

DESCRIPTION

RADIOACTIVE FLUORINE-LABELING PRECURSOR COMPOUND AND METHOD
FOR PRODUCING RADIOACTIVE FLUORINE-LABELED COMPOUND USING
SAME

5

Technical Field

[0001]

The present invention relates a novel radioactive
fluorine-labeling precursor compound and a production
10 method of a radioactive fluorine-labeled compound using the
precursor compound.

Background Art

[0002]

15 Conventionally, a radioactive fluorine-labeling
reaction is often performed by preparing a labeling
precursor compound which is a compound having a leaving
group bonded to a site to be fluorine-labeled of a target
substrate and performing a nucleophilic substitution
20 reaction in which radioactive fluoride ion F is allowed to
react with the labeling precursor compound. In general,
this reaction is performed by using a small amount of
radioactive fluoride ion F with respect to a large amount
of labeling precursor compound. Therefore, purification of
25 the obtained radioactive fluorine-labeled compound is

usually performed by separating a large amount of unreacted labeling precursor compound by a high-performance liquid chromatography (HPLC) method.

[0003]

5 However, the HPLC method is cumbersome and takes time, and thus causes degradation of yield of the object compound in consideration of the half-life of radioactive fluorine of 110 minutes. As an alternative strategy requiring no HPLC purification, Patent Literatures 1 and 2
10 have proposed that a labeled compound is made easy to separate from another species without a compound M (purification site) by modifying a part of a leaving group of the labeling precursor compound with a compound M (purification site), and this compound is allowed to be
15 used as a labeling precursor compound and to react with a nucleophilic agent such as radioactive fluoride ion F.

[0004]

 In addition, the present applicant has already filed a patent application for a labeling precursor compound and
20 a labeling method using a novel leaving group different from the conventional leaving group (Patent Literature 3).

Citation List

Patent Literature

25 [0005]

Patent Literature 1: WO 2009/127372 A

Patent Literature 2: WO 2011/006610 A

Patent Literature 3: JP 2017-52713 A

5 Summary of Invention

[0006]

The method described in Patent Literature 1 is based on the concept that an active group immobilized on a resin chemically acts on the purification site M of the precursor
10 compound after the radioactive fluorination reaction. Therefore, there has been a problem in that radioactive fluorination rate is adversely affected, preparation of resins such as those having a specific active group introduced thereinto is required, or addition of further
15 reaction conditions such as heating or addition of a reagent after the radioactive fluorination reaction is required.

[0007]

The method described in Patent Literature 2 is based
20 on the concept that a difference between logD of a labeling precursor compound and logD of a radioactive labeled compound is 1.5 or more, such that separation of the radioactive labeled compound is easily performed. However, there have been problems in that the type of leaving group
25 disclosed in Patent Literature 2 is limited, designing in

accordance with the characteristics of individual
substrates is difficult, and poisonous chlorosulfonic acid
needs to be used in synthesis. In addition, further
improvement of purity of the separated radioactive labeled
5 compound is required.

[0008]

In addition, the method of Patent Literature 3
requires that the substrate is a compound having a
neopentyl group, but does not focus on any application to a
10 compound having no neopentyl group.

[0009]

An object of the present invention is to provide a
method which enables a leaving group to be flexibly
designed, maintains a radioactive fluorination rate at the
15 same degree as in conventional methods, and can separate
and purify a radioactive fluorine-labeled compound from an
unreacted precursor compound by a simple purification
method after the radioactive fluorination reaction.

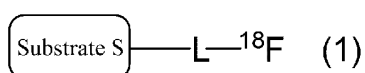
[0010]

20 As a result of diligent research to solve the
problems described above, the present inventors have found
that a method which can maintain a radioactive fluorination
rate at the same degree as in conventional methods and can
separate and purify a radioactive fluorine-labeled compound
25 from an unreacted precursor compound by a simple

purification method after a radioactive fluorination reaction can be provided by introducing a hydrophobic amide tag into a benzene ring of a leaving group formed of a benzenesulfonyloxy group, thereby completing the present invention.

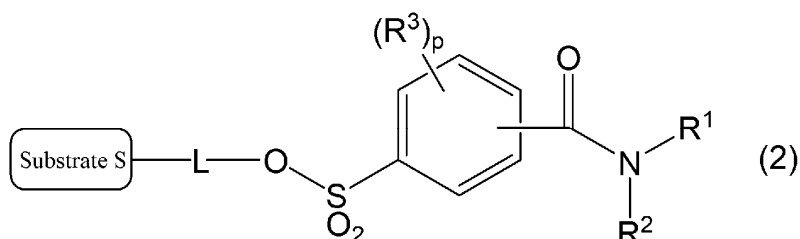
[0011]

That is, according to an aspect of the present invention, there is provided a labeling precursor compound for a radioactive fluorine-labeled compound represented by the following general formula (1):



wherein S represents a substrate, and L represents a straight alkyl group having 1 to 6 carbon atoms, which may contain an ether group,

the labeling precursor compound being represented by the following general formula (2):



wherein S and L are the same as in the general formula (1), R¹ and R² each independently represent a straight or branched alkyl group having 1 to 30 carbon atoms, or a

substituted or unsubstituted monocyclic or condensed polycyclic aryl group,

R³ each independently represent an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon

5 atoms, and

p represents an integer of 0 to 4.

[0012]

In addition, according to another aspect of the present invention, there is provided a production method of
10 a radioactive fluorine-labeled compound, the method including a step of allowing the aforementioned labeling precursor compound to react with [¹⁸F]fluoride ion to obtain the radioactive fluorine-labeled compound represented by the aforementioned general formula (1).

15 [0013]

According to the present invention, since a compound represented by the general formula (2), that is, a compound in which a hydrophobic amide substituent is introduced into a benzene ring of a benzenesulfonyloxy group which is a
20 leaving group, is used as a labeling precursor compound for a radioactive fluorine-labeling reaction, a radioactive fluorination rate is maintained at the same degree as in conventional methods, and a radioactive fluorine-labeled compound can be separated and purified from an unreacted
25 precursor compound by a simple purification method after a

radioactive fluorination reaction.

Description of Embodiments

[0014]

5 1. Radioactive fluorine-labeling precursor compound

A radioactive fluorine-labeling precursor compound of the present invention is a precursor compound for a radioactive fluorine-labeled compound represented by the general formula (1), and has a structure represented by the
10 general formula (2). $\text{clogP}(\text{clogP}_{(1)})$ of the radioactive fluorine-labeled compound represented by the general formula (1) is preferably -1.4 to 5.0 and more preferably 2.0 to 5.0. The labeling precursor compound is designed such that a difference ($\text{clogP}_{(2)} - \text{clogP}_{(1)}$) between
15 $\text{clogP}(\text{clogP}_{(1)})$ of the radioactive fluorine-labeled compound represented by the general formula (1) and $\text{clogP}(\text{clogP}_{(2)})$ of the precursor compound represented by the general formula (2) is preferably 2 or more, more preferably 3 or more, still more preferably 5 or more, and particularly
20 preferably 8 or more. The upper limit thereof is not particularly limited, but the difference between clogPs ($\text{clogP}_{(2)} - \text{clogP}_{(1)}$) is preferably 50 or less and is more practically 30 or less in consideration of solubility of the precursor compound in a reaction solution. By doing so,
25 after the radioactive fluorine-labeling reaction, the

unreacted precursor compound and the targeted radioactive fluorine-labeled compound can be easily separated from each other in a short time by simple column chromatography such as a reverse-phase cartridge column.

5 [0015]

In the present invention, the alkyl group of R^1 and R^2 includes a straight or branched alkyl group having 1 to 30 carbon atoms among which the number of carbon atoms is preferably 4 to 24 and more preferably 8 to 18, and a
10 straight alkyl group is preferable. The monocyclic aryl group of R^1 and R^2 includes a phenyl group, and the condensed polycyclic aryl group of R^1 and R^2 include a naphthyl group, an anthracenyl group, and the like. In the alkyl group and the monocyclic or condensed polycyclic aryl
15 group, a hydrogen atom may be substituted by an alkyl group, an alkoxy group, a halogen atom, or the like. R^1 and R^2 may be the same or different, but are preferably the same group. A group represented by $-\text{CONR}^1\text{R}^2$ of the precursor compound of the present invention may be bonded to any of a meta-
20 position, an ortho-position, and a para-position of the phenyl group, but is preferably bonded to a para-position of the phenyl group.

[0016]

Note that, in the present specification, halogen
25 means fluorine, chlorine, bromine, or iodine.

[0017]

In the present invention, an example of the alkyl group of R^3 includes a straight or branched alkyl group having 1 to 4 carbon atoms, and an example of the alkoxy group of R^3 includes a straight or branched alkoxy group having 1 to 4 carbon atoms. In the precursor compound of the present invention, p represents an integer of 0 to 4, among which p is preferably 0 that is, a case where the phenyl group of the compound represented by the general formula (2) is substituted by no other substituents than $-\text{CONR}^1\text{R}^2$.

[0018]

The radioactive fluorine-labeling precursor compound of the present invention is preferably one represented by the general formula (2) in which $-\text{CONR}^1\text{R}^2$ (R^1 and R^2 each independently preferably represent a straight alkyl group having 1 to 30 carbon atoms, or a substituted or unsubstituted condensed polycyclic aryl group) is bonded to a para-position, and p is 0.

[0019]

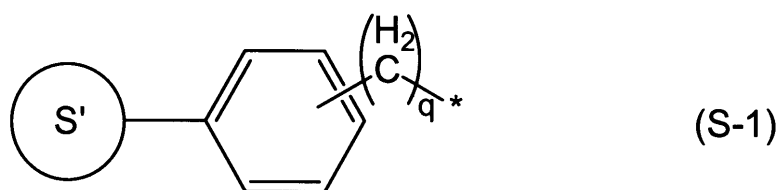
In the present invention, L represents a straight alkyl group (linker) having 1 to 6 carbon atoms, which may contain an ether group. L can be, for example, a group represented by $^*-\text{O}(\text{CH}_2)_n-$, $^*-(\text{CH}_2)_n-$, or $^*-(\text{OCH}_2\text{CH}_2)_m-$ wherein n is an integer of 1 to 5, m is an integer of 1 to

3, and * represents a binding site to S.

