

[Document name] SPECIFICATION

[Title of the invention] Process for production of 1-substituted-2-pyridone-3-carboxylic acid derivative

[Technical field]

[0001]

The present invention relates to a 2-pyridone-3-carbamoyl derivatives having excellent cannabinoid receptor agonist activity, and important intermediates thereof.

[Background art]

[0002]

Patent documents 1 and 2 describe that 2-pyridone-3-carbamoyl derivatives have excellent cannabinoid receptor agonist activity and are useful for allergic diseases. Patent document 3 describes that 2-pyridone-3-carbamoyl derivatives have 5-HT₄ receptor agonist activity. Patent documents 1 to 3 describe a process for producing a 1-substituted-2-pyridone-3-carboxylic acid derivative which is an important intermediate in production of a 2-pyridone-3-carbamoyl derivative, and a process for producing a 2-pyridone-3-carbamoyl derivative from the intermediate, however, there is a room for improvement in reaction yield and/or in operation for obtaining a compound with high purity.

[Patent document 1]

International Publication No.02/53543 pamphlet

[Patent document 2]

International Publication No.2006/046778 pamphlet

[Patent document 3]

International Publication No.2005/073222 pamphlet

[Disclosure of the invention]

[Problem to be solved by the invention]

[0003]

It is an object of the invention to provide simple and convenient process for producing a 2-pyridone-3-carbamoyl derivative having cannabinoid receptor agonist activity and a 1-substituted-2-pyridone-3-carboxylic acid derivative which is an important intermediate thereof.

[Means for solving the problem]

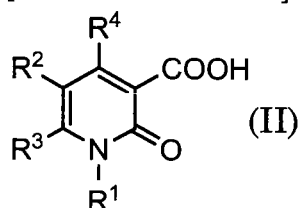
[0004]

In light of these points, the present inventors made diligent efforts, and found process for producing a 2-pyridone-3-carbamoyl derivative having excellent cannabinoid receptor agonist activity, and a 1-substituted-2-pyridone-3-carboxylic acid derivative which is an important intermediate thereof, in a simple and convenient manner with high yield and high purity.

[0005]

That is, the present invention relates to 1) a process for producing a compound represented by general formula (II):

[Chemical formula 2]



wherein



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R¹ represents alkyl which may be substituted with a non-reactive substituent, alkenyl which may be substituted with a non-reactive substituent, or alkynyl which may be substituted with a non-reactive substituent;

R² and R³ each independently represent alkyl, alkyloxyalkyl or alkyloxy; or

R² and R³ taken together with the adjacent carbon atom may form cycloalkene; and

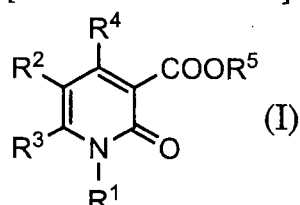
R⁴ represents a hydrogen atom or hydroxy,

comprising Step A and Step B:

[Step A]

hydrolyzing a compound represented by general formula (I):

[Chemical formula 1]



wherein R¹, R², R³, and R⁴ are as defined above, and R⁵ represents alkyl, and

[Step B]

adding alcohol to the hydrolysate of the compound represented by general formula (I) generated in Step A, to obtain a compound represented by general formula (II).

Step A may be conducted in the presence of acid or in the presence of base. When Step A is conducted in the presence of base, acid may be also added after treatment with base. Also in Step B, acid may be added.

The present invention also relates to the following 2) to 18).

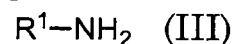
2) The process as described in 1), wherein Step A and Step B are sequentially conducted.

3) The process as described in 1) or 2), further comprising Step C and Step D:

[Step C]

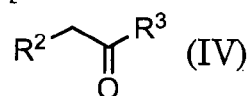
reacting a compound represented by general formula (III):

[Chemical formula 3]



wherein R¹ is as defined in 1), with a compound represented by general formula (IV):

[Chemical formula 4]

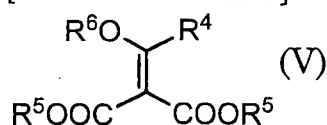


wherein R² and R³ are as defined in 1); and

[Step D]

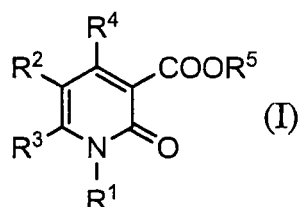
reacting a compound generated in Step C with a compound represented by general formula (V):

[Chemical formula 5]



wherein R⁴ and R⁵ are as defined in 1); and R⁶ represents alkyl, to generate the compound represented by general formula (I):

[Chemical formula 6]



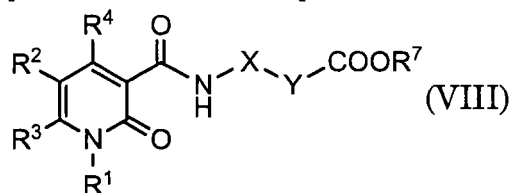
wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in 1).

4) The process as described in 3), wherein R^6 is C1-C2 alkyl.

5) The process as described in any one of 1) to 4), wherein R^5 is C1-C2 alkyl.

6) A process for producing a compound represented by general formula (VIII):

[Chemical formula 14]



wherein R^1 , R^2 , R^3 , and R^4 are as defined in 1); and

R^7 represents a hydrogen atom or alkyl;

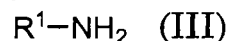
X represents alkylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, alkenylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, alkynylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, cycloalkanediyl which may be substituted with a non-reactive substituent, cycloalkenediyl which may be substituted with a non-reactive substituent, aryldiyl which may be substituted with a non-reactive substituent, heteroaryldiyl which may be substituted with a non-reactive substituent, or nonaromatic heterocyclic diyl which may be substituted with a non-reactive substituent; and

Y represents a single bond, alkylene which may be substituted with a non-reactive substituent, alkenylene which may be substituted with a non-reactive substituent, or alkynylene which may be substituted with a non-reactive substituent, comprising Step C, Step D, Step A, Step B, Step E, and Step F:

[Step C]

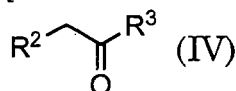
reacting a compound represented by general formula (III):

[Chemical formula 7]



wherein R^1 is as defined in 1), with a compound represented by general formula (IV):

[Chemical formula 8]

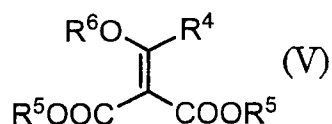


wherein R^2 and R^3 are as defined in 1);

[Step D]

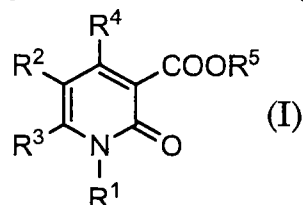
reacting a compound generated in Step C with a compound represented by general formula (V):

[Chemical formula 9]



wherein R^4 and R^5 are as defined in 1); and R^6 is as defined in 3), to generate a compound represented by general formula (I):

[Chemical formula 10]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in 1);

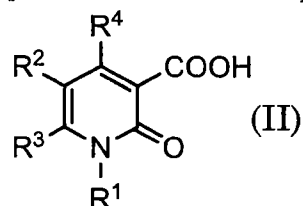
[Step A]

hydrolyzing the compound represented by general formula (I);

[Step B]

adding alcohol to hydrolysate of the compound represented by general formula (I) generated in Step A, to obtain a compound represented by general formula (II):

[Chemical formula 11]

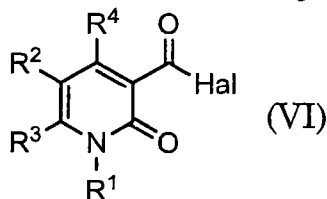


wherein R^1 , R^2 , R^3 , and R^4 are as defined in 1);

[Step E]

reacting the compound represented by general formula (II) with a halogenating reagent, to generate a compound represented by general formula (VI):

[Chemical formula 12]

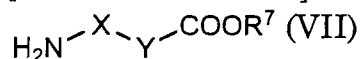


wherein R^1 , R^2 , R^3 and R^4 are as defined in 1); and Hal represents a halogen atom; and

[Step F]

reacting the compound represented by general formula (VI) with a compound represented by general formula (VII):

[Chemical formula 13]



wherein R^7 , X, and Y are as defined above, and subjecting to hydrolysis as needed.

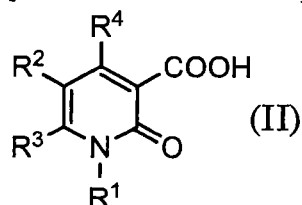
7) The process as described in 6), wherein Step E and Step F are sequentially conducted.

8) The process as described in 6) or 7), wherein Hal is a chlorine atom.

9) The process as described in any one of 6) to 8), wherein R^7 is C1-C2 alkyl.

10) The process as described in any one of 6) to 9), wherein X is alkylene, cycloalkanediyl, arylidiyl, heteroaryldiyl or nonaromatic heterocyclic diyl.

- 11) The process as described in any one of 6) to 10), wherein Y represents a single bond or alkylene.
- 12) The process as described in any one of 3) to 11), wherein Step C, Step D, Step A and Step B are sequentially conducted.
- 13) The process as described in any one of 1) to 12), wherein the compound represented by general formula (II) is obtained in the form of crystals.
- 14) The process as described in any one of 1) to 13), wherein R⁴ is a hydrogen atom.
- 15) The process as described in any one of 1) to 14), wherein R² is C1-C3 alkyl or C1-C3 alkyloxy.
- 16) The process as described in any one of 1) to 15), wherein R³ is C1-C3 alkyl or C1-C3 alkyloxy C1-C3 alkyl.
- 17) The process as described in any one of 1) to 15), wherein R² and R³, taken together with the adjacent carbon atom form cyclooctene.
- 18) The process as described in any one of 1) to 17), wherein R¹ is alkyl which may be substituted with a non-reactive substituent.
- 19) The process as described in any one of 1) to 16) and 18), wherein R¹ is alkyl which may be substituted with a non-reactive substituent, R² is C1-C3 alkyl, R³ is C1-C3 alkyl, R⁴ is a hydrogen atom, and R⁵ is C1-C2 alkyl.
- 20) The process as described in any one of 1) to 14) and 17) to 18), wherein R¹ is alkyl which may be substituted with a non-reactive substituent, R² and R³ taken together with the adjacent carbon atom form cyclooctene, R⁴ is a hydrogen atom, and R⁵ is C1-C2 alkyl.
- 21) The process as described in any one of 1) to 20), wherein the alcohol added to the hydrolysate is isopropanol.
- 22) A process for producing crystals of a compound represented by general formula (II):
[Chemical formula 15]



wherein R¹, R², R³ and R⁴ are as defined in 1), wherein alcohol is added to a solution containing a compound represented by general formula (II).

As a solvent in the solution, a solvent selected from aromatic hydrocarbons (e.g., toluene, xylene), aliphatic carboxylic acid esters (e.g., ethyl acetate, methyl acetate, and butyl acetate), ethers (e.g., diethylether, tetrahydrofuran), ketones (e.g., acetone, ethylmethylketone), N,N-dimethylacetamide, N-methylpyrrolidone, and water may be used as single or in combination.

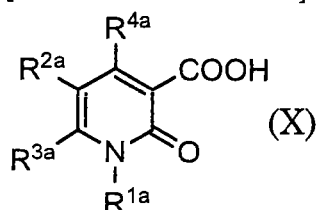
- 23) The process as described in 22), wherein the alcohol is isopropanol.

[0006]

Also, the present invention involves the following (1) to (19).

- (1) A process for producing a compound represented by general formula (X):

[Chemical formula 16]



wherein

R^{1a} represents alkyl which may be substituted with a non-reactive substituent, alkenyl which may be substituted with a non-reactive substituent, or alkynyl which may be substituted with a non-reactive substituent;

R^{2a} and R^{3a} each independently represent alkyl, alkyloxyalkyl or alkyloxy; or

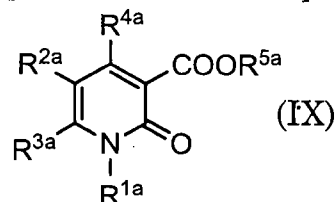
R^{2a} and R^{3a} taken together with the adjacent carbon atom may form cycloalkene; and

R^{4a} represents a hydrogen atom or hydroxy; comprising Step Aa and Step Ba:

[Step Aa]

hydrolyzing a compound represented by general formula (IX):

[Chemical formula 15]



wherein R^{1a} , R^{2a} , R^{3a} , and R^{4a} are as defined above; and R^{5a} represents alkyl, and

[Step Ba]

adding alcohol to the hydrolysate of the compound represented by general formula (IX) generated in Step Aa, to generate crystals of a compound represented by general formula (X).

Step Aa may be conducted in the presence of acid or in the presence of base. When Step Aa is conducted in the presence of base, acid may be added after treatment with base.

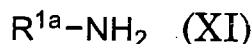
(2) The process as described in (1), wherein Step Aa and Step Ba are sequentially conducted.

(3) The process as described in (1) or (2), further comprising Step Ca and Da:

[Step Ca]

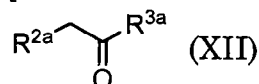
reacting a compound represented by general formula (XI):

[Chemical formula 17]



wherein R^{1a} is as defined in (1), with a compound represented by general formula (XII):

[Chemical formula 18]

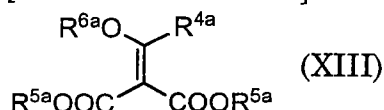


wherein R^{2a} and R^{3a} are as defined in (1); and

[Step Da]

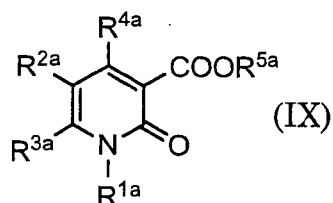
reacting a compound generated in Step Ca with a compound represented by general formula (XIII):

[Chemical formula 19]



wherein R^{4a} and R^{5a} are as defined in (1); and R^6 represents alkyl, to generate a compound represented by general formula (IX):

[Chemical formula 20]



wherein R^{1a} , R^{2a} , R^{3a} , R^{4a} and R^{5a} are as defined in (1).

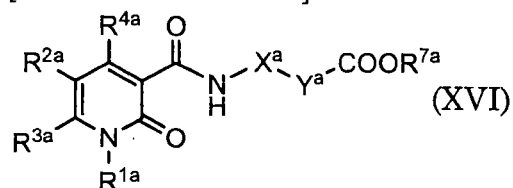
(4) The process as described in (3), wherein Step Ca, Step Da, Step Aa, and Step Ba are sequentially conducted in this order.

(5) The process as described in (3) or (4), wherein R^{6a} is C1-C2 alkyl.

(6) The process as described in any one of (1) to (5), wherein R^{5a} is C1-C2 alkyl.

(7) A process for producing a compound represented by general formula (XVI):

[Chemical formula 28]



wherein R^{1a} , R^{2a} , R^{3a} and R^{4a} are as defined in (1); and

R^{7a} represents a hydrogen atom or alkyl;

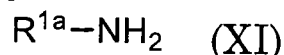
X^a represents alkylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, alkenylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, alkynylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, cycloalkanediyl which may be substituted with a non-reactive substituent, cycloalkenediyl which may be substituted with a non-reactive substituent, aryldiyl which may be substituted with a non-reactive substituent, heteroaryldiyl which may be substituted with a non-reactive substituent, or nonaromatic heterocyclic diyl which may be substituted with a non-reactive substituent; and

Y^a represents a single bond, alkylene which may be substituted with a non-reactive substituent, alkenylene which may be substituted with a non-reactive substituent, or alkynylene which may be substituted with a non-reactive substituent, comprising Step Ca, Step Da, Step Aa, Step Ba, Step Ea, and Step Fa:

[Step Ca]

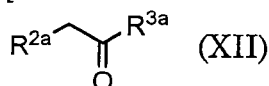
reacting a compound represented by general formula (XI):

[Chemical formula 21]



wherein R^{1a} is as defined in (1), with a compound represented by general formula (XII):

[Chemical formula 22]

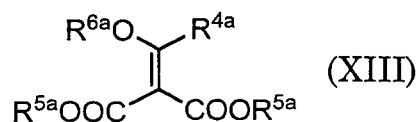


wherein R^{2a} and R^{3a} are as defined in (1);

[Step Da]

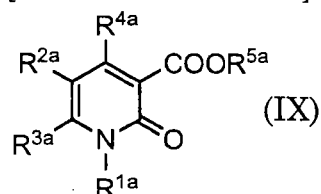
reacting a compound generated in Step Ca with a compound represented by general formula (XIII):

[Chemical formula 23]



wherein R^{4a} and R^{5a} are as defined in (1); and R^{6a} is as defined in (3), to generate a compound represented by general formula (IX):

[Chemical formula 24]



wherein R^{1a} , R^{2a} , R^{3a} , R^{4a} and R^{5a} are as defined in (1);

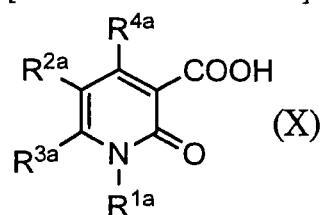
[Step Aa]

hydrolyzing the compound represented by general formula (IX);

[Step Ba]

adding alcohol to the hydrolysate of the compound represented by general formula (IX) generated in Step Aa, to obtain a compound represented by general formula (X):

[Chemical formula 25]

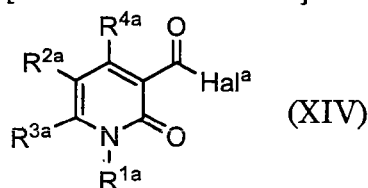


wherein R^{1a} , R^{2a} , R^{3a} and R^{4a} are as defined in (1);

[Step Ea]

reacting the compound represented by general formula (X) with a halogenating reagent to generate a compound represented by general formula (XIV):

[Chemical formula 26]

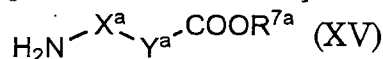


wherein R^{1a} , R^{2a} , R^{3a} and R^{4a} are as defined in (1); and Hal^a represents a halogen atom) and

[Step Fa]

reacting the compound represented by general formula (XIV) with a compound represented by general formula (XV):

[Chemical formula 27]



wherein R^{7a} , X^a , and Y^a are as defined above, and subjecting to hydrolysis as needed.

(8) The process as described in (7), wherein Step Ca, StepDa, StepAa and StepBa are sequentially conducted.

(9) The process as described in (7), wherein Step Ea and StepFa are sequentially conducted.

(10) The process as described in any one of (7) to (9), wherein Hal^a is a chlorine atom.

(11) The process as described in any one of (7) to (10), wherein R^{7a} is C1-C2 alkyl.

- (12) The process as described in any one of (7) to (11), wherein X^a is alkylene, cycloalkanediyl, aryldiyl, heteroaryldiyl or nonaromatic heterocyclic diyl.
- (13) The process as described in any one of (7) to (12), wherein Y^a is a single bond or alkylene.
- (14) The process as described in any one of (1) to (13), wherein R^{4a} is a hydrogen atom.
- (15) The process as described in any one of (1) to (14), wherein R^{2a} is C1-C2 alkyl or C1-C2 alkyloxy.
- (16) The process as described in any one of (1) to (15), wherein R^{3a} is C1-C3 alkyl or C1-C2 alkyloxy C1-C2 alkyl.
- (17) The process as described in any one of (1) to (14), wherein R^{2a} and R^{3a} taken together with the adjacent carbon atom form cyclooctene.
- (18) The process as described in any one of (1) to (17), wherein R^{1a} is alkyl which may be substituted with a non-reactive substituent.
- (19) The process as described in any one of (1) to (18), wherein the alcohol added to the hydrolysate is isopropanol.
- [0007]

Hereinafter, meanings of various terms will be explained. Each term is used in the unified meaning throughout the specification, and has the same meaning when used as single or in combination with other term.

In the present specification, "hetero atom" means oxygen atom, sulfur atom, or nitrogen atom.

In the present specification, "halogen atom" means fluorine atom, chlorine atom, bromine atom or iodine atom.

In the present specification, "alkyl" comprises straight- or branched-chain monovalent hydrocarbons having 1 to 8 carbon atom(s). Example thereof can include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, n-heptyl and n-octyl and the like. C1-C6 alkyl is preferable. When the number of carbons is particularly specified, "alkyl" having carbon number within the range of the number is meant.

As "alkyl" of R^1 and R^{1a} , C1-C6 alkyl is preferred.

As "alkyl" of R^2 and R^{2a} , C1-C4 alkyl is preferred, C1-C3 alkyl is more preferred, and C1-C2 alkyl is most preferred.

As "alkyl" of R^3 and R^{3a} , C1-C4 alkyl is preferred.

As "alkyl" of R^5 and R^{5a} , C1-C4 alkyl is preferred, and C1-C3 alkyl is more preferred.

As "alkyl" of R^6 and R^{6a} , C1-C4 alkyl is preferred, and C1-C2 alkyl is more preferred.

In the present specification, "alkyloxyalkyl" means a group in which different carbon atoms in the "alkyl" are substituted with one or two "alkyloxy" described later. Example thereof can include methyloxymethyl, ethyloxymethyl, n-propyloxymethyl, isopropyloxymethyl, n-butyloxymethyl, 2-methyloxyethyl, 2-ethyloxyethyl, 2-n-propyloxyethyl, 1-isopropyloxyethyl, 1-n-butyloxyethyl, 3-methyloxypropyl, 3-ethyloxypropyl, 3-n-propyloxypropyl, 2-isopropyloxypropyl, 2-n-butyloxypropyl and the like. C1-C4 alkyloxy C1-C4 alkyl can be preferred. C1-C2 alkyloxy C1-C2 alkyl can be more preferred. When the number of carbons is particularly specified, "alkyloxyalkyl" having carbon number within the range of the number is meant.

As "alkyloxyalkyl" of R^2 and R^{2a} , C1-C4 alkyloxy C1-C4 alkyl is preferred, and C1-C2 alkyloxy C1-C2 alkyl is more preferred.

As "alkyloxyalkyl" of R^3 and R^{3a} , C1-C4 alkyloxy C1-C4 alkyl is preferred, and C1-C2 alkyloxy C1-C2 alkyl is more preferred.

In the present specification, "alkenyl" comprises straight- or branched-chain monovalent hydrocarbon groups having 2 to 8 carbon atoms and having one or more double bond(s). Example thereof can include vinyl, allyl, 1-propenyl, 2-butenyl, 2-pentenyl,

2-hexenyl, 2-heptenyl, 2-octenyl and the like. C2-C6 alkenyl is preferred. When the number of carbons is particularly specified, "alkenyl" having carbon number within the range of the number is meant.

As "alkenyl" of R^1 and R^{1a} , C2-C6 alkenyl is preferred.

In the present specification, "alkynyl" comprises straight- or branched-chain monovalent hydrocarbon groups having 2 to 8 carbon atoms and having one or more triple bond(s). Example thereof can include ethynyl, 1-propynyl, 2-propynyl, 2-butylnyl, 2-pentynyl, 2-hexynyl, 2-heptynyl, 2-octynyl and the like. C2-C6 alkynyl is preferred. When the number of carbons is particularly specified, "alkynyl" having carbon number within the range of the number is meant.

As "alkynyl" of R^1 and R^{1a} , C2-C6 alkynyl is preferred.

In the present specification, "cycloalkyl" comprises cycloalkyls having 3 to 8 carbon atoms. Example thereof can include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. C3-C6 cycloalkyl is preferred. When the number of carbons is particularly specified, "cycloalkyl" having carbon number within the range of the number is meant.

In the present specification, "cycloalkenyl" comprises cycloalkenyls having 3 to 8 carbon atoms. Example thereof can include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. C3-C6 cycloalkenyl is preferred. When the number of carbons is particularly specified, "cycloalkenyl" having carbon number within the range of the number is meant.

In the present specification, "cycloalkene" in phrase of " R^2 and R^3 taken together with the adjacent carbon atom may form cycloalkene" comprises 5 to 10-membered cycloalkene having only one double bond between the carbon atom adjacent to R^2 and the carbon atom adjacent to R^3 . Example thereof can include cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclononene, and cyclodecene. C5-C8 cycloalkene is preferred. Cyclooctene is more preferred. When the number of carbons is particularly specified, "cycloalkenyl" having carbon number within the range of the number is meant.

