature for 1 h. The reaction solution was poured into aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved in methanol (30 mL), copper (II) sulfate (0.631 g) was added to the solution and the mixture was stirred at 0 °C for 2 h. To the reaction solution was added brine and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtrated. To the filtrate was added dimethyl sulfoxide (30 mL) and the mixture was concentrated to give a solution of 1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-one (α-hydroxyketone compound) in dimethyl sulfoxide. To a suspension of trimethylsulfoxonium iodide (3.19 g) in dimethyl sulfoxide (30 mL) was added sodium *tert*-butoxide (1.39 g), and the reaction mixture was stirred at room temperature for 30 min. To the obtained mixture a solution of α-hydroxyketone compound in dimethyl sulfoxide was added, and the mixture was stirred at room temperature for 30 min. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate). The product was recrystallized from ethyl acetate/hexane to provide the title compound (647 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 3.5 Hz), 1.97 (1H, d, J = 11.0 Hz), 2.21 (1H, ddd, J = 14.0 Hz, 10.5 Hz, 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 2.80 (1H, dd, J = 11.0 Hz, 9.0 Hz), 2.99-3.04 (1H, m), 3.10 (1H, d, J = 4.5 Hz), 3.24-3.29 (1H, m), 3.47-3.52 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.0 Hz, 4.5 Hz), 6.91 (1H, t, J = 9.0 Hz), 7.04-7.08 (2H, m).

[0913]

Reference Example 626

(3R*,4R*)-6-(4-Bromo-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

Synthesized analogous to Reference Example 625.

^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 3.5 Hz), 1.96 (1H, d, J = 11.0 Hz), 2.21 (1H, ddd, J = 14.0 Hz, 11.0 Hz, 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 2.80 (1H, dd, J = 11.0 Hz, 9.0 Hz), 2.98-3.04 (1H, m), 3.10 (1H, d, J = 4.5 Hz), 3.24-3.29 (1H, m), 3.48-3.52 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.0 Hz, 4.5 Hz), 6.85 (1H, t, J = 9.0 Hz), 7.18-7.20 (2H, m).

[0914]

Reference Example 627

(3R,4R)-6-(4-Bromo-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

To a solution of 1-(4-bromo-2-fluorophenyl)-4-{[*tert*-butyl(diphenyl)silyl]oxy}-1,2,3,6-tetrahydropyridine (34.2 g) in acetonitrile-dimethoxymethane (240-240 mL) were added at 0 °C, 240 mL of buffer (0.05 M aqueous sodium tetraborate decahydrate in 4 x 10^{-4} M aqueous ethylenediamine tetraacetic acid disodium salt), Shi epoxidizing catalyst (6.86 g), and tetrabutylammonium hydrogensulfate (0.910 g). Thereafter, a solution of Oxone (Registered trade mark) (56.8 g) in 300 mL of 4 x 10^{-4} M aqueous ethylenediamine tetraacetic acid disodium salt and a solution of potassium carbonate (53.7 g) in water (300 mL) were added dropwise through two separate addition funnels over 2 h, and then the mixture was stirred at 0 °C for 2 h. To the reaction solution were added ice-cooled hexane and ice-cooled water to extract the product. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved in tetrahydrofuran-water (175-140 mL), 5 N hydrochloric acid (35 mL) was added to the solution, and the mixture was stirred at room temperature for 1 h. To the reaction solution was added water, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtrated. To the filtrate was added dimethyl sulfoxide (160 mL) and the solution was concentrated to give a solution of (R)-1-(4-bromo-2-fluorophenyl)-3-hydroxypiperidin-4-one (α-hydroxyketone compound) in dimethyl sulfoxide. To a suspension of trimethylsulfonium iodide (16.2 g) in dimethyl sulfoxide (160 mL) was added sodium *tert*-butoxide (7.08 g), and the reaction mixture was stirred at room temperature for 30 min. The solution of α-hydroxyketone compound in dimethyl sulfoxide was added to the mixture, and the obtained mixture was stirred at room temperature for 15 min. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and recrystallized from ethyl acetate/hexane to provide the title compound (3.27 g, 99 % ee).

^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 3.5 Hz), 1.96 (1H, d, J = 11.0 Hz), 2.21 (1H, ddd, J = 14.0 Hz, 11.0 Hz, 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 2.80 (1H, dd, J = 11.0 Hz, 9.0 Hz), 2.98-3.04 (1H, m), 3.10 (1H, d, J = 4.5 Hz), 3.24-3.29 (1H, m), 3.48-3.52 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.0 Hz, 4.5 Hz), 6.85 (1H, t, J = 9.0 Hz), 7.18-7.20 (2H, m).

[0915]

Reference Example 628

(3R*,4R*)-6-(4-Bromo-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

Synthesized analogous to Reference Example 625.

^{1}HNMR ($CDCl_3$) δ ppm: 1.76 (1H, dt, J = 14.0 Hz, 4.0 Hz), 2.05 (1H, d, J = 11.0 Hz), 2.09 (1H, ddd, J = 14.0 Hz, 10.0 Hz, 4.5 Hz), 2.69 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.06-3.10 (1H, m), 3.14-3.19 (1H, m), 3.26-3.32 (1H, m), 3.40-3.44 (1H, m), 3.85 (1H, ddd, J = 11.0 Hz, 8.5 Hz, 4.5 Hz), 7.02-7.07 (2H, m).

[0916]

Reference Example 629

(3R,4R)-6-(4-Bromo-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

Synthesized analogous to Reference Example 627.

^{1}HNMR ($CDCl_3$) δ ppm: 1.76 (1H, dt, J = 14.0 Hz, 4.0 Hz), 2.05 (1H, d, J = 11.0 Hz), 2.09 (1H, ddd, J = 14.0 Hz, 10.0 Hz, 4.5 Hz), 2.69 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.06-3.10 (1H, m), 3.14-3.19 (1H, m), 3.26-3.32 (1H, m), 3.40-3.44 (1H, m), 3.85 (1H, ddd, J = 11.0 Hz, 8.5 Hz, 4.5 Hz), 7.02-7.07 (2H, m).

[0917]

Reference Example 630

(3R,4R)-6-(4-Chloro-2-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

Synthesized analogous to Reference Example 627.

^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 3.5 Hz), 1.97 (1H, d, J = 11.0 Hz), 2.21 (1H, ddd, J = 14.0 Hz, 10.5 Hz, 4.5 Hz), 2.72 (1H, d, J = 4.5 Hz), 2.80 (1H, dd, J = 11.0 Hz, 9.0 Hz), 2.99-3.04 (1H, m), 3.10 (1H, d, J = 4.5 Hz), 3.24-3.29 (1H, m), 3.47-3.52 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.0 Hz, 4.5 Hz), 6.91 (1H, t, J = 9.0 Hz), 7.04-7.08 (2H, m).

[0918]

Reference Example 631

($3R^*$,$4R^*$)-6-(4-fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

Synthesized analogous to Reference Example 625.

^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 4.0 Hz), 1.94 (1H, d, J = 11.0 Hz), 2.17 (1H, ddd, J = 14.0 Hz, 10.5 Hz, 4.5 Hz), 2.71 (1H, d, J = 4.5 Hz), 2.83 (1H, dd, J = 11.5 Hz, 9.0 Hz), 3.04-3.09 (1H, m), 3.09 (1H, d, J = 4.5 Hz), 3.34-3.38 (1H, m), 3.60-3.63 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.5 Hz, 4.5 Hz), 6.91-7.00 (4H, m).

[0919]

Reference Example 632

(3R,4R)-6-(4-Fluorophenyl)-1-oxa-6-azaspiro[2.5]octan-4-ol

To a suspension of 1-(4-fluorophenyl)piperidin-4-one (10.3 g) and (S)-5-(pyrrolidin-2-yl)-1H-tetrazole (0.371 g) in N,N-dimethylformamide (100 mL) was added a solution of nitrosobenzene (5.71 g) in N,N-dimethylformamide (100 mL) over 6.5 h at -20 °C, and the reaction mixture was stirred at the same temperature for 1 h. The reaction solution was poured into ice-cooled aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved in methanol (100 mL), copper (II) sulfate (2.55 g) was added to the solution and the mixture was stirred at 0 °C for 2 h. To the reaction solution was added brine, and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtrated. To the filtrate was added dimethyl sulfoxide (100 mL) and the mixture was concentrated to give a solution of (R)-1-(4-fluorophenyl)-3-hydroxypiperidin-4-one (α-hydroxyketone compound) in dimethyl sulfoxide. To a suspension of trimethylsulfonium iodide (12.9 g) in dimethyl sulfoxide (100 mL) was added sodium *tert*-butoxide (5.64 g), and the mixture was stirred at 1 h. To the mixture was added the solution of α-hydroxyketone compound in dimethyl sulfoxide and the reaction mixture was stirred at room temperature for 15 min. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and recrystallized from ethyl acetate/hexane to provide the title compound (1.01 g, > 99 % ee).

^{1}HNMR ($CDCl_3$) δ ppm: 1.74 (1H, dt, J = 14.0 Hz, 4.0 Hz), 1.94 (1H, d, J = 11.0 Hz), 2.17 (1H, ddd, J = 14.0 Hz, 10.5 Hz, 4.5 Hz), 2.71 (1H, d, J = 4.5 Hz), 2.83 (1H, dd, J = 11.5 Hz, 9.0 Hz), 3.04-3.09 (1H, m), 3.09 (1H, d, J = 4.5 Hz), 3.34-3.38 (1H, m), 3.60-3.63 (1H, m), 3.96 (1H, ddd, J = 11.0 Hz, 9.5 Hz, 4.5 Hz), 6.91-7.00 (4H, m).

[0920]

Reference Example 633

tert-Butyl (1S*,6S*)-6-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate

To a solution of *tert*-butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,6-dihydropyridine-1(2H)-carboxylate (3.06 g) in chloroform (30 mL) was added 75 % *meta*-chloroperoxybenzoic acid (2.81 g) and the reaction mixture was stirred at room temperature overnight. After insoluble materials were filtered off, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (2.8 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.96-2.06 (1H, m), 2.07-2.20 (1H, m), 2.59-2.67 (2H, m), 2.96-3.03 (2H, m), 3.06-3.22 (1H, m), 3.25-3.37 (1H, m), 3.51-3.80 (2H, m), 3.82-4.16 (3H, m), 6.42 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.90 (1H, t, J = 9.3 Hz), 7.59 (1H, brs).

[0921]

Reference Example 634

tert-Butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate

Synthesized analogous to Reference Example 633.

^{1}HNMR ($CDCl_3$) δ ppm: 1.46 (9H, s), 1.94-2.04 (1H, m), 2.06-2.18 (1H, m), 2.58-2.68 (2H, m), 2.81-2.91 (2H, m), 3.06-3.20 (1H, m), 3.24-3.39 (1H, m), 3.51-3.79 (2H, m), 3.74 (3H, s), 3.82-4.18 (3H, m), 5.17-5.27 (2H, m), 6.47 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.72-6.78 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.08-7.15 (2H, m).

[0922]

Reference Example 635

tert-Butyl (3R*,4S*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3,4-dihydroxypiperidine-1-carboxylate

To a solution of *tert*-butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (9.3 g) in anisole (0.4 mL) was added trifluoroacetic acid (40 mL) dropwise, the reaction mixture was stirred while heating at 60 °C for 3 h, and the solvent was distilled off. To the residue, methanol (40 mL) and triethylamine (7.6 mL) followed by di-*tert*-butyl dicarbonate (4.6 mL) were added, and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added 5 N aqueous sodium hydroxide and the reaction mixture was stirred at 60 °C for 15 h. After the reaction mixture was allowed to cool to room temperature, the precipitate was collected on a filter and purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (2.0 g).

^{1}HNMR (DMSO-d6) δ ppm: 1.32-1.39 (1H, m), 1.39 (9H, s), 1.66-1.79 (1H, m), 2.40-2.48 (2H, m), 2.86-3.00 (2H, m), 3.38-3.43 (1H, m), 3.52-3.82 (5H, m), 3.86-3.94 (1H, m), 4.82 (1H, brs), 4.86-4.96 (1H, m), 6.54 (1H, dd, J = 9.1 Hz, 3.8 Hz), 6.98 (1H, t, J = 9.2 Hz), 9,98 (1H, brs).

[0923]

Reference Example 636

tert-Butyl (3R*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 43.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.50-1.57 (1H, m), 1.83-1.92 (1H, m), 2.38 (1H, brs), 2.65 (2H, t, J = 7.1 Hz), 2.80-2.91 (2H, m), 3.12-3.24 (1H, m), 3.34-3.51 (1H, m), 3.71-3.79 (2H, m), 3.74 (3H, s), 3.86-4.09 (3H, m), 5.23 (2H, brs), 6.55 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.74-6.78 (2H, m), 6.83 (1H, dd, J = 12.3 Hz, 9.2 Hz), 7.10-7.14 (2H, m).

[0924]

Reference Example 637

tert-Butyl (3R*,4S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 530.

^{1}HNMR ($CDCl_3$) δ ppm: -0.15 (3H, s), 0.09-0.17 (3H, m), 0.76-0.86 (9H, m), 1.46 (9H, s), 1.47-1.55 (1H, m), 1.86-1.97 (1H, m), 2.28 (1H, brs), 2.57-2.70 (2H, m), 2.82-2.90 (2H, m), 3.07-3.39 (2H, m), 3.62-3.72 (2H, m), 3.73 (3H, s), 3.79-3.92 (1H, m), 3.93-4.08 (2H, m), 5.23 (2H, brs), 6.46 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.72-6.78 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.2 Hz), 7.09-7.14 (2H, m).

[0925]

Reference Example 638

5-({(3R*,4S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(trimethylsilyl)oxy]piperidin-4-yl}methoxy)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 539.

^{1}HNMR ($CDCl_3$) δ ppm: -0.17 (3H, s), 0.04 (3H, s), 0.05 (9H, s), 0.81 (9H, s), 1.39-1.45 (1H, m), 1.69-1.77 (1H, m), 2.62 (2H, t, J = 7.0 Hz), 2.65-2.71 (1H, m), 2.79-2.98 (4H, m), 3.12-3.17 (1H, m), 3.61-3.66 (2H, m), 3.73 (3H, s), 3.91 (1H, d, J = 9.4 Hz), 5.12-5.32 (2H, m), 6.41 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.71-6.76 (2H, m), 6.82 (1H, dd, J = 12.6 Hz, 9.2 Hz), 7.08-7.13 (2H, m).

[0926]

Reference Example 639

5-{[(3R*,4S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.11 (3H, s), 0.02 (3H, s), 0.78 (9H, s), 1.60-1.68 (1H, m), 2.19-2.27 (1H, m), 2.30 (1H, brs), 2.59-2.70 (2H, m), 2.83-2.92 (2H, m), 3.11-3.27 (3H, m), 3.32-3.37 (1H, m), 3.73 (3H, s), 3.77-3.81 (1H, m), 3.82-3.86 (1H, m), 4.03-4.09 (1H, m), 5.23 (2H, brs), 6.49 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.81-6.90 (2H, m), 6.98-7.05 (2H, m), 7.09-7.16 (2H, m).

[0927]

Reference Example 640

5-{[(3R*,4S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(2,4-dichlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR ($CDCl_3$) δ ppm: -0.06 (3H, s), 0.01 (3H, s), 0.81 (9H, s), 1.64-1.71 (1H, m), 2.26-2.32 (2H, m), 2.61-2.72 (2H, m), 2.87-2.92 (2H, m), 2.93-2.99 (1H, m), 3.03-3.10 (1H, m), 3.13-3.19 (1H, m),3.40-3.46 (1H, m), 3.76 (3H, s), 3.89 (1H, d, J = 9.0 Hz), 3.92-3.95 (1H, m), 4.10 (1H, d, = 9.0 Hz), 5.26 (2H, brs), 6.53 (1H, dd, J = 9.2 Hz, 3.2 Hz), 6.75-6.80 (2H, m), 6.87 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.97 (1H, d, J = 8.7 Hz), 7.12-7.16 (2H, m), 7.19 (1H, dd, J = 8.7 Hz, 2.5 Hz), 7.37 (1H, d, J = 2.5 Hz).

[0928]

Reference Example 641

5-{[(3R*,4S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-chloro-2,5-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 70.

^{1}HNMR (CDCl$_3$) δ ppm: -0.13 (3H, s), 0.01 (3H, s), 0.75 (9H, s), 1.59-1.64 (1H, m), 2.16-2.24 (1H, m), 2.30 (1H, s), 2.59-2.70 (2H, m), 2.83-2.89 (2H, m), 3.17-3.31 (3H,m), 3.36 (1H, dd,J = 12.7 Hz, 2.2 Hz), 3.73 (3H, s), 3.75 (1H, d, J = 8.9 Hz), 3.79-3.83 (1H, m), 4.04 (1H, d, J = 8.9 Hz), 5.23 (2H, brs), 6.48 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.71 (1H, dd, J = 10.9 Hz, 7.7 Hz), 6.73-6.77 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.03 (1H, dd, J = 11.9 Hz, 7.0 Hz), 7.09-7.14 (2H, m).

[0929]

Reference Example 642

8-Fluoro-1-(4-methoxybenzyl)-5-[(trimethylsilyl)ethinyl]-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, to a solution of 8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl trifluoromethanesulfonate (433 mg), trimethylsilylacetylene (0.166 mL), bis(triphenylphosphine)palladium (II) dichloride (70 mg) and copper (I) iodide (38 mg) in N-methyl-2-pyrrolidone (3 mL) was added triethylamine (0.697 mL), and the mixture was stirred at 50 °C for 18 h. The reaction solution was poured into 1 N hydrochloric acid, and the solution was extracted with dichloromethane. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (222 mg).

^{1}HNMR (CDCl$_3$) δ ppm: 0.25 (9H, s), 2.66-2.69 (2H, m), 3.03-3.06 (2H, m), 3.74 (3H, s), 5.22 (2H, brs), 6.73-6.79 (2H, m), 6.80-6.85 (1H, m), 7.08-7.12 (3H, m).

[0930]

Reference Example 643

5-Ethinyl-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-fluoro-1-(4-methoxybenzyl)-5-[(trimethylsilyl)ethinyl]-3,4-dihydroquinolin-2(1H)-one (220 mg) in tetrahydrofuran (2 mL) was added tetrabutylammonium fluoride (1 M tetrahydrofuran solution) (0.692 mL), and the mixture was stirred at room temperature for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (16 mg).

^{1}HNMR (CDCl$_3$) δ ppm: 2.66-2.70 (2H, m), 3.06-3.09 (2H, m), 3.24 (1H, s), 3.74 (3H, s), 5.22 (2H, brs), 6.74-6.76 (2H, m), 6.83-6.88 (1H, m), 7.09-7.15 (3H, m).

[0931]

Reference Example 644

5-{[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethinyl}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 5-ethinyl-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (166 mg) in tetrahydrofuran (2 mL), n-butyllithium (1.6 M hexane solution) (0.351 mL) was added dropwise at -60 °C, and the reaction mixture was stirred at the same temperature for 1 h. To the mixture was added a solution of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (120 mg) in tetrahydrofuran (1 mL) dropwise, and the reaction mixture was stirred at -60 °C for 2 h, then at room temperature for 18 h. To the reaction solution was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (110 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.97-2.04 (2H, m), 2.08-2.12 (3H, m), 2.67-2.71 (2H, m), 3.04-3.07 (2H, m), 3.21-3.31 (4H, m), 3.74 (3H, s), 5.23 (2H, brs), 6.72-6.77 (2H, m), 6.84-6.89 (3H, m), 7.08-7.12 (3H, m).