[0020]

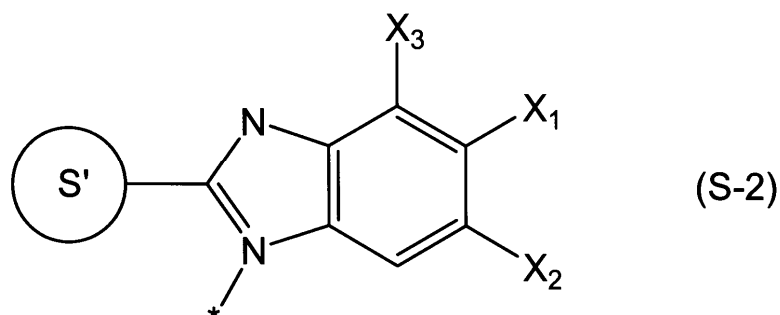
In the present invention, S can be arbitrarily adopted as long as the compound represented by the general
5 formula (1) is one used as a radiopharmaceutical. However, S can be, for example, a group represented by the following formula (S-1) or a group represented by the following formula (S-2).

[0021]



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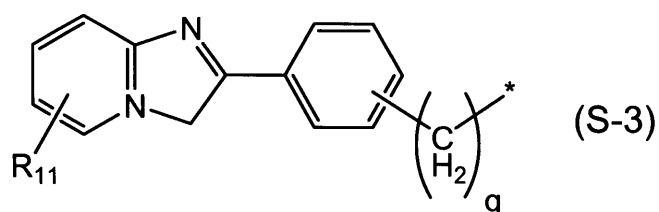
In the formula (S-1), S' is a part of S, q is 0 or 1, and the asterisk is a binding site to L.



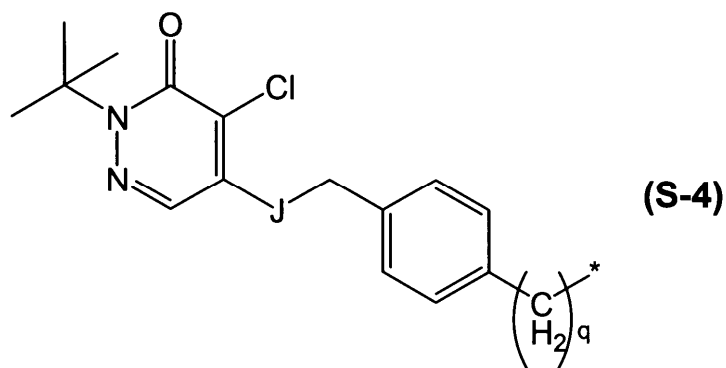
In formula (S-2), S' is a part of S, X₁ and X₃ each
15 independently represent a hydrogen atom or a halogen atom, and X₂ represents a hydrogen atom, a halogen atom, or a nitrile group, but at least one of X₁, X₂, and X₃ is a halogen atom, and the asterisk is a binding site to L.

[0022]

In the present invention, specific examples of the group represented by the formula (S-1) include groups represented by the following formulas (S-3), (S-4), (S-5),
5 and (S-6).

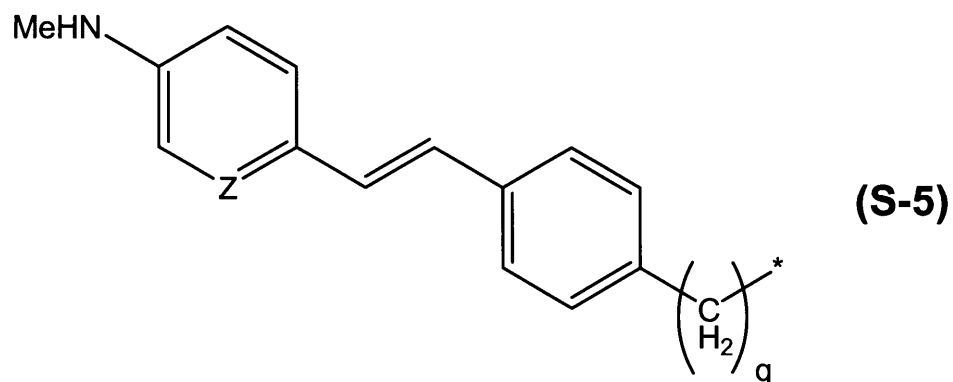


wherein q is the same as in the formula (S-1), R_{11} is a halogen atom, and the asterisk represents a binding site to L.

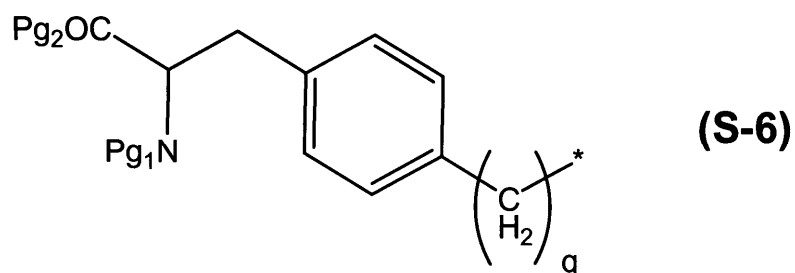


10

wherein q is the same as in the formula (S-1), J is O, S, NH, or NMe, the asterisk represents a binding site to L, and, here, Me represents a methyl group.



wherein q is the same as in the formula (S-1), Z is carbon or nitrogen, Me represents a methyl group, and the asterisk represents a binding site to L.



5

wherein q is the same as in the formula (S-1), Pg₁ represents a protecting group of an amino group, Pg₂ represents a protecting group of a carboxyl group, and the asterisk is a binding site to L.

10 [0023]

In the formula (S-3), q is preferably 1. In addition, in a case where S is a group represented by formula (S-3), L is preferably a group presented by *-O(CH₂)_n- wherein * is a binding site to the formula (S-3), and n is an integer of 1 to 5 and preferably 2 to 4.

15

[0024]

In the formula (S-4), q is preferably 0, and J is preferably 0. In addition, in a case where S is a group represented by the formula (S-4), L is preferably a group presented by $^*\text{-O}(\text{CH}_2)_n\text{-}$ wherein * is a binding site to the
5 formula (S-4), and n is an integer of 1 to 5 and preferably 2.

[0025]

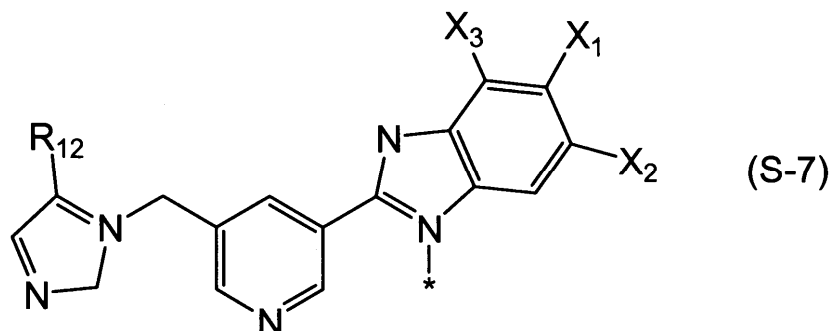
In the formula (S-5), q is preferably 0. In addition, in a case where S is a group represented by the
10 formula (S-5), L is preferably a group presented by $^*\text{-(OCH}_2\text{CH}_2)_m\text{-}$ wherein * is a binding site to the formula (S-5), and m is an integer of 1 to 3 and preferably 3.

[0026]

In the formula (S-6), q is preferably 0. In
15 addition, in a case where S is a group represented by the formula (S-6), L is preferably a group presented by $^*\text{-(CH}_2)_n\text{-}$ wherein * is a binding site to the formula (S-6), and n is an integer of 1 to 5 and preferably 2.

[0027]

20 In addition, in the present invention, a specific example of the group represented by the formula (S-2) includes a group represented by the following formula (S-7).



wherein X_1 , X_2 , and X_3 are the same as in the formula (S-2), R_{12} represents a hydrogen atom, a halogen atom, or CO_2R_a , R_a represents an alkyl group having 1 to 10 carbon atoms, and

5 the asterisk represents a binding site to L.

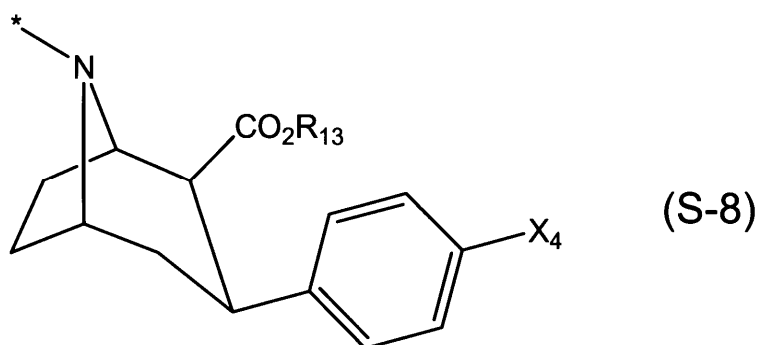
[0028]

In the formula (S-7), R_{12} is preferably a hydrogen atom, X_1 is preferably a hydrogen atom or a halogen atom, X_2 is preferably a halogen atom independently of X_1 , and X_3

10 is preferably a hydrogen atom. In addition, in a case where S is a group represented by the formula (S-7), L is preferably a group represented by $^*-(CH_2)_n-$ wherein * is a binding site to the formula (S-7), and n is an integer of 1 to 5 and preferably 2 or 3.

15 [0029]

In addition, another example which can be adopted as a substrate S includes a group represented by the following formula (S-8).



wherein X_4 is a halogen atom or a methyl group, R_{13} is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, and the asterisk represents a binding site to L.

5 [0030]

In the formula (S-8), X_4 is preferably a halogen atom and R_{13} is preferably a methyl group. In addition, in a case where S is a group represented by the formula (S-7), L is preferably a group presented by $^*-(CH_2)_n-$ wherein * is
 10 a binding site to the formula (S-7), and n is an integer of 1 to 5 and preferably n is 3.