In the present specification, "cycloalkene" in phrase of " R^{2a} and R^{3a} taken together with the adjacent carbon atom may form cycloalkene" comprises 5 to 10-membered cycloalkene having only one double bond between the carbon atom adjacent to R^{2a} and the carbon atom adjacent to R^{3a} . Example thereof can include cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclononene, and cyclodecene. C5-C8 cycloalkene is preferred. Cyclooctene is more preferred. When the number of carbons is particularly specified, "cycloalkenyl" having carbon number within the range of the number is meant.

In the present specification, "alkyloxy" means a group in which "alkyl" as defined above is substituted with one oxygen atom. Example thereof can include methyloxy, ethyloxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy, n-pentyloxy, isopentyloxy, 2-pentyloxy, 3-pentyloxy, n-hexyloxy, isohexyloxy, 2-hexyloxy, 3-hexyloxy, n-heptyloxy, n-octyloxy and the like. C1-C6 alkyloxy is preferred. C1-C4 alkyloxy is more preferred. When the number of carbons is particularly specified, "alkyloxy" having carbon number within the range of the number is meant.

As "alkyloxy" of R^2 and R^{2a} , C1-C4 alkyloxy is preferred, and C1-C2 alkyloxy is more preferred.

As "alkyloxy" of R^3 and R^{3a} , C1-C4 alkyloxy is preferred.

In the present specification, "alkenyloxy" means a group in which "alkenyl" as defined above is substituted with one oxygen atom. Example thereof can include vinyloxy, allyloxy, 1-propenyloxy, 2-butenyloxy, 2-pentenyloxy, 2-hexenyloxy, 2-heptenyloxy, 2-octenyloxy and the like. C2-C6 alkenyloxy is preferred. C2-C4 alkenyloxy is more preferred. When the number of carbons is particularly specified, "alkenyloxy" having carbon number within the

range of the number is meant.

In the present specification, "alkynyloxy" means a group in which "alkynyl" as defined above is substituted with one oxygen atom. Example thereof can include ethynyloxy, 1-propynyloxy, 2-propynyloxy, 2-butyloxy, 2-pentyloxy, 2-hexynyloxy, 2-heptyloxy, 2-octynyloxy and the like. C2-C6 alkynyloxy is preferred. C2-C4 alkynyloxy is more preferred. When the number of carbons is particularly specified, "alkynyloxy" having carbon number within the range of the number is meant.

In the present specification, "cycloalkyloxy" means a group in which "cycloalkyl" as defined above is substituted with one oxygen atom. Example thereof can include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, and cyclooctyloxy. C3-C6 cycloalkyloxy is preferred. When the number of carbons is particularly specified, "cycloalkyloxy" having carbon number within the range of the number is meant.

In the present specification, "alkylthio" means a group in which "alkyl" as defined above is substituted with one sulfur atom. Example thereof can include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, n-pentylthio, isopentylthio, 2-pentylthio, 3-pentylthio, n-hexylthio, isohexylthio, 2-hexylthio, 3-hexylthio, n-heptylthio, n-octylthio and the like. C1-C6 alkylthio is preferred. C1-C4 alkylthio is more preferred. When the number of carbons is particularly specified, "alkylthio" having carbon number within the range of the number is meant.

In the present specification, "alkenylthio" means a group in which "alkenyl" as defined above is substituted with one sulfur atom. Example thereof can include vinylthio, allylthio, 1-propenylthio, 2-butenylthio, 2-pentenylthio, 2-hexenylthio, 2-heptenylthio, 2-octenylthio and the like. C2-C6 alkenylthio is preferred. C2-C4 alkenylthio is more preferred. When the number of carbons is particularly specified, "alkenylthio" having carbon number within the range of the number is meant.

In the present specification, "alkynylthio" means a group in which "alkynyl" as defined above is substituted with one sulfur atom. Example thereof can include ethynylthio, 1-propynylthio, 2-propynylthio, 2-butylnylthio, 2-pentylnylthio, 2-hexynylthio, 2-heptylnylthio, 2-octynylthio and the like. C2-C6 alkynylthio is preferred. C2-C4 alkynylthio is more preferred. When the number of carbons is particularly specified, "alkynylthio" having carbon number within the range of the number is meant.

In the present specification, "cycloalkylthio" comprises a group in which "cycloalkyl" as defined above is substituted with one sulfur atom. Example thereof can include cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cycloheptylthio, and cyclooctylthio. C3-C6 cycloalkylthio is preferred. When the number of carbons is particularly specified, "cycloalkylthio" having carbon number within the range of the number is meant.

In the present specification, "alkylene" means straight- or branched-chain alkylene having 1 to 10 carbon atom(s). Example thereof can include methylene, 1-methyl methylene, 1,1-dimethyl methylene, ethylene, 1-methylethylene, 1-ethylethylene, 1,1-dimethylethylene, 1,2-dimethylethylene, 1,1-diethylethylene, 1,2-diethylethylene, 1-ethyl-2-methylethylene, trimethylene, 1-methyltrimethylene, 2-methyltrimethylene, 1,1-dimethyltrimethylene, 1,2-dimethyltrimethylene, 2,2-dimethyltrimethylene, 1-ethyltrimethylene, 2-ethyltrimethylene, 1,1-diethyltrimethylene, 1,2-diethyltrimethylene, 2,2-diethyltrimethylene, 2-ethyl-2-methyltrimethylene, tetramethylene, 1-methyl tetramethylene, 2-methyl tetramethylene, 1,1-dimethyl tetramethylene, 1,2-dimethyl tetramethylene, 2,2-dimethyl tetramethylene, 2,2-di-n-propyltrimethylene, 1-isobutylethylene, 1-(2,2-dimethylpropyl) methylene, 1-t-butylethylene, 1-isobutyltrimethylene and the like. When the number of carbons is particularly specified, "alkylene" having carbon number within the range of the number is meant.

In the present specification, the phrase of "alkylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent" means a group in which methylene moiety in alkylene of "alkylene which may be substituted with a non-reactive substituent" defined below may be substituted with "hetero atom" as defined above in non-adjacent one or two sites. Examples of "alkylene which may be intervened by a hetero atom" can include methylene, 1-methyl methylene, 1,1-dimethyl methylene, ethylene, 1-methylethylene, 1-ethylethylene, 1,1-dimethylethylene, 1,2-dimethylethylene, 1,1-diethylethylene, 1,2-diethylethylene, 1-ethyl-2-methylethylene, trimethylene, 1-methyltrimethylene, 2-methyltrimethylene, 1,1-dimethyltrimethylene, 1,2-dimethyltrimethylene, 2,2-dimethyltrimethylene, 1-ethyltrimethylene, 2-ethyltrimethylene, 1,1-diethyltrimethylene, 1,2-diethyltrimethylene, 2,2-diethyltrimethylene, 2-ethyl-2-methyltrimethylene, tetramethylene, 1-methyl tetramethylene, 2-methyl tetramethylene, 1,1-dimethyl tetramethylene, 1,2-dimethyl tetramethylene, 2,2-dimethyl tetramethylene, 2,2-di-n-propyltrimethylene, 1-isobutylethylene, 1-(2,2-dimethylpropyl) methylene, 1-t-butylethylene, 1-isobutyltrimethylene, methyleneoxy methylene, methylenethio methylene, methylene (N-methylamino) methylene, ethyleneoxy methylene, ethylenethio methylene, ethylene (N-methylamino) methylene, methyleneoxyethylene, methylenethioethylene, methylene (N-methylamino)ethylene, trimethyleneoxy methylene, trimethyleneoxyethylene, trimethyleneoxytrimethylene, 1-isobutyl methyleneoxy methylene, 1-(2,2-dimethylpropyl) methyleneoxy methylene, 1-t-butyl methyleneoxy methylene, 1-isobutylethyleneoxy methylene, and 1-isobutyl methyleneoxyethylene. When the number of carbons is particularly specified, "alkylene which may be intervened by a hetero atom" having carbon number within the range of the number is meant.

In the present specification, "alkenylene" means straight- or branched-chain alkenylene having 2 to 10 carbon atoms. Example thereof can include ethenylene, 1-methyl ethenylene, 1-ethyl ethenylene, 1,2-dimethyl ethenylene, 1,2-diethyl ethenylene, 1-ethyl-2-methyl ethenylene, propenylene, 1-methyl-2-propenylene, 2-methyl-2-propenylene, 1,1-dimethyl-2-propenylene, 1,2-dimethyl-2-propenylene, 1-ethyl-2-propenylene, 2-ethyl-2-propenylene, 1,1-diethyl-2-propenylene, 1,2-diethyl-2-propenylene, 1-butenylene, 2-butenylene, 1-methyl-2-butenylene, 2-methyl-2-butenylene, 1,1-dimethyl-2-butenylene, 1,2-dimethyl-2-butenylene, 1-isobutyl ethenylene, 1-(2,2-dimethylpropyl)-2-propenylene, 1-t-butyl-2-propenylene, 1-isobutyl-2-propenylene and the like. When the number of carbons is particularly specified, "alkenylene" having carbon number within the range of the number is meant.

The phrase of "alkenylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent" means a group in which methylene moiety of alkylene in "alkenylene which may be substituted with a non-reactive substituent" defined below may be substituted with "hetero atom" as defined above in one or two positions that are not adjacent. Examples of "alkenylene which may be intervened by a hetero atom" can include ethenylene, 1-methyl ethenylene, 1-ethyl ethenylene, 1,2-dimethyl ethenylene, 1,2-diethyl ethenylene, 1-ethyl-2-methyl ethenylene, propenylene, 1-methyl-2-propenylene, 2-methyl-2-propenylene, 1,1-dimethyl-2-propenylene, 1,2-dimethyl-2-propenylene, 1-ethyl-2-propenylene, 2-ethyl-2-propenylene, 1,1-diethyl-2-propenylene, 1,2-diethyl-2-propenylene, 1-butenylene, 2-butenylene, 1-methyl-2-butenylene, 2-methyl-2-butenylene, 1,1-dimethyl-2-butenylene, 1,2-dimethyl-2-butenylene, 1-isobutyl ethenylene, 1-(2,2-dimethylpropyl)-2-propenylene, 1-t-butyl-2-propenylene, 1-isobutyl-2-propenylene, 1-methyl-2-butenyleneoxy methylene, 1-isobutyl-2-butenyleneoxy methylene, 1-(2,2-dimethylpropyl)-2-butenyleneoxy methylene, 1-t-butyl-2-butenyleneoxy methylene and the like. When the number of carbons is particularly specified, "alkenylene

which may be intervened by a hetero atom" having carbon number within the range of the number is meant.

In the present specification, "alkynylene" means straight- or branched-chain alkynylene having 2 to 10 carbon atoms. Example thereof can include ethynylene, propynylene, 1-methyl-2-propynylene, 1-ethyl-2-propynylene, butynylene, 1-methyl-2-butynylene, 2-methyl-3-butynylene, 1,1-dimethyl-2-butynylene, 1,2-dimethyl-3-butynylene, 2,2-dimethyl-3-butynylene, 1-isobutyl ethynylene, 1-(2,2-dimethylpropyl)-propynylene, 1-t-butyl-propynylene, 1-isobutyl-propynylene and the like. When the number of carbons is particularly specified, "alkynylene" having carbon number within the range of the number is meant.

In the present specification, the phrase of "alkynylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent" means a group in which methylene moiety in alkylene of "alkynylene which may be substituted with a non-reactive substituent" defined below may be substituted with "hetero atom" as defined above in one or two positions that are not adjacent. Examples of "alkynylene which may be intervened by a hetero atom" can include ethynylene, propynylene, 1-methyl-2-propynylene, 1-ethyl-2-propynylene, butynylene, 1-methyl-2-butynylene, 2-methyl-3-butynylene, 1,1-dimethyl-2-butynylene, 1,2-dimethyl-3-butynylene, 2,2-dimethyl-3-butynylene, 1-isobutyl ethynylene, 1-(2,2-dimethylpropyl)-propynylene, 1-t-butyl-propynylene, 1-isobutyl-propynylene, 1-methyl-2-butynyleneoxy methylene, 1-isobutyl-2-butynyleneoxy methylene, 1-(2,2-dimethylpropyl)-2-butynyleneoxy methylene, 1-t-butyl-2-butynyleneoxy methylene and the like. When the number of carbons is particularly specified, "alkynylene which may be intervened by a hetero atom" having carbon number within the range of the number is meant.

In the present specification, "aryl" comprises monocyclic or fused cyclic aromatic hydrocarbons. This may be fused at every possible position with the above "cycloalkyl", the above "cycloalkenyl", or "nonaromatic heterocyclic group" defined below. In both cases where aryl is a monocyclic ring and a fused cyclic ring, binding can occur at every position. Example thereof can include phenyl, 1-naphthyl, 2-naphthyl, anthranyl, tetrahydronaphthyl, 1,3-benzodioxolyl, and 1,4-benzodioxanyl. Phenyl, 1-naphthyl, and 2-naphthyl are preferred. Phenyl is more preferred.

In the present specification, "heteroaryl" comprises 5- to 6-membered aromatic rings containing at least one atom optionally selected from oxygen atom, sulfur atom and nitrogen atom in the ring. This may be fused at every possible position with the above "cycloalkyl", the above "aryl", "nonaromatic heterocyclic group" defined below or other heteroaryl. In both cases where heteroaryl is a monocyclic ring and a fused cyclic ring, binding can occur at every position. Example thereof can include pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), imidazolyl (e.g., 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl), oxazolyl (e.g., 2-oxazolyl), thiazolyl (e.g., 2-thiazolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrazinyl (e.g., 2-pyrazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl), tetrazolyl (e.g., 1H-tetrazolyl), oxadiazolyl (e.g., 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), indolizinyl (e.g., 2-indolizinyl, 6-indolizinyl), isoindolyl (e.g., 2-isoindolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), indazolyl (e.g., 3-indazolyl), purinyl (e.g., 8-purinyl), quinolizinyl (e.g., 2-quinolizinyl), isoquinolyl (e.g., 3-isoquinolyl), quinolyl (e.g., 2-quinolyl, 5-quinolyl), phthalazinyl (e.g., 1-phthalazinyl), naphthylidinyl (e.g., 2-naphthylidinyl), quinolanyl (e.g., 2-quinolanyl), quinazolinyl (e.g., 2-quinazolinyl), cinnolinyl (e.g., 3-cinnolinyl), pteridinyl (e.g., 2-pteridinyl), carbazolyl (e.g., 2-carbazolyl, 4-carbazolyl), phenanthridinyl (e.g., 2-phenanthridinyl, 3-phenanthridinyl), acridinyl (e.g., 1-acridinyl, 2-acridinyl),

dibenzofuranyl (e.g., 1-dibenzofuranyl, 2-dibenzofuranyl), benzoimidazolyl (e.g., 2-benzoimidazolyl), benzoisoxazolyl (e.g., 3-benzoisoxazolyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzoxadiazolyl (e.g., 4-benzoxadiazolyl), benzoisothiazolyl (e.g., 3-benzoisothiazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzofuryl (e.g., 3-benzofuryl), benzothienyl (e.g., 2-benzothienyl), dibenzothienyl (e.g., 2-dibenzothienyl), and benzodioxolyl (e.g., 1,3-benzodioxolyl).

In the present specification, "nonaromatic heterocyclic group" comprises 3- to 12-membered nonaromatic heterocyclic groups containing at least one nitrogen atom in the ring, and optionally containing an oxygen atom and/or a sulfur atom. Example thereof can include pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolynyl, pyrazolidinyl, pyrazolynyl, piperidinyl, dihydropyridinyl, tetrahydropyridinyl, piperadynyl, dihydropyrazinyl, tetrahydropyrazinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, and perhydropyrimidinyl.

In the present specification, "aryloxy" comprises groups in which the above "aryl" is substituted with one oxygen atom. Example thereof can include phenyloxy, naphthyloxy and the like.

In the present specification, "arylthio" comprises groups in which the above "aryl" is substituted with one sulfur atom. Example thereof can include phenylthio, naphthylthio and the like.

In the present specification, "heteroaryloxy" comprises groups in which the above "heteroaryl" is substituted with one oxygen atom. Example thereof can include pyrrolyloxy, furyloxy, thienyloxy, imidazolyloxy, pyrazolyloxy, isothiazolyloxy, isoxazolyloxy, oxazolyloxy, thiazolyloxy, pyridyloxy, pyrazinyloxy, pyrimidinyloxy, pyridazinyloxy, tetrazolyloxy, oxadiazolyloxy, thiadiazolyloxy, indolizinyloxy, isoindolyloxy, indolyloxy, indazolyloxy, purinyloxy, quinolizinyloxy, isoquinolyloxy, quinolyloxy, phthalazinyloxy, naphthyridinyloxy, quinolanyloxy, quinazolinyloxy, cinnolinyl oxy, pteridinyl oxy, carbazolyloxy, phenanthridinyl oxy, acridinyloxy, dibenzofuranyloxy, benzoimidazolyloxy, benzoisoxazolyloxy, benzoxazolyloxy, benzoxadiazolyloxy, benzoisothiazolyloxy, benzothiazolyloxy, benzofuryloxy, benzothienyloxy, dibenzothienyloxy, benzodioxolyloxy and the like. Furyloxy, thienyloxy, imidazolyloxy, pyrazolyloxy, isothiazolyloxy, isoxazolyloxy, oxazolyloxy, thiazolyloxy, pyridyloxy, pyrazinyloxy, pyrimidinyloxy, pyridazinyloxy and the like are preferred.

In the present specification, "heteroarylthio" comprises groups in which the above "heteroaryl" is substituted with one sulfur atom. Example thereof can include pyrrolylthio, furylthio, thienylthio, imidazolythio, pyrazolythio, isothiazolythio, isoxazolythio, oxazolythio, thiazolythio, pyridylthio, pyrazinylthio, pyrimidinylthio, pyridazinylthio, tetrazolythio, oxadiazolythio, thiadiazolythio, indolizinythio, isoindolythio, indolythio, indazolythio, purinylthio, quinolizinythio, isoquinolythio, quinolythio, phthalazinylthio, naphthyldinylthio, quinolanythio, quinazolinythio, cinnolinyl thio, pteridinyl thio, carbazolythio, phenanthridinyl thio, acridinylthio, dibenzofuranylthio, benzoimidazolythio, benzoisoxazolythio, benzoxazolythio, benzoxadiazolythio, benzoisothiazolythio, benzothiazolythio, benzofurylthio, benzothienylthio, dibenzothienylthio, benzodioxolythio and the like. Furylthio, thienylthio, imidazolythio, pyrazolythio, isothiazolythio, isoxazolythio, oxazolythio, thiazolythio, pyridylthio, pyrazinylthio, pyrimidinylthio, pyridazinylthio and the like are preferred.

In the present specification, "cycloalkanediyl" means a group having another one bonding hand in the above "cycloalkyl". Example thereof can include cyclopentanedyl, cyclohexanedyl, and cyclooctanedyl.

In the present specification, "cycloalkenediyl" means a group having another one bonding site in the above "cycloalkenyl". Example thereof can include 1-cyclopentenediyl, 1-cyclohexenediyl, 1-cyclooctenediyl and the like.

In the present specification, "aryldiyl" means a group having another one bonding site

in the above "aryl". Example thereof can include phenylene and naphthalenediyl.

In the present specification, "heteroaryldiyl" means a group having another one bonding site in the above "heteroaryl". Example thereof can include pyrrolediyl, furandiyl, thiophenediyl, pyrazolediyl, imidazolediyl, isothiazolediyl, isoxazolediyl, oxazolediyl, thiazolediyl, pyrazinediyl, pyrimidinediyl, pyridazinediyl, oxadiazolediyl, thiadiazolediyl, indolidinediyl, isoindolediyl, indolediyl, indazolediyl, purinediyl, quinolidinediyl, isoquinolidinediyl, quinolidinediyl, phthalazinediyl, naphthyridinediyl, quinolanediyl, quinazoline diyl, cinnolidinediyl, pteridinediyl, carbazolediyl, phenanthridinediyl, acridinediyl, dibenzofurandiyl, benzoxazolonediyl, benzoxadinonediyl, benzoimidazolediyl, benzoisoxazolediyl, benzoxazolediyl, benzoxadiazolediyl, benzoisothiazolediyl, benzothiazolediyl, benzofurandiyl, benzothiophenediyl, dibenzothiophenediyl, benzodioxolanediyl and the like.

In the present specification, "nonaromatic heterocyclic diyl" means a group having another one bonding site in the above "nonaromatic heterocyclic group". Example thereof can include pyrrolidinediyl, pyrrolinediyl, imidazolidinediyl, imidazolidinediyl, pyrazolidinediyl, pyrazolidinediyl, piperidinediyl, dihydropyridinediyl, tetrahydropyridinediyl, piperazinediyl, dihydropyrazinediyl, tetrahydropyrazinediyl, dihydropyrimidinediyl, tetrahydropyrimidinediyl, perhydropyrimidinediyl, tetrahydrofurandiyl, tetrahydrothiophenediyl, N-methylpyrrolidinediyl, tetrahydropyrandiyl, N-methylperhydropyridinediyl and the like.

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In the present specification, example of a non-reactive substituent in "alkyl which may be substituted with a non-reactive substituent" includes trihalomethyl, cycloalkyl optionally substituted with one or two substituent(s) selected from Substituent group A, cycloalkenyl optionally substituted with one or two substituent(s) selected from Substituent group A, alkyloxy optionally substituted with one or two substituent(s) selected from Substituent group B, cycloalkyloxy optionally substituted with one or two substituent(s) selected from Substituent group A, alkylthio optionally substituted with one or two substituent(s) selected from Substituent group B, cycloalkylthio optionally substituted with one or two substituent(s) selected from Substituent group A, aryl optionally substituted with one to three substituent(s) selected from Substituent group C, heteroaryl optionally substituted with one to three substituent(s) selected from Substituent group C, aryloxy optionally substituted with one to three substituent(s) selected from Substituent group C, heteroaryloxy optionally substituted with one to three substituent(s) selected from Substituent group C, arylthio optionally substituted with one to three substituent(s) selected from Substituent group C, heteroarylthio optionally substituted with one to three substituent(s) selected from Substituent group C, pyrrolidino, piperidino, morpholino and the like, and these may be substituted by one or two substituent(s).

Substituent group A: C1-C4 alkyl, trihalomethyl, C1-C4 alkyloxy, C1-C4 alkylthio, phenyl optionally substituted with one to three substituent(s) selected from Substituent group C, phenoxy optionally substituted with one to three substituent(s) selected from Substituent group C, heteroaryl

Substituent group B: trihalomethyl, C1-C4 alkyloxy, C1-C4 alkylthio, phenyl optionally substituted with one to three substituent(s) selected from Substituent group C, phenoxy optionally substituted with one to three substituent(s) selected from Substituent group C, heteroaryl

Substituent group C: halogen atom, C1-C4 alkyl, trihalomethyl, C1-C4 alkyloxy, C1-C4 alkylthio, phenyl optionally substituted by one to three substituent(s) selected from Substituent group C, phenoxy optionally substituted by one to three substituent(s) selected from Substituent group C, heteroaryl

In the present specification, examples of a non-reactive substituent in "alkenyl which may be substituted with a non-reactive substituent", "alkynyl which may be substituted with a non-reactive substituent", "alkylene which may be substituted with a non-reactive substituent", "alkenylene which may be substituted with a non-reactive substituent", and "alkynylene which may be substituted with a non-reactive substituent" include trihalomethyl, cycloalkyl optionally substituted with one or two substituent(s) selected from above Substituent group A, cycloalkenyl optionally substituted with one or two substituent(s) selected from above Substituent group A, aryl optionally substituted with one to three substituent(s) selected from Substituent group C, heteroaryl optionally substituted with one to three substituent(s) selected from Substituent group C and the like, and these may be substituted by one or two substituent(s).

In the present specification, examples of non-reactive substituents in "cycloalkanediyl which may be substituted with a non-reactive substituent" and "cycloalkenediyl which may be substituted with a non-reactive substituent" include alkyl optionally substituted with one or two substituent(s) selected from above Substituent group B, trihalomethyl, cycloalkyl optionally substituted with one or two substituent(s) selected from above Substituent group A, cycloalkenyl optionally substituted with one or two substituent(s) selected from above Substituent group A, aryl optionally substituted with one to three substituent(s) selected from above Substituent group C, heteroaryl optionally substituted with one to three substituent(s) selected from above Substituent group C and the like, and these may be substituted with one or two substituent(s).