[0932]

Reference Example 645

5-{2-[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethinyl}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (0.105 g) in ethanol (2 mL) was added palladium-carbon ethylenediamine complex (palladium 3.5-6.5 %) (50 mg), and the reaction mixture was stirred at room temperature for 1 h under hydrogen atmosphere. The catalyst was filtered off with Celite, and the filtrate was concentrated to provide the title compound (99 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.69 (4H, m), 1.77-1.85 (2H, m), 2.63-2.70 (4H, m), 2.82-2.85 (2H, m), 3.02-3.06 (2H, m), 3.33-3.38 (2H, m), 3.74 (3H, s), 5.21 (2H, s), 6.74-6.77 (2H, m), 6.81-6.90 (4H, m), 7.12 (2H, d, J = 8.5 Hz).

[0933]

Reference Example 646

O-[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl] dimethylcarbamothioate

Under argon atmosphere, to a solution of 8-fluoro-5-hydroxy-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (5.0 g) in N,N-dimethylformamide (50 mL) was added sodium hydride (55 % in oil) (0.796 g) under ice-cooling, and the reaction mixture was stirred at room temperature for 45 min. To the reaction mixture, a solution of dimethylthiocarbamoyl chloride (3.28 g) in N,N-dimethylformamide (5 mL) was added dropwise, and the mixture was stirred at 60 °C for 2.5 h. The reaction solution was poured into cold ammonium chloride aqueous solution, and hexane was added to the mixture and the obtained solution was stirred. The precipitate was collected on a filter to provide the title compound (6.40 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.63-2.68 (2H, m), 2.68-2.73 (2H, m), 3.34 (3H, s), 3.45 (3H, s), 3.74 (3H, s), 5.22 (2H, brs), 6.67 (1H, dd, J = 9.0 Hz, 3.9 Hz), 6.74-6.79 (2H, m), 6.91 (1H, dd, J = 12.4 Hz, 9.0 Hz), 7.09-7.15 (2H, m).

[0934]

Reference Example 647

S-[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl] dimethylcarbamothioate

Under argon atmosphere, a suspension of O-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl] dimethylcarbamothioate (3.0 g) in diphenyl ether (15 mL) was stirred at 200 °C for 5 days. To the reaction solution was added hexane, and after stirring the mixture, the supernatant thereof was removed by decantation. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.15 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.63-2.70 (2H, m), 2.93-3.06 (5H, m), 3.10 (3H, brs), 3.74 (3H, s), 5.20 (2H, brs), 6.75-6.79 (2H, m), 6.90 (1H, dd, J = 12.6 Hz, 8.6 Hz), 7.10-7.14 (2H, m), 7.16 (1H, dd, J = 8.6 Hz, 4.7 Hz).

[0935]

Reference Example 648

8-Fluoro-1-(4-methoxybenzyl)-5-sulfanyl-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere, to a suspension of S-[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl] dimethylcarbamothioate (1.15 g) in methanol/water (1:1) (20 mL) was added 5 N aqueous sodium hydroxide (2.96 mL) and the reaction mixture was heated to reflux for 3 h. The reaction solution was poured into ice water and was made weak acidic with 5 N hydrochloric acid, and the precipitate was collected on a filter. The obtained solid was dissolved into dichloromethane, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was washed with hexane/diisopropyl ether to provide the title compound (0.83 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.63-2.70 (2H, m), 2.90-2.97 (2H, m), 3.24 (1H, s), 3.74 (3H, s), 5.21 (2H, brs), 6.73-6.77 (2H, m), 6.80 (1H, dd, J = 12.7 Hz, 8.7 Hz), 6.98 (1H, dd, J = 8.7 Hz, 4.4 Hz), 7.07-7.12 (2H, m).

[0936]

Reference Example 649

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 453.

^{1}HNMR ($CDCl_3$) δ ppm: 1.67-1.81 (4H, m), 1.99 (1H, s), 2.63-2.69 (2H, m), 2.97-3.04 (4H, m), 3.06-3.11 (2H, m), 3.11-3.17 (2H, m), 3.71 (3H, s), 5.21 (2H, brs), 6.72-6.76 (2H, m), 6.84-6.91 (2H, m), 7.01-7.06 (2H, m), 7.07-7.12 (2H, m), 7.16 (1H, dd, J = 8.7 Hz, 4.5 Hz).

[0937]

Reference Example 650

5-({[1-(4-Chloro-2-fluorophenyl)-4-hydroxy-1-oxidepiperidin-4-yl]methyl}sulfonyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

To a suspension of 5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one (0.25 g) in chloroform (10 mL) was added m-chloroperoxybenzoic acid (contain 25 % water) (0.419 g) and the reaction mixture was stirred at room temperature for 7.5 h. The solvent was distilled off, the residue was washed with saturated aqueous sodium hydrogencarbonate and ethyl acetate, and crystalized from ethyl acetate to provide the title compound (0.25 g).

^{1}HNMR (DMSO-d6) δ ppm: 1.73-1.85 (2H, m), 2.51-2.60 (2H, m), 2.63-2.75 (2H, m), 2.76-2.86 (2H, m), 3.30-3.45 (2H, m), 3.57 (2H, s), 4.10-4.21 (2H, m), 4.70-5.50 (1H, broad signal), 7.37 (1H, t, J = 9.4 Hz), 7.48 (1H, dd, J = 8.9 Hz, 2.2 Hz), 7.58 (1H, dd, J = 8.9 Hz, 5.1 Hz), 7.64 (1H, dd, J = 12.4 Hz, 2.2 Hz), 8.71 (1H, t, J = 9.2 Hz), 10.41 (1H, brs).

[0938]

Reference Example 651

tert-Butyl (3R*,4R*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxy-3-(methylamino) piperidine-1-carboxylate

To *tert*-butyl (1S*,6S*)-6-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (0.39 g) was added 40 % methylamine in methanol (30 mL) and the reaction mixture was heated to reflux for 6 h. The reaction solvent was distilled off to provide the title compound. The compound was used for the next step without further purification.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.49-1.82 (4H, m), 2.42 (3H, s), 2.47-2.57 (1H, m), 2.64 (2H, t, J = 7.9 Hz), 2.99 (2H, t, J = 7.9 Hz), 3.13-3.52 (2H, m), 3.62-4.02 (3H, m), 4.06-4.18 (1H, m), 6.52 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.91 (1H, t, J = 9.3 Hz), 7.66 (1H, brs).

[0939]

Reference Example 652

8-Fluoro-5-{[(3R*,4R*)-4-hydroxy-3-(methylamino) piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one dihydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.81-1.93 (1H, m), 2.30-2.40 (1H, m), 2.42-2.49 (2H, m), 2.70 (3H, brs), 2.89-2.98 (2H, m), 3.10-3.30 (3H, m), 3.46-3.55 (1H, m), 3.56-3.68 (1H, m), 4.09-4.25 (3H, m), 6.63-6.72 (1H, m), 7.03-7.12 (1H, m), 8.91 (1H, brs), 9.51 (1H, brs), 9.59 (1H, brs), 9.83 (1H,brs), 10.05 (1H, brs).

[0940]

Reference Example 653

tert-Butyl (3R*,4R*)-3-amino-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 651.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.49-1.74 (3H, m), 1.79-1.91 (1H, m), 2.26-2.42 (1H, m), 2.64 (2H, t, J = 7.9 Hz), 2.93-3.06 (3H, m), 3.18-3.34 (1H, m), 3.47-3.79 (2H, m), 3.80-3.98 (2H, m), 4.09-4.19 (1H, m), 6.51 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.57 (1H, brs).

[0941]

Reference Example 654

5-{[(3R*,4R*)-3-Amino-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one dihydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.79-1.89 (1H, m), 2.29-2.39 (1H, m), 2.41-2.49 (2H, m), 2.87-2.98 (2H, m), 3.09-3.29 (2H, m), 3.30-3.62 (3H, m), 3.90-3.90 (1H, m), 4.01-4.07 (1H, m), 4.11-4.18 (1H, m), 6.60-6.80 (1H, m), 7.01-7.11 (1H, m), 8.72 (3H, brs), 9.47 (1H, brs), 9.69 (1H, brs), 10.04 (1H, brs).

[0942]

Reference Example 655

tert-Butyl (3S*,4S*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxy-3-methylpiperidine-1-carboxylate

Under argon atmosphere, to a suspension of *tert*-butyl (1S*,6S*)-6-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (0.5 g) and copper (I) bromide-dimethylsulfide complex (0.026 g) in tetrahydrofuran (10 mL) was added dropwise methylmagnesium chloride (3M tetrahydrofuran solution) (1.27 mL) at 0 °C, and the reaction mixture was heated to reflux for 3.5 h. To the reaction solution was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.25 g).

^{1}HNMR (CDCl$_3$) δ ppm: 0.99 (3H, d, J = 7.1 Hz), 1.47 (9H, s), 1.50-1.57 (1H, m), 1.77-1.86 (1H, m), 1.86-2.01 (1H, m), 2.17 (1H, brs), 2.65 (2H, t, J = 7.7 Hz), 2.95-3.03 (2H, m), 3.14-

3.42 (1H, m), 3.45-3.53 (1H, m), 3.59-3.66 (1H, m), 3.68-4.02 (3H, m), 6.47 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.5 Hz), 7.51 (1H, brs).

[0943]

Reference Example 656

8-Fluoro-5-{[(3S*,4S*)-4-hydroxy-3-methylpiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 60.

^{1}HNMR ($CDCl_3$) δ ppm: 1.05 (3H, d, J = 7.2 Hz), 1.48-1.56 (1H, m), 1.56-1.70 (1H, broad signal), 1.83-1.96 (2H, m), 2.20 (1H, brs), 2.60 (1H, dd, J = 12.7 Hz, 5.6 Hz), 2.63-2.67 (2H, m), 2.79-2.86 (1H, m), 3.00 (2H, t, J = 7.7 Hz), 3.03-3.10 (1H, m), 3.21 (1H, dd, J = 12.7 Hz, 3.8 Hz), 3.84-3.93 (2H, m), 6.48 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.57 (1H, brs).

[0944]

Reference Example 657

tert-Butyl (3S*,4R*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxy-3-methoxypiperidine-1-carboxylate

To a suspension of *tert*-butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (0.4 g) in methanol (5 mL) was added sodium methoxide (5M methanol solution) (1.56 mL), and the reaction mixture was stirred at 60 °C for 32 h. To the reaction solution was added acetic acid (0.45 mL) and the solvent was distilled off. Water was added to the residue, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.29 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.42-1.52 (10H, m), 1.77-1.86 (1H, m), 2.32 (1H, brs), 2.60-2.68 (2H, m), 2.79-2.89 (2H, m), 3.03-3.27 (3H, m), 3.33 (3H, brs), 3.69-4.07 (3H, m), 3.74 (3H,s), 4.08-4.32 (1H, m), 5.16-5.28 (2H, m), 6.55 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.78 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

[0945]

Reference Example 658

8-Fluoro-5-{[(3S*,4R*)-4-hydroxy-3-methoxypiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 60.

^{1}HNMR ($CDCl_3$) δ ppm: 1.44-1.51 (1H, m), 1.51-1.70 (1H, broad signal), 1.70-1.79 (1H, m), 2.27 (1H, brs), 2.62-2.67 (2H, m), 2.82-2.90 (3H, m), 2.94-3.02 (1H, m), 3.02-3.09 (2H, m), 3.09-3.14 (1H, m), 3.31 (3H, s), 3.73 (1H, d, J = 9.0 Hz), 3.74 (3H, s), 4.03 (1H, d, J = 9.0 Hz), 5.17-5.28 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.74-6.78 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

[0946]

Reference Example 659

5-{[(3S*,4R*)-1-(3,5-Dichloropyridin-2-yl)-4-hydroxy-3-methoxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 66.

^{1}HNMR ($CDCl_3$) δ ppm: 1.62-1.68 (1H, m), 2.16-2.25 (1H, m), 2.37 (1H, s), 2.62-2.69 (2H, m), 2.85-2.91 (2H, m), 3.28 (3H, s), 3.31-3.40 (2H, m), 3.42-3.48 (1H, m), 3.60-3.67 (1H, m), 3.74 (3H, s), 3.85 (1H, d, J = 9.1 Hz), 3.89-3.97 (1H, m), 4.10 (1H, d, J = 9.1 Hz), 5.16-5.28 (2H, m), 6.57 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.78 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.58 (1H, d, J = 2.3 Hz), 8.10 (1H, d, J = 2.3 Hz).

[0947]

Reference Example 660

tert-Butyl (3R*,4S*)-3-cyano-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

Under argon atmosphere, to a solution of acetonecyanohydrin (0.342 mL) in tetrahydrofuran (4 mL) was added lithium hydride (0.028 g) and the reaction mixture was stirred at room temperature for 2 h. Then, to the mixture was added *tert*-butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (0.6 g) and the reaction mixture was heated to reflux for 7 h. After the reaction solution was allowed to cool to room temperature, water was added thereto, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.53 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.50 (9H, s), 1.62-1.70 (1H, m), 1.86-1.95 (1H, m), 2.50 (1H, s), 2.62-2.69 (2H, m), 2.77-3.03 (3H, m), 3.03-3.31 (1H, m), 3.31-3.60 (1H, m), 3.74 (3H, s), 3.90 (1H, d, J = 9.4 Hz), 3.93-4.49 (3H, m), 5.14-5.31 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.87 (1H, dd, J = 12.5 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

[0948]

Reference Example 661

(3R*,4S*)-4-({[8-Fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-3-carbonitrile

Synthesized analogous to Reference Example 60.

^{1}HNMR ($CDCl_3$) δ ppm: 1.54-1.68 (2H, m), 1.79-1.88 (1H, m), 2.42 (1H, brs), 2.66 (2H, t, J = 7.0 Hz), 2.79-2.92 (3H, m), 2.95-3.02 (1H, m), 3.02-3.11 (1H, m), 3.17 (1H, dd, J = 13.1 Hz, 2.2 Hz), 3.34 (1H, dd, J = 13.1 Hz, 3.1 Hz), 3.74 (3H, s), 3.88 (1H, d, J = 9.4 Hz), 4.10 (1H, d, J = 9.4 Hz), 5.17-5.29 (2H, m), 6.57 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.86 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

[0949]

Reference Example 662

(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-3-carbonitrile

Synthesized analogous to Reference Example 66.

^{1}HNMR ($CDCl_3$) δ ppm: 1.79-1.85 (1H, m), 2.19-2.26 (1H, m), 2.48 (1H, s), 2.68 (2H, t, J = 7.1 Hz), 2.82-2.94 (2H, m), 3.09-3.12 (1H, m), 3.25-3.33 (1H, m), 3.52 (1H, dd, J = 12.9 Hz, 2.8 Hz), 3.65-3.72 (1H, m), 3.74 (3H, s), 3.91-3.97 (1H, m), 3.98 (1H, d, J = 9.4 Hz), 4.20 (1H, d, J = 9.4 Hz), 5.16-5.30 (2H, m), 6.60 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.80 (2H, m), 6.88 (1H, dd, J = 12.5 Hz, 9.1 Hz), 7.10-7.15 (2H, m), 7.65 (1H, d, J = 2.3 Hz), 8.15 (1H, d, J = 2.3 Hz).

[0950]

Reference Example 663

tert-Butyl (3R*,4S*)-3-fluoro-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidine-1-carboxylate

To *tert*-butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate

(0.51 g) was added tetrabutylammonium dihydrogen trifluoride (2.0 g, excess), and the reaction mixture was stirred at 120 °C for 2 days. To the reaction solution was added water and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.36 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.57-1.62 (1H, m), 1.78-1.91 (1H, m), 2.42-2.48 (1H, m), 2.61-2.69 (2H, m), 2.79-2.93 (2H, m), 3.03-3.49 (2H, m), 3.75 (3H, m), 3.75-3.79 (1H, m), 3.90-4.06 (2H, m), 4.21-4.79 (2H, m), 5.16-5.29 (2H, m), 6.54 (1H, dd, J = 9.0 Hz, 3.3 Hz), 6.72-6.79 (2H, m), 6.85 (1H, dd, J = 12.6 Hz. 9.1 Hz), 7.05-7.16 (2H, m).

[0951]

Reference Example 664

8-Fluoro-5-{[(3R*,4S*)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.72-1.80 (1H, m), 1.83-1.92 (1H, m), 2.56-2.65 (2H, m), 2.81-3.02 (2H, m), 3.06-3.20 (2H, m), 3.44-3.56 (1H, m), 3.68 (3H, s), 3.81-3.90 (1H, m), 3.92-4.00 (1H, m), 4.77-4.83 (1H, m), 4.88-4.94 (1H, m), 5.05-5.16 (2H, m), 5.81 (1H, brs), 6.72 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.77-6.85 (2H, m), 6.99 (1H, dd, J = 9.1 Hz, 4.2 Hz), 7.03-7.11 (2H, m), 8.66 (1H, brs), 9.27 (1H, brs).

[0952]

Reference Example 665

5-{[(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 66.

^{1}HNMR (CDCl$_3$) δ ppm: 1.68-1.77 (1H, m), 2.17-2.28 (1H, m), 2.48-2.58 (1H, m), 2.61-2.70 (2H, m), 2.81-2.94 (2H, m), 3.21-3.31 (1H, m), 3.44-3.61 (1H, m), 3.74 (3H, s), 3.75-3.86 (2H, m), 4.02-4.13 (2H, m), 4.56-4.72 (1H, m), 5.16-5.30 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.72-6.80 (2H, m), 6.85 (1H, dd, J = 12.6 Hz. 9.1 Hz), 7.09-7.16 (2H, m), 7.60 (1H, d, J = 2.3 Hz), 8.10 (1H, d, J = 2.3 Hz).

[0953]

Reference Example 666

4-[(Acetyloxy)methyl]-1-(4-methoxybenzyl)-3-methylpyridinium chloride

A solution of (3-methylpyridin-4-yl)methyl acetate (20.4 g) and 4-methoxybenzyl chloride (15.6 mL) in acetonitrile (120 mL) was stirred at 100 °C for 8 h. The reaction solution was allowed to cool to room temperature, and the precipitate was collected on a filter which was washed with ethyl acetate to provide the title compound (23.1 g).

^{1}HNMR (DMSO-d6) δ ppm: 2.20 (3H, s), 2.43 (3H, s), 3.75 (3H, s), 5.36 (2H, s), 5.73 (2H, s), 6.96-7.02 (2H, m), 7.52-7.58 (2H, m), 8.01 (1H, d, J = 8.0 Hz), 9.08 (1H, d, J = 8.0 Hz), 9.16 (1H, s).

[0954]

Reference Example 667

[1-(4-Methoxybenzyl)-5-methyl-1,2,3,6-tetrahydropyridin-4-yl]methyl acetate

To a solution of 4-[(acetyloxy)methyl]-1-(4-methoxybenzyl)-3-methylpyridinium chloride (23.1 g) in methanol (200 mL) was added at -20 °C sodium borohydride (8.86 g), and the reaction mixture was stirred at the same temperature for 30 min. To the reaction solution was added water, the mixture was stirred overnight, the solvent was distilled off, ethyl acetate was added to the residue, and insoluble materials were filtered off. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (6.8 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.66 (3H, s), 2.05 (3H, s), 2.13-2.22 (2H, m), 2.53 (2H, t, J = 7.2 Hz), 2.84-2.90 (2H, m), 3.49-3.54 (2H, m), 3.81 (3H, s), 4.57-4.61 (2H, m), 6.83-6.89 (2H, m), 7.22-7.29 (2H, m).

