

PSMA-TARGETED RADIOPHARMACEUTICAL FOR DIAGNOSING AND TREATING PROSTATE CANCER

BACKGROUND OF THE INVENTION

5

1. Field of the Invention

The present invention relates to a PSMA-targeted radiopharmaceutical for diagnosing and treating prostate cancer.

10

2. Description of the Related Art

Prostate cancer is the most common male cancer in the world and ranks second in mortality. Prostate cancer usually develops in men over 50, and the number
15 of patients increases rapidly with age. It usually progresses slowly, but when it develops into a malignant metastasis, it is extremely difficult to treat. The metastasis usually begins to the lymph nodes, pelvic bones, vertebrae and bladder around
20 prostate cancer and gradually spreads throughout the body.

Prostate-specific antigen test (PSA test) and digital rectal examination are currently used primarily for prostate cancer diagnosis, and
25 transrectal ultrasonography, CT, MRI and WBBS (Whole

body bone scan) imaging are also used. Biopsies for prostate cancer diagnosis are also being conducted. However, in most cases the diagnostic accuracy is low and early diagnosis of the disease is difficult. In addition, it is difficult to determine metastasis and difficult to distinguish from benign diseases such as prostate hyperplasia and prostatitis.

PET (Positron Emission Tomography) is a medical imaging technique that diagnoses a disease using a short half-life radioactive isotope emitting positrons. This technique can be used for early diagnosis of a disease, evaluation of treatment and confirmation of metastasis/recurrence.

[¹⁸F]FDG is a representative PET radiopharmaceutical used for cancer diagnosis because it can observe the enhanced glucose metabolism of cancer cells. However, prostate cancer has a characteristic that it is difficult to detect early or diagnose disease progression because the intake of [¹⁸F]FDG is not high. Choline is a material used for the biosynthesis of phosphatidylcholine, which is essential for cell membrane formation, and [¹¹C]Choline and [¹⁸F]fluorocholine are known to be more suitable for diagnosing prostate cancer than

[¹⁸F]FDG. However, they have low sensitivity to diagnose prostate cancer early, lymph node metastasis, and recurrence, and it is difficult to distinguish prostate cancer from other cancers.

5

Prostate-Specific Membrane Antigen (PSMA) is a protein that is specifically over-expressed in prostate cancer and has an enzyme activity that degrades N-acetyl-L-aspartyl-glutamate (NAAL). It is
10 known that a compound having a glutamic acid-urea-lysine (GUL) structure does not decompose into analogues of NAAL and binds to PSMA very selectively. To date, several compounds with GUL as a basic structure have been developed, and among them, the
15 compounds labeled with F-18 (half-life: 110 minutes) are being developed as PET radiopharmaceuticals for diagnosing prostate cancer.

In addition to F-18, Ga-68 is a radioactive metal that emits positrons, and has a feature of easily
20 complexing with a chelator bound to a precursor, and a ⁶⁸Ga-labeled GUL compound can also be used as a PET radiopharmaceutical for diagnosing prostate cancer.

In the case of a ⁶⁸Ga-labeled GUL compound, it can
25 be used as a prostate cancer targeted therapy by

replacing Ga-68, a positron emitting isotope, with a therapeutic radioactive metal that emits beta rays or alpha particles. In the case of ^{68}Ga -PSMA-617, a ^{68}Ga -labeled compound, a clinical study is underway in
5 which ^{177}Lu -PSMA-617 labeled with Lu-177 (lutetium-177), which emits beta rays, is synthesized instead of Ga-68 and used in prostate cancer patients. It has been reported that most of the prostate cancer that has spread throughout the body is eliminated by
10 repeated administration of 3 times.

In addition, a PSMA-targeted therapy labeled with an alpha-particle-emitting isotope is also being developed, and since it emits more energy than beta
15 rays, the therapeutic effect thereof is better. Representative nuclides include Ac-225 (actinium-225), Bi-213 (bismuth-213), At-211 (astatine-211), etc. Currently, Xofigo® is used to treat prostate cancer that has metastasized to bone, but it is an injection
20 of ^{223}Ra - RaCl_2 (radium dichloride), which has no therapeutic effect on prostate cancer formed other than bone.

The present inventors have completed the present
25 invention after confirming that the new structured

PSMA-targeted compounds labeled with a radioactive metal have high binding force and selectivity to PSMA, and excellent pharmacokinetic properties.

5 **SUMMARY OF THE INVENTION**

 It is an object of the present invention to provide a compound in which a radioactive metal-coupled chelator is coupled to a glutamic acid-urea-
10 lysine compound having excellent binding force to PSMA protein and showing excellent pharmacokinetic properties in vivo, a stereoisomer thereof, a hydrate thereof, or a pharmaceutically acceptable salt thereof.

15 It is another object of the present invention to provide a compound in which a chelator is coupled to a glutamic acid-urea-lysine compound having excellent binding force to PSMA protein and showing excellent pharmacokinetic properties in vivo, a stereoisomer
20 thereof, a hydrate thereof, or a pharmaceutically acceptable salt thereof.

 It is another object of the present invention to provide a composition for diagnosing prostate cancer comprising the compound as an active ingredient.

It is another object of the present invention to provide a pharmaceutical composition for preventing or treating prostate cancer comprising the compound as an active ingredient.

5 It is another object of the present invention to provide a method for treating cancer, comprising a step of administering the compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof to an individual or a subject
10 in need.

It is another object of the present invention to provide the compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof for the treatment of cancer.

15 It is another object of the present invention to provide a use of the compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof for the preparation of a drug for treating cancer.

20

To achieve the above objects, in one aspect of the present invention, the present invention provides a compound represented by formula 1 below, a stereoisomer thereof, a hydrate thereof, or a
25 pharmaceutically acceptable salt thereof.

$$\text{R}_2\text{-C}_6\text{H}_4\text{-L}_4\text{-C(=O)-NH-L}_1\text{-C(=O)-NH-}\left[\text{NH-C(=O)-L}_1\text{-C(=O)-NH-L}_3\text{-Tz-L}_2\text{-W-X-N(R}_1\text{)-U-L}_1\text{-C(=O)-NH-C(=O)-NH-CH(COOH)-CH}_2\text{CH}_2\text{COOH}\right]_n\text{-NH-L}_3\text{-Tz-L}_2\text{-W-X-N(R}_1\text{)-U-L}_1\text{-C(=O)-NH-C(=O)-NH-CH(COOH)-CH}_2\text{CH}_2\text{COOH}$$

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 8;

R₁ is hydrogen, or -L₅-CO₂H, wherein L₅ is -(CH₂)_b-
 wherein b is an integer of 1 ~ 6;

W is a bond, or $-NA_1-$, A_1 is hydrogen, or $-(CH_2)_c-$
 dyl, wherein c is an integer of $0 \sim 3$;

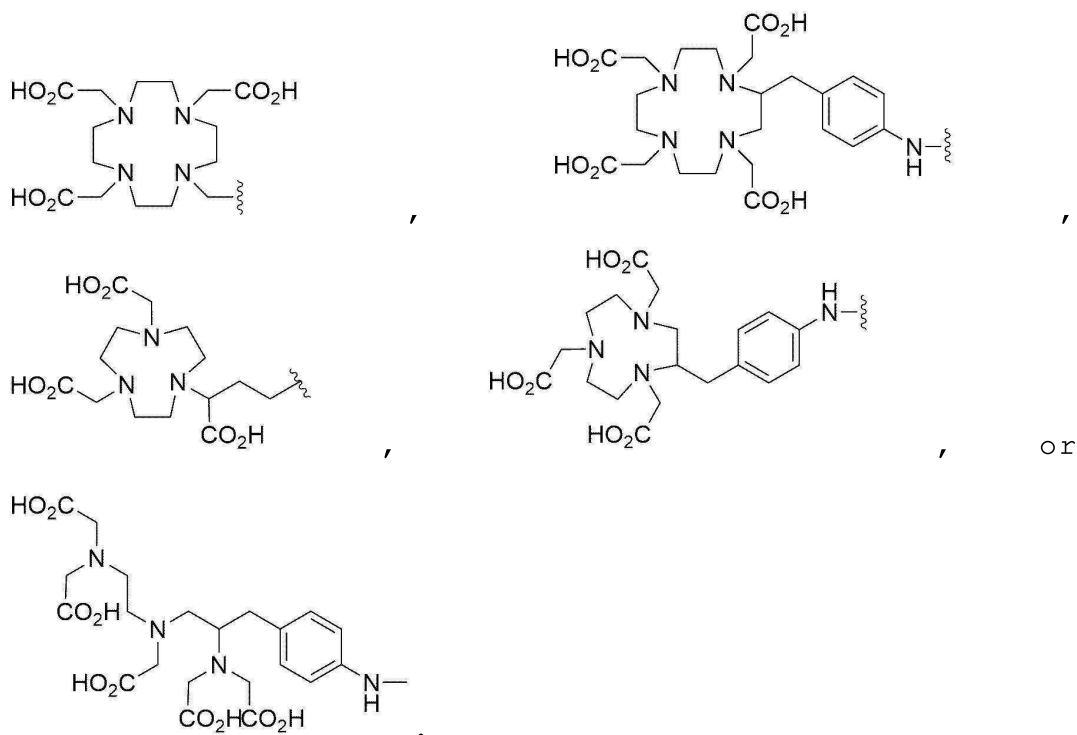
Tz is a bond, , or ;

L₄ is -(CH₂)_e-, wherein e is an integer of 1 ~ 6;
n is an integer of 0 ~ 1;

7

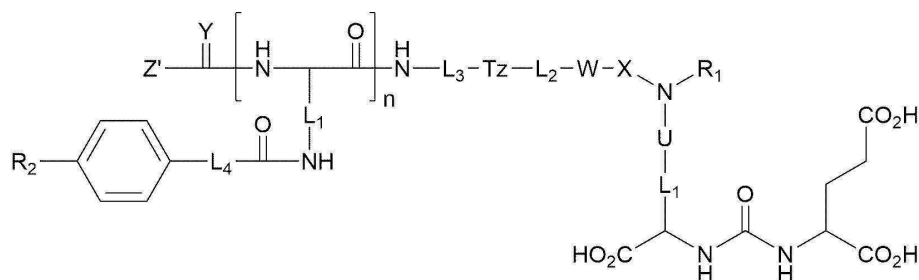
Y is oxygen or sulfur;

Z is a chelator including a radioactive metal,
 wherein the radioactive metal is Ga-68, Cu-64, Cu-67,
 Y-90, Sc-47, In-111, Sn-117m, Lu-177, Bi-212, Bi-213,
 5 Pb-212, Rd-223, or Ac-225, and the chelator is



10 In another aspect of the present invention, the
 present invention provides a compound represented by
 formula 2 below, a stereoisomer thereof, a hydrate
 thereof, or a pharmaceutically acceptable salt
 thereof.

15 [Formula 2]



In formula 2,

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 8;

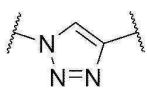
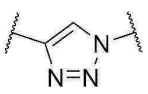
U is a bond, or $-C(O)-$;

5 R_1 is hydrogen, or $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$,
 , wherein b is an integer of 1 ~ 6;

X is a bond, or $-C(O)-$;

W is a bond, or $-NA_1-$, A_1 is hydrogen, or $-(CH_2)_c-$
 pyridyl, wherein c is an integer of 0 ~ 3;

10 L_2 is a bond, or $-(CH_2)_d-$, wherein d is an integer
 of 1 ~ 8;

Tz is a bond, , or ;

L_3 is C_{1-12} straight or branched alkylene, wherein
 one or more carbon atoms in alkylene can be replaced
 15 by oxygen atoms;

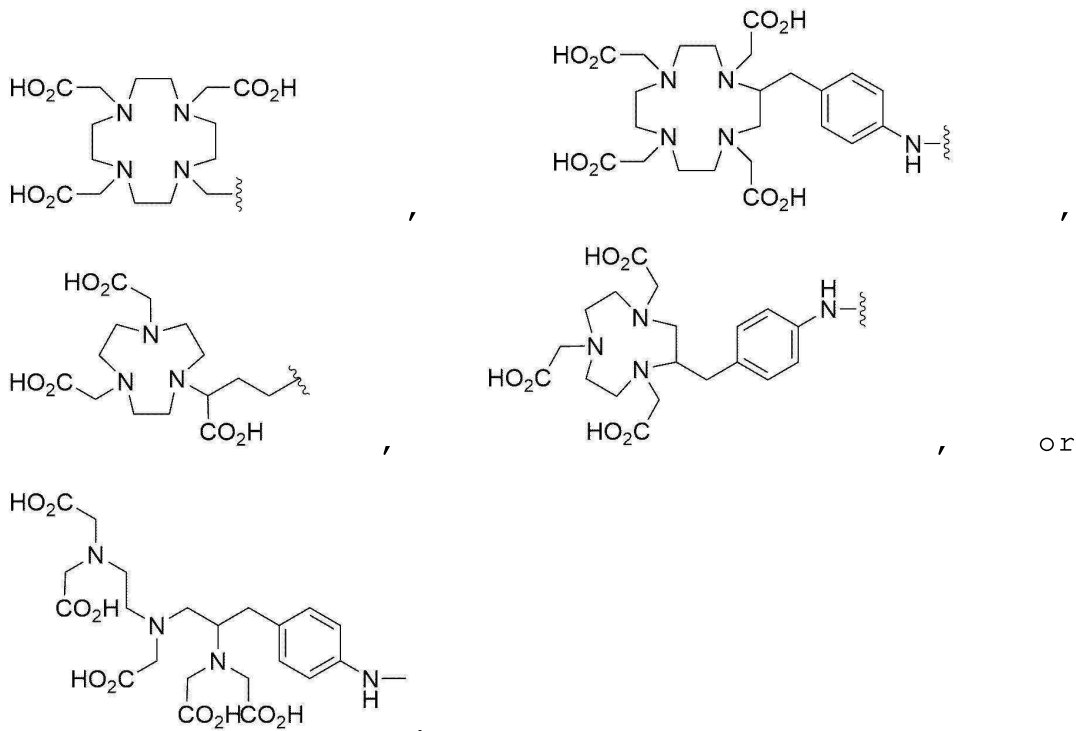
L_4 is $-(CH_2)_e-$, wherein e is an integer of 1 ~ 6;

n is an integer of 0 ~ 1;

R_2 is hydrogen, C_{1-5} straight or branched alkyl,
 or halogen;

20 Y is oxygen or sulfur;

Z' is a chelator, wherein the chelator is



5

In another aspect of the present invention, the present invention provides a composition for diagnosing prostate cancer comprising the compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof as an active ingredient.

In another aspect of the present invention, the present invention provides a pharmaceutical composition for preventing or treating prostate cancer comprising the compound, the stereoisomer thereof, the

hydrate thereof, or the pharmaceutically acceptable salt thereof as an active ingredient.

In another aspect of the present invention, the present invention provides a method for treating
5 cancer, comprising a step of administering the compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof to an individual or a subject in need.

In another aspect of the present invention, the
10 present invention provides the compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof for the treatment of cancer.

In another aspect of the present invention, the
15 present invention provides a use of the compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof for the preparation of a drug for treating cancer.

ADVANTAGEOUS EFFECT

The compounds provided by one aspect of the present invention in which carboxylic acid bound to lysine of Glutamic acid-urea-Lysine (GUL) is introduced form strong salt bridge interaction with the arginine patch at the PSMA protein binding site, resulting in high binding power. These compounds are characterized by rapid background radiation removal effect and low non-specific binding in vivo due to the hydrophilic characteristics of carboxylic acid. In addition, the compounds are ingested at high concentrations in tumors or cancers expressing PSMA protein by maintaining a long residence time in blood.

15

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the results of quantitative analysis of MicroPET/CT images acquired for 270 minutes after the administration of [^{68}Ga]**1e**.

Figure 2 is a graph showing the results of quantitative analysis of MicroPET/CT images acquired for 270 minutes after the administration of [^{68}Ga]**1g**.

Figure 3 is a graph showing the results of quantitative analysis of MicroPET/CT images acquired for 390 minutes after the administration of [⁶⁸Ga]**1h**.

Figure 4 is a graph showing the results of
5 quantitative analysis of MicroPET/CT images acquired for 390 minutes after the administration of [⁶⁸Ga]**1k**.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

10 Hereinafter, the present invention is described in detail.

The embodiments of this invention can be modified in various other forms, and the scope of the present invention is not limited to the embodiments described
15 below. It is well understood by those in the art who has the average knowledge on this field that the embodiments of the present invention are given to explain the present invention more precisely. In addition, the "inclusion" of an element throughout the
20 specification does not exclude other elements, but may include other elements, unless specifically stated otherwise.

In one aspect of the present invention, the
25 present invention provides a pharmaceutical

L_3 is C_{1-12} straight or branched alkylene, wherein one or more carbon atoms in alkylene can be replaced by oxygen atoms;

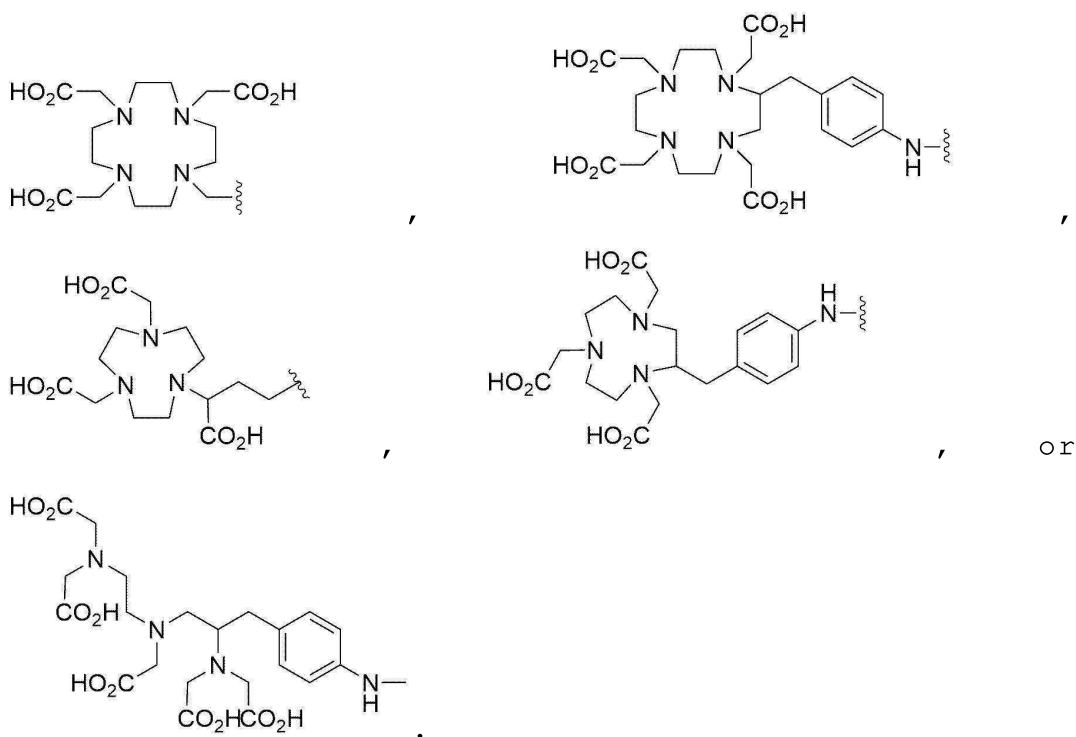
L_4 is $-(CH_2)_e-$, wherein e is an integer of 1 ~ 6;

5 n is an integer of 0 ~ 1;

R_2 is hydrogen, C_{1-5} straight or branched alkyl, or halogen;

Y is oxygen or sulfur;

Z is a chelator including a radioactive metal, 10 wherein the radioactive metal is Ga-68, Cu-64, Cu-67, Y-90, Sc-47, In-111, Sn-117m, Lu-177, Bi-212, Bi-213, Pb-212, Rd-223, or Ac-225, and the chelator is



In another aspect of the present invention,

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 6;

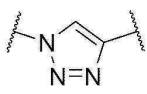
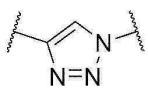
U is a bond, or $-C(O)-$;

5 R_1 is hydrogen, or $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$,
wherein b is an integer of 1 ~ 4;

X is a bond, or $-C(O)-$;

W is a bond, or $-NA_1-$, A_1 is hydrogen, or $-(CH_2)_c-$ -
pyridyl, wherein c is an integer of 0 ~ 1;

10 L_2 is a bond, or $-(CH_2)_d-$, wherein d is an integer
of 1 ~ 6;

Tz is a bond, , or  ;

L_3 is C_{1-12} straight or branched alkylene, wherein
one or more carbon atoms in alkylene can be replaced
15 by oxygen atoms;

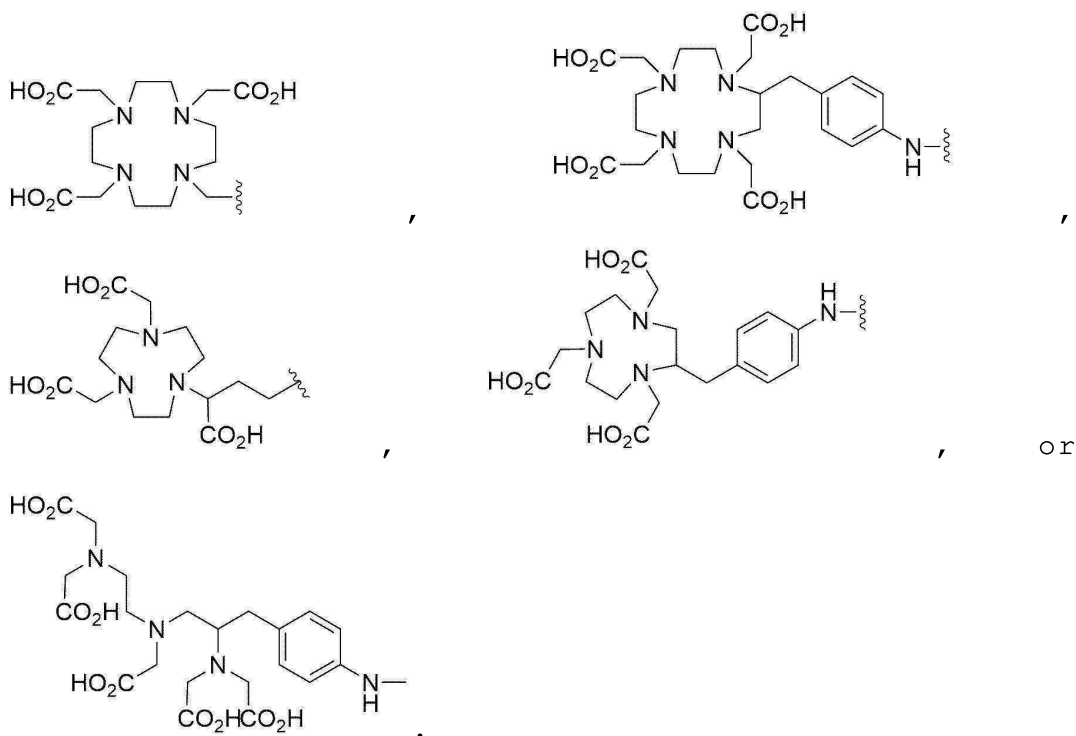
L_4 is $-(CH_2)_e-$, wherein e is an integer of 2 ~ 4;

n is an integer of 0 ~ 1;

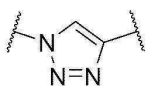
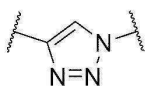
R_2 is hydrogen, C_{1-3} straight or branched alkyl,
or halogen;

20 Y is oxygen or sulfur;

Z is a chelator including a radioactive metal,
wherein the radioactive metal is Ga-68, Cu-64, Cu-67,
Y-90, Sc-47, In-111, Sn-117m, Lu-177, Bi-212, Bi-213,
Pb-212, Rd-223, or Ac-225, and the chelator is



- 5 In another aspect of the present invention,
- L_1 is $-(CH_2)_a-$, wherein a is an integer of 2 ~ 4;
- U is a bond, or $-C(O)-$;
- R_1 is hydrogen, or $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$, wherein b is an integer of 1 ~ 2;
- 10 X is a bond, or $-C(O)-$;
- W is a bond, or $-NA_1-$, wherein A_1 is hydrogen or pyridyl;
- L_2 is a bond, or $-(CH_2)_d-$, wherein d is an integer of 1 ~ 2;

Tz is a bond, , or  ;

L₃ is C₁₋₁₂ straight or branched alkylene, wherein one or more carbon atoms in alkylene can be replaced by oxygen atoms;

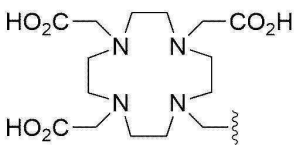
5 L₄ is -(CH₂)₃-;

n is an integer of 0 ~ 1;

R₂ is hydrogen, methyl or halogen;

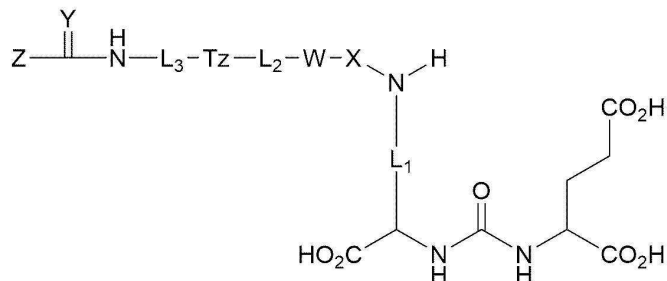
Y is oxygen;

Z is a chelator including a radioactive metal,
10 wherein the radioactive metal is Ga-68, Cu-64, or Lu-

177, and the chelator can be  .