In the present specification, examples of substituents in "aryldiyl which may be substituted with a non-reactive substituent", "heteroaryldiyl which may be substituted with a non-reactive substituent", and "nonaromatic heterocyclic diyl which may be substituted with a non-reactive substituent" include halogen atom, alkyl optionally substituted with one or two substituent(s) selected from above Substituent group B, trihalomethyl, cycloalkyl optionally substituted with one or two substituent(s) selected from above Substituent group A, alkyloxy optionally substituted with one or two substituent(s) selected from above Substituent group B, cycloalkyloxy optionally substituted with one or two substituent(s) selected from above Substituent group A, alkylthio optionally substituted with one or two substituent(s) selected from above Substituent group B, cycloalkylthio optionally substituted with one or two substituent(s) selected from above Substituent group A, aryl optionally substituted with one to three substituent(s) selected from above Substituent group C, heteroaryl optionally substituted with one to three substituent(s) selected from above Substituent group C, aryloxy optionally substituted with one to three substituent(s) selected from above Substituent group C, heteroaryloxy optionally substituted with one to three substituent(s) selected from above Substituent group C, arylthio optionally substituted with one to three substituent(s) selected from above Substituent group C, heteroarylthio optionally substituted with one to three substituent(s) selected from above Substituent group C and the like, and these may be substituted with one or two substituent(s).

In the present specification, "non-reactive substituent" means a substituent that will cause no reaction during reaction in any of Step A to Step F. For example, the substituents as shown above are recited.

In the present specification, "hydrolysate of compound represented by general formula (I)" means a compound represented by general formula (II) or its metal salt (metal is sodium, potassium or lithium) of carboxylic acid.

In the present specification, "hydrolysate of compound represented by general formula (IX)" means a compound represented by general formula (X) or its metal salt (metal is sodium, potassium or lithium) of carboxylic acid.

In the present specification, "hydrolysis" embraces hydrolysis in acidic condition, and

hydrolysis in basic condition. In the case of hydrolysis in basic condition, acid may be also added.

In the present specification, "adding alcohol to hydrolysate" embraces the following cases: 1) after hydrolysis, the reaction solution is extracted with an organic solvent, and alcohol is added to the resultant organic phase; 2) after hydrolysis, an organic solvent is added to the reaction solution and then separated, and alcohol is added to the resultant aqueous phase; 3) after hydrolysis, acid is added to the reaction solution and then extracted with an organic solvent, and alcohol is added to the resultant organic phase; 4) after hydrolysis, acid is added to the reaction solution and an organic solvent is added and then separated, and alcohol is added to the resultant aqueous phase; 5) after hydrolysis, the reaction solution is extracted with an organic solvent, and alcohol and acid are added to the resultant organic layer; and 6) after hydrolysis, an organic solvent is added to the reaction solution and then separated, and alcohol and acid are added to the resultant aqueous phase. As necessary, the solution may be concentrated and/or diluted.

In the present specification, "sequentially conducting Step A and StepB" means that the compound generated after reaction of Step A is used in next Step B without being isolated.

In the present specification, "sequentially conducting Step Aa and Step Ba" means that the compound generated after reaction of Step Aa is used in next Step Ba without being isolated.

In the present specification, "sequentially conducting Step C, Step D, Step A, and Step B" means that the compound generated after reaction of each of Step C, Step D and Step A is respectively used in next Step D, Step A, and Step B without being isolated.

In the present specification, "sequentially conducting Step Ca, Step Da, Step Aa, and Step Ba" means that the compound generated after reaction of each of Step Ca, Step Da and Step Aa is respectively used in next Step Da, Step Aa, and Step Ba without being isolated.

In the present specification, "sequentially conducting Step E and Step F" means that the compound generated after reaction of Step E is used in next Step F without being isolated.

In the present specification, "sequentially conducting Step Ea and Step Fa" means that the compound generated after reaction of Step Ea is used in next Step Fa without being isolated.

[0009]

Preferred substituent groups for R^1 to R^7 , X, Y, and Hal in compounds represented by general formulas (I), (II), (III), (IV), (V), (VI), (VII), and (VIII) are shown by (Ia) to (IIb). Compounds of possible combinations thereof are preferred.

As R^1 , (Ia) alkyl which may be substituted with a non-reactive substituent, alkenyl which may be substituted with a non-reactive substituent, or alkynyl which may be substituted with a non-reactive substituent is preferred, (Ib) alkyl which may be substituted with a non-reactive substituent is more preferred, and (Ic) alkyl which may be substituted with one or two substituent(s) selected from Substituent group D is most preferred.

Substituent group D: trifluoromethyl, C1-C4 alkyloxy, C5-C6 cycloalkyl, phenyl substituted with one to two halogen atom(s), and morpholino

As R^2 , (Id) alkyl, alkyloxyalkyl, or alkyloxy is preferred, (Ie) alkyl or alkyloxy is more preferred, and (If) C1-C3 alkyl is most preferred.

As R^3 , (Ig) alkyl, alkyloxyalkyl, or alkyloxy is preferred, (Ih) alkyl or alkyloxyalkyl is preferred, and (Ii) C1-C3 alkyl is most preferred.

Alternatively, R^2 and R^3 taken together with the adjacent carbon atom form preferably (Ij) 5 to 10-membered cycloalkene having one double bond, and more preferably (Ik) cyclooctene.

As R^4 , (Il) a hydrogen atom or hydroxyl is preferred, and (Im) a hydrogen atom is more preferred.

As R⁵, (In) alkyl is preferred, and (Io) C1-C2 alkyl is more preferred.

As R⁶, (Ip) alkyl is preferred, and (Iq) C1-C2 alkyl is more preferred.

As R⁷, (Ir) a hydrogen atom or alkyl is preferred, and (Is) C1-C2 alkyl is more preferred.

As X, (It) alkylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, alkenylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, alkynylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, cycloalkanediyl which may be substituted with a non-reactive substituent, cycloalkenediyl which may be substituted with a non-reactive substituent, aryldiyl which may be substituted with a non-reactive substituent, heteroaryldiyl which may be substituted with a non-reactive substituent, or nonaromatic heterocyclic diyl which may be substituted with a non-reactive substituent is preferred, and (Iu) alkylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, cycloalkanediyl which may be substituted with a non-reactive substituent, aryldiyl which may be substituted with a non-reactive substituent, heteroaryldiyl which may be substituted with a non-reactive substituent, or nonaromatic heterocyclic diyl which may be substituted with a non-reactive substituent is more preferred, and (Iv) cycloalkanediyl, aryldiyl, heteroaryldiyl which may be substituted with halogen atom, or tetrahydropyrandiyl is most preferred.

As Y, (Iw) a single bond, alkylene which may be substituted with a non-reactive substituent, alkenylene which may be substituted with a non-reactive substituent, or alkynylene which may be substituted with a non-reactive substituent is preferred, (Ix) a single bond or alkylene is more preferred, and (Iy) a single bond or (Iz) C1-C2 alkylene is most preferred.

As Hal, (IIa) halogen atom is preferred, and (IIb) a chlorine atom is more preferred.
[0010]

Preferred substituent groups for R^{1a} to R^{7a}, X^a, Y^a and Hal^a in compounds represented by general formulas (XI), (X), (XI), (XII), (XIII), (XIV), (XV) and (XVI) are shown by (Iaa) to (IIba). Compounds of possible combinations of these are preferred.

As R^{1a}, (Iaa) alkyl which may be substituted with a non-reactive substituent, alkenyl which may be substituted with a non-reactive substituent, or alkynyl which may be substituted with a non-reactive substituent is preferred, (Iba) alkyl which may be substituted with a non-reactive substituent is more preferred, and (Ica) alkyl which may be substituted with one to two substituent(s) selected from Substituent group D is most preferred.

Substituent group D^a: trifluoromethyl, C1-C4 alkyloxy, C5-C6 cycloalkyl, phenyl substituted by one to two halogen atom(s), and morpholino

As R^{2a}, (Ida) alkyl, alkyloxyalkyl, or alkyloxy is preferred, (Iea) alkyl or alkyloxy is more preferred, and (Ifa) C1-C2 alkyl is most preferred.

As R^{3a}, (Iga) alkyl, alkyloxyalkyl, or alkyloxy is preferred, (Iha) alkyl or alkyloxyalkyl is more preferred, and (Iia) C1-C3 alkyl is most preferred.

Alternatively, R^{2a} and R^{3a} taken together with the adjacent carbon atom form (Ija) 5 to 10-membered cycloalkene having one double bond, more preferably (Ika) cyclooctene.

As R^{4a}, (IIa) hydrogen atom or hydroxyl is preferred, and (Ima) a hydrogen atom is more preferred.

As R^{5a}, (Ina) alkyl is preferred, and (Ioa) C1-C2 alkyl is more preferred.

As R^{6a}, (Ipa) alkyl is preferred, and (Iqa) C1-C2 alkyl is more preferred.

As R^{7a}, (Ira) hydrogen atom or alkyl is preferred, and (Isa) C1-C2 alkyl is more preferred.

As X^a, (Ita) alkylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, alkenylene which may be intervened by a hetero

atom and may be substituted with a non-reactive substituent, alkynylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, cycloalkanediyl which may be substituted with a non-reactive substituent, cycloalkenediyl which may be substituted with a non-reactive substituent, aryldiyl which may be substituted with a non-reactive substituent, heteroaryldiyl which may be substituted with a non-reactive substituent, or nonaromatic heterocyclic diyl which may be substituted with a non-reactive substituent is preferred, and (Iua) alkylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, cycloalkanediyl which may be substituted with a non-reactive substituent, aryldiyl which may be substituted with a non-reactive substituent, heteroaryldiyl which may be substituted with a non-reactive substituent, or nonaromatic heterocyclic diyl which may be substituted with a non-reactive substituent is more preferred, and (Iva) cycloalkanediyl, aryldiyl, heteroaryldiyl which may be substituted with a halogen atom, or tetrahydropyrandiyl is most preferred.

As Y^a, (Iwa) a single bond, alkylene which may be substituted with a non-reactive substituent, alkenylene which may be substituted with a non-reactive substituent, or alkynylene which may be substituted with a non-reactive substituent is preferred, and (Ixa) a single bond or alkylene is more preferred, and (Iya) a single bond or (Iza) C1-C2 alkylene is most preferred.

As Hal^a, (IIaa) halogen atom is preferred, and (IIba) chlorine atom is more preferred.

[Effect of the invention]

[0011]

It is useful as a process for obtaining a 2-pyridone-3-carbamoyl derivative having excellent cannabinoid agonist activity and its important intermediate in a simple manner, with high yield and high purity.

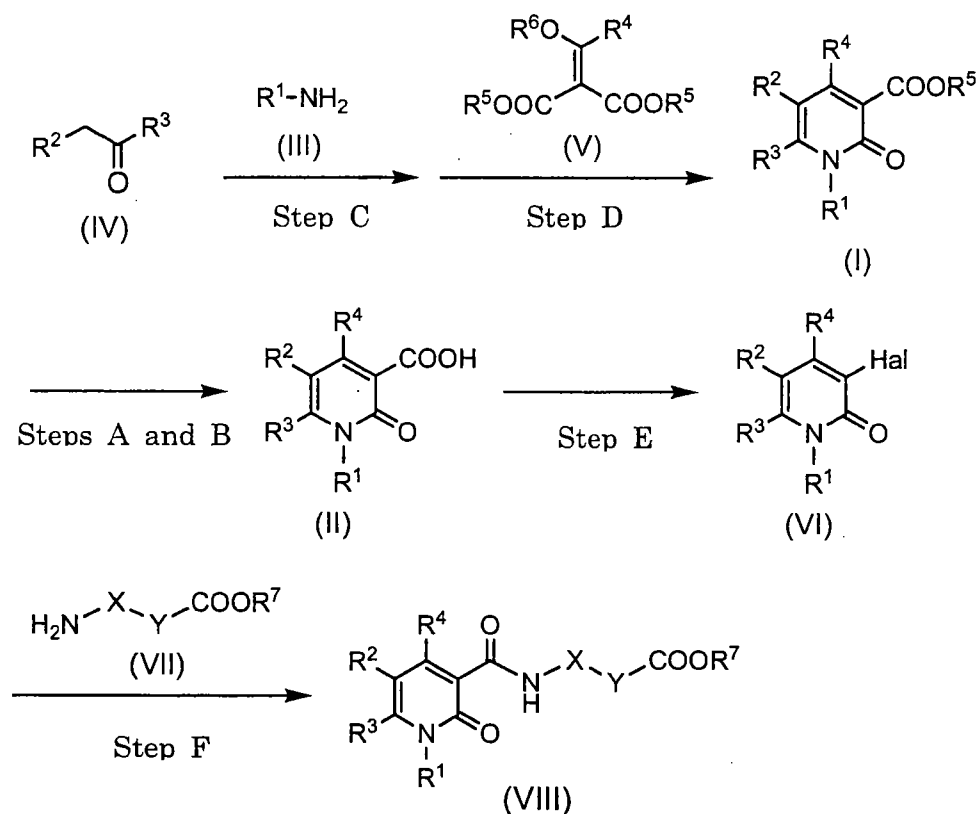
[Best mode for carrying out the invention]

[0012]

A compound of the present invention may be synthesized by any of the methods shown below. In compounds represented by general formulas (I), (II), (III), (IV), (V), (VI), (VII), and (VIII), when they have a asymmetric center, their racemates and/or optically active substances are also involved.

The compounds represented by general formulas (I), (II), (III), (IV), (V), (VI), (VII), and (VIII) may be present in an appropriate salt or solvate form in each step.

[Chemical formula 29]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in 1); R^6 is as defined in 3); R^7 , X, Y, and Hal are as defined in 6).

Step C is a dehydrative condensation step between the compound represented by general formula (IV) and the compound represented by general formula (III).

This step may be carried out in the absence of solvent or in a solvent.

The compound represented by general formula (III) may be used in an amount of 0.1 to 1 mole equivalents, and preferably 0.35 to 0.85 mole equivalents, relative to the compound represented by general formula (IV). When R^2 and R^3 do not cooperate with the adjacent carbon atom, more preferably 0.35 to 0.55 mole equivalents may be used. When R^2 and R^3 together with the adjacent carbon atom form cycloalkene, more preferably 0.65 to 0.85 mole equivalents may be used.

As a reaction solvent, toluene, xylene, chlorobenzene, or mixed solvent thereof, and preferably toluene may be used.

Reaction time may be 30 minutes to 48 hours, and preferably 30 minutes to 10 hours.

Reaction temperature is $50^\circ C$ to the temperature at which reaction solvent is refluxed, and preferably at $100^\circ C$ to the temperature at which reaction solvent is refluxed.

As necessary, acetic acid may be used in an amount of 0.05 to 0.10 mole equivalents, relative to the compound represented by general formula (IV).

After completion of reaction in Step C, the reaction solution may be used in Step D directly or after concentration as is needed. The dehydratively condensed objective compound may be isolated by using a commonly used purification method and used in Step D.

Step D is a ring closure step of the compound obtained in Step C and the compound represented by general formula (V) to generate the compound represented by general formula (I).

This step may be carried out in the absence of solvent or in a solvent.

The compound represented by general formula (V) may be used in an amount of 0.3 to 1.2 mole equivalents, and preferably 0.5 to 1.0 mole equivalents, relative to the compound represented by general formula (IV). When R^2 and R^3 do not cooperate with the adjacent

carbon atom, more preferably 0.55 to 0.75 mole equivalents may be used. When R² and R³ together with the adjacent carbon atom form cycloalkene, more preferably 0.85 to 1.05 mole equivalents may be used.

As a reaction solvent, toluene, xylene, chlorobenzene, or mixed solvent thereof, and preferably toluene may be used.

Reaction time is 30 minutes to 48 hours, and preferably 30 minutes to 16 hours.

Reaction temperature is 50°C to the temperature at which reaction solvent is refluxed, and preferably at 100°C to the temperature at which reaction solvent is refluxed.

After completion of reaction in Step D, the reaction solution may be used in Step A directly or after concentration as is needed. The compound represented by general formula (I) may be used in Step A after extraction, isolation and purification by commonly used methods.

Step A is a step of hydrolyzing the compound represented by general formula (I) obtained in Step D to generate the hydrolysate of the compound represented by general formula (I).

When hydrolysis is conducted in acidic condition, alcohol may be added to the reaction solution and extracted with an organic solvent after hydrolysis. Alternatively, after extracting the reaction solution with an organic solvent, alcohol may be added to the organic phase.

When hydrolysis is conducted in basic condition, acid may be added to the reaction solution to render it acidic after hydrolysis, and then alcohol may be added to the reaction solution and extracted with an organic solvent. Alternatively, after rendering the reaction solution acidic by addition of acid and extracting the reaction solution with an organic solvent, alcohol may be added to the organic phase. When hydrolysate is soluble in the organic phase, alcohol and acid may be added to the organic phase after extracting the reaction solution with an organic solvent. After hydrolysis, the reaction solution may be used directly in the next step, or concentrated as necessary before use in the next step.

As an organic solvent, ethyl acetate, and toluene are preferred.

A) When hydrolysis is conducted in acidic condition, acid may be used in an amount of 0.25 to 10 mole equivalents, and preferably 1 to 3 mole equivalents, relative to the compound represented by general formula (I).

As acid, hydrochloric acid or sulfuric acid may be used. Reaction solvent, reaction time, reaction temperature, precipitation time of crystals, precipitation temperature of crystals and so on may be as same as those of the case where hydrolysis is conducted in basic condition described below.

B) When hydrolysis is conducted in basic condition, the base may be used in an amount of 0.25 to 3 mole equivalents, preferably 0.8 to 2.5 mole equivalents, and more preferably 1.2 to 2 mole equivalents, relative to the compound represented by general formula (I).

As base, sodium hydroxide, potassium hydroxide, or lithium hydroxide, and preferably sodium hydroxide may be used. Base may be used in solid state or as an aqueous solution.

As a reaction solvent, alcohol (methanol, ethanol, n-propanol, or isopropanol)/water or mixed solvent of toluene/alcohol (methanol, ethanol, n-propanol, or isopropanol)/water, and preferably toluene/methanol/water or methanol/water may be used.

Reaction time may be 0.25 to 8 hours, and preferably 0.5 to 2 hours.

Reaction temperature may be 10°C to 70°C, and preferably 20°C to 60°C.

After completion of hydrolysis, the reaction solution may be washed with toluene as needed, to obtain the phase (aqueous phase or organic phase) in which the hydrolysate of the compound represented by general formula (I) is dissolved.

As acid to be added to the reaction solution or the phase in which the hydrolysate of the compound represented by general formula (I) is dissolved, hydrochloric acid or sulfuric

acid, and preferably sulfuric acid may be used.

Step B is a step of generating crystals of the compound represented by general formula (II) by adding alcohol to hydrolysate of the compound represented by general formula (I) generated in Step A.

As alcohol to be added, methanol, ethanol, n-propanol, isopropanol, or mixed solvent thereof, and preferably isopropanol may be used.

Crystals may be allowed to precipitate for 0.25 to 12 hours, and preferably for 0.25 to 2 hours.

Crystals may be allowed to precipitate at -10°C to 25°C, and preferably at -5°C to 5°C.

Step C, Step D, and Step A may be sequentially conducted without conducting isolation.

Step E is a step of reacting the compound represented by general formula (II) with a halogenating agent to generate the compound represented by general formula (VI).

The halogenating agent may be used in an amount of 0.5 to 2 mole equivalents, and preferably 0.8 to 1.5 mole equivalents, relative to the compound represented by general formula (II).

As a reaction solvent, toluene, tetrahydrofuran, N,N-dimethylformamide, N-methylpyrrolidone, or mixed solvent thereof, and preferably mixed solvent of toluene/N-methylpyrrolidone or tetrahydrofuran/N,N-dimethylformamide may be used.

Reaction time may be 0.25 to 12 hours, and preferably 0.25 to 2 hours.

Reaction temperature may be 10°C to 50°C, and preferably 20°C to 30°C.

After completion of reaction of Step E, the reaction solution may be used in Step F directly or after concentration as needed.

Step F is a step of reacting the compound represented by general formula (VI) with the compound represented by general formula (VII) or its acid salt in the presence of base to generate the compound represented by general formula (VIII).

The compound represented by general formula (VII) or its acid salt may be used in an amount of 0.5 to 2 mole equivalents, and preferably 0.8 to 1.5 mole equivalents, relative to the compound represented by general formula (VI).

As acid salt, hydrochloric acid salt, hydrobromic acid salt, or sulfuric acid salt, and preferably hydrochloric acid salt may be used.

The base may be used in an amount of 0.5 to 2 mole equivalents, and preferably 0.8 to 1.5 mole equivalents, relative to the compound represented by general formula (VI).

As a reaction solvent, toluene, tetrahydrofuran, N,N-dimethylformamide, N-methylpyrrolidone, or mixed solvent thereof, and preferably mixed solvent of toluene/N-methylpyrrolidone or tetrahydrofuran/N,N-dimethylformamide may be used.

Reaction time may be 0.25 to 12 hours, and preferably 0.25 to 2 hours.

Reaction temperature may be 10°C to 50°C, and preferably 20°C to 30°C.

When R⁷ is a hydrogen atom, after completion of reaction in Step F, crystals may be allowed to precipitate. If necessary, crystals may be allowed to precipitate by adding alcohol, and methanol, ethanol, n-propanol, isopropanol, or mixed solvent thereof, preferably isopropanol may be used.

Crystals may be allowed to precipitate for 0.25 to 12 hours, and preferably for 0.25 to 2 hours.

Crystals may be allowed to precipitate at -10°C to 25°C, and preferably at -5°C to 5°C.

When R⁷ is alkyl, likewise Step A, hydrolysis is conducted in acidic condition or in the presence of base, and the compound represented by general formula (VIII) wherein R⁷ is a hydrogen atom can be obtained.

If necessary, likewise Step B, crystals may be allowed to precipitate by adding alcohol, and methanol, ethanol, n-propanol, isopropanol, or mixed solvent thereof, preferably

isopropanol may be used.

Crystals may be allowed to precipitate for 0.25 to 12 hours, and for 0.25 to 2 hours.

Crystals may be allowed to precipitate at -10°C to 25°C, and preferably at -5°C to 5°C.

[0013]

In the present specification, "solvate" comprises, for example, solvate with organic solvent, hydrate and the like. When solvate with organic solvent is formed, it may be coordinated with an arbitrary number of organic solvent molecules. When hydrate is formed, it may be coordinated with an arbitrary number of water molecules. Hydrate is preferred.

In the present specification, examples of "salts of the compounds represented by general formulas (I), (II), (III), (IV), (V), (VI), (VII), and (VIII)" include salts of the compounds represented by general formula (I), (II), (III), (IV), (V), (VI), (VII), and (VIII) with alkaline metal (lithium, sodium, potassium and the like), alkaline earth metal (magnesium, calcium and the like), ammonium, organic base and amino acid, or inorganic acid (hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and the like), and organic acid (acetic acid, citric acid, maleic acid, fumaric acid, benzene sulfonic acid, para toluene sulfonic acid and the like). These salts may be formed by commonly used methods.

[0014]

X-ray diffraction patterns of the crystals of the compounds represented by general formula (II) and general formula (VIII) generated by the aforementioned process may be obtained by powder X-ray analysis.

The crystals are easy to handle in conducting the above production process, or in producing a pharmaceutical composition containing the compound represented by formula (VIII) as an active ingredient, and have high purity, so that they are useful crystals for production of pharmaceutical composition.

X-ray diffraction patterns of the crystals of the compounds represented by formula (II) and formula (VIII) will be shown in later-described Examples 1 to 20 (X-ray diffraction measuring condition: tube lamp CuK α ray, tube voltage 40Kv, tube current 40 mA or 50 mA, $d\sin\theta = n\lambda$ (n is an integer, d is lattice spacing (unit: angstrom), θ is diffraction angle (unit: degree))).

These crystals are characterized by respective diffraction angle or lattice spacing.

[0015]

Hereinafter, the present invention will be explained in more detail by way of Examples and Test Examples, however, the present invention will not be limited thereto.

In Examples, the following abbreviations will be used.