[0031]

Examples of the radioactive labeled compound of the general formula (1) obtained from the labeling precursor
 15 compound of the present invention include various compounds which are used as a radiopharmaceutical, preferably a diagnostic drug by a positron emission tomography (PET) method. For example, in a case where the formula (S-3) is adopted as the substrate S, an amyloid affinity compound

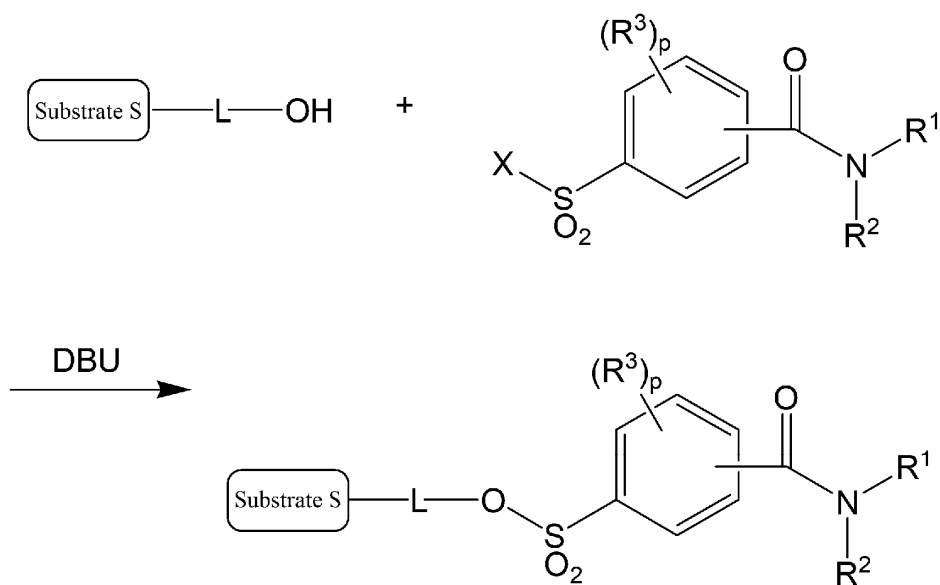
disclosed in WO 2007/135890 A may be mentioned. In addition, in a case where the formula (S-4) is adopted as the substrate S, a compound for imaging myocardial perfusion (for example, Flurpiridaz and the like) disclosed
5 in WO 2005/079391 A may be mentioned by way of example. In addition, in a case where the formula (S-5) is adopted as the substrate S, a compound for imaging amyloid, such as Florbetapir and Florbetaben may be mentioned by way of example. In addition, in a case where the formula (S-6) is
10 adopted as the substrate S, a compound for imaging a tumor, such as O-(2-fluoroethyl)-L-tyrosine (FET) may be mentioned by way of example. In addition, in a case where the formula (S-7) is adopted as the substrate S, a compound for image diagnosis of adrenal gland disease disclosed in
15 WO 2015/199205 A may be mentioned by way of example. In addition, in a case where the formula (S-7) is adopted as the substrate S, a compound for mapping a monoamine reuptake site (for example, FP-CIT) disclosed in WO 99/01184 A may be mentioned by way of example.

20 [0032]

The radioactive fluorine-labeling precursor compound of the present invention can be produced by, for example, acting a sulfonyl fluoride corresponding to a leaving group and diazabicycloundecene (DBU) on a compound (OH form) in
25 which a hydroxyl group is bonded to a site where

radioactive fluorine is to be introduced, as shown in SCHEME 1 below. Note that, in SCHEME 1 below, S, L, R¹ to R³, and p are the same as those mentioned above concerning the general formula (2), and X is a halogen atom.

5 [0033]



SCHEME 1

[0034]

2. Production method of radioactive fluorine-labeled compound using radioactive fluorine-labeling precursor compound

10 compound

According to the present invention, a radioactive fluorine-labeled compound represented by the general formula (1) can be produced by a step of allowing a radioactive fluorine-labeling precursor compound

15 represented by the general formula (2) to react with

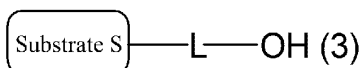
[¹⁸F]fluoride ion (radioactive fluorine labeling reaction step).

[0035]

The radioactive fluorine labeling reaction is preferably performed in the presence of a base in an inert solvent. Specifically, the compound represented by the general formula (1) can be obtained by performing the reaction in an appropriate solvent such as an aprotic solvent, e.g., acetonitrile, N,N-dimethylformamide or dimethyl sulfoxide at a temperature of 20 to 120°C using a [¹⁸F]fluoride ion aqueous solution produced from [¹⁸O]water by cyclotron as the [¹⁸F]fluoride ion and using a base exemplified by tetrabutylammonium or potassium carbonate/Kryptofix 222. The radioactive fluorine labeling reaction can be performed with a synthesis apparatus equipped with a reaction vessel and a shield. In addition, the synthesis apparatus may be an automatic synthesis apparatus in which all steps are automated.

[0036]

In the above reaction step, by-products such as an unreacted precursor compound (that is, a compound represented by the general formula (2)) and an OH form represented by the following general formula (3) coexist with the target compound represented by the general formula (1).



wherein S and L are the same as in the general formula (1).

[0037]

The purification of the target compound represented
5 by the general formula (1) can be performed in accordance
with a solid phase extraction method using a reverse-phase
cartridge column. Specifically, the unreacted precursor
compound (that is, the compound represented by the general
formula (2)) is usually higher in lipophilicity, in other
10 words, higher in hydrophobicity than the target compound
represented by the general formula (1). Accordingly, a
method utilizing such a difference in hydrophobicity may be
used, which may be exemplified by a method in which a
reaction mixture obtained in the radioactive fluorine
15 labeling reaction step is added to a reverse-phase
cartridge column filled with octadecyl silica gel or the
like, [¹⁸F]fluoride ion is separated, and then an
appropriate elution solvent is allowed to pass through the
above column, such that the compound of the general formula
20 (1) which is the object compound can be eluted to be
separated and collected. Examples of the elution solvent
include water-soluble solvents such as acetonitrile,
ethanol, t-butanol and methanol, or a mixed liquid of these
with water. The compound of the general formula (1) which

is the collected target compound can be subjected to deprotection and the like, if necessary, to be an object compound.

5 Examples

[0038]

Hereinafter, the present invention is described more specifically by way of examples; however, the present invention is not limited only to the following examples.

10 [0039]

It is to be noted that in the following examples, the names of individual compounds used in experiments are defined as shown in Table 1.

[0040]

Table 1: Compound No. and Structural Formula

Compound	Structure
Precursor Compound 1	
Precursor Compound 2	
Precursor Compound 3	
Precursor Compound 4	
Precursor Compound 5	
Precursor Compound 6	
Unlabeled Compound 1	

[0041]

5 In the examples, the molecular structure of the individual compounds was identified based on nuclear magnetic resonance (NMR) spectra. AVANCE III HD (manufactured by BRUKER Japan K.K.) was used as an NMR apparatus and deuterated chloroform was used as a solvent.

10 ^1H -NMR was measured at a resonance frequency of 500 MHz.

^{13}C -NMR was measured at a resonance frequency of 125 MHz.

All chemical shifts are given in terms of ppm on a delta scale (δ). Fine splittings of signals were indicated using abbreviations (s: singlet, d: doublet, t: triplet, dd: double doublet, dt: double triplet, dq: double quartet, m: multiplet, and br: broad).

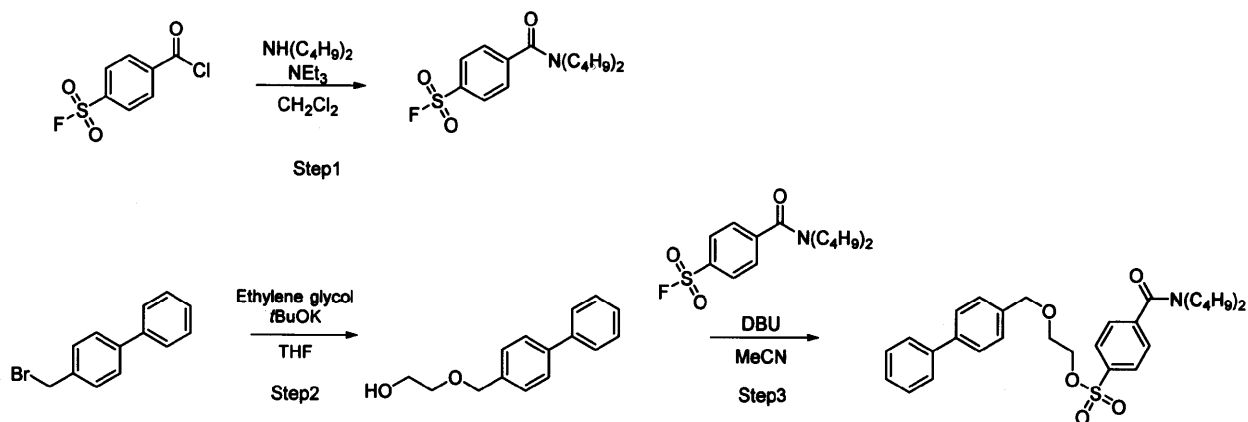
Hereinafter, the term "room temperature" in the examples means 25°C.

In a synthesis example of each compound, each step in the compound synthesis was repeated plural times if necessary to secure an amount required for use as an intermediate or the like in other syntheses.

[0042]

Example 1: Synthesis of precursor compound 1

According to the following scheme, 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl-4-(dibutylcarbamoyle)benzenesulfonate (precursor compound 1) was synthesized.



[0043]

Step 1: Synthesis of 4-(dibutylcarbamoyl)benzenesulfonic acid fluoride

Dibutylamine (280 μ L, 1.60 mmol) was dissolved in
5 dichloromethane (12 mL), triethylamine (0.25 mL, 1.8 mmol)
was added to the resulting solution, the solution was
cooled to 0°C, and then 4-fluorosulfonyl benzoic acid
chloride (233 mg, 1.05 mmol) was added to the cooled
solution and the solution was stirred at 0°C for 5 hours.

