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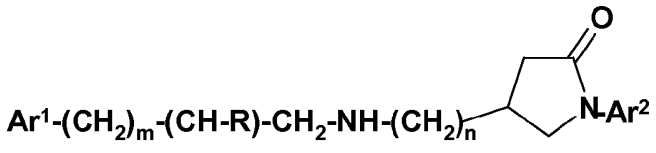
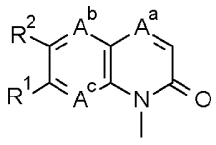
(54) **Title**: PYRROLIDINE DERIVATIVES WITH ANTIBACTERIAL PROPERTIES



(I)



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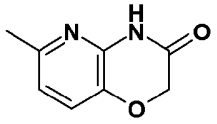

(3)

(57) **Abstract**: Provided is a compound of Formula (I) or a salt thereof: Formula (I) wherein R, m, n, R1, R2, Aa-Ac are defined as in the claims and Ar^{1} represents a bicyclic heterocyclic group of the following formula: Formula (2) Ar ^{2} represents a bicyclic heterocyclic group of the formula: [Formula 3] having antibacterial activity.

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PYRROLIDINE DERIVATIVES WITH ANTIBACTERIAL PROPERTIES

Field of the Invention

The present invention relates to a novel compound, a salt, or a hydrate thereof having excellent antibacterial activity against Gram-positive bacteria and Gram-negative bacteria and also being excellent in terms of safety, and an antibacterial agent containing the same.

Background of the Invention

To date, various antibiotics and synthetic antibacterial agents have been used for the treatment of infectious diseases in medical field. However, in recent years, there have appeared resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), quinolone-resistant *Escherichia coli*, carbapenem-resistant *Klebsiella pneumoniae*, or multiple drug resistant *Pseudomonas aeruginosa*. Since these bacteria are resistant to many of the existing antibiotics and antibacterial agents, the treatment of patients affected with these bacteria has assumed a global importance.

Accordingly, there is a need for the development of an antibacterial agent in a different category, which has a structure different from those of the existing antibacterial agents.

As such antibacterial compounds in a different category, there have been known a group of compounds, which have two aromatic rings that may be heterocyclic rings, and which comprise a heterocyclic ring, such as oxazolidinone, as a structural moiety for connecting these aromatic rings to each other (see Patent Literatures 1 to 13, for example). However, it has been considered that the compounds having such a structure must be improved in terms of safety, in order to apply them to clinical field. There has not been known a compound having a structure, in which pyrrolidinone is comprised in the connecting structue of the two aromatic rings, with respect to the above described compounds.

[Citation List]

[Patent Literature]

[Patent Literature 1] International Publication WO 2002/50040
[Patent Literature 2] International Publication WO 2004/50036
[Patent Literature 3] International Publication WO 2008/26172
[Patent Literature 4] International Publication WO 2008/126024
[Patent Literature 5] International Publication WO 2008/126034
[Patent Literature 6] International Publication WO 2009/77989
[Patent Literature 7] International Publication WO 2009/104147
[Patent Literature 8] International Publication WO 2009/104159
[Patent Literature 9] International Publication WO 2010/15985
[Patent Literature 10] International Publication WO 2010/41194
[Patent Literature 11] International Publication WO 2010/41218
[Patent Literature 12] International Publication WO 2010/41219
[Patent Literature 13] International Publication WO 2013/21363

Summary of the Invention

[Problems to be Solved by the Invention]

There is a need for the development of an agent, which exhibits wide and strong antibacterial activity against Gram-positive bacteria, Gram-negative bacteria, and the resistant bacteria thereof, and also having the excellent safety.

[Means for Solving the Problems]

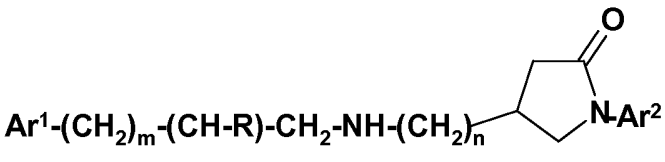
As a result of intensive studies, the present inventors have found that a compound represented by formula (I), a salt, or a hydrate thereof as described below, which has two heteroaryl groups at both ends of a molecule thereof and which comprises pyrrolidinone in a structural moiety for connecting these groups to each other, exhibits wide and strong antibacterial activity against Gram-positive

bacteria and Gram-negative bacteria and also has excellent safety, thereby completing the present invention.

Specifically, the invention of the present application includes the following [1]:

[1] A compound represented by the following formula (I) or a salt thereof:

[Formula 1]



(I)

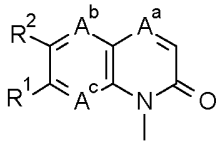
wherein R represents hydrogen atom;

m represents an integer of 1 or 2;

n represents an integer of 0 or 1

Ar^1 represents a bicyclic heterocyclic group represented by the following formula:

[Formula 2]



R^1 represents a methoxy group, a difluoromethoxy group, a halogen atom, or a cyano group;

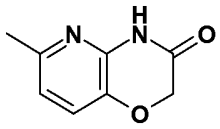
R^2 represents a hydrogen atom or a halogen atom;

A^a represents nitrogen;

A^b and A^c represent CH;

Ar^2 represents a bicyclic heterocyclic group represented by the following formula:

[Formula 3]



In addition, the invention of the present application includes the following [2] to [11].

[2] The compound or a salt thereof according to [1], wherein the sum of m and n is 1, 2 or 3.

[3] The compound or a salt thereof according to [1] or [2], wherein R^1 represents a methoxy group.

[4] The compound or a salt thereof according to [1] or [2], wherein R^1 represents a difluoromethoxy group.

[5] The compound or a salt thereof according to [1] or [2], wherein R^1 represents a cyano group.

[6] The compound or a salt thereof according to [1] or [2], wherein both R^1 and R^2 represent a halogen atom.

[7] The compound or a salt thereof according to [1] or [2], wherein both R^1 and R^2 represent a fluorine atom.

[8] A compound or salt thereof according to [1], which is selected from:

3-Oxo-4-(3-{[(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]amino}propyl)-3,4-dihydroquinoxaline-6-carbonitrile,

3-Oxo-4-[3-({[(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]methyl}amino)propyl]-3,4-dihydroquinoxaline-6-carbonitrile,

6-[(4*R*)-4-({3-[7-(difluoromethoxy)-2-oxoquinoxalin-1(2*H*)-yl]propyl}amino)-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one,

6-{(4*R*)-4-[({3-[7-(difluoromethoxy)-2-oxoquinoxalin-1(2*H*)-yl]propyl}amino)methyl]-2-oxopyrrolidin-1-yl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one,

6-[(4*R*)-4-{[4-(6,7-difluoro-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-2-one,

6-[(4*R*)-4-{[4-(7-methoxy-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one,

6-[(4*R*)-4-{[4-(7-Difluoromethoxy-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one.

[9] A pharmaceutical agent comprising the compound or a salt thereof according to any of [1] to [8] as its effective ingredient.

[10] A therapeutic agent for infectious diseases, which comprises the compound or a salt thereof according to any of [1] to [8] as its effective ingredient.

[11] A method for treatment of infectious diseases, which comprises administrating the compound or a salt thereof according to any of [1] to [8].

The compound , a salt thereof, or a hydrate thereof of the invention of the present application, namely, a compound having two heteroaryl groups at both ends of a molecule thereof and comprising pyrrolidinone in a structural part for connecting these groups to each other, exhibits wide and strong antibacterial activity against Gram-positive bacteria and Gram-negative bacteria, and is excellent in terms of safety. Accordingly, the compound of the present invention is anticipated to exhibit excellent efficacy for the treatment and/or prevention of infectious diseases, and thus it is useful.

Detailed Description of the Invention

The compound having the structure (I) contains bicyclic aromatic heterocyclic substitutents (heteroaryl group; in the present application, each may be abbreviated as Ar^1 or Ar^2.) at both end of the molecule, and the two heteroaryl group is connected by the substructure unit containing pyrrolidinone group.

In case of Ar^1, this contains amide structure at its 1 and 2 position, which is cyclic amide structure with 2-oxo group. The nitrogen atom within that amide structure is the position for the connection to Ar^2.

In case of Ar^2, this contains cyclic amide structure whose amide structure is constituted at 3 and 4 position with 3-oxo group. Ar^2 is connected directly at 6

position to pyrrolidinone moiety present in the connecting structure moiety, and moreover on the nitrogen atom of said pyrrolidinone (these position numbers are counted based on the structure wherein A^a to A^c in Ar^1 is C-H and when Ar^2 is 1,4-benzoxazine.).

Furthre, Ar^1 has the substiturents of R^1 and R^2, wherein R^1 represents a methoxy group, a difluoromethoxy group, a halogen atom, or a cyano group; R^2 represents a hydrogen atom or a halogen atom. When R^1 or R^2 is a halogen atom, chlorine atom or fluorine atom is preferable, more preferably, fluorine atom.

Next, a structure for connecting Ar^1 and Ar^2 to each other will be described.

One characteristic of the compound of the present invention is that this structure contains pyrrolidinone. The pyrrolidinone is preferably 2-pyrrolidinone. This pyrrolidinone preferably has a structure in which Ar^2 is connected to the structure on a nitrogen atom thereof. Moreover, Ar^1 also binds to the structure on a carbon atom of the pyrrolidinone ring *via* another connecting moiety. The connecting position of the connecting moiety to Ar^1 on this 2-pyrrolidine ring is preferably 4-position therof. Further, there arose two kinds of isomers according to the mode of connection at the 4 position of pyrrolidinone, all of such isomers are included in the present invention.

The connecting moiety to Ar^1 is characterized in that it contains an amino group. It is preferable that this amino group is directly connected to the 4-position of 2-pyrrolidinone or connected to it *via* one methylene group. The connecting moiety from this amino group to Ar^1 is composed of a methylene chain containing 3 to 4 carbon atoms.

Thus, the following structures are constructed:

Ar^1-CH_2-CH_2-CH_2-NH-(2-Pyrrolidinone-1-Ar^2-4-yl)

Ar^1-CH_2-CH_2-CH_2-CH_2-NH-(2-Pyrrolidinone-1-Ar^2-4-yl)

Ar^1-CH_2-CH_2-CH_2-NH-CH_2-(2-Pyrrolidinone-1-Ar^2-4-yl)

Ar^1-CH_2-CH_2-CH_2-CH_2-NH-CH_2-(2-Pyrrolidinone-1-Ar^2-4-yl)

[(2-Pyrrolidinone-1-Ar^2-4-yl) represents that 4-position is the connecting position of the 2-pyrrolidinone to which Ar^2 is bonded at 1 position.]

The invention of the present application includes the following compounds, but are not limited to:

3-Oxo-4-(3-{[(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]amino}propyl)-3,4-dihydroquinoxaline-6-carbonitrile,

3-Oxo-4-[3-({[(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]methyl}amino)propyl]-3,4-dihydroquinoxaline-6-carbonitrile,

6-[(4*R*)-4-({3-[7-(difluoromethoxy)-2-oxoquinoxalin-1(2*H*)-yl]propyl}amino)-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one,

6-{(4*R*)-4-[({3-[7-(difluoromethoxy)-2-oxoquinoxalin-1(2*H*)-yl]propyl}amino)methyl]-2-oxopyrrolidin-1-yl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one,

6-[(4*R*)-4-{[4-(6,7-difluoro-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-2-one,

6-[(4*R*)-4-{[4-(7-methoxy-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one,

6-[(4*R*)-4-{[4-(7-Difluoromethoxy-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one, a salt thereof or a solvate thereof.

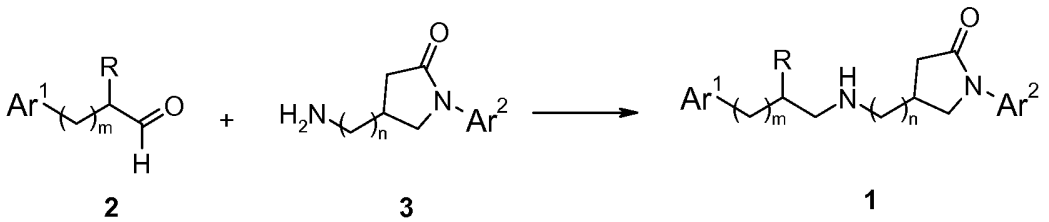
Next, a method for producing the compound of the present invention will be described.

The compound represented by the formula (1) of the present invention (which may be abbreviated as compound 1. The compound of the other structure with different number will be abbreviated in the same way.) is produced by various methods. For example, it can be produced by the following method.

For example, the compound represented by the formula (1) of the present invention can be produced by performing a reductive alkylation reaction (a reductive amination reaction) between compound 2 as an aldehyde compound and compound 3 as an amine compound (Scheme 1). That is to say, an imine compound or an iminium compound, which is once generated from the reaction between the compound 2 and the compound 3, or an iminium compound, is

reduced, so that it can be converted to the compound 1. This reaction may be carried out either as a one-pot reaction or as a stepwise reaction.

[Formula 4]



2 3 1

Scheme 1

This reaction can be carried out by the method described in Advanced Organic Chemistry, 4th edition (written by Jerry March), pp. 898-900, 1991, John Wiley & Sons, Inc. etc., or by methods equivalent thereto. As a reducing agent used in this reaction, a hydrogenated complex compound can preferably be used. As such a hydrogenated complex compound, a boron-containing compound is adequate, and examples of such a boron-containing compound include sodium borohydride, sodium triacetoxy borohydride, and sodium cyano borohydride. In addition, catalytic reduction using a metal catalyst such as palladium carbon, Raney nickel, platinum oxide or palladium black can preferably be used. As a reduction reaction, reduction using a boron-containing hydrogenated complex compound is simply carried out, and thus it can preferably be used.

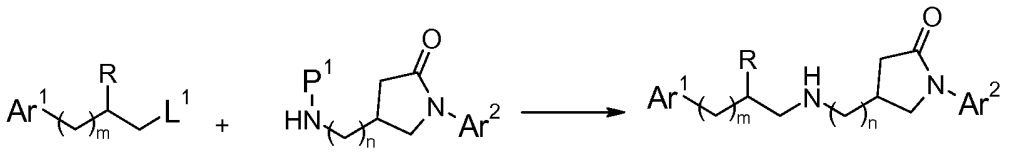
With regard to a reaction temperature, both an imine/iminium ion formation reaction and a reduction reaction can be carried out within a temperature range between -100°C and 150°C, and preferably between -20°C and 50°C.

Various functional groups of the compounds 2 and 3 may be protected by suitable protective groups during the present reaction, as desired. After completion of the reaction, such functional groups are deprotected, so that the compounds can be induced to the compound 1.

Moreover, the compound 1 can also be produced by allowing compound 5 to react with compound 4 having a leaving group L^1 and performing an alkylation

reaction on the amino group of a pyrrolidinone compound, as described below (Scheme 2).

[Formula 5]



4 5 1

Scheme 2

This reaction can be carried out by the method described in Advanced Organic Chemistry, 4th edition (written by Jerry March), pp. 411-413 and pp. 425-427, 1991, John Wiley & Sons, Inc., or by the method described in Chemical Communications, 2004, pp. 353-359, etc., or by methods equivalent thereto. This reaction is generally carried out in the presence of a base. Examples of an available base include: inorganic bases such as potassium carbonate or cesium carbonate; organic bases such as triethylamine or *N,N*-diisopropylethylamine; and sodium hydride, lithium *N,N*-diisopropylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, and potassium hexamethyldisilazide.

The reaction can be carried out within a temperature range between -100°C and 250°C, and preferably between -20°C and 150°C.

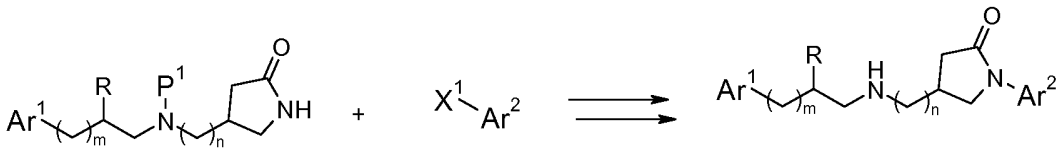
P^1 may be either hydrogen or a protective group. Examples of such a protective group include: aralkyl group-type protective groups such as a benzyl group, a benzhydryl group and a trityl group; acyl group (alkylcarbonyl, aralkylcarbonyl, arylcarbonyl, etc.)-type protective groups such as a formyl group, a trifluoroacetyl group and a trichloroacetyl group; alkyloxycarbonyl- and aralkyloxycarbonyl-type protective groups such as a benzyloxycarbonyl group and a *tert*-butoxycarbonyl group; and other protective groups such as a tosyl group, a nosyl group, a *tert*-butylsulfinyl group and a sulfo group. Such a protective group is removed under suitable conditions after completion of the present alkylation reaction, so that the compounds can be induced to the compound 1. Examples of

the leaving group L^1 include: leaving groups such as a mesyloxy group, a tosyloxy group, a trifluoroacetoxy group and a trifluoromethanesulfonyloxy group; as well as a halogen atom.

Various functional groups of the compounds 4 and 5 may be protected by suitable protective groups during the present reaction, as desired. In this case, such functional groups are deprotected after completion of the reaction, so that the compounds can be induced to the compound 1.

Furthermore, the compound 1 can also be produced by carrying out a cross-coupling reaction between a lactam compound 6 and a compound 7, so as to introduce an aromatic ring on the nitrogen atom of the lactam compound (Scheme 3).

[Formula 6]



6 7 1

Scheme 3

This reaction can be carried out by the method described in Strategic Applications of Name Reactions in Organic Synthesis (edited by L. Kuerti *et al.*), pp. 70-71, 2005, Elsevier Inc., Metal-Catalyzed Cross-Coupling Reactions, Vol. 2, 2nd edition (edited by Armin de meijere *et al.*), pp. 699-760, 2004, WILEY-VCH Verlag GmbH & Co., KGaA Publishing Company, or Journal of The American Chemical Society, Vol. 124, No. 25, pp. 7421-7428, 2002, etc., or by methods equivalent thereto.

X^1 may be a tosyloxy group, a mesyloxy group, a trifluoromethanesulfonyloxy group, etc., as well as a halogen atom such as chlorine, bromine or iodine.

Various functional groups of the compounds 6 and 7 may be protected by suitable protective groups during the present reaction, as desired. Such

protectivel groups are deprotected after completion of the reaction, so that the compounds can be induced to the compound 1.