[0955]

Reference Example 668

tert-Butyl 4-(hydroxymethyl)-5-methyl-3,6-dihydropyridine-1(2H)-carboxylate

To a solution of [1-(4-methoxybenzyl)-5-methyl-1,2,3,6-tetrahydropyridin-4-yl]methyl acetate (0.33 g) in dichloromethane (10 mL) was added 2-chloroethyl chloroformate (0.19 mL) and the reaction mixture was stirred at 50 °C for 5 h. The solvent was distilled off and to the residue was added methanol (10 mL) and the reaction mixture was stirred at 70 °C for 2 h. After the reaction was completed, the solvent was distilled off, and the residue was dissolved in methanol (10 mL). To the solution were added triethylamine (0.48 mL) and di-*tert*-butyl dicarbonate (0.39 mL), and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added 2 N aqueous sodium hydroxide (10 mL), the reaction mixture was stirred at 1 h, to which an aqueous solution of 2 M citric acid was added and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.20 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.50-1.65 (2H, m), 1.71 (3H, s), 2.20-2.30 (2H, m), 3.45-3.55 (2H, m), 4.16 (2H, brs).

[0956]

Reference Example 669

tert-Butyl 4-(chloromethyl)-5-methyl-3,6-dihydropyridine-1(2H)-carboxylate

To a solution of *tert*-butyl 4-(hydroxymethyl)-5-methyl-3,6-dihydropyridine-1(2H)-carboxylate (3.57 g) in acetonitrile (50 mL) were added triethylamine (3.06 mL) and methanesulfonyl chloride (1.46 mL) at 0 °C, and the reaction mixture was stirred at room temperature overnight. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (2.53 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.74 (3H, s), 2.15-2.28 (2H, m), 3.45-3.55 (2H, m), 3.73-3.86 (2H, m), 4.07-4.12 (2H, m).

[0957]

Reference Example 670

tert-Butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-5-methyl-3,6-dihydropyridine-1(2H)-carboxylate

Synthesized analogous to Reference Example 495.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.69 (3H, brs), 2.16-2.26 (2H, m), 2.58-2.66 (2H, m), 2.81-2.89 (2H, m), 2.44-2.54 (2H, m), 3.74 (3H, s), 3.76-3.84 (2H, m), 4.42-4.47 (2H, m), 5.18-5.26 (2H, m), 6.51 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.78 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

[0958]

Reference Example 671

tert-Butyl (1S*,6S*)-6-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-1-methyl-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate

Synthesized analogous to Reference Example 633.

^{1}HNMR ($CDCl_3$) δ ppm: 1.37 (3H, s), 1.46 (9H, s), 2.02-2.20 (2H, m), 2.60-2.69 (2H, m), 2.81-2.95 (2H, m), 3.14-3.47 (2H, m), 3.48-3.76 (2H, m), 3.74 (3H, s), 3.93-4.08 (2H, m), 5.17-5.29 (2H, brs), 6.50 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.82 (1H, dd, J = 12.4 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

[0959]

Reference Example 672

tert-Butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxy-3-methylpiperidine-1-carboxylate

Synthesized analogous to Reference Example 499.

^{1}HNMR ($CDCl_3$) δ ppm: 1.47 (9H, s), 1.64 (3H, s), 1.66-1.75 (1H, m), 1.77-1.85 (1H, m), 2.58-2.71 (2H, m), 2.73-2.92 (3H, m), 2.93-3.00 (1H, m), 3.02-3.26 (2H, m), 3.65-3.84 (2H, m), 3.74 (3H, s), 3.96-4.09 (1H, m), 4.13-4.18 (1H, m), 5.12-5.33 (2H, m), 6.55 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.80 (2H, m), 6.85 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.09-7.16 (2H, m).

[0960]

Reference Example 673

5-{[(3S*,4S*)-3,4-Dihydroxy-3-methylpiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.22 (3H, s), 1.93-2.08 (2H, m), 2.55-2.65 (2H, m), 2.77-3.12 (6H, m), 3.38-3.50 (2H, m), 3.68 (3H, s), 3.78-3.85 (1H, m), 4.11-4.19 (1H, m), 5.10 (2H, brs), 6.77 (1H, dd, J = 9.4 Hz, 3.3 Hz), 6.78-6.86 (2H, m), 6.99 (1H, dd, J = 13.1 Hz, 9.1 Hz), 7.04-7.12 (2H, m), 8.81 (1H, brs), 8.95 (1H, brs).

[0961]

Reference Example 674

5-{[(3S*,4S*)-1-(3,5-Dichloropyridin-2-yl)-3,4-dihydroxy-3-methylpiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 66.

^{1}HNMR ($CDCl_3$) δ ppm: 1.37 (3H, s), 1.86-1.96 (1H, m), 2.02-2.12 (1H, m), 2.61-2.69 (2H, m), 2.84-2.93 (2H, m), 3.05 (1H, brs), 3.31-3.51 (4H, m), 3.60-3.74 (1H, m), 3.75 (3H, s), 3.93 (1H, d, J = 9.4 Hz), 4.14 (1H, d, J = 9.4 Hz), 5.14-5.32 (2H, m), 6.58 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.73-6.80 (2H, m), 6.86 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.09-7.17 (2H, m), 7.63 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

[0962]

Reference Example 675

5-{[(3S*,4S*)-1-(4-Chloro-2-fluorophenyl)-3,4-dihydroxy-3-methylpiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Under nitrogen atmosphere, to a solution of 5-{[(3S*,4S*)-3,4-dihydroxy-3-methylpiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride (0.36 g), 1-bromo-4-chloro-2-fluorobenzene (0.19 g), triethylamine (0.16 mL) and cesium carbonate (0.72 g) in toluene (6 mL) were added 2,2'-

bis(diphenylphosphino)-1,1'-binaphthyl (41 mg) and tris(dibenzylideneacetone)dipalladium (0) (20 mg), and the reaction mixture was stirred at 100 °C overnight. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (42 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.45 (3H, s), 1.89-2.05 (2H, m), 2.59-2.72 (2H, m), 2.79-3.08 (6H, m), 3.09-3.15 (2H, m), 3.74 (3H, s), 3.89 (1H, d, J = 9.2 Hz), 4.17 (1H, d, J = 9.2 Hz), 5.14-5.32 (2H, m), 6.58 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.80 (2H, m), 6.82-6.93 (2H, m), 7.01-7.08 (2H, m), 7.09-7.17 (2H, m).

[0963]

Reference Example 676

1-(2-Chloro-4-fluorophenyl)-3-fluoro-4,4-dimethoxypiperidine

Synthesized analogous to Reference Example 205.

^{1}HNMR ($CDCl_3$) δ ppm: 1.91-1.98 (1H, m), 2.10-2.18 (1H, m), 2.80-2.88 (1H, m), 3.06-3.22 (2H, m), 3.30 (3H, s), 3.34 (3H, s), 3.39-3.49 (1H, m), 4.57-4.71 (1H, m), 6.90-6.95 (1H, m), 7.02 (1H, dd, J = 8.9 Hz, 5.5 Hz), 7.12 (1H, dd, J = 8.3 Hz, 2.9 Hz).

[0964]

Reference Example 677

1-(2-Chloro-4-fluorophenyl)-3-fluoropiperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR (CDCl$_3$) δ ppm: 2.58-2.66 (1H, m), 2.81-2.91 (1H, m), 3.03-3.16 (2H, m), 3.49-3.56 (1H, m), 3.85-3.92 (1H, m), 5.18 (1H, ddd, J = 48.0 Hz, 10.3 Hz, 6.9 Hz), 6.95-7.01 (1H, m), 7.05 (1H, dd, J = 8.9 Hz, 5.4 Hz), 7.19 (1H, dd, J = 8.2 Hz, 2.9 Hz).

[0965]

Reference Example 678

1-(4-Chloro-2-fluorophenyl)-3-fluoro-4,4-dimethoxypiperidine

Synthesized analogous to Reference Example 205.

^{1}HNMR (CDCl$_3$) δ ppm: 1.92-1.98 (1H, m), 2.06-2.15 (1H, m), 2.86-2.93 (1H, m), 3.11-3.26 (2H, m), 3.28 (3H, s), 3.33 (3H, s), 3.55-3.63 (1H, m), 4.56-4.69 (1H, m), 6.84-6.90 (1H, m), 7.00-7.07 (2H, m).

[0966]

Reference Example 679

1-(4-Chloro-2-fluorophenyl)-3-fluoropiperidin-4-one

Synthesized analogous to Reference Example 251.

^{1}HNMR (CDCl$_3$) δ ppm: 2.61-2.68 (1H, m), 2.77-2.86 (1H, m), 3.09-3.22 (2H, m), 3.60-3.67 (1H, m), 3.93-4.01 (1H, m), 5.05-5.20 (1H, m), 6.90-6.95 (1H, m), 7.06-7.14 (2H, m).

[0967]

Reference Example 680

(3R*,4S*)-6-(4-Chloro-2-fluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

Under argon atmosphere, to a solution of trimethylsulfoxonium iodide (2.00 g) in dimethyl sulfoxide (20 mL) was added sodium *tert*-butoxide (0.834 g), and the reaction mixture was stirred at room temperature for 30 min. To the mixture was added a solution of 1-(4-chloro-2-fluorophenyl)-3-fluoropiperidin-4-one (2.03 g) in dimethyl sulfoxide (10 mL), and the mixture was stirred at room temperature for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and the title compound (1.03 g) was obtained from lower polarity fractions.

^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.71 (1H, m), 2.26-2.35 (1H, m), 2.80 (1H, dd, J = 4.6 Hz, 1.9 Hz), 3.00 (1H, d, J = 4.6 Hz), 3.16-3.29 (2H, m), 3.31-3.50 (2H, m), 4.32 (1H, ddd, J = 48.0 Hz, 5.1 Hz, 3.1 Hz), 6.88-6.94 (1H, m), 7.03-7.10 (2H, m).

[0968]

Reference Example 681

(3R*,4R*)-6-(4-Chloro-2-fluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

From higher polarity fractions of Reference Example 680, the title compound (0.48 g) was obtained.

^{1}HNMR ($CDCl_3$) δ ppm: 1.90-2.03 (2H, m), 2.78 (1H, dd, J = 4.6 Hz, 3.4 Hz), 3.03 (1H, d, J = 4.6 Hz), 3.16-3.28 (2H, m), 3.32-3.47 (2H, m), 4.65 (1H, ddd, J = 48.0 Hz, 7.3 Hz, 3.9 Hz), 6.89-6.94 (1H, m), 7.04-7.10 (2H, m).

[0969]

Reference Example 682

(3R*,4S*)-6-(2-Chloro-4-fluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

The reaction and purification analogous to Reference Example 680 and 681 gave the title compound from lower polarity fractions.

^{1}HNMR ($CDCl_3$) δ ppm: 1.74-1.83 (1H, m), 2.16-2.26 (1H, m), 2.78 (1H, dd, J = 4.7 Hz, 2.1 Hz), 3.03 (1H, d, J = 4.7 Hz), 3.08-3.19 (2H, m), 3.24-3.43 (2H, m), 4.41 (1H, ddd, J = 48.5 Hz, 5.7 Hz, 3.4 Hz), 6.93-6.98 (1H, m), 7.04 (1H, dd, J = 8.9 Hz, 5.5 Hz), 7.15 (1H, dd, J = 8.3 Hz, 2.9 Hz).

[0970]

Reference Example 683

($3R^*,4R^*$)-6-(2-Chloro-4-fluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

The reaction and purification analogous to Reference Example 680 and 681 gave the title compound from higher polarity fractions.

^{1}HNMR ($CDCl_3$) δ ppm: 1.80-1.90 (1H, m), 2.02-2.13 (1H, m), 2.78 (1H, dd, J = 4.8 Hz, 2.6 Hz), 3.07 (1H, d, J = 4.8 Hz), 3.08-3.17 (2H, m), 3.18-3.27 (1H, m), 3.37-3.46 (1H, m), 4.75 (1H, ddd, J = 47.9 Hz, 8.3 Hz, 4.1 Hz), 6.93-6.99 (1H, m), 7.05 (1H, dd, J = 8.9 Hz, 5.5 Hz), 7.15 (1H, dd, J = 8.3 Hz, 2.9 Hz).

[0971]

Reference Example 684

1-(4-Chloro-2,6-difluorophenyl)-4-[(trimethylsilyl)oxy]-1,2,3,6-tetrahydropyridine

Under argon atmosphere, a solution of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (1 g), chlorotrimethylsilane (1.55 mL) and triethylamine (2.84 mL) in N,N-dimethylformamide (5 mL) was stirred at 70 °C for 15 h, and the solvent was distilled off. To the residue was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (1.28 g).

^{1}HNMR ($CDCl_3$) δ ppm: 0.21 (9H, s), 2.18-2.25 (2H, m), 3.27-3.34 (2H, m), 3.62-3.68 (2H, m), 4.86-4.90 (1H, m), 6.83-6.91 (2H, m).

[0972]

Reference Example 685

1-(4-Chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one

Under argon atmosphere, to a solution of 1-(4-chloro-2,6-difluorophenyl)-4-[(trimethylsilyl)oxy]-1,2,3,6-tetrahydropyridine (1.28 g) in acetonitrile (15 mL) was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1.57 g) under ice-cooling, and the mixture was stirred at the same temperature for 1 h, then at room temperature for 1.5 h. To the reaction solution was added saturated aqueous sodium hydrogencarbonate, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.76 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.55-2.65 (1H, m), 2.74-2.84 (1H, m), 3.38-3.50 (3H, m), 3.78-3.86 (1H, m), 5.08 (1H, ddd, J = 48.3 Hz, 10.1 Hz, 6.8 Hz), 6.90-6.99 (2H, m).

[0973]

Reference Example 686

(3R*,4S*)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

The reaction and purification analogous to Reference Example 680 and 681 gave the title compound from lower polarity fractions.

^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.72 (1H, m), 2.18-2.26 (1H, m), 2.77 (1H, dd, J = 4.7 Hz, 2.0 Hz), 2.99 (1H, d, J = 4.7 Hz), 3.20-3.28 (1H, m), 3.30-3.44 (2H, m), 3.52-3.63 (1H, m), 4.29 (1H, ddd, J = 48.5 Hz, 5.6 Hz, 3.2 Hz), 6.86-6.93 (2H, m).

[0974]

Reference Example 687

(3R*,4R*)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

The reaction and purification analogous to Reference Example 680 and 681 gave the title compound from higher polarity fractions.

^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.90 (1H, m), 1.97-2.05 (1H, m), 2.76 (1H, dd, J = 4.7 Hz, 3.7 Hz), 3.00 (1H, d, J = 4.7 Hz), 3.15-3.22 (1H, m), 3.34-3.54 (3H, m), 4.56 (1H, ddd, J = 48.3 Hz, 6.9 Hz, 3.9 Hz), 6.86-6.94 (2H, m).

[0975]

Reference Example 688

(3R)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one

Under argon atmosphere, to a suspension of N-fluorobenzenesulfonimide (2.0 g) and sodium carbonate (1.01 g) in tetrahydrofuran (10 mL) was added a solution of 9-epi-9-amino-9-deoxydihydroquinidine (9-epi-DHQDA) (0.413 g), trichloroacetic acid (0.218 g) and water (0.023 mL) in tetrahydrofuran (15 mL) at -20 °C, and the mixture was stirred for 10 min. To the mixture was added 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (3.12 g), and the reaction mixture was stirred at the same temperature for 16 h, then at -10 °C for 24 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.26 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.57-2.65 (1H, m), 2.75-2.84 (1H, m), 3.38-3.50 (3H, m), 3.78-3.86 (1H, m), 5.00-5.16 (1H, m), 6.92-6.98 (2H, m).

[0976]

Reference Example 689

(3S)-1-(4-Chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one

By the procedure analogous to Reference Example 688, with 9-epi-9-amino-9-deoxydihydroquinine (9-epi-DHQA) as catalyst, the title compound was obtained.

^{1}HNMR ($CDCl_3$) δ ppm: 2.57-2.65 (1H, m), 2.75-2.84 (1H, m), 3.38-3.50 (3H, m), 3.78-3.86 (1H, m), 5.00-5.16 (1H, m), 6.92-6.98 (2H, m).

[0977]

Reference Example 690

(3S,4R)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

The reaction and purification analogous to Reference Examples 680 and 681 with (3R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one (1.20 g) were done. The material obtained from lower polarity fractions was recrystallized from ethanol/water to provide the title compound (0.47 g, 97 % ee).

^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.72 (1H, m), 2.18-2.26 (1H, m), 2.77 (1H, dd, J = 4.7 Hz, 2.0 Hz), 2.99 (1H, d, J = 4.7 Hz), 3.20-3.28 (1H, m), 3.30-3.44 (2H, m), 3.52-3.63 (1H, m), 4.29 (1H, ddd, J = 48.5 Hz, 5.6 Hz, 3.2 Hz), 6.86-6.93 (2H, m).

[0978]

Reference Example 691

(3R,4R)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

The material obtained from higher polarity fractions of Reference Example 690 was recrystallized from hexane to provide the title compound (0.24 g, 91 % ee).

^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.90 (1H, m), 1.97-2.05 (1H, m), 2.76 (1H, dd, J = 4.7 Hz, 3.7 Hz), 3.00 (1H, d, J = 4.7 Hz), 3.15-3.22 (1H, m), 3.34-3.54 (3H, m), 4.56 (1H, ddd, J = 48.3 Hz, 6.9 Hz, 3.9 Hz), 6.86-6.94 (2H, m).

[0979]

Reference Example 692

(3R,4S)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

The reaction and purification analogous to Reference Example 680 and 681 with (3S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoropiperidin-4-one (1.19 g) were done. The material obtained from lower polarity fractions was recrystallized from ethanol/water to provide the title compound (0.43 g, 96 % ee).

^{1}HNMR ($CDCl_3$) δ ppm: 1.64-1.72 (1H, m), 2.18-2.26 (1H, m), 2.77 (1H, dd, J = 4.7 Hz, 2.0 Hz), 2.99 (1H, d, J = 4.7 Hz), 3.20-3.28 (1H, m), 3.30-3.44 (2H, m), 3.52-3.63 (1H, m), 4.29 (1H, ddd, J = 48.5 Hz, 5.6 Hz, 3.2 Hz), 6.86-6.93 (2H, m).

[0980]

Reference Example 693

(3S,4S)-6-(4-Chloro-2,6-difluorophenyl)-4-fluoro-1-oxa-6-azaspiro[2.5]octane

The material obtained from higher polarity fractions of Reference Example 692 was recrystallized from ethanol/water to provide the title compound (0.22 g, 86 % ee).

^{1}HNMR (CDCl$_3$) δ ppm: 1.82-1.90 (1H, m), 1.97-2.05 (1H, m), 2.76 (1H, dd, J = 4.7 Hz, 3.7 Hz), 3.00 (1H, d, J = 4.7 Hz), 3.15-3.22 (1H, m), 3.34-3.54 (3H, m), 4.56 (1H, ddd, J = 48.3 Hz, 6.9 Hz, 3.9 Hz), 6.86-6.94 (2H, m).

[0981]

Reference Example 694

(3R*,4R*)-4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)piperidin-3-ol

To a solution of (3R*,4R*)-1-benzyl-4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-piperidin-3-ol (11.6 g) in ethanol (100 mL) was added 20 % palladium hydroxide on carbon (1.16 g, 10wt %) , and the reaction mixture was stirred under hydrogen atmosphere at 50 °C for 2 h. After the reaction solution was allowed to cool to room temperature, palladium hydroxide was filtered off with Celite, and the solvent of the filtrate was distilled off to provide the title compound (8.66 g).