In another aspect of the present invention, the compound represented by formula 1 can be a compound
15 represented by formula 1-1 below.

[Formula 1-1]



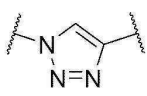
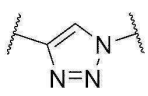
In formula 1-1,

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 8;

X is a bond, or $-C(O)-$;

W is a bond or $-NA_1-$, wherein A_1 is hydrogen or $-(CH_2)_c$ -pyridyl, wherein c is an integer of 0 ~ 3;

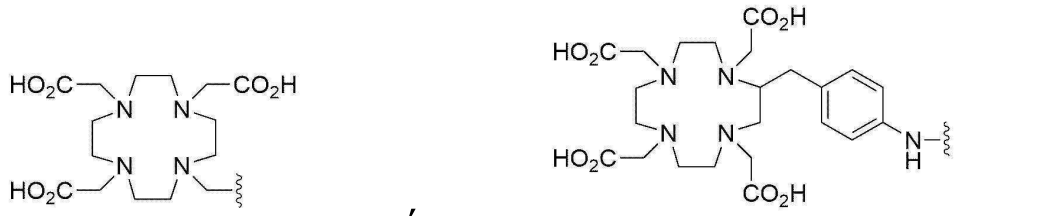
5 L_2 is a bond or $-(CH_2)_d-$, wherein d is an integer of 1 ~ 8;

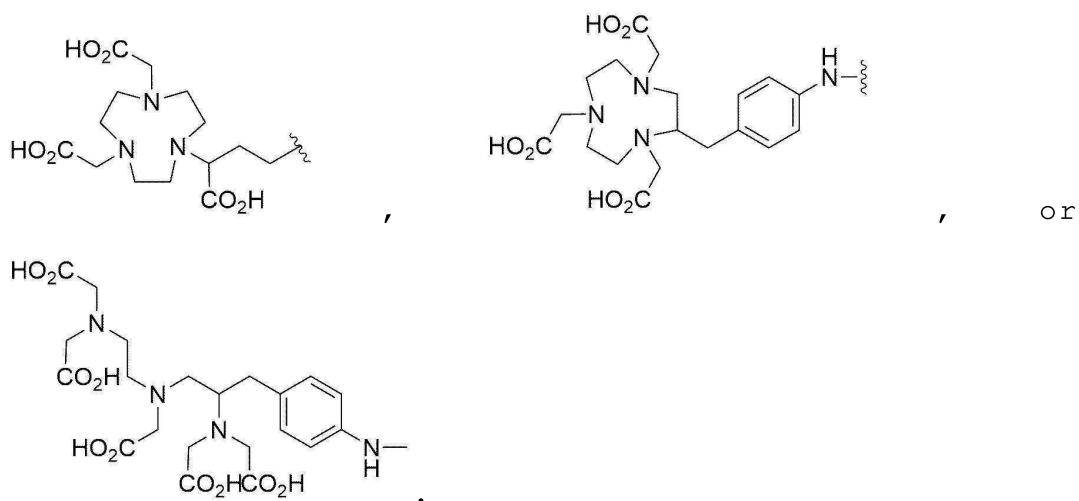
Tz is a bond, , or  ;

L_3 is C_{1-12} straight or branched alkylene, wherein one or more carbon atoms in alkylene can be replaced
10 by oxygen atoms;

Y is oxygen or sulfur;

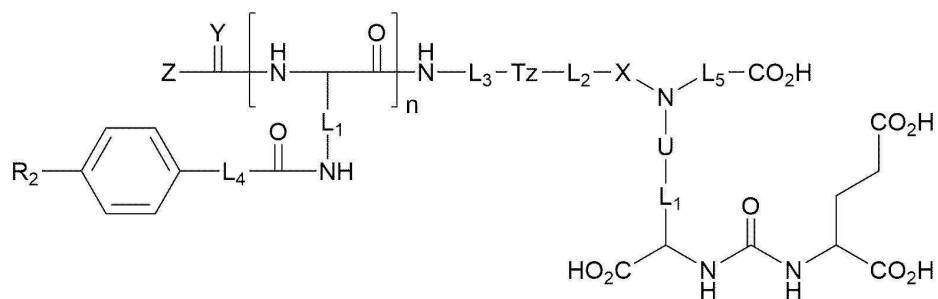
Z is a chelator including a radioactive metal, wherein the radioactive metal is Ga-68, Cu-64, Cu-67, Y-90, Sc-47, In-111, Sn-117m, Lu-177, Bi-212, Bi-213,
15 Pb-212, Rd-223, or Ac-225, and the chelator is





In another aspect of the present invention, the compound represented by formula 1 can be a compound represented by formula 1-2 below.

[Formula 1-2]



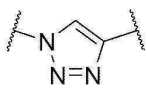
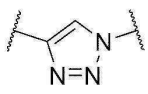
In formula 1-2,

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 8;

U is a bond, or $-C(O)-$;

X is a bond, or $-C(O)-$;

L₂ is a bond or -(CH₂)_d-, wherein d is an integer of 1 ~ 8;

Tz is a bond, , or ;

L₃ is C₁₋₁₂ straight or branched alkylene, wherein
 5 one or more carbon atoms in alkylene can be replaced
 by oxygen atoms;

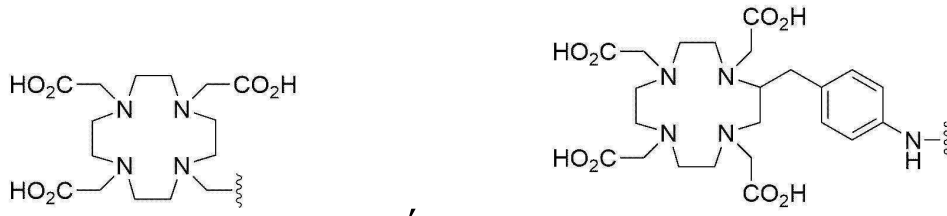
L₄ is -(CH₂)_e-, wherein e is an integer of 1 ~ 6;

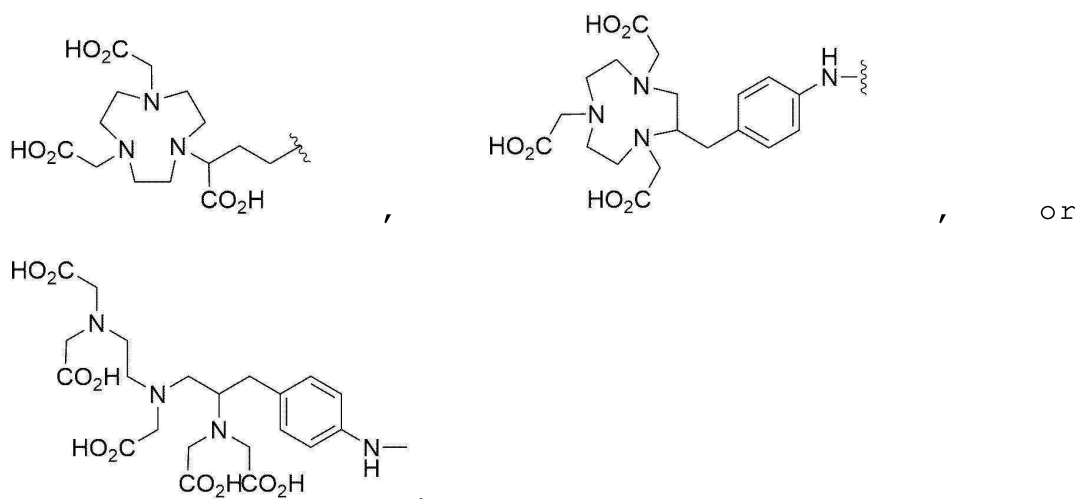
n is an integer of 0 ~ 1;

R₂ is hydrogen, C₁₋₅ straight or branched alkyl,
 10 or halogen;

Y is oxygen or sulfur;

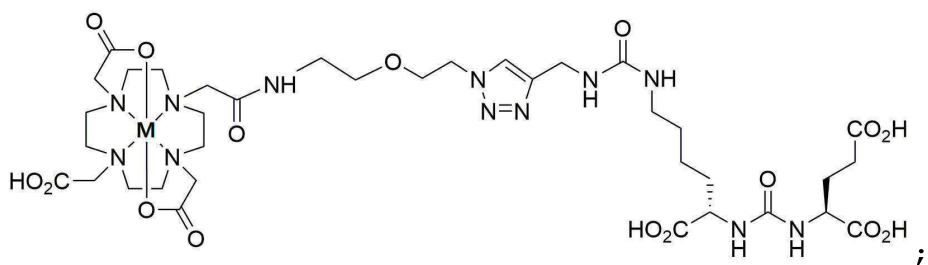
Z is a chelator including a radioactive metal,
 wherein the radioactive metal is Ga-68, Cu-64, Cu-67,
 Y-90, Sc-47, In-111, Sn-117m, Lu-177, Bi-212, Bi-213,
 15 Pb-212, Rd-223, or Ac-225, and the chelator is





In another aspect of the present invention, the
 5 compound represented by formula 1 can be any one
 compound selected from the group consisting of the
 following compounds.

(1)



10

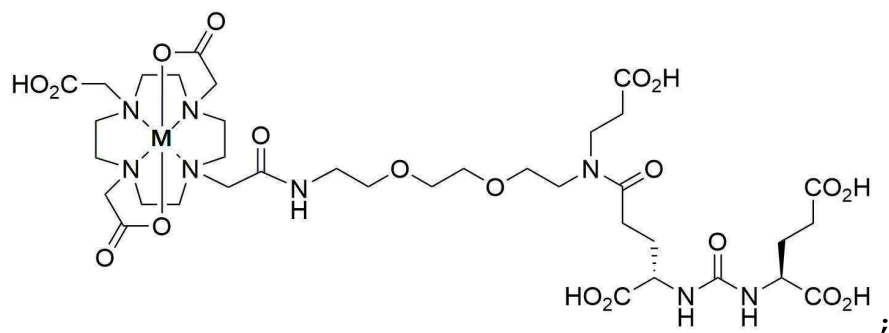
(2)



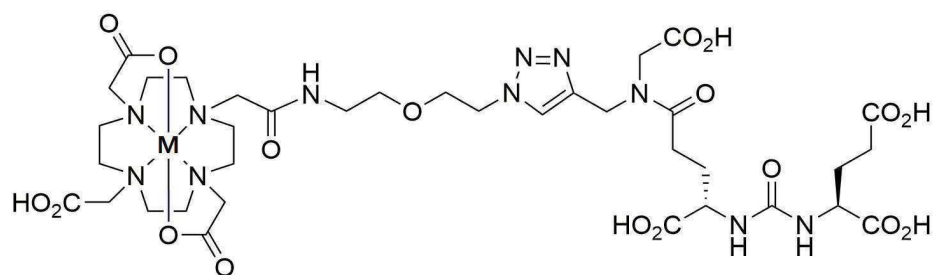








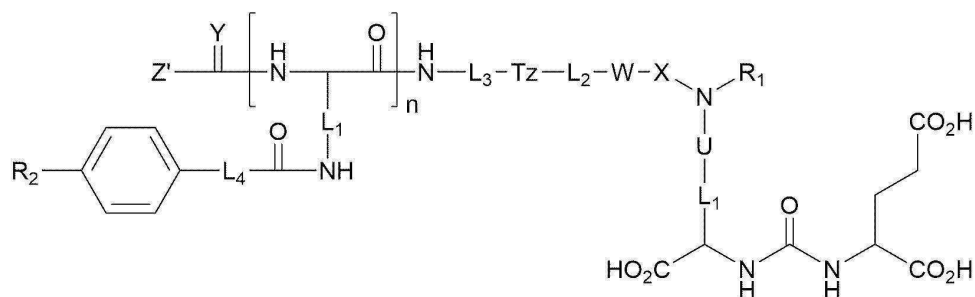
(16)



(At this time, in the above formulas, M is a
 5 radioactive metal, and the radioactive metal is as
 defined in formula 1.).

In another aspect of the present invention, the
 present invention provides a compound represented by
 10 formula 2 below, a stereoisomer thereof, a hydrate
 thereof, or a pharmaceutically acceptable salt
 thereof.

[Formula 2]



In formula 2,

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 8;

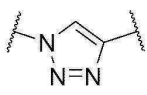
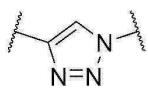
U is a bond, or $-C(O)-$;

5 R_1 is hydrogen or $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$,
wherein b is an integer of 1 ~ 6;

X is a bond, or $-C(O)-$;

W is a bond or $-NA_1-$, and A_1 is hydrogen or $-(CH_2)_c$ -pyridyl, wherein c is an integer of 0 ~ 3;

10 L_2 is a bond or $-(CH_2)_d-$, wherein d is an integer
of 1 ~ 8;

Tz is a bond, , or ;

L_3 is C_{1-12} straight or branched alkylene, wherein
one or more carbon atoms in alkylene can be replaced
15 by oxygen atoms;

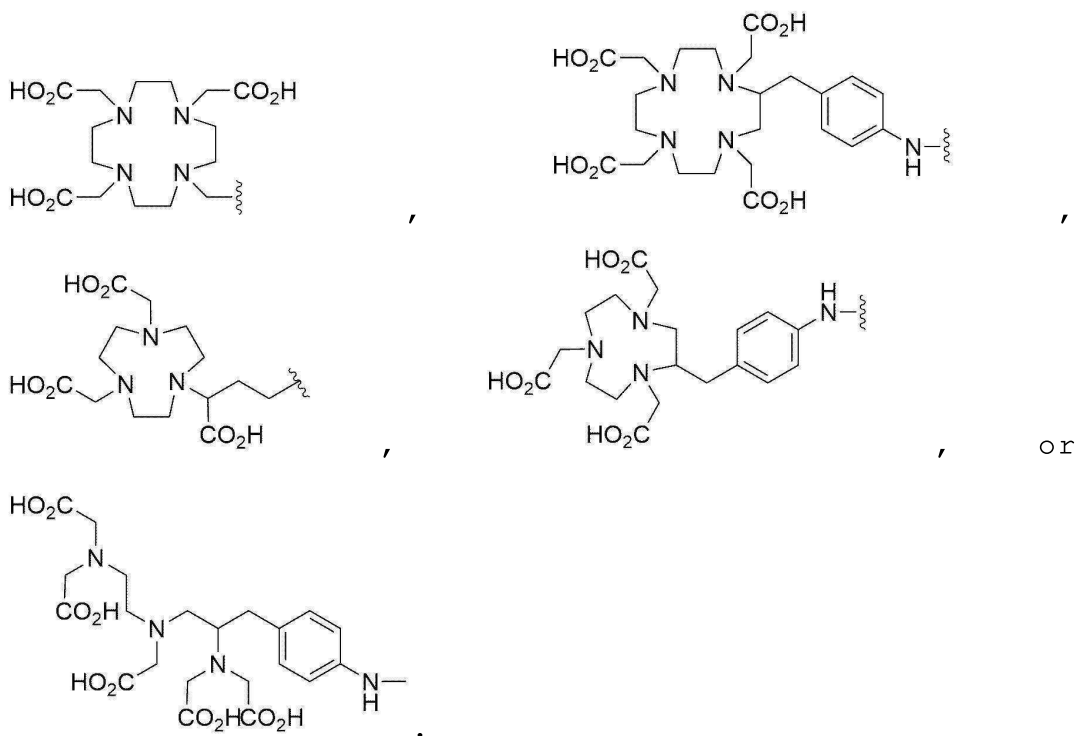
L_4 is $-(CH_2)_e-$, wherein e is an integer of 1 ~ 6;

n is an integer of 0 ~ 1;

R_2 is hydrogen, C_{1-5} straight or branched alkyl,
or halogen;

Y is oxygen or sulfur;

Z' is a chelator, and the chelator is



In another aspect of the present invention,

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 6;

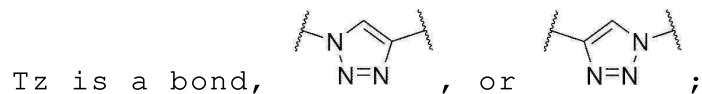
U is a bond, or $-C(O)-$;

10 R_1 is hydrogen or $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$, wherein b is an integer of 1 ~ 4;

X is a bond, or $-C(O)-$;

W is a bond or $-NA_1-$, and A_1 is hydrogen or $-(CH_2)_c$ -pyridyl, wherein c is an integer of 0 ~ 1;

L_2 is a bond or $-(CH_2)_d-$, wherein d is an integer of 1 ~ 6;



L_3 is C_{1-12} straight or branched alkylene, wherein
5 one or more carbon atoms in alkylene can be replaced
by oxygen atoms;

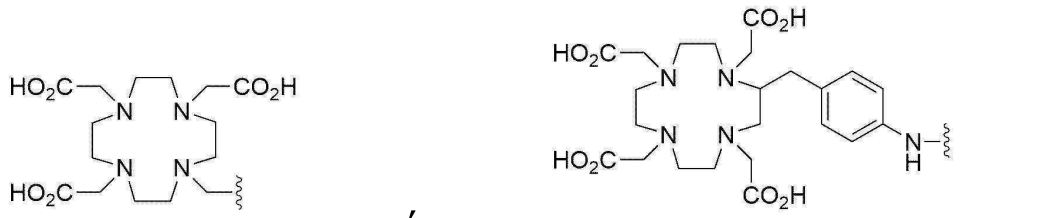
L_4 is $-(CH_2)_e-$, wherein e is an integer of 2 ~ 4;

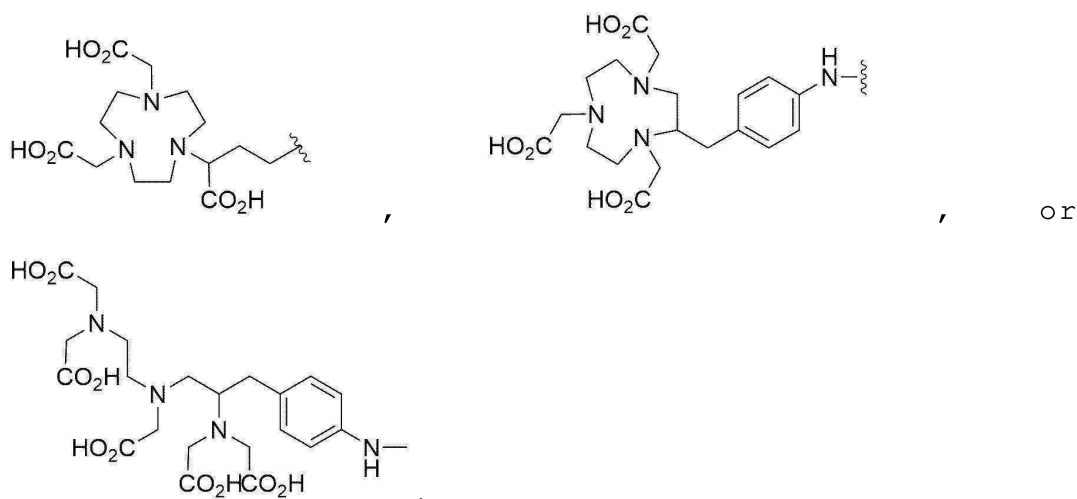
n is an integer of 0 ~ 1;

R_2 is hydrogen, C_{1-3} straight or branched alkyl,
10 or halogen;

Y is oxygen or sulfur;

Z' is a chelator, and the chelator can be





In another aspect of the present invention,

5 L_1 is $-(CH_2)_a-$, wherein a is an integer of 2 ~ 4;

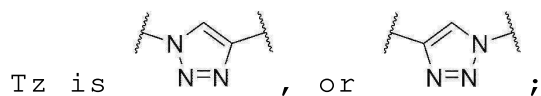
U is a bond, or $-C(O)-$;

R_1 is hydrogen or $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$,
wherein b is an integer of 1 ~ 2;

X is a bond, or $-C(O)-$;

10 W is a bond or $-NA_1-$, and A_1 is hydrogen or
pyridyl;

L_2 is a bond or $-(CH_2)_d-$, wherein d is an integer
of 1 ~ 2;



15 L_3 is C_{1-12} straight or branched alkylene, wherein
one or more carbon atoms in alkylene can be replaced
by oxygen atoms;

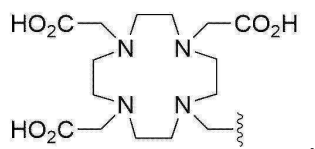
L_4 is $-(CH_2)_3-$;

n is an integer of $0 \sim 1$;

R_2 is hydrogen, methyl, or halogen;

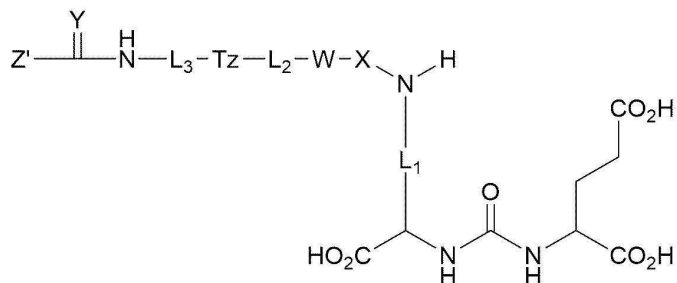
Y is oxygen;

5 Z' is a chelator, and the chelator can be



In another aspect of the present invention, the compound represented by formula 2 can be a compound
10 represented by formula 2-1 below.