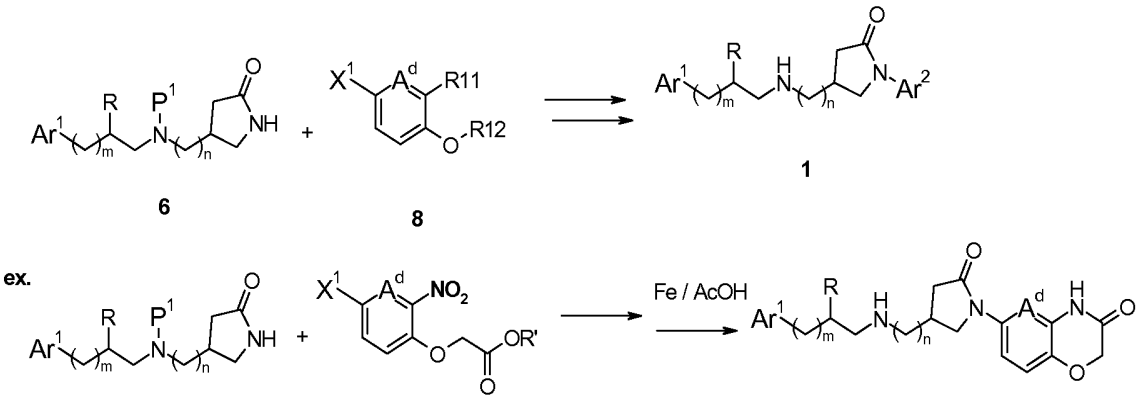
This coupling reaction may be carried out in the presence of a catalyst compound, which is composed of a metal atom and a ligand compound. Examples of such a metal constituting the catalyst include palladium and copper. These metals can be added to the reaction in the form of palladium(II) acetate, tris(dibenzilideneacetone)dipalladium(0), copper(I) iodide, etc. When the catalyst metal is palladium for instance, examples of such a ligand constituting the catalyst compound include BINAP and S-Phos. When the catalyst metal is copper for instance, examples of such a ligand include *N,N'*-dimethylethylenediamine and trans-1,2-diaminocyclohexane. A catalyst compound may be prepared by mixing a catalyst metal with a ligand compound before initiation of the reaction. Alternatively, the catalyst metal and the ligand compound may be added to the reaction mixture, separately, so that a catalyst compound may be generated in the reaction mixture. This coupling reaction is preferably carried out in the presence of a base, as well as the catalyst compound. Examples of an available base include inorganic bases such as potassium carbonate, cesium carbonate, and potassium phosphate.

The reaction can be carried out within a temperature range between 0°C and 250°C, and preferably between 50°C and 150°C.

Moreover, it may also be possible that a cross-coupling reaction be carried out between the compound 6 and a compound 8 having a monocyclic structure, instead of the compound 7 having a fused ring structure, and that functional groups R11 and R12 be then converted, so as to construct a condensed ring structure, and that the compounds be induced to the compound 1 (Scheme 4, wherein A^d is N). R11 may be a nitro group, a halogen atom, or the like, which can be then converted to an amino group. R12 may be, for example, hydrogen, a suitable protective group, an alkoxycarbonylmethyl group, or the like. For example, when R11 is a nitro group and R12 is an alkoxycarbonylmethyl group,

the compounds may be converted to the compound 1 by carrying out a heat treatment in the presence of iron/acetic acid, or a catalytic reductive reaction.

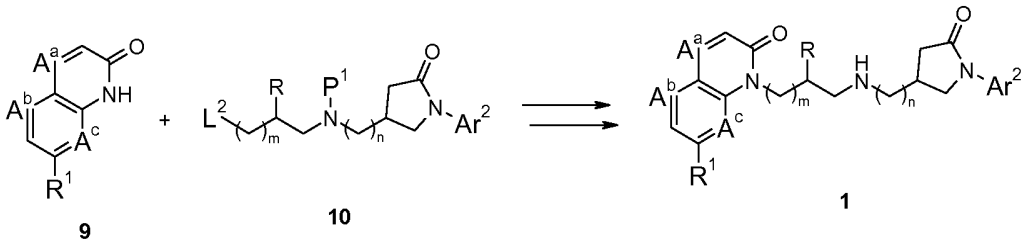
[Formula 7]



Scheme 4

Further, the compound 1 can also be produced by allowing compound 9 to react with compound 10, so as to carry out an alkylation reaction on the nitrogen atom of a cyclic amide, as described below (Scheme 5).

[Formula 8]



Scheme 5

This reaction can be carried out by the method described in Advanced Organic Chemistry, 4th edition (written by Jerry March), pp. 425-427, 1991, John Wiley & Sons, Inc., etc., or by methods equivalent thereto.

This reaction may be carried out in the presence of a base. Examples of an available base include: inorganic bases such as potassium carbonate, cesium carbonate or potassium phosphate; organic bases such as triethylamine or *N,N*-diisopropylethylamine; and sodium hydride, lithium *N,N*-diisopropylamide, lithium

hexamethyldisilazide, sodium hexamethyldisilazide, and potassium hexamethyldisilazide.

The reaction can be carried out within a temperature range between -100°C and 200°C, and preferably between -20°C and 150°C.

Examples of the leaving group L^2 include: leaving groups such as a mesyloxy group, a tosyloxy group, a trifluoroacetoxy group and a trifluoromethanesulfonyloxy group; as well as a halogen atom.

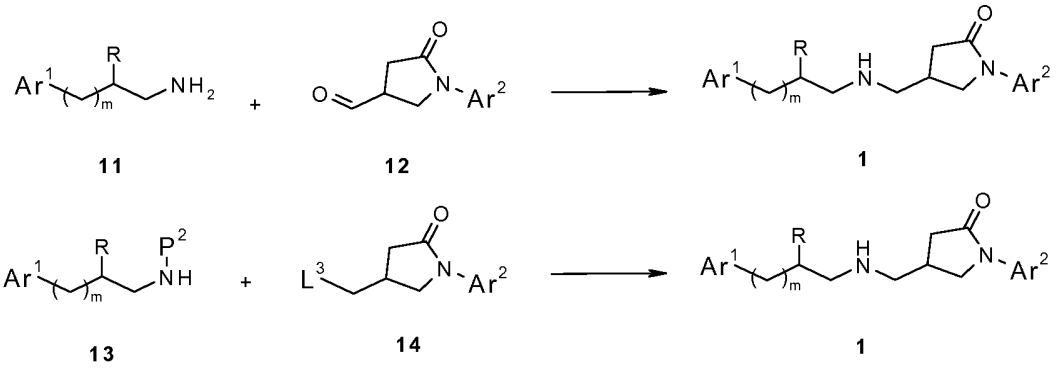
Various functional groups of the compounds 9 and 10 may be protected by suitable protective groups during the present reaction, as desired. In this case, such protective groups are deprotected after completion of the reaction, so that the compounds can be induced to the compound 1.

Moreover, when n = 1, the compound 1 can be produced by carrying out a reductive alkylation reaction (a reductive amination reaction) between a compound 11 as an amine compound and a compound 12 as an aldehyde compound, as described below. Furthermore, the compound 1 can also be produced by carrying out an alkylation reaction between a compound 13 that may be protected by a protective group P^2 and a compound 14 having a leaving group L^3 (Scheme 6). The reductive alkylation reaction (reductive amination reaction) can be carried out by the same method as that applied to produce the compound 1 from the above described compound 2 and amine compound 3. Furthermore, the alkylation reaction can be carried out by the same method as that applied to produce the compound 1 from the compound 4 and the compound 5. Herein, P^2 may be hydrogen, and it may also be an aralkyl-type protective group such as a benzyl group, a benzhydryl group or a trityl group, an acyl-type protective group such as a formyl group, a trifluoroacetyl group or a trichloroacetyl group, an alkyloxycarbonyl- or aralkyloxycarbonyl-type protective group such as a benzyloxycarbonyl group or a *tert*-butoxycarbonyl group, or another protective group such as a tosyl group, a nosyl group, a *tert*-butylsulfinyl group or a sulfo group. Such a protective group is removed under suitable conditions after completion of the present alkylation reaction, so that the compounds can be

induced to the compound 1. Examples of the leaving group L^3 include: leaving groups such as a mesyloxy group, a tosyloxy group, a trifluoroacetoxy group and a trifluoromethanesulfonyloxy group; as well as a halogen atom.

Various functional groups of the compounds 11, 12, 13 and 14 may be protected by suitable protective groups during the present reaction, as desired. Such protective groups are deprotected after completion of the reaction, so that the compounds can be induced to the compound 1.

[Formula 9]



Scheme 6

Still further, the compound 1 can be produced by carrying out a reaction between a compound 15 as an oxylan compound and a compound 16 as an amine compound that may be protected by a protective group P^3, as described below (Scheme 7). This reaction can be carried out by the method described in Advanced Organic Chemistry, 4th edition (written by Jerry March), p. 416, 1991, John Wiley & Sons, Inc., etc., or by methods equivalent thereto.

This reaction can be carried out in the presence or absence of a suitable solvent. In addition, a suitable reagent may be added to the reaction system. Examples of an available solvent include: alcohols such as methanol, ethanol and isopropyl alcohol; ethers such as tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxypropane; aromatic hydrocarbons such as toluene and benzene; esters such as ethyl acetate; water; N,N-dimethylformamide; and acetonitrile. Moreover, these solvent can also be used in the form of a mixed solvent. Examples of the reagent that can be added to the reaction system include: Broensted acids such

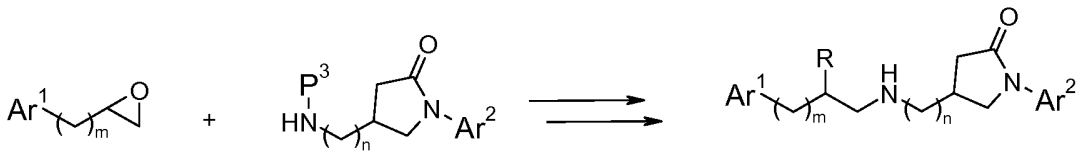
as hydrogen chloride, acetic acid, trifluoroacetic acid, and tosic acid; alkali such as potassium carbonate, sodium carbonate, sodium hydrogen carbonate, and cesium carbonate; Lewis acids such as lithium tetrafluoroborate, lithium perchlorate, ytterbium(III) triflate, bismuth(III) chloride, and zinc(II) chloride; and strong bases such as sodium hydride, lithium diisopropylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, and P4-phosphazene.

The reaction can be carried out within a temperature range between -100°C and 200°C, and preferably between -80°C and 150°C.

Herein, P^3 may be hydrogen, and it may also be an aralkyl-type protective group such as a benzyl group, a benzhydryl group or a trityl group, an acyl-type protective group such as a formyl group, a trifluoroacetyl group or a trichloroacetyl group, an alkyl- or aralkyloxycarbonyl-type protective group such as a benzyloxycarbonyl group or a tert-butoxycarbonyl group, or another protective group such as a tosyl group, a nosyl group, a tert-butylsulfinyl group or a sulfo group. Such a protective group is removed under suitable conditions after completion of the present reaction, so that the compounds can be induced to the compound 1.

Various functional groups of the compounds 15 and 16 may be protected by suitable protective groups during the present reaction, as desired. Such protective groups are deprotected after completion of the reaction, so that the compounds can be induced to the compound 1.

[Formula 10]



Scheme 7

The hydroxy group present in a compound thus formed can be converted to methylene group using appropriate known methods of synthetic organic chemistry.

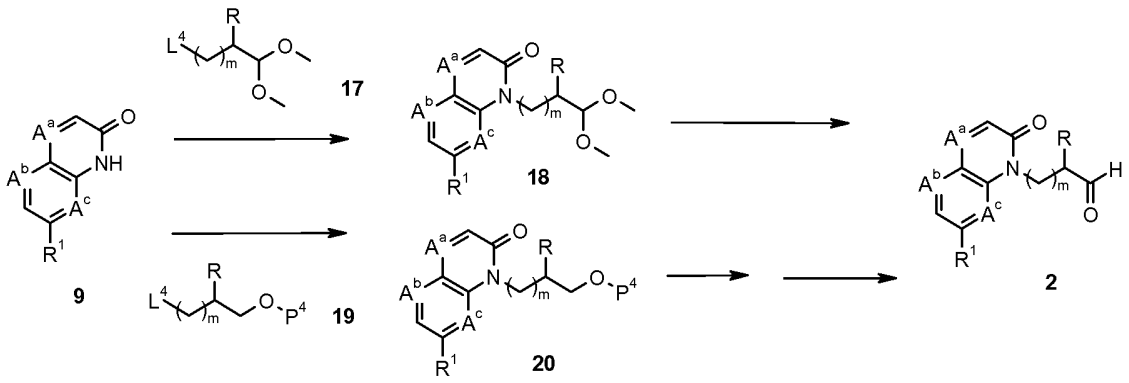
Next, a method for producing each synthetic intermediate compound will be described.

[Compound 2]

Compound 2 can be produced by the method described in International Publication WO2009/104159, or by methods equivalent thereto, for example (Scheme 8). That is to say, for example, a compound 17, in which a formyl group is protected by a protective group such as dimethylacetal, and a compound 9 are subjected to an alkylation reaction, and the formyl-protective group is then removed from the obtained compound 18, so as to produce the compound 2. The leaving group L^4 may be a halogen atom, or may also be a leaving group such as a mesyloxy group, a tosyloxy group, a trifluoroacetoxy group or a trifluoromethanesulfonyloxy group.

Moreover, a compound 19, in which a hydroxy group is protected by a protective group P^4, and a compound 9 are subjected to an alkylation reaction. Thereafter, the protective group P^4 is then removed from the obtained compound 20, and the hydroxy group is oxidized to a formyl group, so as to produce the compound 2. Various functional groups of the compounds 9, 17, 18, 19 and 20 may be protected by suitable protective groups during these reactions, as desired. The protective groups can be removed at an appropriate stage.

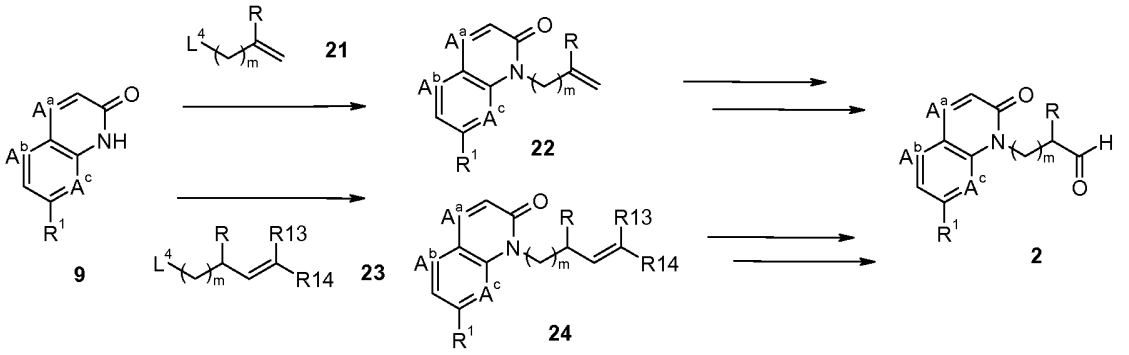
[Formula 11]



Scheme 8

Furthermore, for example, the alkylation reaction of the compound 9 is carried out with compounds 21, 23 and the like, which are unsaturated compounds. Thereafter, hydroboration/oxidation is carried out on the unsaturated bond of the obtained compound 22, or a reaction such as conversion to diol/oxidative fission is carried out on a compound 24, so that the compound 2 can also be produced (Scheme 9). Herein, each of R13 and R14 is hydrogen, an alkyl group, etc. Various functional groups of the compounds 9, 21, 22, 23 and 24 may be protected by suitable protective groups during these reactions, as desired. The protective groups can be removed at an appropriate stage.

[Formula 12]



Scheme 9

The compound 9 in Scheme 9 can be produced by the method described in International Publication WO2006/134378, International Publication

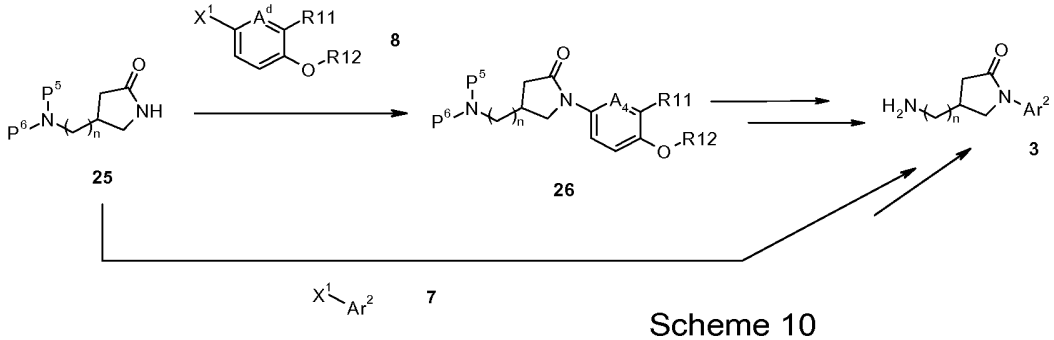
WO2006/137485, International Publication WO2009/1126, etc. or by methods equivalent thereto.

Some of the compounds 17, 19, 21 and 23 are commercially available, and thus, they can be used. Also, compounds, which are not commercially available, can be produced by generally known methods of synthetic organic chemistry.

[Compound 3]

Compound 3 can be produced by performing a cross-coupling reaction between a compound 25 and a compound 8, and then converting the functional groups R11 and R12 of the obtained compound 26. Alternatively, the compound 3 can be produced by performing a cross-coupling reaction between a compound 25 and a compound 7 (Scheme 10). Herein, each of protective group P^5 or P^6 is hydrogen or a protective group. When they are protective groups, they can be removed at an appropriate stage. As reaction conditions for these cross-coupling reactions, there can be applied the same reaction conditions as the reaction conditions for the production of the compound 1 from the compounds 6 and 7, or the reaction conditions for the production of the compound 1 from the compounds 6 and 8, which are described above. Various functional groups of the compounds 7, 8, 25 and 26 may be protected by suitable protective groups during these reactions, as desired. The protective groups can be removed at an appropriate stage.

[Formula 13]



Scheme 10

The compounds 7 and 8 can be produced by the method described in International Publication WO2010/41194, International Publication

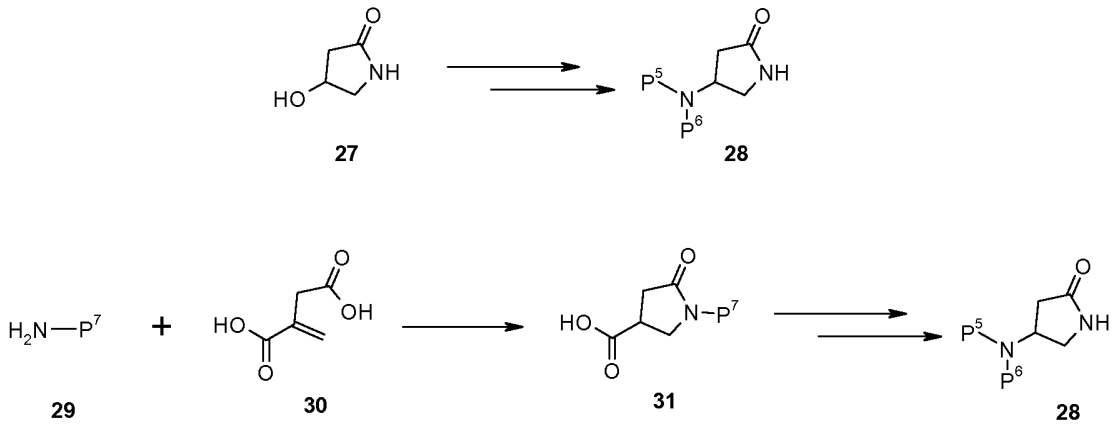
WO2007/118130, International Publication WO2007/16610, etc. or by methods equivalent thereto.