10 After completion of the reaction, the reaction solution was
added to 1 mol/L hydrochloric acid and extraction with
ethyl acetate was performed two times. The combined ethyl
acetate layer was washed with a saturated aqueous sodium
hydrogen carbonate solution and a saturated saline solution,
15 dried with anhydrous magnesium sulfate, and concentrated
under reduced pressure, and then the obtained crude product
was purified by silica gel column chromatography (eluent:
hexane/ethyl acetate = 3 : 1) to obtain 4-
(dibutylcarbamoyl)benzenesulfonic acid fluoride (191 mg,
20 0.61 mmol).

$^1\text{H-NMR}$: δ 8.06 (d, 2H, $J=8.5\text{Hz}$), 7.59 (d, 2H, $J=8.0\text{Hz}$),
3.51 (t, 2H, $J=7.5\text{Hz}$), 3.13 (t, 2H, $J=7.5\text{Hz}$), 1.69-1.63 (m, 2H),
1.58 (m, 2H), 1.52-1.46 (m, 2H), 1.43-1.38 (m, 2H), 1.19-
1.11 (m, 2H), 0.99 (t, 3H, $J=7.5\text{Hz}$), 0.81 (t, 3H, $J=7.5\text{Hz}$)

25 [0044]

Step 2: Synthesis of 2-([1,1'-biphenyl]-4-ylmethoxy)ethanol

Potassium t-butoxide (444 mg, 4.4 mmol) was dissolved in ethylene glycol (4.4 mL, 78.9 mmol), a solution obtained by dissolving 4-(bromomethyl)-1,1'-
5 biphenyl (1.8 g, 4.386 mmol) in tetrahydrofuran (20 mL) was added to the resulting solution, and the solution was stirred at 65°C for 6.5 hours. Potassium t-butoxide (101 mg, 1.1 mmol) was added and stirred at 65°C for 1.5 hours. After completion of the reaction, the reaction solution was
10 added to 0.1 mol/L hydrochloric acid and extraction with ethyl acetate was performed two times. The combined ethyl acetate layer was washed with water, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure, and then the obtained crude product was purified by silica
15 gel column chromatography (eluent: hexane/ethyl acetate = 3 : 1) to obtain 2-([1,1'-biphenyl]-4-ylmethoxy)ethanol (967 mg, 4.24 mmol).

$^1\text{H-NMR}$: δ 7.60-7.58 (m, 4H), 7.46-7.41 (m, 4H), 7.37-7.34 (m, 1H), 4.61 (s, 2H), 3.79 (dd, 2H, $J=6.0, 4.0\text{Hz}$),
20 3.64 (dd, 2H, $J=6.0, 4.0\text{Hz}$)
[0045]

Step 3: Synthesis of precursor compound 1

2-([1,1'-biphenyl]-4-ylmethoxy)ethanol (52 mg, 0.22 mmol) was dissolved in acetonitrile (2.0 mL), the solution
25 was cooled to 0°C, and then diazabicycloundecene (79 μL ,

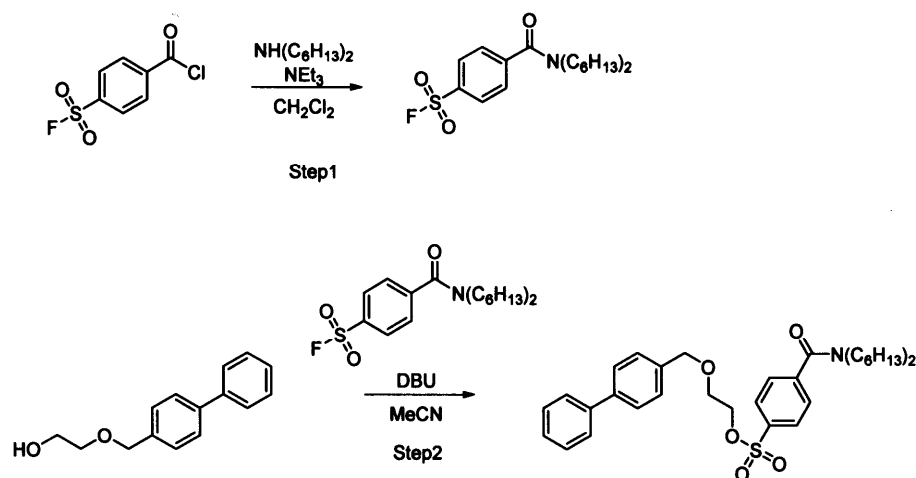
0.50 mmol) and 4-(dibutylcarbamoyl)benzenesulfonic acid fluoride (88 mg, 0.26 mmol) were added to the cooled solution and the solution was stirred at room temperature for 1 hour. After completion of the reaction, water was added to the reaction solution and extraction with ethyl acetate was performed two times. The combined ethyl acetate layer was washed with water and a saturated saline solution, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure, and then the obtained crude product was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 75/25) to obtain the precursor compound 1 (70 mg, 0.14 mmol).

$^1\text{H-NMR}$: δ 7.95 (d, 2H, $J=8.5\text{Hz}$), 7.60-7.56 (m, 4H), 7.49 (d, 2H, $J=8.5\text{Hz}$), 7.46-7.43 (m, 2H), 7.37-7.35 (m, 3H), 4.54 (s, 2H), 4.25 (t, 2H, $J=4.5\text{Hz}$), 3.70 (t, 2H, $J=4.5\text{Hz}$), 3.49 (t, 2H, $J=7.5\text{Hz}$), 3.11 (t, 2H, $J=7.5\text{Hz}$), 1.68-1.60 (m, 2H), 1.49-1.36 (m, 4H), 1.18-1.08 (m, 2H) 0.98 (t, 3H, $J=7.3\text{Hz}$), 0.78 (t, 3H, $J=7.3\text{Hz}$)

[0046]

Example 2: Synthesis of precursor compound 2

According to the following scheme, 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl-4-(dihexylcarbamoyl)benzenesulfonate (precursor compound 2) was synthesized.



[0047]

Step 1: Synthesis of 4-(di-hexylcarbamoyl)benzenesulfonic acid fluoride

5 Dihexylamine (176 μL , 0.75 mol) was dissolved in dichloromethane (12 mL), triethylamine (0.13 mL, 1.25 mmol) was added to the resulting solution, the solution was cooled to 0°C , and then 4-fluorosulfonyl benzoic acid chloride (151 mg, 0.68 mmol) was added to the cooled
10 solution and the solution was stirred at 0°C for 3 hours. After completion of the reaction, the reaction solution was added to 1 mol/L hydrochloric acid and extraction with ethyl acetate was performed two times. The combined ethyl acetate layer was washed with a saturated aqueous sodium
15 hydrogen carbonate solution and a saturated saline solution, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure, and then the obtained crude product was purified by silica gel column chromatography (eluent:

hexane/ethyl acetate = 3 : 1) to obtain 4-(dihexylcarbamoyl)benzenesulfonic acid fluoride (181 mg, 0.49 mmol).

δ 8.06 (d, 2H, J=8.5Hz), 7.59 (d, 2H, J=8.0Hz),
5 3.49 (t, 2H, J=7.5Hz), 3.12 (t, 2H, J=7.5Hz), 1.70-1.64 (m, 2H),
1.52-1.48 (m, 2H), 1.40-1.32 (m, 6H) 1.25-1.18 (m, 2H), 1.18-
1.08 (m, 4H), 0.93-0.90 (m, 3H), 0.84 (t, 3H, J=7.3z)
[0048]

Step 2: Synthesis of precursor compound 2

10 2-([1,1'-biphenyl]-4-ylmethoxy)ethanol (50 mg, 0.22 mmol) was dissolved in acetonitrile (2.0 mL), the solution was cooled to 0°C, and then diazabicycloundecene (79 μ L, 0.50 mmol) and 4-(dibutylcarbamoyl)benzenesulfonic acid fluoride (85 mg, 0.22 mmol) were added to the cooled
15 solution and the solution was stirred at room temperature for 1 hour. After completion of the reaction, water was added to the reaction solution and extraction with ethyl acetate was performed two times. The combined ethyl acetate layer was washed with water and a saturated saline
20 solution, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure, and then the obtained crude product was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 3 : 1) to obtain the precursor compound 2 (83 mg, 0.14 mmol).

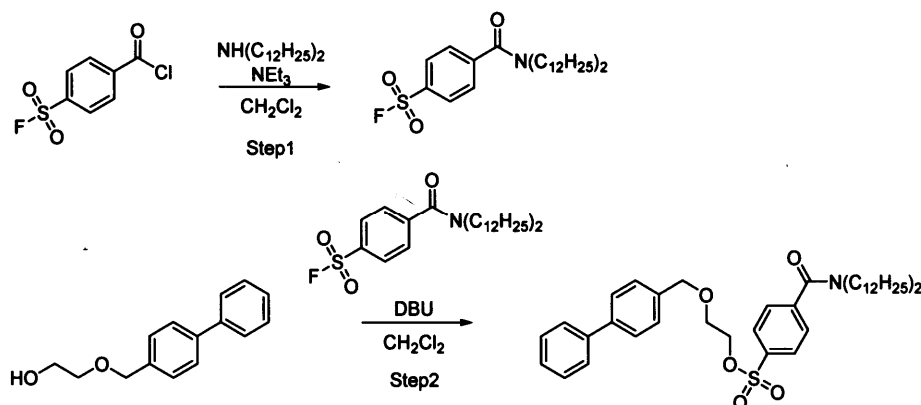
25 $^1\text{H-NMR}$: δ 7.96 (d, 2H, J=8.5Hz), 7.60-7.57 (m, 4H),

7.48 (d, 2H, J=8.5Hz), 7.46-7.42 (m, 2H), 7.37-7.33 (m, 3H),
 4.54 (s, 2H), 4.25 (t, 2H, J=4.8Hz), 3.70 (t, 2H, J=4.8Hz),
 3.47 (t, 2H, J=7.8Hz), 3.10 (t, 2H, J=7.5Hz), 1.68-1.60 (m, 2H),
 1.49-1.30 (m, 6H), 1.25-1.17 (m, 2H), 1.17-1.08 (m, 4H) 0.93-
 5 0.90 (m, 3H), 0.83 (t, 3H, J=7.3z)

[0049]

Example 3: Synthesis of precursor compound 3

According to the following scheme, 2-([1,1'-
 biphenyl]-4-ylmethoxy)ethyl-4-
 10 (didodecylcarbamoyl)benzenesulfonate (precursor compound 3)
 was synthesized.