Me: methyl

Et: ethyl

DMF: N,N-dimethylformamide

THF: tetrahydrofuran

DMSO: dimethylsulfoxide

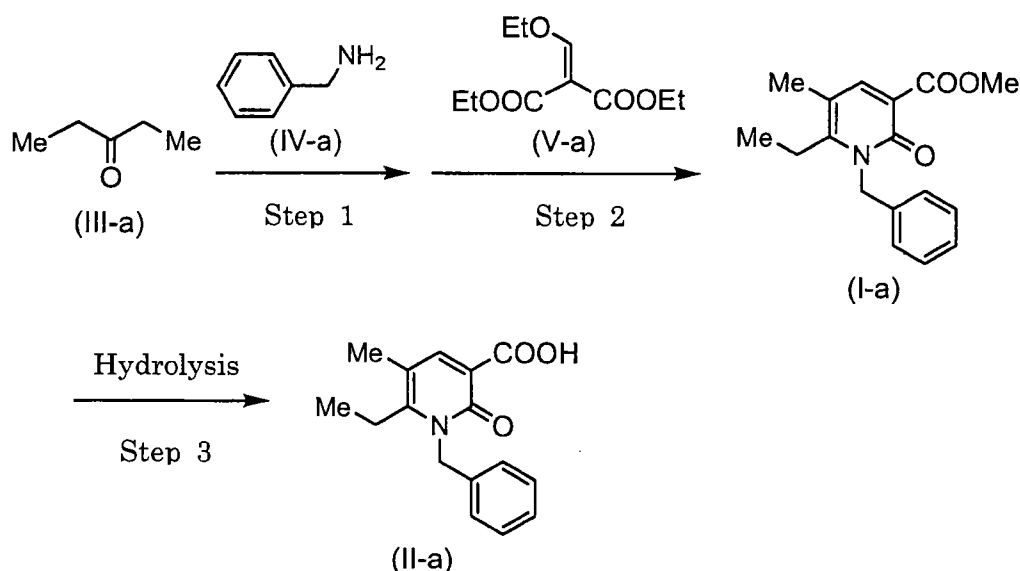
TMS: tetramethylsilane

[Examples]

[0016]

Example 1: Synthesis of Compound (II-a)

[Chemical formula 30]



Step 1

A solution of a compound (III-a, 39.1 g, 0.454 mol) and a compound (IV-a, 20.3 g, 0.189 mol) in toluene (142 mL) was refluxed under dehydrating condition for 5.5 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution. This concentrated solution was used in the next reaction.

Step 2

To the concentrated solution obtained in Step 1 was added a compound (V-a, 61.3 g, 0.283 mol), and stirred at 120°C for 8 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution containing a compound (I-a). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added methanol (60 mL), and 24% sodium hydroxide aqueous solution (38 mL), and stirred at 25°C for 0.5 hour. The reaction solution was concentrated under reduced pressure, and washed with toluene (213 mL). To the aqueous phase were added 61% sulfuric acid (3.3 g), and then 31% sulfuric acid (26 g) to render it acidic, and extracted with ethyl acetate (144 mL). The extract was concentrated under reduced pressure, then 2-propanol (24 mL) was added, and allowed to crystallize at 0°C for 0.5 hour. The precipitated crystals were collected by filtration, and dried to obtain a compound (II-a, 36.6 g, 71.4%).

Melting point: 114°C

NMR (CDCl₃, TMS): 1.18 (t, 3H, J= 7.7), 2.24 (s, 3H), 2.73 (q, 2H, J= 7.5), 5.49 (br s, 2H), 7.09 (m, 2H), 7.29 - 7.38 (m, 3H), 8.38 (s, 1H), 14.53 (br s, 1H)

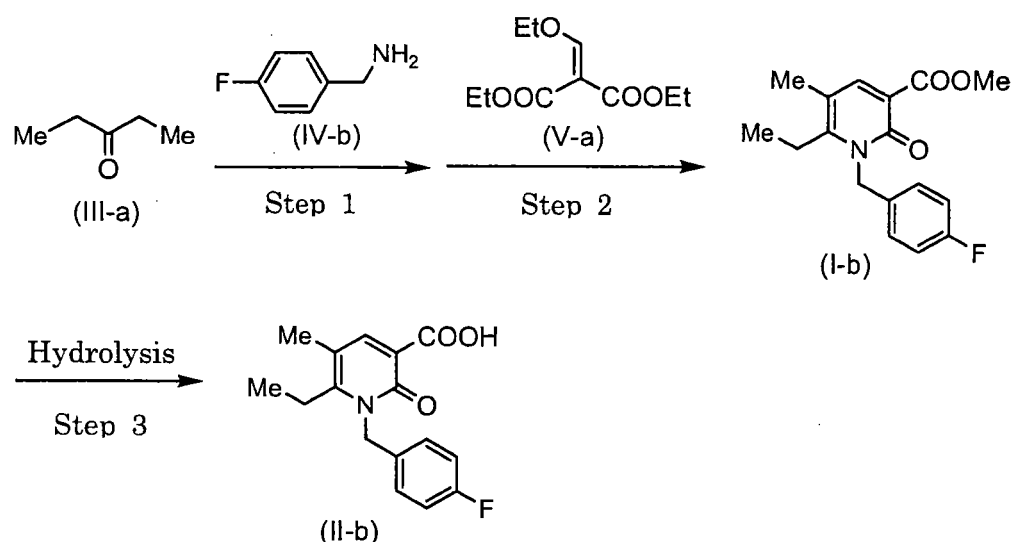
A result of powder X-ray diffraction is shown in Table 1 and Fig. 1.

Diffraction angles of major peaks: 2θ = 10.5, 15.1, 19.5, 21.7, 25.2 degrees

[Table 1]

2θ	Peak search set width	d value	Intensity	Relative intensity
10.240	0.118	8.6314	8850	19
10.540	0.165	8.3864	48120	100
11.540	0.188	7.6618	21325	45
13.600	0.165	6.5055	13748	29
14.080	0.165	6.2848	4192	9
14.340	0.165	6.1714	5617	12
15.100	0.188	5.8625	33417	70
16.380	0.188	5.4071	3875	9
17.280	0.212	5.1275	25265	53
18.100	0.165	4.8970	4247	9
18.620	0.165	4.7614	16650	35
19.160	0.118	4.6284	5147	11
19.460	0.188	4.5577	29203	61
20.200	0.165	4.3924	4033	9
21.480	0.141	4.1335	16787	35
21.740	0.165	4.0846	27045	57
22.040	0.118	4.0297	19158	40
22.220	0.165	3.9974	22852	48
22.800	0.212	3.8971	6607	14
23.220	0.188	3.8275	9807	21
23.580	0.141	3.7699	4500	10
25.220	0.188	3.5283	42992	90
26.160	0.188	3.4036	6208	13
26.500	0.188	3.3607	6187	13
27.420	0.188	3.2500	4648	10
27.860	0.188	3.1997	17108	36
28.460	0.188	3.1336	11918	25
28.960	0.165	3.0806	4882	11
29.520	0.188	3.0234	5660	12
30.260	0.141	2.9512	5187	11
30.500	0.165	2.9285	7170	15
30.940	0.212	2.8878	7727	17
33.180	0.188	2.6978	5917	13
33.480	0.141	2.6743	3375	8
33.580	0.118	2.6666	3507	8
35.120	0.235	2.5531	3668	8
36.540	0.259	2.4571	4177	9
37.840	0.282	2.3756	5530	12
38.800	0.329	2.3190	5273	11

Example 2: Synthesis of Compound (II-b)
[Chemical formula 31]



Step 1

A solution of a compound (III-a, 39.1 g, 0.454 mol) and a compound (IV-b, 23.7g, 0.189 mol) in toluene (142 mL) was refluxed under dehydrating condition for 5 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution. This concentrated solution was used in the next reaction.

Step 2

To the concentrated solution obtained in Step 1 was added a compound (V-a, 61.3 g, 0.283 mol), and stirred at 117°C for 8 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution containing a compound (I-b). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added methanol (60 mL), and 26% sodium hydroxide aqueous solution (43.7 g), and stirred at 25°C for 0.5 hour. The reaction solution was concentrated under reduced pressure, and washed with toluene (213 mL). To the aqueous phase were added 61% sulfuric acid (3.3 g), and then 31% sulfuric acid (26 g) to render it acidic, and extracted with ethyl acetate (144 mL). After washing with water (95 mL), the extract was concentrated under reduced pressure, then 2-propanol (24 mL) was added, and allowed to crystallize at 0°C for 0.5 hour. The precipitated crystals were collected by filtration, and dried to obtain compound (II-b, 35.9 g, 65.6%).

Melting point: 110 to 111°C

NMR (DMSO- d_6 , TMS): 1.05 (t, 3H, J= 7.5), 2.24 (s, 3H), 2.75 (q, 2H, J= 7.5), 5.48 (s, 2H), 7.15 - 7.25 (m, 4H), 8.32 (s, 1H), 14.68 (s, 1H)

A result of powder X-ray diffraction is shown in Table 2 and Fig. 2.

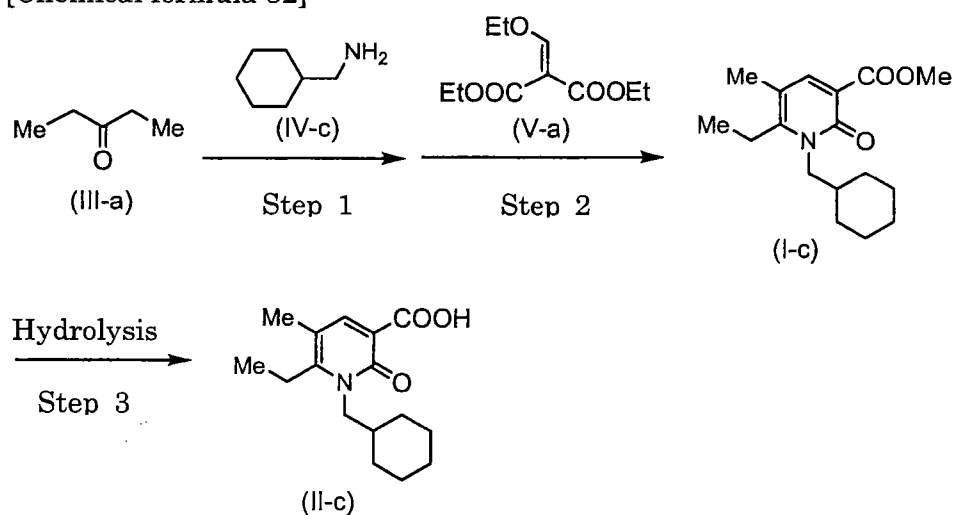
Diffraction angles of major peaks: $2\theta = 13.7, 19.0, 24.2, 26.4, 27.8$ degrees

[Table 2]

2	θ	Peak search set width	d value	Intensity	Relative intensity
10.820	0.188	8.1700	13027	17	
12.200	0.188	7.2487	3957	6	
13.240	0.141	6.6816	17142	23	
13.720	0.306	6.4489	77085	100	
14.580	0.165	6.0704	3063	4	
15.060	0.212	5.8780	5818	8	
15.780	0.165	5.6114	10943	15	
17.160	0.165	5.1631	7473	10	
18.040	0.188	4.9132	27957	37	
18.960	0.188	4.6768	48507	63	
20.440	0.165	4.3414	15035	20	
21.740	0.188	4.0846	9210	12	
22.700	0.141	3.9140	6683	9	
22.900	0.118	3.8803	5162	7	
23.320	0.188	3.8113	7670	10	
24.180	0.212	3.6777	34875	46	
25.140	0.141	3.5394	3605	5	
25.700	0.235	3.4635	18045	24	
26.420	0.188	3.3707	34753	46	
27.760	0.188	3.2110	39982	52	
28.240	0.188	3.1575	3567	5	
29.360	0.188	3.0395	3997	6	
29.820	0.235	2.9937	17890	24	
30.380	0.165	2.9398	4750	7	
31.900	0.118	2.8031	3463	5	
32.160	0.188	2.7810	5760	8	
32.880	0.212	2.7217	5135	7	
33.900	0.212	2.6421	3972	6	
36.380	0.212	2.4675	3473	5	
37.320	0.235	2.4075	4157	6	

Example 3: Synthesis of Compound (II-c)

[Chemical formula 32]



Step 1

A solution of a compound (III-a, 39.1 g, 0.454 mol) and a compound (IV-c, 21.4 g, 0.189 mol) in toluene (142 mL) was refluxed under dehydrating condition for 5 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution. This concentrated solution was used in the next reaction.

Step 2

To the concentrated solution obtained in Step 1 was added a compound (V-a, 61.3 g, 0.283 mol), and stirred at 117°C for 8 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution containing a compound (I-c). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added methanol (60 mL) and 24% sodium hydroxide aqueous solution (38.4 mL), and stirred at 25°C for 0.5 hour. The reaction solution was concentrated under reduced pressure, and washed with toluene (213 mL). To the aqueous phase were added 61% sulfuric acid (3.3 g) and then 31% sulfuric acid (26 g) to render it acidic, and extracted with ethyl acetate (144 mL). After washing with water (95 mL), the extract was concentrated under reduced pressure, then 2-propanol (24 mL) was added, and allowed to crystallize at 0°C for 0.5 hour. The precipitated crystals were collected by filtration, and dried to obtain a compound (II-c, 37.5 g, 71.5%).

Melting point: 131°C

NMR (DMSO- d_6 , TMS): 1.00 - 1.30 (m, 5H), 1.22 (t, 3H, J= 7.5), 1.55 - 1.90 (m, 6H), 2.24 (s, 3H), 2.82 (q, 2H, J= 7.2), 3.90 - 4.20 (m, 2H), 8.29 (s, 1H)

A result of powder X-ray diffraction is shown in Table 3 and Fig. 3.

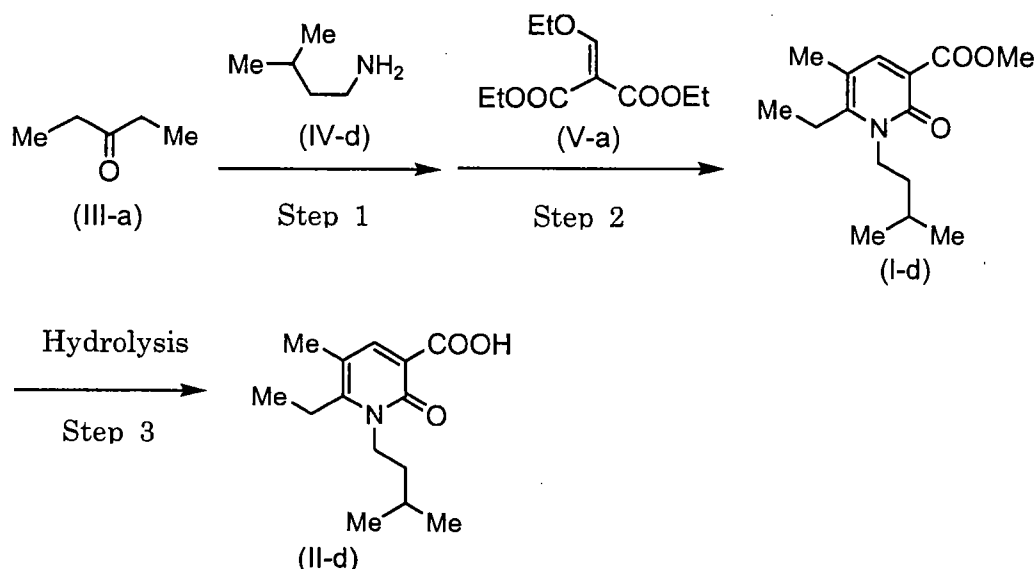
Diffraction angles of major peaks: $2\theta = 9.8, 14.5, 20.4, 21.9, 25.6$ degrees

[Table 3]

2 θ	Peak search set width d value	Intensity	Relative Intensity
9.160	0.165 9.6465	26548	44
9.780	0.141 9.0363	60607	100
11.380	0.165 7.7692	15588	26
12.700	0.188 6.9645	9470	16
14.520	0.259 6.0953	37578	62
15.200	0.188 5.8241	10905	18
17.860	0.165 4.9623	9370	16
18.420	0.165 4.8126	10147	17
19.240	0.165 4.6093	8260	14
19.800	0.235 4.4802	15892	27
20.440	0.165 4.3414	28042	47
21.940	0.188 4.0478	27668	46
22.520	0.188 3.9449	22020	37
22.940	0.165 3.8736	8088	14
24.000	0.188 3.7048	4438	8
24.320	0.353 3.6568	6000	10
24.980	0.188 3.5617	19927	33
25.580	0.188 3.4795	29438	49
27.020	0.212 3.2972	10233	17
28.060	0.165 3.1773	4480	8
29.160	0.212 3.0599	12447	21
30.140	0.188 2.9626	3910	7
30.900	0.188 2.8915	6073	11
32.080	0.165 2.7878	6487	11

Example 4: Synthesis of Compound (II-d)

[Chemical formula 33]



Step 1

A solution of a compound (III-a, 39.1 g, 0.454 mol) and a compound (IV-d, 16.5 g, 0.189 mol) in toluene (142 mL) was refluxed under dehydrating condition for 8 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution. This concentrated solution was used in the next reaction.

Step 2

To the concentrated solution obtained in Step 1 was added a compound (V-a, 61.3 g, 0.283 mol), and stirred at 120°C for 8 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution containing a compound (I-d). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added with methanol (60 mL) and 24% sodium hydroxide aqueous solution (38.4 mL), and stirred at 25°C for 0.5 hour. The reaction solution was concentrated under reduced pressure, and washed with toluene (213 mL). To the aqueous phase were added 61% sulfuric acid (3.3 g) and then 31% sulfuric acid (26 g) to render it acidic, and extracted with ethyl acetate (144 mL). After washing with water (95 mL), the extract was concentrated under reduced pressure, then 2-propanol (24 mL) was added, and allowed to crystallize at 0°C for 0.5 hour. The precipitated crystals were collected by filtration, and dried to obtain a compound (II-d, 28.2 g, 59.3%).

Melting point: 106°C

NMR (DMSO- d_6 , TMS): 1.02 (d, 6H, $J = 6.6$), 1.28 (t, 3H, $J = 7.5$), 1.56 - 1.66 (m, 2H), 1.78 (m, 1H), 2.23 (s, 3H), 2.79 (q, 2H, $J = 7.5$), 4.10 - 4.21 (m, 2H), 8.28 (s, 1H)

A result of powder X-ray diffraction is shown in Table 4 and Fig. 4.

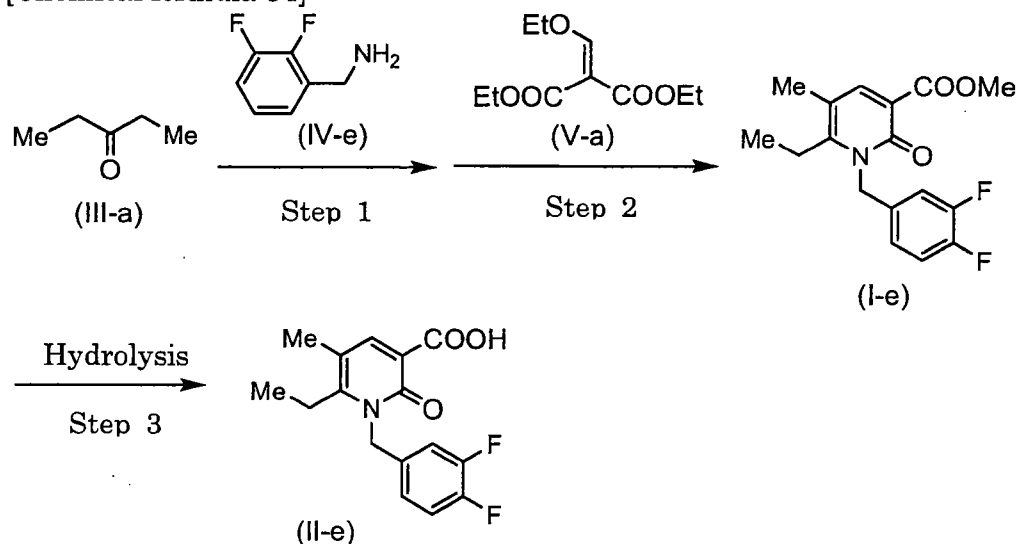
Diffraction angles of major peaks: $2\theta = 10.1, 10.8, 21.3, 26.0$ degrees

[Table 4]

2 θ	Peak search set width	d value	Intensity	Relative intensity
10.140	0.188	8.7163	65433	100
10.760	0.165	8.2154	32057	49
12.920	0.165	6.8464	7662	12
14.120	0.165	6.2671	13083	20
15.740	0.141	5.6255	3253	5
16.060	0.165	5.5142	10022	16
18.000	0.188	4.9240	15025	23
18.680	0.165	4.7462	11157	18
19.740	0.165	4.4937	10558	17
20.380	0.188	4.3540	4202	7
20.900	0.188	4.2468	14033	22
21.260	0.188	4.1757	38532	59
21.660	0.188	4.0995	16912	26
21.860	0.118	4.0625	8093	13
22.440	0.188	3.9588	11630	18
22.960	0.188	3.8703	6895	11
23.320	0.188	3.8113	9763	15
24.500	0.165	3.6304	3357	6
25.120	0.188	3.5421	16370	26
25.360	0.118	3.5092	8232	13
26.020	0.188	3.4216	27965	43
28.000	0.188	3.1840	3812	6
29.260	0.141	3.0497	3793	6
31.080	0.188	2.8751	12482	20
31.720	0.306	2.8186	4427	7
32.440	0.165	2.7576	3503	6
33.140	0.165	2.7010	4107	7
33.500	0.212	2.6728	8705	14

Example 5: Synthesis of Compound (II-e)

[Chemical formula 34]



Step 1

A solution of a compound (III-a, 58.6 g, 0.681 mol) and a compound (IV-e, 27.1g, 0.189 mol) in toluene (142 mL) was refluxed under dehydrating condition for 5 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution. This concentrated solution was used in the next reaction.

Step 2

The concentrated solution obtained in Step 1 was added with a compound (V-a, 61.3 g, 0.283 mol) and stirred at 117°C for 8 hours. The reaction solution was concentrated under reduced pressure, and a concentrated solution containing a compound (I-e) was obtained. This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added methanol (59 mL) and 24% sodium hydroxide aqueous solution (38.6 mL), and stirred at 25°C for 0.5 hour. The reaction solution was concentrated under reduced pressure, and washed with toluene (212 mL). To the aqueous phase were added 61% sulfuric acid (3.3 g), and then 31% sulfuric acid (26 g) to render it acidic, and extracted with ethyl acetate (144 mL). After washing with water (95 mL), the extract was concentrated under reduced pressure, then 2-propanol (24 mL) was added, and allowed to crystallize at 0°C for 0.5 hour. The precipitated crystals were collected by filtration, and dried to obtain a compound (II-e, 39.6 g, 68.1%).

Melting point: 131 to 132°C

¹H-NMR (CDCl₃, TMS): 1.21 (t, 3H, J= 7.7), 2.25 (s, 3H), 2.73 (q, 2H, J= 7.4), 5.42 (br s, 2H), 6.86 (m, 1H), 6.96 (ddd, 1H, J= 10.8, 7.4 and 2.3), 7.15 (dt, 1H, J= 9.9 and 8.3), 8.39 (s, 1H), 14.31 (br s, 1H)

A result of powder X-ray diffraction is shown in Table 5 and Fig. 5.