When n = 0 (compound 28), the compound 25 may be commercially available. The compound 28 can also be produced by the method described in International Publication WO2004/022536. Alternatively, the compound 25 can also be induced from a commercially available 4-hydroxy-2-pyrrolidinone derivative such as a compound 27, for example (Scheme 11). Specifically, a series of reactions, such as mesylation, azidation, and reduction of an azide group, are carried out on the compound 27, so that it can be induced to a compound 28. The lactam portion of a commercially available 4-hydroxy-2-pyrrolidinone derivative used as a raw material may be protected, as appropriate, and such a protective group may be removed at an appropriate stage. Moreover, this 4-hydroxy-2-pyrrolidinone derivative may be an optically active substance, and using such an optically active substance, an optically active compound 1 can be produced. Furthermore, the compound 28 can be produced by synthesizing a compound 31 from a compound 29 as a primary amine and an itaconic acid 30, and then converting the carboxy group thereof to an amino group. Various functional groups of the compounds 28, 29, 30 and 31 may be protected by suitable protective groups during these reactions, as desired. The protective groups may be removed at an appropriate stage.

As such a compound 29, 4-methoxyaniline or benzylamine, in which the P^7 portion thereof functions as a protective group that can be removed later, or optically active 1-phenylethylamine, 1-(4-methoxyphenyl)ethylamine, and the like can preferably be used. In addition, using an optically active compound as such a compound 29, a stereoisomer can be easily separated on the basis of the steric configuration of the 4-position of pyrrolidine at the stage of, for example, the compound 31, an ester compound thereof or the like. Even in a case in which a compound that is not optically active is used, a steroisomer can be separated by column chromatography using a column capable of separating an optical isomer. In order to synthesize the compound 31 from the compounds 29 and 30, a mixture

of the compounds 29 and 31 is heated, or such compounds are heated together with a suitable solvent such as benzene, toluene, water or alcohol. During such treatments, a suitable catalyst such as tosic acid can be coexisted. Otherwise, using a Dean-Stark apparatus or the like, water generated as a result of the reaction may be removed. The carboxy group of the compound 31 can be converted to an amino group, for example, by performing a series of reactions such as acid azide synthesis/Curtius rearrangement/carbamate synthesis (Cbz protection using benzyl alcohol and tert-butanol, or the synthesis of a Boc-protected amino group)/deprotection. Otherwise, after the carboxy group has been converted to an amide group, it can be converted to an amino group by Hofmann rearrangement or the like. When the P^7 group is a 4-methoxyphenyl group, a 1-(4-methoxyphenyl)ethyl group or the like, for example, deprotection can be carried out under oxidative conditions using diammonium cerium(IV) nitrate or the like, or under acidic conditions using trifluoroacetic acid or the like, or other conditions. When it is a benzyl group, a 1-phenylethyl group or the like, deprotection can be carried out under reaction conditions for Birch reduction or the like.

[Formula 14]

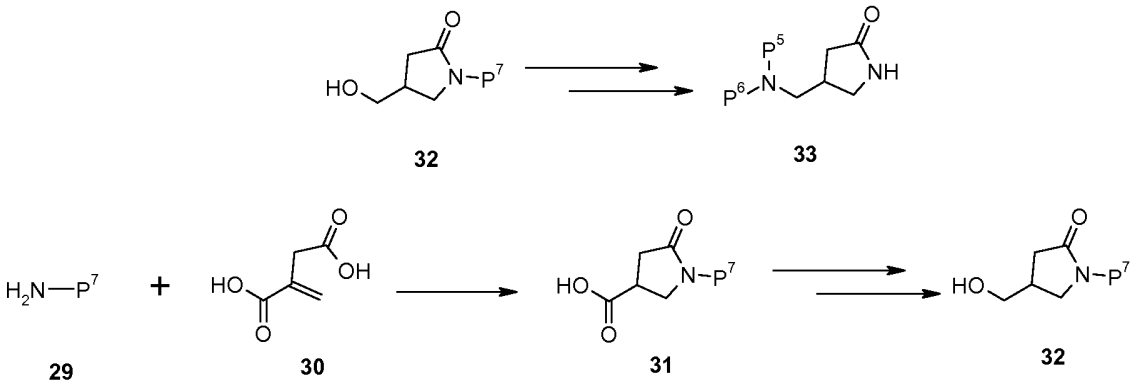


Scheme 11

When n = 1 (compound 33), the compound 25 may be commercially available. Alternatively, the compound 25 can also be induced from a commercially available 4-(hydroxymethyl)-2-pyrrolidinone derivative such as a

compound 32, for example (Scheme 12). Specifically, a series of reactions, such as mesylation, azidation, and reduction of an azide group, are carried out on the compound 32, so that it can be induced to the compound 33. The lactam part of a commercially available 4-(hydroxymethyl)-2-pyrrolidinone derivative used as a raw material may be protected, as appropriate, and such a protective group may be removed at an appropriate stage. Moreover, this 4-(hydroxymethyl)-2-pyrrolidinone derivative may be an optically active substance, and using such an optically active substance, an optically active compound 1 can be produced. The compound 32 may be commercially available, and it can also be produced by synthesizing the compound 31 from the compound 29 as a primary amine and the itaconic acid 30, and then reducing the carboxy group. This reductive reaction can be carried out under ordinary reductive conditions for converting a carboxy group to a hydroxymethyl group, or the carboxy group can also be reduced mediated by a carboxylic acid ester compound.

[Formula 15]



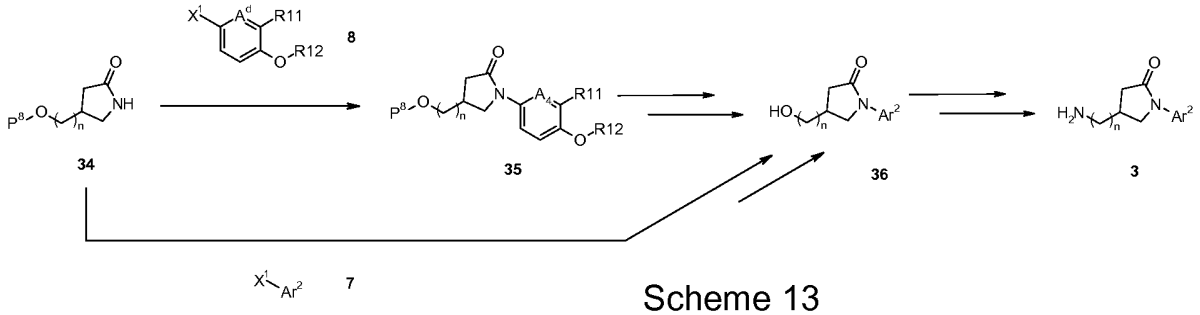
Scheme 12

Moreover, the compound 3 can be produced by carrying out a cross-coupling reaction between a hydroxy compound 34 that may be protected and a compound 7 or a compound 8, and then converting the hydroxy group to an amino group at an appropriate stage (Scheme 13). Herein, a protective group P^8 is hydrogen or a protective group. When the protective group P^8 is a protective group, it can be removed at an appropriate stage. As reaction conditions for

these cross-coupling reactions, there can be applied the same reaction conditions as the reaction conditions for the production of the compound 1 from the compounds 6 and 7, or the reaction conditions for the production of the compound 1 from the compounds 6 and 8, which are described above. Various functional groups of the compounds 7, 8, 34, 35 and 36 may be protected by suitable protective groups during these reactions, as desired. The protective groups can be removed at an appropriate stage.

Some of compounds 34 are commercially available. Also, compounds 34, which are not commercially available, can be produced by generally known methods of synthetic organic chemistry, using the compounds 31, 32 or the like, or using commercially available reagents.

[Formula 16]



Scheme 13

[Compound 4]

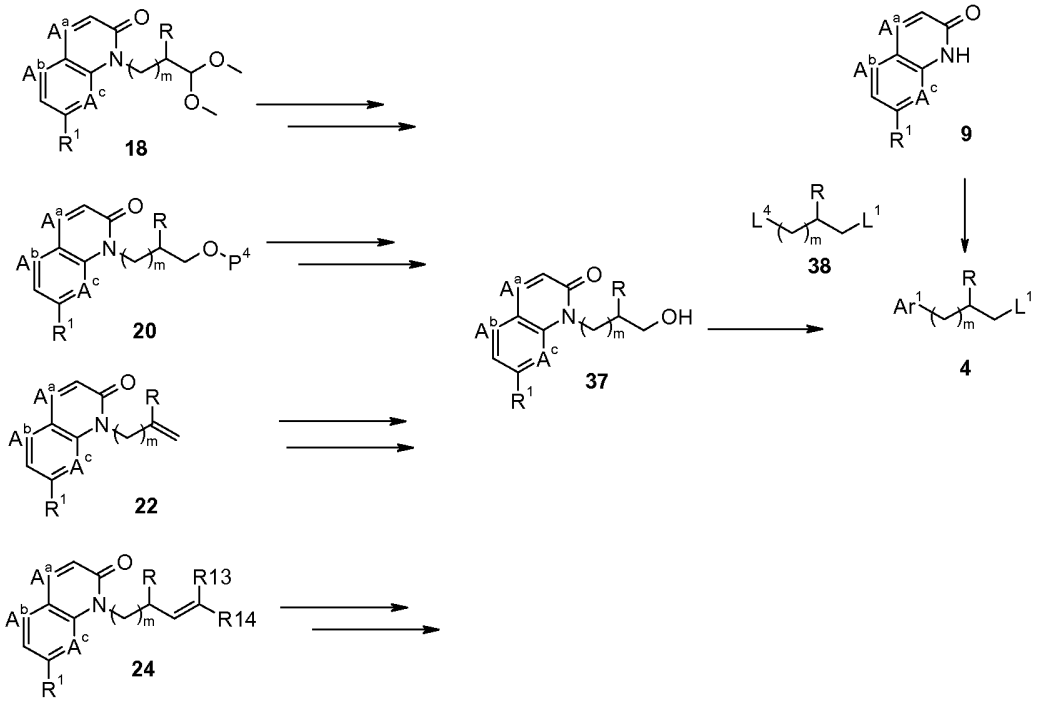
Compound 4 can be produced by a method similar to the method for producing the compound 2 (Scheme 14). That is to say, for example, deacetalization/reduction of an aldehyde functional group is performed on the compound 18 that is a synthetic intermediate of the compound 2, so as to convert the compound 18 to a compound 37 that is an alcohol compound. Thereafter, the hydroxy group of the compound 37 is converted to a leaving group, so as to produce the compound 4. Production of this compound 37 facilitates the production of the compound 4. Alternatively, the compound 37 can also be obtained by deprotective the hydroxy group of the compound 20 that is a synthetic intermediate of the compound 2. Moreover, the compound 37 can also be synthesized by performing hydroboronation on the compound 22 that is a synthetic

intermediate of the compound 2, or by performing ozone oxidation/reduction treatment on the compound 24 that is a synthetic intermediate of the compound 2, or by conversion to diol/oxidative fission/reduction of an aldehyde group. On the other hand, the compound 4 can also be produced by carrying out a selective alkylation reaction on the compound 9, using a compound 38 having two leaving groups.

During a series of reactions, various functional groups of all of these compounds may be protected by suitable protective groups, as desired. Thereafter, the protective groups can be removed at an appropriate stage.

Some of compounds 38 in Scheme 14 are commercially available. Also, compounds 38, which are not commercially available, can be produced by generally known methods of synthetic organic chemistry, using commercially available reagents.

[Formula 17]



Scheme 14

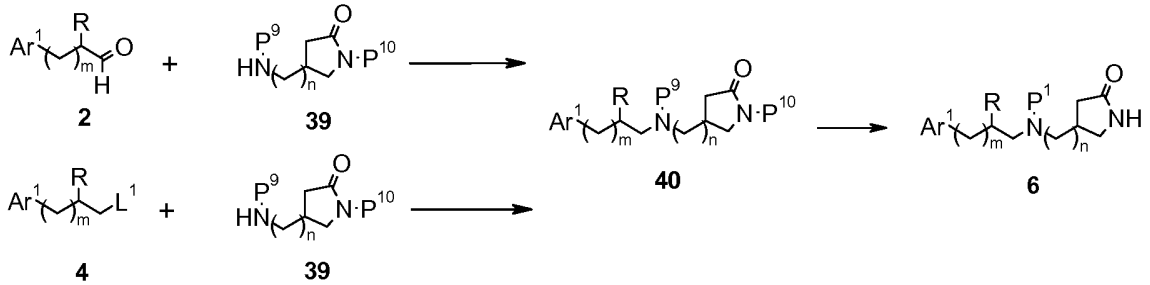
[Compound 5]

Compound 5 may be the compound 3 itself, or it may be produced by a method similar to the method for producing the compound 3 or may easily be induced from the compound 3.

[Compound 6]

Compound 6 can be produced by carrying out a reductive amination (reductive alkylation) reaction between a pyrrolidinone derivative that may be protected, such as a compound 39, and the compound 2. It can also be produced by carrying out an alkylation reaction between the compound 4 and the compound 39 or the like (Scheme 15). P^9 and P^{10} are protective groups, and they may be hydrogen unless it affects the reaction. P^{10} is preferably an acyl group, an alkoxycarbonyl group, a benzyl group, a substituted benzyl group, a 1-phenylethyl group, a 1-(substituted)phenylethyl group or the like, which can be removed later. P^9 is an aralkyl-type protective group such as a benzyl group. When the compound 39 is used in the alkylation reaction, P^9 may be various types of protective groups capable of stabilizing anion, such as an acyl, alkoxycarbonyl, sulfonyl or sulfenyl group. During these reactions, various functional groups of all of these compounds may be protected by suitable protective groups, as desired. Thereafter, the protective groups can be removed at an appropriate stage.

[Formula 18]

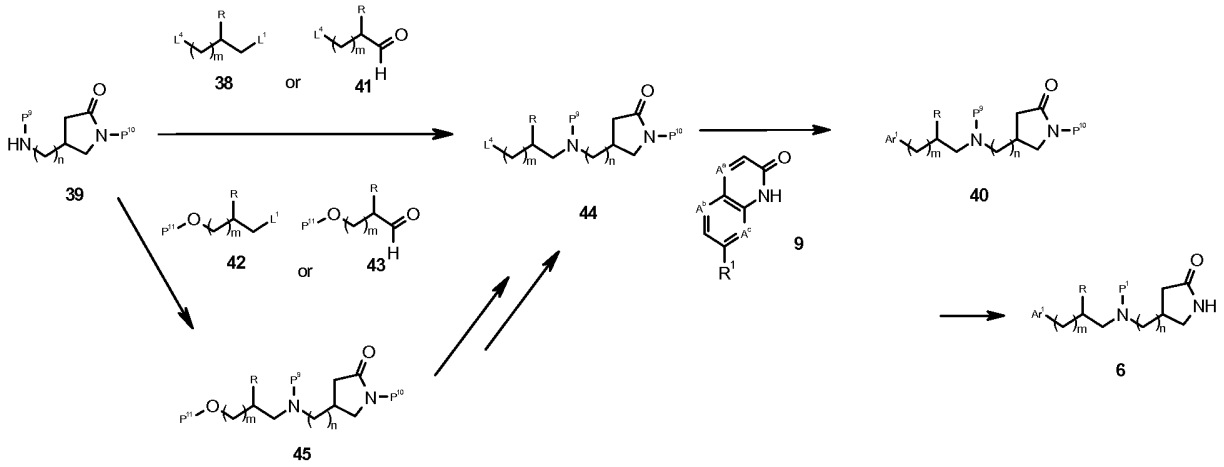


Scheme 15

Also, the compound 6 can be produced by performing a reaction, such as reductive alkylation or alkylation, between the pyrrolidinone compound 39 or the like that may be protected and a suitable compound such as a compound 38, 41,

42 or 43, then performing, as necessary, the removal of the protective group, conversion to a leaving group, etc., so as to induce it to a compound 44, and then carrying out the alkylation reaction of the compound 44 with a compound 9 (Scheme 16). P^{11} may be an alcohol protective group, and it may also be hydrogen unless it affects the reaction. During these reactions, various functional groups of all of these compounds may be protected by suitable protective groups, as desired. Thereafter, the protective groups can be removed at an appropriate stage.

[Formula 19]



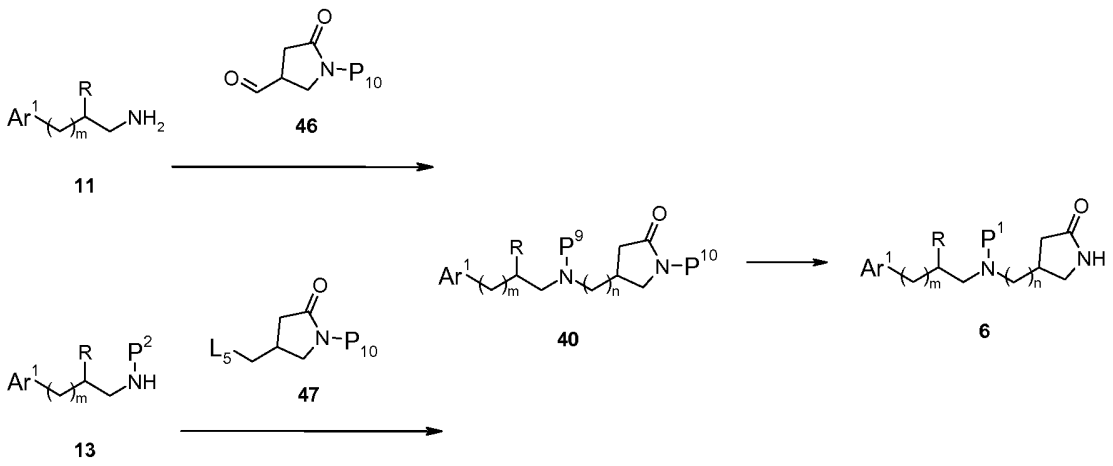
Scheme 16

The compound 39 in Schemes 15 and 16 may be the above described compound 25 itself, or it may also be synthesized from the compound 25 or may be synthesized by a method similar to the method for synthesizing the compound 25. In addition, some of the compounds 41, 42 and 43 are commercially available. Also, the compounds, which are not commercially available, can be produced by generally known methods of synthetic organic chemistry, using commercially available reagents.