^{1}HNMR (CDCl$_3$) δ ppm: 0.09 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 1.00-1.13 (1H, m), 1.45-1.72 (3H, m), 2.42 (1H, dd, J = 11.7 Hz, 10.0 Hz), 2.56 (1H, dt, J = 2.8 Hz, 12.3 Hz), 2.97-3.04 (1H, m), 3.17-3.24 (1H, m), 3.50-3.58 (1H, m), 3.62 (1H, t, J = 9.6 Hz), 3.69-3.77 (1H, m), 3.94-4.30 (1H, m).

[0982]

Reference Example 695

(3R*,4R*)-4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-1-(2,4-dichlorophenyl)piperidin-3-ol

Synthesized analogous to Reference Example 68.

^{1}HNMR ($CDCl_3$) δ ppm: 0.11 (3H, s), 0.12 (3H, s), 0.92 (9H, s), 1.35-1.48 (1H, m), 1.59-1.76 (2H, m), 2.50 (1H, dd, J = 10.8 Hz, 9.8 Hz), 2.59 (1H, dt, J = 2.6 Hz, 11.8 Hz), 3.26-3.35 (1H, m), 3.43-3.51 (1H, m), 3.71 (1H, t, J = 9.6 Hz), 3.79-3.90 (2H, m), 4.16-4.20 (1H, m), 6.96 (1H, d, J = 8.6 Hz), 7.18 (1H, dd, J = 8.6 Hz, 2.3 Hz), 7.35 (1H, d, J = 2.3 Hz).

[0983]

Reference Example 696

(3R*,4R*)-1-(2,4-Dichlorophenyl)-4-(hydroxymethyl)piperidin-3-ol

To a solution of (3R*,4R*)-4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-1-(2,4-dichlorophenyl)piperidin-3-ol (1.67 g) in tetrahydrofuran (12 mL) was added a solution of 1 M tetrabutylammonium fluoride in tetrahydrofuran (5.1 mL), and the reaction mixture was stirred at room temperature overnight. After the solvent was distilled off, water was added to the residue and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.11 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.40-1.54 (1H, m), 1.66-1.79 (2H, m), 2.36-2.34 (1H, m), 2.53 (1H, dd, J = 10.8 Hz, 9.7 Hz), 2.62 (1H, dt, J = 2.5 Hz, 11.7 Hz), 3.12-3.19 (1H, m), 3.26-3.34 (1H, m), 3.42-3.49 (1H, m), 3.75-3.93 (3H, m), 6.96 (1H, d, J = 8.6 Hz), 7.18 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.36 (1H, d, J = 2.5 Hz).

[0984]

Reference Example 697

[(3R*,4R*)-1-(2,4-Dichlorophenyl)-3-hydroxypiperidin-4-yl]methyl 4-methylbenzenesulfonate

To a solution of (3R*,4R*)-1-(2,4-dichlorophenyl)-4-(hydroxymethyl)piperidin-3-ol (1.11 g) in dichloromethane (12 mL) were added *para*-toluenesulfonyl chloride (0.84 g) and N,N,N',N'-tetramethyl-1,3-diaminopropane (0.94 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. To the reaction solution was added water and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.0 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.77 (2H, m), 1.81-1.87 (1H, m), 2.05-2.10 (1H, m), 2.46 (3H, m), 2.48-2.64 (2H, m), 3.21-3.29 (1H, m), 3.40-3.48 (1H, m), 3.71-3.81 (1H, m), 4.14-4.20 (1H, m), 4.23-4.30 (1H, m), 6.92 (1H, d, J = 8.6 Hz), 7.17 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.35 (1H, d, J = 2.4 Hz), 7.36-7.40 (2H, m), 7.80-7.85 (2H, m).

[0985]

Reference Example 698

(3R*,4R*)-4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-1-(4-chloro-2-fluorophenyl)piperidin-3-ol

Synthesized analogous to Reference Example 68.

^{1}HNMR ($CDCl_3$) δ ppm: 0.11 (3H, s), 0.12 (3H, s), 0.92 (9H, s), 1.33-1.45 (1H, m), 1.58-1.75 (2H, m), 2.52 (1H, t, J = 10.5 Hz), 2.63 (1H, dt, J = 2.5 Hz, 12.0 Hz), 3.34-3.41 (1H, m), 3.49-3.56 (1H, m), 3.69 (1H, t, J = 9.7 Hz), 3.78-3.87 (2H, m), 4.17-4.20 (1H, m), 6.83-6.91 (1H, m), 7.00-7.07 (2H, m).

[0986]

Reference Example 699

(3R*,4R*)-1-(4-Chloro-2-fluorophenyl)-4-(hydroxymethyl)piperidin-3-ol

Synthesized analogous to Reference Example 696.

^{1}HNMR (CDCl$_3$) δ ppm: 1.37-1.51 (1H, m), 1.65-1.77 (2H, m), 2.18-2.29 (1H, m), 2.55 (1H, t, J = 10.5 Hz), 2.65 (1H, dt, J = 2.6 Hz, 12.0 Hz), 3.05-3.08 (1H, m), 3.33-3.40 (1H, m), 3.48-3.56 (1H, m), 3.73-3.91 (3H, m), 6.84-6.91 (1H, m), 7.05-7.08 (2H, m).

[0987]

Reference Example 700

4-methylbenzenesulfonic acid [(3R*,4R*)-1-(4-Chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methyl ester

Synthesized analogous to Reference Example 697.

^{1}HNMR (CDCl$_3$) δ ppm: 1.57-1.75 (2H, m), 1.78-1.85 (1H, m), 2.06-2.11 (1H, m), 2.46 (3H, m), 2.47-2.66 (2H, m), 3.28-3.36 (1H, m), 3.47-3.53 (1H, m), 3.69-3.79 (1H, m), 4.13-4.19 (1H, m), 4.24-4.30 (1H, m), 6.80-6.87 (1H, m), 7.00-7.07 (2H, m), 7.34-7.39 (2H, m), 7.78-7.84 (2H, m).

[0988]

Reference Example 701

(3R*,4R*)-4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-1-(4-chloro-2,5-difluorophenyl)piperidin-3-ol

Synthesized analogous to Reference Example 68.

^{1}HNMR (CDCl$_3$) δ ppm: 0.11 (3H, s), 0.12 (3H, s), 0.92 (9H, s), 1.31-1.44 (1H, m), 1.58-1.75 (2H, m), 2.50 (1H, t, J = 10.6 Hz), 2.64 (1H, dt, J = 2.5 Hz, 12.0 Hz), 3.35-3.43 (1H, m), 3.52-3.59 (1H, m), 3.68 (1H, t, J = 9.6 Hz), 3.77-3.85 (2H, m), 4.16-4.19 (1H, m), 6.73 (1H, dd, J = 10.7 Hz, 7.6 Hz), 7.05 (1H, dd, J = 11.6 Hz, 6.9 Hz).

[0989]

Reference Example 702

(3R*,4R*)-1-(4-Chloro-2,5-difluorophenyl)-4-(hydroxymethyl)piperidin-3-ol

Synthesized analogous to Reference Example 696.

^{1}HNMR (CDCl$_3$) δ ppm: 1.37-1.50 (1H, m), 1.66-1.78 (2H, m), 2.15-2.24 (1H, m), 2.53 (1H, t, J = 10.5 Hz), 2.65 (1H, dt, J = 2.6 Hz, 12.1 Hz), 3.16-3.23 (1H, m), 3.35-3.43 (1H, m), 3.51-3.59 (1H, m), 3.73-3.90 (3H, m), 6.73 (1H, dd, J = 10.6 Hz, 7.6 Hz), 7.06 (1H, d, J = 11.6 Hz, 6.9 Hz).

[0990]

Reference Example 703

[(3R*,4R*)-1-(4-Chloro-2,5-difluorophenyl)-3-hydroxypiperidin-4-yl]methyl 4-methylbenzenesulfonate

Synthesized analogous to Reference Example 697.

^{1}HNMR (CDCl$_3$) δ ppm: 1.59-1.75 (2H, m), 1.78-1.86 (1H, m), 2.04-2.08 (1H, m), 2.46 (3H, m), 2.47-2.64 (2H, m), 3.31-3.39 (1H, m), 3.50-3.57 (1H, m), 3.69-3.78 (1H, m), 4.11-4.18 (1H, m), 4.26-4.32 (1H, m), 6.70 (1H, dd, J = 10.6 Hz, 7.6 Hz), 7.06 (1H, dd, J = 11.5 Hz, 6.8 Hz), 7.33-7.40 (2H, m), 7.78-7.84 (2H, m).

[0991]

Reference Example 704

tert-Butyl 4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-1-carboxylate

Synthesized analogous to Reference Example 495.

^{1}HNMR ($CDCl_3$) δ ppm: 1.23-1.35 (2H, m), 1.47 (9H, s), 1.75-1.83 (2H, m), 1.90-2.03 (1H, m), 2.59-2.66 (2H, m), 2.69-2.83 (2H, m), 2.98 (2H, t, J = 7.7 Hz), 3.78 (2H, d, J = 6.3 Hz), 4.05-4.28 (2H, m), 6.43 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.51 (1H, brs).

[0992]

Reference Example 705

8-Fluoro-5-(piperidin-4-ylmethoxy)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 60.

^{1}HNMR ($CDCl_3$) δ ppm: 1.24-1.36 (2H, m), 1.49-1.77 (1H, broad signal), 1.77-1.84 (2H, m), 1.87-1.99 (1H, m), 2.58-2.70 (4H, m), 2.99 (2H, t, J = 7.7 Hz), 3.09-3.17 (2H, m), 3.77 (2H, d, J = 6.3 Hz), 6.43 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.89 (1H, t, J = 9.5 Hz), 7.53 (1H, brs).

[0993]

Reference Example 706

tert-Butyl (3S*,4S*)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-3-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 495.

^{1}HNMR ($CDCl_3$) δ ppm: 1.42-1.46 (1H, m), 1.47 (9H, s), 1.77-1.85 (1H, m), 1.86-1.95 (1H, m), 2.41-2.52 (1H, m), 2.53-2.83 (4H, m), 2.89-3.03 (2H, m), 3.57-3.67 (1H, m), 4.00-4.42 (4H, m), 6.49 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.91 (1H, t, J = 9.4 Hz), 7.59 (1H, brs).

[0994]

Reference Example 707

8-Fluoro-5-{[(3S*,4S*)-3-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one hydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.68-1.79 (1H, m), 1.83-1.91 (1H, m), 1.92-1.99 (1H, m), 2.42-2.49 (2H, m), 2.58-2.69 (1H, m), 2.81-2.94 (3H, m), 3.19-3.30 (2H, m), 3.42-3.46 (1H, m), 3.72-3.80 (1H, m), 4.00-4.07 (2H, m), 6.60 (1H, dd, J = 9.2 Hz, 3.8 Hz), 7.03 (1H, t, J = 9.4 Hz), 8.83-8.95 (1H, m), 8.97-9.08 (1H, m), 10.04 (1H, brs).

[0995]

Reference Example 708

(3R*,4S*)-1-(3,5-Dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidin-3-yl 4-nitrobenzoate

To a solution of 5-{[(3S*,4S*)-1-(3,5-dichloropyridin-2-yl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one (1.0 g) in tetrahydrofuran (20 mL) were added 4-nitrobenzoic acid (0.49 g), triphenylphosphine (0.89 g) and diethyl azodicarboxylate (1.55 mL) , and the reaction mixture was stirred at room temperature overnight. The solvent was distilled off, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) and further purified by basic silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.0 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.85-1.92 (1H, m), 2.12-2.22 (1H, m), 2.41-2.50 (1H, m), 2.61 (2H, d, J = 7.7 Hz), 2.92-3.03 (2H, m), 3.05-3.12 (1H, m), 3.13-3.18 (1H, m), 3.91-3.96 (2H, m), 4.00-4.07 (1H, m), 4.32-4.39 (1H, m), 5.53-5.56 (1H, m), 6.39 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.84 (1H, t, J = 9.5 Hz), 7.46 (1H, d, J = 2.3 Hz), 7.59 (1H, brs), 8.04-8.08 (3H, m), 8.22-8.26 (2H, m).

[0996]

Reference Example 709

tert-Butyl (3R*,4R*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3-hydroxypiperidine-1-carboxylate

Synthesized analogous to Reference Example 495.

^{1}HNMR ($CDCl_3$) δ ppm: 1.36-1.45 (1H, m), 1.46 (9H, s), 1.74-1.93 (2H, m), 2.36-2.48 (1H, m), 2.50-2.92 (6H, m), 3.55-3.66 (1H, m), 3.74 (3H, s), 3.96-4.39 (4H, m), 5.15-5.31 (2H, m), 6.53 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.73-6.79 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.2 Hz), 7.09-7.16 (2H, m).

[0997]

Reference Example 710

8-Fluoro-5-{[(3R*,4R*)-3-hydroxypiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.66-1.98 (3H, m), 2.55-2.69 (3H, m), 2.79-2.93 (3H, m), 3.18-3.28 (2H, m), 3.68 (3H, s), 3.70-3.81 (1H, m), 3.97-4.03 (2H, m), 5.04-5.16 (2H, m), 5.45-5.55 (1H, m), 6.71 (1H, dd, J = 9.2 Hz, 3.3 Hz), 6.78-6.84 (2H, m), 6.98 (1H, dd, J = 13.1 Hz, 9.1 Hz), 7.03-7.10 (2H, m), 8.86-9.26 (2H, m).

[0998]

Reference Example 711

5-{[(3R*,4R*)-1-(2,4-Dichlorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 526.

^{1}HNMR (CDCl$_3$) δ ppm: 1.65-1.78 (1H, m), 1.87-1.98 (2H, m), 2.41-2.45 (1H, m), 2.54-2.73 (4H, m), 2.79-2.95 (2H, m), 3.28-3.36 (1H, m), 3.47-3.54 (1H, m), 3.74 (3H, s), 3.86-3.95 (1H, m), 4.01-4.16 (2H, m), 5.15-5.32 (2H, m), 6.56 (1H, dd, J = 9.2 Hz, 3.4H), 6.73-6.80 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.94 (1H, d, J = 8.6 Hz), 7.10-7.16 (2H, m), 7.19 (1H, dd, J = 8.6 Hz, 2.4 Hz), 7.37 (1H, d, J = 2.4 Hz).

[0999]

Reference Example 712

5-{[(3R*,4R*)-1-(4-Chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 526.

^{1}HNMR (CDCl$_3$) δ ppm: 1.65-1.77 (1H, m), 1.85-1.96 (2H, m), 2.31-2.35 (1H, m), 2.55-2.75 (4H, m), 2.81-2.93 (2H, m), 3.36-3.43 (1H, m), 3.53-3.60 (1H, m), 3.74 (3H, s), 3.84-3.94 (1H, m), 4.02-4.12 (2H, m), 5.18-5.30 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.4H), 6.73-6.79 (2H, m), 6.80-6.92 (2H, m), 7.02-7.09 (2H, m), 7.10-7.16 (2H, m).

[1000]

Reference Example 713

5-{[(3R*,4R*)-1-(4-Chloro-2,5-difluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 526.

^{1}HNMR (CDCl$_3$) δ ppm: 1.55-1.76 (2H, m), 1.86-1.95 (1H, m), 2.41-2.49 (1H, m), 2.56-2.73 (3H, m), 2.80-2.89 (2H, m), 3.33-3.39 (1H, m), 3.46-3.62 (2H, m), 3.68 (3H, s), 3.96-4.04 (1H, m), 4.06-4.13 (1H, m), 5.04-5.16 (3H, m), 6.70 (1H, dd, J = 9.2 Hz, 3.4H), 6.77-6.84 (2H, m), 6.98 (1H, dd, J = 13.2 Hz, 9.1 Hz), 7.02-7.13 (3H, m), 7.50 (1H, dd, J = 12.1 Hz, 7.1 Hz).

[1001]

Reference Example 714

5-{[1-(3,5-Dichloropyridin-2-yl)-4-methoxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere, to a solution of 5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (0.35 g) and methyl iodide (0.078 mL) in N,N-dimethylformamide (7 mL)was added sodium hydride (55 % in oil) (0.030 g) under ice-cooling, and the reaction mixture was stirred at the same temperature for 2 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate, the organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.33 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.80-1.89 (2H, m), 1.98-2.04 (2H, m), 2.61-2.68 (2H, m), 2.87-2.94 (2H, m), 3.16-3.26 (2H, m), 3.32 (3H, s), 3.54-3.61 (2H, m), 3.74 (3H, s), 3.87 (2H, s), 5.23

(2H, brs), 6.52 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.17 (2H, m), 7.59 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

[1002]

Reference Example 715

8-Fluoro-5-{[4-(hydroxymethyl)piperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere at -70 °C, to a solution of 1-tert-butyl 4-ethyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-1,4-dicarboxylate (1.50 g) in tetrahydrofuran (15 mL) was added sodium triethylborohydride (1 M tetrahydrofuran solution) (6.05 mL) dropwise, and the reaction mixture was stirred for 9 h while allowing to warm to room temperature slowly. Then, brine was added to the mixture, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give 1-*tert*-butyl 4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-(hydroxymethyl)piperidine-1-carboxylate (alcohol compound). The obtained alcohol compound was dissolved into ethyl acetate (4 mL), and 4 N hydrochloric acid/ethyl acetate (4 mL) was added to the mixture. After stirring the mixture at room temperature for 2 h, the solvent was distilled off. The residue was dissolved into water, the reaction mixture was made basic with aqueous sodium hydroxide, and the solution was extracted with dichloromethane. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off, the residue was purified by silica gel column chromatography (basic silica gel: dichloromethane/methanol) to provide the title compound (0.15 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.54-1.63 (4H, m), 1.63-1.74 (2H, m), 2.61-2.67 (2H, m), 2.81-2.91 (6H, m), 3.71 (2H, s), 3.74 (3H, s), 3.84 (2H, s), 5.23 (2H, brs), 6.55 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.78 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.11-7.15 (2H, m).

[1003]

Reference Example 716

5-{[1-(3,5-Dichloropyridin-2-yl)-4-(hydroxymethyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 66.

^{1}HNMR (CDCl$_3$) δ ppm: 1.65-1.73 (1H, m), 1.75-1.82 (4H, m), 2.60-2.68 (2H, m), 2.82-2.89 (2H, m), 3.28-3.35 (4H, s), 3.74 (3H, s), 3.77 (2H, brs), 3.91 (2H, s), 5.23 (2H, brs), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.74-6.79 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.11-7.16 (2H, m), 7.60 (1H, d, J = 2.3 Hz), 8.11 (1H, d, J = 2.3 Hz).

[1004]

Reference Example 717

Methyl [1-(3,5-Dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidin-4-yl]carbamate

To a solution of 1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid (0.86 g) in 1,4-dioxane (8 mL) were added triethylamine (0.214 mL) and diphenylphosphoryl azide (0.331 mL), and the mixture was refluxed for 2 h. The solvent was distilled off and to the residue was added methanol (20 mL), and the reaction mixture was refluxed for 15 h. The solvent was distilled off, the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.82 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.91-2.00 (2H, m), 2.22-2.30 (2H, m), 2.61-2.67 (2H, m), 2.83-2.89 (2H, m), 3.09-3.17 (2H, m), 3.56-3.60 (2H, m), 3.61 (3H, s), 3.74 (3H, s), 4.08 (2H, s), 4.64 (1H, s), 5.22 (2H, brs), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.61 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

[1005]

Reference Example 718

Methyl [1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidin-4-yl]methylcarbamate

To a solution of methyl [1-(3,5-dichloropyridin-2-yl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidin-4-yl]carbamate (0.3 g) in N,N-dimethylformamide (3 mL) was added methyl iodide (0.061 mL), then sodium hydride (55 % in oil) (0.032 g) was added under ice-cooling, and the reaction mixture was stirred at room temperature for 4 h. To the reaction solution was added ammonium chloride aqueous solution, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.31 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.08-2.18 (2H, m), 2.60-2.68 (4H, m), 2.81-2.87 (2H, m), 3.07 (3H, s), 3.18-3.26 (2H, m), 3.44-3.51 (2H, m), 3.64 (3H, s), 3.74 (3H, s), 4.18 (2H, s), 5.22 (2H, brs), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.82 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.60 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

[1006]

Reference Example 719

Methyl [1-(3,5-Dichloropyridin-2-yl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidin-4-yl]methylcarbamate

Synthesized analogous to Reference Example 119.