[0050]

Step 1: Synthesis of 4-(didodecylcarbamoyl)benzenesulfonic 15 acid fluoride

Didodecylamine (500 mg, 2.70 mmol) was dissolved in dichloromethane (23 mL), triethylamine (0.63 mL, 4.50 mmol) was added to the resulting solution, the solution was cooled to 0°C, and then 4-fluorosulfonyl benzoic acid

chloride (500 mg, 2.25 mmol) was added to the cooled solution and the solution was stirred at room temperature for 18 hours. After completion of the reaction, 1 mol/L hydrochloric acid was added to the reaction solution and
5 extraction with ethyl acetate was performed three times. The combined ethyl acetate layer was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated saline solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure, and then
10 the obtained crude product was purified by silica gel column chromatography (eluent: toluene/ethyl acetate = 40 : 1) to obtain 4-(didodecylcarbamoyl)benzenesulfonic acid fluoride (627 mg, 1.16 mmol).

$^1\text{H-NMR}$: δ 8.05 (d, 2H, $J=8.3\text{Hz}$), 7.59 (d, 2H, $J=8.3\text{Hz}$),
15 3.49 (t, 2H, $J=7.6\text{Hz}$), 3.11 (t, 2H, $J=7.4\text{Hz}$), 1.65 (br, 2H),
1.49 (br, 2H), 1.35-1.09 (m, 36H), 0.88 (t, 6H, $J=6.7\text{Hz}$)
[0051]

Step 2: Synthesis of 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl-4-(didodecylcarbamoyl)benzenesulfonate (precursor compound
20 3)

2-([1,1'-biphenyl]-4-ylmethoxy)ethanol (32 mg, 0.14 mmol) was dissolved in dichloromethane (1.4 mL), the solution was cooled at 0°C , and then diazabicycloundecene (50 μL , 0.33 mmol) and 4-

25 (didodecylcarbamoyl)benzenesulfonic acid fluoride (90 mg,

0.17 mmol) were added to the cooled solution and the solution was stirred at room temperature for 18 hours. After completion of the reaction, water was added to the reaction solution and extraction with chloroform was performed three times. The combined ethyl acetate layer was dried with anhydrous sodium sulfate, and concentrated under reduced pressure, and then the obtained crude product was purified by silica gel column chromatography (eluent: chloroform) to obtain 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl-4-(didodecylcarbamoyl)benzenesulfonate (54 mg, 0.07 mmol).

$^1\text{H-NMR}$: δ 7.96-7.94 (m, 2H), 7.60-7.57 (m, 4H), 7.49-7.42 (m, 4H), 7.37-7.35 (m, 3H), 4.54 (s, 2H), 4.25 (t, 2H, $J=4.6\text{Hz}$), 3.70 (t, 2H, $J=4.6\text{Hz}$), 3.47 (t, 2H, $J=7.6\text{Hz}$), 3.09 (t, 2H, $J=7.2\text{Hz}$), 1.63 (br, 2H), 1.46 (br, 2H), 1.35-1.07 (m, 36H), 0.88-0.87 (m, 6H)

[0052]

Example 4: Synthesis of precursor compound 4

According to the following scheme, 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl-4-(dioctadecylcarbamoyl)benzenesulfonate (precursor compound 4) was synthesized.

Step 1: Synthesis of 4-
(dioctadecylcarbamoyl)benzenesulfonic acid fluoride

Diocetadecylamine (282 mg, 0.54 mmol) was dissolved in dichloromethane (1 mL), triethylamine (0.13 mL, 0.90 mmol) was added to the resulting solution, the solution was cooled to 0°C, and then 4-fluorosulfonyl benzoic acid chloride (100 mg, 0.45 mmol) was added to the cooled solution and the solution was stirred at room temperature for 18 hours. After completion of the reaction, water was added to the reaction solution and extraction with chloroform was performed three times. The combined chloroform layer was dried with anhydrous sodium sulfate, and concentrated under reduced pressure, and then the obtained crude product was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 5/1) to obtain 4-(diocetadecylcarbamoyl)benzenesulfonic acid fluoride (208 mg, 0.29 mmol).

$^1\text{H-NMR}$: δ 8.05 (d, 2H, $J=8.4\text{Hz}$), 7.60 (d, 2H, $J=8.4\text{Hz}$),
3.49 (t, 2H, $J=7.6\text{Hz}$), 3.11 (t, 2H, $J=7.6\text{Hz}$), 1.66 (br, 2H),
1.49 (br, 2H), 1.36-1.10 (m, 60H), 0.88 (t, 6H, $J=7.0$)
[0054]

5 Step 2: Synthesis of 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl-
4-(dioctadecylcarbamoyl)benzenesulfonate (precursor
compound 4)

2-([1,1'-biphenyl]-4-ylmethoxy)ethan-1-ol (30 mg,
0.13 mmol) was dissolved in dichloromethane (1.3 mL), the
10 solution was cooled to 0°C , and then diazabicycloundecene
(47 μL , 0.32 mmol) and 4-
(dioctadecylcarbamoyl)benzenesulfonic acid fluoride (112 mg,
0.16 mmol) were added to the cooled solution and the
solution was stirred at room temperature for 18 hours.
15 After completion of the reaction, water was added to the
reaction solution and extraction with chloroform was
performed three times. The combined chloroform layer was
dried with anhydrous sodium sulfate, and concentrated under
reduced pressure, and then the obtained crude product was
20 purified by silica gel column chromatography (eluent:
chloroform) to obtain 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl-
4-(dioctadecylcarbamoyl)benzenesulfonate (63 mg, 0.07 mmol).

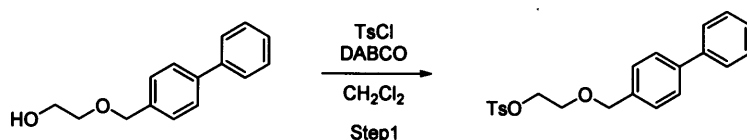
$^1\text{H-NMR}$: δ 7.96-7.94 (m, 2H), 7.60-7.57 (m, 4H), 7.49-
7.42 (m, 4H), 7.37-7.35 (m, 3H), 4.54 (s, 2H),
25 4.25 (t, 2H, $J=4.7\text{Hz}$), 3.70 (t, 2H, $J=4.7\text{Hz}$), 3.50-3.45 (m, 2H),

3.10-3.08 (m, 2H), 1.64-1.62 (m, 2H), 1.47-1.46 (m, 2H), 1.34-1.04 (m, 60H), 0.88 (t, 6H, J=6.75Hz)

[0055]

5 Comparative Example 1: Synthesis of 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl-4-methylbenzenesulfonate (precursor compound 5)

According to the following scheme, the precursor compound 5 was synthesized.



10 [0056]

Step 1: Synthesis of 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl-4-methylbenzenesulfonate

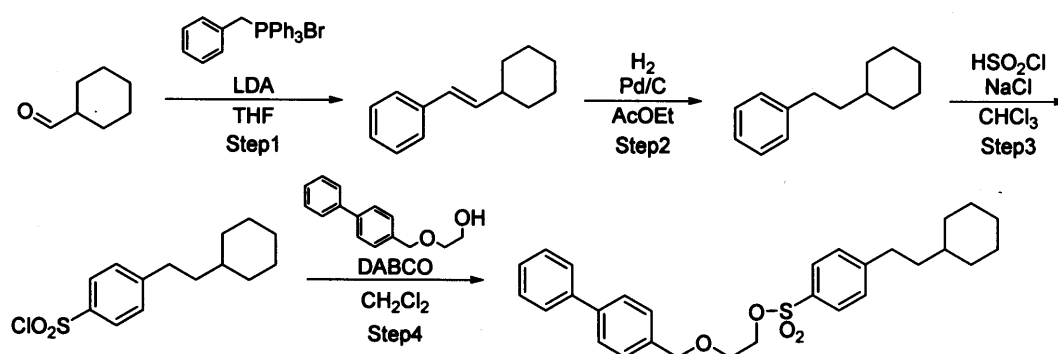
2-([1,1'-biphenyl]-4-ylmethoxy)ethanol (55 mg, 0.24 mmol) was dissolved in dichloromethane (2 mL), and 1,4-diazabicyclo[2,2,2]octane (86 mg, 0.77 mmol) and p-toluenesulfonyl chloride (69 mg, 0.36 mmol) were added to the resulting solution and the solution was stirred at room temperature for 4.5 hours. After completion of the reaction, water was added to the reaction solution and
15
20 extraction with ethyl acetate was performed two times. The combined ethyl acetate layer was dried with anhydrous magnesium sulfate, and concentrated under reduced pressure, and then the obtained crude product was purified by silica

gel column chromatography (eluent: hexane/ethyl acetate = 3 : 1) to obtain 4-methylbenzenesulfonic acid 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl (64 mg, 0.17 mmol).

$^1\text{H-NMR}$: δ 7.81 (d, 2H, $J=8.0\text{Hz}$), 7.60-7.54 (m, 4H), 7.47-7.43 (m, 2H), 7.37-7.30 (m, 5H), 4.53 (s, 2H), 4.22 (t, 2H, $J=4.8\text{Hz}$), 3.70 (t, 2H, $J=4.8\text{Hz}$), 2.43 (s, 3H) [0057]

Comparative Example 2: Synthesis of precursor compound 6

According to the following scheme, 4-(2-cyclohexylethyl)benzenesulfonic acid 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl (precursor compound 6) was synthesized.