Moreover, when n = 1, the compound 6 can be produced by carrying out a reductive alkylation (reductive amination) reaction between a compound 11 and a compound 46 or by carrying out an alkylation reaction between a compound 13

and a compound 47 (Scheme 17). Various functional groups of all of these compounds may be protected by suitable protective groups, and thereafter, the protective groups can be removed at an appropriate stage.

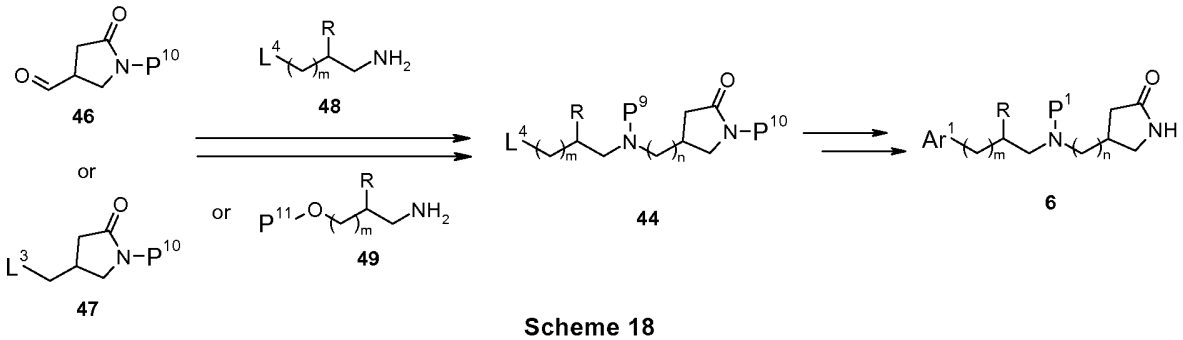
[Formula 20]



Scheme 17

Furthermore, when n = 1, the compound 6 can be produced by first carrying out a reductive alkylation (reductive amination) reaction between a compound 46 and a compound 48 or a compound 49, so as to obtain a compound 44, and then applying a method similar to that in Scheme 16 (Scheme 18). This compound 44 can also be obtained by carrying out an alkylation reaction between the compound 47 and the compound 48 or the compound 49, and then carrying out, as necessary, the removal of the protective group, conversion of the hydroxy group to a leaving group, etc. Various functional groups of all of these compounds may be protected by suitable protective groups, and thereafter, the protective groups can be removed at an appropriate stage.

[Formula 21]



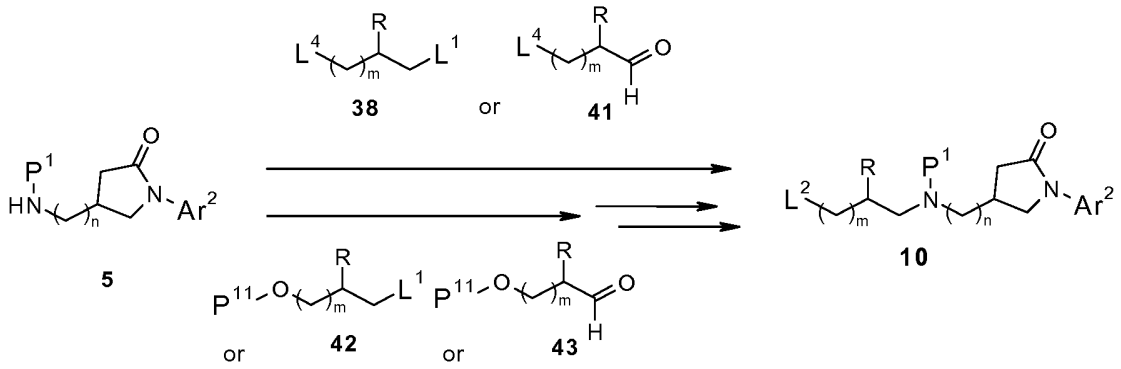
Scheme 18

The compounds 46 and 47 in Schemes 17 and 18 can be produced from the above described compounds 31, 32 and 34, etc. by generally known methods of synthetic organic chemistry. Some of the compounds 48 and 49 are commercially available. The compounds, which are not commercially available, can be produced by generally known methods of synthetic organic chemistry, using commercially available reagents.

[Compound 10]

Compound 10 can be produced by carrying out an alkylation reaction between a compound 5 and a suitable compound such as a compound 38 or 42, and then carrying out, as necessary, the removal of the protective group, conversion to a leaving group, etc. (Scheme 19). Alternatively, the compound 10 can also be produced by carrying out a reaction, such as reductive alkylation, between the compound 5 and a suitable compound such as a compound 41 or 43, and then carrying out, as necessary, the removal of the protective group, conversion to a leaving group, etc., as described above (Scheme 19). A leaving group L^4 may be either identical to or different from L^2. When the leaving group L^4 is different from L^2, L^4 can be converted to L^2 later. Various functional groups of all of these compounds may be protected by suitable protective groups, as desired, during these reactions, and thereafter, the protective groups can be removed at an appropriate stage.

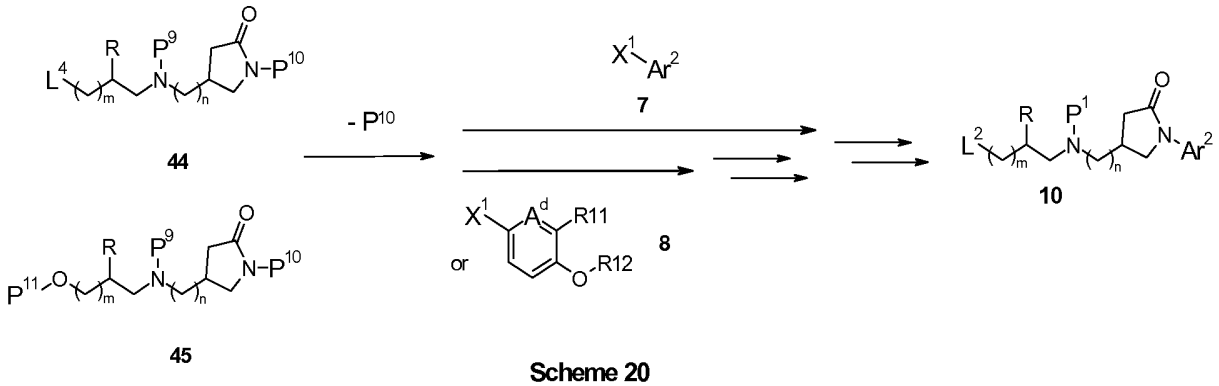
[Formula 22]



Scheme 19

Moreover, the compound 10 can also be produced by removing a protective group P^{10} from a compound 44 or 45, then carrying out a cross-coupling reaction of the compound 44 or 45 with a compound 7 or a compound 8, and then converting various functional groups, as necessary (Scheme 20). Various functional groups of all of these compounds may be protected by suitable protective groups, as desired, during these reactions, and thereafter, the protective groups can be removed at an appropriate stage.

[Formula 23]

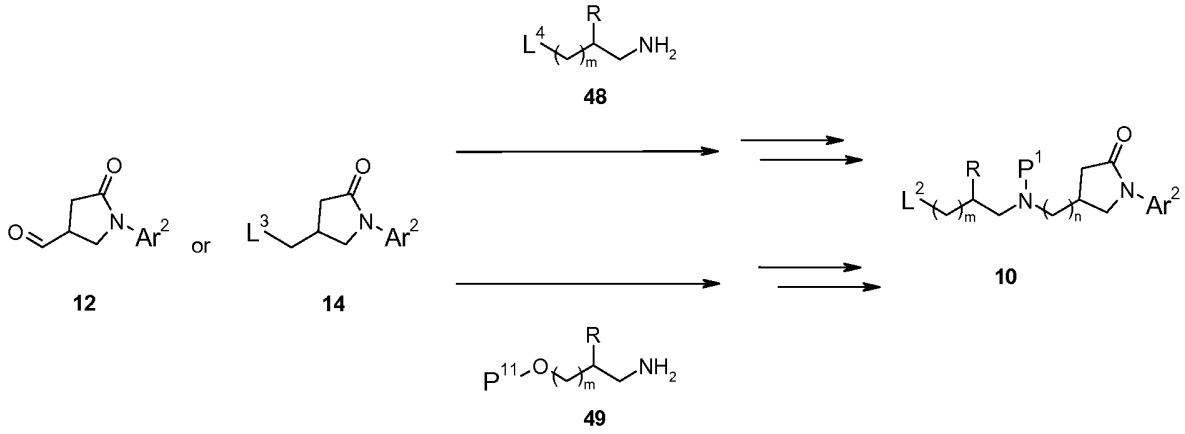


Scheme 20

Furthermore, when n = 1, the compound 10 can be produced by carrying out a reductive alkylation reaction between a compound 12 and a compound 48 or a compound 49, or carrying out an alkylation reaction between a compound 14 and the compound 48 or the compound 49, and then carrying out, as necessary, conversion of protective groups or functional groups (Scheme 21). Various functional groups of all of these compounds may be protected by suitable

protective groups, as desired, during these reaction, and thereafter, the protective groups can be removed at an appropriate stage.

[Formula 24]



Scheme 21

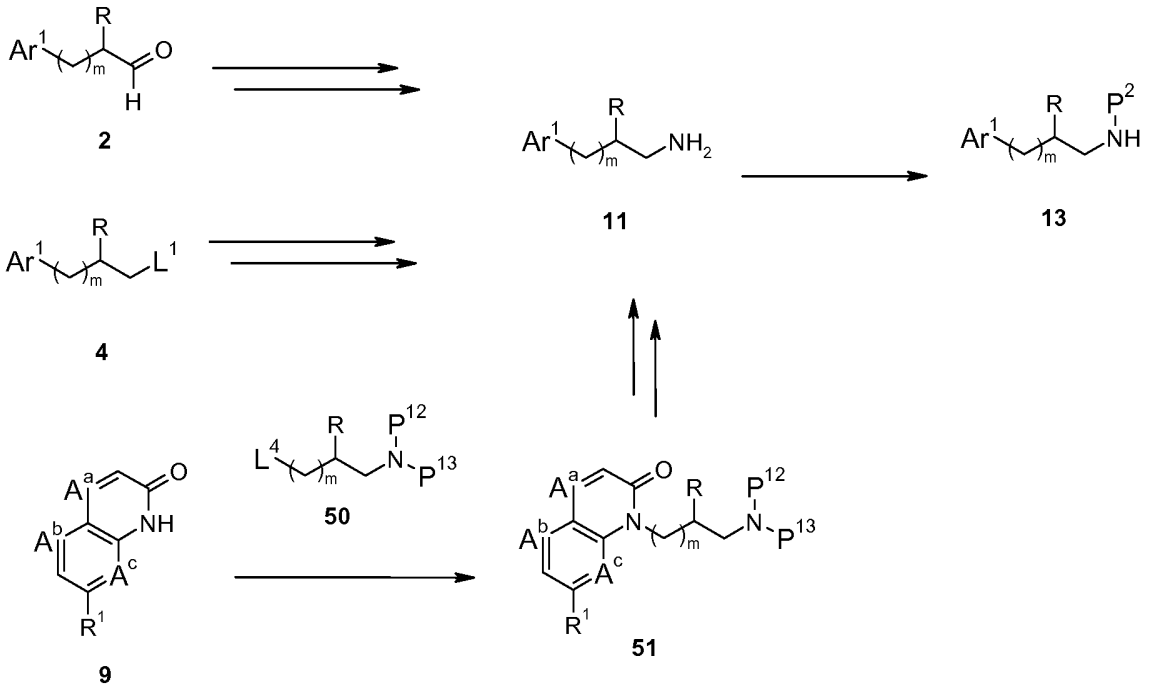
Some of the compounds 48 and 49 in Scheme 21 are commercially available. The compounds, which are not commercially available, can be produced by generally known methods of synthetic organic chemistry, using commercially available reagents.

[Compounds 11 and 13]

Compound 11 or 13 can be produced by carrying out reductive alkylation on a compound 2 using ammonium acetate, or by carrying out such reductive alkylation on the compound 2 using benzylamine and then removing a benzyl group, etc. Moreover, the compound 11 or 13 can also be produced by carrying out azidation/reduction reaction on a compound 4 (Scheme 22). Furthermore, the compound 11 or 13 can also be produced by carrying out an alkylation reaction between a compound 9 and a compound 50 having an amine functional group that may be protected. P^{12} and P^{13} are protective groups for amine. P^{12} and P^{13} may be hydrogen unless it affects the reaction. Various functional groups of all of these compounds may be protected by suitable protective groups, as desired, during these reaction, and thereafter, the protective groups can be removed at an appropriate stage.

Some of the compounds 50 in Scheme 22 are commercially available. The compounds, which are not commercially available, can be produced by generally known methods of synthetic organic chemistry, using commercially available reagents.

[Formula 25]



Scheme 22

[Compounds 12 and 14]

Compounds 12 and 14 can be produced from the compounds 35, 36, etc. by generally known methods of synthetic organic chemistry.

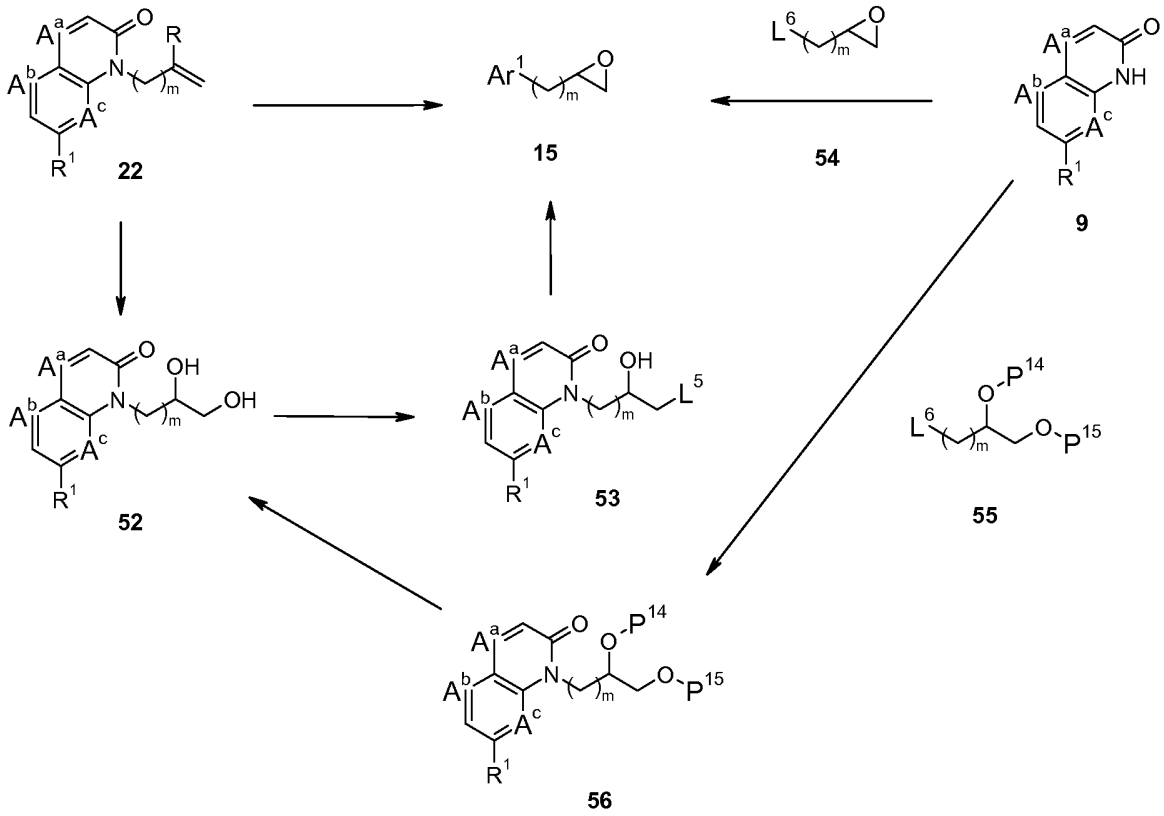
[Compound 15]

Compound 15 can be synthesized by epoxidizing the olefin structure of a compound 22, for example. In addition, the compound 15 can also be synthesized by converting the olefin structure of the compound 22 to dihydroxy (compound 52), then selectively converting a primary alcohol to a leaving group L^5 (compound 53), and then allowing suitable alkali to react on the compound (Scheme 23). Moreover, the compound 15 can also be synthesized by carrying out an alkylation reaction between a compound 9 and a compound 54 having an oxylan structure. Furthermore, the compound 15 can also be synthesized by

carrying out an alkylation reaction between the compound 9 and a compound 55 in which two hydroxy groups are appropriately protected, and then going through compound 56, 52 and 53. Various functional groups of all of these compounds may be protected by suitable protective groups, as desired, during these reaction, and thereafter, the protective groups can be removed at an appropriate stage.

Some of the compounds 54 or 55 in Scheme 23 are commercially available. The compounds, which are not commercially available, can be produced by generally known methods of synthetic organic chemistry, using commercially available reagents.

[Formula 26]



Scheme 23

[Compound 16]

Compound 16 may be the compound 3 or 5 itself, or it can be produced from the compound 3, 5, or the like by generally known methods of synthetic organic

chemistry. Alternatively, the compound 16 can be produced by a method similar to the method for producing the compounds 3, 5 and the like.

Protective groups used in the above described reactions can be selected from the following groups in accordance with common knowledge in this technical field.

Protective groups for amino groups are not particularly limited, as long as they are commonly used in this technical field. Examples of such protective groups for amino groups include: alkoxycarbonyl groups such as a tert-butoxycarbonyl group and a 2,2,2-trichloroethoxycarbonyl group; aralkyloxycarbonyl groups such as a benzyloxycarbonyl group, a paramethoxybenzyloxycarbonyl group, and a paranitrobenzyloxycarbonyl group; acyl groups such as an acetyl group, a methoxyacetyl group, a trifluoroacetyl group, a chloroacetyl group, a pivaloyl group, a formyl group, and a benzoyl group; alkyl groups or aralkyl groups such as a tert-butyl group, a benzyl group, a paranitrobenzyl group, a paramethoxybenzyl group, and a triphenylmethyl group; ethers such as a methoxymethyl group, a tert-butoxymethyl group, a tetrahydropyranyl group, and a 2,2,2-trichloroethoxymethyl group; (alkyl and/or aralkyl)-substituted silyl groups such as a trimethylsilyl group, an isopropyldimethylsilyl group, a tert-butyldimethylsilyl group, a tribenzylsilyl group, and a tert-butyldiphenylsilyl group; arylsulfonyl groups such as a p-toluenesulfonyl group, a benzenesulfonyl group, and a 2-nitrobenzenesulfonyl group (nosyl group); sulfinyl groups such as a benzenesulfinyl group, a p-toluenesulfinyl group, and a tert-butylsulfinyl group; and a sulfo group and an allyl group. The acyl group may be an alkylcarbonyl group, an arylcarbonyl group, or an aralkylcarbonyl group.