[Formula 2-1]



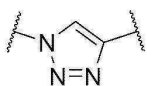
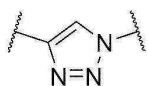
In formula 2-1,

L_1 is $-(CH_2)_a-$, wherein a is an integer of $1 \sim 8$;

15 X is a bond, or $-C(O)-$;

W is a bond or $-NA_1-$, and A_1 is hydrogen or $-(CH_2)_c$ -pyridyl, wherein c is an integer of $0 \sim 3$;

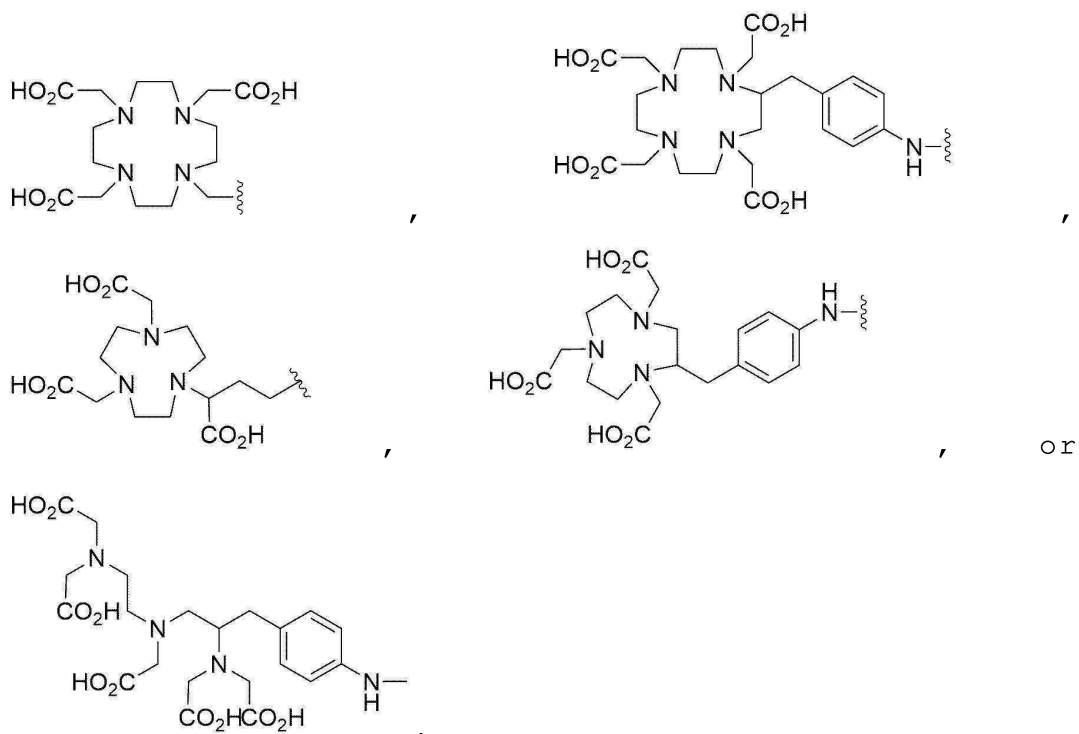
L_2 is a bond or $-(CH_2)_d-$, wherein d is an integer of $1 \sim 8$;

Tz is a bond, , or  ;

L₃ is C₁₋₁₂ straight or branched alkylene, wherein one or more carbon atoms in alkylene can be replaced by oxygen atoms;

5 Y is oxygen or sulfur;

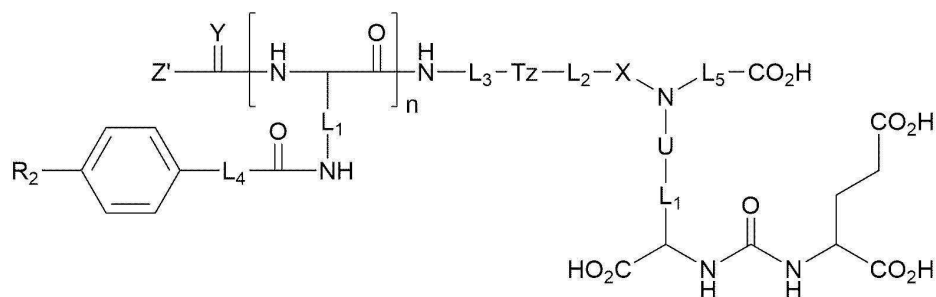
Z' is a chelator, and the chelator is



10

In another aspect of the present invention, the compound represented by formula 2 can be a compound represented by formula 2-2 below.

[Formula 2-2]



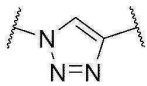
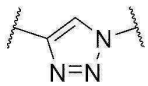
In formula 2-2,

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 8;

U is a bond, or $-C(O)-$;

5 X is a bond, or $-C(O)-$;

L_2 is a bond or $-(CH_2)_d-$, wherein d is an integer of 1 ~ 8;

Tz is a bond, , or ;

L_3 is C_{1-12} straight or branched alkylene, wherein
10 one or more carbon atoms in alkylene can be replaced by oxygen atoms;

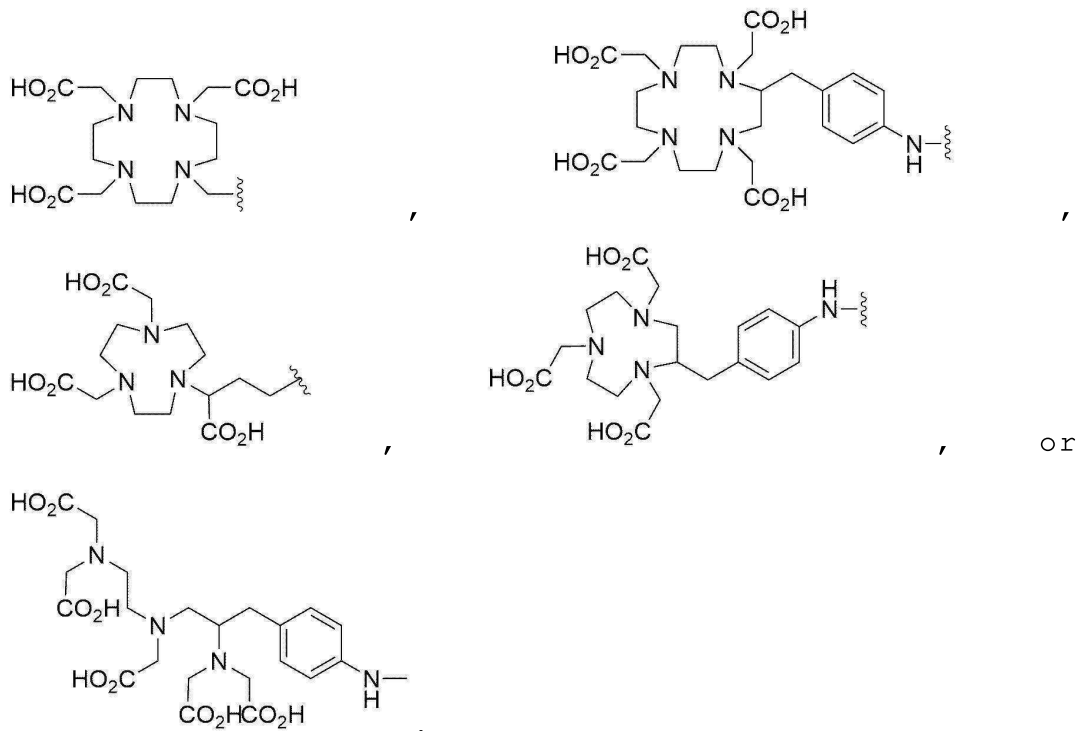
L_4 is $-(CH_2)_e-$, wherein e is an integer of 1 ~ 6;

n is an integer of 0 ~ 1;

R_2 is hydrogen, C_{1-5} straight or branched alkyl,
15 or halogen;

Y is oxygen or sulfur;

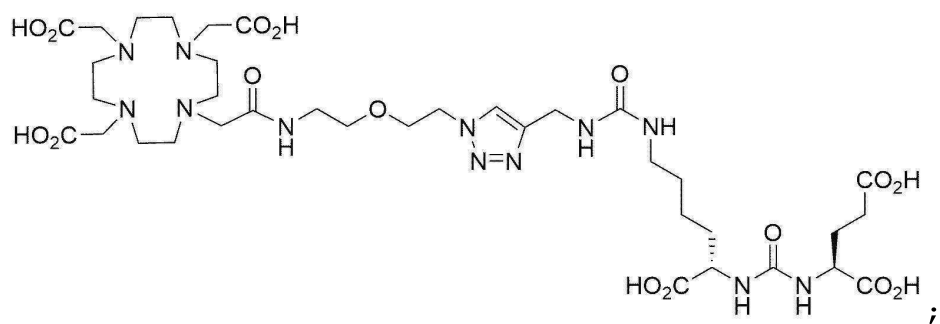
Z' is a chelator, and the chelator is



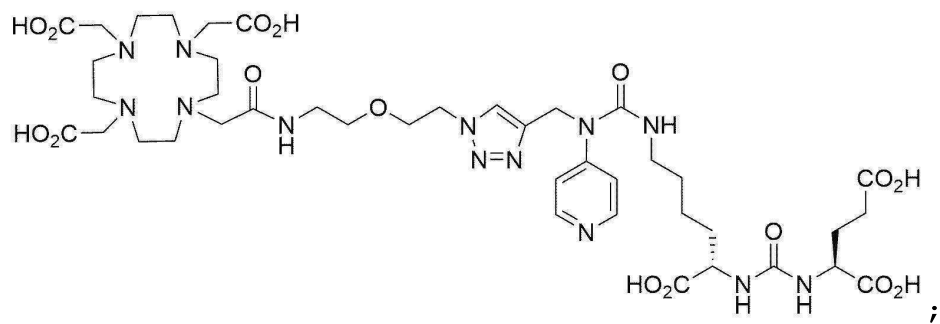
5

In another aspect of the present invention, the compound represented by formula 2 can be any one compound selected from the group consisting of the following compounds.

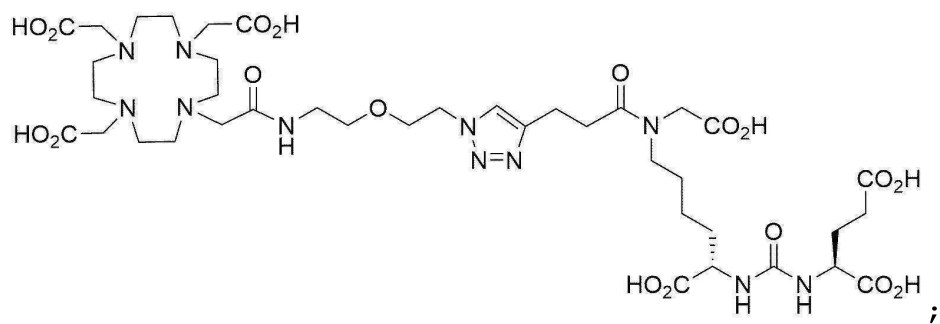
10 (1)



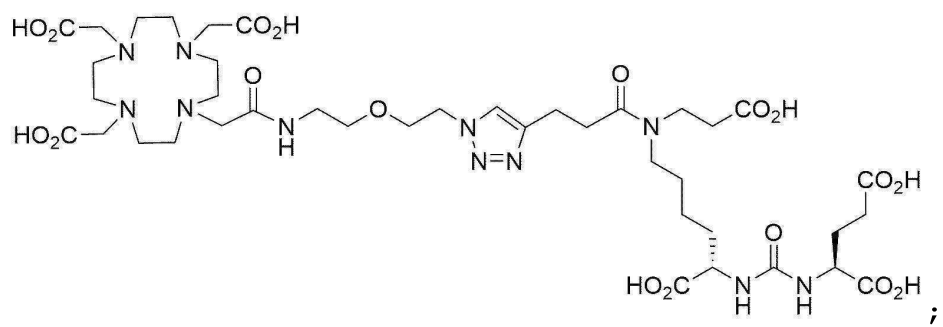
(2)



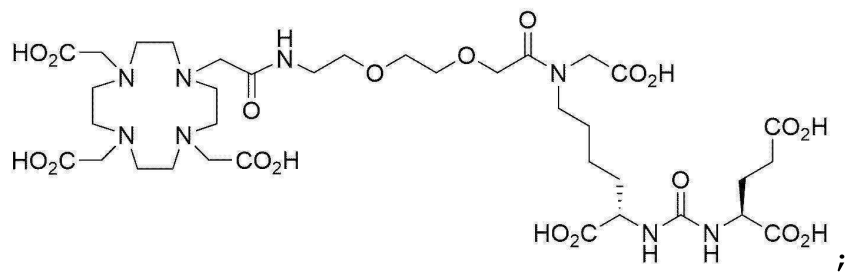
(3)



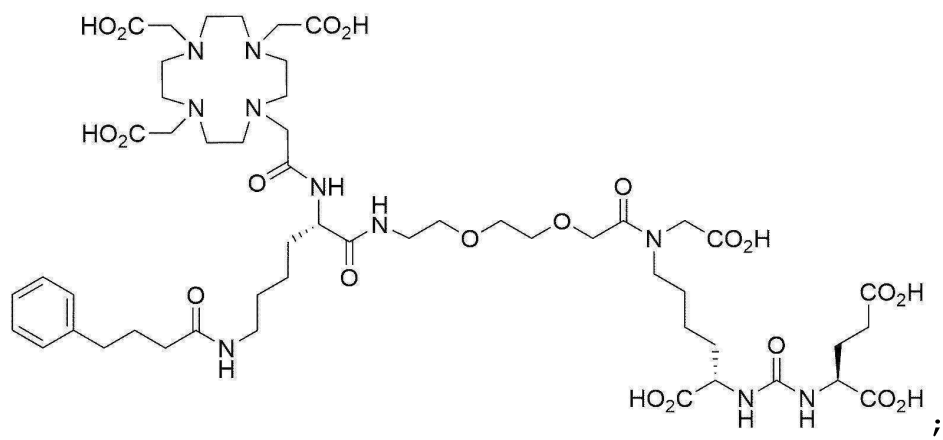
(4)



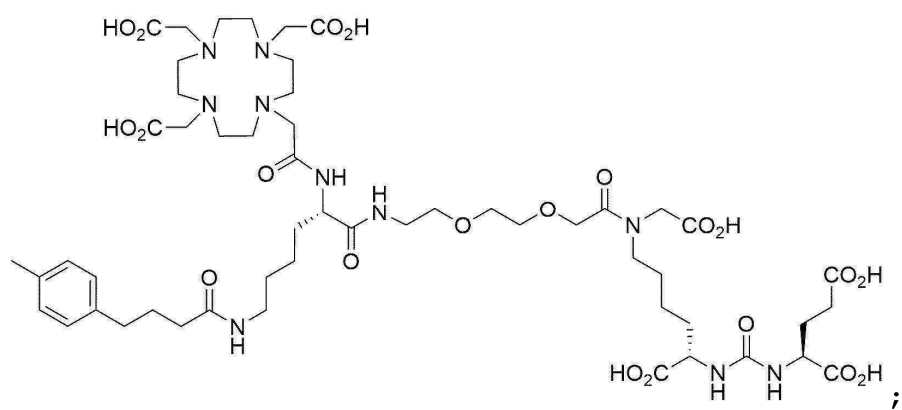
(5)



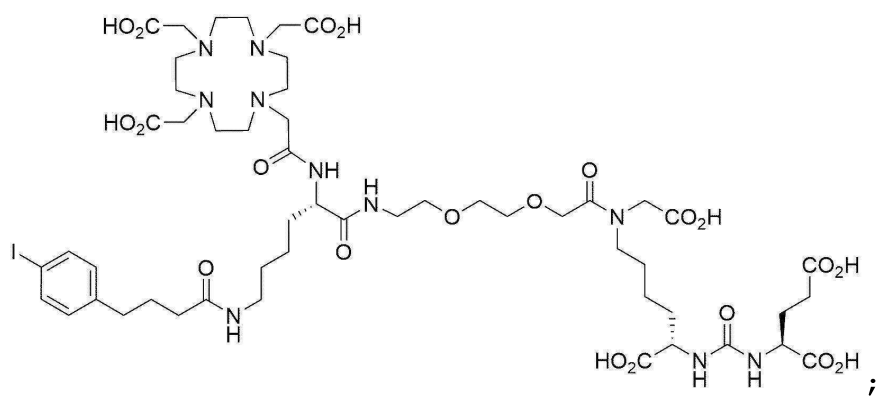
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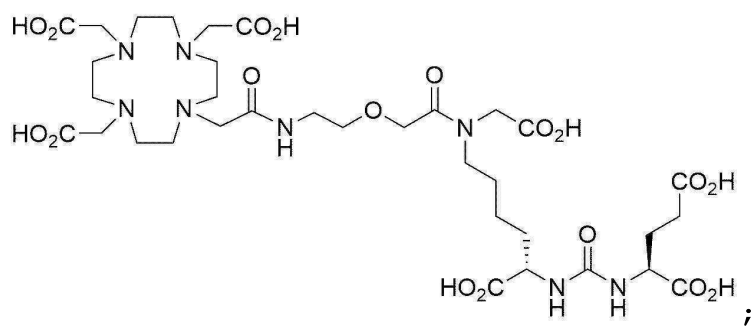
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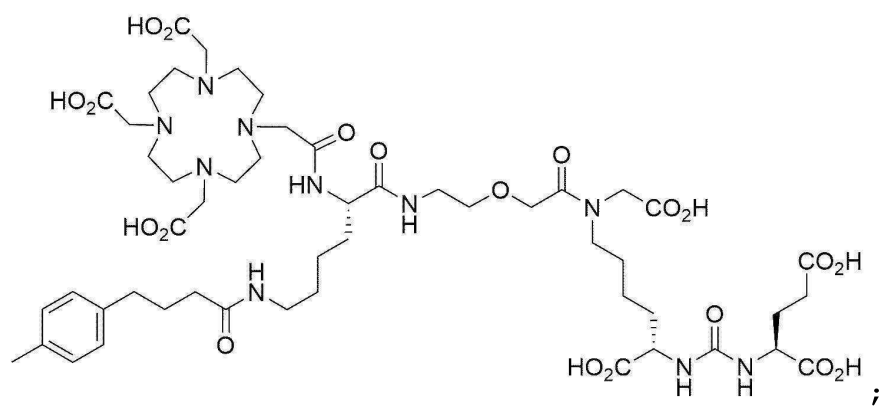
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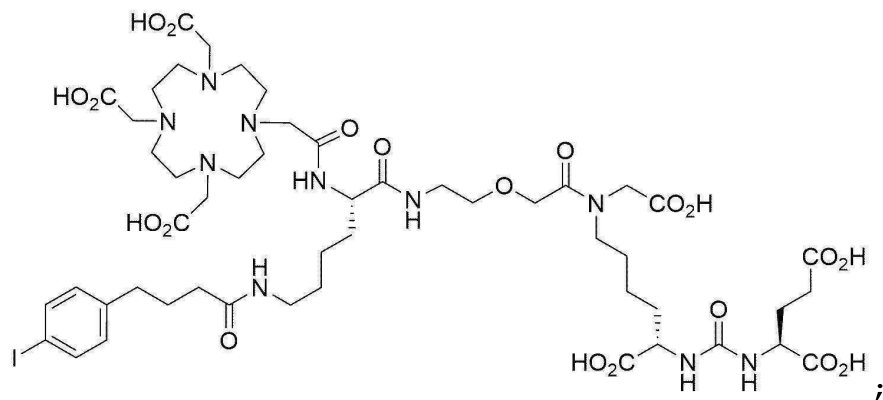
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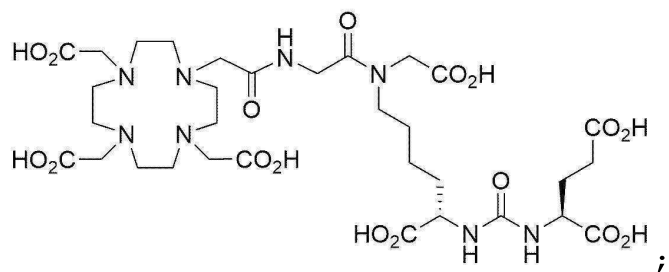
(10)



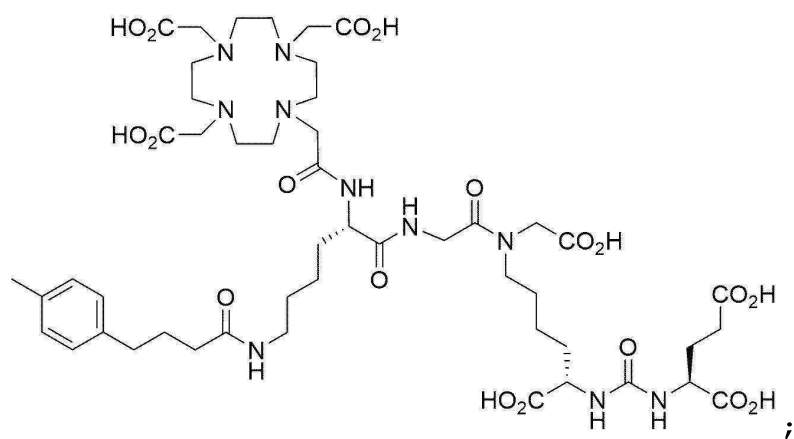
(11)



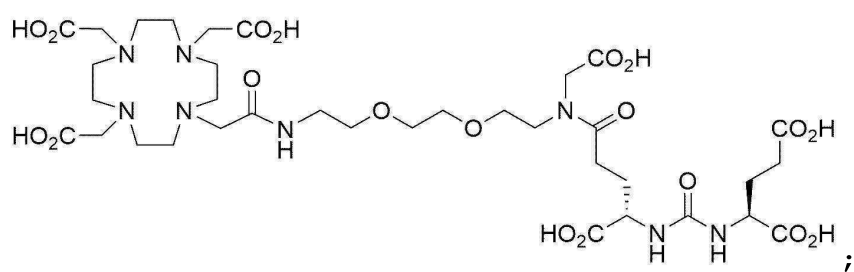
(12)



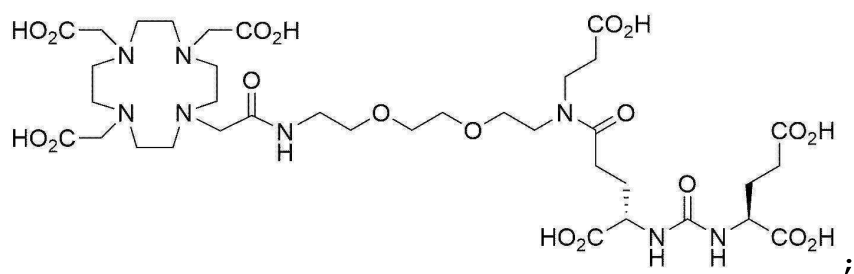
(13)



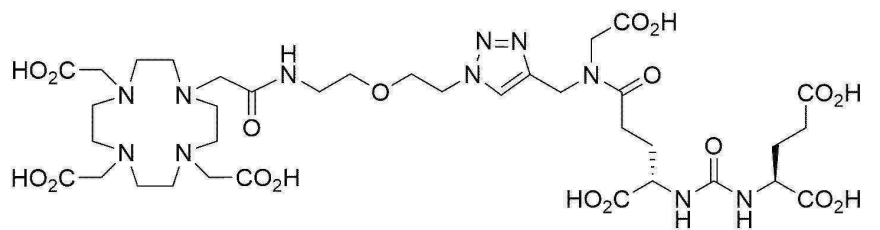
(14)



(15)



(16)



The compound represented by formula 1 or formula
 2 of the present invention can be used as a form of a
 5 pharmaceutically acceptable salt, in which the salt is
 preferably acid addition salt formed by
 pharmaceutically acceptable free acids. The acid
 addition salt herein can be obtained from inorganic
 acids such as hydrochloric acid, nitric acid,
 10 phosphoric acid, sulfuric acid, hydrobromic acid,
 hydroiodic acid, nitrous acid, and phosphorous acid;
 non-toxic organic acids such as aliphatic
 mono/dicarboxylate, phenyl-substituted alkanoate,
 hydroxy alkanoate, alkandioate, aromatic acids, and
 15 aliphatic/aromatic sulfonic acids; or organic acids
 such as acetic acid, benzoic acid, citric acid, lactic
 acid, maleic acid, gluconic acid, methanesulfonic
 acid, 4-toluenesulfonic acid, tartaric acid, and
 fumaric acid. The pharmaceutically non-toxic salts are
 20 exemplified by sulfate, pyrosulfate, bisulfate,
 sulphite, bisulphite, nitrate, phosphate, monohydrogen

phosphate, dihydrogen phosphate, metaphosphate,
pyrophosphate, chloride, bromide, iodide, fluoride,
acetate, propionate, decanoate, caprylate, acrylate,
formate, isobutylate, caprate, heptanoate, propiolate,
5 oxalate, malonate, succinate, suberate, cabacate,
fumarate, maliate, butyne-1,4-dioate, hexane-1,6-
dioate, benzoate, chlorobenzoate, methylbenzoate,
dinitrobenzoate, hydroxybenzoate, methoxybenzoate,
phthalate, terephthalate, benzenesulfonate,
10 toluenesulfonate, chlorobenzenesulfonate,
xylenesulfonate, phenylacetate, phenylpropionate,
phenylbutylate, citrate, lactate, hydroxybutylate,
glycolate, malate, tartrate, methanesulfonate,
propanesulfonate, naphthalene-1-sulfonate,
15 naphthalene-2-sulfonate, and mandelate.

The acid addition salt in this invention can be
prepared by the conventional method known to those in
the art. For example, the derivative represented by
formula 1 or formula 2 is dissolved in an organic
20 solvent such as methanol, ethanol, acetone,
methylenechloride, and acetonitrile, to which organic
acid or inorganic acid is added to induce
precipitation. Then, the precipitate is filtered and
dried to give the salt. Or the solvent and the
25 excessive acid are distilled under reduced pressure,

and dried to give the salt. Or the precipitate is crystallized in an organic solvent to give the same.