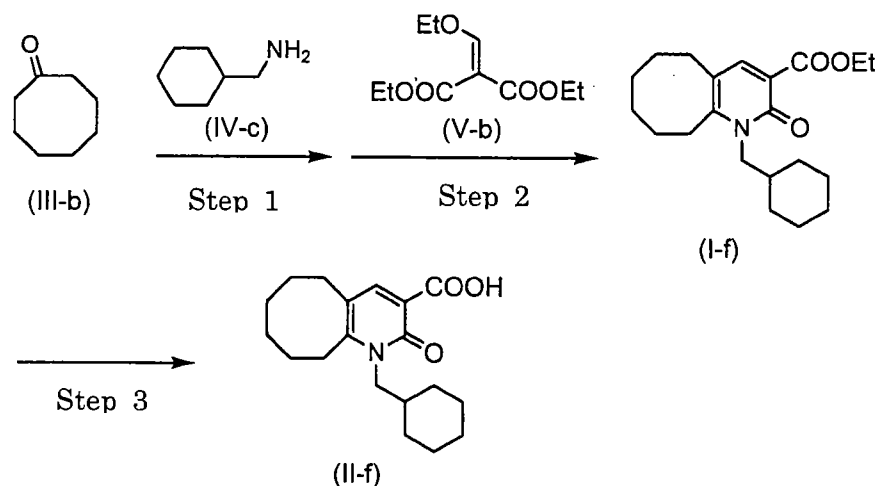
Diffraction angles of major peaks: 2θ = 13.4, 13.8, 19.0, 24.3, 27.9 degrees

[Table 5]

2	θ	Peak search set width	d value	Intensity	Relative intensity
10.800		0.188	8.1850	19250	40
12.040		0.188	7.3447	5348	12
13.400		0.188	6.6022	27512	57
13.800		0.188	6.4117	48528	100
15.040		0.165	5.8857	4795	10
15.840		0.165	5.5902	8180	17
17.020		0.165	5.2052	3640	8
17.980		0.188	4.9294	18187	38
19.020		0.188	4.6622	22233	46
20.160		0.188	4.4010	5250	11
21.820		0.306	4.0698	4742	10
22.480		0.165	3.9518	3413	8
22.820		0.188	3.8937	5980	13
23.400		0.188	3.7985	5430	12
24.260		0.212	3.6657	22273	46
25.620		0.212	3.4741	12558	26
26.460		0.188	3.3657	21558	45
26.900		0.165	3.3117	4582	10
27.880		0.188	3.1974	30877	64
28.480		0.165	3.1314	3447	8
29.800		0.188	2.9957	18477	39
30.240		0.353	2.9531	6155	13
31.620		0.212	2.8273	4927	11
32.840		0.188	2.7250	3157	7
33.340		0.212	2.6852	3182	7
39.800		0.212	2.2630	3738	8

Example 6: Synthesis of Compound (II-f)

[Chemical formula 35]



Step 1

A solution of a compound (III-b, 10.0g, 0.079 mol) and a compound (IV-c, 8.97 g, 0.079 mol) in toluene (100 mL) was refluxed under dehydrating condition for 7 hours.

Step 2

To the reaction solution obtained in Step 1 was added a compound (V-b, 20.56 g, 0.095 mol), and refluxed under heating for 16 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution containing a compound (I-f). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added methanol (150 mL) and 2N sodium hydroxide aqueous solution (79 mL, 0.158 mol), and stirred at 25°C for 3 hours. The reaction solution was concentrated under reduced pressure, toluene and water were added, and an aqueous phase was separated. To the aqueous phase was added 5N hydrochloric acid (34 mL), and extracted with ethyl acetate. The extract was concentrated under reduced pressure, 2-propanol (40 mL) was added, and stirred at 0°C for 1 hour to allow crystallization. The precipitated crystals were collected by filtration, and dried to obtain a compound (II-f, 15.5 g, 61.6%).

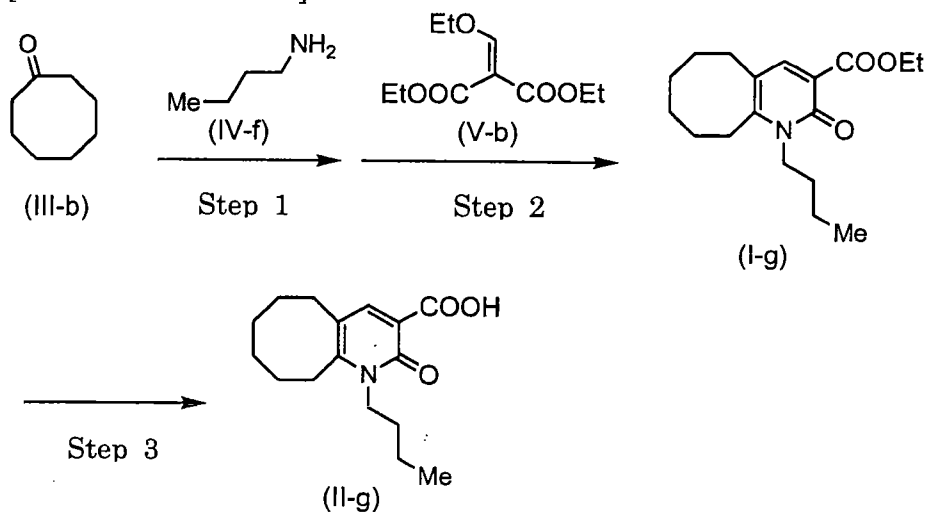
NMR (CDCl₃, TMS): 1.05 - 1.71 (m, 19H), 2.70 - 2.74 (m, 2H), 2.98 - 3.01 (m, 2H), 4.06 (bs, 2H), 8.21 (s, 1H), 14.96 (s, 1H)

A result of powder X-ray diffraction is shown in Table 6 and Fig. 6.

Diffraction angles of major peaks: 2θ = 10.2, 11.4, 15.0, 18.2, 20.6, 21.5 degrees
[Table 6]

2 θ	d value	Intensity	Relative intensity
10.225	8.64424	75.6	68.3
11.368	7.777	72.3	65.4
14.963	5.91599	70.3	63.5
15.34	5.7713	32.9	29.7
15.857	5.58444	21.2	19.2
17.052	5.19562	34.5	31.2
18.15	4.88349	72.3	65.4
18.713	4.73784	15	13.6
19.73	4.49593	26.2	23.7
20.074	4.41965	42.2	38.1
20.565	4.31529	111	100
21.196	4.18823	43.8	39.6
21.466	4.13617	83.3	75.3
21.975	4.04138	27.9	25.2
22.823	3.89325	62.6	56.6
23.408	3.79726	50.8	45.9
23.748	3.74359	49.8	45.1
24.105	3.68889	26.5	24
26.736	3.33161	14.3	13
28.598	3.11872	12.4	11.2
28.892	3.08773	11.8	10.7
29.557	3.01971	13.5	12.2
29.82	2.99372	13	11.7
31.52	2.83599	16.1	14.6
33.017	2.71078	11.3	10.2
33.454	2.67632	9.61	8.7
34.817	2.57465	8.55	7.7
35.301	2.54042	8.78	7.9
35.937	2.49694	8.51	7.7
36.337	2.47034	6.89	6.2
37.262	2.4111	6.34	5.7
38.3	2.34809	7.61	6.9

Example 7: Synthesis of Compound (II-g)
[Chemical formula 36]



Step 1

A solution of a compound (III-b, 30.0 g, 0.238 mol) and a compound (IV-f, 20.9 g, 0.286 mol) in toluene (80 mL) was refluxed under dehydrating condition for 5.5 hours.

Step 2

To the reaction solution obtained in Step 1 was added a compound (V-b, 51.5 g, 0.238 mol), and refluxed under heating at 2 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution containing a compound (I-g). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added methanol (200 mL), tetrahydrofuran (200 mL), and 2N sodium hydroxide aqueous solution (149 mL), and after completion of reaction, a similar operation as in Example 1 was conducted, and methanol (200 mL) was added to the obtained crystalline concentrated residue to carry out recrystallization. The precipitated crystals were collected by filtration, and dried to obtain a compound (II-g, 47.9 g, 72.5%).

NMR (DMSO- d_6 , TMS): 1.00 (t, 3H, $J=7.5$), 1.35 - 1.55 (m, 6H), 1.60 - 1.86 (m, 6H), 2.63 - 2.71 (m, 2H), 2.90 - 2.99 (m, 2H), 3.99 - 4.21 (m, 2H), 8.27 (s, 1H), 14.78 (br s, 1H)

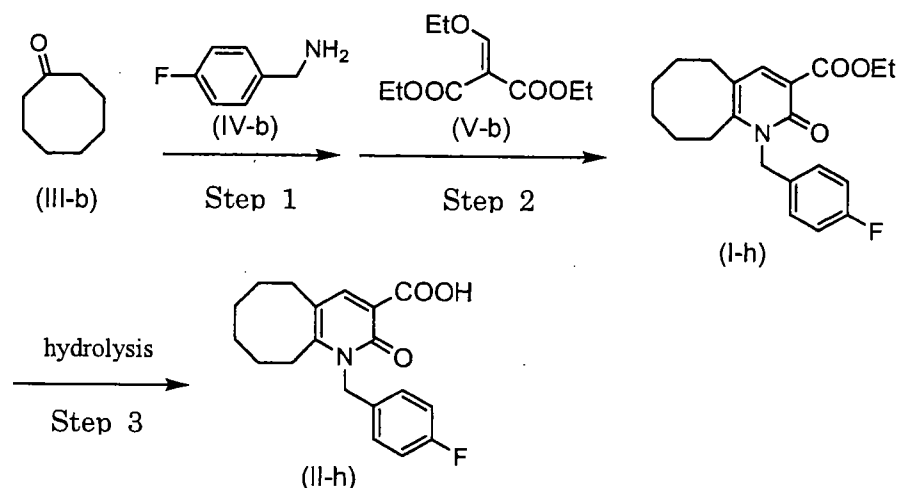
A result of powder X-ray diffraction is shown in Table 7 and Fig. 7.

Diffraction angles of major peaks: $2\theta = 9.2, 9.7, 10.0, 15.5, 19.7$ degrees

[Table 7]

2 θ	d value	Intensity	Relative intensity
9.157	9.64983	515	100
9.74	9.0733	82.4	16
9.998	8.83963	165	32
10.701	8.26016	16.5	3.2
14.051	6.29757	24.7	4.8
15.129	5.8512	37.9	7.4
15.504	5.71047	77.8	15.1
16.271	5.44302	20.2	3.9
17.419	5.08702	8.46	1.6
18.146	4.88461	43.7	8.5
18.432	4.80948	32.7	6.4
18.749	4.7289	25.2	4.9
19.4	4.57168	41.5	8
19.66	4.51179	80.8	15.7
20.188	4.39506	33.8	6.6
20.53	4.32258	47.7	9.3
21.466	4.13612	77.1	15
22.073	4.02376	22.6	4.4
22.349	3.97472	20.2	3.9
22.882	3.88329	10.6	2.1
23.449	3.79069	23.4	4.5
24.491	3.63169	29	5.6
24.807	3.5861	27.9	5.4
25.1	3.54492	16.3	3.2
26.069	3.41533	18	3.5
26.504	3.3602	12.2	2.4
27.549	3.23514	8.93	1.7
28.49	3.13036	11.8	2.3
28.914	3.08543	17.5	3.4
29.707	3.00485	13.6	2.6
30.226	2.95439	13.9	2.7
30.66	2.91355	14.9	2.9
30.92	2.88962	35.6	6.9
31.382	2.84813	8.82	1.7
31.978	2.79642	18.2	3.5
32.236	2.77461	14.7	2.9
32.916	2.71881	7.92	1.5
34.088	2.62797	7.28	1.4
34.783	2.57704	9.52	1.8
35.37	2.53563	10.3	2
36.075	2.48769	6.57	1.3
38.451	2.33925	8.15	1.6
38.959	2.30987	6.79	1.3

Example 8: Synthesis of Compound (II-h)
[Chemical formula 37]



Step 1

A solution of a compound (III-b, 10.0 g, 0.079 mol) and a compound (IV-b, 11.9 g, 0.095 mol) in toluene (100 mL) was refluxed under dehydrating condition for 7 hours.

Step 2

To the reaction solution obtained in Step 1 was added a compound (V-b, 23.99 g, 0.111 mol) and refluxed for 15 hours under heating. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution containing a compound (I-h). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 we added methanol (150 mL), and 2N sodium hydroxide aqueous solution (79 mL, 0.158 mol), and stirred at 25°C for 2 hours. The reaction solution was concentrated under reduced pressure, and toluene and water were added, and an aqueous phase was separated. To the aqueous phase were added 2-propanol (35 mL), and 34 mL of 5N hydrochloric acid, and stirred at 25°C for 1 hour to allow crystallization. The precipitated crystals were collected by filtration, and dried to obtain a compound (II-h, 19.8 g, 76.0%).

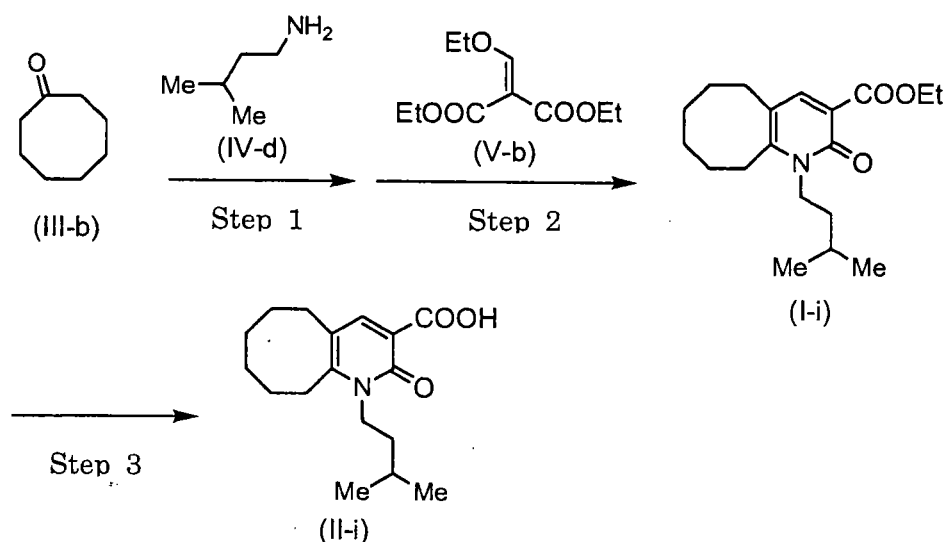
NMR (DMSO- d_6 , TMS): 1.20 - 1.45 (m, 4H), 1.55 - 1.63 (m, 4H), 2.70 - 2.80 (m, 2H), 2.85-2.95 (m, 2H), 5.47 (s, 2H), 7.18 (d, 4H, $J = 8.1$), 8.29 (s, 1H), 14.7 (s, 1H)

A result of powder X-ray diffraction is shown in Table 8 and Fig. 1.

Diffraction angles of major peaks: $2\theta = 13.2, 18.7, 19.5, 20.0, 22.7$ degrees [Table 8]

2 θ	d value	Intensity	Relative intensity
7.566	11.67471	15	9.6
10.77	8.20772	15.4	9.9
12.192	7.25359	41.7	26.7
13.203	6.70005	84.9	54.4
14.048	6.29902	25.7	16.4
14.683	6.02792	7.87	5
15.147	5.8443	48.2	30.8
17.193	5.15322	39	24.9
17.799	4.97912	11.3	7.2
18.657	4.75212	136	86.8
19.469	4.55556	101	64.7
20.022	4.43099	156	100
21.775	4.0781	33.4	21.4
22.332	3.97759	18.2	11.6
22.707	3.91287	96.4	61.7
23.972	3.70907	37.4	23.9
24.275	3.66343	45.2	28.9
25.153	3.5375	34.9	22.3
25.995	3.42484	32.8	21
26.297	3.38625	14.7	9.4
26.62	3.34582	11.4	7.3
27.171	3.27922	14.4	9.2
28.373	3.14302	9.63	6.2
28.98	3.07852	10.4	6.7
29.205	3.05527	13.4	8.6
30.55	2.92382	8.97	5.7
30.839	2.89702	14.1	9
31.677	2.82234	14.7	9.4
32.168	2.78033	9.8	6.3
32.465	2.75559	15.4	9.8
32.75	2.7322	8.08	5.2
33.771	2.6519	8.76	5.6
34.306	2.6118	13.7	8.8
34.966	2.56396	13.7	8.8
36.025	2.49102	17	10.9
39.509	2.27902	16.6	10.6

Example 9: Synthesis of Compound (II-i)
[Chemical formula 38]



Step 1

A solution of a compound (III-b, 10.1 g, 0.0800 mol) and a compound (IV-d, 6.98 g, 0.0800 mol) in toluene (100 mL) was refluxed under dehydrating condition for 6 hours.

Step 2

To the reaction solution obtained in Step 1 was added a compound (V-b, 20.8 g, 0.0960 mol), and refluxed under heating for 15 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution containing a compound (I-i). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added methanol (86 mL) and tetrahydrofuran (86 mL), and 2N sodium hydroxide aqueous solution (80.0 mL), and stirred at 25°C for 3 hours. The reaction solution was concentrated under reduced pressure, and toluene and water were added, and an aqueous phase was separated. The obtained aqueous phase was added to a mixed solution of 5N hydrochloric acid (40 mL) and ethyl acetate (300 mL), and extracted with ethyl acetate (50 mL). The extract was concentrated under reduced pressure, 2-propanol (8 mL) was added, and stirred at 25°C for 15 hours to allow crystallization. The precipitated crystals were collected by filtration, and dried to obtain a compound (II-i, 12.1 g, 52.0%).

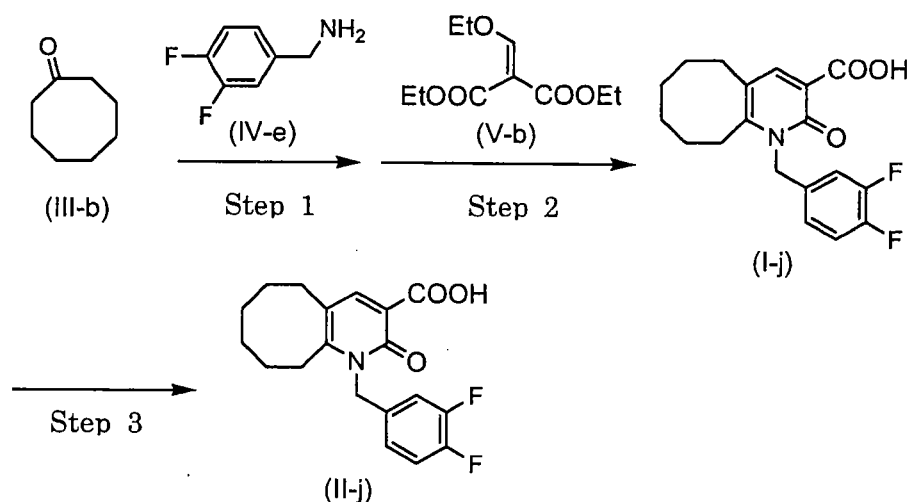
NMR (DMSO- d_6): 0.95 (d, 6H, $J=6.6$), 1.33 (brs, 2H), 1.43 (brs, 2H), 1.50 - 1.60 (m, 4H), 1.71 - 1.78 (m, 3H), 2.70 (m, 2H), 2.97 (m, 2H), 4.14 (m, 2H), 8.19 (s, 1H), 14.9 (s, 1H)

A result of powder X-ray diffraction is shown in Table 9 and Fig. 9.

Diffraction angles of major peaks: $2\theta = 8.4, 9.8, 14.3, 20.3, 21.8$ degrees
[Table 9]

2 θ	d value	Intensity	Relative intensity
8.353	10.57689	232	100
9.833	8.98789	211	90.9
13.02	6.79412	6.61	2.9
13.585	6.51263	9.94	4.3
14.328	6.17642	96.4	41.6
15.338	5.77198	25.4	11
15.666	5.65203	51.9	22.4
16.078	5.50794	12.6	5.4
16.586	5.34029	35.5	15.3
17.345	5.10841	29.8	12.9
19.34	4.58573	63.5	27.4
19.572	4.532	114	49.4
20.319	4.36688	71.5	30.9
20.668	4.29392	20.5	8.8
21.371	4.15431	24.4	10.5
21.771	4.0789	71.3	30.8
22.525	3.94392	15.7	6.8
23.241	3.82401	19	8.2
24.12	3.68663	67.3	29.1
24.791	3.58837	38.5	16.6
25.156	3.53711	10.5	4.6
25.8	3.45029	8.02	3.5
27.238	3.2713	8.36	3.6
28.016	3.18219	10.3	4.5
29.022	3.07416	42.1	18.2
29.417	3.03379	10.4	4.5
29.859	2.98982	19.3	8.4
30.463	2.93195	15	6.5
30.925	2.88921	9.75	4.2
31.742	2.81665	9.82	4.2
32.534	2.74985	10.1	4.4
32.892	2.72077	13.8	5.9
33.51	2.67202	7.83	3.4
34.2	2.61964	9.04	3.9
34.484	2.59868	8.55	3.7
35.75	2.50956	8.67	3.7
36.751	2.44343	8.08	3.5
37.722	2.38277	11.8	5.1
39.205	2.29599	9.1	3.9
39.765	2.26492	7.78	3.4

Example 10: Synthesis of Compound (II-j)
[Chemical formula 39]



Step 1

A solution of a compound (III-b, 10.6 g, 0.084 mol) and a compound (IV-e, 10.0 g, 0.070 mol) in toluene (80 mL) was refluxed under dehydrating condition for 7 hours.

Step 2

To the reaction solution obtained in Step 1 was added a compound (V-b, 15.9 g, 0.074 mol), and refluxed under heating for 7 hours. The reaction solution was concentrated under reduced pressure to obtain a concentrated solution containing a compound (I-j). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added methanol (70 mL), and a solution of sodium hydroxide (8.38 g) in water (40 mL), and stirred at room temperature for 1 hour. After completion of reaction, a similar operation as in Example 1 was conducted, and methanol (100 mL) was added to the obtained crystalline concentrated residue and concentrated to 50 g, and left standing at 0°C. The precipitated crystals were collected by filtration, washed with a small amount of cold methanol, and dried to obtain compound (II-j, 12.5 g, 51.7%).

NMR (DMSO- d_6 , TMS): 1.37 - 1.55 (m, 4H), 1.65 - 1.80 (m, 4H), 2.64 - 2.72 (m, 2H), 2.82 - 2.91 (m, 2H), 5.42 (s, 2H), 6.85 (m, 1H), 6.95 (m, 1H), 7.15 (m, 1H), 8.38 (s, 1H), 14.34 (br s, 1H)

A result of powder X-ray diffraction is shown in Table 10 and Fig. 10.

Diffraction angles of major peaks: $2\theta = 14.6, 15.7, 17.9, 23.5, 26.8, 27.7$ degrees

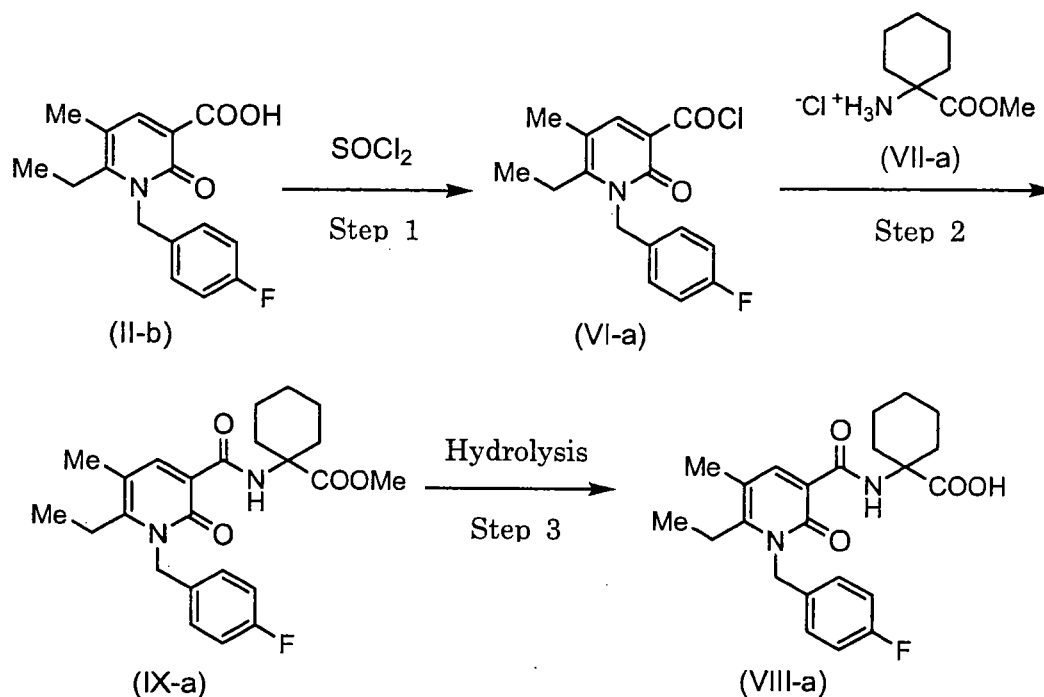
[Table 10]

2 θ	d value	Intensity	Relative intensity
8.874	9.95659	8.86	1.2
9.756	9.05824	32.6	4.3
10.305	8.57703	47.9	6.4
11.144	7.93334	51.1	6.8
12.553	7.04558	28.5	3.8
12.919	6.84683	9.64	1.3
13.851	6.38822	13.2	1.8
14.621	6.05345	134	17.8
15.313	5.78145	41.5	5.5
15.731	5.62873	148	19.7
17.352	5.10646	90.8	12.1
17.9	4.95135	751	100
19.655	4.51293	27.7	3.7
20.749	4.27748	58.3	7.8
21.418	4.14532	13.1	1.7
21.857	4.06297	87.7	11.7
22.607	3.92993	14.1	1.9
23.513	3.78048	216	28.8
24.278	3.66308	116	15.4
25.212	3.52939	8.67	1.2
25.957	3.42984	14	1.9
26.267	3.39	20	2.7
26.794	3.32453	128	17.1
27.652	3.22326	160	21.3
27.965	3.18785	57.8	7.7
28.673	3.11081	15	2
29.929	2.98303	29.2	3.9
30.87	2.89423	9.3	1.2
31.709	2.81953	47.4	6.3
32.895	2.72054	10.5	1.4
34.761	2.57864	21.3	2.8
35.43	2.53147	21.3	2.8
35.996	2.49297	9.23	1.2
37.007	2.42715	10.1	1.3
37.632	2.38823	7.93	1.1
38.335	2.34608	9.16	1.2
39.15	2.29909	8.46	1.1

[0017]

Example 11: Synthesis of Compound (VIII-a)

[Chemical formula 40]



Step 1

To a solution of a compound (II-b, 7.35 g, 25.4 mmol) obtained in Example 2 in toluene (8.7 mL) and N-methylpyridone (8.7 mL) were added thionyl chloride (3.32 g, 27.9 mmol), and stirred at 25°C for 0.5 hour to obtain a reaction solution containing a compound (VI-a). This reaction solution was used in the next reaction.