^{1}HNMR ($CDCl_3$) δ ppm: 2.10-2.19 (2H, m), 2.61-2.71 (4H, m), 2.97 (2H, t, J = 7.7 Hz), 3.10 (3H, s), 3.18-3.27 (2H, m), 3.46-3.53 (2H, m), 3.66 (3H, s), 4.23 (2H, s), 6.46 (1H, dd, J = 9.1

Hz, 4.0 Hz), 6.90 (1H, t, J = 9.5 Hz), 7.48 (1H, brs), 7.61 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

[1007]

Reference Example 720

5-{[4-(Aminooxy)-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Under argon atmosphere, to a solution of 5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one (0.694 g) in N,N-dimethylformamide (7 mL) was added sodium hydride (55 % in oil) (0.059 g) under ice-cooling, and the mixture was stirred at room temperature for 30 min. To the reaction solution was added O-mesitylenesulfonylhydroxylamine (0.32 g) under ice-cooling, and the mixture was stirred at the same temperature for 30 min, and then at room temperature for 18 h. To the reaction solution was added ammonium chloride aqueous solution, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.30 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.78-1.87 (2H, m), 2.06-2.13 (2H, m), 2.61-2.68 (2H, m), 2.88-2.94 (2H, m), 3.11-3.19 (2H, m), 3.53-3.61 (2H, m), 3.74 (3H, s), 3.95 (2H, s), 4.95 (2H, s), 5.23 (2H, brs), 6.56 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.78 (2H, m), 6.83 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.59 (1H, d, J = 2.3 Hz), 8.12 (1H, d, J = 2.3 Hz).

[1008]

Reference Example 721

5-Fluoro-2-[4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidin-1-yl]benzonitrile

To a solution of 8-fluoro-5-[(4-hydroxypiperidin-4-yl)methoxy]-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride (1.0 g) in water (10 mL) was added 5 N aqueous sodium hydroxide (1 mL) to make the reaction residue basic, and the solution was extracted with dichloromethane. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. To the residue were added 2,5-difluorobenzonitrile (0.463 g), potassium carbonate (0.460 g) and N-methyl-2-pyrrolidone (5 mL), and the mixture was stirred at 100 °C for 24 h. To the reaction solution was added ammonium chloride aqueous solution and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.83 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.87-2.01 (4H, m), 2.02 (1H, s), 2.63-2.69 (2H, m), 2.86-2.92 (2H, m), 3.16-3.25 (2H, m), 3.28-3.34 (2H, m), 3.74 (3H, s), 3.82 (2H, s), 5.24 (2H, brs), 6.53 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.06 (1H, dd, J = 9.1 Hz, 4.6 Hz), 7.11-7.16 (2H, m), 7.20-7.25 (1H, m), 7.28 (1H, dd, J = 7.8 Hz, 3.0 Hz).

[1009]

Reference Example 722

5-Fluoro-2-[4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxypiperidin-1-yl]pyridine-3-carbonitrile

Synthesized analogous to Reference Example 721.

^{1}HNMR ($CDCl_3$) δ ppm: 1.82-1.91 (4H, m), 2.05 (1H, s), 2.63-2.69 (2H, m), 2.84-2.91 (2H, m), 3.42-3.51 (2H, m), 3.74 (3H, s), 3.80 (2H, s), 3.99-4.07 (2H, m), 5.23 (2H, brs), 6.51 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.78 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.15 (2H, m), 7.54 (1H, dd, J = 7.3 Hz, 3.1 Hz), 8.24 (1H, d, J = 3.1 Hz).

[1010]

Reference Example 723

2-[4-(Aminooxy)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidin-1-yl]-5-fluorobenzonitrile

Synthesized analogous to Reference Example 720.

^{1}HNMR (CDCl$_3$) δ ppm: 1.84-1.94 (2H, m), 2.13-2.20 (2H, m), 2.62-2.68 (2H, m), 2.88-2.95 (2H, m), 3.02-3.10 (2H, m), 3.24-3.30 (2H, m), 3.74 (3H, s), 3.96 (2H, s), 4.95 (2H, s), 5.24 (2H, brs), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.74-6.79 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.03 (1H, dd, J = 9.1 Hz, 4.6 Hz), 7.11-7.16 (2H, m), 7.19-7.24 (1H, m), 7.28 (1H, dd, J = 7.8 Hz, 3.0 Hz).

[1011]

Reference Example 724

2-[4-(Aminooxy)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidin-1-yl]-5-fluoropyridine-3-carbonitrile

Synthesized analogous to Reference Example 720.

^{1}HNMR (CDCl$_3$) δ ppm: 1.74-1.84 (2H, m), 2.09-2.17 (2H, m), 2.61-2.67 (2H, m), 2.86-2.93 (2H, m), 3.28-3.38 (2H, m), 3.74 (3H, s), 3.94 (2H, s), 3.94-4.01 (2H, m), 4.97 (2H, s), 5.23 (2H, brs), 6.54 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.10-7.16 (2H, m), 7.53 (1H, dd, J = 7.3 Hz, 3.1 Hz), 8.24 (1H, d, J = 3.1 Hz).

[1012]

Reference Example 725

tert-Butyl 4-cyano-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-1-carboxylate

Synthesized analogous to Reference Example 59.

^{1}HNMR (CDCl$_3$) δ ppm: 1.47 (9H, s), 1.55-1.63 (2H, m), 2.04-2.09 (2H, m), 2.63-2.69 (2H, m), 2.86-2.94 (2H, m), 3.00-3.20 (2H, m), 3.74 (3H, s), 3.90 (2H, s), 4.05-4.40 (2H, m), 5.23 (2H, brs), 6.45 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.74-6.79 (2H, m), 6.84 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.10-7.15 (2H, m).

[1013]

Reference Example 726

4-{[(8-Fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}piperidine-4-carbonitrile

To a mixture of *tert*-butyl 4-cyano-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-1-carboxylate (0.92 g) and anisole (0.382 mL) was added trifluoroacetic acid (10 mL), and the mixture was stirred at 65-70 °C for 2 h, and then the solvent was distilled off. To the residue was added ethyl acetate, and the insoluble precipitate was collected on a filter. The obtained solid was suspended in water (20 mL), to which 5 N aqueous sodium hydroxide (0.35 mL) was added and insoluble crystal was collected on a filter to provide the title compound (0.46 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.55-1.69 (3H, m), 2.06-2.12 (2H, m), 2.65 (2H, t, J = 7.7 Hz), 2.99-3.08 (4H, m), 3.11-3.18 (2H, m), 3.94 (2H, s), 6.42 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.51 (1H, brs).

[1014]

Reference Example 727

5-{[1-(2,4-Dichlorophenyl)-4-(hydroxymethyl)piperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

To a suspension of 1-(2,4-dichlorophenyl)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)piperidine-4-carboxylic acid (397 mg) in tetrahydrofuran (8 mL) was added triethylamine (0.104 mL), then ethyl chlorocarbonate (0.068 mL) was added dropwise under ice-cooling, and the reaction mixture was stirred for 1 h. The precipitate was filtered off, and to the filtrate was added a solution of sodium borohydride (77 mg) in water (3 mL), and the solution was stirred at room temperature for 1 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was distilled off to provide the title compound (304 mg).

^{1}HNMR ($CDCl_3$) δ ppm: 1.70 (1H, t, J = 5.6 Hz), 1.77-1.86 (4H, m), 2.63-2.66 (2H, m), 2.84-2.87 (2H, m), 3.01 (4H, t, J = 5.5 Hz), 3.74 (3H, s), 3.77 (2H, d, J = 5.5 Hz), 3.91 (2H, s), 5.23 (2H, brs), 6.57 (1H, dd, 9.2 Hz, 3.2 Hz), 6.77 (2H, d, 8.7 Hz), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 6.96 (1H, d, J = 8.6 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.18 (1H, dd, J = 8.6 Hz, 2.5 Hz), 7.36 (1H, d, J = 2.5 Hz).

[1015]

Reference Example 728

tert-Butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-4-hydroxy-3-methoxypiperidine-1-carboxylate

To a solution of *tert*-butyl (3S*,4S*)-4-({[8-fluoro-1-(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl]oxy}methyl)-3,4-dihydroxypiperidine-1-carboxylate (1.06 g) in tetrahydrofuran (10 mL) was added sodium *tert*-butoxide (0.23 g) and the mixture was stirred at room temperature for 30 min. At the same temperature methyl iodide (0.15 mL) and N-methyl-2-pyrrolidone (2 mL) were added to the mixture and the solution was stirred at room temperature overnight. The solvent was distilled off, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.40 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.48 (9H, s), 1.68-1.76 (1H, m), 1.77-1.89 (1H, m), 2.36-2.42 (1H, m), 2.60-2.68 (2H, m), 2.78-3.02 (3H, m), 3.08-3.19 (1H, m), 3.33-3.40 (1H, m), 3.38 (3H, m), 3.64-3.71 (1H, m), 3.74 (3H, s), 3.78-3.90 (1H, m), 3.91-3.96 (1H, m), 4.16-4.40 (1H, m), 5.16-5.28 (2H, m), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.79 (2H, m), 6.83 (1H, dd, J = 12.7 Hz, 9.0 Hz), 7.09-7.16 (2H, m).

[1016]

Reference Example 729

8-Fluoro-5-{[(3S*,4S*)-4-hydroxy-3-methoxypiperidin-4-yl]methoxy}-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one hydrochloride

Synthesized analogous to Reference Example 456.

^{1}HNMR (DMSO-d6) δ ppm: 1.71-1.79 (1H, m), 1.93-2.06 (1H, m), 2.59-2.60 (2H, m), 2.83-3.06 (4H, m), 3.09-3.19 (1H, m), 3.25 (3H, s), 3.56-3.61 (1H, m), 3.68 (3H, s), 3.70-3.76 (1H, m), 3.99-4.20 (2H, m), 5.04-5.15 (2H, m), 5.22 (1H, brs), 6.70 (1H, dd, J = 9.2 Hz, 3.4 Hz), 6.77-6.84 (2H, m), 7.00 (1H, dd, J = 13.0 Hz, 9.1 Hz), 7.04-7.10 (2H, m), 8.76 (1H, brs), 8.93 (1H, brs).

[1017]

Reference Example 730

5-{[(3S*,4S*)-1-(3,5-Dichloropyridin-2-yl)-4-hydroxy-3-methoxypiperidin-4-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 66.

^{1}HNMR (CDCl$_3$) δ ppm: 1.81-1.87 (1H, m), 2.03-2.12 (1H, m), 2.42-2.46 (1H, m), 2.61-2.68 (2H, m), 2.81-2.94 (2H, m), 2.98-3.05 (1H, m), 3.15-3.23 (1H, m), 3.39 (3H, s), 3.62-3.69 (2H, m), 3.72-3.77 (1H, m), 3.74 (3H, s), 3.91-4.02 (2H, m), 5.18-5.28 (2H, m), 6.55 (1H, dd, J = 9.1 Hz, 3.3 Hz), 6.73-6.79 (2H, m), 6.84 (1H, dd, J = 12.8 Hz, 9.0 Hz), 7.10-7.17 (2H, m), 7.62 (1H, d, J = 2.3 Hz), 8.13 (1H, d, J = 2.3 Hz).

[1018]

Reference Example 731

1-(4-Chloro-2,6-difluorophenyl)-4-ethylidenepiperidine

To a solution of ethyltriphenylphosphonium bromide (1.81 g) in tetrahydrofuran (12 mL), n-butyllithium (1.6 M hexane solution) (3.05 mL) was added dropwise at 0 °C, and the reaction mixture was stirred for 10 min. To the mixture was added a solution of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (1 g) in tetrahydrofuran (4 mL), and the mixture was stirred at room temperature for 1 h. To the reaction solution was added aqueous saturated ammonium chloride, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (852 mg).

^{1}HNMR (CDCl$_3$) δ ppm: 1.61 (3H, d, J = 6.9 Hz), 2.26-2.36 (4H, m), 3.09-3.21 (4H, m), 5.25-5.30 (1H, m), 6.82-6.89 (2H, m).

[1019]

Reference Example 732

1-(4-Chloro-2,6-difluorophenyl)-4-[1-hydroxyethyl]piperidin-4-ol

Synthesized analogous to Reference Example 504.

^{1}HNMR (CDCl$_3$) δ ppm: 1.22 (3H, d, J = 6.6 Hz), 1.57-1.62 (1H, m), 1.67-1.81 (3H, m), 1.86-1.89 (2H, m), 3.06 (2H, d, J = 11.8 Hz), 3.36-3.44 (2H, m), 3.60-3.66 (1H, m), 6.83-6.90 (2H, m).

[1020]

Reference Example 733

1-[1-(4-Chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl 4-methylbenzenesulfonate

Synthesized analogous to Reference Example 697.

^{1}HNMR (CDCl$_3$) δ ppm: 1.26 (3H, d, J = 6.4 Hz), 1.50-1.57 (1H, m), 1.62-1.67 (4H, m), 2.46 (3H, s), 2.95-3.03 (2H, m), 3.31-3.39 (2H, m), 4.51 (1H, q, J = 6.4 Hz), 6.82-6.89 (2H, m), 7.36 (2H, d, J = 8.0 Hz), 7.81 (2H, d, J = 8.0 Hz).

[1021]

Reference Example 734

(3R*,5R*)-1-(4-Chloro-2,6-difluorophenyl)-3,5-dihydroxypiperidin-4-one

To a suspension of 1-(4-chloro-2,6-difluorophenyl)piperidin-4-one (5.00 g) and DL-proline (0.703 g) in N,N-dimethylformamide (50 mL), a solution of nitrosobenzene (2.18 g) in N,N-dimethylformamide (50 mL) was added over 5 h at 0 °C, and the mixture was stirred at the same temperature for 2 h. The reaction solution was poured into ice-cooled aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was dissolved into methanol (50 mL), and copper (II) sulfate (0.975 g) was added to the solution at 0 °C, and the mixture was stirred at the same temperature for 2 h. To the reaction solution was added brine, and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound. The compound was used for the next step without further purification.

^{1}HNMR ($CDCl_3$) δ ppm: 3.26-3.30 (2H, m), 3.59-3.63 (2H, m), 4.57-4.59 (2H, m), 6.95-7.00 (2H, m).

[1022]

Reference Example 735

(4R*,8R*)-6-(4-Chloro-2,6-difluorophenyl)-1-oxa-6-azaspiro[2.5]octane-4,8-diol

Synthesized analogous to Reference Example 623.

^{1}HNMR ($CDCl_3$) δ ppm: 2.01 (1H, d, J = 10.5 Hz), 2.74 (1H, d, J = 8.0 Hz), 2.94 (1H, d, J = 4.5 Hz), 3.06 (1H, d, J = 4.5 Hz), 3.08-3.16 (2H, m), 3.38-3.43 (1H, m), 3.50-3.52 (1H, m), 3.65-3.70 (1H, m), 4.12-4.17 (1H, m), 6.90-6.98 (2H, m).

[1023]

Reference Example 736

8-(4-Chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol

To a solution of 4-chloro-2-fluoro-1-iodobenzene (1.01 mL) in tetrahydrofuran (20 ml), a solution of 2 M isopropylmagnesium chloride tetrahydrofuran (4.29 mL) was added dropwise under argon atmosphere at -30 °C, and the mixture was stirred at from -30 to -20 °C for 5 min, then at room temperature for 2 h. To the reaction solution at -5 °C was added 1,4-dioxaspiro[4.5]decan-8-one (1.47 g), and the reaction mixture was stirred at room temperature overnight. The reaction solution was poured into aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.16 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.63-1.74 (2H, m,), 1.80-1.91 (2H, m), 1.97 (1H, d, J = 4.2 Hz), 2.04-2.16 (2H, m), 2.26-2.39 (2H, m), 3.99 (4H, t, J = 2.3 Hz), 7.07 (1H, dd, J = 12.0 Hz, 2.1 Hz), 7.12 (1H, dd, J = 8.5 Hz, 2.2 Hz), 7.48 (1H, t, J = 8.7 Hz).

[1024]

Reference Example 737

4-(4-Chloro-2-fluorophenyl)-4-[(4-methoxybenzyl)oxy]cyclohexanone

Under argon atmosphere, to a solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (6.51 g) in N,N-dimethylformamide (65ml) was added sodium hydride (50 % in oil) (2.18 g) under ice-cooling, and the mixture was stirred at the same temperature for 30 min. To the mixture was added α-chloro-4-methoxytoluene (6.16 mL) and the solution was stirred at room temperature for 3 h. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography to provide 8-(4-chloro-2-fluorophenyl)-8-[(4-methoxybenzyl)oxy]-1,4-dioxaspiro[4.5]decane as oil (9.06 g). The oil was dissolved into tetrahydrofuran (130 mL), and to the solution was added 5 N hydrochloric acid (33 mL), and the mixture was stirred at room temperature for 5 h. The reaction solution was poured into potassium carbonate aqueous solution, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (7.64 g).

^{1}HNMR (CDCl$_3$) δ ppm: 2.21-2.42 (4H, m), 2.55-2.66 (2H, m), 2.76-2.90 (2H, m), 3.81 (3H, s), 4.23 (2H, s), 6.85-6.93 (2H, m), 7.13 (1H, dd, J = 11.7 Hz, 2.1 Hz), 7.17 (1H, m), 7.22-7.29 (2H, m), 7.40 (1H, t, J = 8.5 Hz).

[1025]

Reference Example 738

6-(4-Chloro-2-fluorophenyl)-6-[(4-methoxybenzyl)oxy]-1-oxaspiro[2.5]octane

Synthesized analogous to Reference Example 623.

^{1}HNMR (CDCl$_3$) δ ppm: 1.15-1.23 (2H, m), 2.15-2.26 (2H, m), 2.29-2.38 (2H, m), 2.38-2.50 (2H, m), 2.71 (2H, s), 3.81 (3H, s), 4.12 (2H, s), 6.84-6.93 (2H, m), 7.05-7.13 (1H, dd, J = 11.7 Hz, 2.1 Hz), 7.13-7.18 (1H, dd, J = 8.4 Hz, 2.1 Hz), 7.22-7.30 (2H, m), 7.38 (1H, t, J = 8.5 Hz).

[1026]

Reference Example 739

4-Chloro-2-fluoro-1-{1-[(4-methoxybenzyl)oxy]-4-methylidenecyclohexyl}benzene

To a suspension of methyltriphenylphosphonium bromide (5.59 g) in tetrahydrofuran (42 mL) was added potassium *tert*-butoxide (1.55 g) under argon atmosphere, and the mixture was stirred at room temperature for 1 h. To the mixture was added a solution of 4-(4-chloro-2-fluorophenyl)-4-[(4-methoxybenzyl)oxy]cyclohexanone (4.36 g) in tetrahydrofuran (10 mL), and the reaction mixture was stirred at room temperature overnight. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (3.90 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.86-2.00 (2H, m), 2.17-2.27 (2H, m), 2.30-2.40 (2H, m), 2.52-2.64 (2H, m), 3.80 (3H, s), 4.16 (2H, s), 4.65-4.71 (2H, m), 6.83-6.90 (2H, m), 7.08 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.10-7.16 (1H, m), 7.21-7.28 (2H, m), 7.36 (1H, t, J = 8.5 Hz).