A pharmaceutically acceptable metal salt can be prepared by using a base. Alkali metal or alkali earth metal salt is obtained by the following processes:
5 dissolving the compound in excessive alkali metal hydroxide or alkali earth metal hydroxide solution; filtering non-soluble compound salt; evaporating the remaining solution and drying thereof. At this time,
10 the metal salt is preferably prepared in the pharmaceutically suitable form of sodium, potassium, or calcium salt. And the corresponding silver salt is prepared by the reaction of alkali metal or alkali earth metal salt with proper silver salt (ex; silver
15 nitrate).

In addition, the present invention includes not only the compound represented by formula 1 or formula 2 but also a pharmaceutically acceptable salt thereof, and a solvate, an optical isomer, or a hydrate
20 possibly produced from the same.

In another aspect of the present invention, the present invention provides a composition for diagnosing prostate cancer comprising the compound
25 represented by formula 1, the stereoisomer thereof,

the hydrate thereof, or the pharmaceutically acceptable salt thereof as an active ingredient.

The composition for diagnosing prostate cancer can diagnose prostate cancer by selectively binding
5 the compound to PSMA (Prostate-Specific Membrane Antigen) over-expressed in prostate cancer cells.

In another aspect of the present invention, the present invention provides a pharmaceutical
10 composition for preventing or treating prostate cancer comprising the compound represented by formula 1, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof as an active ingredient.

15

The compound represented by formula 1 and the pharmaceutically acceptable salt thereof can be administered orally or parenterally and be used in general forms of pharmaceutical formulation. That is,
20 the compound represented by formula 1 and the pharmaceutically acceptable salt thereof can be prepared for oral or parenteral administration by mixing with generally used diluents or excipients such as fillers, extenders, binders, wetting agents,
25 disintegrating agents and surfactants. Solid

formulations for oral administration are tablets, pills, powders, granules and capsules. These solid formulations are prepared by mixing one or more compounds of the present invention with one or more
5 suitable excipients such as starch, calcium carbonate, sucrose or lactose, gelatin, etc. Except for the simple excipients, lubricants, for example magnesium stearate, talc, etc, can be used. Liquid formulations for oral administrations are suspensions, solutions,
10 emulsions and syrups, and the above-mentioned formulations can contain various excipients such as wetting agents, sweeteners, aromatics and preservatives in addition to generally used simple diluents such as water and liquid paraffin.
15 Formulations for parenteral administration are sterilized aqueous solutions, water-insoluble excipients, suspensions and emulsions. Water insoluble excipients and suspensions can contain, in addition to the active compound or compounds, propylene glycol,
20 polyethylene glycol, vegetable oil like olive oil, injectable ester like ethylolate, etc.

The pharmaceutical composition comprising the compound represented by formula 1 or the
25 pharmaceutically acceptable salt thereof as an active

ingredient of the present invention can be administered by parenterally and the parenteral administration includes subcutaneous injection, intravenous injection, intramuscular injection or
5 intrathoracic injection.

To prepare the composition as a formulation for parenteral administration, the compound represented by formula 1 or the pharmaceutically acceptable salt thereof of the present invention is mixed with a
10 stabilizer or a buffering agent to produce a solution or suspension, which is then formulated as ampoules or vials. The composition herein can be sterilized and additionally contains preservatives, stabilizers, wettable powders or emulsifiers, salts and/or buffers
15 for the regulation of osmotic pressure, and other therapeutically useful materials, and the composition can be formulated by the conventional mixing, granulating or coating method.

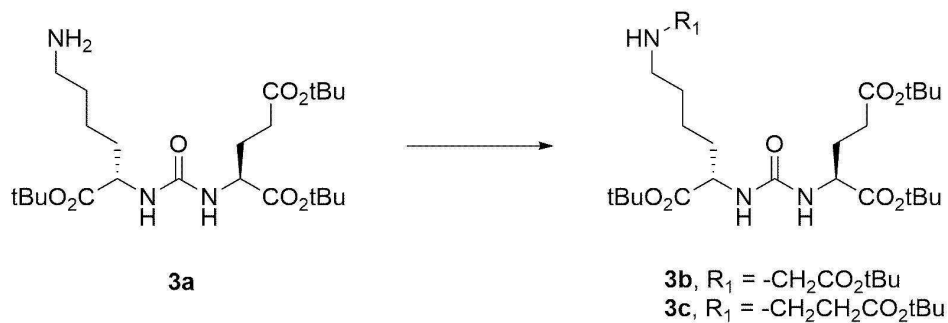
The formulations for oral administration are
20 exemplified by tablets, pills, hard/soft capsules, solutions, suspensions, emulsions, syrups, granules, elixirs, and troches, etc. These formulations can include diluents (for example, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, and/or
25 glycine) and lubricants (for example, silica, talc,

stearate and its magnesium or calcium salt, and/or
 polyethylene glycol) in addition to the active
 ingredient. Tablets can include binding agents such as
 magnesium aluminum silicate, starch paste, gelatin,
 5 methylcellulose, sodium carboxymethylcellulose and/or
 polyvinylpyrrolidone, and if necessary disintegrating
 agents such as starch, agarose, alginic acid or its
 sodium salt or azeotropic mixtures and/or absorbents,
 coloring agents, flavours, and sweeteners can be
 10 additionally included thereto.

Hereinafter, the present invention will be
 described in detail by the following examples.

However, the following examples are only for
 15 illustrating the present invention, and the contents
 of the present invention are not limited thereto.

<Example 1> Preparation of compounds 3b and 3c



20 **Preparation of compound 3b**

The compound **3a** (5.2 g, 10.66 mmol) was dissolved in dichloromethane (100 mL) and cooled to 0°C, to which tert-butyl bromoacetate (1.9 mL, 12.8 mmol) was slowly added. The mixture was maintained at 0°C, to which triethylamine (2.2 mL, 16 mmol) was slowly added, and the mixture was stirred while gradually raising the temperature to room temperature. After stirring the mixture for 3 hours, water (50 mL) was added thereto, and the organic compound was extracted with dichloromethane (50 mL, twice). The collected organic layer was treated with anhydrous sodium sulfate, concentrated under reduced pressure and purified by column chromatography (5% methanol/dichloromethane) to give the compound **3b** (3.36 g, 52%).

¹H NMR (400 MHz, CDCl₃) δ 1.39–1.53 (m, 36H), 1.55–1.89 (m, 5H), 2.02–2.10 (m, 1H), 2.22–2.37 (m, 2H), 2.54–2.58 (m, 2H), 3.27 (s, 2H), 4.28–4.36 (m, 2H), 5.07–5.10 (m, 2H);

¹³C NMR (100 MHz, CDCl₃) δ 22.6, 27.9, 28.0, 28.1, 28.2, 28.5, 29.6, 31.6, 32.8, 49.0, 51.7, 53.0, 53.5, 80.5, 81.1, 81.6, 82.0, 156.8, 171.9, 172.1, 172.4, 172.5;

MS (ESI) m/z 602 [M+H]⁺

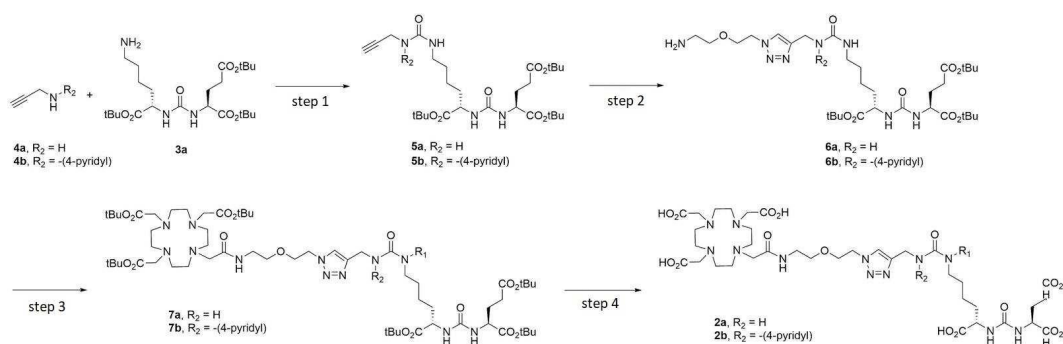
Preparation of compound 3c

The compound **3a** (500 mg, 1.03 mmol) was dissolved in ethanol (10 mL), followed by stirring at 0°C for 10 minutes. Tert-butyl acrylate (0.38 mL, 2.58 mmol) was slowly added thereto, followed by stirring at 0°C for 20 hours. Upon completion of the reaction, the solvent was removed, and the concentrate was separated by column chromatography (8% methanol/dichloromethane) to give the compound **3c** (0.23 g, 37%).

¹H NMR (400 MHz, CDCl₃) δ 1.40 (s, 9H), 1.41 (s, 9H), 1.43 (s, 18H), 1.48–1.65 (m, 3H), 1.70–1.86 (m, 2H), 2.00–2.07 (m, 1H), 2.21–2.36 (m, 2H), 2.48 (t, *J* = 6.6 Hz, 2H), 2.58–2.69 (m, 2H), 2.86 (t, *J* = 6.6 Hz, 2H), 4.26–4.34 (m, 2H), 5.26 (dd, *J* = 13.0, 8.2 Hz, 2H);

MS (ESI) *m/z* 616 [M+H]⁺

<Example 2> Preparation of compounds 2a and 2b



Step 1: Preparation of compound 5a

Triphosgene (107 mg, 0.36 mmol) was dissolved in acetonitrile (5.0 mL), to which the compound **3a** (500 mg, 1.03 mmol) dissolved in acetonitrile was slowly added at 0°C. Then, triethylamine (0.50 mL, 3.61 mmol) was added thereto, followed by stirring for 30 minutes. Propargylamine (**4a**, 0.072 mL, 1.13 mmol) was added thereto at 0°C. After 15 minutes, the mixture was stirred at room temperature for 1 hour, concentrated under reduced pressure, and then water was added thereto. The organic compound was repeatedly extracted 3 times using ethyl acetate. The collected organic solvent was dried over anhydrous sodium sulfate, concentrated under reduced pressure and separated by column chromatography (2% methanol/dichloromethane) to give the compound **5a** (492 mg, 84%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 1.25-1.30 (m, 2H), 1.44 (s, 18H), 1.48 (s, 9H), 1.51-1.60 (m, 3H), 1.67-1.76 (m, 1H), 1.80-1.90 (m, 1H), 2.05-2.13 (m, 1H), 2.18 (t, *J* = 2.6 Hz, 1H), 2.29-2.40 (m, 2H), 3.06-3.12 (m, 5 1H), 3.30-3.36 (m, 1H), 3.95-4.06 (m, 2H), 4.08-4.14 (m, 1H), 4.36 (sext, *J* = 4.4 Hz, 1H), 5.64 (d, *J* = 7.6 Hz, 1H), 5.69 (t, *J* = 5.2 Hz, 1H), 5.89 (t, *J* = 5.4 Hz, 1H), 6.11 (d, *J* = 8.4 Hz, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 23.4, 27.7, 27.8, 27.9, 10 28.0, 29.6, 29.7, 31.7, 32.1, 39.4, 53.3, 54.2, 70.5, 80.7, 81.4, 81.5, 83.1, 158.0, 158.2, 172.0, 172.3, 174.6;

MS (ESI) *m/z* 569 [M+H]⁺

15 **Step 1: Preparation of compound 5b**

The compound **4b** (200 mg, 1.51 mmol) was dissolved in acetonitrile (5.0 mL), to which 4-nitrophenyl chloroformate (305 mg, 1.51 mmol) was slowly added at 0°C. Triethylamine (0.50 mL, 3.61 mmol) was added 20 thereto, followed by stirring for 30 minutes. The compound **3a** (886 mg, 1.82 mmol) dissolved in acetonitrile (10 mL) was slowly added thereto at 0°C, to which diisopropylethylamine (0.324 mL, 1.82 mmol) was added. After 15 minutes, the mixture was stirred 25 at 100°C for 12 hours. After cooling the mixture to

room temperature, water was added thereto. The organic compound was repeatedly extracted 3 times using ethyl acetate. The collected organic solvent was dried over anhydrous sodium sulfate, concentrated under reduced
5 pressure and separated by column chromatography (5% methanol/dichloromethane) to give the compound **5b** (836 mg, 86%) as a colorless liquid.

^1H NMR (400 MHz, CDCl_3) δ 1.27–1.37 (m, 2H), 1.43
10 (s, 9H), 1.45 (s, 18H), 1.50–1.55 (m, 2H), 1.59–1.65 (m, 1H), 1.72–1.88 (m, 2H), 2.01–2.10 (m, 1H), 2.27–2.34 (m, 1H), 2.35 (t, J = 2.4 Hz, 1H), 2.16 (q, J = 6.7 Hz, 2H), 4.25–4.34 (m, 2H), 4.50 (ddd, J = 25.2, 18.0, 2.4 Hz, 2H), 5.21 (t, J = 5.8 Hz, 1H), 5.48 (s,
15 1H), 5.50 (s, 1H), 7.32 (dd, J = 4.8, 1.6 Hz, 2H), 8.59 (d, J = 6.4 Hz, 2H);

^{13}C NMR (100 MHz, CDCl_3) δ 22.4, 27.9, 28.0, 28.1, 28.3, 29.4, 31.6, 32.4, 38.2, 40.7, 52.9, 53.3, 72.9, 79.3, 80.5, 81.6, 82.0, 119.5, 149.6, 151.2, 155.3,
20 157.1, 172.3, 172.4, 172.5;

MS (ESI) m/z 646 $[\text{M}+\text{H}]^+$

Step 2: Preparation of compound 6a

The compound **5a** (0.8 g, 1.4 mmol) and 2-
25 aminoethyl, 2'-azidoethyl ether (0.37 g, 2.81 mmol)

were dissolved in ethanol (20 mL), to which 1 M CuSO₄ (0.28 mL, 0.28 mmol) and 2 M sodium ascorbate (0.21 mL, 0.42 mmol) were added, followed by stirring for 1 hour. The reactant was filtered and the solvent was
5 eliminated under reduced pressure. The concentrate was separated by NH silica gel column chromatography (2% methanol/dichloromethane) to give the compound **6a** (0.45 g, 46%).

10 MS (ESI) m/z 699 [M+H]⁺

Step 2: Preparation of compound 6b

The compound **6b** (450 mg, 42%) was obtained by the same manner as described in the preparation of the
15 compound **6a** except that the compound **5b** (880 mg, 1.4 mmol), 2-aminoethyl, 2'-azidoethyl ether (0.26 g, 2.00 mmol), 1 M CuSO₄ (0.27 mL, 0.27 mmol) and 2 M sodium ascorbate (0.20 mL, 0.41 mmol) were used.

20 MS (ESI) m/z 776 [M+H]⁺

Step 3: Preparation of compound 7a

DOTA-tris(tBu) ester (0.44 g, 0.77 mmol) was dissolved in dichloromethane (15 mL), to which
25 hydroxybenzotriazole (HOBt, 0.13 g, 0.97 mmol), TBTU

(0.31 g, 0.97 mmol) and diisopropylethylamine (0.224 mL, 0.13 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **6a** (0.45 g, 0.64 mmol) dissolved in dichloromethane (5 mL) was added thereto, followed by stirring 1 hour. The reaction was terminated by adding water (20 mL), and the organic compound was extracted using dichloromethane (20 mL x 2). The organic solvent was concentrated under reduced pressure, and the concentrate was separated by column chromatography (4% methanol/dichloromethane) to give the compound **7a** (0.32 g, 40%).

¹H NMR (400 MHz, methanol-d₄) δ 1.45-1.50 (m, 69H), 1.52-1.74 (m, 4H), 1.74-1.85 (m, 2H), 1.98-2.09 (m, 4H), 2.25-2.38 (m, 6H), 3.09-3.16 (m, 6H), 3.35-3.43 (m, 4H), 3.47-3.56 (m, 4H), 3.61-3.68 (m, 2H), 3.81-3.86 (m, 4H), 4.11-4.15 (m, 2H), 4.18-4.25 (m, 2H), 4.36-4.38 (m, 4H), 4.55 (t, J = 4.8 Hz, 4H), 7.84 (s, 0.7H), 7.86 (s, 0.3H);

MS (ESI) m/z 1254 [M+H]⁺

Step 3: Preparation of compound **7b**

The compound **7b** (0.15 g, 29%) was obtained by the same manner as described in the preparation of the

compound **7a** except that DOTA-tris(tBu) ester (270 mg, 0.46 mmol), hydroxybenzotriazole (HOBt, 0.078 g, 0.58 mmol), TBTU (0.19 g, 0.58 mmol), diisopropylethylamine (0.134 mL, 0.77 mmol), and the compound **6b** (0.30 g, 0.39 mmol) were used.

^1H NMR (400 MHz, methanol- d_4) δ 1.35–1.49 (m, 63H), 1.60–1.68 (m, 1H), 1.73–1.85 (m, 4H), 1.99–2.08 (m, 3H), 2.27–2.34 (m, 4H), 3.20–3.26 (m, 8H), 3.51 (t, J = 5.6 Hz, 4H), 3.69–3.78 (m, 5H), 3.81–3.83 (m, 1H), 4.09–4.23 (m, 1H), 4.46–4.56 (m, 4H), 5.03 (s, 4H), 7.41 (d, J = 6.8 Hz, 2H), 7.94 (s, 1H), 8.43 (d, J = 6.4 Hz, 2H);

MS (ESI) m/z 1331 $[\text{M}+\text{H}]^+$

15

Step 4: Preparation of compound **2a**

The compound **7a** (300 mg, 0.24 mmol) was added to 70% trifluoroacetic acid/dichloromethane (6 mL), followed by stirring for 5 hours. Diethyl ether (20 mL) was added thereto to precipitate, and it was separated using a centrifuge. The mixture was separated by HPLC and dried using a lyophilizer to give the compound **2a** (115 mg, 52%) as a solid.

¹H NMR (400 MHz, D₂O) δ 1.31-1.44 (m, 2H), 1.45-1.55 (m, 2H), 1.66-1.75 (m, 1H), 1.79-1.88 (m, 1H), 1.93-2.02 (m, 1H), 2.14-2.22 (m, 1H), 2.52 (t, *J* = 7.2 Hz, 2H), 3.11 (t, *J* = 6.8 Hz, 3H), 3.14-3.55 (m, 26H),
5 3.58 (t, *J* = 5.2 Hz, 3H), 3.62-3.93 (m, 6H), 3.96 (t, *J* = 5.6 Hz, 4H), 4.18 (dd, *J* = 13.6, 4.8 Hz, 1H), 4.27 (dd, *J* = 14.4, 5.2 Hz, 1H), 4.39 (s, 2H), 4.61 (t, *J* = 5.2 Hz, 2H), 7.93 (s, 1H);

MS (ESI) *m/z* 918 [M+H]⁺

10

Step 4: Preparation of compound 2b

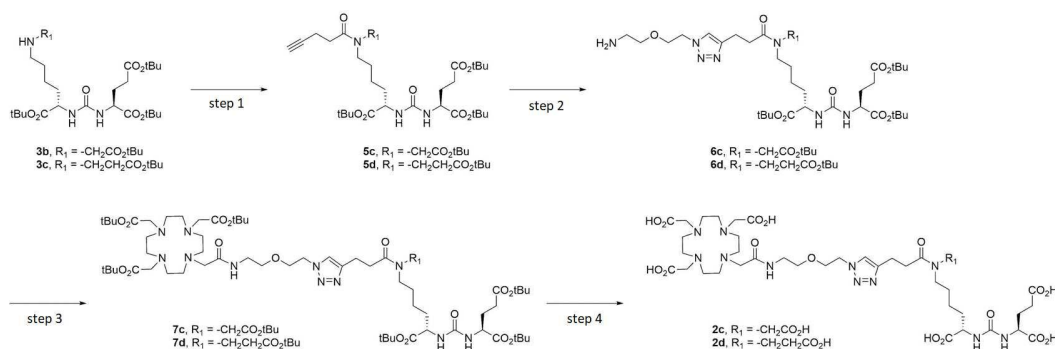
The compound **2b** (10 mg, 48%) was obtained by the same manner as described in the preparation of the compound **2a** as a solid except that the compound **7a** (28
15 mg, 21 μmol) and 70% trifluoroacetic acid/dichloromethane (0.4 mL) were used.

¹H NMR (400 MHz, D₂O) δ 1.31-1.44 (m, 4H), 1.51-1.62 (m, 2H), 1.64-1.75 (m, 1H), 1.79-1.87 (m, 1H),
20 1.90-1.99 (m, 1H), 2.11-2.19 (m, 1H), 2.49 (t, *J* = 7.6 Hz, 2H), 2.90-3.48 (m, 18H), 5.52 (t, *J* = 5.2 Hz, 3H), 3.61-3.88 (m, 6H), 3.92 (t, *J* = 4.8 Hz, 3H), 4.16 (dd, *J* = 14.0, 5.2 Hz, 1H), 4.25 (dd, *J* = 14.4, 5.2 Hz, 1H), 4.59 (t, *J* = 4.4 Hz, 2H), 5.19 (s, 2H), 7.60 (d,

$J = 7.2 \text{ Hz}$, 2H), 8.03 (s, 1H), 8.42 (d, $J = 7.2 \text{ Hz}$, 2H);

MS (ESI) m/z 995 $[M+H]^+$

5 <Example 3> Preparation of compounds 2c and 2d



Step 1: Preparation of compound 5c

4-Pentaenoic acid (82 mg, 0.83 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0°C, to which N,N'-dicyclohexylcarbodiimide (190 mg, 0.91 mmol) and the compound **3c** (0.5 g, 0.83 mmol) were added, followed by stirring at room temperature for 1 hour. The organic layer was filtered several times and the solvent was eliminated under reduced pressure. The concentrate was separated by column chromatography (30% ethylacetate/*n*-hexane) to give the compound **5c** (0.29 g, 52%).

¹H NMR (400 MHz, CDCl₃) δ 1.34–1.67 (m, 39H),
1.68–2.02 (m, 5H), 2.16–2.32 (m, 2H), 2.37–2.56 (m,
5H), 3.22 (t, J = 7.2 Hz, 1H), 3.29 (t, J = 7.6 Hz,
1H), 3.82–3.90 (m, 2H), 4.17–4.29 (m, 2H), 5.49–5.52
5 (m, 1.5H), 5.60 (d, J = 8.0 Hz, 0.5 Hz);

MS (ESI) *m/z* 704 [M+Na]⁺

Step 1: Preparation of compound 5d

The compound **5d** (0.18 g, 79%) was obtained by the
10 same manner as described in the preparation of the
compound **5c** except that 4-pentaenoic acid (32 mg, 0.32
mmol), N,N'-dicyclohexylcarbodiimide (74 mg, 0.36
mmol), and the compound **3c** (0.20 g, 0.32 mmol) were
used.

15

¹H NMR (400 MHz, CDCl₃) δ 1.41–1.43 (m, 27), 1.44
(s, 9H), 1.51–1.63 (m, 3H), 1.76–1.88 (m, 2H), 1.93–
1.96 (m, 1H), 2.01–2.08 (m, 1H), 2.20–2.36 (m, 2H),
2.46–2.53 (m, 5H), 2.57–2.60 (m, 1H), 3.26 (dt, J =
20 21.2, 7.7 Hz, 2H), 3.52 (q, J = 7.2 Hz, 2H), 4.24–4.35
(m, 2H), 5.05 (dd, J = 16.4, 8.0 Hz, 1H), 5.33 (dd, J
= 61.2, 8.0 Hz, 1H);

MS (ESI) *m/z* 718 [M+Na]⁺

25

Step 2: Preparation of compound 6c

The compound **5c** (0.26 g, 0.38 mmol) and 2-aminoethyl, 2'-azidoethyl ether (60 mg, 0.46 mmol) were dissolved in ethanol (5 mL), to which 1 M CuSO₄ (0.076 mL, 0.076 mmol) and 2 M sodium ascorbate (0.057 mL, 0.11 mmol) were added, followed by stirring for 1 hour. The reactant was filtered and the solvent was eliminated under reduced pressure. The concentrate was separated by NH silica gel column chromatography (3% methanol/dichloromethane) to give the compound **6c** (0.27 g, 87%).