Step 2

To the reaction solution obtained in Step 1 was added a solution of a compound (VII-a, 5.90 g, 30.5 mmol) and triethylamine (3.1 g, 30.5 mmol) in toluene (18.5 mL) and N-methylpyridone (18.5 mL). Then after addition of triethylamine (5.66 g, 55.9 mmol), the resultant solution was stirred at 25°C for 0.5 hour to obtain a reaction solution containing a compound (IX-a). After washing with 6% sulfuric acid (34.6 g), 4% sodium hydroxide (32.2 g), and purified water (14.5 mL), the solution was concentrated under reduced pressure. This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added with methanol (25.9 mL) and 36% sodium hydroxide aqueous solution (7.06g), and stirred at 50°C for 4 hours. The reaction solution was concentrated under reduced pressure, and 2-propanol (54.6 g) and 10% sulfuric acid (68.5 g) were added to render it acidic, and allowed to crystallize at 25°C for 0.3 hour. The precipitated crystals were collected by filtration, and dried to obtain a compound (VIII-a, 9.78g, 92.9%).

Melting point: 237 to 238°C

NMR (DMSO- d_6 , TMS): 1.05 (t, 3H, $J = 7.8\text{Hz}$), 1.15 - 2.10 (m, 10H), 2.19 (s, 3H), 2.67 (dd, 2H, $J = 7.2$ and 15 Hz), 5.42 (s, 2H), 7.13 - 7.22 (m, 4H), 8.19 (s, 1H), 10.14 (s, 1H), 12.17 (br, 1H)

A result of powder X-ray diffraction is shown in Table 11 and Fig. 11.

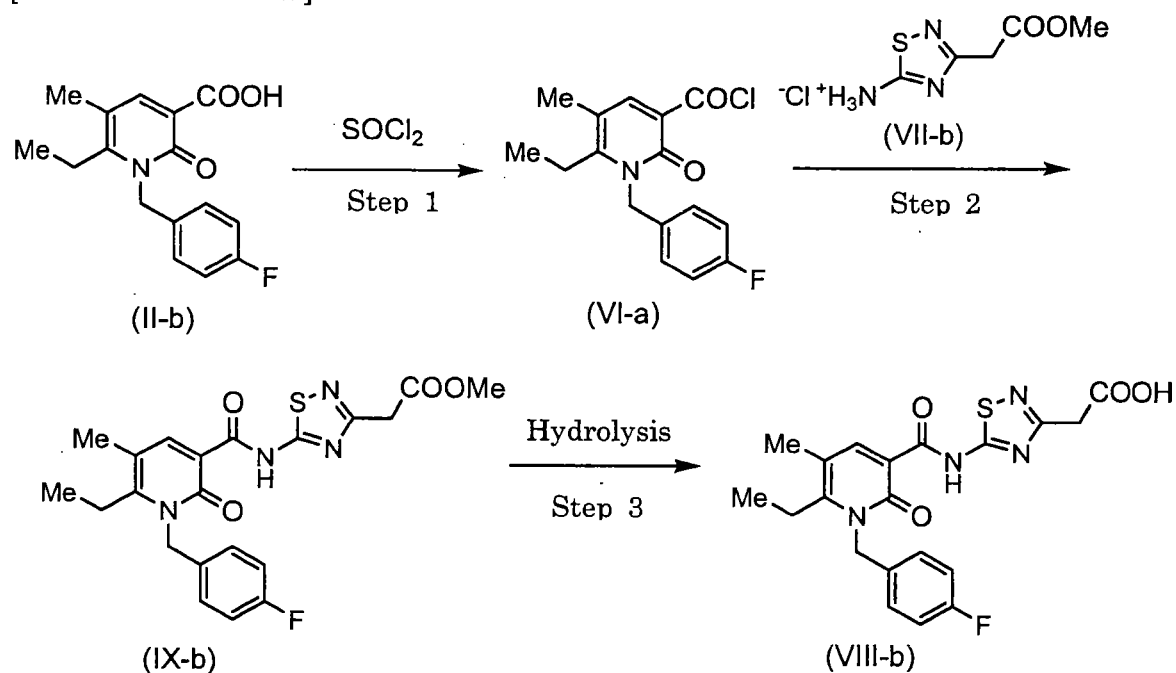
Diffraction angles of major peaks: $2\theta = 9.4, 17.8, 18.5, 20.9, 38.4$ degrees

[Table 11]

2 θ	Peak search set width	d value	Intensity	Relative intensity
9.440	0.212	9.3610	4298	48
9.840	0.212	8.9813	3378	38
12.840	0.212	6.8888	812	10
13.220	0.235	6.6917	1666	19
14.860	0.212	5.9566	848	10
15.720	0.235	5.6326	2123	24
17.820	0.235	4.9733	6841	76
18.540	0.235	4.7818	3695	42
19.520	0.282	4.5439	1781	20
20.880	0.235	4.2509	3834	43
21.700	0.259	4.0920	1333	15
22.340	0.235	3.9762	2230	25
22.840	0.235	3.8903	1643	19
23.140	0.212	3.8406	1489	17
23.740	0.188	3.7448	557	7
24.320	0.188	3.6568	636	8
24.640	0.212	3.6100	729	9
25.800	0.306	3.4503	3163	36
26.540	0.259	3.3558	1019	12
28.500	0.259	3.1293	1697	19
29.000	0.235	3.0764	1039	12
29.340	0.212	3.0416	768	9
29.780	0.235	2.9976	574	7
30.280	0.259	2.9493	819	10
32.920	0.282	2.7185	362	5
35.300	0.188	2.5405	487	6
36.140	0.259	2.4833	376	5
38.400	0.306	2.3422	9001	100
39.160	0.306	2.2985	602	7

Example 12: Synthesis of Compound (VIII-b)

[Chemical formula 41]



Step 1

To a solution of a compound (II-b, 7.36 g, 25.4 mmol) obtained in Example 2 in DMF

(1.0 mL) and THF (73.6 mL) was added with thionyl chloride (3.3 g, 27.9 mmol), and stirred at 25°C for 0.5 hour to obtain a reaction solution containing a compound (VI-a). This reaction solution was used in the next reaction.

Step 2

To the reaction solution obtained in Step 1 were added a compound (VII-b, 5.85 g, 27.9 mmol), pyridine (20.1 g, 254 mmol), and dimethylaminopyridine (620 mg, 5.1 mmol), stirred at 25°C for 20 hours, then 14% hydrochloric acid (134.6 g) was added, and extracted with ethyl acetate (217 mL). The extract was washed with water (74 mL) and 5% aqueous sodium hydrogen carbonate (74 mL). The extract was concentrated under reduced pressure to obtain a concentrated solution containing a compound (IX-b). This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added THF (35.7 mL), methanol (25.5 mL), and 1N sodium hydroxide aqueous solution (45.9 mL), and stirred at 0°C for 2 hours. To the solution was added 2N hydrochloric acid (25.2 mL) to render it acidic, added water (40 mL), and then allowed to crystallize at 0°C for 0.5 hour. The precipitated crystals were collected by filtration, and dried to obtain a compound (VIII-b, 9.04g, 91.7%).

Melting point: 202 to 203°C

NMR (DMSO- d_6 , TMS): 1.06 (t, 3H, J= 7.5 Hz), 2.24 (s, 3H), 2.75 (q, 2H, J= 7.5Hz), 3.79 (s, 2H), 5.49 (br-s, 2H), 7.13 - 7.28 (m, 4H), 8.42 (s, 1H), 13.65 (s, 1H)

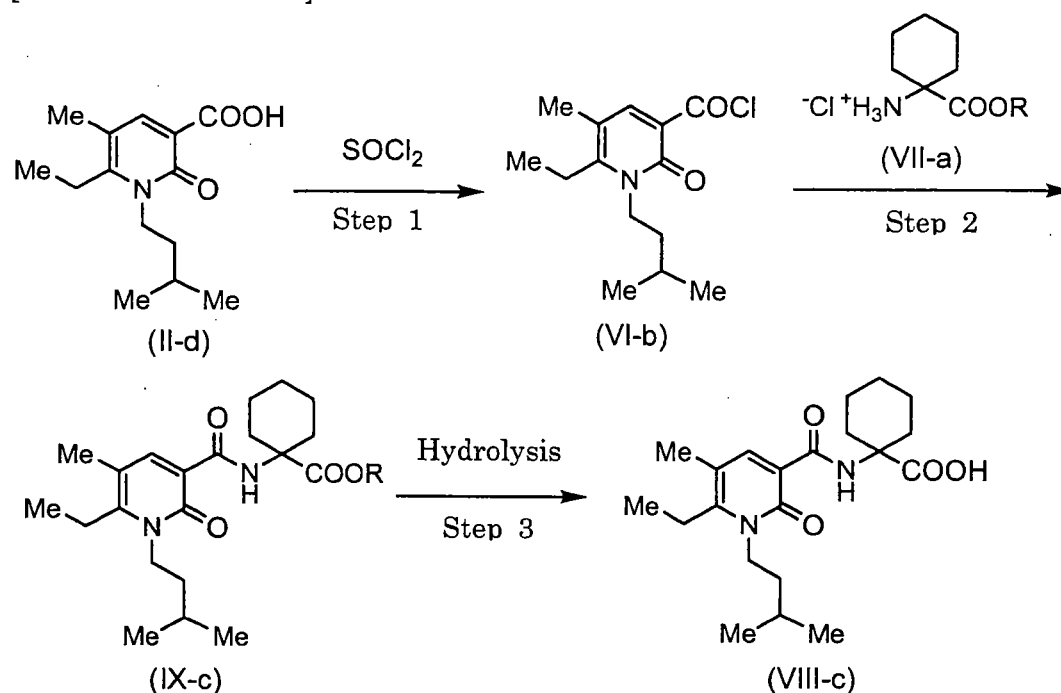
A result of powder X-ray diffraction is shown in Table 12 and Fig. 12.

Diffraction angles of major peaks: $2\theta = 8.5, 18.4, 23.9, 25.2$ degrees

[Table 12]

2 θ	Peak search	set width	d value	Intensity	Relative intensity
8.000	0.165	11.0424	577	8	
8.540	0.188	10.3454	2579	35	
10.720	0.188	8.2459	1016	14	
11.140	0.188	7.9360	417	6	
11.880	0.188	7.4433	235	4	
15.400	0.188	5.7490	1058	15	
16.160	0.165	5.4803	871	12	
16.340	0.188	5.4203	1307	18	
16.940	0.188	5.2296	955	13	
17.740	0.212	4.9956	444	6	
18.380	0.212	4.8230	3168	43	
19.440	0.212	4.5624	1097	15	
20.120	0.212	4.4097	517	7	
20.680	0.188	4.2915	762	11	
21.000	0.188	4.2268	809	11	
21.960	0.188	4.0442	289	4	
22.840	0.188	3.8903	435	6	
23.080	0.188	3.8504	473	7	
23.480	0.188	3.7857	679	10	
23.880	0.212	3.7232	3440	47	
25.160	0.212	3.5366	2355	32	
25.920	0.259	3.4346	456	7	
27.240	0.235	3.2711	1477	20	
28.380	0.259	3.1422	1786	24	
29.260	0.259	3.0497	781	11	
30.960	0.447	2.8860	405	6	
34.700	0.235	2.5830	357	5	
38.360	0.235	2.3446	7443	100	

Example 13: Synthesis of Compound (VIII-c)
[Chemical formula 42]



Step 1

To a solution of a compound (II-d, 6.38 g, 25.4 mmol) obtained in Example 4 in toluene (10.7 mL) and N-methylpyridone (10.7 mL) was added thionyl chloride (3.32 g, 27.9 mmol), and stirred at 25°C for 0.5 hour to obtain a reaction solution containing a compound (VI-d). This reaction solution was used in the next reaction.

Step 2

To the reaction solution obtained in Step 1 was added a solution of a compound (VII-a, 5.41 g, 27.9 mmol) and triethylamine (2.83 g, 27.9 mmol) in toluene (15.9 mL) and N-methylpyridone (15.9 mL). Then after adding triethylamine (5.66 g, 55.9 mmol), the solution was stirred at 25°C for 1 hour to obtain a reaction solution containing a compound (IX-c). After washing with 6% sulfuric acid (30.3 g), 4% sodium hydroxide (28.3 g), and water (12.6 mL), the solution was concentrated under reduced pressure. This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added methanol (22.7 mL), and 36% sodium hydroxide aqueous solution (7.06g), and stirred at 50°C for 4 hours. The reaction solution was concentrated under reduced pressure, 2-propanol (60.3 mL) and 10% sulfuric acid (68.5 g) were added to render it acidic, and allowed to crystallize at 0°C for 1.5 hours. The precipitated crystals were collected by filtration, and dried to obtain a compound (VIII-d, 7.77 g, 81.3%).

Melting point: 170 to 171°C

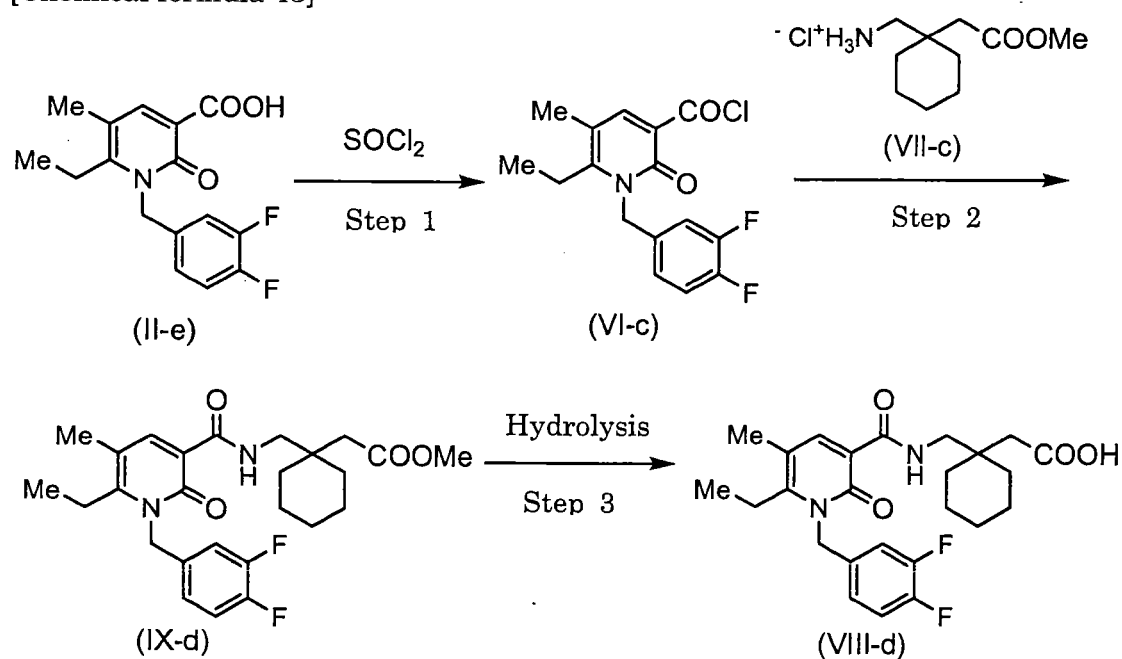
NMR (DMSO- d_6 , TMS): 0.97 (d, 6H, $J = 6.6$), 1.18 (s, 3H, $J = 7.5$), 1.26 - 1.78 (m, 8H), 2.16 (s, 3H), 2.75 (q, 2H, $J = 7.5$), 4.09 (m, 2H), 8.09 (s, 1H), 10.24 (s, 3H)

A result of powder X-ray diffraction is shown in Table 13 and Fig. 13.

Diffraction angles of major peaks: $2\theta = 10.9, 13.3, 20.4, 22.7$ degrees
 [Table 13]

2θ	Peak search set width	d value	Intensity	Relative intensity
8.200	0.188	10.7735	1992	18
9.320	0.141	9.4812	570	5
9.600	0.165	9.2053	1527	14
10.900	0.188	8.1102	9876	86
13.300	0.188	6.6516	5380	47
14.940	0.165	5.9249	604	6
15.660	0.235	5.6541	646	6
16.440	0.212	5.3875	2045	18
17.080	0.306	5.1871	2255	20
17.580	0.212	5.0407	2161	19
18.660	0.235	4.7513	864	8
19.300	0.212	4.5952	2117	19
19.880	0.212	4.4624	1848	17
20.400	0.212	4.3498	2649	24
21.700	0.188	4.0920	2470	22
22.000	0.188	4.0369	2234	20
22.340	0.165	3.9762	1512	14
22.720	0.259	3.9106	2561	23
24.340	0.212	3.6539	780	7
26.020	0.212	3.4216	2090	19
26.620	0.235	3.3459	1382	13
27.040	0.212	3.2948	658	6
28.760	0.165	3.1016	671	6
30.440	0.165	2.9341	569	5
30.620	0.165	2.9173	546	5
32.360	0.188	2.7643	544	5
33.500	0.259	2.6728	734	7
37.640	0.165	2.3878	693	7
38.420	0.188	2.3411	11499	100

Example 14: Synthesis of Compound (VIII-d)
 [Chemical formula 43]



Step 1

To a solution of a compound (II-e, 7.81 g, 25.4 mmol) obtained in Example 5 in toluene (18 mL) and N-methylpyridone (18 mL) was added thionyl chloride (3.33 g, 28.0 mmol), and stirred at 25°C for 0.5 hour to obtain a reaction solution containing a compound (VI-c). This reaction solution was used in the next reaction.

Step 2

To the reaction solution obtained in Step 1 were added a compound (VII-c, 6.20 g, 28.0 mmol), toluene (10.8 mL), N-methylpyridone (10.8 mL), and triethylamine (8.49 g, 83.9 mmol), and stirred at 25°C for 0.5 hour to obtain a reaction solution containing a compound (IX-e). After washing with 6% sulfuric acid (37.3 g), 4% sodium hydroxide (33.7 g), and water (15.6 mL), the solution was concentrated under reduced pressure. This concentrated solution was used in the next reaction.

Step 3

To the concentrated solution obtained in Step 2 were added THF (42 mL), methanol (30 mL), and 1N sodium hydroxide aqueous solution (50.8 mL), and stirred at 50°C for 3 hours. To the solution was added 2N hydrochloric acid (25.4 mL) to render it acidic, added water (24 mL), and allowed to crystallize at 0°C for 0.3 hour. The precipitated crystals were collected by filtration, and dried to obtain a compound (VIII-d, 10.6 g, 90.7%).

Melting point: 194 to 195°C

NMR (DMSO- d_6 , TMS): 1.04 (t, 3H, J = 7.5), 1.22 - 1.58 (m, 10H), 2.17 (s, 2H), 2.18 (s, 3H), 2.65 (q, 2H, J = 7.5), 3.40 (d, 2H, J = 6.3), 5.43 (brs, 2H), 7.11-7.21 (m, 4H), 8.25 (s, 1H), 9.94 (t, 1H, J = 5.7), 12.15 (brs, 1H)

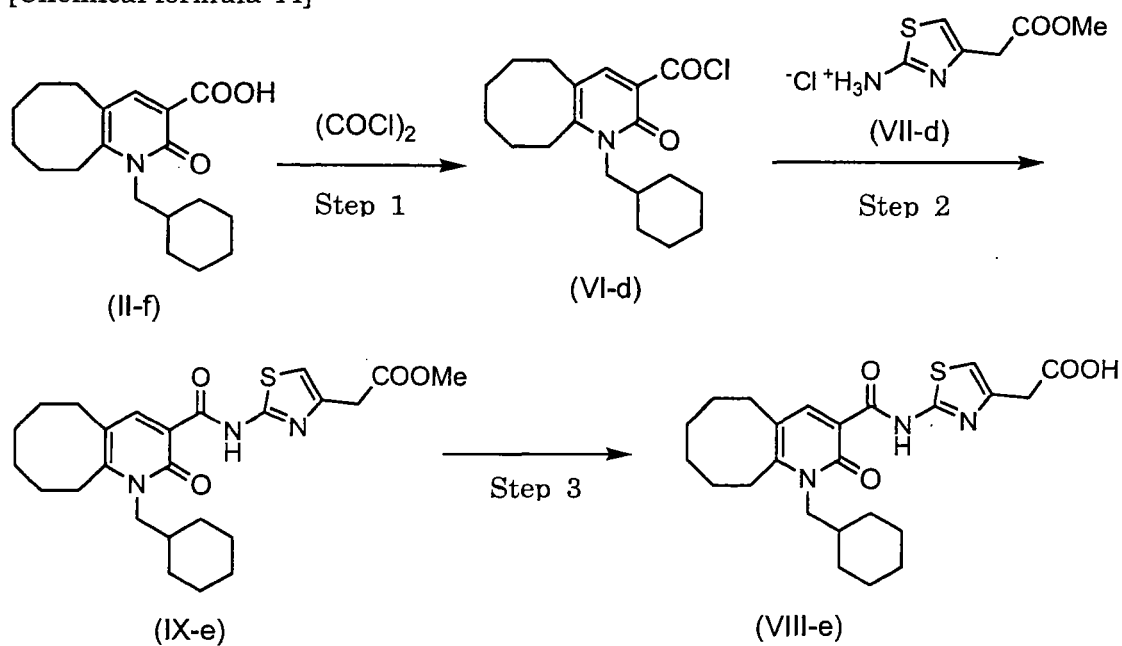
A result of powder X-ray diffraction is shown in Table 14 and Fig. 14.

Diffraction angles of major peaks: $2\theta = 4.7, 12.8, 15.8, 17.5, 24.3, 25.7$ degrees

[Table 14]

2 θ	Peak search set width	d value	Intensity	Relative intensity
4.860	0.188	18.1675	3176	29
8.380	0.212	10.5425	948	9
9.680	0.212	9.1294	639	6
12.800	0.212	6.9103	2899	27
14.200	0.212	6.2320	506	5
15.760	0.235	5.6184	2737	25
17.460	0.235	5.0750	11143	100
17.860	0.212	4.9623	520	5
18.520	0.235	4.7869	958	9
19.740	0.235	4.4937	592	6
20.940	0.165	4.2388	999	9
21.140	0.188	4.1992	1224	11
22.220	0.259	3.9974	2380	22
24.280	0.235	3.6628	3118	28
25.220	0.376	3.5283	1152	11
25.720	0.235	3.4609	2840	26
26.460	0.235	3.3657	726	7
28.180	0.282	3.1641	294	3
28.660	0.235	3.1122	770	7
29.260	0.165	3.0497	398	4
29.540	0.329	3.0214	765	7
29.900	0.165	2.9859	389	4
30.340	0.353	2.9436	358	4
31.480	0.259	2.8395	340	4
32.000	0.259	2.7945	1035	10
33.700	0.282	2.6574	387	4
37.560	0.212	2.3927	322	3
38.420	0.306	2.3411	8222	74
39.320	0.188	2.2895	327	3

Example 15: Synthesis of Compound (VIII-e)
[Chemical formula 44]



Step 1

To a solution of a compound (II-f, 800 mg, 2.52 mmol) obtained in Example 6 in

tetrahydrofuran (8 mL) were added oxalyl chloride (352 mg, 2.77 mmol) and dimethylformamide (2 drops), and stirred at 25°C for 1 hour to obtain a reaction solution containing a compound (VI-d). This reaction solution was used in the next reaction.