[1027]

Reference Example 740

4-(4-Chloro-2-fluorophenyl)-1-(hydroxymethyl)-4-[(4-methoxybenzyl)oxy]cyclohexanol

To a solution of 4-chloro-2-fluoro-1-{1-[(4-methoxybenzyl)oxy]-4-methylidenecyclohexyl}benzene (0.30 g) in acetone/water (6 mL/1.5 mL) were added N-methylmorpholine (0.24 g) and Osmium Oxide, Immobilized Catalyst I (content: 7 %) (0.030 g, 8.31 μM), and the reaction mixture was stirred at room temperature overnight. Insoluble materials were filtered off, and the filtrate was concentrated. Water was added to the residue, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.28 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.51-1.68 (2H, m), 1.69-1.86 (2H, m), 1.86-2.30 (6H, m), 3.49 (0.6H, d, J = 5.1 Hz), 3.63 (1.4H, d, J = 5.4 Hz), 3.80 (3H, s), 4.09 (0.6H, s), 4.14 (1.4H, s), 6.83 (2H, m), 7.09 (1H, dd, J = 11.9 Hz, 2.1 Hz), 7.13 (1H, dd, J = 8.4 Hz, 2.1 Hz), 7.17-7.28 (2H, m), 7.32-7.42 (1H, m).

[1028]

Reference Example 741

{*cis*-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-[(4-methoxybenzyl)oxy]cyclohexyl}methyl 4-methylbenzenesulfonate

Synthesized analogous to Reference Example 697.

^{1}HNMR (CDCl$_3$) δ ppm: 1.61-1.71 (2H, m), 1.80-2.00 (4H, m), 2.11 (1H, s), 2.12-2.23 (2H, m), 2.45 (3H, s), 3.80 (3H, s), 4.04 (2H, s), 4.10 (2H, s), 6.82-6.89 (2H, m), 7.05-7.15 (2H, m), 7.18-7.22 (2H, m), 7.31 (1H, t, J = 8.5 Hz), 7.36 (2H, d, J = 8.0 Hz), 7.76-7.84 (2H, m).

[1029]

Reference Example 742

(3s,6s)-6-(4-Chloro-2-fluorophenyl)-6-[(4-methoxybenzyl)oxy]-1-oxaspiro[2.5]octane

A solution of {*cis*-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-[(4-methoxybenzyl)-oxy]cyclohexyl}methyl 4-methylbenzenesulfonate (1.09 g) and 1,8-diazabicyclo[5.4.0]undecene (0.36 mL) in ethyl acetate (11 mL) was stirred at room temperature overnight. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.68 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.21-1.34 (2H, m), 2.07-2.19 (2H, m), 2.32-2.47 (4H, m), 2.67 (2H, s), 3.81 (3H, s), 4.16 (2H, s), 6.83-6.92 (2H, m), 7.11 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.13-7.20 (1H, m), 7.22-7.30 (2H, m), 7.40 (1H, t, J = 8.5 Hz).

[1030]

Reference Example 743

8-(4-Chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene

A solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (0.30 g) and (methoxycarbonylsulfamoyl)triethylammonium hydroxide (0.50 g) in tetrahydrofuran (6 mL) was stirred, under argon atmosphere, at room temperature for 1 h. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.25 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.90 (2H, t, J = 6.5 Hz), 2.44-2.49 (2H, m), 2.57-2.63 (2H, m), 3.99-4.05 (4H, m), 5.83-5.87 (1H, m), 7.03-7.09 (2H, m), 7.19 (1H, t, J = 8.4 Hz).

[1031]

Reference Example 744

8-(4-Chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decane

To a solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (1.18 g) in ethyl acetate (12 mL) was added platinum oxide (60 mg) under argon atmosphere, and the reaction mixture was stirred at room temperature for 7 h under hydrogen atmosphere. Insoluble materials were filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.60 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.63-1.92 (8H, m), 2.82-2.94 (1H, m), 3.98 (4H, s), 7.04 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.07 (1H, dd, J = 8.3 Hz, 2.0 Hz), 7.19 (1H, t, J = 8.2 Hz).

[1032]

Reference Example 745

4-(4-Chloro-2-fluorophenyl)cyclohexanone

A solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decane (2.95 g) and 5 N hydrochloric acid (15 mL) in tetrahydrofuran (59 mL) was stirred at room temperature for 5 h, then under heated to reflux for 5 h. The reaction solution was concentrated, and potassium carbonate aqueous solution was added to the residue, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.95 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.81-2.02 (2H, m), 2.13-2.27 (2H, m), 2.45-2.60 (4H, m), 3.26-3.39 (1H, m), 7.02-7.20 (3H, m).

[1033]

Reference Example 746

4-Chloro-2-fluoro-1-(4-methylidenecyclohexyl)benzene

Synthesized analogous to Reference Example 739.

^{1}HNMR ($CDCl_3$) δ ppm: 1.44-1.59 (2H, m), 1.83-1.99 (2H, m), 2.09-2.24 (2H, m), 2.38-2.47 (2H, m), 2.94-3.05 (1H, m), 4.68 (2H, t, J = 1.7 Hz), 7.03 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.06 (1H, dd, J = 8.3 Hz, 2.1 Hz), 7.12 (1H, t, J = 8.1 Hz).

[1034]

Reference Example 747

4-(4-Chloro-2-fluorophenyl)-1-(hydroxymethyl)cyclohexanol

Synthesized analogous to Reference Example 740.

^{1}HNMR ($CDCl_3$) δ ppm: 1.40-1.65 (4H, m), 1.68-1.78 (0.5H, m), 1.78-1.91 (2.5H, m), 1.91-1.99 (1.5H, m), 1.99-2.11 (1.5H, m), 2.76-2.99 (1H, m), 3.48 (0.5H, d, J = 5.9 Hz), 3.70 (1.5H, d, J = 5.9 Hz), 7.00-7.25 (3H, m).

[1035]

Reference Example 748

[*cis*-4-(4-Chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methyl 4-methylbenzenesulfonate

To a solution of 4-(4-chloro-2-fluorophenyl)-1-(hydroxymethyl)cyclohexanol (1.96 g) in dichloromethane (20 mL) were added p-toluenesulfonyl chloride (1.74 g) and N,N,N',N'-tetramethyl-1,3-propanediamine (2.52 mL) under ice-cooling, and the mixture was stirred at the same temperature for 3 h. To the reaction solution was added water, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.45 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.39-1.52 (2H, m), 1.63-1.73 (2H, m), 1.75-1.92 (5H, m), 2.46 (3H, s), 2.71-2.87 (1H, m), 3.87 (2H, s), 7.02 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.07 (1H, dd, J = 8.4 Hz, 1.9 Hz), 7.18 (1H, t, J = 8.2 Hz), 7.37 (2H, d, J = 8.1 Hz), 7.77-7.85 (2H, m).

[1036]

Reference Example 749

[*trans*-4-(4-Chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methyl 4-methylbenzenesulfonate

To a solution of 4-(4-chloro-2-fluorophenyl)-1-(hydroxymethyl)cyclohexanol (1.96 g) in dichloromethane (20 mL) were added p-toluenesulfonyl chloride (1.74 g) and N,N,N',N'-tetramethyl-1,3-propanediamine (2.52 mL) under ice-cooling, and the reaction mixture was stirred at the same temperature for 3 h. To the reaction solution was added water, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.97 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.29-1.44 (2H, m), 1.51-1.68 (2H, m), 1.71-1.85 (2H, m), 1.88-2.02 (2H, m), 2.17 (1H, s), 2.46 (3H, s), 2.72-2.83 (1H, m), 4.12 (2H, s), 6.96-7.11 (3H, m), 7.38 (2H, d, J = 8.0 Hz), 7.79-7.89 (2H, m).

[1037]

Reference Example 750

(3r,6r)-6-(4-Chloro-2-fluorophenyl)-1-oxaspiro[2.5]octane

Synthesized analogous to Reference Example 742.

^{1}HNMR ($CDCl_3$) δ ppm: 1.33-1.48 (2H, m), 1.62-1.77 (2H, m), 1.94-2.15 (4H, m), 2.66 (2H, s), 2.85-2.97 (1H, m), 7.03 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.07 (1H, dd, J = 8.4 Hz, 1.9 Hz), 7.16 (1H, t, J = 8.1 Hz).

[1038]

Reference Example 751

(3s,6s)-6-(4-Chloro-2-fluorophenyl)-1-oxaspiro[2.5]octane

Synthesized analogous to Reference Example 742.

^{1}HNMR ($CDCl_3$) δ ppm: 1.32-1.43 (2H, m), 1.77-1.95 (4H, m), 2.01-2.16 (2H, m), 2.71 (2H, s), 2.88-3.00 (1H, m), 7.05 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.10 (1H, dd, J = 8.4 Hz, 2.3 Hz), 7.21 (1H, t, J = 8.2 Hz).

[1039]

Reference Example 752

5-{[*cis*-4-(4-Chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 453.

^{1}HNMR (CDCl$_3$) δ ppm: 1.56-1.66 (2H, m), 1.70-1.79 (2H, m), 1.85-1.99 (5H, m), 2.62-2.70 (2H, m), 2.81-2.93 (3H, m), 3.74 (3H, s), 3.77 (2H, s), 5.24 (2H, brs), 6.52 (1H, dd, J = 7.3 Hz, 3.4 Hz), 6.73-6.79 (2H, m), 6.84 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.05 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.10 (1H, dd, J = 8.5 Hz, 1.9 Hz), 7.12-7.15 (2H, m), 7.23 (1H, t, J = 8.0 Hz).

[1040]

Reference Example 753

5-{[4-(4-Chloro-2-fluorophenyl)cyclohex-1-en-1-yl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR (CDCl$_3$) δ ppm: 1.76-1.90 (1H, m), 1.90-2.00 (1H, m), 2.10-2.31 (3H, m), 2.31-2.41 (1H, m), 2.60-2.69 (2H, m), 2.83-2.97 (2H, m), 3.05-3.19 (1H, m), 3.73 (3H, s), 4.35 (2H, s), 5.23 (2H, brs), 5.82-5.90 (1H, m), 6.52 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.71-6.79 (2H, m), 6.82 (1H, dd, J = 12.8 Hz, 9.1 Hz), 7.00-7.11 (2H, m), 7.10-7.18 (3H, m).

[1041]

Reference Example 754

5-{[(1R*,2R*,4R*)-4-(4-Chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 740.

^{1}HNMR (CDCl$_3$) δ ppm: 1.62-1.74 (2H, m), 1.77-1.93 (2H, m), 1.93-2.08 (2H, m), 2.20 (1H, d, J = 5.8 Hz), 2.48 (1H, d, J = 0.7 Hz), 2.61-2.71 (2H, m), 2.81-3.00 (3H, m), 3.74 (3H, s), 3.88-3.93 (1H, m), 3.94 (2H, s), 5.14-5.34 (2H, m), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-

6.79 (2H, m), 6.85 (1H, dd, J = 12.7 Hz, 9.1 Hz), 7.06 (1H, dd, J = 10.1 Hz, 2.1 Hz), 7.09-7.16 (3H, m), 7.21 (1H, t, J = 8.1 Hz).

[1042]

Reference Example 755

5-{[(1R*,2R*,4S*)-4-(4-Chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-1-(4-methoxybenzyl)-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 740.

^{1}HNMR ($CDCl_3$) δ ppm: 1.58-1.67 (1H, m), 1.78-1.94 (3H, m), 1.98-2.15 (2H, m), 2.56-2.69 (4H, m), 2.83-2.92 (2H, m), 3.31-3.42 (1H, m), 3.74 (3H, s), 4.04 (2H, s), 4.08 (1H, brs), 5.24 (2H, brs), 6.56 (1H, dd, J = 9.1 Hz, 3.4 Hz), 6.73-6.80 (2H, m), 6.86 (1H, dd, J = 12.6 Hz, 9.1 Hz), 7.00-7.09 (2H, m), 7.09-7.17 (3H, m).

[1043]

Reference Example 756

5-({4-(4-Chloro-2-fluorophenyl)-4-[(4-methoxybenzyl)oxy]cyclohex-1-en-1-yl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 595.

^{1}HNMR ($CDCl_3$) δ ppm: 1.86-2.01 (1H, m), 2.25-2.44 (3H, m), 2.54-2.62 (2H, m), 2.63-2.82 (2H, m), 2.96 (2H, t, J = 7.7 Hz), 3.79 (3H, s), 4.17 (2H, s), 4.39 (2H, brs), 5,78 (1H, brs), 6.42 (1H, dd, J = 9.1 Hz, 4.0 Hz), 6.77-6.94 (3H, m), 7.05-7.15 (2H, m), 7.15-7.20 (2H, m), 7.29 (1H, t, J = 8.6 Hz), 7.51 (1H, brs).

[1044]

Reference Example 757

5-({(1R*,2R*)-4-(4-Chloro-2-fluorophenyl)-1,2-dihydroxy-4-[(4-methoxybenzyl)oxy]-cyclohexyl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one

Synthesized analogous to Reference Example 740.

^{1}HNMR ($CDCl_3$) δ ppm: 1.77-2.46 (6H, m), 2.48-2.69 (4H, m), 2.78-2.95 (2H, m), 3.81 (3H, s), 3.93 (1H, d, J = 8.9 Hz), 4.00 (1H, d, J = 8.9 Hz), 4.10 (2H, s), 4.19-4.33 (1H, m), 6.49 (1H, dd, J = 9.0 Hz, 3.9 Hz), 6.80-6.95 (3H, m), 7.09-7.24 (4H, m), 7.33-7.42 (1H, m), 7.51 (1H, brs).

[1045]

Reference Example 758

(1R*,2R*,5S*)-5-(4-Chloro-2-fluorophenyl)-2-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-2-hydroxy-5-[(4-methoxybenzyl)oxy]cyclohexyl acetate

To a solution of 5-({(1R*,2R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxy-4-[(4-methoxybenzyl)oxy]cyclohexyl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one (1.39 g) in pyridine (14 mL) was added acetic anhydride(0.28 mL), and the reaction mixture was stirred at 50-60 °C for 4 h. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (0.67 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.70-1.80 (1H, m), 2.07 (3H, s), 2.14-2.22 (2H, m), 2.23-2.25 (1H, m), 2.27-2.37 (1H, m), 2.38-2.52 (3H, m), 2.58 (1H, dd, J = 12.9 Hz, 4.3 Hz), 2.72-2.91 (2H, m), 3.73-3.88 (5H, m), 4.06 (1H, d, J = 10.3 Hz), 4.39 (1H, d, J = 10.3 Hz), 5.49 (1H, dd, J =

11.6 Hz, 4.4 Hz), 6.41 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.81-6.92 (3H, m), 7.12 (1H, dd, J = 11.6 Hz, 2.0 Hz), 7.15 (1H, dd, J = 8.4 Hz, 2.1 Hz), 7.27-7.32 (2H, m), 7.38 (1H, t, J = 8.4 Hz), 7.54 (1H, brs).

[1046]

Reference Example 759

(1R*,2R*,5R*)-5-(4-Chloro-2-fluorophenyl)-2-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-2-hydroxy-5-[(4-methoxybenzyl)oxy]cyclohexyl acetate

To a solution of 5-({(1R*,2R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxy-4-[(4-methoxybenzyl)oxy]cyclohexyl}methoxy)-8-fluoro-3,4-dihydroquinolin-2(1H)-one (1.39 g) in pyridine (14 mL) was added acetic anhydride (0.28 mL), and the reaction mixture was stirred at 50-60 °C for 4 h. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate) to provide the title compound (0.29 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.50-1.64 (1H, m), 1.81-1.92 (1H, m), 2.08 (3H, s), 2.15-2.34 (3H, m), 2.48-2.73 (5H, m), 2.84-2.94 (1H, m), 3.73 (2H, s), 3.78 (3H, s), 4.04 (1H, d, J = 10.4 Hz), 4.19 (1H, d, J = 10,.4 Hz), 5.10 (1H, dd, J = 12.0 Hz, 4.4 Hz), 6.34 (1H, dd, J = 9.1 Hz, 3.9 Hz), 6.79 (3H, m), 7.08-7.15 (2H, m), 7.17 (1H, dd, J = 11.9 Hz, 2.1 Hz), 7.24 (1H, dd, J = 8.5 Hz, 2.1 Hz), 7.48 (1H, brs), 7.71 (1H, t, J = 8.5 Hz).

[1047]

Reference Example 760

Dimethyl 4-(4-chloro-2-fluorophenyl)-4-cyanoheptanedioate

A solution of 4-chloro-2-fluorophenylacetonitrile (10.00 g), methyl acrylate (53.1 mL) and Triton B (2.68 mL) in acetonitrile (200 mL) was heated to reflux for 8 h. The reaction solution was concentrated, and 2 N hydrochloric acid was added to the residue. The solution was extracted with diethyl ether, the organic layer was washed with water and potassium carbonate aqueous solution, and dried over anhydrous sodium sulfate, and then the solvent was distilled off to provide the title compound (20.2 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.10-2.23 (2H, m), 2.29-2.43 (2H, m), 2.46-2.66 (4H, m), 3.62 (6H, s), 7.06-7.30 (2H, m), 7.50 (1H, t, J = 8.5 Hz).

[1048]

Reference Example 761

Methyl 5-(4-chloro-2-fluorophenyl)-5-cyano-2-oxocyclohexanecarboxylate

To a solution of dimethyl 4-(4-chloro-2-fluorophenyl)-4-cyanoheptanedioate (20.15 g) in 1,2-dimethoxyethane (202 mL) was added sodium hydride (50 % in oil) (8.49 g) under argon atmosphere at 0 °C, and the mixture was stirred at the same temperature for 5 min, then at room temperature for 10 min, and then heated to reflux for 1 h. The reaction solution was poured into aqueous saturated ammonium chloride, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (14.04 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.23-2.54 (3H, m), 2.66-2.89 (2H, m), 3.01-3.17 (1H, m), 3.79 (3H, s), 7.15-7.26 (2H, m), 7.38-7.50 (1H, m), 12.25 (1H, s).

[1049]

Reference Example 762

1-(4-Chloro-2-fluorophenyl)-4-oxocyclohexanecarbonitrile

To a solution of methyl 5-(4-chloro-2-fluorophenyl)-5-cyano-2-oxocyclohexanecarboxylate (14.04 g) in dimethyl sulfoxide (112 mL) were added sodium chloride (14.04 g) and water (18 mL), and the reaction mixture was stirred at 140-150 °C for 8 h. To the reaction solution was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (10.2 g).

^{1}HNMR ($CDCl_3$) δ ppm: 2.34-2.45 (2H, m), 2.51-2.65 (4H, m), 2.84-2.98 (2H, m), 7.18-7.25 (2H, m), 7.48 (1H, t, J = 8.5 Hz).

[1050]

Reference Example 763

(3r,6r)-6-(4-Chloro-2-fluorophenyl)-1-oxaspiro[2.5]octane-6-carbonitrile

Synthesized analogous to Reference Example 623.

^{1}HNMR ($CDCl_3$) δ ppm: 1.35-1.49 (2H, m), 2.23-2.34 (4H, m), 2.45-2.60 (2H, m), 2.78 (2H, s), 7.13-7.24 (2H, m), 7.41 (1H, t, J = 8.6 Hz).