Protective groups for hydroxy groups are not particularly limited, as long as they are commonly used in this technical field. Examples of such protective groups for hydroxy groups include: alkyl groups such as a tert-butyl group and an allyl group; aralkyl groups such as a benzyl group, a paramethoxybenzyl group, a 3,4-dimethoxybenzyl group, a paranitrobenzyl group, a diphenylmethyl group, and

a triphenylmethyl group; 1-(alkoxy)alkyl or 1-(aralkoxy)alkyl groups such as a methoxymethyl group, a 2-(trimethylsilyl)ethoxymethyl group, a tetrahydropyranyl group, a 1-ethoxyethyl group, a tert-butoxymethyl group, and a benzyloxymethyl group; (alkyl and/or aralkyl)-substituted silyl groups such as a trimethylsilyl group, a triethylsilyl group, a triisopropylsilyl group, a tert-butyldimethylsilyl group, and a tert-butyldiphenylsilyl group; acyl groups such as a formyl group, an acetyl group, a chloroacetyl group, a trichloroacetyl group, a trifluoroacetyl group, a pivaloyl group, a benzoyl group, and a 2,4,6-trimethylbenzoyl group; oxycarbonyl groups such as a methoxymethyloxycarbonyl group, a 9-fluorenylmethyloxycarbonyl group, a 2,2,2-trichloroethyloxycarbonyl group, a 2-(trimethylsilyl)ethyloxycarbonyl group, an isobutyloxycarbonyl group, an allyloxycarbonyl group, a paranitrophenyloxycarbonyl group, a benzyloxycarbonyl group, a paramethoxybenzyloxycarbonyl group, and a paranitrobenzyloxycarbonyl group; and sulfonyl groups such as a methanesulfonyl group and a paratoluenesulfonyl group. When two hydroxy groups are present adjacent to each other, having a 1,2- or 1,3-relation, the two hydroxy groups may be simultaneously protected. Examples of such a protective group include: cyclic acetals/ketals such as a methylidene group, a tert-butylmethylidene group, an isopropylidene group, and a benzylidene group; and orthoesters such as a methoxymethylene group.

Protective groups for carbonyl groups are not particularly limited, as long as they are commonly used in this technical field. Examples of such protective groups for carbonyl groups include: noncyclic acetals/ketals such as a dimethylacetal group; cyclic acetals/ketals such as 1,3-dioxane, 1,3-dioxolane, chiral or achiral 4,5-dimethyl-1,3-dioxolane, chiral or achiral 4,5-diphenyl-1,3-dioxolane, and trans-1,2-cyclohexanediol ketal; thioacetals/thioketals such as dimethyl dithioacetal, 1,3-dithiane, and 1,3-dithiolane; cyanohydrins such as O-trimethylsilylcyanohydrin and O-acetylcyanohydrin; hydrazones such as N,N-dimethylhydrazone and tosylhydrazone; and oximes such as O-methyloxime and O-benzyloxime.

Protective groups for carboxy groups are not particularly limited, as long as they are commonly used in this technical field. Examples of such protective groups for carboxy groups include: alkyl esters such as methyl ester, an ethyl ester, a tert-butyl ester, a 9-fluorenylmethyl ester, a cyanomethyl ester, a cyclohexyl ester, an allyl ester, a methoxymethyl ester, a tetrahydropyranyl ester, a 2-(trimethylsilyl)ethoxymethyl ester, a benzyloxymethyl ester, a pivaloyloxymethyl ester, a phenacyl ester, a 2,2,2-trichloroethyl ester, and a 2-(trimethylsilyl)ethyl ester; aralkyl esters such as a benzyl ester, a diphenylmethyl ester, a triphenylmethyl ester, a 2,4,6-trimethylbenzyl ester, an orthonitrobenzyl ester, a paranitrobenzyl ester, and a paramethoxybenzyl ester; aryl esters such as a phenyl ester, a 2,6-dimethylphenyl ester, a 2,6-di-tert-butyl-4-methylphenyl ester, and a pentafluorophenyl ester; silyl esters such as a trimethylsilyl ester, a triethylsilyl ester, a triisopropylsilyl ester, and a tert-butyldimethylsilyl ester; and ortho esters such as a triethoxymethyl group.

Protective groups for N-mono-substituted amide groups are not particularly limited, as long as they are commonly used in this technical field. Examples of such protective groups for N-mono-substituted amide groups include: substituted alkyl groups such as an allyl group, a tert-butyl group, a methoxymethyl group, a benzyloxymethyl group, a 2,2,2-trichloroethyl group, a tert-butyldimethylsilyloxymethyl group, a pivaloyloxymethyl group, and a cyanomethyl group; aralkyl groups such as a benzyl group, a 4-methoxybenzyl group, a 2,4-dimethoxybenzyl group, an ortho-nitrobenzyl group, a triphenylmethyl group, an (R)-1-phenylethyl group, an (S)-1-phenylethyl group, an (R)-1-(4-methoxyphenyl)ethyl group, and an (S)-1-(4-methoxyphenyl)ethyl group; substituted aryl groups such as a 4-methoxyphenyl group and a 3,4-dimethoxyphenyl group; alkyl/aralkyloxy groups such as a methoxy group and a benzyloxy group; substituted silyl groups such as a triisopropylsilyl group and a tert-butyldimethylsilyl group; carbamates such as a tert-butoxycarbonyl group, a benzyloxycarbonyl group, and a methoxycarbonyl group; and sulfonyl groups such as a paratoluenesulfonyl group.

Bases used in the above described reactions can be selected from the following substances in accordance with common knowledge in this technical field. Specifically, examples of such bases include: alkaline metal or alkaline-earth metal hydrides (e.g. lithium hydride, sodium hydride, potassium hydride, and calcium hydride); alkaline metal or alkaline-earth metal amides (e.g. lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, and potassium hexamethyldisilazide); alkaline metal or alkaline-earth metal lower alkoxides (e.g. sodium methoxide, sodium ethoxide, and potassium t-butoxide); alkaline metal or alkaline-earth metal hydroxides (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, or barium hydroxide); alkaline metal, alkaline-earth metal, or silver carbonates (e.g. sodium carbonate, potassium carbonate, cesium carbonate, and silver carbonate); alkaline metal hydrogencarbonates (e.g. sodium hydrogen carbonate, and potassium hydrogen carbonate); alkyl lithium (e.g. n-butyl lithium) or alkyl Grignard (e.g. methyl magnesium bromide); inorganic bases such as silver oxide, or amines (e.g. triethylamine, diisopropylethylamine, and N-methylmorpholine); organic bases such as basic heterocyclic compounds (e.g. 4-dimethylaminopyridine, imidazole, 2,6-lutidine, collidine, 1,8-diazabicyclo[5,4,0]undec-7-ene, 1,5-diazabicyclo[4,3,0]non-5-ene, and 1,4-diazabicyclo[2,2,2]octane); and phosphazenes such as P4-phosphazene.

The solvents used in the above described reactions can be selected from the following solvents in accordance with common knowledge in this technical field. Examples of such solvents include alcohol solvents, ether solvents, halogen solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, and water. These solvents may be used in combination of the two or more types thereof.

The compound of the present invention may be either a free compound or an acid-adduct salt. Examples of such an acid-adduct salt include: halogen acid salts such as a hydrofluorde, a hydrochloride, a hydrobromide, and a hydriodide; inorganic acid salts such as a hydrochloride, a nitrate, a perchlorate, a sulfate,

and a phosphate; lower alkanesulfonates such as a methanesulfonate, a trifluoromethanesulfonate, and an ethanesulfonate; arylsulfonates such as a benzenesulfonate and a p-toluenesulfonate; and organic acid salts such as an acetate, a malate, a lactate, a fumarate, a succinate, a citrate, an ascorbate, a tartrate, an oxalate, and a maleate.

There may be a case in which the compound of the present invention contains water molecules in the crystals thereof or it absorbs water content and has adsorption water, so that it becomes a hydrate, for example, during a crystal-generating step or a purification step, or by being left in the atmosphere. Such a hydrate is also included in the salt of the present invention.

The compound of the present invention has one or more asymmetric carbon atoms in the molecule thereof, and optical isomers are present. These isomers and a mixture of these isomers are all represented by a single formula, namely, general formula (I). Accordingly, the compound of the present invention includes all of such optical isomers and a mixture containing optical isomers at any given ratio.

The present invention may also include a compound, in which one or more atoms constituting the compound of the present invention are substituted with isotopes of the atoms. There are two types of isotopes, namely, a radioisotope and a stable isotope. Examples of such an isotope include: hydrogen isotopes (^{2}H and ^{3}H), carbon isotopes (^{11}C, ^{13}C and ^{14}C), nitrogen isotopes (^{13}N and ^{15}N), oxygen isotopes (^{15}O, ^{17}O and ^{18}O), and a fluorine isotope (^{18}F). A composition comprising a compound labeled with an isotope is useful, for example, as a therapeutic agent, a preventive agent, a study reagent, an assay reagent, a diagnostic agent, an in vivo diagnostic imaging reagent, etc. A compound labeled with an isotope is also included in the compound of the present invention, and the mixtures containing such isotope-labeled compounds at any given ratio are also all included in the compound of the present invention. The compound of the present invention, which is labeled with an isotope, can be produced by a method well known in the present technical field, for example, using an isotope-

labeled raw material, instead of a raw material used in the production method of the present invention as described later.

Since the salt and/or crystal of the present invention has strong antibacterial action, it can be used as a pharmaceutical agent for humans, animals and fish, or as an agricultural chemical or a preservative agent for food products. When the compound of the invention of the present application is used as a pharmaceutical agent for human bodies, the dosage thereof is set from 100 mg to 10000 mg, and more preferably from 300 to 5000 mg, per adult per day. On the other hand, the dosage of the compound of the present invention for use in animals is different depending on the purpose of administration, the size of an animal to be treated, the type of pathogen infected, and the degree of symptom. The dosage is generally set from 1 to 200 mg, and more preferably from 5 to 100 mg, per kg of body weight of the animal per day. Such a daily dosage is administered to the animal once a day, or divided over 2 to 4 administrations. It is to be noted that a daily dosage may exceed the aforementioned amount.

The salt and/or crystal of the invention of the present application is active on a wide range of microorganisms that cause various types of infectious diseases. Thus, the salt and/or crystal of the present invention is able to treat, prevent or alleviate diseases caused by these pathogens. Examples of bacteria or bacteria-like microorganisms, for which the compound of the invention of the present application is effective, include Staphylococcus, Streptococcus pyogenes, Streptococcus haemolyticus, Enterococcus, Diplococcus pneumoniae, Peptostreptococcus, Neisseria gonorrhoeae, Escherichia coli, Citrobacter, Shigella, Klebsiella pneumoniae, Enterobacter, Serratia, Proteus, Pseudomonas aeruginosa, Haemophilus influenzae, Acinetobacter, Campylobacter, Mycoplasma, and Chlamydia trachomatis.

Examples of diseases caused by these pathogens include folliculitis, furuncle, carbuncle, erysipelas, cellulitis, lymphangitis (lymphadenitis), whitlow, subcutaneous abscess, hidradenitis, acne conglobata, infectious atheroma, anal abscess, mastitis, superficial secondary infection of external injury/burn

injury/operative wound, pharyngolarynx, acute bronchitis, tonsillitis, chronic bronchitis, bronchiectasis, diffuse panbronchiolitis, secondary infection of chronic respiratory disease, pneumonia, pyelonephritis, cystitis, prostatitis, epididymitis, gonorrheal urethritis, nongonococcal urethritis, cholecystitis, cholangitis, bacillary dysentery, enteritis, uterine adnexitis, intrauterine infection, bartholinitis, blepharitis, hordeolum, dacryocystitis, meibomianitis, corneal ulcer, otitis media, sinusitis, periodontoclasia, pericoronitis, jaw inflammation, peritonitis, endocarditis, septicemia, meningitis, and skin infection.

Moreover, examples of acid-fast bacteria, for which the salt and/or crystal of the invention of the present application is effective, include a group of tubercle bacillus (*Mycobacterium tuberculosis*, *M. bovis*, and *M. africanum*) and a group of atypical mycobacteria (*M. kansasii*, *M. marinum*, *M. scrofulaceum*, *M. avium*, *M. intracellulare*, *M. xenopi*, *M. fortuitum*, and *M. chelonae*). Based on causative microorganisms, mycobacterial infections caused by these pathogens are broadly divided into three types of infections, namely, tuberculosis, atypical mycobacteriosis and leprosy. Tuberculosis is observed in the thoracic cavity, trachea/bronchus, lymph node, whole body, articulation of the bone, meninges/brain, digestive organs (bowel/liver), skin, mammary gland, eye, middle ear/pharynx, urinary tract, male genital organ, female genital organ, as well as in the lung. A main organ affected with atypical mycobacteriosis (non-tuberculous mycobacterial infection) is lung, and other organs affected with this disease include local lymph node, skin soft tissues, articulation of the bone, and whole body.

Furthermore, the salt and/or crystal of the invention of the present application is useful for various types of microorganisms causing infectious diseases of animals, such as genus Escherichia, genus Salmonella, genus Pasteurella, genus Haemophilus, genus Bordetella, genus Staphylococcus, and genus Mycoplasma. Examples of specific disease that infects Aves include colibacillosis, white diarrhea, avian paratyphoid, fowl cholera, infectious coryza, staphylococcosis, and mycoplasma infection. Examples of specific disease that

infects swine include colibacillosis, salmonellosis, pasteurellosis, hemophilus infection, atrophic rhinitis, exudative dermatitis, and mycoplasma infection. Examples of specific disease that infects bovine include colibacillosis, salmonellosis, hemorrhagic septicemia, mycoplasma infection, contagious bovine pleuropneumonia, and mastitis. Examples of specific disease that infects dog include coliform septicemia, salmonella infection, hemorrhagic septicemia, pyometra, and cystitis. Examples of specific disease that infects cat include exudative pleurisy, cystitis, chronic rhinitis, hemophilus infection, kitty diarrhea, and mycoplasma infection.

A pharmaceutical agent comprising the salt and/or crystal of the present invention as an active ingredient is preferably provided in the form of a pharmaceutical composition comprising the salt and/or crystal of the present invention used as an active ingredient and one or two or more types of additives used for pharmaceutical agents. The pharmaceutical agent of the present invention is not particularly limited in terms of administration form, and it can be administered orally or parenterally.

An antibacterial agent comprising the salt and/or crystal of the invention of the present application can be prepared by selecting a suitable pharmaceutical agent depending on its administration method, according to a commonly used method for preparing various types of pharmaceutical agents. Examples of the dosage form of an antibacterial agent comprising the compound of the present invention as a main agent include a tablet, a powder, a granule, a capsule, a solution, a syrup, an elixir, and an oily or aqueous suspension. In the case of an injection, a stabilizer, an antiseptic, a solubilizing agent, a pH adjuster, an isotonizing agent, etc. may be added to the pharmaceutical agent. A solution that may comprise the aforementioned agents may be contained in a vessel and may be then freeze-dried to prepare a solid agent, which is a pharmaceutical agent prepared when used. Otherwise, a single dosage amount of agent may be contained in a vessel, or several dosage amounts of agents may also be contained in a single vessel. Examples of an external preparation include a

solution, a suspension, an emulsion, an ointment, a gel, a cream, a lotion, and a spray. In the case of a solid agent, it may comprise pharmaceutically acceptable additives as well as an active compound. Examples of such additives include fillers, binders, disintegrators, solution promoters, wetting agents, and lubricants. Examples of a liquid agent include a solution, a suspension, and an emulsion. Such a liquid agent may comprise a suspending agent, an emulsifier, and the like as additives.

[Examples]

Hereinafter, the present invention will be described more in detail in the following examples and the like. However, these examples are not intended to limit the scope of the present invention.

[Reference Example 1] 4-Chloro-3-nitrobenzonitrile

In dry acetonitrile (40 ml) was dissolved 4-chlorobenzonitrile (4g, 29.2 mmol), and nitronium tetrafluoroborate (7.7g, 58.39 mmol) was added therto at 0 °C. The reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was poured into cold water. The white solid precipitated out was collected by filtration, and the filterate was washed with water and dried. The compound (4.0g, 75.47%) thus obtained was used for next step without purification.

[Reference Example 2] Ethyl *N*-(4-cyano-2-nitrophenyl)glycinate

In dry acetonitrile (40 ml) were dissolved 4-chloro-3-nitrobenzonitrile (4.0 g, 21.98 mmol), ethyl glycinate hydrochloride (4.6 g, 32.97 mmol) and diisopropyl ethylamine (10.9 ml, 65.94 mmol) in microwave vial and the mixture was irradiated at 125 °C for 30 minutes. The solvent was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to yield 4.0g (73.13%) of the title compound.

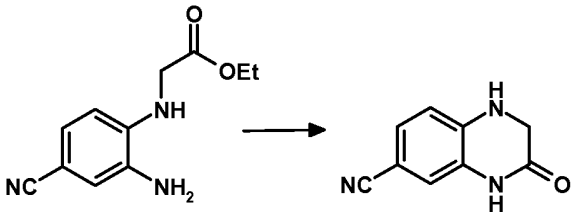
^{1}H-NMR(400MHz,$CDCl_3$)δ:1.33(t,J=7.2Hz,3H),4.13(d,J=5.2Hz,2H),4.32(q,J=7.2Hz,2H),6.77 (d,J=9.2Hz,1H),7.65(dd,J=9.2,2.0Hz,1H),8.55(d,J=2.0Hz,1H),8.81(s, 1H).

[Reference Example 3] Ethyl *N*-(2-amino-4-cyanophenyl)glycinate

Ethyl *N*-(4-cyano-2-nitrophenyl)glycinate (1.0 g, 4.02 mmol) was dissolved in dry methanol (30 ml) and palladium carbon (0.3 g, 30% w/w) was added. The reaction mixture was stirred under hydrogen atmosphere for 1.5 hour. After complete consumption of starting material, the reaction mixture was filtered and washed with methanol. The filtrate and washings were concentrated under reduced pressure to yield crude product (0.88 g), which was used as such for next step without purification.

[Reference Example 4] 3-Oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

[Formula 27]



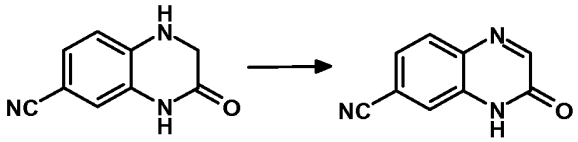
Ethyl *N*-(2-amino-4-cyanophenyl)glycinate (Reference Example 3, 0.88 g) was dissolved in ethanol (10 ml) and acetic acid (1.0 ml) was added to it. The reaction mixture was heated at 80 °C for 1 hour. The solvent was removed under reduced pressure to yield crude product (0.75 g), which was used as such for next step.