[0058]

Step 4: Synthesis of precursor compound 6

2-([1,1'-diphenyl]-4-ylmethoxy)-ethanol (50.6 mg, 0.222 mmol) was dissolved in dichloromethane (2.0 mL) and cooled to 0°C, and then the resultant solution was supplemented with a solution in which 1,4-diazabicyclo[2.2.2]octane (37.4 mg, 0.333 mmol) was dissolved in dichloromethane (2.0 mL) together with 4-(2-

cyclohexyl-ethyl)-benzenesulfonyl chloride (76.4 mg, 0.266 mmol) obtained by performing the Steps 1 to 3 in accordance with the method described in Example 1 of WO 2011/006610 A. After stirring for 30 minutes, the reaction was stopped by
5 addition of a saturated aqueous sodium hydrogen carbonate solution and extraction with dichloromethane was performed three times. The combined dichloromethane layer was washed with water and a saturated saline solution, dried over sodium sulfate, and concentrated under reduced pressure.

10 The obtained crude product was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 4 : 1) to obtain 4-(2-cyclohexylethyl)benzenesulfonic acid 2-([1,1'-biphenyl]-4-ylmethoxy)ethyl (75.6 mg, 0.158 mmol).

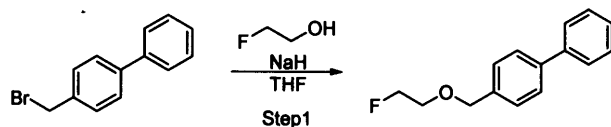
$^1\text{H-NMR}$: δ 7.81 (d, 2H, $J=8.4\text{Hz}$), 7.59-7.55 (m, 4H),

15 7.44 (t, 2H, $J=7.6\text{Hz}$), 7.37-7.30 (m, 5H), 4.53 (s, 2H), 4.23 (t, 2H, $J=4.8\text{Hz}$), 3.70 (t, 2H, $J=4.8\text{Hz}$), 2.67 (t, 2H, $J=8.2\text{Hz}$), 1.74-1.64 (m, 5H), 1.51-1.47 (m, 2H), 1.25-1.13 (m, 4H), 0.96-0.88 (m, 2H)

[0059]

20 Reference Example 1: Synthesis of unlabeled compound 1

According to the following scheme, 4-([2-fluoroethoxy)methyl]-1,1'-biphenyl (unlabeled compound 1) was synthesized.



[0060]

Step 1: Synthesis of 4-([2-fluoroethoxy]methyl)-1,1'-biphenyl

5 2-Fluoroethanol (86 mg, 0.77 mmol) was dissolved in tetrahydrofuran (1.4 mL) and cooled to 0°C, and sodium hydride (3.2 mg, 0.14 mmol) was added to the cooled solution and the solution was stirred for 10 minutes. Subsequently, 4-(bromomethyl)-1,1'-biphenyl (50 mg, 0.20 mmol) was added and stirred at room temperature for 18 hours. After completion of the reaction, a saturated aqueous ammonium chloride solution was added to the reaction solution and extraction with chloroform was performed three times. The combined chloroform layer was washed with water, dried with anhydrous sodium sulfate, concentrated under reduced pressure, and then the obtained crude product was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 10/1) to obtain 4-([2-fluoroethoxy]methyl)-1,1'-biphenyl (5.8 mg, 0.03 mmol).

¹H-NMR: δ 7.60-7.58 (m, 4H), 7.45-7.42 (m, 4H), 7.36-7.33 (m, 1H), 4.65 (s, 2H), 4.61 (dt, 2H, J=47.7Hz, 4.2Hz), 3.76 (dt, 2H, J=29.4Hz, 4.2Hz)

[0061]

Example 5: Preparation of radioactive fluorinated 4-[(2-[¹⁸F]fluoroethoxy)methyl]-1,1'-biphenyl using precursor compounds 1 to 4

5 An aqueous potassium carbonate solution (50 µmol/L, 0.2 mL) and a solution of Kryptofix 222 (trade name, manufactured by Merck KGaA) (12 mg, 37.2 µmol) dissolved in acetonitrile (0.6 mL) were added to [¹⁸F]fluoride ion-containing [¹⁸O]water. The resulting solution was heated at
10 110°C in a flow of argon gas to evaporate water, and then supplemented with acetonitrile (0.5 mL x 3) and azeotropically evaporated to dryness. A solution of each of the precursor compounds 1 to 6 (8 µmol) synthesized in accordance with the methods shown in Examples 1 to 6
15 dissolved in acetonitrile (0.5 mL) was added to the dried residue, and the mixture was heated at 90°C for 5 minutes. After completion of the reaction, the mixture was analyzed by a thin layer chromatography (TLC) under the following conditions, and then water for injection (10 mL) was added
20 to the mixture. Then, the mixture was allowed to pass through Sep-Pak (registered trademark) C18 Plus (trade name, manufactured by Nippon Waters K.K.), such that 4-[(2-[¹⁸F]fluoroethoxy)methyl]-1,1'-biphenyl was absorbed and collected onto the corresponding column. After the column
25 was washed with water (10 mL), a mixed liquid (4 mL) of

water/acetonitrile = 1:3 was allowed to pass through the column to elute 4-[(2-[¹⁸F]fluoroethoxy)methyl]-1,1'-biphenyl.

The 4-[(2-[¹⁸F]fluoroethoxy)methyl]-1,1'-biphenyl
5 obtained by the operation described above was subjected to an HPLC analysis under the following conditions. Note that the identification was performed by confirming whether or not its R_f value on the TLC plate is the same as that of the unlabeled compound of 4-[(2-fluoroethoxy)methyl]-1,1'-
10 biphenyl synthesized with Reference Example 1.

[0062]

TLC condition

Plate: TLC glass plate Silica gel 60F₂₅₄

Developing solvent: hexane/ethyl acetate = 3 : 1

15 HPLC condition

Column: CAPCELLPAKC18MGII (trade name, manufactured by Shiseido Company, Limited, particle size: 5 μm, size: 4.6 mmφ x 150 mm)

Mobile phase: 20 mmol/L ammonium acetate buffer
20 solution (pH = 6.0)/acetonitrile = 70/30 → 30/70 (0 → 30 minutes), 30/70 (30 → 45 minutes), 30/70 → 1/99 (45 → 46 minutes), 1/99 (46 → 100 minutes)

Flow rate: 1.0 mL/min

Detector: ultraviolet-visible absorption photometer
25 (detection wavelength: 254 nm)

[0063]

Comparative Example 3: Preparation of radioactive
fluorinated 4-[(2-[¹⁸F]fluoroethoxy)methyl]-1,1'-biphenyl
using conventional precursor compound

5 The preparation was performed in the same manner as
in Example 5 except that, as a precursor compound, the
precursor compound 5 or 6 synthesized in accordance with
the method shown in Comparative Example 1 or 2 was used.

[0064]

10 Evaluation 1: Evaluation of labeling reaction for fluorine-
labeled compound

Table 2 shows the amounts of radioactivity used in
Example 5 and Comparative Example 3, and the amount of
radioactivity and [¹⁸F] fluorination rate of the obtained
15 product (4-[(2-[¹⁸F]fluoroethoxy)methyl]-1,1'-biphenyl). A
peak area ratio of 4-[(2-[¹⁸F]fluoroethoxy)methyl]-1,1'-
biphenyl subjected to the TLC analysis after completion of
the reaction was taken as a [¹⁸F] fluorination rate.

As shown in Table 2, by using the precursor
20 compounds 1 to 4 of the Examples, the approximately same
[¹⁸F] fluorination rate as those of the conventional
precursor compounds 5 and 6 was obtained.

[0065]

Table 2

	Radioactivity of [^{18}F]F $^-$ water used (Value corrected at start of synthesis)	Amount of radioactivity of product (Measurement time)	[^{18}F] fluorination rate at the time of completing reaction
Precursor Compound 1	443 MBq	241 MBq (44 minutes after start of synthesis)	75%
Precursor Compound 2	234 MBq	177 MBq (44 minutes after start of synthesis)	82%
Precursor Compound 3	488 MBq	250 MBq (35 minutes after start of synthesis)	67%
Precursor Compound 4	676 MBq	276 MBq (41 minutes after start of synthesis)	65%
Precursor Compound 5	158 MBq	78.4 MBq (65 minutes after start of synthesis)	78%
Precursor Compound 6	507 MBq	256 MBq (60 minutes after start of synthesis)	66%

[0066]

Evaluation 2: Evaluation of impurities

5 Table 3 shows the evaluation results obtained by an HPLC analysis of the amount of nonradioactive impurities in the 4-[(2-[^{18}F]fluoroethoxy)methyl]-1,1'-biphenyl obtained

in Example 5 and Comparative Example 3. A mixed amount of the precursor compound was quantitatively determined with a calibration curve prepared using a standard sample. In addition, a collection rate was shown as a collection rate with respect to the amount of precursor compound used in the radioactive fluorination reaction. The amount of impurities having unknown structures was converted to the amount of OH form (2-([1,1'-biphenyl]-4-ylmethoxy)ethan-1-ol) for evaluation.

As a result, as shown in Table 3, all of the precursor compounds 1 to 4 of the Examples showed smaller amounts of precursor contamination than the conventional precursor compounds 5 and 6. In addition, the precursor compounds 1, 3, and 4 were also smaller in amounts of nonradioactive impurities having unknown structures than the conventional compound.