[1051]

Reference Example 764

8-(4-Chloro-2-fluorophenyl)-8-methoxy-1,4-dioxaspiro[4.5]decane

To a solution of 8-(4-chloro-2-fluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (2.00 g) in N,N-dimethylformamide (20 mL) was added sodium hydride (50 % in oil) (0.670 g) under argon atmosphere at 0 °C, and the reaction mixture was stirred at the same temperature for 30 min. Then to the mixture was added iodomethane (0.868 mL) and the solution was stirred at room temperature for 1 h. The reaction solution was poured into water, and the solution was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.98 g).

^{1}HNMR (CDCl$_3$) δ ppm: 1.60-1.70 (2H, m), 1.93-2.05 (2H, m), 2.05-2.21 (4H, m), 3.07 (3H, s), 3.88-4.04 (4H, m), 7.00-7.09 (1H, dd, J = 11.8 Hz, 2.2 Hz), 7.11 (1H, m), 7.31 (1H, t, J = 8.5 Hz).

[1052]

Reference Example 765

4-(4-Chloro-2-fluorophenyl)-4-methoxycyclohexanone

Synthesized analogous to Reference Example 745.

^{1}HNMR (CDCl$_3$) δ ppm: 2.20-2.39 (4H, m), 2.42-2.55 (2H, m), 2.70-2.84 (2H, m), 3.19 (3H, s), 7.11 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.15-7.20 (1H, m), 7.34 (1H, t, J = 8.5 Hz).

[1053]

Reference Example 766

4-Chloro-2-fluoro-1-(1-methoxy-4-methylidenecyclohexyl)benzene

Synthesized analogous to Reference Example 739.

^{1}HNMR (CDCl$_3$) δ ppm: 1.83-1.99 (2H, m), 2.12-2.28 (4H, m), 2.41-2.56 (2H, m), 3.11 (3H, s), 4.68 (2H, t, J = 1.7 Hz), 7.06 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.09-7.15 (1H, m), 7.30 (1H, t, J = 8.5 Hz).

[1054]

Reference Example 767

4-(4-Chloro-2-fluorophenyl)-1-(hydroxymethyl)-4-methoxycyclohexanol

Synthesized analogous to Reference Example 740.

^{1}HNMR ($CDCl_3$) δ ppm: 1.46-1.64 (1H, m), 1.67-2.25 (9H, m), 3.05 (1H, s), 3.10 (2H, s), 3.51 (0.6H, d, J = 5.2 Hz), 3.63 (1.4H, d, J = 5.6 Hz), 7.00-7.17 (2H, m), 7.28-7.36 (1H, m).

[1055]

Reference Example 768

[*trans*-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methyl 4-methylbenzenesulfonate

To a solution of 4-(4-chloro-2-fluorophenyl)-1-(hydroxymethyl)-4-methoxycyclohexanol (1.48 g) in dichloromethane (15 mL) were added N,N,N',N'-tetramethyl-1,3-propanediamine (1.704 mL) and p-toluenesulfonyl chloride (1.17 g), and the reaction mixture was stirred at room temperature for 1 h. To the reaction solution was added brine, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (0.53 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.49-1.62 (2H, m), 1.65-1.78 (2H, m), 1.80 (1H, s), 1.97-2.03 (2H, m), 2.09-2.22 (2H, m), 2.46 (3H, s), 3.00 (3H, s), 3.89 (2H, s), 7.06 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.09-7.15 (1H, m), 7.28 (1H, t, J = 7.9 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.77-7.85 (2H, m).

[1056]

Reference Example 769

[*cis*-4-(4-Chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methyl 4-methylbenzenesulfonate

To a solution of 4-(4-chloro-2-fluorophenyl)-1-(hydroxymethyl)-4-methoxycyclohexanol (1.48 g) in dichloromethane (15 mL) were added N,N,N',N'-tetramethyl-1,3-propanediamine (1.704 mL) and p-toluenesulfonyl chloride (1.173 g), and the reaction mixture was stirred at room temperature for 1 h. To the reaction solution was added brine, and the solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the title compound (1.41 g).

^{1}HNMR ($CDCl_3$) δ ppm: 1.60-1.69 (2H, m), 1.73-1.93 (4H, m), 1.98-2.08 (2H, m), 2.11 (1H, s), 2.45 (3H, s), 3.06 (3H, s), 4.04 (2H, s), 7.06 (1H, dd, J = 12.2 Hz, 2.2 Hz), 7.12 (1H, dd, J = 8.5 Hz, 2.2 Hz), 7.25 (1H, t, J = 8.5 Hz), 7.33-7.40 (2H, m), 7.76-7.85 (2H, m).

[1057]

Reference Example 770

(3r,6r)-6-(4-Chloro-2-fluorophenyl)-6-methoxy-1-oxaspiro[2.5]octane

Synthesized analogous to Reference Example 742.

^{1}HNMR ($CDCl_3$) δ ppm: 1.11-1.22 (2H, m), 2.09-2.26 (4H, m), 2.31-2.43 (2H, m), 2.72 (2H, s), 3.09 (3H, s), 7.09 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.13 (1H, dd, J = 8.5 Hz, 2.2 Hz), 7.31 (1H, t, J = 8.5 Hz).

[1058]

Reference Example 771

(3s,6s)-6-(4-Chloro-2-fluorophenyl)-6-methoxy-1-oxaspiro[2.5]octane

Synthesized analogous to Reference Example 742.

^{1}HNMR ($CDCl_3$) δ ppm: 1.12-1.30 (2H, m), 1.97-2.13 (2H, m), 2.18-2.35 (4H, m), 2.66 (2H, s), 3.12 (3H, s), 7.08 (1H, dd, J = 11.8 Hz, 2.1 Hz), 7.14 (1H, dd, J = 8.5 Hz, 2.1 Hz), 7.34 (1H, t, J = 8.5 Hz).

[1059]

Reference Example 772

8-(4-Chloro-2,6-difluorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol

Synthesized analogous to Reference Example 736.

^{1}HNMR ($CDCl_3$) δ ppm: 1.61-1.70 (2H, m), 2.08-2.14 (4H, m), 2.29-2.43 (2H, m), 2.53 (1H, t, J = 5.5 Hz), 3.93-4.01 (4H, m), 6.86-6.95 (2H, m).

[1060]

Reference Example 773

4-(4-Chloro-2,6-difluorophenyl)-4-hydroxycyclohexanone

Synthesized analogous to Reference Example 745.

^{1}HNMR ($CDCl_3$) δ ppm: 2.27-2.40 (2H, m), 2.40-2.55 (4H, m), 2.86-2.98 (3H, m), 6.94-7.00 (2H, m).

[1061]

Reference Example 774

1-(4-Chloro-2,6-difluorophenyl)-4-methylidenecyclohexanol

Synthesized analogous to Reference Example 739.

^{1}HNMR ($CDCl_3$) δ ppm: 2.02-2.25 (6H, m), 2.54-2.70 (3H, m), 4.68 (2H, t, J = 1.7 Hz), 6.81-6.96 (2H, m).

[1062]

Reference Example 775

1-(4-Chloro-2,6-difluorophenyl)-4-(hydroxymethyl)cyclohexane-1,4-diol

Synthesized analogous to Reference Example 740.

^{1}HNMR (DMSO-d6) δ ppm: 1.22-1.31 (0.5H, m), 1.40-1.52 (1.5H, m), 1.56-1.72 (1.5H, m), 1.75-1.96 (2.5H, m), 2.01-2.11 (1.5H, m), 2.17-2.33 (0.5H, m), 3.15 (0.5H, d, J = 5.6 Hz), 3.28 (1.5H, d, J = 5.9 Hz), 3.86 (0.25H, s), 4.06 (0.75H, s), 4.38 (0.75H, t, J = 5.9 Hz), 4.47 (0.25H, t, J = 5.6 Hz), 5.00 (0.25H, s), 5.20 (0.75H, s), 7.15-7.29 (2H, m).

[1063]

Reference Example 776

[*trans*-4-(4-Chloro-2,6-difluorophenyl)-1,4-dihydroxycyclohexyl]methyl 4-methylbenzenesulfonate

To a solution of 1-(4-chloro-2,6-difluorophenyl)-4-(hydroxymethyl)cyclohexane-1,4-diol (1.59 g) in dichloromethane (32 mL) were added N,N,N',N'-tetramethyl-1,3-propanediamine (1.81 mL) and p-toluenesulfonyl chloride (1.24 g), and the reaction mixture

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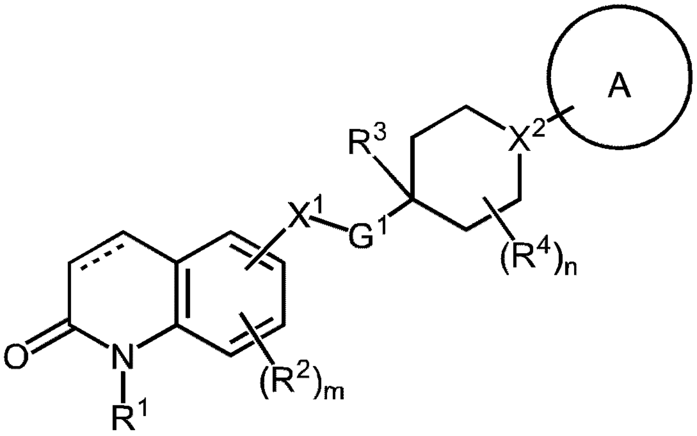
CLAIMS:

1. A compound of the general formula (1) for use for diagnosing, preventing, or treating tuberculosis:



(1)

or a pharmaceutically acceptable salt thereof,

wherein **R^1** is

(1) hydrogen,

(2) amino, or amino having one or two of the same or different C_{1-6} alkyl or

(3) C_{1-6} alkyl;

R^2 is

(1) halogen,

(2) amino, or amino having one or two of the same or different C_{1-6} alkyl,

(3) C_{1-6} alkyl,

(4) C_{1-6} alkoxy or

(5) hydroxy;

m is an integer of 0 to 3;

provided that when m is 2 or 3, R^2s are the same or different from each other;

X^1 is $-CH_2-$, -O-, $-N(R^5)-$, -S-, -SO- or $-SO_2-$;

R^5 is

(1) hydrogen,

(2) C_{1-6} alkyl or

(3) C_{1-7} alkanoyl;

G^1 is C_{1-6} alkylene;

R^3 is

(1) hydrogen,

(2) carboxy,
(3) halogen,
(4) C_{1-6} alkyl, or C_{1-6} alkyl having one or more hydroxy,
(5) cyano,
(6) amino, or amino having one or two substituents independently selected from:
  (a) C_{1-6} alkyl and
  (b) -C(=O)-R^6 or
(7) -O-R^7;

R^6 is

(1) C_{1-6} alkoxy or
(2) C_{1-6} alkyl, or C_{1-6} alkyl having amino or amino having one or two of the same or different C_{1-6} alkyl;

R^7 is

(1) hydrogen,
(2) amino,
(3) C_{1-7} alkanoyl or
(4) C_{1-6} alkyl;

R^4 is

(1) amino, or amino having one or two of the same or different C_{1-6} alkyl,
(2) halogen,
(3) cyano,
(4) C_{1-6} alkyl,
(5) oxo,
(6) -O-R^8 or
(7) -O-C(=O)-R^9;

R^8 is

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) -PH(=O)OH or
(4) benzyl, or benzyl having one or more of the same or different C_{1-6} alkoxy;

R^9 is

(1) C_{1-6} alkyl,
(2) -G^2-COOH,
(3) amino, or amino having one or two of the same or different C_{1-6} alkyl,

(4) C_{1-6} alkoxy or

(5) pyrazinyl;

G^2 is C_{1-6} alkylene;

n is an integer of 0 to 8;

provided that when n is 2 or more, each of R^4s, R^8s, R^9s, and G^2s are the same or different from each other and R^4s are substituted on the same or different carbon atom;

X^2 is N, CH, or CR^4, wherein multiple R^4s in formula (1) are the same or different from each other;

Ring A is

(1) phenyl, or phenyl having one or more substituents, or

(2) heterocyclyl selected from the group consisting of pyridyl, N-oxide pyridyl, thienyl, quinolyl, isoquinolyl, benzothienyl, quinoxalinyl, benzofuryl, benzodioxolyl, benzooxazolyl, and benzoimidazolyl, or said heterocyclyl which has one or more substituents,

wherein the substituents are independently selected from:

(a) halogen;

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) C_{1-6} alkyl, or C_{1-6} alkyl having one or more substituents independently selected from:

(i) halogen,

(ii) hydroxy,

(iii) C_{1-6} alkoxy, and

(iv) aryloxy, or aryloxy having one or more of the same or different halogen, wherein the aryloxy is selected from the group consisting of phenyloxy, naphthyloxy, anthryloxy, and phenanthryloxy;

(f) C_{1-6} alkoxy, or C_{1-6} alkoxy having one or more substituents independently selected from the group consisting of:

(i) halogen,

(ii) C_{1-6} alkoxy, or C_{1-6} alkoxy having one or more of the same or different C_{1-6} alkoxy,

(iii) aryloxy, or aryloxy having one or more of the same or different halogen, wherein the aryloxy is selected from phenyloxy, naphthyloxy, anthryloxy, and phenanthryloxy,

(iv) heterocyclyl, or heterocyclyl having one or more of the same or different C_{1-6} alkyl or C_{1-6} alkyl having one or more of the same or different halogen, wherein the heterocyclyl is 3- to 12-membered monocyclic or polycyclic heterocyclyl comprising 1 to 5 heteroatoms selected from oxygen, sulfur, and nitrogen, and

(v) amino, or amino having one or two of the same or different C_{1-6} alkyl;

(g) C_{1-6} alkoxycarbonyl;

(h) C_{1-6} alkylsulfanyl;

(i) aryl, or aryl having one or more of the same or different halogen, wherein the aryl is selected from the group consisting of phenyl, naphthyl, anthryl, and phenanthryl;

(j) phenyloxy, naphthyloxy, anthryloxy, or phenanthryloxy; and

(k) aralkyloxy, or aralkyloxy having one or more substituents independently selected from:

(i) halogen,

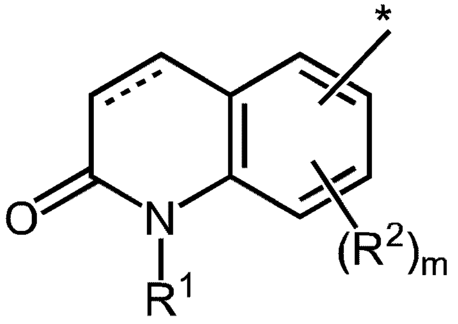
(ii) C_{1-6} alkyl, or C_{1-6} alkyl having one or more of the same or different halogen, and

(iii) C_{1-6} alkoxy, or C_{1-6} alkoxy having one or more of the same or different halogen, wherein the aralkyloxy is selected from benzyloxy, 1-phenylethyloxy, 2-phenylethyloxy, 1-naphthylmethyloxy, and 2-naphthylmethyloxy; and

a moiety of formula:

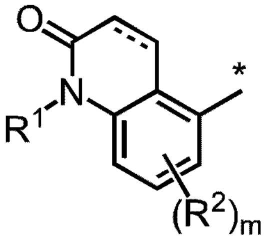
represents single bond or double bond.

2. The compound for use according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the following partial structure (X) in the general formula (1):

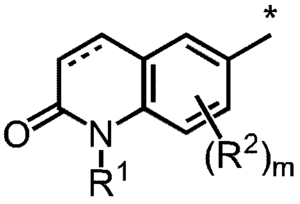


,

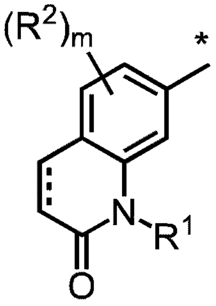
wherein * is binding point to X^1; and R^1, R^2 and m are as defined in claim 1, is any one of the structures selected from the group consisting of the following formulae (X1) to (X6):



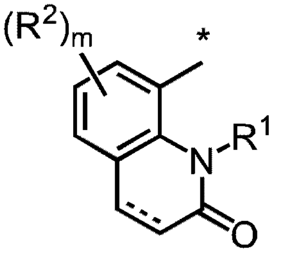
(X1)



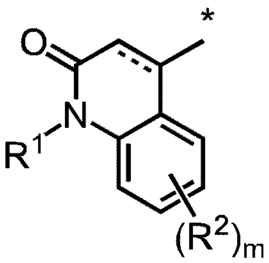
(X2)



(X3)

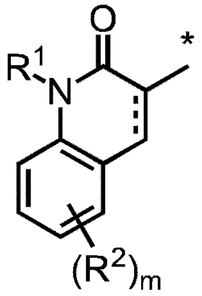


(X4)



(X5)

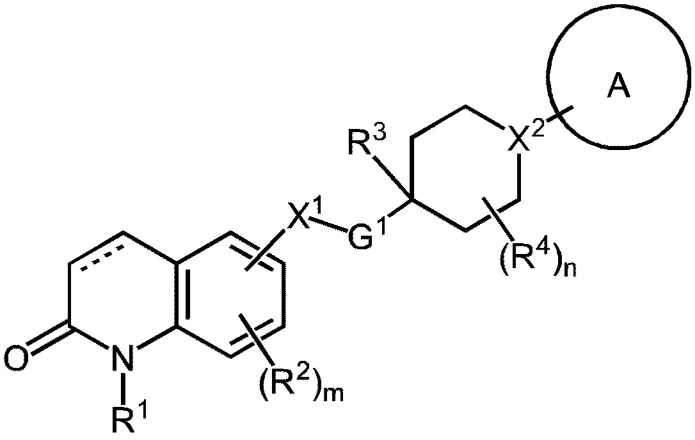
and



(X6)

wherein *, R^1, R^2 and m are as defined above.