¹H NMR (400 MHz, methanol-d₄) δ 1.37-1.55 (m, 36H), 1.56-1.70 (m, 2H), 1.71-1.94 (m, 2H), 1.95-2.14 (m, 2H), 2.24-2.40 (m, 2H), 2.58-2.91 (m, 2H), 2.92-3.12 (m, 2H), 3.33-3.48 (m, 4H), 3.49-3.76 (m, 4H), 3.77-3.92 (m, 2H), 3.96 (s, 1H), 4.45-4.28 (m, 3H), 4.46-4.65 (m, 1H);

MS (ESI) *m/z* 813 [M+H]⁺

Step 2: Preparation of compound **6d**

The compound **6d** (60.0 mg, 50%) was obtained by the same manner as described in the preparation of the compound **6c** except that the compound **5d** (0.10 g, 0.14 mmol), 2-aminoethyl, 2'-azidoethyl ether (21 mg, 0.16

mmol), 1 M CuSO₄ (0.030 mL, 0.030 mmol) and 2 M sodium ascorbate (0.020 mL, 0.040 mmol) were used.

¹H NMR (400 MHz, CDCl₃) δ 1.23–1.30 (m, 2H), 1.40
5 (s, 18H), 1.42 (s, 18H), 1.68 (s, 6H), 1.74–1.87 (m, 2H), 1.99–2.09 (m, 1H), 2.24–2.35 (m, 2H), 2.41–2.47 (m, 2H), 2.70–2.75 (m, 1H), 2.96–3.08 (m, 2H), 3.20–3.31 (m, 2H), 3.28–3.54 (m, 3H), 3.81 (t, *J* = 8.0 Hz, 2H), 4.24–4.42 (m, 2H), 4.47–4.55 (m, 2H), 5.59 (dd, *J*
10 = 53.4, 7.4 Hz, 1H), 5.77 (dd, *J* = 37.6, 8.4 Hz, 1H), 7.53 (d, *J* = 16.4 Hz, 1H);

MS (ESI) *m/z* 826 (M+H)⁺

Step 3: Preparation of compound 7c

15 DOTA-tris(*t*Bu) ester (84 mg, 0.015 mmol) was dissolved in dichloromethane (5 mL), to which hydroxybenzotriazole (HOBt, 25 mg, 0.019 mmol), TBTU (59 mg, 0.019 mmol) and diisopropylethylamine (0.042 mL, 0.25 mmol) were added, followed by stirring at
20 room temperature for 10 minutes. The compound **6c** (100 mg, 0.12 mmol) dissolved in dichloromethane (2 mL) was added thereto, followed by stirring 1 hour. The reaction was terminated by adding water (10 mL), and the organic compound was extracted using
25 dichloromethane (10 mL x 2). The reactant was dried

over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was separated by column chromatography (3% methanol/dichloromethane) to give the compound **7c** (95 mg, 56%).

5

^1H NMR (400 MHz, methanol- d_4) δ 1.42–1.65 (m, 63H), 1.71–1.85 (m, 2H), 1.95–3.69 (m, 40H), 3.74 (s, 3H), 3.79–3.92 (m, 2H), 3.96 (s, 1H), 4.11–4.20 (m, 3H), 4.50–4.58 (m, 2H);

10 MS (ESI) m/z 1388 $[\text{M}+\text{Na}]^+$

Step 3: Preparation of compound **7d**

The compound **7d** (51 mg, 61%) was obtained by the same manner as described in the preparation of the
15 compound **7c** except that DOTA-tris(*t*Bu) ester (29 mg, 0.073 mmol) was dissolved in dichloromethane (5 mL) and hydroxybenzotriazole (HOBt, 12 mg, 0.091 mmol), TBTU (29 mg, 0.091 mmol), diisopropylethylamine (15.86 μL , 91.07 μmol) and the compound **6d** (50 mg, 60.5 μmol)
20 were used.

^1H NMR (400 MHz, CDCl_3) δ 0.75–0.94 (m, 2H), 1.23–1.61 (m, 63H), 1.69 (s, 5H), 1.77–1.87 (m, 2H), 2.00–2.08 (m, 3H), 2.21 (bs, 2H), 2.27–2.37 (m, 3H), 2.41–
25 2.48 (m, 4H), 2.78 (s, 4H), 2.94–3.06 (m, 3H), 3.20–

3.38 (m, 5H), 3.43-3.56 (m, 4H), 3.60 (t, $J = 5.2$ Hz, 2H), 3.66-3.75 (m, 5H), 3.80 (t, $J = 4.8$ Hz, 2H), 4.19 (d, $J = 4.0$ Hz, 2H), 4.25-4.34 (m, 2H), 4.50-4.54 (m, 2H), 5.47 (dd, $J = 26.8, 8.0$ Hz, 1H), 5.66 (dd, $J =$
5 12.4, 8.4 Hz, 1H), 7.71 (d, $J = 41.2$ Hz, 1H)

MS (ESI) m/z 1381 $[M+H]^+$

Step 4: Preparation of compound 2c

The compound **7c** (60 mg, 0.044 mmol) was added to
10 70% trifluoroacetic acid/dichloromethane (2 mL),
followed by stirring for 4 hours. Diethyl ether (20 mL) was added thereto to precipitate, and it was separated using a centrifuge. The mixture was separated by HPLC and dried using a lyophilizer to
15 give the compound **2c** (25 mg, 58%) as a solid.

^1H NMR (400 MHz, D_2O) δ 1.10-1.30 (m, 2H), 1.31-1.50 (m, 2H), 1.52-1.63 (m, 1H), 1.64-1.76 (m, 1H), 1.78-1.89 (m, 1H), 1.99-2.09 (m, 1H), 2.36-2.40 (m,
20 2H), 2.62-2.65 (m, 1H), 2.77-2.80 (m, 2H), 2.95-2.98 (m, 3H), 3.00-3.19 (m, 7H), 3.21-3.42 (m, 11H), 3.46-3.47 (m, 3H), 3.49-3.72 (m, 4H), 3.82-3.86 (m, 3H), 3.95 (s, 2H), 4.01-4.15 (m, 4H), 4.53-4.56 (m, 2H), 7.84 (s, 1H);

25 MS (ESI) m/z 974 $[M+H]^+$

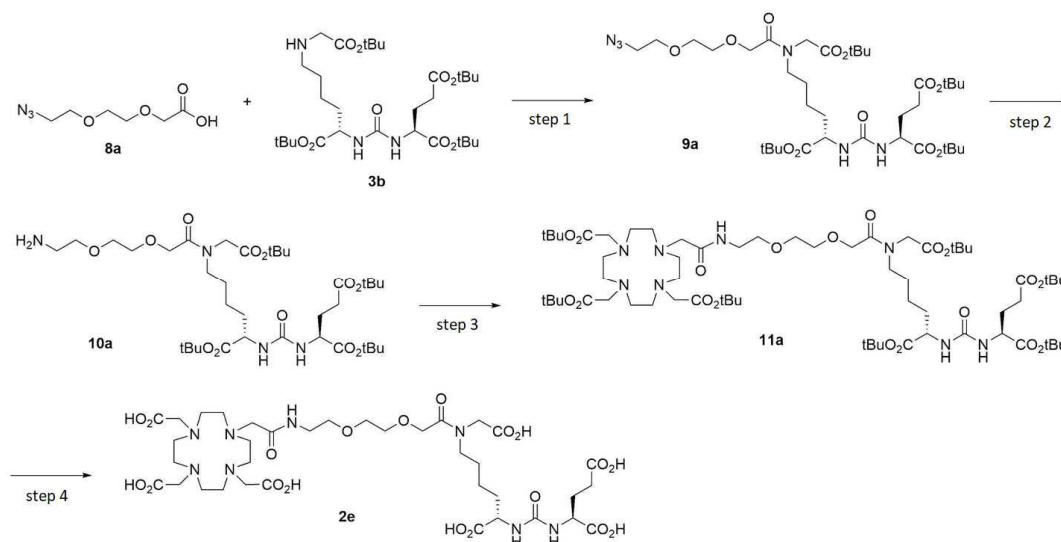
Step 4: Preparation of compound 2d

The compound **2d** (19 mg, 66%) was obtained by the same manner as described in the preparation of the compound **2c** as a solid except that the compound **7d** (40 mg, 0.029 mmol) was used.

¹H NMR (400 MHz, D₂O) δ 1.25-1.42 (m, 2H), 1.44-1.64 (m, 2H), 1.65-1.76 (m, 1H), 1.78-1.91 (m, 1H), 10 1.92-2.04 (m, 1H), 2.14-2.22 (m, 0.5H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 1.5H), 2.64 (t, *J* = 7.2 Hz, 1H), 2.81 (t, *J* = 7.2 Hz, 1H), 2.88 (t, *J* = 7.2 Hz, 1H), 3.03-3.07 (m, 3H), 3.08-3.54 (m, 19H), 3.55-3.65 (m, 7H), 3.66-3.87 (m, 4H), 3.96 (t, *J* = 4.8 15 Hz, 4H), 4.17-4.22 (m, 1H), 4.25-4.28 (m, 1H), 4.62-4.64 (m, 2H), 7.92 (s, 0.6H), 7.93 (s, 0.4H);

MS (ESI) *m/z* 974 [M+H]⁺

<Example 4> Preparation of compound 2e



Step 1: Preparation of compound **9a**

The compound **3b** (600 mg, 0.997 mmol) synthesized in Example 1 was dissolved in dichloromethane (10 mL), to which N,N'-dicyclohexylcarbodiimide (DCC, 226 mg, 1.04 mmol) was slowly added at room temperature. 2-(2-(2-Azidoethoxy)ethoxy)acetic acid **8a** ($\text{N}_3-(\text{CH}_2\text{CH}_2\text{O})_2-\text{CH}_2\text{COOH}$, 226 mg, 1.20 mmol) was slowly added thereto, followed by stirring for 1 hour. Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent was dried over anhydrous sodium sulfate, concentrated under reduced pressure and separated by column chromatography (60% ethylacetate/n-hexane) to give the compound **9a** (520 mg, 67%) as a colorless liquid.

¹H NMR (400 MHz, methanol-d₄) δ 1.44-1.49 (m, 36H), 1.50-1.57 (m, 2H), 1.58-1.71 (m, 2H), 1.73-1.84 (m, 2H), 2.00-2.09 (m, 1H), 2.25-2.38 (m, 2H), 3.33-
5 3.39 (m, 4H), 3.65-3.72 (m, 6H), 3.96 (d, *J* = 1.2 Hz, 1H), 4.11-4.22 m, 3H), 4.33 (s, 2H), 6.32-6.36 (m, 1H);

MS (ESI) *m/z* 773 [M+H]⁺

10 **Step 2: Preparation of compound 10a**

The compound **9a** (490 mg, 0.634 mmol) synthesized in step 1 above was dissolved in ethanol (20 mL), to which 10% palladium on carbon (67 mg) was added, followed by stirring for 12 hours under hydrogen. The
15 reaction solution was filtered, washed with ethanol, and concentrated under reduced pressure. The concentrate was separated by column chromatography (4% methanol/dichloromethane, NH silica gel) to give the compound **10a** (425 mg, 90%) as a colorless liquid.

20

¹H NMR (400 MHz, methanol-d₄) δ 1.34-1.39 (m, 2H), 1.44-1.49 (m, 36H), 1.51-1.65 (m, 4H), 1.73-1.84 (m, 2H), 2.00-2.07 (m, 1H), 2.31 (q, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 5.2 Hz, 2H), 3.33-3.40 (m, 1H), 3.52 (q, *J* =
25 5.2 Hz, 2H), 3.61-3.66 (m, 3H), 3.69-3.71 (m, 1H),

3.97 (d, $J = 1.2$ Hz, 1H), 4.11 (s, 1H), 4.13-4.21 (m, 2H), 4.32 (s, 2H);

MS (ESI) m/z 747 $[M+H]^+$

5 **Step 3: Preparation of compound 11a**

DOTA-tris(tBu) ester (55 mg, 0.096 mmol) was dissolved in dichloromethane (2.0 mL), to which hydroxybenzotriazole (HOBt, 22 mg, 0.160 mmol), TBTU (52 mg, 0.160 mmol) and diisopropylethylamine (0.042
10 mL, 0.241 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **10a** (60 mg, 0.080 mmol) synthesized in step 2 above dissolved in dichloromethane (2.0 mL) was added thereto, followed by stirring at room temperature for 1 hour.
15 Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent was dried over anhydrous sodium sulfate, concentrated under reduced pressure and separated by column
20 chromatography (3% methanol/dichloromethane) to give the compound **11a** (75 mg, 71%) as a colorless liquid.

^1H NMR (400 MHz, methanol- d_4) δ 1.44-1.50 (m, 63H), 1.54-1.65 (m, 4H), 1.73-1.82 (m, 2H), 2.00-2.09
25 (m, 3H), 2.15-2.34 (m, 6H), 2.59-3.25 (br s, 16H),

3.38-3.40 (m, 2H), 3.55-3.57 (m, 3H), 3.62 (s, 2H),
3.63-3.69 (m, 3H), 3.97 (s, 2H), 4.08 (s, 2H), 4.09-
4.21 (m, 3H), 4.31 (s, 2H);

MS (ESI) m/z 1302 [M+H]⁺

5

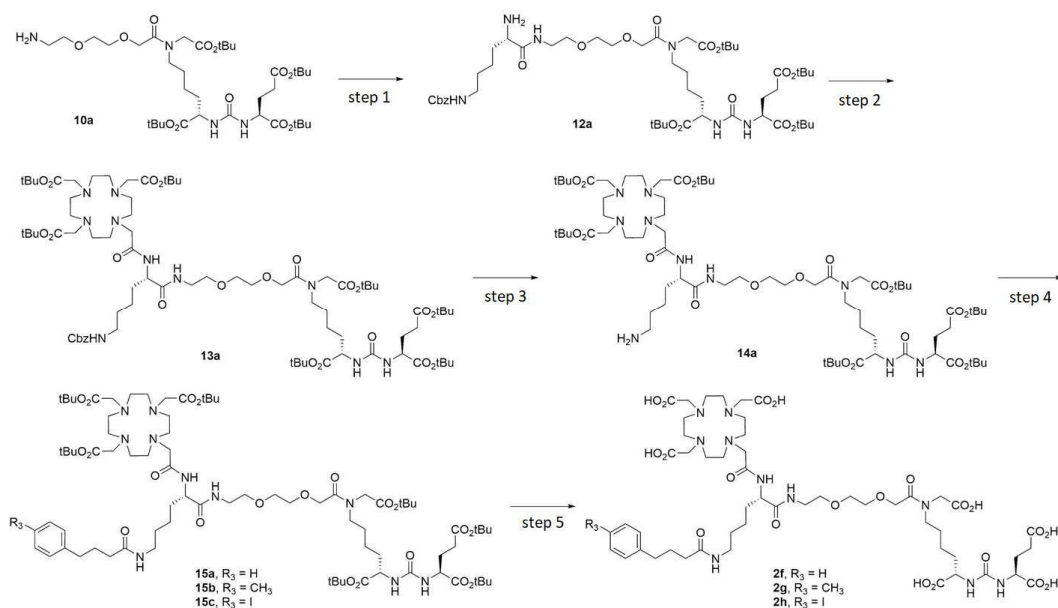
Step 4: Preparation of compound 2e

The compound **11a** (50 mg, 0.038 mmol) synthesized
in step 3 above was dissolved in 70% trifluoroacetic
acid/dichloromethane (0.5 mL), followed by stirring at
10 room temperature for 4 hours. The reactant was
concentrated under reduced pressure and separated by
high performance liquid chromatography (HPLC) to give
the compound **2e** (26 mg, 74%) as a white solid.

15 ¹H NMR (400 MHz, D₂O) δ 1.16-1.30 (m, 2H), 1.36-
1.50 (m, 2H), 1.52-1.62 (m, 1H), 1.64-1.73 (m, 1H),
1.76-1.86 (m, 1H), 1.98-2.06 (m, 1H), 2.35 (td, J =
7.2, 1.6 Hz, 2H), 2.86-3.38 (m, 20H), 3.48-3.60 (m,
10H), 3.70-3.91 (br s, 3H), 3.96 (s, 2H), 4.00-4.12
20 (m, 3H), 4.25 (s, 2H);

MS (ESI) m/z 910 [M+2H]⁺

<Example 5> Preparation of compounds 2f, 2g and 2h



Step 1: Preparation of compound 12a

Lysine (Fmoc-Lys(Z)-OH, 275 mg, 0.546 mmol) was dissolved in dichloromethane (10 mL), to which
 5 hydroxybenzotriazole (HOBt, 123 mg, 0.1910 mmol), TBTU (292 mg, 0.910 mmol) and diisopropylethylamine (0.238 mL, 1.37 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **10a** (340 mg, 0.455 mmol) synthesized in step 2 of Example 4
 10 dissolved in dichloromethane (5.0 mL) was added thereto, followed by stirring at room temperature for 1 hour. Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent
 15 was dried over anhydrous sodium sulfate, concentrated

under reduced pressure and separated by column chromatography (2% methanol/dichloromethane). Dichloromethane (15 mL) was added to the obtained compound, to which piperidine (0.043 mL, 0.438 mmol) was added, followed by stirring at room temperature for 24 hours. The reactant was concentrated under reduced pressure, and the concentrate was separated by column chromatography (3% methanol/dichloromethane, NH silica gel) to give the compound **12a** (480 mg, 84%) as a colorless liquid.

^1H NMR (400 MHz, methanol- d_4) δ 1.34–1.39 (m, 2H), 1.44–1.48 (m, 36H), 1.50–1.70 (m, 10 H), 1.72–1.84 (m, 2H), 2.00–2.08 (m, 1H), 2.24–2.38 (m, 2H), 3.11 (t, J = 6.8 Hz, 2H), 3.33–3.41 (m, 4H), 3.55 (q, J = 5.2 Hz, 2H), 3.61–3.68 (m, 4H), 3.96 (d, J = 1.6 Hz, 1H), 4.08 (d, J = 1.2 Hz, 1H), 4.10–4.21 (m, 3H), 4.31 (s, 1H), 5.06 (s, 2H), 7.27–7.32 (m, 1H), 7.33–7.34 (m, 4H);

MS (ESI) m/z 1010 $[\text{M}+\text{H}]^+$

Step 2: Preparation of compound 13a

DOTA-tris(*t*Bu) ester (211 mg, 0.369 mmol) was dissolved in dichloromethane (10 mL), to which hydroxybenzotriazole (HOBt, 83 mg, 0.614 mmol), TBTU (197 mg, 0.614 mmol) and diisopropylethylamine (0.161

mL, 0.921 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **12a** (310 mg, 0.307 mmol) synthesized in step 1 above dissolved in dichloromethane (5.0 mL) was added thereto, followed by stirring at room temperature for 1 hour. Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent was dried over anhydrous sodium sulfate, concentrated under reduced pressure and separated by column chromatography (5% methanol/dichloromethane) to give the compound **13a** (323 mg, 67%) as a colorless liquid.

^1H NMR (400 MHz, methanol- d_4) δ 1.36-1.39 (m, 2H), 1.44-1.49 (m, 63H), 1.51-1.73 (m, 8H), 1.75-1.84 (m, 2H), 2.00-2.07 (m, 3H), 2.08-2.26 (m, 4H), 2.28-2.36 (m, 3H), 2.38-3.05 (br s, 12H), 3.11 (t, J = 6.6 Hz, 2H), 3.16-3.28 (m, 4H), 3.36 (t, J = 6.6 Hz, 2H), 3.38-3.52 (br s, 3H), 3.54 (q, J = 4.0 Hz, 2H), 3.58-3.68 (m, 5H), 3.97 (d, J = 4.4 Hz, 1H), 4.07 (s, 1H), 4.09-4.22 (m, 3H), 4.26-4.28 (m, 1H), 4.31 (s, 1H), 5.06 (s, 2H), 7.26-7.32 (m, 1H), 7.33-7.38 (m, 4H);

MS (ESI) m/z 1565 $[\text{M}+2\text{H}]^+$

Step 3: Preparation of compound 14a

The compound **13a** (300 mg, 0.192 mmol) synthesized in step 2 above was dissolved in ethanol (20 mL), to which 10% palladium on carbon (20 mg) was added, followed by stirring for 2 hours under hydrogen. The
5 reaction solution was filtered, washed with ethanol, and concentrated under reduced pressure. The concentrate was separated by column chromatography (4% methanol/dichloromethane, NH silica gel) to give the compound **14a** (260 mg, 95%) as a colorless liquid.

10

^1H NMR (400 MHz, methanol- d_4) δ 1.33-1.42 (m, 4H), 1.44-1.49 (m, 63H), 1.51-1.57 (m, 4H), 1.59-1.73 (m, 4H) 1.74-1.85 (m, 3H), 2.00-2.08 (m, 3H), 2.09-2.27 (br s, 4H), 2.29-2.38 (m, 3H), 2.60-2.65 (m, 2H), 2.68
15 (t, J = 7.2 Hz, 2H), 2.73-2.94 (br s, 7H), 3.05-3.17 (br s, 3H), 3.25-3.28 (m, 2H), 3.34-3.39 (m, 2H), 3.43 (br s, 1H), 3.47-3.39 (m, 1H), 3.53-3.57 (m, 3H), 3.63 (s, 2H), 3.65-3.68 (m, 2H), 3.98 (d, J = 5.6 Hz, 1H), 4.09 (s, 1H), 4.11-4.22 (m, 3H), 4.32 (s, 2H);

20 MS (ESI) m/z 1430 $[\text{M}+\text{H}]^+$

Step 4: Preparation of compound 15a

4-Phenylbutyric acid (8.4 mg, 0.050 mmol) was dissolved in dichloromethane (1.0 mL), to which
25 hydroxybenzotriazole (HOBt, 11 mg, 0.084 mmol), TBTU

(27 mg, 0.084 mmol) and diisopropylethylamine (0.022 mL, 0.126 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **14a** (60 mg, 0.042 mmol) synthesized in step 3 above dissolved
5 in dichloromethane (1.0 mL) was added thereto, followed by stirring at room temperature for 2 hours. Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent was
10 dried over anhydrous sodium sulfate, concentrated under reduced pressure and separated by column chromatography (4% methanol/dichloromethane) to give the compound **15a** (17 mg, 26%) as a colorless liquid.

15 ^1H NMR (400 MHz, methanol- d_4) δ 1.44–1.48 (m, 63H), 1.51–1.71 (m, 6H), 1.74–1.84 (m, 4H), 1.86–1.94 (m, 2H), 1.98–2.15 (m, 6H), 2.19 (t, J = 7.4 Hz, 2H), 2.24–2.34 (m, 3H), 2.36–3.04 (br s, 3H), 2.61 (t, J = 7.8 Hz, 2H), 2.63–3.04 (br s, 10H), 3.12–3.19 (m, 3H),
20 3.25–3.26 (m, 4H), 3.35–3.37 (m, 4H), 3.47–3.56 (m, 5H), 3.59–3.68 (m, 4H), 3.97 (d, J = 4.0 Hz, 1H), 4.08–4.22 (m, 4H), 4.31 (s, 2H), 7.1–7.18 (m, 3H), 7.24–7.27 (m, 2H);

MS (ESI) m/z 1577 $[\text{M}+\text{H}]^+$

Step 4: Preparation of compound 15b

The compound **15b** (17 mg, 26%) was obtained by the same manner as described in the preparation of the compound **15a** as a colorless liquid except that 4-(p-
5 tolyl)butyric acid (12 mg, 0.063 mmol), hydroxybenzotriazole (HOBt, 14 mg, 0.106 mmol), TBTU (34 mg, 0.106 mmol), diisopropylethylamine (0.028 mL, 0.159 mmol) and the compound **14a** (76 mg, 0.053 mmol) synthesized in step 3 above were used.

10

MS (ESI) m/z 1590 [M+H]⁺

Step 4: Preparation of compound 15c

The compound **15c** (36 mg, 51%) was obtained by the
15 same manner as described in the preparation of the compound **15a** as a colorless liquid except that 4-(p-iodophenyl)butyric acid (15 mg, 0.050 mmol), hydroxybenzotriazole (HOBt, 11 mg, 0.084 mmol), TBTU (27 mg, 0.084 mmol), diisopropylethylamine (0.022 mL,
20 0.126 mmol) and the compound **14a** (60 mg, 0.042 mmol) synthesized in step 3 above were used.