^{1}H-NMR(400MHz,DMSO-d_6)δ:3.90(d,J=1.6Hz,2H),6.68(d,J=8.4Hz,1H), 6.94(d,J=2.0Hz,1H),7.16(dd,J=8.4,2.0Hz,1H),10.50(s,1H).

MS (-ve mode):172 (M-H).

[Reference Example 5] 3-Oxo-3,4-dihydroquinoxaline-6-carbonitrile

[Formula 28]



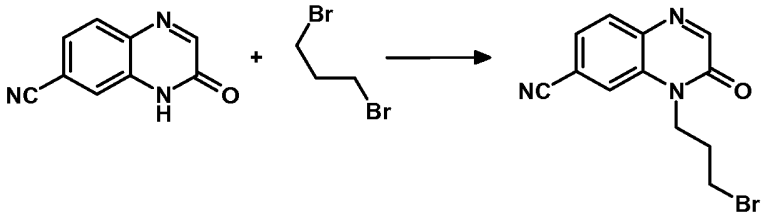
In dry methanol (25 ml) was dissolved 3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (0.55 g, 3.18 mmol). To this, potassium carbonate (0.66 g, 4.77 mmol) and iodine (0.97 g 3.82 mmol) were added at room temperature and stirred at the same temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in water and quenched with aqueous sodium dithionite till iodine color disappeared. Aqueous layer was extracted with ethyl acetate (x3), and the extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield 0.49g (90.74%) of the title compound.

^{1}H-NMR(400MHz,DMSO-d_6)δ:7.64(d,J=1.6Hz,1H),7.70(dd,J=8.4,2.0Hz,1H), 7.95(d,J=8.4Hz,1H), 8.31(s,1H),12.70(s,1H).

MS (-ve mode):170(M-H).

[Reference Example 6] 4-(3-Bromopropyl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

[Formula 29]

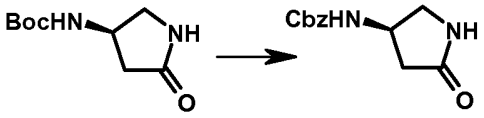


Dibromopropane (2.5 ml, 24.85 mmol) and potassium hydroxide (0.33 g, 5.96 mmol) was taken in dry dimethylsulfoxide (10 ml). To above reaction mixture was added 3-oxo-3,4-dihydroquinoxaline-6-carbonitrile (Reference Example 5, 0.85 g, 4.97 mmol)portion wise at 0 °C. The reaction mixture was stirred at room temperature for 2.0 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine solution. Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (ethyl acetate/hexane) to yield 0.3g (20.69%) of the title compound.

^{1}H-NMR(400MHz,DMSO-d_6)δ:2.18(t,J=7.2Hz,2H),3.66(t,J=7.2Hz,2H), 4.30(t,J=7.2Hz,2H),7.79(dd,J=8.4,1.6Hz,1H),7.99(d,J=8.0Hz,1H),8.25(d,J=1.2Hz,1H),8.36(s,1H).

[Reference Example 7] Benzyl [(3*R*)-5-oxopyrrolidin-3-yl]carbamate

[Formula 30]



In a two neck round bottom flask (100 ml), trifluoroacetic acid and dichloromethane (1:2, 30 ml) was taken and cooled to 5-10 °C. To this was added *tert*-butyl [(3*R*)-5-oxopyrrolidin-3-yl]carbamate (20g, 0.1moles) portion wise over a period of 20 minutes. The reaction temperature was slowly raised to room temperature and stirred for 6 hours. After complete consumption of starting material, the reaction mixture was concentrated and excess trifluoroacetic acid was removed using high vacuum pump to yeild crude oily residue of (4*R*)-4-aminopyrrolidin-2-one (11g).

In tetrahydrofuran and water (1:1, 100 ml) was then dissolved (4*R*)-4-aminopyrrolidin-2-one (11g, 0.11 moles) and the mixture was cooled to 5-10 °C.

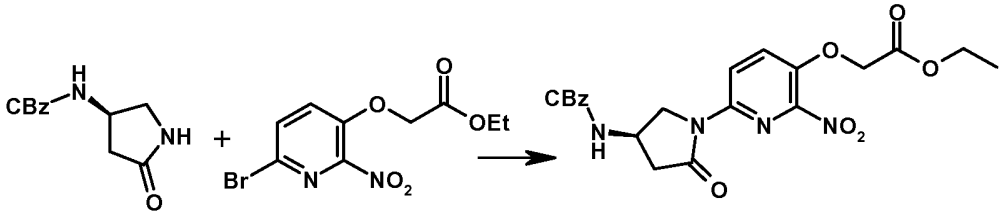
To this solution was added solid sodium bicarbonate till the effervescence stopped and pH of the reaction mixture was neutral. Benzyl chloroformate (44.88 ml, 50% in toluene, 0.132 moles) was then added dropwise to this reaction mixture at the same temperature. The reaction mixture was slowly warmed to room temperature and stirred for 8 hours. After complete consumption of starting amine, reaction mixture was extracted with ethyl acetate (x3) and combined organic layer was dried over anhydrous sodium sulphate. The extarct was concentrated to yield semi solid compound which was further triturated with diethyl ether and hexane (50%, 250 ml) to yield 20g (85%) of the title compound as off-white solid.

^{1}H-NMR(400MHz,$CDCl_3$)δ:2.22(m,1H),2.69(m,1H),3.27(m,1H),3.72(m,1H), 4.48(bs,1H),5.10(bs,2H),5.71(bs,2H),7.30(m,5H).

MS: 235$(M+H)^+$.

[Reference Example 8] Ethyl ({6-[(4*R*)-4-{[(benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl]-2-nitropyridin-3-yl}oxy)acetate

[Formula 31]



Benzyl [(3*R*)-5-oxopyrrolidin-3-yl]carbamate (10 g, 0.042 moles) and ethyl [(6-bromo-2-nitropyridin-3-yl)oxy]acetate (20.8 g, 0.068 moles) were taken in three neck round bottom flask (1L) and to it 1,4-dioxane (600 ml) was added under argon atmosphere. To this reaction vessel was added cuprous iodide (6.5 g, 0.034 moles), cesium carbonate (42 g, 0.128 moles) and *N,N'*-dimethylethylene diamine (3.4 ml, 0.034 moles) and then degassed with argon gas for 10 minutes. The reaction mixture was then refluxed at 100-110 °C for 3 hours, followed by evaporation to yield oily residue, which was dissolved in ethyl acetate (1000 ml). The organic layer was washed with water (x2), dried over anhydrous sodium

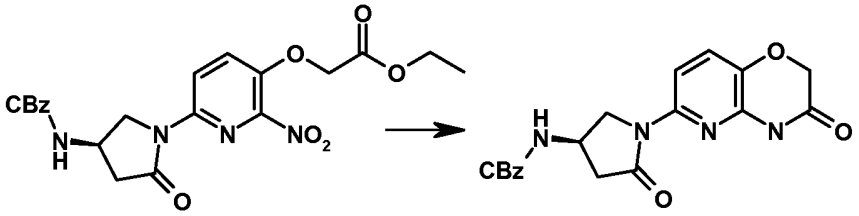
sulphate, filtered and then concentrated to yield brown oily crude compound which was purified by a fast filtration column chromatography on combiflash (ethyl acetate/hexane) to yield 11.5g (61%) of the title compound.

^{1}H-NMR(400MHz,$CDCl_3$)δ:1.32(m,2H),2.65(m,1H),3.12(m,1H),3.75(s,3H), 3.92(m,1H),4.35(m,1H),4.5(bs,1H),4.77(bs,2H),5.20(s,3H),7.33(m,5H),7.50(d,9.2Hz,1H),8.60(d,9.2Hz,1H).

MS: 459$(M+H)^+$

[Reference Example 9] Benzyl [(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]carbamate

[Formula 32]



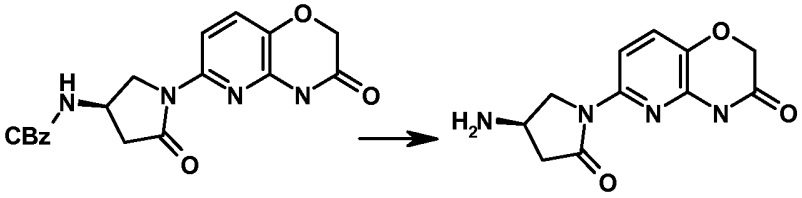
Ethyl ({6-[(4*R*)-4-{[(benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl]-2-nitropyridin-3-yl}oxy)acetate (10 g, 0.021 moles) and iron powder (6 g, 0.109 moles) were taken in a three neck round bottom flask (1L). To this reaction vessel was added acetic acid (100 ml) and ethanol (500 ml) and then stirred vigorously at 70-80 °C for 3 hours. After complete consumption of starting material, the reaction mixture was evaporated and to the residue cold water (250 ml) was added. The mixture was then cooled to 10-15 °C and solid sodium bicarbonate was added to it till the pH of the solution was neutral. The mixture was then extracted with dichloromethane and ethyl acetate (x5). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to yield off-white solid compound which was triturated with diethyl ether (100 ml) to yield 9g (98%) of the title compound as off-white solid.

^{1}H-NMR(400MHz,DMSO-d_6)δ:2.46(m,2H),2.92(m,1H),3.82(m,1H),4.11(m,1H),4.15(bs,1H),4.60(s,2H),5.03(s,2H),7.35 (m,5H),7.85(m,2H),11.17(s,1H).

MS: 383(M+H)$^+$

[Reference Example 10] 6-[(4*R*)-4-amino-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one

[Formula 33]



Benzyl [(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]carbamate (10 g, 0.026 moles) was taken in a round bottom flask (500 ml) and to it methanol (250 ml) was added followed by addition of palladium on carbon (5g, 50% w/w) and it was stirred at room temperature under hydrogen balloon for 2 hours. After complete consumption of starting material, the reaction mixture was filtered through Buchner funnel and washed with methanol (500 ml). The organic layer was then evaporated to yield off-white solid which was purified by triturating in diethyl ether (50 ml) to yield 6g (98%) of the title compound.

^{1}H-NMR(400MHz,DMSO-d_6)δ:0.93(m,1H),2.25(m,1H),2.76(m,1H),3.63(m,4H), 3.97(m,1H), 4.60(s,2H),7.39(d,8.8Hz,1H),7.84(d,8.8Hz,1H).

MS: 249(M+H)$^+$

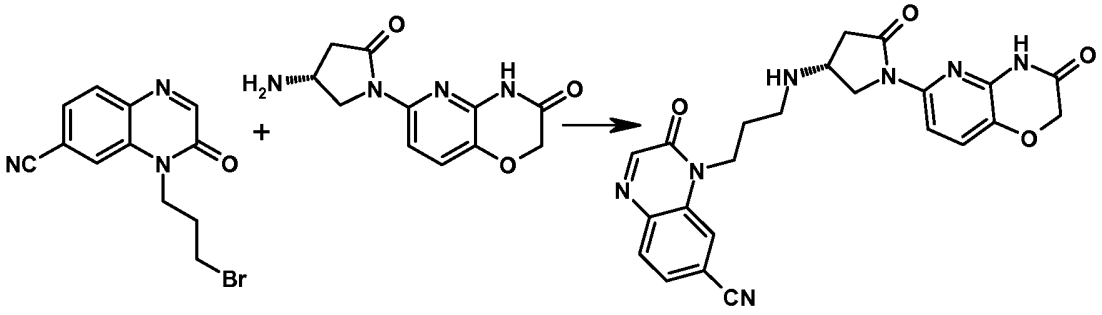
[Reference Example 11] 6-[(4*R*)-4-(aminomethyl)-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one (7.7g) was prepared in a similar manner and in similar yields using benzyl {[(3*R*)-5-oxopyrrolidin-3-yl]methyl}carbamate (12g).

^{1}H-NMR(400MHz,DMSO-d_6)δ:2.45(m,2H),2.63(m,3H),3.67(m,1H),4.01(m,1H),4.60(s,2H),7.39 (d,8.8Hz,1H),7.81(d,8.8Hz,1H).

MS: 263$(M+H)^+$

[Example 1] 3-Oxo-4-(3-{[(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]amino}propyl)-3,4-dihydroquinoxaline-6-carbonitrile

[Formula 34]



In dry *N,N*-dimethylformamide (2.0 ml) were dissolved 4-(3-bromopropyl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (Reference Example 6, 0.150 g, 0.51 mmol), 6-[(4*R*)-4-amino-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one (Reference Example 10, 0.127 g, 0.51 mmol) and diisopropyl ethylamine (0.3 ml, 1.02 mmol). The reaction mixture was stirred at 50 °C for 16 hours. The reaction mixture was poured in water and extracted with ethyl acetate, the extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The obtained crude product was purified by preparative thin layer chromatography (methanol/dichloromethane) to yield 20 mg (8.48%) of the title compound.

^{1}H-NMR(400MHz,DMSO-d_6)δ:1.79(bs,2H),2.37(m,1H),2.61(bs,2H),2.79(m,1H), 3.38(d,J=6.8Hz,2H),3.74(bs,1H),4.01(bs,1H),4.26(bs,2H),4.60(s,2H),7.39(d,J=8.8 Hz,1H), 7.78(d,J=8.0Hz,1H),7.83(d,J=8.4Hz,1H),7.98(d,J=8.0Hz,1H), 8.27(s,1H), 8.36(s,1H),11.16(bs, 1H).

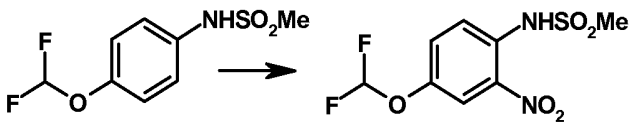
MS:460(M+H)$^+$.

[Example 2] 3-Oxo-4-[3-({[(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]methyl}amino)propyl]-3,4-dihydroquinoxaline-6-carbonitrile was prepared in a similar fashion as in Example 1 using 6-[(4*R*)-4-(aminomethyl)-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one (Reference Example 11, 0.127 g, 0.51 mmol).
^{1}H-NMR(400MHz,DMSO-d_6)δ:1.79(bs,2H),2.61(bs,4H),3.50(m,2H),3.68(m,1H), 4.02(m,2H),4.26(m,2H),4.35(m,1H),4.59(s,2H),7.38(d,J=8.8Hz,1H),7.80(m,2), 7.99(d,J=8.0Hz,1H),8.28(s,1H),8.38(s,1H).
MS:474(M+H)$^+$.

[Reference Example 12] *N*-[4-(Difluoromethoxy)phenyl]methanesulfonamide

In tetrahydrofuran (10 ml) was dissolved 4-difluoromethoxyaniline (1.0 g, 6.29 mmol). To this, pyridine (1.0 ml, 12.58 mmol) and methane sulfonyl chloride (0.7 ml, 9.43 mmol) were added at 0-5 °C and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with water and brine solution. Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product (1.5 g) was used as such for next step.
^{1}H-NMR(400MHz,DMSO-d_6)δ:2.97(s,3H),7.16(d,J=8.8Hz,2H),7.16(t,J=74.4Hz,1H), 7.24 (d,J=9.2Hz,2H),9.77(s,1H).

[Reference Example 13] *N*-[4-(Difluoromethoxy)-2-nitrophenyl]methanesulfonamide
[Formula 35]



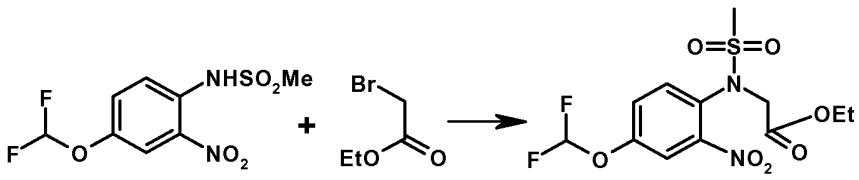
In chloroform (15 ml) was dissolved *N*-[4-(difluoromethoxy)phenyl]methanesulfonamide (Reference Example 7, 1.7 g, 7.17 mmol), and acetic anhydride (1.0 ml, 10.76 mmol) was added thereto at room temperature and the mixture was heated to 60 °C. To this, nitric acid (0.4 ml, 8.61 mmol) was added drop-wise over a period of 3 minutes at the same temperature. The heating was continued for additional 30 minutes and the mixture was then cooled to room temperature, poured into water and extracted with ethyl acetate (x3). The organic extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product 1.7g (84.16%) was used without purification for next step.

^{1}H-NMR(400MHz,DMSO-d_6)δ:3.11(s,3H),7.35(t,J=73.2Hz,1H),7.59(dd,J=8.8,2.8Hz,1H), 7.66(d,J=8.8Hz,1H),7.86(d,J=2.8Hz,1H),9.83(s,1H).

MS (-ve mode): 281(M-H).

[Reference Example 14] Ethyl *N*-[4-(difluoromethoxy)-2-nitrophenyl]-*N*-(methylsulfonyl)glycinate

[Formula 36]

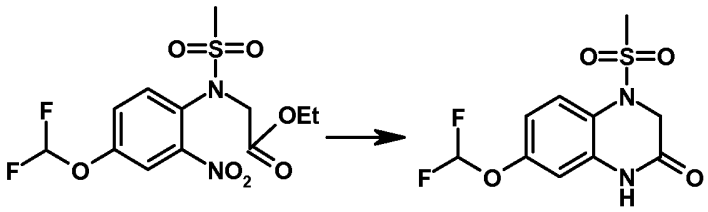


N-[4-(Difluoromethoxy)-2-nitrophenyl]methanesulfonamide (1.1 g, 3.90 mmol) and potassium carbonate (0.65 g, 4.68 mmol) were taken in dry *N,N*-dimethylformamide (5 ml), followed by addition of ethyl bromo acetate (0.6 ml, 4.68 mmol) at room temperature and the mixture was stirred at the same temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic extract was washed with water and brine solution and dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane) to yield 1.2g (83.33%) of the title compound.

^{1}H-NMR(400MHz,DMSO-d_6)δ:1.20(t,7.2Hz,3H),3.16(s,3H),4.16(q,7.2Hz,2H),4.52(bs,2H), 7.44(t,J=72.8Hz,1H), 7.64(dd,J=8.8,3.2Hz,1H), 7.89(d,J=8.8Hz,1H),7.93(d,J=3.2Hz,1H). MS: 369$(M+H)^+$.