3. A compound of the general formula (1):



(1)

or a salt thereof,

wherein **R¹** is

(1) hydrogen,

(2) amino, or amino having one or two of the same or different C_{1-6} alkyl or

(3) C_{1-6} alkyl;

R^2 is

(1) halogen,

(2) amino, or amino having one or two of the same or different C_{1-6} alkyl,

(3) C_{1-6} alkyl,

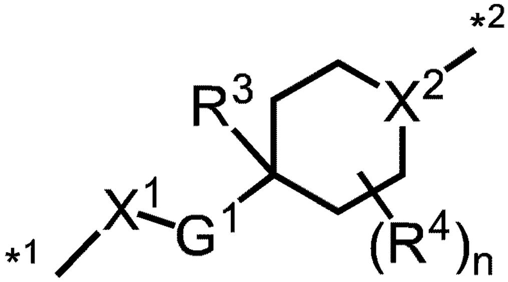
(4) C_{1-6} alkoxy or

(5) hydroxy;

m is an integer of 0 to 3;

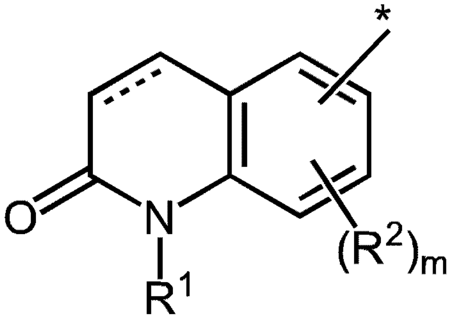
provided that when m is 2 or 3, R^2s are the same or different from each other;

the following partial structure (Y) in the general formula (1):



(Y)

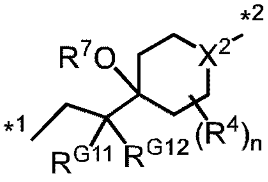
wherein *1 is binding point to the following partial structure of Formula (X) in the general formula (1):

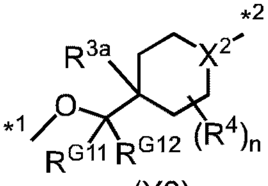


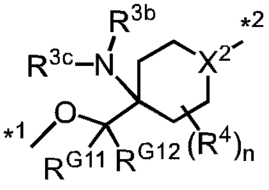
(X)

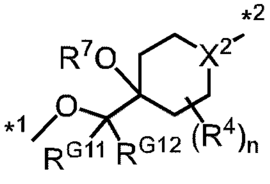
; *2 is binding point to Ring A and * is binding point to X^1,

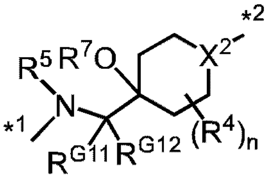
is any one of the structures selected from the group consisting of the following formulae (Y1) to (Y8):

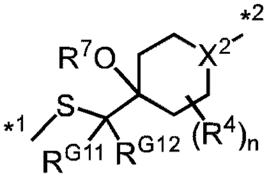

(Y1)

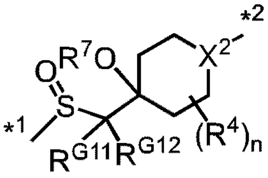

(Y2)


(Y3)

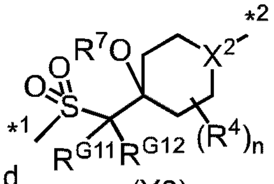

(Y4)


(Y5)


(Y6)


(Y7)

and


(Y8)

,

wherein $\mathbf{R^{3a}}$ is (1) hydrogen, (2) carboxy, (3) halogen, (4) C_{1-6} alkyl, or C_{1-6} alkyl having one or more hydroxy, or (5) cyano;

$\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are each independently (1) hydrogen, (2) C_{1-6} alkyl, or (3) -C(=O)-R^6;

$\mathbf{R^{G11}}$ and $\mathbf{R^{G12}}$ are each independently hydrogen or C_{1-6} alkyl;

the total number of carbon atoms in R^{G11} and R^{G12} is 0 to 5;

$\mathbf{R^5}$ is

(1) hydrogen,

(2) C_{1-6} alkyl or

(3) C_{1-7} alkanoyl;

$\mathbf{R^6}$ is

(1) C_{1-6} alkoxy or

(2) C_{1-6} alkyl, or C_{1-6} alkyl having amino or amino having one or two of the same or different C_{1-6} alkyl;

$\mathbf{R^7}$ is

(1) hydrogen,

(2) amino,

(3) C_{1-7} alkanoyl or

(4) C_{1-6} alkyl;

$\mathbf{R^4}$ is

(1) amino, or amino having one or two of the same or different C_{1-6} alkyl,

(2) halogen,

(3) cyano,

(4) C_{1-6} alkyl,

(5) oxo,

(6) -O-R^8 or

(7) -O-C(=O)-R^9;

R^8 is

(1) hydrogen,

(2) C_{1-6} alkyl,

(3) -PH(=O)OH or

(4) benzyl, or benzyl having one or more of the same or different C_{1-6} alkoxy;

R^9 is

(1) C_{1-6} alkyl,

(2) -G^2-COOH,

(3) amino, or amino having one or two of the same or different C_{1-6} alkyl,

(4) C_{1-6} alkoxy or

(5) pyrazinyl;

G^2 is C_{1-6} alkylene;

n is an integer of 0 to 8;

provided that when n is 2 or more, each of R^4s, R^8s, R^9s, and G^2s are the same or different from each other and R^4s are substituted on the same or different carbon atom;

X^2 is N, CH, or CR^4, wherein multiple R^4s in formula (1) are the same or different from each other;

Ring A is

(1) phenyl, or phenyl having one or more substituents, or

(2) heterocyclyl selected from the group consisting of pyridyl, N-oxide pyridyl, thienyl, quinolyl, isoquinolyl, benzothienyl, quinoxalinyl, benzofuryl, benzodioxolyl, benzooxazolyl, and benzoimidazolyl, or said heterocyclyl which has one or more substituents,

wherein the substituents are independently selected from:

(a) halogen;

(b) cyano;

(c) nitro;

(d) hydroxy;

(e) C_{1-6} alkyl, or C_{1-6} alkyl having one or more substituents independently selected from:

  (i) halogen,

  (ii) hydroxy,

  (iii) C_{1-6} alkoxy, and

(iv) aryloxy, or aryloxy having one or more of the same or different halogen, wherein the aryloxy is selected from the group consisting of phenyloxy, naphthyloxy, anthryloxy, and phenanthryloxy;

(f) C_{1-6} alkoxy, or C_{1-6} alkoxy having one or more substituents independently selected from the group consisting of:

(i) halogen,

(ii) C_{1-6} alkoxy, or C_{1-6} alkoxy having one or more of the same or different C_{1-6} alkoxy,

(iii) aryloxy, or aryloxy having one or more of the same or different halogen, wherein the aryloxy is selected from phenyloxy, naphthyloxy, anthryloxy, and phenanthryloxy,

(iv) heterocyclyl, or heterocyclyl having one or more of the same or different C_{1-6} alkyl or C_{1-6} alkyl having one or more of the same or different halogen, wherein the heterocyclyl is 3- to 12-membered monocyclic or polycyclic heterocyclyl comprising 1 to 5 heteroatoms selected from oxygen, sulfur, and nitrogen, and

(v) amino, or amino having one or two of the same or different C_{1-6} alkyl;

(g) C_{1-6} alkoxycarbonyl;

(h) C_{1-6} alkylsulfanyl;

(i) aryl, or aryl having one or more of the same or different halogen, wherein the aryl is selected from the group consisting of phenyl, naphthyl, anthryl, and phenanthryl;

(j) phenyloxy, naphthyloxy, anthryloxy, or phenanthryloxy; and

(k) aralkyloxy, or aralkyloxy having one or more substituents independently selected from:

(i) halogen,

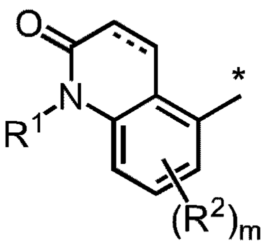
(ii) C_{1-6} alkyl, or C_{1-6} alkyl having one or more of the same or different halogen, and

(iii) C_{1-6} alkoxy, or C_{1-6} alkoxy having one or more of the same or different halogen, wherein the aralkyloxy is selected from benzyloxy, 1-phenylethyloxy, 2-phenylethyloxy, 1-naphthylmethyloxy, and 2-naphthylmethyloxy; and

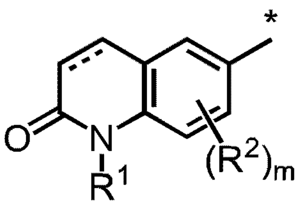
a moiety of formula:

represents single bond or double bond.

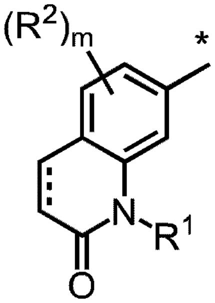
4. The compound according to claim 3, or a salt thereof, wherein the partial structure (X) is any one of the structures selected from the group consisting of the following formulae (X1) to (X6):



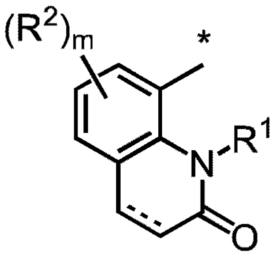
(X1)



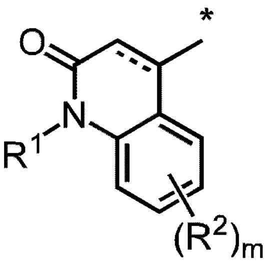
(X2)



(X3)

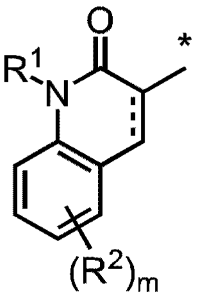


(X4)



(X5)

and



(X6)

wherein *, R^1, R^2 and m are as defined in claim 3.

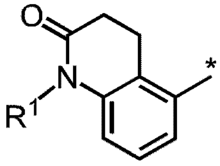
5. The compound of claim 3 or 4, or a salt thereof, wherein **R^1** is hydrogen.

6. The compound of any one of claims 3 to 5, or a salt thereof, wherein **R^2** is halogen.

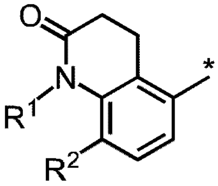
7. The compound of any one of claims 3 to 6, or a salt thereof, wherein **m** is 0, 1 or 2.

8. The compound of any one of claims 3 to 7, or a salt thereof, wherein **n** is 0, 1 or 2.

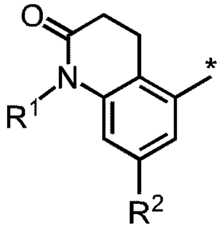
9. The compound of claim 3, or a salt thereof, wherein the partial structure (X) is a structure of a formula selected from the group consisting of the formulae (X1-1), (X1-2), (X1-3), (X1-4), (X1-6), and (X1-7):



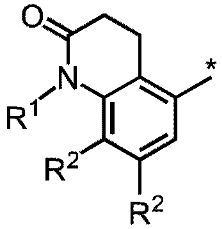
(X1-1)



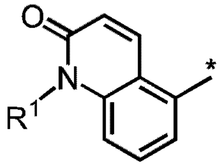
(X1-2)



(X1-3)

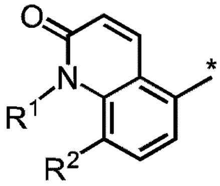


(X1-4)



(X1-6)

and



(X1-7)

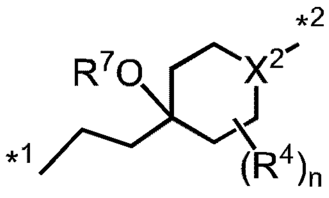
wherein * is binding point to X^1;

R^1 is hydrogen;

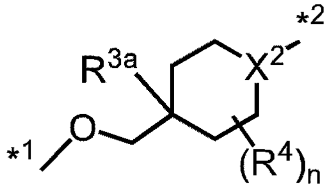
R^2 is (1) halogen or (2) C_{1-6} alkyl;

provided that when R^2 is multiple, each of them is the same or different from each other;

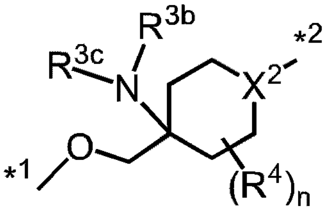
the partial structure (Y) is a structure of a formula selected from the group consisting of the formulae (Y1-1), (Y2-1), (Y3-1), (Y4-1), (Y5-1), and (Y6-1):



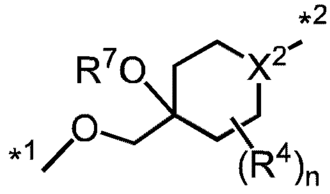
(Y1-1)



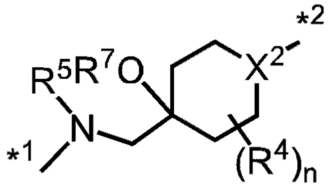
(Y2-1)



(Y3-1)

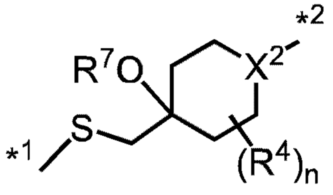


(Y4-1)



(Y5-1)

and



(Y6-1)

wherein *1 is binding point to the partial structure of Formula (X);

*2 is binding point to Ring A;

R^5 is hydrogen;

R^{3a} is (1) hydrogen or (2) halogen;

R^{3b} and **R^{3c}** are each hydrogen;

R^7 is hydrogen;

R^4 is (1) halogen, (2) -O-R^8, (3) -O-C(=O)-R^9, or (4) cyano;

R^8 is (1) hydrogen or (2) C_{1-6} alkyl;

R^9 is (1) C_{1-6} alkyl or (2) C_{1-6} alkoxy;

n is an integer of 0 to 2;

provided that when n is 2, each of R^{4}s, R^{8}s, and R^{9}s are the same or different from each other and R^{4}s are substituted on the same or different carbon atom;

X^2 is N, CH, or CR^4, wherein multiple R^{4}s in formula (1) are the same or different from each other; and

Ring A is phenyl or pyridyl, or phenyl or pyridyl which has 1 to 3 groups independently selected from the group consisting of:

(a) halogen;

(b) C_{1-6} alkoxy or C_{1-6} alkoxy having (i) halogen and (ii) C_{1-6} alkoxy; and

(c) aralkyloxy or aralkyloxy having one or more of the same or different C_{1-6} alkoxy or C_{1-6} alkoxy having one or more of the same or different halogen; or

quinolyl, or quinolyl having 1 to 2 halogen.

10. The compound of claim 3, which is selected from the group consisting of the following compounds:

5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one,

5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one,

5-{[1-(4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}quinolin-2(1H)-one,

8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

8-fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one,

8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, 5-{[(3S,4S)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(3-bromo-6-chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4S)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R*,4R*)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H)-one,

5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R*,4R*)-1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate,

(3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate,

5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{2-[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[trans-4-(4-chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[cis-4-(4-chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(1R*,2R*,4R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(1R,2R,4S)-4-(4-chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

trans-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxycyclohexanecarbonitrile, and

5-{[trans-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

11. The compound of claim 3, which is selected from the group consisting of the following compounds:

5-{[4-amino-1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one,

5-{[4-amino-1-(4-chloro-2-fluorophenyl)piperidin-4-yl]methoxy}-8-chloroquinolin-2(1H)-one,

5-{[1-(4-chlorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, 5-{[1-(4-ethoxy-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}quinolin-2(1H)-one,

8-chloro-5-{[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

8-fluoro-5-{[1-(2-fluoro-4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

8-chloro-5-({1-[4-chloro-2-fluoro-5-(2-methoxyethoxy)phenyl]-4-hydroxypiperidin-4-yl}methoxy)-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one,

8-chloro-7-fluoro-5-{[4-hydroxy-1-(2,4,6-trifluorophenyl)piperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(3,5-dichloropyridin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(4-chloro-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(3-bromo-6-chloroquinolin-2-yl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4S)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-chloro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R*,4R*)-1-(4-bromo-2-fluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoroquinolin-2(1H)-one,

5-({[1-(3,5-dichloropyridin-2-yl)-4-hydroxypiperidin-4-yl]methyl}amino)-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(3,5-dichloropyridin-2-yl)piperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[1-(3,5-dichloropyridin-2-yl)-4-fluoropiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R*,4R*)-1-(4-chloro-2-fluorophenyl)-3-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(3S,4S)-1-(4-chloro-2,6-difluorophenyl)-3-fluoro-4-hydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl ethyl carbonate,

(3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate,

5-({[1-(4-chloro-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methyl}sulfanyl)-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{2-[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]ethyl}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[trans-4-(4-chloro-2-fluorophenyl)-1,4-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[cis-4-(4-chloro-2-fluorophenyl)-1-hydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, 5-{[(1R*,2R*,4R*)-4-(4-chloro-2-fluorophenyl)-1,2-dihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

5-{[(1R,2R,4S)-4-(4-chloro-2-fluorophenyl)-1,2,4-trihydroxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one,

trans-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxycyclohexanecarbonitrile, and

5-{[trans-4-(4-chloro-2-fluorophenyl)-1-hydroxy-4-methoxycyclohexyl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one.

12. The compound of claim 3, which is 8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

13. The compound of claim 3, which is 8-chloro-5-{[1-(4-chloro-2,6-difluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-3,4-dihydroquinolin-2(1H)-one.

14. The compound of claim 3, which is 5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

15. The compound of claim 3, which is 5-{[1-(4-bromo-2-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7,8-difluoro-3,4-dihydroquinolin-2(1H)-one.

16. The compound of claim 3, which is 5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

17. The compound of claim 3, which is 5-{[1-(2,4-dichloro-5-fluorophenyl)-4-hydroxypiperidin-4-yl]methoxy}-7-fluoro-8-methyl-3,4-dihydroquinolin-2(1H)-one.

18. The compound of claim 3, which is 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof.

19. The compound of claim 3, which is 5-{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one.

20. The compound of claim 3, which is (3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate, or a salt thereof.

21. The compound of claim 3, which is (3R,4R)-1-(4-chloro-2-fluorophenyl)-4-{[(8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]methyl}-4-hydroxypiperidin-3-yl acetate.

22. A pharmaceutical composition, comprising the compound of any one of claims 3 to 10, 12, 14, 16, 18 and 20, or a pharmaceutically acceptable salt thereof, or the compound of claim 11, 13, 15, 17, 19 or 21, and a pharmaceutically acceptable carrier.

23. A medicament for diagnosing, preventing, or treating tuberculosis, comprising the compound of any one of claims 3 to 10, 12, 14, 16, 18 and 20, or a pharmaceutically acceptable salt thereof, or the compound of claim 11, 13, 15, 17, 19 or 21, and a pharmaceutically acceptable carrier.

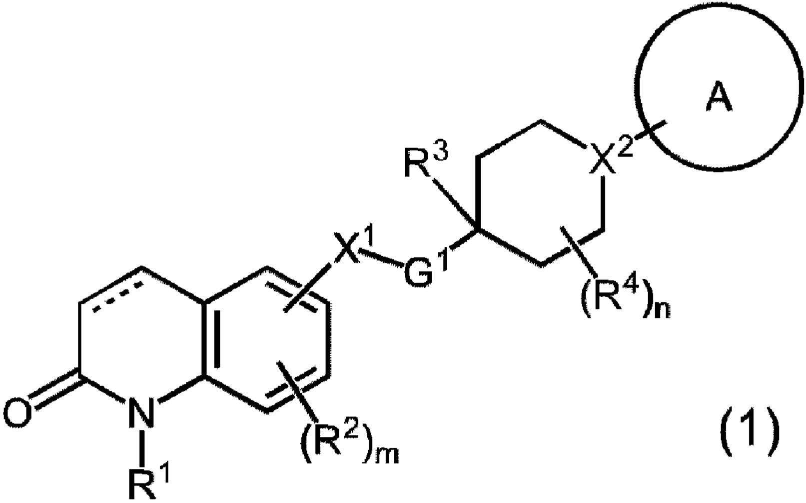
24. The compound of any one of claims 3 to 10, 12, 14, 16, 18 and 20, or a pharmaceutically acceptable salt thereof, or the compound of claim 11, 13, 15, 17, 19 or 21, for use in diagnosing, preventing, or treating tuberculosis.

25. Use of the compound of any one of claims 3 to 10, 12, 14, 16, 18 and 20, or a pharmaceutically acceptable salt thereof, or the compound of claim 11, 13, 15, 17, 19 or 21, in the manufacture of a medicament for diagnosing, preventing, or treating tuberculosis.

26. Use of an effective amount of the compound of any one of claims 3 to 10, 12, 14, 16, 18 and 20, or a pharmaceutically acceptable salt thereof, or the compound of claim 11, 13, 15, 17, 19 or 21, for diagnosing, preventing, or treating tuberculosis in a patient.

27. Use according to claim 25 or 26, for the treatment of tuberculosis in combination with delamanid, bedaquiline or delamanid and bedaquiline.

28. The compound of any one of claims 3 to 10, 12, 14, 16, 18 and 20, wherein the salt is a pharmaceutically acceptable salt.



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