¹H NMR (400 MHz, methanol-d₄) δ 1.44-1.48 (m, 63H), 1.51-1.57 (m, 4H), 1.58-1.70 (m, 3H), 1.71-1.82
25 (m, 3H), 1.84-1.92 (m, 3H), 1.93-2.15 (m, 5H), 2.18

(t, J = 7.6 Hz, 2H), 2.20-2.34 (m, 5H), 2.36-2.56 (br s, 3H), 2.58 (t, J = 7.6 Hz, 2H), 2.61-2.76 (br s, 3H), 2.81 (s, 2H), 2.86-3.09 (br s, 5H), 3.11-3.18 (m, 3H), 3.20-3.26 (m, 3H), 3.35-3.39 (m, 2H), 3.42-3.48
5 (br s, 2H), 3.53 (q, J = 4.0 Hz, 2H), 3.62 (s, 2H), 3.64-3.69 (m, 3H), 3.97 (d, J = 3.6 Hz, 1H), 4.08 (s, 1H), 4.10-4.23 (m, 4H), 4.31 (s, 2H), 6.32-6.36 (m, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H);

10 MS (ESI) m/z 1702 $[M+H]^+$

Step 5: Preparation of compound 2f

The compound **15a** (14 mg, 0.0089 mmol) synthesized in step 4 above was dissolved in 70% trifluoroacetic acid/dichloromethane (0.5 mL), followed by stirring at
15 room temperature for 1 hour. The reactant was concentrated under reduced pressure, and the concentrate was separated by high performance liquid chromatography (HPLC) to give the compound **2f** (7 mg,
20 67%) as a white solid.

^1H NMR (400 MHz, D_2O) δ 1.22-1.31 (m, 4H), 1.39 (p, J = 7.4 Hz, 2H), 1.42-1.51 (m, 2H), 1.57-1.73 (m, 4H), 1.79 (p, J = 7.6 Hz, 2H), 1.82-1.89 (m, 1H),
25 2.01-2.09 (m, 1H), 2.13 (t, J = 7.2 Hz, 2H), 2.39 (t,

$J = 7.2$ Hz, 2H), 2.51 (t, $J = 7.4$ Hz, 2H), 2.53–3.00 (br s, 3H), 3.03 (t, $J = 6.8$ Hz, 2H), 3.09–3.43 (m, 18H), 3.47 (q, $J = 5.2$ Hz, 2H), 3.48–3.60 (m, 6H), 3.61–3.91 (br s, 5H), 3.96 (s, 2H), 4.00–4.16 (m, 3H),
5 4.25 (s, 2H), 7.13–7.17 (m, 3H), 7.22–7.27 (m, 2H);

MS (ESI) m/z 1183 $[M+H]^+$, 1181 $[M-H]^-$

Step 5: Preparation of compound 2g

The compound **2g** (10 mg, 36%) was obtained by the
10 same manner as described in the preparation of the
compound **2f** as a white solid except that the compound
15b (37 mg, 0.023 mmol) synthesized in step 4 above
and 70% trifluoroacetic acid/dichloromethane (0.5 mL)
were used.

15

^1H NMR (400 MHz, D_2O) δ 1.14–1.26 (m, 4H), 1.35 (p, $J = 6.8$ Hz, 2H), 1.39–1.48 (m, 2H), 1.50–1.63 (m, 3H), 1.66–1.69 (m, 1H), 1.72 (p, $J = 7.2$ Hz, 2H), 1.82 (p, $J = 7.2$ Hz, 1H), 2.01 (p, $J = 7.0$ Hz, 1H), 2.08
20 (t, $J = 7.2$ Hz, 2H), 2.15 (s, 3H), 2.35 (t, $J = 7.2$ Hz, 2H), 2.43 (t, $J = 7.4$ Hz, 2H), 2.66–2.98 (br s, 2H), 2.99 (t, $J = 6.6$ Hz, 2H), 3.01–3.40 (m, 18H), 3.44 (q, $J = 5.0$ Hz, 2H), 3.48–3.56 (m, 5H), 3.57–3.88 (br s, 6H), 3.92 (s, 2H), 3.98–4.12 (m, 4H), 4.21 (s,

2H), 7.01 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H);

MS (ESI) m/z 1198 $[M+H]^+$, 1196 $[M-H]^-$

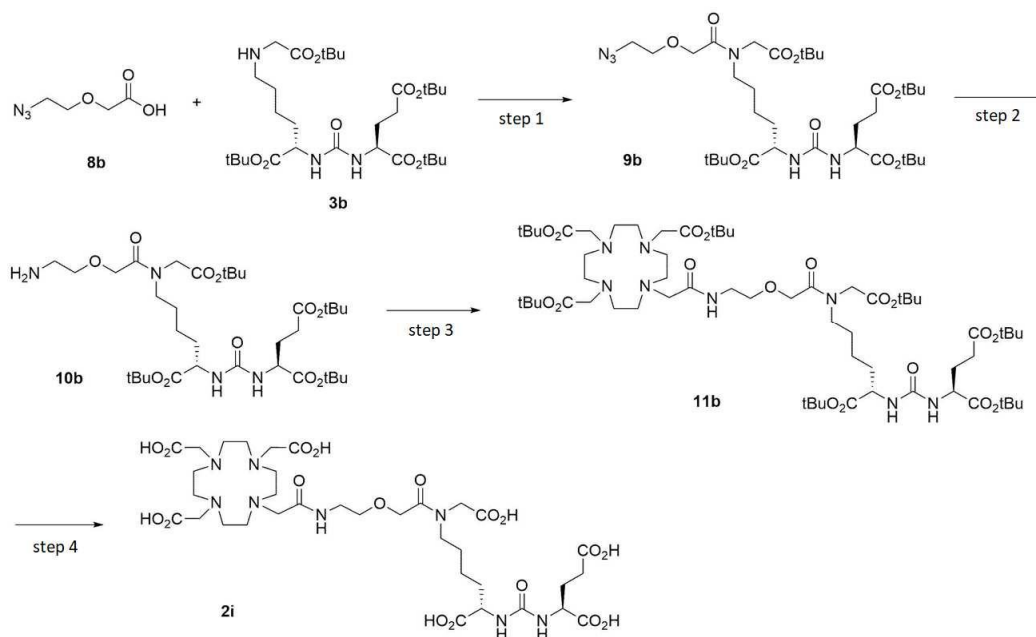
5 **Step 5: Preparation of compound 2h**

The compound **2h** (13 mg, 54%) was obtained by the same manner as described in the preparation of the compound **15a** as a white solid except that the compound **15c** (30 mg, 0.018 mmol) synthesized in step 4 above
10 and 70% trifluoroacetic acid/dichloromethane (0.5 mL) were used.

^1H NMR (400 MHz, D_2O) δ 1.18-1.30 (m, 4H), 1.37 (p, J = 6.8 Hz, 2H), 1.41-1.52 (m, 2H), 1.54-1.67 (m, 3H), 1.70-1.74 (m, 1H), 1.78 (t, J = 7.4 Hz, 2H),
15 1.81-1.90 (m, 1H), 1.98-2.07 (m, 1H), 2.11 (t, J = 7.2 Hz, 2H), 2.39 (t, J = 7.2 Hz, 2H), 2.48 (t, J = 7.4 Hz, 2H), 3.00 (t, J = 6.8 Hz, 2H), 3.02-3.26 (m, 17H), 3.29-3.35 (m, 2H), 3.48 (q, J = 4.4 Hz, 2H), 3.52-3.58
20 (m, 6H), 3.60-3.93 (br s, 7H), 3.97 (s, 2H), 4.03-4.17 (m, 3H), 4.25 (s, 2H), 6.95 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H);

MS (ESI) m/z 1309 $[M+H]^+$, 1307 $[M-H]^-$

25 **<Example 6> Preparation of compound 2i**



Step 1: Preparation of compound **9b**

The compound **3b** (691 mg, 1.15 mmol) synthesized in Example 1 was dissolved in dichloromethane (10 mL), to which N,N'-dicyclohexylcarbodiimide (DCC, 3710 mg, 1.79 mmol) was slowly added at room temperature. 2-(2-Azidoethoxy)acetic acid **8b** ($\text{N}_3\text{-CH}_2\text{CH}_2\text{O-CH}_2\text{COOH}$, 200 mg, 1.38 mmol) was added thereto, followed by stirring for 1 hour. Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent was dried over anhydrous sodium sulfate, concentrated under reduced pressure and separated by column chromatography (40% ethylacetate/n-hexane) to give the compound **9b** (670 mg, 80%) as a colorless liquid.

^1H NMR (400 MHz, methanol- d_4) δ 1.44-1.51 (m, 36H), 1.52-1.67 (m, 4H), 1.71-1.84 (m, 2H), 2.00-2.09 (m, 1H), 2.25-2.38 (m, 2H), 3.36 (q, J = 7.5 Hz, 2H),
5 3.41-3.45 (m, 2H), 3.66 (t, J = 5.0 Hz, 1H), 3.71 (t, J = 5.0 Hz, 1H), 3.97 (d, J = 0.8 Hz, 1H), 4.11 (d, J = 1.2 Hz, 1H), 4.12-4.23 (m, 3H), 4.32 (s, 2H), 6.34 (p, J = 4.2 Hz, 2H);

MS (ESI) m/z 729 $[\text{M}+\text{H}]^+$

10

Step 2: Preparation of compound 10b

The compound **9b** (650 mg, 0.892 mmol) synthesized in step 1 above was dissolved in ethanol (20 mL), to which 10% palladium on carbon (95 mg) was added,
15 followed by stirring for 12 hours under hydrogen. The reaction solution was filtered, washed with ethanol, and concentrated under reduced pressure. The concentrate was separated by column chromatography (2% methanol/dichloromethane, NH silica gel) to give the
20 compound **10b** (573 mg, 91%) as a colorless liquid.

^1H NMR (400 MHz, methanol- d_4) δ 1.37-1.42 (m, 2H), 1.44-1.49 (m, 36H), 1.51-1.67 (m, 4H), 1.71-1.84 (m, 2H), 1.99-2.09 (m, 1H), 2.29-2.34 (m, 2H), 2.84 (p, J = 5.2 Hz, 2H), 3.35-3.40 (m, 1H), 3.54 (t, J = 5.4 Hz,
25

1H), 3.59 (t, J = 5.4 Hz, 1H), 3.98 (d, J = 0.8 Hz, 1H), 4.07 (s, 1H), 4.09–4.21 (m, 2H), 4.31 (s, 2H);

MS (ESI) m/z 703 $[M+H]^+$

5 **Step 3: Preparation of compound 11b**

DOTA-tris(tBu) ester (82 mg, 0.143 mmol) was dissolved in dichloromethane (2.0 mL), to which hydroxybenzotriazole (HOBt, 32 mg, 0.239 mmol), TBTU (77 mg, 0.239 mmol) and diisopropylethylamine (0.062
10 mL, 0.358 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **10b** (84 mg, 0.120 mmol) synthesized in step 2 above dissolved in dichloromethane (2.0 mL) was added thereto, followed by stirring at room temperature for 1 hour.
15 Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent was dried over anhydrous sodium sulfate, concentrated under reduced pressure and separated by column
20 chromatography (2% methanol/dichloromethane) to give the compound **11b** (65 mg, 43%) as a colorless liquid.

^1H NMR (400 MHz, methanol- d_4) δ 1.44–1.49 (m, 63H), 1.51–1.54 (m, 2H), 1.57–1.65 (m, 2H), 1.75–1.84
25 (m, 2H), 2.04–2.09 (m, 2H), 2.30–2.34 (m, 2H), 2.81–

3.25 (br s, 18H), 3.35-3.54 (br s 7H), 3.55 (t, J = 5.4 Hz, 2H), 3.61 (t, J = 5.2 Hz, 2H), 3.98 (s, 2H), 4.06 (s, 1H), 4.10-4.22 (m, 2H), 4.29 (s, 2H);

MS (ESI) m/z 1258 $[M+H]^+$

5

Step 4: Preparation of compound 2i

The compound **11b** (55 mg, 0.044 mmol) synthesized in step 3 above was dissolved in 70% trifluoroacetic acid/dichloromethane (0.5 mL), followed by stirring at
10 room temperature for 4 hours. The reactant was concentrated under reduced pressure, and the concentrate was separated by high performance liquid chromatography (HPLC) to give the compound **2i** (17 mg, 45%) as a white solid.

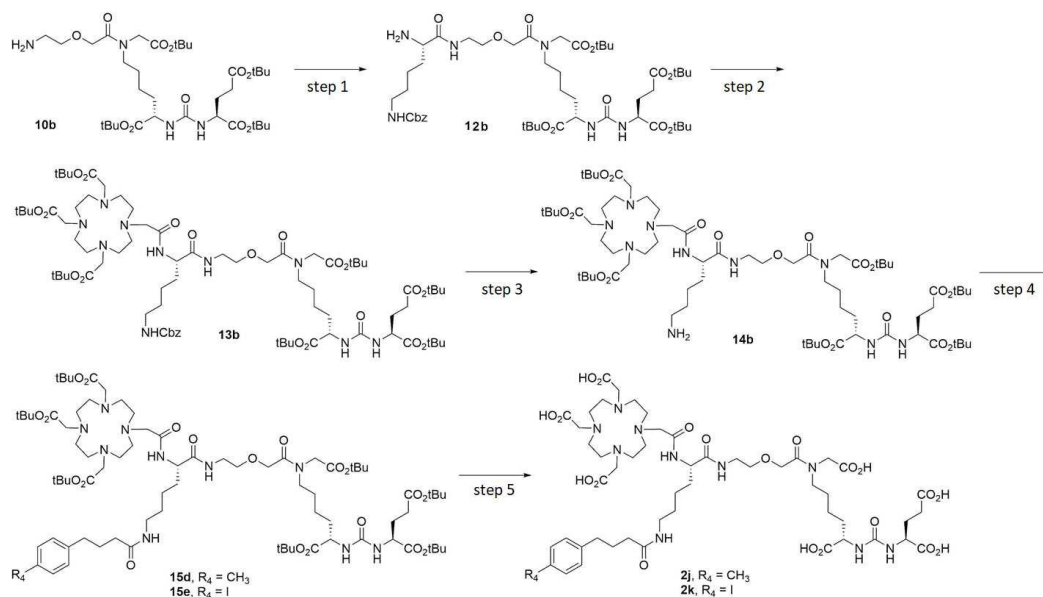
15

^1H NMR (400 MHz, D_2O) δ 1.20-1.34 (m, 2H), 1.42-1.54 (m, 2H), 1.56-1.65 (m, 1H), 1.70-1.77 (m, 1H), 1.86 (p, J = 7.4 Hz, 1H), 2.05 (p, J = 7.2 Hz, 1H), 2.39 (t, J = 7.2 Hz, 2H), 2.84-3.49 (m, 20H), 3.51 (t, J = 5.0 Hz, 1H), 3.55 (t, J = 4.0 Hz, 1H), 3.58-3.62 (br s, 4H), 3.63-3.95 (br s, 3H), 4.00 (s, 2H), 4.05 (s, 1H), 4.07-4.17 (m, 2H), 4.29 (s, 2H);

MS (ESI) m/z 865 $[M+H]^+$, 863 $[M-H]^-$

25

<Example 7> Preparation of compounds 2j and 2k



Step 1: Preparation of compound 12b

Lysine (Fmoc-Lys(Z)-OH, 386 mg, 0.768 mmol) was dissolved in dichloromethane (10 mL), to which

5 hydroxybenzotriazole (HOBt, 173 mg, 1.28 mmol), TBTU (411 mg, 1.28 mmol) and diisopropylethylamine (0.335 mL, 1.92 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **10b** (450 mg, 0.640 mmol) synthesized in step 2 of Example 6

10 dissolved in dichloromethane (5.0 mL) was added thereto, followed by stirring at room temperature for 1 hour. Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent

15 was dried over anhydrous sodium sulfate, concentrated

under reduced pressure and separated by column chromatography (2% methanol/dichloromethane). Dichloromethane (15 mL) was added to the obtained compound, to which piperidine (0.050 mL, 0.505 mmol) was added, followed by stirring at room temperature for 24 hours. The reactant was concentrated under reduced pressure, and the concentrate was separated by column chromatography (3% methanol/dichloromethane, NH silica gel) to give the compound **12b** (380 mg, 61%) as a colorless liquid.

^1H NMR (400 MHz, methanol- d_4) δ 1.33–1.41 (m, 4H), 1.44–1.48 (m, 36H), 1.51–1.72 (m, 8H), 1.74–1.84 (m, 2H), 1.99–2.08 (m, 1H), 2.24–2.38 (m, 2H), 3.11 (t, J = 6.8 Hz, 2H), 3.24–3.28 (m, 1H), 3.34–3.46 (m, 3H), 3.55 (t, J = 5.4 Hz, 1H), 3.60 (t, J = 5.4 Hz, 1H), 3.96 (s, 1H), 4.05 (d, J = 1.2 Hz, 1H), 4.16–4.22 (m, 3H), 4.29 (s, 1H), 5.05 (s, 2H), 7.26–7.32 (m, 1H), 7.33–7.38 (m, 4H);

MS (ESI) m/z 966 $[\text{M}+\text{H}]^+$

Step 2: Preparation of compound 13b

DOTA-tris(*t*Bu) ester (271 mg, 0.472 mmol) was dissolved in dichloromethane (10 mL), to which hydroxybenzotriazole (HOBt, 106 mg, 0.787 mmol), TBTU

(253 mg, 0.787 mmol) and diisopropylethylamine (0.206 mL, 1.18 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **12b** (380 mg, 0.394 mmol) synthesized in step 1 above dissolved
5 in dichloromethane (5.0 mL) was added thereto, followed by stirring at room temperature for 1 hour. Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent was
10 dried over anhydrous sodium sulfate, concentrated under reduced pressure and separated by column chromatography (3% methanol/dichloromethane) to give the compound **13b** (487 mg, 81%) as a colorless liquid.

15 ^1H NMR (400 MHz, methanol- d_4) δ 1.44-1.49 (m, 63H), 1.51-1.53 (m, 2H), 1.59-1.66 (m, 4H), 1.75-1.84 (m, 4H), 2.01-2.09 (m, 3H), 2.10-2.26 (br s, 4H), 2.27-2.34 (m, 3H), 2.38-2.94 (br s, 12H), 2.95-3.21 (m, 6H), 3.23-3.27 (m, 2H), 3.32-3.64 (m, 8H), 3.99-
20 4.08 (m, 2H), 4.11-4.22 (m, 3H), 4.30 (s, 2H), 5.06 (s, 2H), 7.28-7.31 (m, 1H), 7.33-7.34 (m, 4H);

MS (ESI) m/z 1520 $[\text{M}+\text{H}]^+$

Step 3: Preparation of compound 14b

The compound **13b** (467 mg, 0.307 mmol) synthesized in step 2 above was dissolved in ethanol (20 mL), to which 10% palladium on carbon (33 mg) was added, followed by stirring for 2 hours under hydrogen. The reaction solution was filtered, washed with ethanol, and concentrated under reduced pressure. The concentrate was separated by column chromatography (2% methanol/dichloromethane, NH silica gel) to give the compound **14b** (366 mg, 86%) as a colorless liquid.

10

^1H NMR (400 MHz, methanol- d_4) δ 1.44–1.49 (m, 63H), 1.51–1.67 (m, 8H), 1.74–1.84 (m, 3H), 1.89–2.00 (br s, 1H), 2.01–2.08 (m, 2H), 2.09–2.26 (br s, 5H), 2.29–2.34 (m, 2H), 2.36–2.62 (br s, 5H), 2.63–2.68 (m, 2H), 2.70–3.22 (br s 10H), 3.26 (t, J = 7.6 Hz, 2H), 3.39 (t, J = 7.2 Hz, 2H), 3.42–3.73 (m, 6H), 3.95–4.06 (m, 2H), 4.08–4.21 (m, 4H), 4.32 (s, 2H);

MS (ESI) m/z 1386 $[\text{M}+\text{H}]^+$

20 **Step 4: Preparation of compound 15d**

4-(p-Tolyl)butyric acid (11 mg, 0.059 mmol) was dissolved in dichloromethane (1.0 mL), to which hydroxybenzotriazole (HOBt, 13 mg, 0.098 mmol), TBTU (32 mg, 0.098 mmol) and diisopropylethylamine (0.026 mL, 0.147 mmol) were added, followed by stirring at

25

room temperature for 10 minutes. The compound **14b** (68 mg, 0.049 mmol) synthesized in step 3 above dissolved in dichloromethane (1.0 mL) was added thereto, followed by stirring at room temperature for 2 hours.
5 Water was added to the reactant, and then the organic compound was repeatedly extracted 3 times using dichloromethane. The collected organic solvent was dried over anhydrous sodium sulfate, concentrated under reduced pressure and separated by column
10 chromatography (4% methanol/dichloromethane) to give the compound **15d** (60 mg, 42%) as a colorless liquid.

Step 4: Preparation of compound 15e

The compound **15e** (36 mg, 51%) was obtained by the
15 same manner as described in the preparation of the compound **15a** as a colorless liquid except that 4-(p-iodophenyl)butyric acid (32 mg, 0.104 mmol), hydroxybenzotriazole (HOBt, 23 mg, 0.173 mmol), TBTU (56 mg, 0.173 mmol), diisopropylethylamine (0.045 mL,
20 0.260 mmol) and the compound **14b** (120 mg, 0.087 mmol) synthesized in step 3 above were used.

¹H NMR (400 MHz, CDCl₃) δ 0.82-0.96 (m, 2H), 0.97-
1.14 (m, 2H), 1.16-1.37 (m, 6H), 1.42-1.50 (m, 63 H),
25 1.53-1.69 (m, 2H), 1.71-1.96 (m, 5H), 1.99-2.10 (m,

3H), 2.11–2.38 (m, 11H), 2.41–2.68 (m, 6H), 2.81 (s, 3H), 2.82–3.11 (br s, 7H), 3.16–3.33 (m, 5H), 3.35–3.61 (m, 5H), 3.63–3.75 (m, 2H), 3.90 (s, 2H), 4.10 (d, $J = 3.2$ Hz, 1H), 4.24–4.35 (m, 3H), 5.60 (q, $J = 7.6$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 2H), 7.55 (d, $J = 8.0$ Hz, 2H);

MS (ESI) m/z 1658 $[M+H]^+$

Step 5: Preparation of compound 2j

The compound **15d** (24 mg, 0.016 mmol) synthesized in step 4 above was dissolved in 70% trifluoroacetic acid/dichloromethane (0.5 mL), followed by stirring at room temperature for 1 hour. The reactant was concentrated under reduced pressure, and the concentrate was separated by high performance liquid chromatography (HPLC) to give the compound **2j** (6.7 mg, 37%) as a white solid.

^1H NMR (400 MHz, D_2O) δ 1.16–1.28 (m, 4H), 1.35–1.48 (m, 4H), 1.52–1.64 (m, 3H), 1.65–1.70 (m, 1H), 1.74 (t, $J = 7.6$ Hz, 2H), 1.79–1.87 (m, 1H), 2.00–2.05 (m, 1H), 2.10 (t, $J = 7.0$ Hz, 2H), 2.16 (s, 3H), 2.36 (t, $J = 6.6$ Hz, 2H), 2.44 (t, $J = 7.2$ Hz, 2H), 2.82–3.10 (m, 8H), 3.11–3.27 (m, 9H), 3.28–3.38 (m, 4H), 3.39–3.49 (m, 4H), 3.50–3.80 (m, 7H), 3.93 (s, 2H),

3.98-4.12 (m, 3H), 4.19 (s, 2H), 7.02 (d, $J = 8.0$ Hz, 2H), 7.06 (d, $J = 7.2$ Hz, 2H);

MS (ESI) m/z 1153 $[M+H]^+$, 1151 $[M-H]^-$

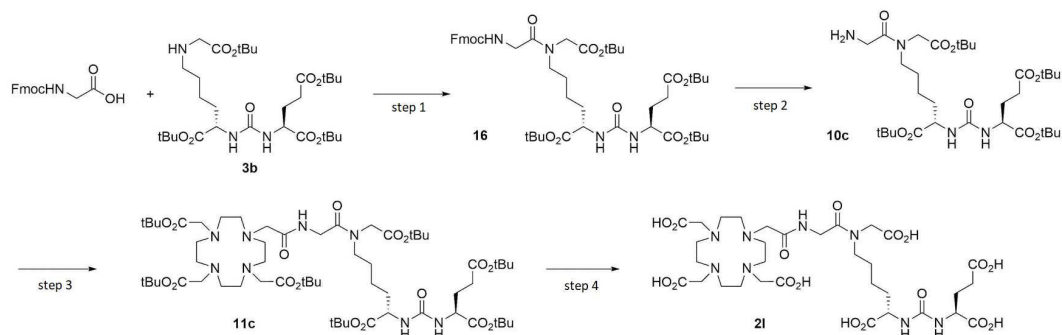
5 **Step 5: Preparation of compound 2k**

The compound **2k** (4.0 mg, 53%) was obtained by the same manner as described in the preparation of the compound **2j** as a white solid except that the compound **15e** (10 mg, 0.0060 mmol) synthesized in step 4 above
10 was used.