[0067]

Table 3

	Mixed amount of precursor compound (Collection rate)	Mixed amount of nonradioactive impurities* having unknown structures (Collection rate)
Precursor Compound 1	11 µg/mL (1%)	335 µg/mL (32%)
Precursor Compound 2	12 µg/mL (1%)	401 µg/mL (34%)
Precursor Compound 3	Lower than detection limit * (0%)	310 µg/mL (21%)
Precursor Compound 4	Lower than detection limit * (0%)	290 µg/mL (26%)
Precursor Compound 5	303µg/mL (40%)	354 µg/mL (46%)
Precursor Compound 6	60µg/mL (6%)	191 µg/mL (20%)

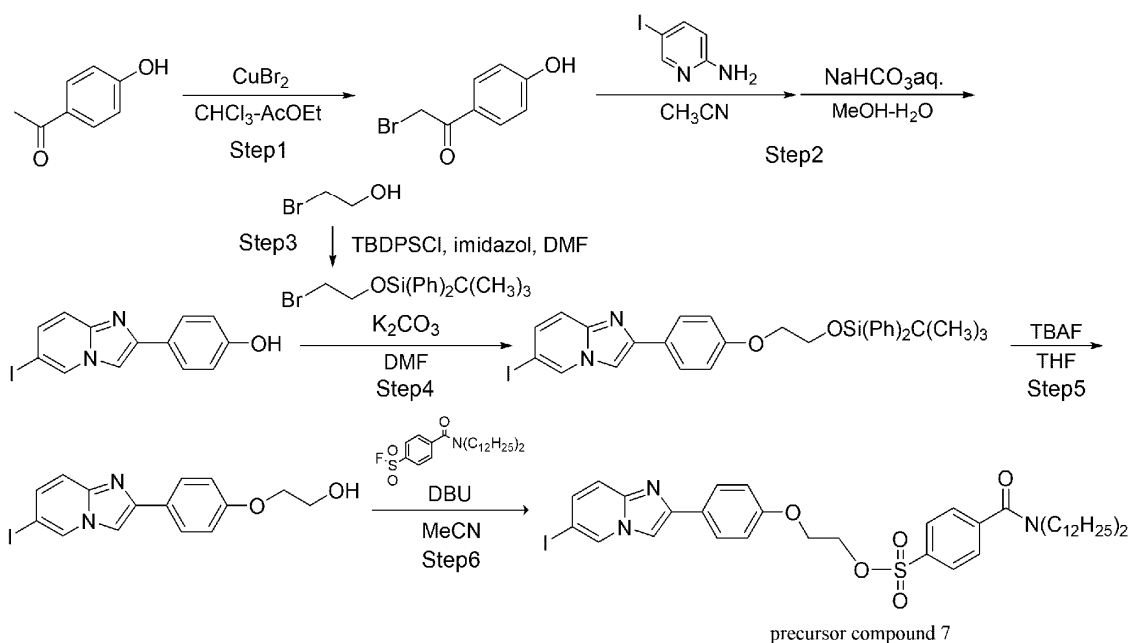
*Detection limit: 1 µg/mL

5 [0068]

Example 6: Synthesis of precursor compound 7

According to the following scheme, 2-(4-(6-imidazo[1,2-a]pyridine-2-yl)phenoxy)ethyl-4-(didodecylcarbamoyl)benzenesulfonate (precursor compound 7)

10 was synthesized.



[0069]

Step 6: Synthesis of precursor compound 7

2-[4'-(2-hydroxyethoxy)phenyl]-6-iodoimidazo[1,2-a]pyridine (100 mg, 0.263 mmol) obtained by performing the Steps 1 to 5 in accordance with the method described in Example II-14 of WO 2007/135890 A was dissolved in acetonitrile (10.0 mL) and cooled to 0°C, and then the resultant solution was supplemented with a solution in which 1,8-diazabicyclo[5.4.0]undecene (78.6 μL , 0.526 mmol) was dissolved in acetonitrile (2.0 mL) together with 4-didodecylcarbamoyl benzene sulfonic acid fluoride (185 mg, 0.342 mmol) obtained by performing the Step 1 in accordance with the method described in Example 3. After warming to room temperature and stirring for 3 hours, the reaction was

stopped by addition of water and extraction with ethyl acetate was performed three times. The combined ethyl acetate layer was washed with a saturated aqueous sodium hydrogen carbonate solution, water, and a saturated saline solution, dried over sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (eluent: chloroform) to obtain 2-(4-(6-imidazo[1,2-a]pyridine-2-yl)phenoxy)ethyl-4-(didodecylcarbamoyl)benzenesulfonate (198 mg, 0.220 mmol) (precursor compound 7).

$^1\text{H-NMR}$: δ 8.37 (s, 1H), 7.98 (d, 2H, $J=8.4\text{Hz}$), 7.84 (d, 2H, $J=8.8\text{Hz}$), 7.7 (s, 1H), 7.52 (d, 2H, $J=8.4\text{Hz}$), 7.40 (d, 1H, $J=9.4\text{Hz}$), 7.32 (d, 1H, $J=9.4\text{Hz}$), 6.88 (d, 2H, $J=8.8\text{Hz}$), 4.42 (t, 2H, $J=4.6\text{Hz}$), 3.48 (t, 2H, $J=4.6\text{Hz}$), 3.48 (t, 2H, $J=7.6\text{Hz}$), 3.11 (t, 2H, $J=7.6\text{Hz}$), 1.65-1.45 (m, 12H), 1.36-1.08 (m, 29H), 0.89-0.86 (m, 5H)
[0070]

Example 7: Synthesis of amyloid beta imaging agent

An amyloid beta imaging agent, 2-[4'-(2''-[^{18}F]fluoroethoxy)phenyl]-6-iodoimidazo[1,2-a]pyridine (^{18}F labeled compound 1-9 in WO 2007/135890 A) was produced by using the precursor compound 7 synthesized in accordance with the method shown in Example 6.

An aqueous potassium carbonate solution (66 $\mu\text{mol/L}$, 0.3 mL) and a solution of Kryptofix 222 (trade name,

manufactured by Merck KGaA) (15 mg, 39.9 μ mol) dissolved in acetonitrile (1.5 mL) were added to [18 F]fluoride ion-containing [18 O]water (the amount of radioactivity: 533 MBq, the value corrected at the start of synthesis). The

5 resulting solution was heated at 110°C in a flow of argon gas to evaporate water, and then supplemented with acetonitrile (0.5 mL x 3) and azeotropically evaporated to dryness. A solution of the precursor compound 7 (30 mg, 33 μ mol) synthesized with the example described above

10 dissolved in dimethyl sulfoxide (0.5 mL) was added to the mixture and heated at 110°C for 10 minutes. After completion of the reaction, water for injection (10 mL) was added to the mixture, and the mixture was allowed to pass through Sep-Pak (registered trademark) C18 Plus (trade name,

15 manufactured by Nippon Waters K.K.). Then, the column was washed with water (10 mL) and a mixed liquid (2 mL) of water/acetonitrile = 1:1, and then 2-[4'-(2''-[18 F]fluoroethoxy)phenyl]-6-iodoimidazo[1,2-a]pyridine was eluted with a mixed liquid (3 mL) of water/acetonitrile =

20 1 : 3. The obtained amount of radioactivity was 186 MBq (58 minutes after the start of synthesis). In addition, as a result of the HPLC analysis under the following conditions, it was confirmed that 4 μ g/mL of the unreacted precursor compound 7 was mixed. In case where a toluene

25 sulfonic acid ester group is used as a leaving group,

instead of the sulfonic acid ester group having an alkyl amide tag introduced according to the present invention, a mixed amount of the unreacted precursor compound was 650 µg/mL. Thus, it was confirmed that an amyloid beta imaging agent low in contamination of the unreacted precursor compound was able to be synthesized by the present invention even without the HPLC purification.

[0071]

HPLC condition

Column: YMC-Pack Pro C8 (trade name, manufactured by YMC CO., LTD., particle size: 5 µm, size: 4.6 mmφ × 150 mm)

Mobile phase: 10 mmol/L ammonium formate buffer solution (pH3)/acetonitrile = 100/0 → 70/30 (0 → 20 minutes), 70/30 → 10/90 (20 → 30 minutes), 10/90 (30 → 70 minutes)

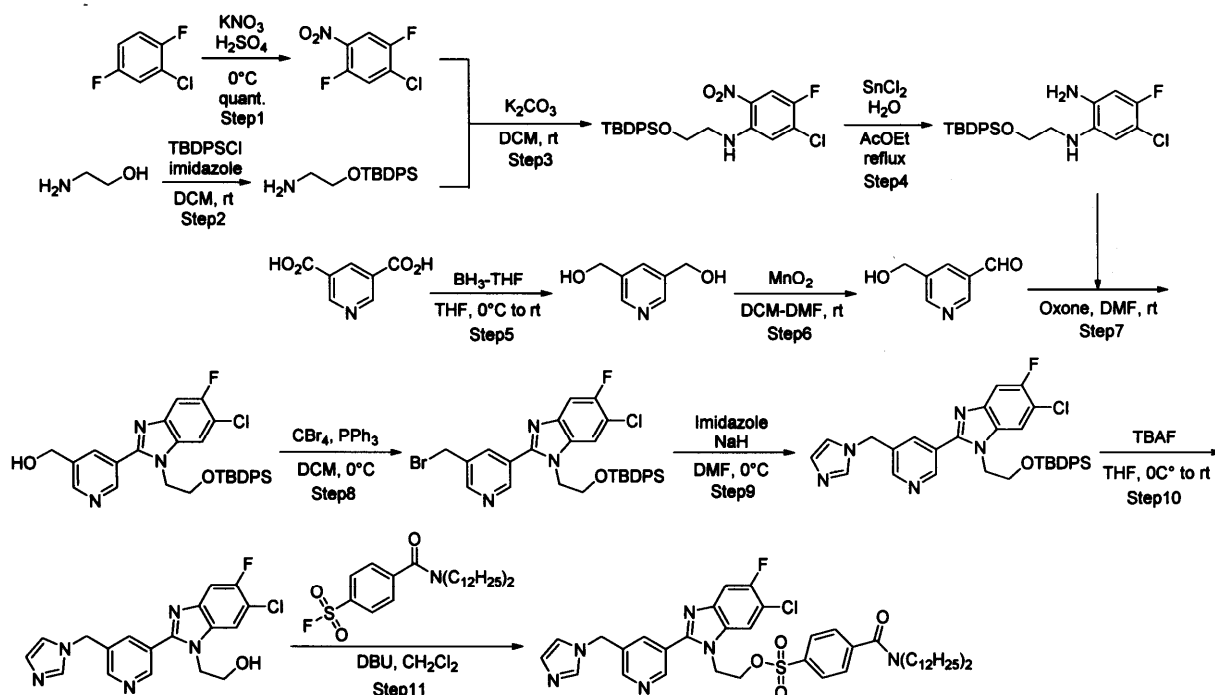
Flow rate: 1.0 mL/min

Detector: ultraviolet-visible absorption photometer (detection wavelength: 260 nm)

[0072]

Example 8: Synthesis of precursor compound 8

According to the following scheme, 2-(2-{5-[(1H-imidazole-1-yl)methyl]pyridine-3-yl}-6-chloro-5-fluoro-1H-benzimidazole-1-yl)ethyl-4-(didodecylcarbamoyl)benzenesulfonate (precursor compound 8) was synthesized.