Step 2

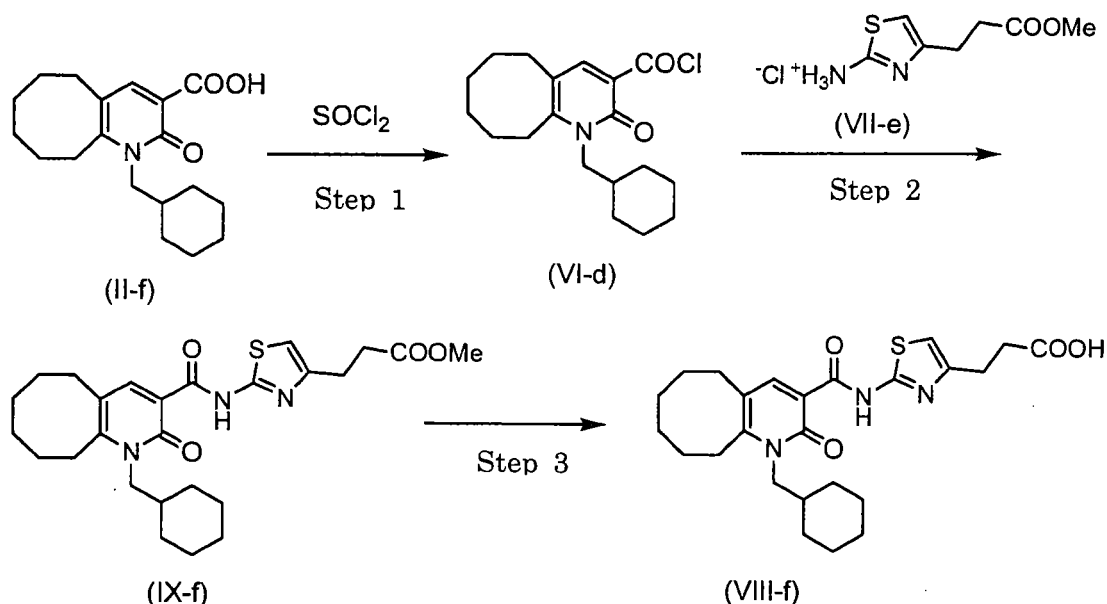
To the reaction solution obtained in Step 1 were added with a compound (VII-d, 516 mg, 2.77 mmol) and triethylamine (0.798 g, 7.89 mmol). The solution was stirred at 25°C for 2 hours to obtain a reaction solution containing a compound (IX-e). To the solution was added with diluted hydrochloric acid, extracted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, and purified water (14.5 mL), and then concentrated under reduced pressure. The residue was recrystallized from acetone-hexane to obtain IX-e (577 mg, 47%).

Step 3

To IX-e (350 mg, 0.72 mmol) obtained in Step 2 were added methanol (3 mL), tetrahydrofuran (3 mL) and 1N sodium hydroxide aqueous solution (2.2 mL, 2.2 mmol), and stirred for 2 hours at room temperature. To the solution was added diluted hydrochloric acid to render it acidic, extracted with ethyl acetate, and washed with water. The organic phase was concentrated, the residue was recrystallized from acetone-hexane, and the precipitated crystals were collected by filtration, and dried to obtain a compound (VIII-e, 370 mg, 80.9%). NMR (CDCl₃, TMS): 1.00 - 1.90 (m, 19H), 2.62 - 2.73 (m, 2H), 2.90 - 3.00 (m, 2H), 3.90 - 4.20 (br, 2H), 5.68 (br, 1H), 7.46 (br, 1H), 8.35 (s, 1H), 8.91 (s, 1H), 13.64 (s, 1H). A result of powder X-ray diffraction is shown in Table 15 and Fig. 15. Diffraction angles of major peaks: 2θ = 6.9, 14.0, 19.4, 21.6 degrees [Table 15]

2 θ	d value	Intensity	Relative intensity
6.949	12.71033	69.4	100
9.383	9.4175	19.8	28.6
9.976	8.85919	6.77	9.8
10.494	8.42308	6.46	9.3
10.842	8.15343	13.2	19
11.195	7.89695	7.49	10.8
11.687	7.56596	13	18.8
12.927	6.84278	10.8	15.6
13.652	6.48101	7.87	11.3
13.984	6.32766	51.8	74.6
15.096	5.86399	23.7	34.1
15.575	5.68475	10.9	15.8
16.531	5.35819	19	27.4
16.903	5.24084	7.62	11
17.856	4.96333	24.1	34.7
18.43	4.81014	30.6	44.1
19.354	4.58237	64.3	92.7
19.995	4.43699	9.79	14.1
20.529	4.32276	32.5	46.9
21.057	4.21553	16.5	23.8
21.594	4.11181	48.7	70.2
21.78	4.07719	35.5	51.2
22.495	3.94922	23.1	33.2
23.35	3.80645	11.1	16.1
25.334	3.51274	12.3	17.7
26.345	3.38018	15.9	22.9
27.262	3.26852	7.63	11
27.908	3.19429	10.3	14.9
28.811	3.09624	11.6	16.8
29.656	3.00984	8.7	12.5
31.556	2.8328	11.9	17.1
32.193	2.77826	6.21	8.9
32.632	2.74186	6.26	9
33.814	2.64866	7.25	10.4
34.344	2.60901	8.31	12
35.005	2.56119	6.12	8.8
36.622	2.45176	7.11	10.2
37.24	2.41248	6.2	8.9
38.748	2.32197	10.3	14.8

Example 16: Synthesis of Compound (VIII-f)
[Chemical formula 45]



Step 1

To a suspension of a compound (II-f, 0.73 g, 2.30 mmol) obtained in Example 6 in THF (3.5 mL) were added thionyl chloride (300 mg, 2.53 mmol) and DMF (2 drops), and stirred at 25°C for 0.5 hour to obtain a reaction solution containing a compound (VI-d). This reaction solution was used in the next reaction.

Step 2

The reaction solution obtained in Step 1 was slowly added dropwise to a solution of a compound (VII-e, 529 mg, 2.53 mmol), triethylamine (815 mg, 8.05 mmol), and tetrahydrofuran (4 mL), and stirred at 25°C for 1.5 hours. To the solution was added diluted hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water and 5% aqueous sodium hydrogen carbonate. The extract was concentrated under reduced pressure, and methanol was added to the obtained residue to obtain a compound (IX-f, 832 mg, 74.2%).

Step 3

To the compound (IX-f, 832 mg, 1.71 mmol) obtained in Step 2 were added THF (2 mL), methanol (1.5 mL), and 1N sodium hydroxide aqueous solution (2.5 mL), and stirred at room temperature for 3 hours. To the reaction solution were added toluene and water, and the aqueous phase was separated. To the separated aqueous phase was added diluted hydrochloric acid to render it acidic, and generated crystals were collected by filtration, and dried to obtain an objective compound (VIII-f, 838 mg, quantitative).

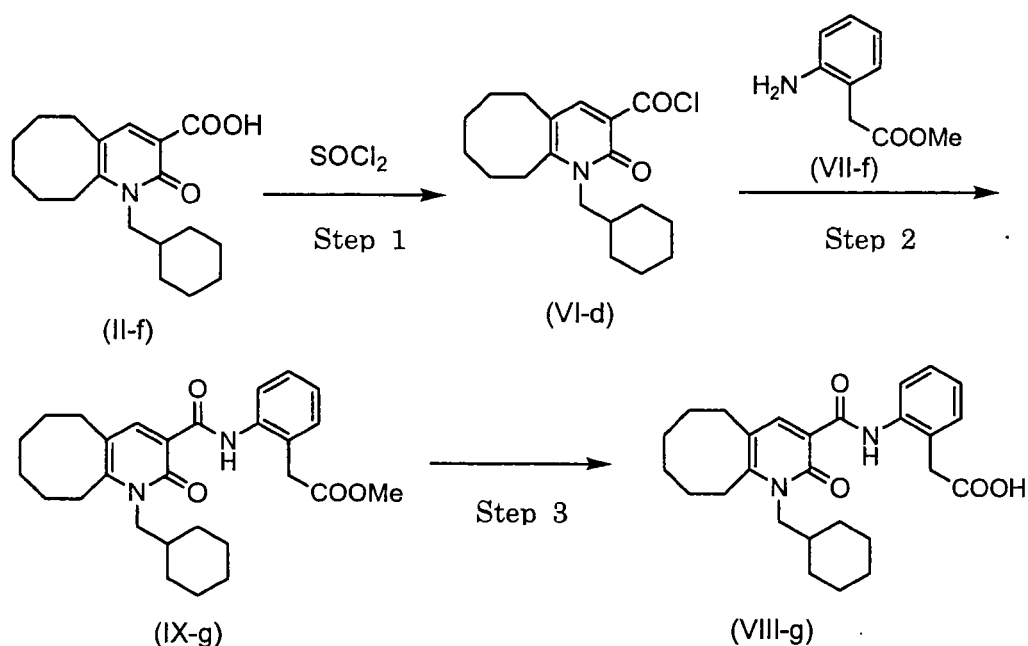
NMR (DMSO-d_6 , TMS): 1.04 - 1.88 (m, 19H), 2.60 (t, 2H, $J = 7.5$), 2.71 (t-like, 2H), 2.84 (t, 2H, $J = 7.5$), 3.00 (t-like, 2H), 4.07 (brd, 2H), 6.86 (s, 1H), 8.28 (s, 1H), 12.15 (br, 1H), 13.43 (s, 1H). A result of powder X-ray diffraction is shown in Table 16 and Fig. 16.

Diffraction angles of major peaks: $2\theta = 12.9, 19.9, 20.4, 21.2$ degrees

[Table 16]

2 θ	d value	Intensity	Relative intensity
8.852	9.98183	17.6	16.8
10.352	8.53796	10.8	10.3
11.18	7.90788	12.8	12.2
11.557	7.65022	24	23
12.378	7.14502	17.7	16.9
12.896	6.8589	54.7	52.3
13.529	6.53961	28.1	26.8
14.554	6.08113	26.1	24.9
14.937	5.92591	8.7	8.3
16.278	5.44072	19.6	18.7
17.059	5.19342	48.5	46.3
17.7	5.00682	21.4	20.4
18.735	4.73242	15.1	14.4
19.018	4.66255	21.2	20.2
19.937	4.44975	68.6	65.5
20.441	4.34118	105	100
20.764	4.27442	40.4	38.6
21.224	4.18275	54.3	51.8
21.855	4.06333	37.1	35.4
22.324	3.97903	12	11.4
23.186	3.833	31.8	30.4
24.18	3.6776	21.4	20.4
24.815	3.58502	17.9	17
26.771	3.32733	9.96	9.5
27.751	3.21199	9.41	9
28.115	3.17129	7.64	7.3
28.69	3.109	9.85	9.4
29.415	3.03399	11.2	10.7
31.776	2.81376	8.94	8.5
32.046	2.79062	8.99	8.6
32.698	2.73647	7.7	7.4
34.257	2.61544	6.36	6.1
36.77	2.44222	6.31	6
37.503	2.39615	6.75	6.4
38.905	2.31298	7.03	6.7
39.776	2.26429	8.36	8

Example 17: Synthesis of Compound (VIII-g)
[Chemical formula 46]



Step 1

To a suspension of a compound (II-f, 1.00 g, 3.15 mmol) obtained in Example 6 in THF (5 mL) was added thionyl chloride (410 mg, 3.45 mmol) and DMF (2 drops), and stirred at 25°C for 0.5 hour to obtain a reaction solution containing a compound (VI-d). This reaction solution was used in the next reaction.

Step 2

The reaction solution obtained in Step 1 was slowly added dropwise to a solution of a compound (VII-f, 786 mg, 4.76 mmol), triethylamine (958 mg, 9.47 mmol) and tetrahydrofuran (5 mL), stirred at 25°C for 1.5 hours, then added diluted hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water and 5% aqueous sodium hydrogen carbonate. The extract was concentrated under reduced pressure to obtain a residue (1.57 g) containing a compound (IX-g). This residue was used in the next reaction.

Step 3

To the residue (1.57 g) obtained in Step 2 were added THF (7.8 mL), methanol (7.8 mL), and 2N sodium hydroxide aqueous solution (4.73 mL), and stirred at room temperature for 1.5 hours. To the reaction solution were added toluene and water, and the aqueous phase was separated. To the separated aqueous phase was added diluted hydrochloric acid to render it acidic, and extracted with ethyl acetate. The organic phase was washed with water, dried, and the solvent was distilled off to obtain an oily residue. To the residue was added ether to be crystallized, and then recrystallized from acetone-hexane to obtain a compound (VIII-g, 917 mg, 65%).

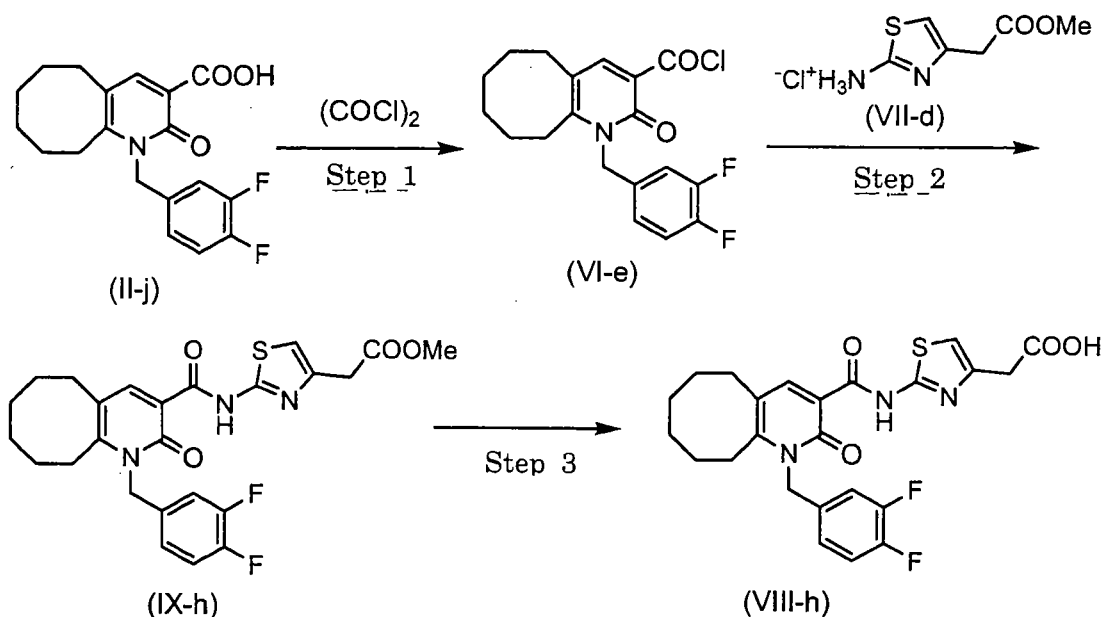
NMR (DMSO- d_6 , TMS): 1.04 - 1.84 (m, 19H), 2.63 - 2.75 (m, 2H), 2.90 - 3.05 (m, 2H), 3.67 (s, 2H), 3.95 - 4.20 (m, 2H), 7.09 (m, 1H), 7.23 - 7.32 (m, 2H), 8.06 (d, 1H, $J = 8.1$), 8.24 (s, 1H), 12.08 (s, 1H), 12.37 (br s, 1H)

A result of powder X-ray diffraction is shown in Table 17 and Fig. 17.

Diffraction angles of major peaks: $2\theta = 6.6, 9.8, 13.2, 16.1, 20.1, 20.9, 24.1$ degrees [Table 17]

2 θ	d value	Intensity	Relative intensity
6.558	13.4674	67.4	59.6
7.285	12.12488	21.1	18.7
9.765	9.05037	76.6	67.8
10.226	8.64285	53.2	47.1
10.548	8.37979	11.8	10.4
13.197	6.70345	67.4	59.6
14.067	6.29065	33.8	29.9
14.915	5.93493	21.4	18.9
16.05	5.51758	59.1	52.3
16.888	5.24575	9.95	8.8
18.351	4.83054	38.7	34.3
19.031	4.6595	32.1	28.4
19.37	4.57858	32.2	28.5
19.708	4.50103	37.4	33.1
20.09	4.41622	91.7	81.2
20.855	4.25595	104	92.2
22.339	3.97649	30.2	26.7
22.87	3.88526	24.4	21.6
24.09	3.69114	113	100
25.31	3.51598	30.5	27
25.778	3.45322	12.3	10.9
26.5	3.36071	9.03	8
27.674	3.22072	8	7.1
28.341	3.14647	10	8.8
28.75	3.10262	12.9	11.4
29.803	2.99537	10.3	9.1
30.402	2.93767	13.3	11.8
30.97	2.88513	11.9	10.5
32.176	2.77966	8.35	7.4
32.92	2.71848	7.08	6.3
34.161	2.62251	14.1	12.5
34.764	2.5784	7.62	6.7
35.746	2.50978	6.53	5.8
36.454	2.4627	7.46	6.6
37.348	2.40576	8.57	7.6
38.582	2.3316	5.86	5.2

Example 18: Synthesis of Compound (VIII-h)
[Chemical formula 47]



Step 1

To a solution of a compound (II-j, 500 mg, 1.44 mmol) obtained in Example 10 in tetrahydrofuran (5 mL) were added oxalyl chloride (201 mg, 1.58 mmol) and dimethylformamide (1 drop), and stirred at 25°C for 1 hour to obtain a reaction solution containing a compound (VI-e). This reaction solution was used in the next reaction.

Step 2

The reaction solution obtained in Step 1 was slowly added to a solution of a compound (VII-d, 320 mg, 1.72 mmol) and triethylamine (0.435 g, 4.30 mmol) in tetrahydrofuran (5 mL). The solution was stirred at 25°C for 2 hours to obtain a reaction solution containing a compound (IX-h). To the solution was added diluted hydrochloric acid, extracted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and purified water, and then concentrated under reduced pressure. The residue was recrystallized from acetone-hexane to obtain IX-h (600 mg, 81%).

Step 3

To IX-h (580 mg, 1.12 mmol) obtained in Step 2 were added methanol (3.4 mL), tetrahydrofuran (3.4 mL) and 1N sodium hydroxide aqueous solution (3.4 mL, 3.4 mmol), and stirred for 1.5 hours at room temperature. To the solution was added diluted hydrochloric acid to render it acidic, and extracted with ethyl acetate, and the organic phase was washed with water. The organic phase was dried, concentrated, the residue was recrystallized from acetone-hexane, and the precipitated crystals were collected by filtration and dried to obtain a compound (VIII-h, 520 mg, 95.2%).

NMR (DMSO-d_6 , TMS): 1.27 - 1.49 (m, 4H), 1.55 - 1.72 (m, 4H), 2.67 - 2.80 (m, 2H), 2.85 - 2.97 (m, 2H), 3.60 (s, 2H), 5.48 (br s, 2H), 6.96 - 7.04 (m, 1H), 7.03 (s, 1H), 7.30 - 7.46 (m, 2H), 8.38 (s, 1H), 12.39 (br s, 1H), 13.26 (s, 1H)

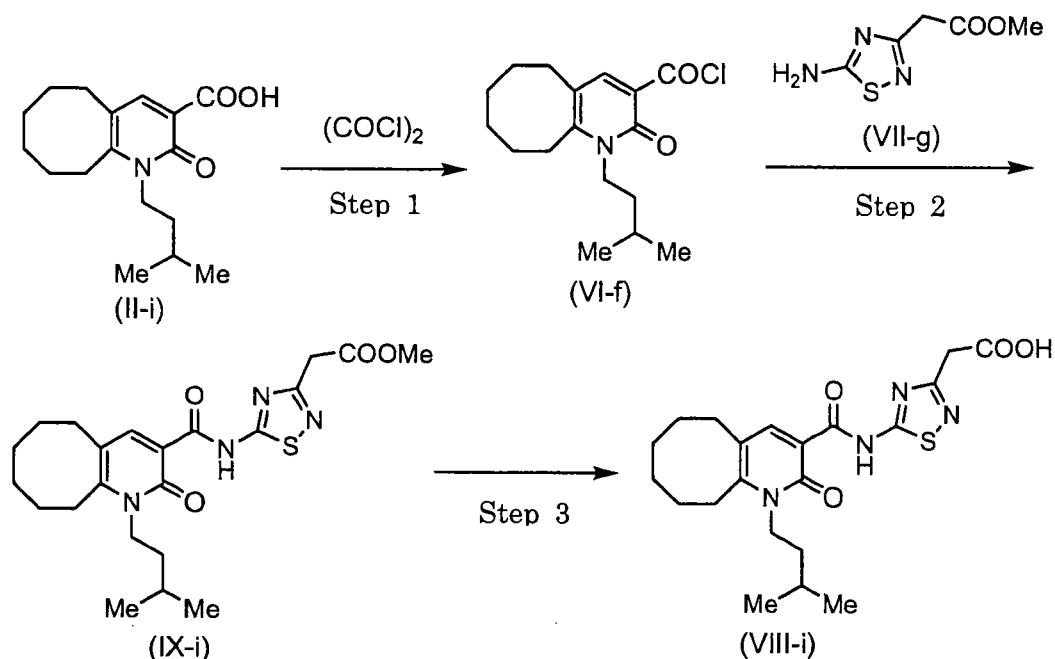
A result of powder X-ray diffraction is shown in Table 18 and Fig. 18.

Diffraction angles of major peaks: $2\theta = 10.0, 17.9, 18.7, 20.6, 21.5, 21.9$ degrees

[Table 18]

2 θ	d value	Intensity	Relative intensity
6.93	12.74467	14.9	17.7
9.22	9.58399	4.7	5.6
9.965	8.86909	48.7	57.7
10.694	8.26601	8.06	9.6
11.435	7.73216	10.8	12.8
11.783	7.50413	6.36	7.5
12.246	7.22174	14.4	17.1
12.897	6.85834	23.2	27.5
13.897	6.36718	14.9	17.6
14.948	5.92164	35.4	42
16.764	5.28428	8.47	10
17.855	4.96368	45.9	54.3
18.48	4.79715	26.4	31.3
18.728	4.7343	75.2	89.2
19.652	4.51364	14.5	17.2
20.595	4.30904	53.8	63.7
21.536	4.12277	75.5	89.5
21.871	4.06047	84.4	100
22.893	3.88147	18.4	21.8
24.118	3.687	8.55	10.1
24.732	3.59682	11.6	13.7
25.731	3.45937	7.53	8.9
26.261	3.39075	30.9	36.6
27.083	3.28971	8.25	9.8
27.799	3.20653	9.91	11.7
28.488	3.13054	25.4	30
30.135	2.96313	11.6	13.7
30.827	2.89811	12.7	15.1
31.354	2.85067	9.67	11.5
32.333	2.76655	5.56	6.6
32.827	2.72603	11.9	14.1
33.707	2.6568	5	5.9
36.292	2.47327	9.49	11.2
36.823	2.43882	7.03	8.3
37.19	2.41562	7.76	9.2
37.769	2.37988	8.61	10.2
39.238	2.29409	6.65	7.9
39.846	2.26049	5.73	6.8

Example 19: Synthesis of Compound (VIII-i)
[Chemical formula 48]



Step 1

To a solution of a compound (II-i, 300 mg, 1.03 mmol) obtained in Example 9 and tetrahydrofuran (3 mL) were added with oxalyl chloride (143 mg, 1.13 mmol) and dimethylformamide (1 drop), and stirred at 25°C for 0.5 hour to obtain a reaction solution containing a compound (VI-f). This reaction solution was used in the next reaction.

Step 2

The reaction solution obtained in Step 1 was slowly added to a solution of a compound (VII-g, 260 mg, 1.24 mmol) and pyridine (3 mL). The solution was stirred at 25°C for 14 hours to obtain a reaction solution containing a compound (IX-i). To the solution was added diluted hydrochloric acid, extracted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and purified water, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate (1:2)) to obtain IX-I as a pale yellow solid (350 mg, 76.1%).