^1H NMR (400 MHz, D_2O) δ 1.15-1.27 (m, 4H), 1.28-1.36 (m, 2H), 1.38-1.48 (m, 2H), 1.54-1.64 (m, 3H), 1.66-1.68 (m, 1H), 1.74 (p, $J = 7.4$ Hz, 2H), 1.79-1.87
15 (m, 1H), 1.98-2.03 (m, 1H), 2.08 (t, $J = 7.0$ Hz, 2H), 2.36 (t, $J = 7.4$ Hz, 2H), 2.43 (t, $J = 7.2$ Hz, 2H), 2.71-2.87 (br s, 3H), 2.96 (t, $J = 6.6$ Hz, 2H), 3.03-3.33 (m, 17H), 3.38-3.49 (m, 3H), 3.52-3.89 (br s, 6H), 3.94 (d, $J = 4.4$ Hz, 2H), 4.00-4.14 (m, 4H), 4.19
20 (s, 2H), 6.90 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.0$ Hz, 2H);

MS (ESI) m/z 1266 $[M+H]^+$, 1264 $[M-H]^-$

<Example 8> Preparation of compound 2l



Step 1: Preparation of compound 16

Fmoc-Gly-OH (0.49 g, 1.66 mmol) was dissolved in dichloromethane (10 mL), to which N,N'-
 5 dicyclohexylcarbodiimide (0.34 g, 1.66 mmol) was added, followed by stirring at 0°C for 10 minutes. The compound **3b** (0.50 g, 0.83 mmol) dissolved in dichloromethane (10 mL) was slowly added to the reaction mixture, followed by stirring at 0°C for 1.5
 10 hours. The reaction mixture was filtered, washed with dichloromethane several times, and the solvent was eliminated under reduced pressure. The concentrate was separated by column chromatography (35%-50% ethylacetate/*n*-hexane) to give the compound **16** (0.45
 15 g, 61%).

¹H NMR (400 MHz, CDCl₃) δ 1.05-1.21 (m, 2H), 1.38 (s, 9H), 1.40 (s, 9H), 1.43 (s, 9H), 1.45 (s, 9H), 1.56-1.62 (m, 2H), 1.64-1.71 (m, 2H), 1.75-1.86 (m, 2H), 1.88-1.94 (m, 2H), 2.19-2.35 (m, 2H), 3.16-3.29
 20

3.88-4.02 (m, 2H), 4.19-4.28 (m, 2H), 4.29-4.40 (m, 3H), 5.23 (dt, J = 64.4, 12.0 Hz, 2H), 5.96 (dt, J = 105.2, 4.4 Hz, 1H), 7.27-7.30 (m, 2H), 7.37 (t, J = 13.4 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.74 (d, J =
5 7.2 Hz, 2H);

MS (ESI) m/z 881 $[M+H]^+$

Step 2: Preparation of compound 10c

The compound **16** (0.40 g, 0.45 mmol) was dissolved
10 in dichloromethane (10 mL), to which piperidine (0.1 mL, 1.01 mmol) was added, followed by stirring at room temperature for 1.5 hours. The reaction mixture was concentrated under reduced pressure, and the concentrate was separated by column chromatography (5%
15 methanol/dichloromethane) to give the compound **10c** (0.19 g, 63%).

^1H NMR (400 MHz, CDCl_3) δ 1.41 (s, 9H), 1.43 (s, 9H), 1.46 (s, 9H), 1.47 (s, 9H) 1.53-1.64 (m, 2H) 1.75-
20 1.89 (m, 2H), 2.02-2.11 (m, 2H), 2.24-2.38 (m, 2H), 3.23 (t, J = 7.4 Hz, 2H), 3.63 (s, 2H), 3.69 (s, 2H), 3.84-3.97 (m, 2H), 4.22-4.37 (m, 2H), 5.46-5.84 (m, 2H);

MS (ESI) m/z 659 $[M+H]^+$

25

Step 3: Preparation of compound 11c

DOTA-tris(tBu) ester (31 mg, 55 μ mol) was dissolved in dichloromethane (0.6 mL), to which hydroxybenzotriazole (HOBT, 9 mg, 68 μ mol), TBTU (22 mg, 68 μ mol) and diisopropylethylamine (16 μ L, 91 μ mol) were added, followed by stirring at room temperature for 10 minutes. The compound **10c** (30 mg, 45.5 μ mol) dissolved in dichloromethane (0.3 mL) was added thereto, followed by stirring at room temperature for 1 hour. The reaction was terminated by adding water (10 mL), and the organic compound was extracted using dichloromethane (10 mL X 3). The reactant was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the concentrate was separated by column chromatography (5% methanol/dichloromethane) to give the compound **11c** (47.4 mg, 86%).

^1H NMR (400 MHz, CDCl_3) δ 1.46 (s, 9H), 1.47 (s, 27H), 1.48 (s, 27H), 1.68 (s, 6H), 1.73–1.80 (m, 1H), 1.78–1.90 (m, 1H), 2.04–2.15 (m, 3H), 2.20–2.48 (m, 6H), 2.83 (s, 9H), 3.00 (bs, 3H), 3.27 (t, J = 7.4 Hz, 2H), 3.32–3.41 (m, 2H), 3.44–3.54 (m, 2H), 3.91–4.14 (m, 3H), 4.20–4.40 (m, 2H), 5.25–5.34 (m, 1H), 5.46 (dd, J = 7.4 Hz, 1H);

MS (ESI) m/z 1213 $[M+H]^+$

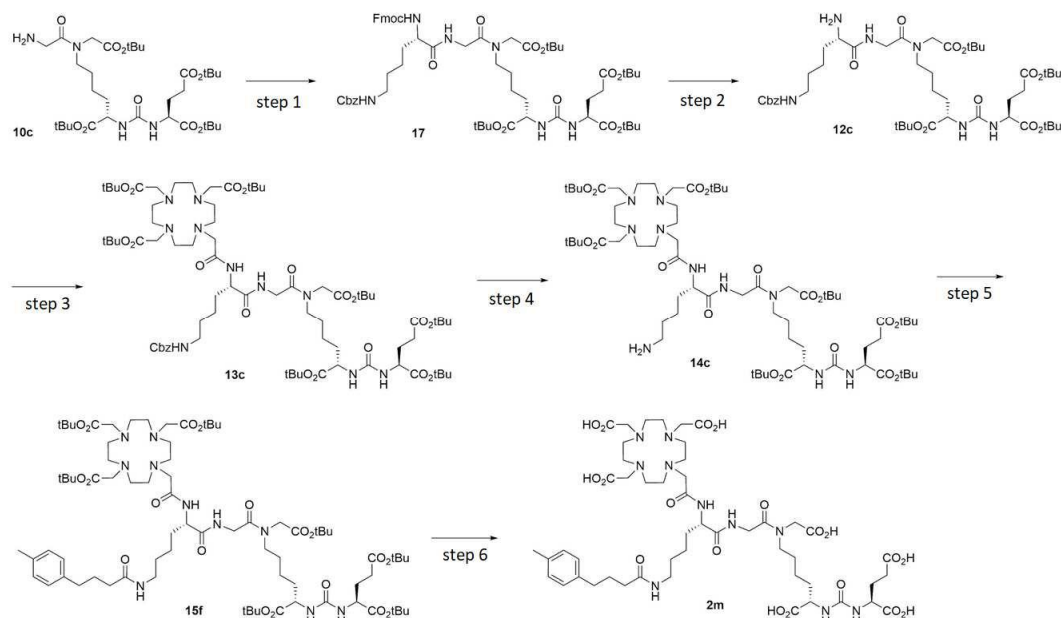
Step 4: Preparation of compound 21

The compound **11c** (40 mg, 32.96 μmol) was added to
5 70% trifluoroacetic acid/dichloromethane (1 mL),
followed by stirring for 5 hours. After dropping the
reaction mixture in diethyl ether (40 mL) to make a
precipitate, it was separated using a centrifuge.
Then, the compound **21** (15 mg, 55%) was obtained by
10 high performance liquid chromatography (HPLC).

^1H NMR (400 MHz, D_2O) δ 1.29–1.38 (m, 2H), 1.46
(bs, 1H), 1.54–1.62 (m, 2H), 1.63–1.70 (m, 1H), 1.75–
1.82 (m, 1H), 1.83–1.93 (m, 1H), 2.05–2.13 (m, 1H),
15 2.42 (t, $J = 7.2$ Hz, 2H), 2.70–3.89 (br, 22H), 3.94
(s, 1H), 3.99 (s, 1H), 4.04 (s, 2H), 4.07–4.12 (1H),
4.12–4.15 (m, 2H), 4.18 (t, $J = 4.4$ Hz, 2H)

MS (ESI) m/z 821 $[M+H]^+$

20 <Example 9> Preparation of compound 2m



Step 1: Preparation of compound 17

Fmoc-Lys(Z)-OH (183 mg, 0.36 mmol) was dissolved in dichloromethane (1 mL), to which
 5 hydroxybenzotriazole (HOBt, 62 mg, 0.46 mmol), TBTU (146 mg, 0.46 mmol) and diisopropylethylamine (106 μ L, 0.61 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **10c** (0.20 g, 0.30 mmol) dissolved in dichloromethane (1 mL) was
 10 added thereto, followed by stirring for 4 hours. The reaction was terminated by adding water (10 mL), and the organic compound was extracted using dichloromethane (10 mL X 3). The reactant was dried over anhydrous sodium sulfate, concentrated under
 15 reduced pressure, and the concentrate was separated by

column chromatography (5% methanol/dichloromethane) to give the compound **17** (268 mg, 77%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 1.19-1.29 (m, 2H), 1.37-
5 1.46 (m, 36H), 1.49-1.55 (m, 2H), 1.57-1.63 (m, 2H),
1.68 (s, 3H), 1.77-1.84 (m, 2H), 2.00-2.10 (m, 2H),
2.22-2.35 (m, 2H), 3.10-3.23 (m, 3H), 3.79-3.99 (m,
3H), 4.13 (s, 1H), 4.18-4.26 (m, 2H), 4.32-4.42 (m,
3H), 5.05 (s, 2H), 5.37-5.87 (m, 3H), 7.02 (d, *J* = 22
10 Hz, 1H), 7.23-7.40 (m, 8H), 7.54-7.60 (m, 2H), 7.73
(q, *J* = 6.1 Hz, 2H)

MS (ESI) *m/z* 1165 [M+Na]⁺

Step 2: Preparation of compound **12c**

15 The compound **17** (250 mg, 0.22 mmol) was dissolved
in CH₂Cl₂ (1 mL), to which piperidine (64.80 μL, 0.66
mmol) was added, followed by stirring at room
temperature for 5 hours. After eliminating the solvent
from the reaction mixture under reduced pressure, the
20 concentrate was subjected to column chromatography to
give the compound **12c** (170 mg, 84%) as a colorless
liquid.

¹H NMR (400 MHz, CDCl₃) δ 1.24-1.36 (m, 2H), 1.45
25 (s, 9H), 1.47 (s, 9H), 1.48 (s, 18H), 1.52-1.59 (m,

4H), 1.71 (s, 4H), 1.77-1.89 (m, 3H), 2.04-2.13 (m, 1H), 2.25-2.39 (m, 2H), 3.15-3.25 (m, 2H), 3.26-3.34 (m, 1H), 3.85-4.05 (m, 2H), 4.12-4.20 (m, 2H), 4.26-4.41 (m, 2H), 5.06-5.16 (m, 3H), 5.51 (ddd, $J = 49.3$, 5 29.4, 8.1 Hz, 2H), 7.37 (d, $J = 4.4$ Hz, 4H), 7.92 (s, 1H);

MS (ESI) m/z 922 $[M+H]^+$

Step 3: Preparation of compound 13c

10 DOTA-tris(tBu) ester (99 mg, 0.119 mmol) was dissolved in dichloromethane (0.5 mL), to which hydroxybenzotriazole (HOBt, 23 mg, 0.261 mmol), TBTU (56 mg, 0.261 mmol) and diisopropylethylamine (30 μ L, 347 μ mol) were added, followed by stirring at room 15 temperature for 10 minutes. The compound **12c** (160 mg, 0.174 mmol) dissolved in dichloromethane (1.6 mL) was added thereto, followed by stirring for 1 hour. The reaction was terminated by adding water (10 mL), and the organic compound was extracted using 20 dichloromethane (10 mL X 3). The reactant was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the concentrate was separated by column chromatography (5% methanol/dichloromethane) to give the compound **13c** (180 mg, 72%) as a colorless 25 liquid.

¹H NMR (400 MHz, CDCl₃) δ 1.28-1.33 (m, 3H), 1.45 (s, 9H), 1.46 (s, 9H), 1.47 (s, 9H), 1.47 (s, 9H), 1.48 (s, 18H), 1.49 (s, 9H), 1.79 (s, 8H), 2.04-2.15 (m, 5H), 2.25-2.41 (m, 5H), 2.59 (bs, 3H), 2.83 (bs, 4H), 2.95 (bs, 3H), 3.18-3.28 (m, 5H), 3.47 (bs, 4H), 3.92 (dd, *J* = 44.0, 18.4 Hz, 2H), 4.04-4.24 (m, 2H), 4.33-4.39 (m, 3H), 5.10 (d, *J* = 3.2 Hz, 2H), 7.15 (d, *J* = 18.4 Hz, 1H), 7.30-7.37 (m, 4H), 7.46 (s, 1H);

10 MS (ESI) *m/z* 1498 [M+Na]⁺

Step 4: Preparation of compound 14c

Palladium (10% Palladium on carbon, 6 mg, 5.8 μmol) was put in a round bottom flask, which was closed with a septum, and filled with hydrogen gas in vacuo. The compound **13c** (170 mg, 115 μmol) dissolved in methanol (2 mL) was loaded in a reaction vessel, followed by stirring at room temperature for 15 hours. The reactant was filtered with celite, concentrated under reduced pressure, and the concentrate was separated by NH-silica gel column chromatography (0-1% methanol/dichloromethane) to give the compound **14c** (117 mg, 76%) as a colorless liquid.

20

¹H NMR (400 MHz, CDCl₃) δ 1.14-1.28 (m, 3H), 1.36 (s, 18H), 1.41 (s, 18H), 1.44 (s, 27H), 1.53-1.62 (m, 4H), 1.68-1.83 (m, 5H), 1.97-2.09 (m, 4H), 2.10-2.37 (m, 7H), 2.40-2.69 (m, 6H), 2.70-3.10 (m, 7H), 3.15-3.26 (m, 2H), 3.31-3.65 (m, 4H), 3.78-3.95 (m, 2H), 4.01-4.13 (m, 2H), 4.21-4.35 (m, 3H), 5.37-5.55 (m, 2H), 7.17 (d, *J* = 28.8 Hz, 1H), 7.52 (bs, 1H);
MS (ESI) *m/z* 1365 [M+Na]⁺

10 **Step 5: Preparation of compound 15f**

4-(*p*-Tolyl)butyric acid (16 mg, 89 μmol) was dissolved in dichloromethane (1 mL), to which hydroxybenzotriazole (HOBt, 15 mg, 112 μmol), TBTU (36 mg, 112 μmol) and DIEA (26 μL, 149 μmol) were added, followed by stirring at room temperature for 10 minutes. The compound **14c** (100 mg, 75 μmol) dissolved in dichloromethane (2 mL) was added thereto, followed by stirring for 1.5 hours. The reaction was terminated by adding water (10 mL), and the organic compound was extracted using dichloromethane (10 mL X 3). The reactant was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the concentrate was separated by column chromatography to give the compound **15f** (69 mg, 86%) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 1.26-1.32 (m, 2H), 1.35-1.40 (m, 27H), 1.42-1.47 (m, 36H), 1.52-1.59 (m, 4H), 1.79-1.96 (m, 6H), 2.00-2.08 (m, 4H), 2.10-2.20 (m, 2H), 2.21-2.41 (m, 14H), 2.54-2.62 (m, 6H), 2.78 (s, 3H), 2.83-2.95 (m, 2H), 3.20 (s, 3H), 3.28-3.62 (m, 4H), 3.73-3.88 (m, 2H), 3.93-4.03 (m, 2H), 4.13-4.25 (m, 2H), 4.27-4.33 (m, 2H), 5.35-5.61 (m, 2H), 7.05 (d, *J* = 1.6 Hz, 4H)

10 MS (ESI) *m/z* 1524 [M+Na]⁺

Step 6: Preparation of compound 2m

The compound **15f** (86 mg, 57 μmol) obtained in step 5 above was added to 70% trifluoroacetic acid/dichloromethane (1 mL), followed by stirring for 6 hours. After dropping the reaction mixture in diethyl ether (40 mL) to make a precipitate, it was separated using a centrifuge. The mixture was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound **2m** (44 mg, 69%) as a white solid.

15
20

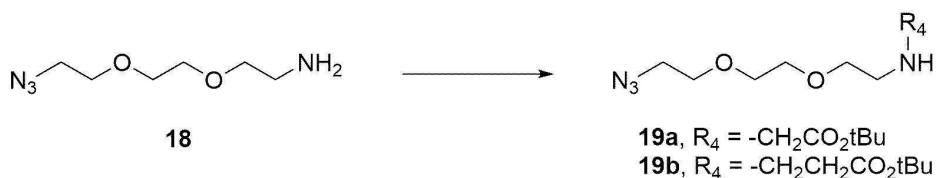
¹H NMR (400 MHz, D₂O) δ 1.36-1.41 (m, 4H), 1.46-1.53 (m, 3H), 1.54-1.59 (m, 2H), 1.66-1.75 (m, 2H), 1.77-1.88 (m, 4H), 1.90-1.99 (m, 1H), 2.10-2.16 (m,

25

1H), 2.21 (t, J = 7.2 Hz, 2H), 2.27 (s, 3H), 2.48 (t, J = 7.6 Hz, 2H), 2.53 (t, J = 7.6 Hz, 2H), 2.93-3.56 (br, 20H), 3.71 (bs, 3H), 3.87 (s, 1H), 3.91 (s, 1H), 3.98 (s, 1H), 4.04 (t, J = 8.6 Hz, 3H), 4.12 (s, 1H),
 5 4.13-4.19 (m, 2H), 4.22-4.26 (m, 1H), 4.30 (bs, 1H), 7.15 (q, J = 7.9 Hz, 4H);

MS (ESI) m/z 1109 $[M-H]^-$

<Example 10> Preparation of compound 19



10

Preparation of compound 19a

The compound **18** (500 mg, 2.87 mmol) was dissolved in dichloromethane (5 mL) and cooled to 0°C, to which triethylamine (0.6 mL, 4.31 mmol) was added. Tert-butyl bromoacetate (620 mg, 3.16 mmol) dissolved in dichloromethane (5 mL) was slowly added thereto, followed by stirring at room temperature for 18 hours. The reaction was terminated by adding water (10 mL), and the organic compound was extracted using
 15 dichloromethane (10 mL X 2). The reactant was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the concentrate was separated by
 20

column chromatography (2% methanol/dichloromethane) to give the compound **19a** (0.46 g, 55%).

^1H NMR (400 MHz, CDCl_3) δ 1.45 (s, 9H), 2.78 (t, J = 4.8 Hz, 2H), 3.31 (s, 2H), 3.38 (t, J = 5.6 Hz, 2H), 3.68–3.59 (m, 9H);

^{13}C NMR (100 MHz, CDCl_3) δ 28.1, 48.7, 50.6, 51.7, 56.6, 76.7, 77.0, 77.3, 81.0, 171.5;

MS (ESI) m/z 289 $[\text{M}+\text{H}]^+$

10

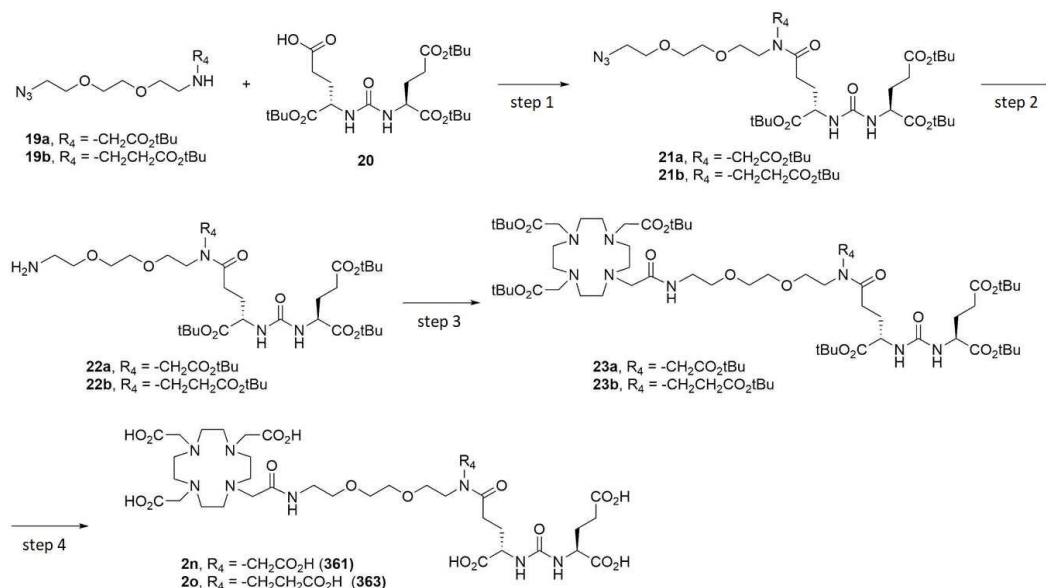
Preparation of compound **19b**

The compound **18** (300 mg, 1.72 mmol) was dissolved in ethanol (10 mL) and cooled to 0°C, to which tert-butyl acrylate (220 mg, 1.72 mmol) was slowly added. After gradually raising the temperature of the mixture to room temperature, the mixture was stirred for 18 hours. The organic solvent was eliminated under reduced pressure, and the concentrate was separated by column chromatography (5% methanol/dichloromethane) to give the compound **19b** (380 mg, 73%).

^1H NMR (400 MHz, CDCl_3) δ 1.43 (s, 9H), 2.42 (t, J = 6.4 Hz, 2H), 2.79 (t, J = 5.6 Hz, 2H), 2.85 (t, J = 6.4 Hz, 2H), 3.38 (t, J = 4.8 Hz, 2H), 3.58 (t, J = 5.2 Hz, 2H), 3.62–3.68 (m, 6H);

^{13}C NMR (100 MHz, CDCl_3) δ 28.1, 35.9, 45.2, 49.1, 50.7, 76.7, 77.0, 77.3, 80.4, 172.0;
MS (ESI) m/z 303 $[\text{M}+\text{H}]^+$

5 <Example 11> Preparation of compounds 2n and 2o



Step 1: Preparation of compound 21a

The compound **20** (180 mg, 0.36 mmol) was dissolved in dichloromethane (5 mL) and cooled to 0°C , to which
10 N,N'-dicyclohexylcarbodiimide (DCC, 83 mg, 0.40 mmol) and the compound **19a** (110 mg, 0.36 mmol) were added, followed by stirring at room temperature for 1 hour. The organic layer was filtered several times, and the solvent was eliminated under reduced pressure. The
15 concentrate was separated by column chromatography (5%

methanol/dichloromethane) to give the compound **21a**
(250 mg, 91%).

¹H NMR (400 MHz, CDCl₃) δ 1.43 (s, 9H), 1.44 (s,
5 9H), 1.45 (s, 9H), 1.46 (s, 9H), 1.79-1.86 (m, 1H),
2.01-2.20 (m, 3H), 2.26-2.36 (m, 3H), 2.44-2.55 (m,
1H), 2.77 (br, 1H), 3.40 (t, *J* = 6.4 Hz, 2H), 3.56-
3.74 (m, 9H), 4.03 (dd, *J* = 44.0, 17.2 Hz, 2H), 4.22-
4.35 (m, 2H);

10 MS (ESI) *m/z* 759 [M+H]⁺

Step 1: Preparation of compound 21b

The compound **21b** (275 mg, 87%) was obtained by
the same manner as described in the preparation of the
15 compound **21a** except that the compound **20** (200 mg, 0.41
mmol), *N,N'*-dicyclohexylcarbodiimide (DCC, 102 mg,
0.49 mmol) and the compound **19b** (200 mg, 0.41 mmol)
were used.