[Reference Example 15] 7-(difluoromethoxy)-4-(methylsulfonyl)-3,4-dihydroquinoxalin-2(1*H*)-one

[Formula 37]

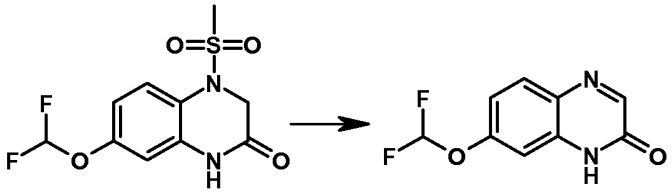


Ethyl *N*-[4-(difluoromethoxy)-2-nitrophenyl]-*N*-(methylsulfonyl)glycinate (1.8 g, 4.89 mmol) was dissolved in dry methanol (20 ml), followed by addition of palladium on carbon (0.5 g, 30% w/w). The reaction mixture was stirred under hydrogen atmosphere for 4 hours. The reaction mixture was filtered and washed with methanol. The filtrate and washings were concentrated under reduced pressure to yield crude product, which was purified by silica gel column chromatography (ethyl acetate/hexane) to yield 1.0g (64.10%) of the title compound.

^{1}H-NMR(400MHz,DMSO-d_6)δ:2.98(s,3H),4.25(s,2H),6.81(d,J=2.8Hz,1H), 6.87(dd,J=8.8,2.4Hz,1H), 7.22(t,J=73.6Hz,1H), 7.44(d,J=8.4Hz,1H),10.91(s,1H). MS(-ve mode): 291(M-H).

[Reference Example 16] 7-(Difluoromethoxy)quinoxalin-2(1*H*)-one

[Formula 38]



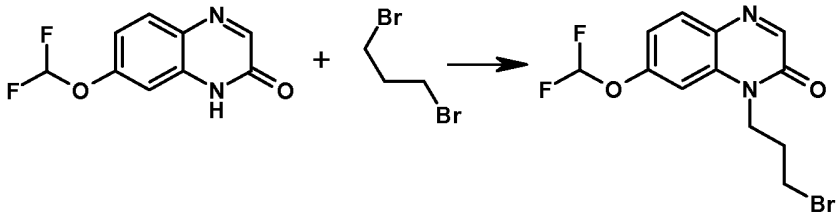
In dioxane (10 ml) was dissolved 7-(difluoromethoxy)-4-(methylsulfonyl)-3,4-dihydroquinoxalin-2(1*H*)-one (1.0 g, 3.43 mmol), and to this, cesium carbonate (0.65 g, 2.06 mmol) was added and stirred at 100 °C overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane, and the solution was washed with water and brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield 0.9 g of the crude product.

^{1}H-NMR(400MHz,DMSO-d_6)δ:7.06(dd,J=8.8,2.8Hz,1H),7.14(d,J=2.8Hz,1H), 7.37(t,J=73.6Hz,1H), 7.79(d,J=8.8Hz,1H),8.08(s,1H).

MS(-ve mode): 211(M-H).

[Reference Example 17] 1-(3-Bromopropyl)-7-(difluoromethoxy)quinoxalin-2(1*H*)-one

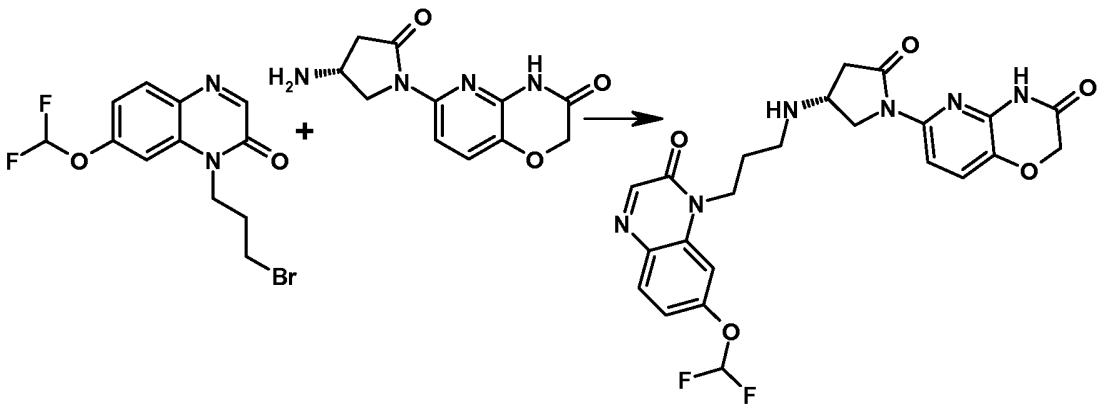
[Formula 39]



Dibromo propane (1.2 ml, 11.89 mmol) and potassium hydroxide (0.16 g, 2.83 mmol) was taken in dry dimethylsulfoxide (10 ml). To the above reaction mixture was added portion wise 7-(difluoromethoxy)quinoxalin-2(1*H*)-one (0.5 g, 2.36 mmol) at 10 °C. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine solution. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane) to yield 0.27g (34.62%) of the title compound.

[Example 3] 6-[(4*R*)-4-({3-[7-(difluoromethoxy)-2-oxoquinoxalin-1(2*H*)-yl]propyl}amino)-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one

[Formula 40]



In dry *N,N*-dimethylformamide (2.0 ml) were dissolved 1-(3-bromopropyl)-7-(difluoromethoxy)quinoxalin-2(1*H*)-one (Reference Example 17, 0.135 g, 0.405 mmol), 6-[(4*R*)-4-amino-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one (Reference Example 10, 0.1 g, 0.405 mmol) and diisopropyl ethylamine (0.13 ml, 0.81 mmol). The reaction mixture was stirred at 50 °C for 16 hours. The reaction mixture was poured in water and extracted with ethyl acetate (x3), the extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography (methanol/dichloromethane) to yield 25mg (12.32%) of the title compound.

^{1}H-NMR(400MHz,DMSO-d_6)δ:1.78(m,2H),2.39(m,2H),2.60(bs,2H),2.79(dd,J=15.2,7.2Hz,1H), 3.38(bs,1H),3.74(m,1H),4.01(dd,J=10.8,6.4Hz,1H),4.24(t,J=7.2Hz,2H),4.60(s,2H),7.20(dd,J=8 .8,2.4Hz,1H),7.39(d,J=8.8Hz,1H),7.44(d,J=2.4Hz,1H),7.46(t,J=73.6Hz,1H),7.83(d,J=8.8Hz,1), 7.89(d,J=8.8Hz,1H),8.18(s,1H),11.17(bs,1H).

MS: 501$(M+H)^+$.

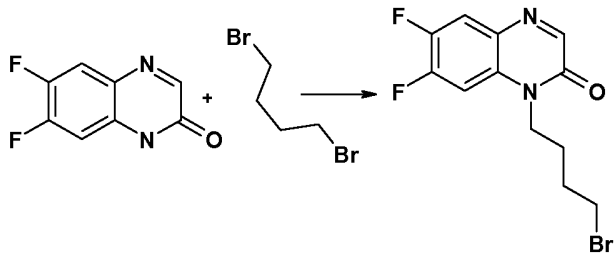
[Example 4] 6-{(4*R*)-4-[({3-[7-(difluoromethoxy)-2-oxoquinoxalin-1(2*H*)-yl]propyl}amino)methyl]-2-oxopyrrolidin-1-yl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one was prepared in a similar fashion as in Example 3 using 6-[(4*R*)-4-(aminomethyl)-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one (Reference Example 11, 0.106 g, 0.405 mmol).

^{1}H-NMR(400MHz,DMSO-d_6)δ:1.79(m,2H),2.08(s,1H),2.45(m,2H),2.63(bs,5H), 3.67(dd,J=10.8,6.4Hz,1H),4.03(m,1H),4.24(bs,2H),4.60(s,2H),7.21(dd,J=8.8,2.4Hz,1H), 7.39(d,J=8.8Hz,1H),7.45(d,J=2.4Hz,1H),7.47(t,J=73.6Hz,1H),7.82(d,J=8.8Hz,1H), 7.90(d,J=8.8Hz,1H), 8.20(s,1H),11.17(bs,1H).

MS: 515$(M+H)^+$.

[Reference Example 18] 1-(4-Bromobutyl)-6,7-difluoroquinoxalin-2(1*H*)-one

[Formula 41]

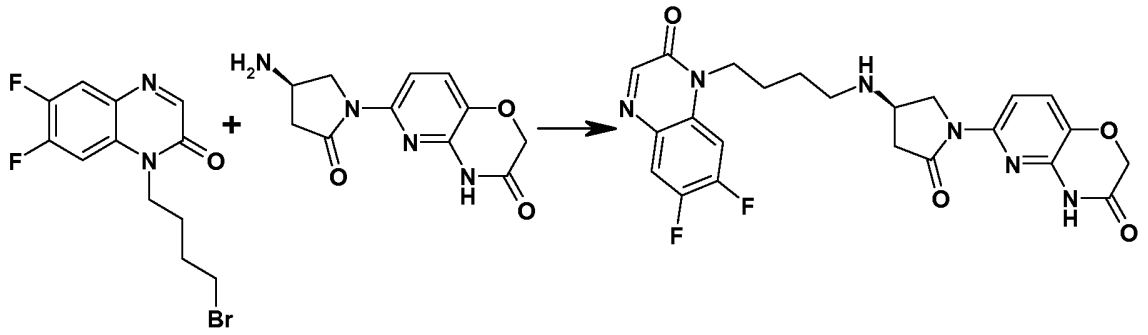


In dry *N,N*-dimethylformamide (30 ml) was taken 6,7-difluoroquinoxalin-2(1*H*)-one (5 g, 27.45 mmol), followed by portion-wise addition of lithium hydride (260 mg, 32.9 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour, then 1,4-dibromobutane (4.9 ml, 41.4 mmol) was slowly added thereto. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was then diluted with ethyl acetate and water and extracted with ethyl acetate (x3). The organic extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane) to yield 3.5 g (40.2%) of the title compound.

^{1}H-NMR(400MHz,DMSO-d_6)δ:1.71-1.78(m,2H),1.87-1.95(m,2H),3.57-3.60(t,J=6.6Hz,2H), 4.20(t,J=7.6Hz,2H),7.87-7.99(m,2H),8.24(s,1H).

[Example 5] 6-[(4*R*)-4-{[4-(6,7-difluoro-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-2-one

[Formula 42]



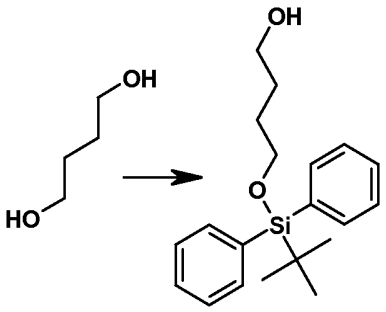
In dry *N,N*-dimethylformamide (2.0 ml) were taken 1-(4-bromobutyl)-6,7-difluoroquinoxalin-2(1*H*)-one (Reference Example 18, 0.300 g, 0.946 mmol), 6-[(4*R*)-4-amino-2-oxopyrrolidin-1-yl]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-2-one (Reference Example 10, 0.400 g, 1.6 mmol) and diisopropyl ethylamine (0.265 ml, 1.69 mmol). The reaction mixture was heated at 80 °C for 4 hours. The reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography (methanol/dichloromethane) to yield 100mg (20%) of the title compound.

^{1}H-NMR(400MHz,DMSO-d_6)δ:1.50(m,2H),1.65(m,2H),2.37(m,1H),2.54(m,3H), 2.77(dd,J=7.2Hz,J=16.8Hz,1H),3.71(bs,1H),3.98(bs,1H),4.16(t,J=7.5Hz,2H),4.59(s,2H), 7.37(d,J=8.8Hz,1H),7.81(d,J=8.4Hz,1H),7.88(dd,J=5.2Hz,J=7.6Hz,1H), 7.97(dd,J=2.0Hz,J=8.4Hz,1H),8.24(s,1H),11.16(bs,1H).

MS: 485$(M+H)^+$.

[Reference Example 19] 4-{[*Tert*-butyl(diphenyl)silyl]oxy}butan-1-ol

[Formula 43]

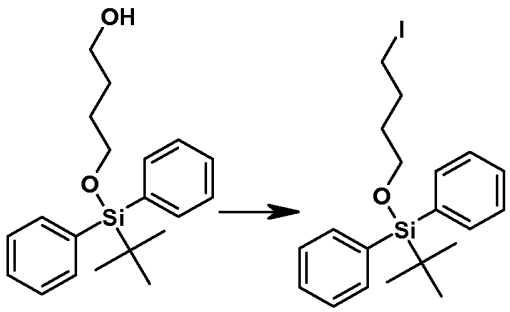


To a stirred solution of butane-1,4-diol (50 g, 0.554 mol) in tetrahydrofuran (500 ml), sodium hydride (22.19 g, 0.554 mol) was added portion wise at 0 °C under argon atmosphere and the reaction mixture was stirred at 0 °C for 30 minutes. To this, *tert*-butyl diphenylsilyl chloride (1726 ml, 0.665 mol) was added drop-wise maintaining temperature at 0 °C over a period of 30 minutes and the mixture was stirred at 0 °C for 1 hour. Water (200 ml) was added drop-wise maintaining temperature at 0 °C, followed by addition of ethyl acetate (300 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (x3). The organic layer was dried and concentrated to dryness. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane) to yield 125g (68.68%) of the title compound.

^{1}H-NMR(400MHz,$CDCl_3$)δ:0.90(s,9H),1.64(m,2H),1.70(m,2H),3.72(m,2H),3.72(m,2H), 7.42(m,6H),7.64(dd,J=1.2Hz,J=6.4Hz,4H).

[Reference Example 20] *Tert*-butyl(4-iodobutoxy)diphenylsilane

[Formula 44]

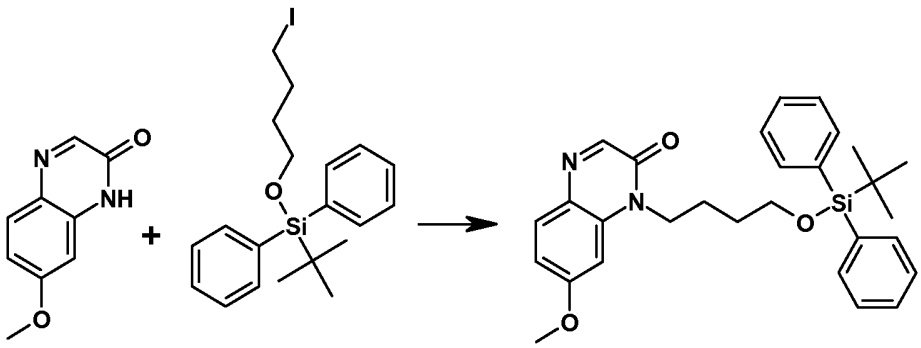


To a stirred solution of 4-[*tert*-butyl(diphenyl)silyl]butan-1-ol (125 g, 0.381mol) in dry toluene (1250 ml), imidazole (25.94 g, 381 mmol) and triphenyl phosphine (149.77 g, 0.571mol) were added portion wise at room temperature under argon atmosphere and the reaction mixture was stirred for about 10 minutes. Then, iodine (145 g, 0.571mol) was added portion-wise at 0 °C, the temperature was maintained at 0 °C and after addition the reaction mixture was stirred for about 30 minutes at room temperature. The reaction mixture was cooled to 0 °C and then saturated sodium thiosulphate solution (800 ml) was added. The reaction mixture was then extracted with ethyl acetate (x2), the pooled ethyl acetate extracts were dried and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane) to obtain 80g (47.90%) of the title compound.

^{1}H-NMR(400MHz,$CDCl_3$)δ:0.90(s,9H),1.64(m,2H),1.96(m,2H),3.18(m,2H),3.67(m,2H), 7.42(m,6H),7.64(dd,J=1.2Hz,J=6.4Hz,4H).

[Reference Example 21] 1-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)-7-methoxyquinoxalin-2(1*H*)-one

[Formula 45]



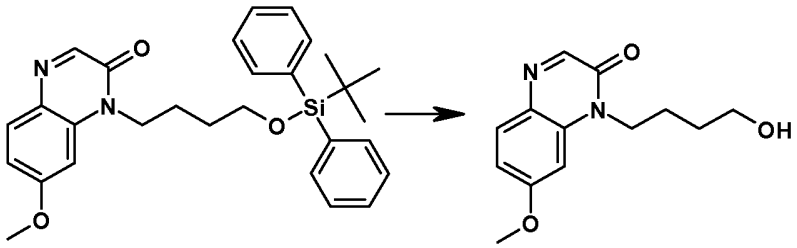
To a stirred solution of 7-methoxyquinoxalin-2(1*H*)-one (3 g, 1.7 mol) in dry *N,N*-dimethylformamide (30 ml), lithium hydride (0.148 g, 1.8 mol) was added at 0 °C under argon atmosphere and then the reaction mixture was allowed to stir at room temperature for about 30 minutes. *Tert*-butyl(4-iodobutoxy)diphenylsilane (Reference Example 15, 8.95 g, 2.0 mol) dissolved in dry *N,N*-dimethylformamide (15 ml) was added drop-wise at room temperature and allowed to stir overnight at room temperature. The reaction mixture was cooled to 0 °C, water (20 ml) was added drop-wise, followed by ethyl acetate (20 ml). The mixture was filtered through celite to remove solid impurities and washed with ethyl acetate (50 ml). The two layers obtained were separated and the ethyl acetate layer was dried and concentrated up to dryness. The crude product was purified by column using combiflash (ethyl acetate/hexane) to yield 2.5g (30.19%) of the title compound.

^{1}H-NMR(400MHz,$CDCl_3$)δ:0.90(s,9H),1.69(m,2H),1.85(m,2H),3.72(m,2H),3.93(s,3H), 4.25(m,2H),6.76(d,J=2.4Hz,1H),6.94(dd,J=9.2Hz,J=2.4Hz,1H),7.42(m,6H), 7.64(dd,J=1.2Hz,J=6.4Hz,4H),7.79(d,J=9.2Hz,1H),8.13(s,1H).

MS: 487$(M+H)^+$.

[Reference Example 22] 1-(4-hydroxybutyl)-7-methoxyquinoxalin-2(1*H*)-one

[Formula 46]



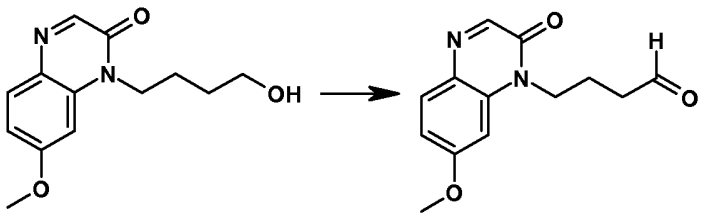
To a stirred solution of 1-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)-7-methoxyquinoxalin-2(1*H*)-one (2.5 g, 1.1 mol) in dry tetrahydrofuran (25 ml), tetra-n-butylammonium fluoride (1M, tetrahydrofuran solution; 10.28 ml, 10.2 mol) was added drop-wise at 0 °C under argon atmosphere and the reaction mixture allowed to stir at room temperature for 1 hour. The reaction mixture was cooled to 0 °C, water (10 ml) was slowly added to it followed by addition of ethyl acetate (20 ml). The two layers were separated and ethyl acetate layer was dried over anhydrous sodium sulphate and concentrated to dryness. The obtained crude product was purified using combiflash (ethyl acetate/hexane) to yield 1.2g (94.48%) of the title compound.