Step 3

To IX-i (340 mg, 0.76 mmol) obtained in Step 2 were added methanol (2.3 mL), tetrahydrofuran (2.3 mL) and 1N sodium hydroxide aqueous solution (2.3 mL, 2.3 mmol), and stirred for 1 hour at room temperature. To the solution was added diluted hydrochloric acid to render it acidic, and extracted with ethyl acetate, and the organic phase was washed with water. The organic phase was dried, and concentrated, and the residue was recrystallized from acetone-hexane, and the precipitated crystals were collected by filtration, and dried to obtain a compound (VIII-i, 250 mg, 76.1%).

NMR (DMSO-d₆, TMS): 0.98 (d, 6H, J= 6.6), 1.26 - 1.86 (m, 11H), 2.65 - 2.80 (m, 2H), 2.90 - 3.05 (m, 2H), 3.81(s, 2H), 4.10 - 4.25 (m, 2H), 8.32 (s, 1H), 12.65 (br s, 1H), 13.84 (s, 1H)

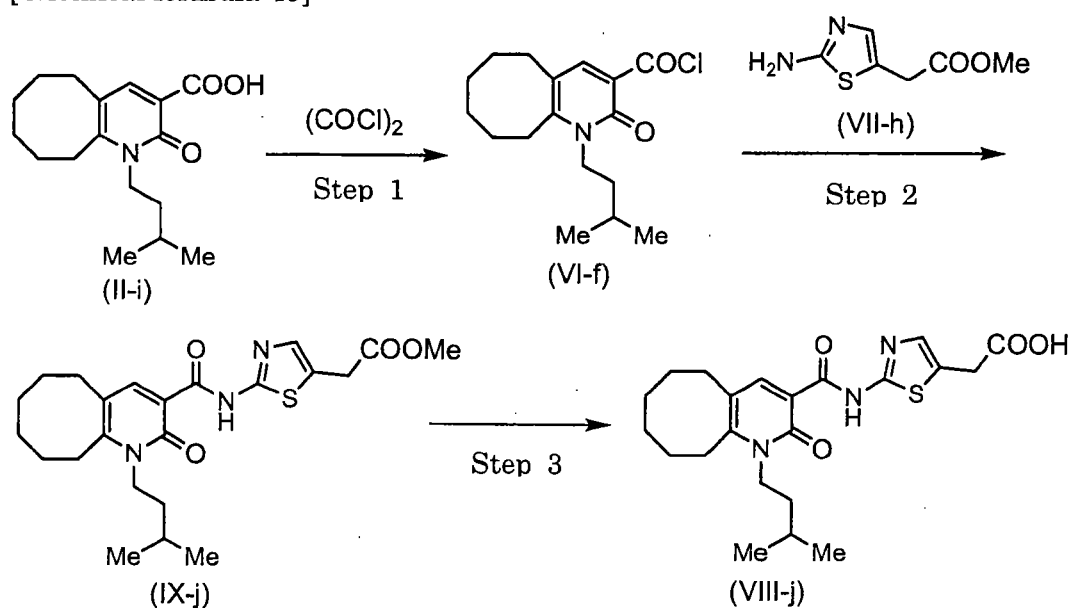
A result of powder X-ray diffraction is shown in Table 19 and Fig. 19.

Diffraction angles of major peaks: 2θ = 10.4, 18.0, 20.7, 21.0 degrees

[Table 19]

2 θ	d value	Intensity	Relative intensity
7.156	12.34303	7.55	1
10.477	8.43668	789	100
11.78	7.50651	6.6	0.8
13.103	6.75132	24.8	3.1
14.007	6.31735	16.9	2.1
14.36	6.16303	8.91	1.1
15.704	5.63842	17.8	2.3
17.15	5.16619	29.1	3.7
18.016	4.91976	63.8	8.1
18.596	4.76749	28.4	3.6
20.691	4.28929	60.7	7.7
20.988	4.22917	52.9	6.7
21.547	4.12084	17.2	2.2
22.62	3.92757	13	1.7
23.018	3.86056	9.8	1.2
23.629	3.76217	10.8	1.4
24.281	3.66264	8.27	1
24.867	3.5776	29.2	3.7
26.363	3.37783	16.3	2.1
27.151	3.28156	17.2	2.2
28.762	3.10138	7.19	0.9
29.739	3.00163	11.5	1.5
30.329	2.94461	13.5	1.7
31.724	2.81822	15.7	2
33.979	2.63617	10	1.3
38.848	2.31625	5	0.6

Example 20: Synthesis of Compound (VIII-j)
[Chemical formula 49]



Step 1

To a solution of a compound (II-i, 300 mg, 1.03 mmol) obtained in Example 4 and tetrahydrofuran (3 mL) were added oxalyl chloride (143 mg, 1.13 mmol) and dimethylformamide (1 drop), and stirred at 25°C for 0.5 hours to obtain a reaction solution

containing a compound (VI-f). This reaction solution was used in the next reaction.

Step 2

The reaction solution obtained in Step 1 was slowly added to a solution of a compound (VII-h, 310 mg, 1.22 mmol), triethylamine (415 mg, 4.1 mmol) and tetrahydrofuran (3 mL). The solution was stirred at 25°C for 14 hours to obtain a reaction solution containing a compound (IX-j). To the solution was added diluted hydrochloric acid, extracted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and purified water, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate (2:1)) to obtain IX-j (350 mg, 76.3%).

Step 3

To IX-j (340 mg, 0.76 mmol) obtained in Step 2 were added methanol (2.3 mL), tetrahydrofuran (2.3 mL) and 1N sodium hydroxide aqueous solution (2.3 mL, 2.3 mmol), and stirred for 2.5 hours at room temperature. To the solution was added diluted hydrochloric acid to render it acidic, and extracted with ethyl acetate, and the organic phase was washed with water. The organic phase was dried, concentrated, and the residue was recrystallized from acetone-hexane, and the precipitated crystals were collected by filtration, and dried to obtain a compound (VIII-j, 230 mg, 70.1%).

NMR (DMSO- d_6 , TMS): 0.98 (d, 6H, $J = 6.6$), 1.26 - 1.84 (m, 11H), 2.65 - 2.77 (m, 2H), 2.90 - 3.03 (m, 2H), 3.82 (s, 2H), 4.10 - 4.25 (m, 2H), 7.31 (s, 1H), 8.24 (s, 1H), 12.63 (br s, 1H), 13.39 (s, 1H)

A result of powder X-ray diffraction is shown in Table 20 and Fig. 20.

Diffraction angles of major peaks: $2\theta = 9.1, 12.1, 18.0, 18.3, 19.7$ degrees

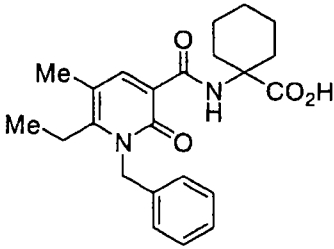
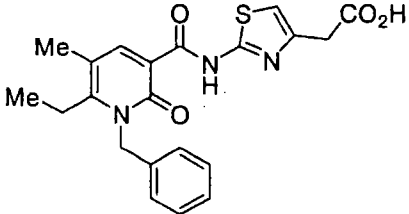
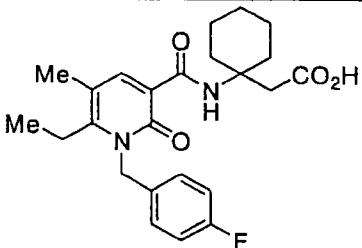
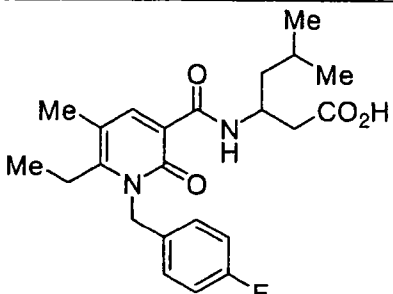
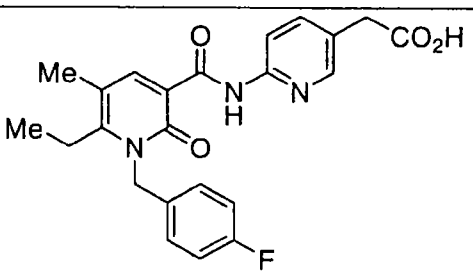
[Table 20]

2 θ	d value	Intensity	Relative intensity
8.59	10.2848	6.48	2.1
9.103	9.70638	94.3	30
11.69	7.56398	15.7	5
12.143	7.28278	314	100
12.676	6.9775	13.1	4.2
14.963	5.91566	19.1	6.1
16.459	5.38127	12.2	3.9
17.536	5.05318	119	38
18.007	4.9222	93.9	29.9
18.255	4.85589	87.4	27.8
18.522	4.78638	44.1	14.1
18.935	4.68288	44.2	14.1
19.503	4.54787	53.1	16.9
19.704	4.50176	60.6	19.3
19.96	4.44466	33.2	10.6
20.349	4.36048	29.4	9.4
20.579	4.31244	35	11.2
21.386	4.15142	14.6	4.7
22.764	3.90315	28.2	9
23.736	3.7455	18.3	5.8
23.954	3.71186	23.3	7.4
24.316	3.65734	13.7	4.4
24.783	3.58953	13.5	4.3
25.843	3.4447	8.89	2.8
26.668	3.33999	47.2	15
27.399	3.25242	10.2	3.2
28.948	3.08184	11.7	3.7
29.136	3.0624	9.3	3
30.006	2.97557	9.05	2.9
30.971	2.88499	24.8	7.9
31.478	2.83971	6.16	2
32.29	2.77007	9.95	3.2
34.289	2.61305	15.6	5
34.762	2.57857	12.3	3.9
35.325	2.53873	6.28	2
35.734	2.5106	7.04	2.2
37.371	2.40432	6.61	2.1
39.096	2.30212	7.75	2.5

[0018]

Compounds (VIII-k) to (VIII-nn) were synthesized in a similar manner as in Examples 1 to 20. Structural formulas are shown in Table 21 to Table 26.

[Table 21]

Compound No.	Structural formula	Melting point °C
V I I I - k		230-232
V I I I - l		203-205
V I I I - m		204-205
V I I I - n		204-205
V I I I - o		185-186

[Table 22]

Compound No.	Structural formula	Melting point °C
V I I I - p		228-230
V I I I - q		186-188
V I I I - r		136-138
V I I I - s		155-160
V I I I - t		126-128

[Table 23]

Compound No.	Structural formula	Melting point °C
V I I I - u		147-149
V I I I - v		175-176
V I I I - z		187-188
V I I I - x		222-224
V I I I - y		157-159

[Table 24]

Compound No.	Structural formula	NMR (DMSO-d ₆ , TMS) δ
V I I I - z		1.04-1.88(m, 19H), 2.70(brt, 2H), 2.99(brt, 2H), 3.49(s, 2H), 4.05(br, 2H), 6.78-6.79(m, 2H), 8.23(s, 1H), 12.88(s, 1H)
V I I I - a a		1.0-1.8(m, 19H), 2.72(br·s, 2H), 3.01(br·s, 2H), 3.81(s, 2H), 4.07(br·s, 2H), 8.33(s, 1H), 12.6(br·s, 1H), 13.8(br·s, 1H)
V I I I - b b		CDC13: 0.94(t, 3H, J=7.2), 1.05-1.88(m, 25H), 2.60-2.82(m, 4H), 2.93(t, 2H, J=6.0), 4.00(bs, 1H), 4.31(bs, 1H), 8.33(s, 1H), 10.4(s, 1H)
V I I I - c c		CDC13: 0.90(t, 3H, J=6.9), 1.00-1.90(m, 27H), 2.60-2.80(m, 4H), 2.93(t, 2H, J=6.0), 4.00(bs, 1H), 4.25-4.37(m, 1H), 8.33(s, 1H), 10.4(s, 1H)
V I I I - d d		1.00-1.90(m, 19H), 2.65-2.77(m, 2H), 2.93-3.07(m, 2H), 3.61(s, 2H), 3.95-4.15(br, 2H), 8.29(s, 1H), 12.20-13.00(br, 1H), 13.64(s, 1H)

[Table 25]

Compound No.	Structural formula	NMR (DMSO-d ₆ , TMS) δ
V I I I - e e		1.02-1.86(m, 19H), 2.62-2.75(m, 2H), 2.92-3.05(m, 2H), 3.85-4.15(br, 2H), 5.43(m, 1H), 8.18(s, 1H), 10.83(d, 1H, J=9.0), 14.22(brs, 1H)
V I I I - f f		1.26-1.68(m, 18H), 2.17(s, 2H), 2.67(br s, 2H), 2.81(br s, 2H), 3.40(d, 2H, J=6.3), 5.41(br s, 2H), 6.86(m, 1H), 7.25(ddd, 1H, J=1.9, 7.7 and 2.3), 7.39(dt, 1H, J=10.8 and 8.4), 8.23(s, 1H), 9.89(t, 1H, J=6.0), 12.06(br s, 1H)
V I I I - g g		1.25-1.50(m, 4H), 1.57-1.70(m, 4H), 2.67-2.77(m, 2H), 2.85-2.95(m, 2H), 3.60(s, 2H), 5.48(s, 2H), 7.12-7.26(m, 4H), 7.72(dd, 1H, J=2.4, 8.4), 8.19(d, 1H, J=2.1), 8.23(d, 1H, J=8.4), 8.38(s, 1H), 12.47(s, 1H)
V I I I - h h		1.26-1.50(m, 4H), 1.55-1.73(m, 4H), 2.66-2.78(m, 2H), 2.83-2.95(m, 2H), 3.60(s, 2H), 5.46(s, 2H), 6.96(m, 1H), 7.26-7.48(m, 2H), 7.72(dd, 1H, J=2.4, 8.4), 8.19(d, 1H, J=2.4), 8.23(d, 1H, J=8.4), 8.37(s, 1H), 12.43(s, 1H), 12.44(br s, 1H)
V I I I - i i		1.20-2.20(m, 12H), 2.60-2.95(m, 4H), 2.86(s, 2H), 3.48(t, 2H, J=10.5), 3.60-3.75(m, 2H), 5.30-5.55(m, 2H), 6.82-7.48(m, 2H), 8.20(s, 1H), 9.98(s, 1H)

[Industrial applicability]
[0019]

The inventors have found a process for producing an important intermediate of a

2-pyridone-3-carbamoyl derivative having excellent cannabinoid receptor agonist activity in a simple manner with high yield and high purity, and also have found a process for producing a 2-pyridone-3-carbamoyl derivative with high yield and high purity by using the important intermediate.

[Brief explanation of drawings]

[0020]

[Fig. 1] Powder X-ray diffraction pattern and peak values of compound (II-a) crystals obtained in Example 1 are shown. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 2] Powder X-ray diffraction pattern and peak values of compound (II-b) crystals obtained in Example 2 are shown. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 3] Powder X-ray diffraction pattern and peak values of compound (II-c) crystals obtained in Example 3 are shown. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 4] Powder X-ray diffraction pattern and peak values of compound (II-d) crystals obtained in Example 4 are shown. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 5] Powder X-ray diffraction pattern and peak values of compound (II-e) crystals obtained in Example 5 are shown. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 6] Powder X-ray diffraction pattern and peak values of compound (II-f) crystals obtained in Example 6 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 7] Powder X-ray diffraction pattern and peak values of compound (II-g) crystals obtained in Example 7 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 8] Powder X-ray diffraction pattern and peak values of compound (II-h) crystals obtained in Example 8 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 9] Powder X-ray diffraction pattern and peak values of compound (II-i) crystals obtained in Example 9 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 10] Powder X-ray diffraction pattern and peak values of compound (II-j) crystals obtained in Example 10 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 11] Powder X-ray diffraction pattern and peak values of compound (VIII-a) crystals obtained in Example 11 are shown. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 12] Powder X-ray diffraction pattern and peak values of compound (VIII-b) crystals obtained in Example 12 are shown. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 13] Powder X-ray diffraction pattern and peak values of compound (VIII-c) crystals obtained in Example 13 are shown. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 14] Powder X-ray diffraction pattern and peak values of compound (VIII-d) crystals obtained in Example 14 are shown. The vertical axis represents intensity (unit: cps), and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 15] Powder X-ray diffraction pattern and peak values of compound (VIII-e) crystals obtained in Example 15 are shown. The vertical axis represents intensity (unit: cps), and the

horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 16] Powder X-ray diffraction pattern and peak values of compound (VIII-f) crystals obtained in Example 16 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 17] Powder X-ray diffraction pattern and peak values of compound (VIII-g) crystals obtained in Example 17 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 18] Powder X-ray diffraction pattern and peak values of compound (VIII-h) crystals obtained in Example 18 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

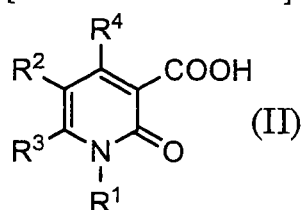
[Fig. 19] Powder X-ray diffraction pattern and peak values of compound (VIII-i) crystals obtained in Example 19 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Fig. 20] Powder X-ray diffraction pattern and peak values of compound (VIII-j) crystals obtained in Example 20 are shown. The vertical axis represents intensity, and the horizontal axis represents diffraction angle (2θ , unit: degrees).

[Document name] Claims

[Claim 1] A process for producing a compound represented by general formula (II):

[Chemical formula 2]



wherein

R¹ represents alkyl which may be substituted with a non-reactive substituent, alkenyl which may be substituted with a non-reactive substituent, or alkynyl which may be substituted with a non-reactive substituent;

R² and R³ each independently represent alkyl, alkyloxyalkyl or alkyloxy; or

R² and R³ taken together with the adjacent carbon atom may form cycloalkene; and

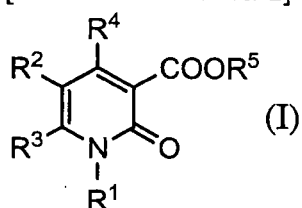
R⁴ represents a hydrogen atom or hydroxy,

comprising Step A and Step B:

[Step A]

hydrolyzing a compound represented by general formula (I):

[Chemical formula 1]



wherein

R¹, R², R³, and R⁴ are as defined above, and

R⁵ represents alkyl, and

[Step B]

adding alcohol to the hydrolysate of the compound represented by general formula (I) generated in Step A to obtain the compound represented by general formula (II).

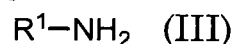
[Claim 2] The process according to claim 1, wherein Step A and Step B are sequentially conducted.

[Claim 3] The process according to claim 1 or 2, further comprising Step C and Step D:

[Step C]

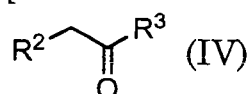
reacting a compound represented by general formula (III):

[Chemical formula 3]



wherein R¹ is as defined in claim 1, with a compound represented by general formula (IV):

[Chemical formula 4]



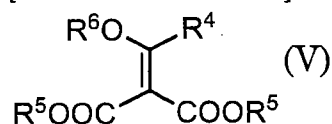
wherein R² and R³ are as defined in claim 1; and

[Step D]

reacting a compound generated in Step C with a compound represented by general

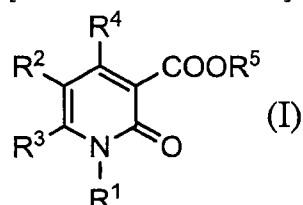
formula (V):

[Chemical formula 5]



wherein R^4 and R^5 are as defined in claim 1 and R^6 represents alkyl, to generate the compound represented by general formula (I):

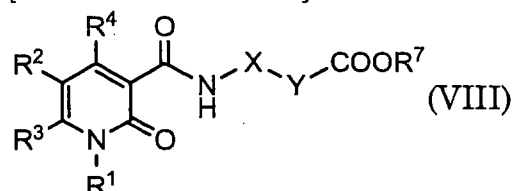
[Chemical formula 6]



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined in claim 1.

[Claim 4] A process for producing a compound represented by general formula (VIII):

[Chemical formula 14]



wherein R^1 , R^2 , R^3 , and R^4 are as defined in claim 1; and

R^7 represents a hydrogen atom or alkyl;

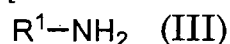
X represents alkylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, alkenylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, alkynylene which may be intervened by a hetero atom and may be substituted with a non-reactive substituent, cycloalkanediyl which may be substituted with a non-reactive substituent, cycloalkenediyl which may be substituted with a non-reactive substituent, aryldiyl which may be substituted with a non-reactive substituent, heteroaryldiyl which may be substituted with a non-reactive substituent, or nonaromatic heterocyclic diyl which may be substituted with a non-reactive substituent; and

Y represents a single bond, alkylene which may be substituted with a non-reactive substituent, alkenylene which may be substituted with a non-reactive substituent, or alkynylene which may be substituted with a non-reactive substituent,, comprising Step C, Step D, Step A, Step B, Step E, and Step F:

[Step C]

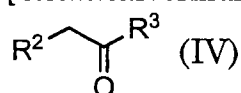
reacting a compound represented by general formula (III):

[Chemical formula 7]



wherein R^1 is as defined in claim 1, with a compound represented by general formula (IV):

[Chemical formula 8]

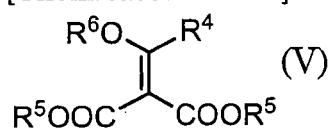


wherein R² and R³ are as defined in claim 1;

[Step D]

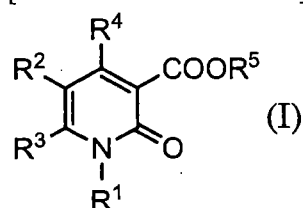
reacting a compound generated in Step C with a compound represented by general formula (V):

[Chemical formula 9]



wherein R⁴ and R⁵ are as defined in claim 1; and R⁶ is as defined in claim 3, to generate a compound represented by general formula (I):

[Chemical formula 10]



wherein R¹, R², R³, R⁴, and R⁵ are as defined in claim 1;

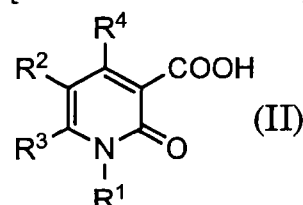
[Step A]

hydrolyzing the compound represented by general formula (I);

[Step B]

adding alcohol to the hydrolysate of the compound represented by general formula (I) generated in Step A to obtain a compound represented by general formula (II):

[Chemical formula 11]

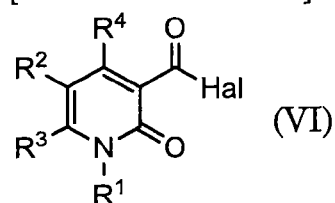


wherein R¹, R², R³, and R⁴ are as defined in claim 1;

[Step E]

reacting the compound represented by general formula (II), with a halogenating reagent to generate a compound represented by general formula (VI):

[Chemical formula 12]

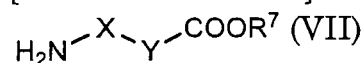


wherein R¹, R², R³ and R⁴ are as defined in claim 1; and Hal represents a halogen atom; and

[Step F]

reacting the compound represented by general formula (VI) with a compound represented by general formula (VII):

[Chemical formula 13]



wherein R⁷, X, and Y are as defined above, and subjecting to hydrolysis as needed.

[Claim 5] The process according to claim 3 or 4, wherein Step C, Step D, Step A and Step B are sequentially conducted.

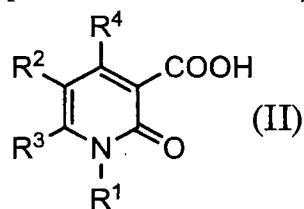
[Claim 6] The process according to any one of claims 1 to 5, wherein the compound represented by general formula (II) is obtained in the form of crystals.

[Claim 7] The process according to any one of claims 1 to 6, wherein R¹ is alkyl which may be substituted with a non-reactive substituent, R² is C1-C2 alkyl, R³ is C1-C3 alkyl, R⁴ is a hydrogen atom, and R⁵ is C1-C2 alkyl.

[Claim 8] The process according to any one of claims 1 to 6, wherein R¹ is alkyl which may be substituted with a non-reactive substituent, R² and R³ taken together with the adjacent carbon atom form cyclooctene, R⁴ is a hydrogen atom, and R⁵ is C1-C2 alkyl.

[Claim 9] The process according to claim 7 or 8, wherein the alcohol to be added is isopropanol.

[Claim 10] A process for producing crystals of a compound represented by general formula (II):
[Chemical formula 15]



wherein R¹, R², R³ and R⁴ are as defined in claim 1, wherein alcohol is added to a solution containing a compound represented by general formula (II).

[Claim 11] The process according to claim 10, wherein the alcohol is isopropanol.