[0073]

Step 1: Synthesis of precursor compound 8

5 2-{6-chloro-5-fluoro-2-[5-(imidazole-1-ylmethyl)pyridine-3-yl]benzimidazole-1-yl}ethanol (57.3 mg, 0.154 mmol) obtained by performing the Steps 1 to 10 in accordance with the method described in Example 2 of WO 2015/199205 A was dissolved in dichloromethane (0.54 mL) and cooled to 0°C, and then the resultant solution was supplemented with a solution in which 1,8-diazabicyclo[5.4.0]undecene (55.3 µL, 0.370 mmol) was dissolved in dichloromethane (1.0 mL) together with 4-didodecylcarbamoyl benzene sulfonic acid fluoride (100 mg, 0.185 mmol) obtained by performing the Step 1 in accordance

with the method described in Example 3. After warming to room temperature and stirring for 1 hour, the reaction was stopped by addition of water and extraction with dichloromethane was performed three times. The combined
5 dichloromethane layer was washed with water and a saturated saline solution, dried over sodium sulfate, and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (eluent: dichloromethane) to obtain 2-(2-{5-[(1H-imidazole-
10 1-yl)methyl]pyridine-3-yl}-6-chloro-5-fluoro-1H-benzimidazole-1-yl)ethyl-4-(didodecylcarbamoyl)benzenesulfonate (precursor compound 8) (94 mg, 0.105 mmol).

$^1\text{H-NMR}$: δ 8.85 (d, 1H, $J=2.1\text{Hz}$), 8.63 (d, 1H, $J=2.1\text{Hz}$),
15 7.84 (dd, 1H, $J=2.1, 2.1\text{Hz}$), 7.66 (d, 2H, $J=8.4\text{Hz}$),
7.66 (s, 1H), 7.59 (d, 1H, $J=9.0\text{Hz}$), 7.43 (d, 2H, $J=8.4\text{Hz}$),
7.40 (d, 1H, $J=6.1\text{Hz}$), 7.14 (t, 1H, $J=1.2\text{Hz}$), 7.00 (t, 1H, $J=1.2\text{Hz}$),
5.29 (s, 2H), 4.47 (t, 2H, 5.2Hz) 4.25 (t, 2H, $J=5.2\text{Hz}$),
3.47 (t, 2H, $J=7.5\text{Hz}$), 3.07 (t, 2H, $J=7.5\text{Hz}$), 1.65 (br, 2H), 1.47-
20 1.43 (m, 2H), 1.36-1.06 (m, 36H), 0.88-0.86 (m, 6H)
[0074]

Example 9: Synthesis of aldosterone synthase imaging agent

An aldosterone synthase imaging agent, 6-chloro-5-fluoro-1-(2-[^{18}F]fluoroethyl)-2-[5-(imidazole-1-ylmethyl)pyridine-3-yl]benzimidazole (^{18}F labeled compound
25

100 in WO 2015/199205 A) was produced by using the precursor compound 8 synthesized with the method shown in Example 8.

An aqueous potassium carbonate solution (50 $\mu\text{mol/L}$,
5 0.25 mL) and a solution of Kryptofix 222 (trade name, manufactured by Merck KGaA) (14 mg, 37.2 μmol) dissolved in acetonitrile (0.7 mL) were added to [^{18}F]fluoride ion-containing [^{18}O]water (the amount of radioactivity: 533 MBq, the value corrected at the start of synthesis). The
10 resulting solution was heated at 110°C in a flow of argon gas to evaporate water, and then supplemented with acetonitrile (0.5 mL x 3) and azeotropically evaporated to dryness. A solution of the precursor compound 7 (8.5 mg, 9.5 μmol) synthesized with the example described above
15 dissolved in dimethyl sulfoxide (0.5 mL) was added to the mixture and heated at 110°C for 10 minutes. After completion of the reaction, water for injection (10 mL) was added to the mixture, and the mixture was allowed to pass through Sep-Pak (registered trademark) C18 Plus (trade name,
20 manufactured by Nippon Waters K.K.). Then, the column was washed with water (10 mL), and then 6-chloro-5-fluoro-1-(2-[^{18}F]fluoroethyl)-2-[5-(imidazole-1-ylmethyl)pyridine-3-yl]benzimidazole was eluted with a mixed liquid (5 mL) of water/acetonitrile = 1:1. The obtained amount of
25 radioactivity was 141 MBq (44 minutes after the start of

synthesis). In addition, as a result of the HPLC analysis under the following conditions, it was confirmed that the unreacted precursor compound 8 was able to be removed to less than a detection limit value. In case where a toluene sulfonic acid ester group is used as a leaving group, instead of the sulfonic acid ester group having an alkyl amide tag introduced according to the present invention, a mixed amount of the unreacted precursor compound was 115 µg/mL. Thus, it was confirmed that an aldosterone synthase imaging agent low in contamination of the unreacted precursor compound was able to be synthesized by the present invention even without the HPLC purification.

[0075]

HPLC condition

Column: XBridge Phenyl (trade name, manufactured by Nippon Waters K.K., particle size: 3.5 µm, size: 4.6 mmφ x 100 mm)

Mobile phase: 10 mmol/L ammonium carbonate solution/methanol = 50/50 → 35/65 (0 → 10 minutes), 35/65 → 0/100 (10 → 25 minutes), 0/100 (25 → 50 minutes)

Flow rate: 1.0 mL/min

Detector: ultraviolet-visible absorption photometer (detection wavelength: 254 nm)

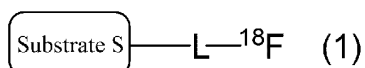
[0076]

This application claims priority based on Japanese

Patent Application No. 2017-042783 filed on March 7, 2017,
the disclosure of which is incorporated herein in its
entirety.

CLAIMS

1. A labeling precursor compound for a radioactive fluorine-labeled compound represented by the following general formula (1):

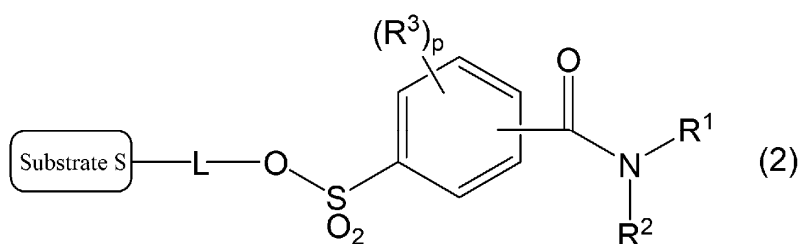


wherein S represents a substrate, and

L represents a straight alkyl group having 1 to 6 carbon atoms, which may contain an ether group,

the labeling precursor compound being represented by

10 the following general formula (2):



wherein S and L are the same as in the general formula (1),

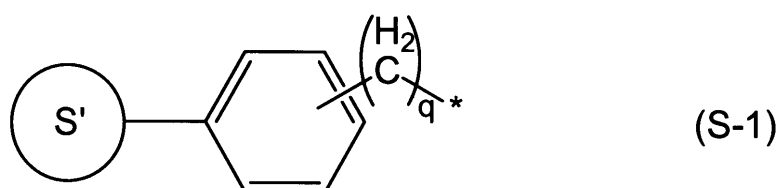
R¹ and R² each independently represent a straight or branched alkyl group having 1 to 30 carbon atoms, or a substituted or unsubstituted monocyclic or condensed polycyclic aryl group,

R³ each independently represent an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and

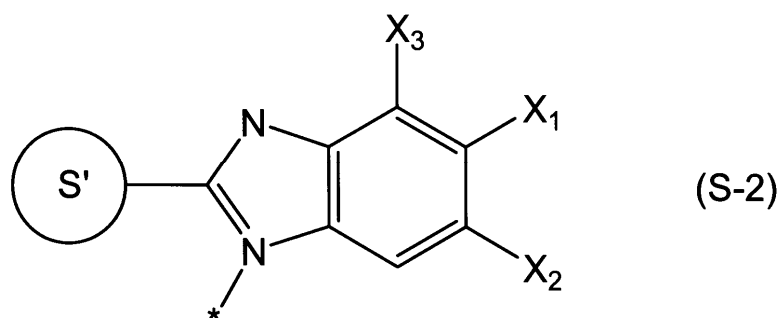
20 p represents an integer of 0 to 4.

2. The labeling precursor compound according to claim 1,
wherein the radioactive fluorine-labeled compound
represented by the general formula (1) has a clogP of -1.4
to 5.0, and a difference in clogP between the radioactive
5 fluorine-labeled compound represented by the general
formula (1) and the precursor compound represented by the
general formula (2) is 2 or more.

3. The labeling precursor compound according to claim 1
10 or 2, wherein, in the general formulas (1) and (2), S is a
group represented by the following formula (S-1) or (S-2):



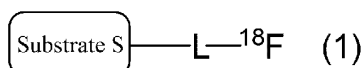
wherein, in the formula (S-1), S' is a part of S, q is 0 or
1, and the asterisk is a binding site to L,



15 wherein, in the formula (S-2), S' is a part of S, X₁ and X₃
each independently represent a hydrogen atom or a halogen
atom, and X₂ represents a hydrogen atom, a halogen atom, or

a nitrile group, but at least one of X_1 , X_2 , and X_3 is a halogen atom, and the asterisk is a binding site to L.

4. A production method of a radioactive fluorine-labeled compound, comprising a step of allowing a labeling precursor compound according to any one of claims 1 to 3 to react with $[^{18}\text{F}]$ fluoride ion to obtain a radioactive fluorine-labeled compound represented by the following general formula (1):



wherein S represents a substrate, and
L represents a straight alkyl group having 1 to 6 carbon atoms, which may contain an ether group.

15 5. The production method according to claim 4, further comprising:

a step of adding a reaction mixture containing a radioactive fluorine-labeled compound represented by the general formula (1) to a reverse-phase cartridge column, said reaction mixture being obtained by the reaction of the labeling precursor compound with $[^{18}\text{F}]$ fluoride ion; and

a step of eluting the radioactive fluorine-labeled compound represented by the general formula (1) from the reverse-phase cartridge column.