^{1}H-NMR(400MHz,$CDCl_3$)δ:1.70(m,2H),1.88(m,2H),3.77(m,2H),3.93(s,3H), 4.27(m,2H),6.82(d,J=2.8Hz,1H),6.93(dd,J=8.8Hz,J=2.4Hz,1H),7.80(d,J=8.8Hz,1H) ,8.13(s,1H).

MS: 285$(M+H)^+$.

[Reference Example 23] 4-(7-Methoxy-2-oxoquinoxalin-1(2*H*)-yl)butanal

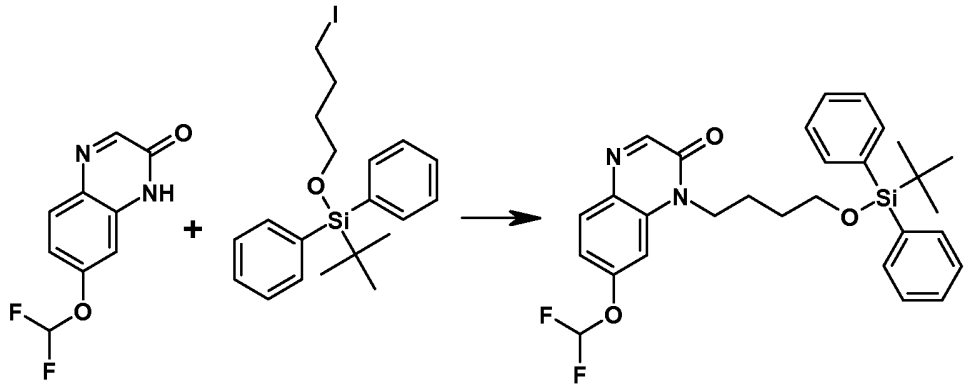
[Formula 47]



To a stirred solution of 1-(4-hydroxybutyl)-7-methoxyquinoxalin-2(1*H*)-one (0.2 g, 0.080 mol) in dichloromethane (10 ml), Dess Martin periodinane (0.683 g, 0.161 mol) was added portion wise at 0 °C under argon atmosphere and the reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was cooled to 0 °C and its pH was adjusted to 7 by adding saturated sodium bicarbonate solution, followed by saturated sodium thiosulphate solution (15 ml). The two layers were separated and the aqueous layer was extracted with dichloromethane. The dichloromethane layers were pooled, dried over anhydrous sodium sulphate and concentrated to dryness. The crude product (0.2 g) obtained was used as such for next step.

[Reference Example 24] 1-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)-7-difluoromethoxyquinoxalin-2(1*H*)-one

[Formula 48]



To a stirred solution of 7-difloromethoxyquinoxalin-2(1*H*)-one (1 g, 0.47 mol) in dry *N,N*-dimethylformamide (10 ml), lithium hydride (0.041 g, 0.51 mol) was added at 0 °C under argon atmosphere and the reaction mixture was stirred at room temperature for about 30 minutes. To this, *tert*-butyl(4-iodobutoxy)diphenylsilane (Reference Example 15, 2.5 g, 0.56 mol) dissolved in dry *N,N*-dimethylformamide (5 ml) was added drop-wise at room temperature then the reaction mixture was allowed to stir overnight. The reaction mixture was

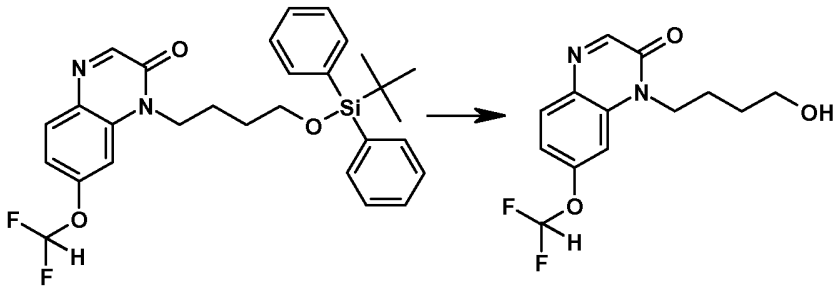
cooled to 0 °C, water (20 ml) was added drop-wise followed by ethyl acetate (20 ml) and it was filtered through a celite. The two layers were separated, ethyl acetate layer was dried and concentrated to dryness. The crude product obtained was purified using Combiflash (ethyl aceate/hexane) to yield 1.0g (40.65%) of the title compound.

^{1}H-NMR(400MHz,$CDCl_3$)δ:0.90(s,9H),1.64(m,2H),1.86(m,2H),3.72(m,2H), 4.22(m,2H),6.58(t,J=72.8Hz,1H),7.07(d,J=2.4Hz,1H),7.10(dd,J=8Hz,J=2.4Hz,1H), 7.42(m,6H),7.64(dd,J=2.4Hz,J=8Hz,4H),7.88(d,J=8Hz,1H),8.24(s,1H).

MS: 523$(M+H)^+$.

[Reference Example 25] 1-(4-hydroxybutyl)-7-difluoromethoxyquinoxalin-2(1*H*)-one

[Formula 49]

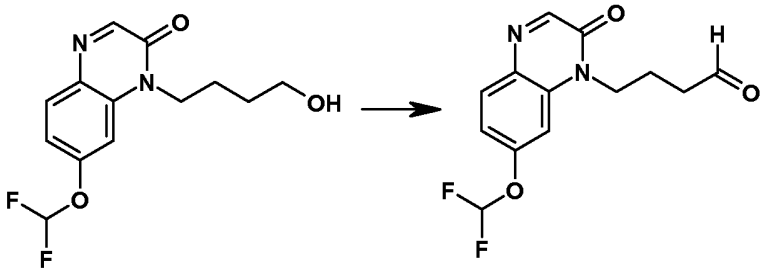


To a stirred solution of 1-(4-{[*tert*-butyl(diphenyl)silyl]oxy}butyl)-7-difluoromethoxyquinoxalin-2(1*H*)-one (1.0 g, 0.383 mol) in dry tetrahydrofuran (10 ml), tetra-*n*-butylammonium fluoride (1M tetrahydrofuran solution; 7.6 ml, 0.766 mol) was added drop-wise at 0 °C under argon atmosphere and the reaction mixture was stirred at room temperature for about 1 hour. The reaction mixture was cooled to 0 °C, water (5 ml) was added drop-wise followed by ethyl acetate (10 ml). The two layers were separated. The ethyl acetate layer was dried and concentrated to dryness. The crude product obtained was purified using Combiflash in (ethyl acetate/hexane) to yield 0.4g (74.07%) of the title compound.

^{1}H-NMR(400MHz,$CDCl_3$)δ:1.69(m,2H),1.85(m,2H),3.77(m,2H),4.27(m,2H),6.58 (dd,J=72.8Hz,1H),7.13(dd,J=8.8Hz,J=2.4Hz,2H),7.88(d,J=8.8Hz,1H),8.25(s,1H).

[Reference Example 26] 4-(7-Difluoromethoxy-2-oxoquinoxalin-1(2*H*)-yl)butanal

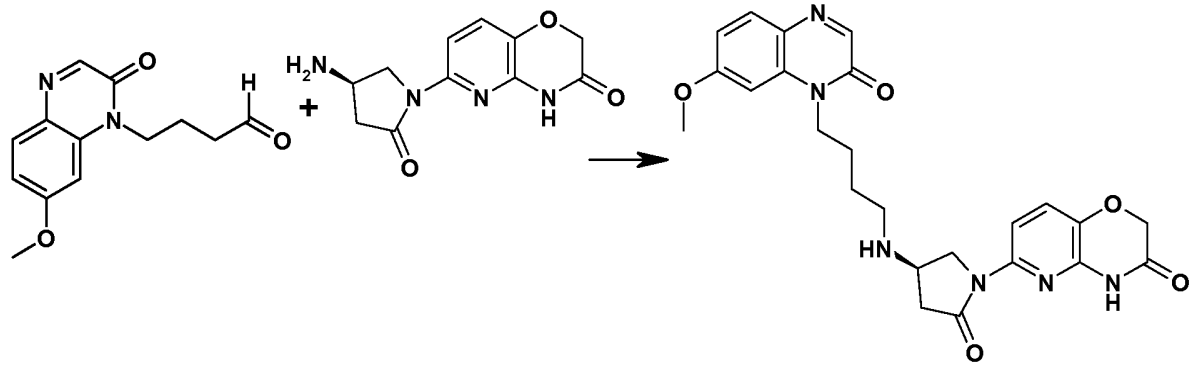
[Formula 50]



To a stirred solution of 1-(4-hydroxybutyl)-7-difluoromethoxyquinoxalin-2(1*H*)-one (0.3 g, 0.105 mol) in dichloromethane (10 ml), Dess Martin Periodinane (0.895 g, 0.211 mol) was added portion wise at 0 °C under argon atmosphere and the reaction mixture was stirred at room temperature for about 2 hours. The reaction mixture was cooled to 0 °C, saturated sodium bicarbonate solution was added till pH was neutral and then saturated sodium thiosulphate solution (10 ml) was added. The two layers were separated, aqueous layer was extracted with dichloromethane (x3), pooled, dried and concentrated to yield the crude product (0.3 g), which was used as such for next step.

[Example 6] 6-[(4*R*)-4-{[4-(7-methoxy-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one

[Formula 51]



A solution of 4-(7-methoxy-2-oxoquinoxalin-1(2*H*)-yl)butanal (Reference Example 23, 0.2 g, 0.08 mol) and 6-[(4*R*)-4-amino-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one (Reference Example 10, 0.201 g, 0.08 mol) in a mixture of tetrahydrofuran and methanol (1:1, 10 ml) was stirred under argon atmosphere for about 30 minutes. The reaction mixture was cooled to 0 °C, sodium triacetoxy borohydride (0.258 g, 1.8 mol) was added portion wise and allowed to stir at room temp for about 2 hours. The reaction mixture was cooled to 0 °C, saturated sodium bicarbonate solution was added till pH was neutral and filtered through a celite. The celite was washed with water (5 ml) and then the organic layer was evaporated. The residue was extracted with methanol (5%) in dichloromethane (x2) and the combined organic extract was dried and concentrated up to dryness. The crude product thus obtained was purified using Combiflash (methanol/dichloromethane) to obtain 0.135g (34.79%) of the title compound.

^{1}H-NMR(400MHz,$CDCl_3$)δ:
1.67(m,2H),1.85(m,2H),2.54(dd,J=4,17.2Hz,1H),2.83(m,3H),3.54(m,1H),3.93(s,3H), 4.05(m,2H),4.25(m,2H),4.60(s,2H),6.76(d,J=2.8Hz,1H),6.90(dd,J=9.2Hz,J=2.4Hz,1H), 7.14(d,8.8Hz,1H),7.78(d,J=8.8Hz,1H),7.91(d,J=8.8Hz,1H), 8.10(s,1H),9.60(bs,1H).
MS: 479$(M+H)^+$ and 477$(M-H)^-$.

[Example 7] 6-[(4*R*)-4-{[4-(7-Difluoromethoxy-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one [0.08 g (21.97%)] was prepared in a similar manner as in Example 6 using 4-(7-difluoromethoxy-2-oxoquinoxalin-1(2*H*)-yl)butanal (Reference Example 26, 0.2 g, 0.070 mol) and 6-[(4*R*)-4-amino-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one (Reference Example 10, 0.175 g, 0.070 mol).

^{1}H-NMR(400MHz,$CDCl_3$)δ:1.69(m,2H),1.85(m,2H),2.54(dd,J=4.4,17.2Hz,1H),2.83(m,3H), 3.54(m,1H),3.93(m,1H),4.05(m,1H),4.25(m,2H),4.60(s,2H),6.63(d,J=72.8Hz,1H),7.10(dd,J=7. 6Hz,2H),7.17(d,8.8Hz,1H),7.88(d,J=9.2Hz,1H),7.93(d,J=8.8Hz,1H),8.22(s,1H),8.9(bs,1H).
MS: 515$(M+H)^+$.

The measurement method of antibacterial activity of the compound of the present invention was carried out in accordance with the standard methods specified by Japanese Society of Chemotherapy, and the results are shown in MIC (μg/mL) (Table 1).

[Table 1]

Compound/bacteria	MRSA DB00026
Example 2	0.125
Example 4	0.03
Example 7	<0.008

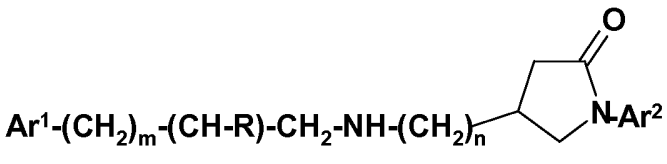
[Industrial Applicability]

The compound of the invention of the present application, a salt thereof, or a hydrate thereof exhibits wide and strong antibacterial activity against Gram-positive bacteria and Gram-negative bacteria, and it also has excellent safety. Thus, the compound of the present invention, a salt thereof, or a hydrate thereof is anticipated to exhibit excellent effects for the treatment and/or prevention of infectious diseases.

Claims:

[Claim 1] A compound represented by the following formula (I) or a salt thereof:

[Formula 1]



(I)

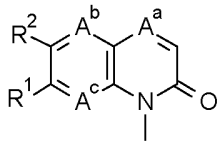
wherein R represents hydrogen atom;

m represents an integer of 1 or 2;

n represents an integer of 0 or 1

Ar^1 represents a bicyclic heterocyclic group represented by the following formula:

[Formula 2]



wherein:

A^a represents nitrogen;

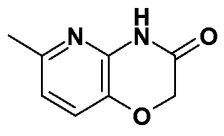
A^b and A^c represent CH;

R^1 represents a methoxy group, a difluoromethoxy group, a halogen atom, or a cyano group;

R^2 represents a hydrogen atom or a halogen atom;

Ar^2 represents a bicyclic heterocyclic group represented by the following formula:

[Formula 3]



[Claim 2] The compound or a salt thereof according to claim [1], wherein the sum of m and n is 1, 2 or 3.

[Claim 3] The compound or a salt thereof according to claim [1] or [2], wherein R^1 represents a methoxy group.

[Claim 4] The compound or a salt thereof according to claim [1] or [2], wherein R^1 represents a difluoromethoxy group.

[Claim 5] The compound or a salt thereof according to claim [1] or [2], wherein R^1 represents a cyano group.

[Claim 6] The compound or a salt thereof according to claim [1] or [2], wherein both R^1 and R^2 represent a halogen atom.

[Claim 7] The compound or a salt thereof according to claim [6], wherein both R^1 and R^2 represent a fluorine atom.

[Claim 8] A compound or salt thereof according to claim [1], which is selected from:

3-Oxo-4-(3-{[(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]amino}propyl)-3,4-dihydroquinoxaline-6-carbonitrile,

3-Oxo-4-[3-({[(3*R*)-5-oxo-1-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)pyrrolidin-3-yl]methyl}amino)propyl]-3,4-dihydroquinoxaline-6-carbonitrile,

6-[(4*R*)-4-({3-[7-(difluoromethoxy)-2-oxoquinoxalin-1(2*H*)-yl]propyl}amino)-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one,

6-{(4*R*)-4-[({3-[7-(difluoromethoxy)-2-oxoquinoxalin-1(2*H*)-yl]propyl}amino)methyl]-2-oxopyrrolidin-1-yl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one,

6-[(4*R*)-4-{[4-(6,7-difluoro-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-2-one,

6-[(4*R*)-4-{[4-(7-methoxy-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one,

6-[(4*R*)-4-{[4-(7-Difluoromethoxy-2-oxoquinoxalin-1(2*H*)-yl)butyl]amino}-2-oxopyrrolidin-1-yl]-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one.

[Claim 9] A pharmaceutical agent comprising the compound or a salt thereof according to any of the preceeding claims [1] to [8] as its effective ingredient.

[Claim 10] A therapeutic agent for infectious diseases, which comprises the compound or a salt thereof according to any of the preceeding claims [1] to [8] as its effective ingredient.

[Claim 11] A method for treatment of infectious diseases, which comprises administrating the compound or a salt thereof according to any of the preceeding claims [1] to [8].

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/055160

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/04 A61K31/5383 A61P31/04
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/104159 A1 (ACTELION PHARMACEUTICALS LTD [CH]; HUBSCHWERLEN CHRISTIAN [FR]; RUEEDI) 27 August 2009 (2009-08-27) page 95; claims; examples	1-11
A	WO 2010/041219 A1 (ACTELION PHARMACEUTICALS LTD [CH]; EGGER VERENA [CH]; GUDE MARKUS [CH]) 15 April 2010 (2010-04-15) page 71, line 6 - page 72, line 10; claims; example 26	1-11

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2013	26/11/2013

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

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/055160

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 992 628 A1 (GLAXO GROUP LTD [GB]) 19 November 2008 (2008-11-19) examples 50, 52-55, 61-64, 67-83, 98-102, 113-116, 142-146, 200-230, 231-236, 249, 261, 262, 272, 277 (in particular example 231); page 212, line 1 - page 213, line 15; claims	1-11
A	WO 02/070540 A2 (SMITHKLINE BEECHAM CORP [US]; AUBART KELLY M [US]; XIANG JIA-NING [US]) 12 September 2002 (2002-09-12) page 29; claims; examples	1-11
A	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KANBAK, SEDA AKSU ET AL: "Synthesis of new 4(1H)-pyridinone derivatives and their", XP002715469, retrieved from STN Database accession no. 2009:1301870 abstract & KANBAK, SEDA AKSU ET AL: "Synthesis of new 4(1H)-pyridinone derivatives and their", REVISTA DE CHIMIE (BUCHAREST, ROMANIA) (2009), 60(9), 888-892 CODEN: RCBUAU; ISSN: 0034-7752, 2009,	1-11
X,P	WO 2012/108376 A1 (DAIICHI SANKYO CO LTD [JP]; INAGAKI HIROAKI; FUJISAWA TETSUNORI; ITOH) 16 August 2012 (2012-08-16) examples	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/055160

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2009104159 A1	27-08-2009
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		EP 2346862 A1	27-07-2011
		ES 2395491 T3	13-02-2013
		JP 2012505201 A	01-03-2012
		US 2011195949 A1	11-08-2011
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		EA 200970140 A1	30-06-2009
		EP 1992628 A1	19-11-2008
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