20 MS (ESI) *m/z* 773 [M+H]⁺

Step 2: Preparation of compound 22a

The compound **21a** (200 mg, 0.26 mmol) was
dissolved in methanol (8 mL), to which palladium (10%
25 Palladium on carbon, 13 mg, 13 μmol) was added. The

reaction flask was filled with hydrogen gas, followed by stirring at room temperature for 1 hour. After passing the reaction product through celite, the solvent was eliminated under reduced pressure, and the
5 concentrate was separated by column chromatography (8% methanol/dichloromethane) to give the compound **22a** (120 mg, 63%).

^1H NMR (400 MHz, methanol- d_4) δ 1.45 (s, 9H),
10 1.47–1.49 (m, 27H), 1.76–1.94 (m, 2H), 2.01–2.13 (m, 2H), 2.27–2.39 (m, 3H), 2.55–2.60 (m, 2H), 2.79–2.81 (m, 2H), 3.35 (s, 1H), 3.52 (t, J = 5.2 Hz, 2H), 3.55–3.65 (m, 8H), 4.04 (dd, J = 17.6, 4.8 Hz, 1H), 4.14–4.22 (m, 3H);

15 MS (ESI) m/z 733 $[\text{M}+\text{H}]^+$

Step 2: Preparation of compound **22b**

The compound **22b** (210 mg, 90%) was obtained by the same manner as described in the preparation of the
20 compound **22a** except that the compound **21b** (240 mg, 0.32 mmol) and palladium (10% Palladium on carbon, 17 mg, 16 μmol) were used.

^1H NMR (400 MHz, methanol- d_4) δ 1.45 (s, 18H),
25 1.48 (s, 18H), 1.59–1.63 (m, 1H), 1.68–1.75 (m, 2H),

1.79-1.91 (m, 4H), 2.03-2.14 (m, 2H), 2.30-2.36 (m, 2H), 2.48-2.62 (m, 3H), 2.80-2.82 (m, 2H), 3.43-3.70 (m, 12H), 4.14-4.20 (m, 2H);

MS (ESI) m/z 747 $[M+H]^+$

5

Step 3: Preparation of compound 23a

DOTA-tris(tBu) ester (38 mg, 65 μ mol) was dissolved in dichloromethane (7 mL), to which hydroxybenzotriazole (HOBt, 110 mg, 82 μ mol), TBTU (26
10 mg, 82 μ mol) and diisopropylethylamine (19 μ L, 0.11 mmol) were added, followed by stirring for 10 minutes. The compound **22a** (40 mg, 55 μ mol) dissolved in dichloromethane (3 mL) was added thereto, followed by stirring for 1 hour. The reaction was terminated by
15 adding water (10 mL), and the organic compound was extracted using dichloromethane (10 mL X 2). The reactant was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the concentrate was separated by column chromatography (5%
20 methanol/dichloromethane) to give the compound **23a** (60 mg, 70%) as a white solid.

^1H NMR (400 MHz, methanol- d_4) δ 1.40-1.57 (m, 63H), 1.76-2.87 (m, 26H), 3.36-3.63 (m, 17H), 3.74 (s,

1H), 4.04 (d, J = 8.0 Hz, 2H), 4.14-4.24 (m, 3H),
6.34-6.38 (m, 1H);

MS (ESI) m/z 1288 $[M+H]^+$

5 **Step 3: Preparation of compound 23b**

The compound **23b** (60 mg, 68%) was obtained by the same manner as described in the preparation of the compound **23a** except that DOTA-tris(tBu) ester (46 mg, 80 μ mol), hydroxybenzotriazole (HOBt, 14 mg, 0.10 mmol), TBTU (32 mg, 0.10 mmol), diisopropylethylamine
10 (24 μ L, 0.13 mmol) and the compound **22b** (50 mg, 67 μ mol) were used.

^1H NMR (400 MHz, methanol- d_4) δ 1.09-1.24 (m, 12H), 1.29-1.43 (m, 10H), 1.45-1.53 (m, 41H), 1.57-1.63 (m, 4H), 1.66-1.76 (m, 7H), 1.80-1.91 (m, 8H), 2.03-2.12 (m, 2H), 2.25-2.37 (m, 2H), 2.44-2.64 (m, 4H), 2.82 (s, 9H), 3.35-3.49 (m, 5H), 3.52-3.69 (m, 7H), 4.14-4.22 (m, 2H);

20 MS (ESI) m/z 1302 $[M+H]^+$

Step 4: Preparation of compound 2n

The compound **23a** (45 mg, 35 μ mol) was added to 70% trifluoroacetic acid/dichloromethane (1 mL),
25 followed by stirring for 7 hours. After dropping the

reaction mixture in diethyl ether (20 mL) to make a precipitate, it was separated using a centrifuge. The mixture was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to
5 give the compound **2n** (22 mg, 70%) as a solid.

^1H NMR (400 MHz, D_2O) δ 1.93–2.02 (m, 2H), 2.14–2.22 (m, 2H), 2.45–2.54 (m, 3H), 2.63–2.68 (m, 2H), 2.88–3.56 (m, 18H), 3.57–3.72 (m, 11H), 3.73–3.85 (m,
10 3H), 3.86–4.10 (m, 3H), 4.16 (s, 1H), 4.21–4.31 (m, 3H);

MS (ESI) m/z 895 $[\text{M}+\text{H}]^+$

Step 4: Preparation of compound **2o**

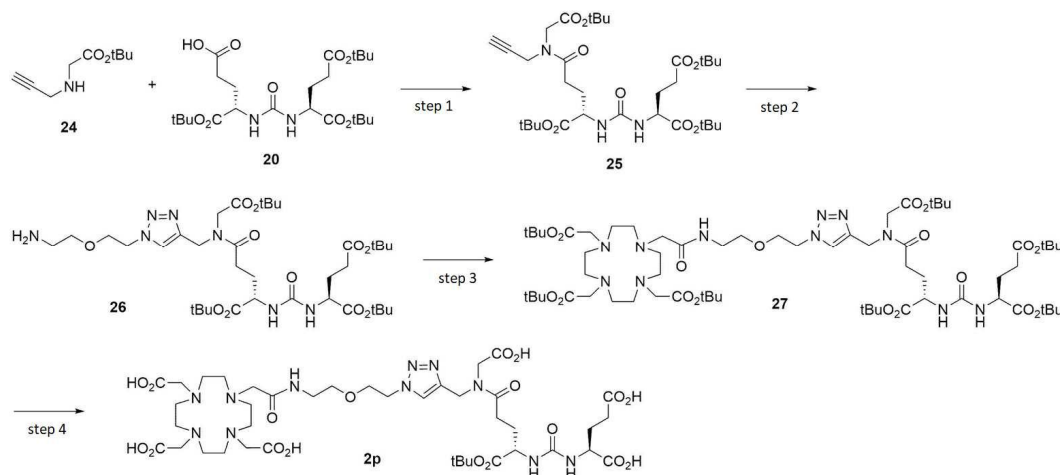
15 The compound **2o** (17 mg, 48%) was obtained by the same manner as described in the preparation of the compound **2n** except that the compound **23b** (50 mg, 38 μmol) and 70% trifluoroacetic acid/dichloromethane (1 mL) were used.

20

^1H NMR (400 MHz, D_2O) δ 1.92–2.03 (m, 2H), 2.15–2.25 (m, 2H), 2.48–2.68 (m, 5H), 2.71–2.75 (m, 1H), 2.92–3.53 (m, 18H), 3.55–3.86 (m, 17H), 3.87–4.17 (m, 3H), 4.22–4.31 (m, 2H);

25 MS (ESI) m/z 909 $[\text{M}+\text{H}]^+$

<Example 12> Preparation of compound 2p



Step 1: Preparation of compound 25

5 The compound **20** (500 mg, 1.02 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0°C, to which N,N'-dicyclohexylcarbodiimide (DCC, 230 mg, 1.12 mmol) and the compound **24** (170 mg, 1.02 mmol) were added, followed by stirring at room temperature for 1 hour.

10 The organic layer was filtered several times, and the solvent was eliminated under reduced pressure. The concentrate was separated by column chromatography (30% ethylacetate/*n*-hexane) to give the compound **25** (450 mg, 69%).

15

¹H NMR (400 MHz, CDCl₃) δ 1.37–1.50 (m, 36H), 1.81–1.90 (m, 1H), 1.96–2.25 (m, 4H), 2.28–2.39 (m,

3H), 2.51–2.56 (m, 1H), 4.01–4.10 (m, 2H), 4.14–4.21 (m, 2H), 4.24–4.36 (m, 3H), 5.51 (br, 1H), 5.75 (br, 1H);

MS (ESI) m/z 774 $[M+H]^+$

5

Step 2: Preparation of compound 26

The compound **25** (350 mg, 0.55 mmol) and 2-aminoethyl 2'-azidoethyl ether (110 mg, 0.82 mmol) were dissolved in ethanol (10 mL), to which 1 M CuSO₄ (0.11 mL, 0.11 mmol) and 2 M sodium ascorbate (0.082 mL, 0.16 mmol) were added, followed by stirring for 1 hour. The reactant was filtered and the solvent was eliminated under reduced pressure. The concentrate was separated by NH silica gel column chromatography (3% methanol/dichloromethane) to give the compound **26** (250 mg, 59%).

¹H NMR (400 MHz, methanol-d₄) δ 1.41–1.51 (m, 37H), 1.78–1.90 (m, 2H), 2.03–2.16 (m, 2H), 2.29–2.42 (m, 3H), 2.67–2.71 (m, 1H), 3.12 (q, J = 5.2 Hz, 2H), 3.65–3.70 (m, 2H), 3.88–3.94 (m, 2H), 4.01 (d, J = 6.0 Hz, 1H), 4.16–4.22 (m, 3H), 4.52–4.64 (m, 3H), 4.69–4.75 (m, 1H), 7.95 (s, 0.6H), 8.07 (s, 0.5H);

MS (ESI) m/z 770 $[M+H]^+$

25

Step 3: Preparation of compound 27

DOTA-tris(tBu) ester (36 mg, 62 μ mol) was dissolved in dichloromethane (5 mL), to which hydroxybenzotriazole (DCC, 11 mg, 78 μ mol), TBTU (25
5 mg, 78 μ mol) and diisopropylethylamine (18 μ L, 0.10 mmol) were added, followed by stirring at room temperature for 10 minutes. The compound **26** (40 mg, 52 μ mol) dissolved in dichloromethane (1 mL) was added thereto, followed by stirring for 1 hour. The reaction
10 was terminated by adding water (10 mL), and the organic compound was extracted using dichloromethane (10 mL X 2). The reactant was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the concentrate was separated by column
15 chromatography (3% methanol/dichloromethane) to give the compound **27** (50 mg, 72%).

^1H NMR (400 MHz, methanol- d_4) δ 1.40-1.52 (m, 63H), 1.55-1.66 (m, 1H), 1.76-1.97 (m, 4H), 2.02-2.28
20 (m, 9H), 2.29-2.48 (m, 8H), 2.68-2.72 (m, 3H), 3.35-3.41 (m, 4H), 3.48-3.71 (m, 4H), 3.81-3.87 (m, 3H), 3.94-4.08 (m, 1H), 4.13-4.23 (m, 4H), 4.52-4.59 (m, 3H), 4.64-4.75 (m, 2H), 7.92 (s, 0.6H), 8.05 (s, 0.4H);

25 MS (ESI) m/z 1325 $[\text{M}+\text{H}]^+$

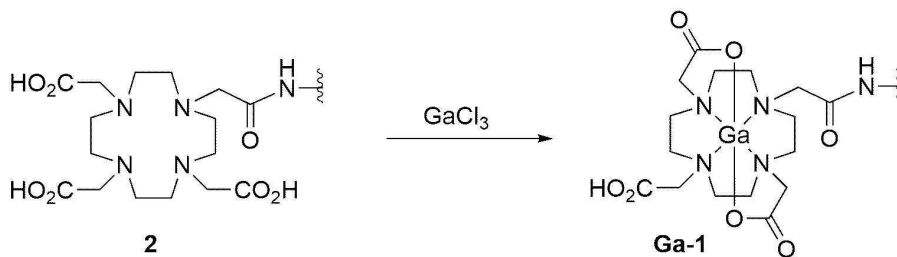
Step 4: Preparation of compound 2p

The compound **27** (43 mg, 32 μmol) was added to 70% trifluoroacetic acid/dichloromethane (1 mL), followed by stirring for 7 hours. After dropping the reaction mixture in diethyl ether (20 mL) to make a precipitate, it was separated using a centrifuge. The mixture was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound **2p** (22 mg, 73%) as a solid.

^1H NMR (400 MHz, D_2O) δ 1.90–2.03 (m, 2H), 2.12–2.23 (m, 2H), 2.43–2.53 (m, 3H), 2.72–2.78 (m, 1H), 2.99–3.46 (m, 16H), 3.52–3.59 (m, 3H), 3.62–4.10 (m, 9H), 4.14 (s, 1H), 4.19–4.35 (m, 3H), 4.57–4.63 (m, 2H), 4.65–4.74 (m, 2H), 4.77 (s, 2H), 7.95 (s, 0.4H), 8.04 (s, 0.6H);

MS (ESI) m/z 932 $[\text{M}+\text{H}]^+$

<Example 13> Preparation of Ga-1



Preparation of compound Ga-1a

The compound **2a** (10 mg, 11 μ mol) was dissolved in water (0.6 mL), to which gallium trichloride (19 mg, 0.11 mmol) dissolved in water (0.6 mL) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1a** (6 mg, 56%) as a solid.

10

^1H NMR (400 MHz, D_2O) δ 1.34–1.51 (m, 4H), 1.64–1.73 (m, 1H), 1.77–1.86 (m, 1H), 1.91–2.00 (m, 1H), 2.12–2.20 (m, 1H), 2.50 (t, J = 7.2 Hz, 2H), 3.10 (t, J = 6.8 Hz, 2H), 3.31–3.43 (m, 10H), 3.52–3.57 (m, 6H), 3.65 (s, 2H), 3.78 (s, 2H), 3.84–3.94 (m, 8H), 4.00–4.03 (m, 2H), 4.16 (dd, J = 14.0, 5.2 Hz, 1H), 4.24 dd, J = 14.0, 5.2 Hz, 1H), 4.38 (s, 2H), 4.57 (t, J = 4.8 Hz, 2H), 7.88 (s, 1H);

MS (ESI) m/z 984 $[\text{M}+\text{H}]^+$

20

Preparation of compound Ga-1b

The compound **2b** (19 mg, 19 μ mol) was dissolved in water (0.8 mL), to which gallium trichloride (33 mg, 0.19 mmol) dissolved in water (0.8 mL) was added, followed by stirring at 70°C for 1 hour. The reaction

25

solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1b** (13 mg, 64%) as a solid.

5

^1H NMR (400 MHz, D_2O) δ 1.28–1.42 (m, 3H), 1.50–1.57 (m, 2H), 1.65–1.73 (m, 1H), 1.77–1.86 (m, 1H), 1.89–1.99 (m, 1H), 2.10–2.20 (m, 1H), 2.48 (t, J = 7.2 Hz, 2H), 3.27–3.42 (m, 11H), 3.49–3.57 (m, 6H), 3.67
10 (s, 2H), 3.78 (s, 2H), 3.83–3.92 (m, 8H), 4.00–4.03 (m, 2H), 4.15 (dd, J = 14.0, 4.8 Hz, 1H), 4.24 ((dd, J = 14.0, 4.8 Hz, 1H), 4.58 (t, J = 4.8 Hz, 2H), 5.19 (s, 2H), 7.62 (d, J = 7.6 Hz, 2H), 8.01 (s, 1H), 8.42 (d, J = 7.6 Hz, 2H);

15 MS (ESI) m/z 1061 $[\text{M}+\text{H}]^+$

Preparation of compound Ga-**1c**

The compound **2c** (10 mg, 10 μmol) was dissolved in water (1 mL), to which gallium trichloride (18 mg, 100
20 μmol) dissolved in water (1 mL) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1c** (6 mg,
25 58%) as a solid.

¹H NMR (400 MHz, D₂O) δ 1.28-1.42 (m, 2H), 1.44-1.62 (m, 2H), 1.64-1.77 (m, 1H), 1.78-1.90 (m, 1H), 1.93-2.23 (m, 1H), 2.50-2.54 (m, 2H), 2.72-2.75 (m, 0.5H), 2.87-2.90 (m, 1.5H), 3.01-3.07 (m, 2H), 3.36-3.44 (m, 12H), 3.54-3.59 (m, 6H), 3.69 (s, 2H), 3.77 (s, 2H), 3.85-3.94 (m, 8H), 4.00-4.12 (m, 4H), 4.16-4.29 (m, 3H), 4.57-4.60 (m, 2H), 7.81 (s, 1H);

MS (ESI) *m/z* 1041 [M+H]⁺

10

Preparation of compound Ga-1d

The compound **2d** (6 mg, 6 μmol) was dissolved in water (0.8 mL), to which gallium trichloride (14 mg, 80 μmol) dissolved in water (0.8 mL) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1d** (4 mg, 62%) as a solid.

20

¹H NMR (400 MHz, D₂O) δ 1.26 -1.43 (m, 2H), 1.44-1.60 (m, 2H), 1.66-1.78 (m, 1H), 1.79-1.91 (m, 1H), 1.94-1.20 (m, 1H), 2.15-2.24 (m, 1H), 2.48-2.67 (m, 4H), 2.79-2.88 (m, 2H), 3.01-3.09 (m, 2H), 3.28-3.49 (m, 11H), 3.52-3.65 (m, 8H), 3.70 (s, 2H), 3.79 (s,

25

2H), 3.84-3.99 (m, 7H), 4.05 (d, $J = 10.8$ Hz, 2H),
4.18-4.29 (m, 2H), 4.60 (t, $J = 5.2$ Hz, 2H), 7.82 (s,
0.6H), 7.84 (s, 0.4H);

MS (ESI) m/z 1055 $[M+H]^+$

5

Preparation of compound Ga-1e

The compound **2e** (16 mg, 18 μ mol) was dissolved in
distilled water (0.5 mL), to which gallium trichloride
(16 mg, 91 μ mol) was added, followed by stirring at
10 70°C for 1 hour. The reaction solution was filtered.
The filtrate was separated by high performance liquid
chromatography (HPLC) and dried using a lyophilizer to
give the compound Ga-**1e** (15 mg, 86%) as a white solid.

15 ^1H NMR (400 MHz, D_2O) δ 1.17-1.32 (m, 2H), 1.37-
1.51 (m, 2H), 1.53-1.62 (m, 1H), 1.65-1.75 (m, 1H),
1.82 (p, $J = 7.4$ Hz, 1H), 2.01 (p, $J = 7.6$ Hz, 1H),
2.35 (t, $J = 7.2$ Hz, 2H), 3.00-3.30 (m, 12H), 3.36-
3.41 (m, 4H), 3.47 (q, $J = 4.8$ Hz, 2H), 3.51-3.60 (m,
20 6H), 3.65 (s, 2H), 3.73 (s, 4H), 3.76-3.79 (m, 2H),
3.85-3.88 (m, 2H), 3.97 (s, 2H), 4.01-4.12 (m, 3H),
4.24 (s, 2H);

MS (ESI) m/z 975 $[M+H]^+$

25

Preparation of compound Ga-1f

The compound **2f** (3.8 mg, 3.2 μ mol) synthesized in step 5 of Example 5 was dissolved in distilled water (0.5 mL), to which gallium trichloride (3.0 mg, 17 μ mol) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1f** (2.7 mg, 68%) as a white solid.

10

^1H NMR (400 MHz, D_2O) δ 1.20-1.31 (m, 4H), 1.36-1.50 (m, 5H), 1.54-1.74 (m, 5H), 1.76-1.84 (m, 2H), 1.85-1.96 (m, 1H), 1.99-2.04 (m, 2H), 2.13 (t, J = 7.4 Hz, 2H), 2.35 (t, J = 7.2 Hz, 2H), 2.51 (t, J = 7.0 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 3.15-3.28 (m, 9H), 3.33-3.44 (m, 8H), 3.46-3.50 (m, 3H), 3.55-3.58 (m, 3H), 3.65-3.70 (m, 3H), 3.75-3.81 (m, 4H), 3.87 (s, 2H), 3.92-4.12 (m, 5H), 4.26 (s, 2H), 7.14-7.17 (m, 3H), 7.24-7.27 (m, 2H);

20

MS (ESI) m/z 1252 $[\text{M}+2\text{H}]^+$, 1248 $[\text{M}-2\text{H}]^-$

Preparation of compound Ga-1g

The compound **2g** (4.4 mg, 3.7 μ mol) synthesized in step 5 of Example 5 was dissolved in distilled water (0.5 mL), to which gallium trichloride (4.0 mg, 23

25

μmol) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-1g (2.0 mg, 43%) as a white solid.

¹H NMR (400 MHz, D₂O) δ 1.12-1.28 (m, 4H), 1.32-1.37 (m, 2H), 1.40-1.48 (m, 2H), 1.49-1.62 (m, 3H), 1.64-1.70 (m, 1H), 1.73 (p, *J* = 7.4 Hz, 2H), 1.77-1.86 (m, 1H), 1.99-2.05 (m, 1H), 2.08 (t, *J* = 7.2 Hz, 2H), 2.15 (s, 3H), 2.36 (t, *J* = 7.6 Hz, 2H), 2.43 (t, *J* = 6.8 Hz, 2H), 2.96-3.03 (m, 2H), 3.04-3.28 (m, 1H), 3.30-3.47 (m, 8H), 3.84-3.91 (m, 2H), 3.92-3.40 (m, 2H), 4.03-4.08 (m, 2H), 4.09-4.14 (m, 1H), 4.23 (s, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H);

MS (ESI) *m/z* 1265 [M+H]⁺, 1263 [M-H]⁻

Preparation of compound Ga-1h

The compound 2h (6.0 mg, 4.6 μmol) synthesized in step 5 of Example 5 was dissolved in distilled water (0.5 mL), to which gallium trichloride (6.0 mg, 34.1 μmol) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate

was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1h** (5.4 mg, 86%) as a solid.

5 ¹H NMR (400 MHz, D₂O) δ 1.21-1.30 (m, 4H), 1.33-1.38 (m, 2H), 1.40-1.51 (m, 2H), 1.54-1.75 (m, 4H), 1.82 (p, *J* = 7.4 Hz, 2H), 1.83-1.89 (m, 1H), 2.03-2.08 (m, 1H), 2.12 (t, *J* = 7.2 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 1H), 2.48 (t, *J* = 7.2 Hz, 1H), 3.00 (t, *J* = 6.6
10 Hz, 2H), 3.13-3.33 (m, 11H), 3.39-3.52 (m, 8H), 3.55-3.60 (m, 6H), 3.66-3.74 (m, 3H), 3.97 (s, 2H), 4.00-4.17 (m, 3H), 4.27 (s, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H);

MS (ESI) *m/z* 1375 [M+H]⁺, 1373 [M-H]⁻

15

Preparation of compound Ga-**1i**

The compound **2i** (7.0 mg, 8.1 μmol) synthesized in step 4 of Example 6 was dissolved in distilled water (0.5 mL), to which gallium trichloride (7.0 mg, 40
20 μmol) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1i** (6.0 mg, 79%) as a white
25 solid.

¹H NMR (400 MHz, D₂O) δ 1.22-1.33 (m, 2H), 1.40-1.52 (m, 2H), 1.56-1.64 (m, 1H), 1.68-1.76 (m, 1H), 1.85 (p, *J* = 7.2 Hz, 1H), 2.04 (p, *J* = 7.2 Hz, 1H),
5 2.38 (t, *J* = 7.2 Hz, 2H), 3.17-3.34 (m, 11H), 3.41-3.43 (m, 4H), 3.48-3.53 (m, 2H), 3.58 (s, 4H), 3.76 (s, 4H), 3.79 (s, 2H), 3.88-3.91 (m, 2H), 3.97 (s, 2H), 4.06-4.14 (m, 3H), 4.26 (s, 2H);

MS (ESI) *m/z* 933 [M+2H]⁺, 929 [M-2H]⁻

10

Preparation of compound Ga-1j

The compound **2j** (4.4 mg, 3.8 μmol) synthesized in step 5 of Example 7 was dissolved in distilled water (0.5 mL), to which gallium trichloride (4.0 mg, 23
15 μmol) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1j** (2.3 mg, 49%) as a white
20 solid.

¹H NMR (400 MHz, D₂O) δ 1.20-1.30 (m, 4H), 1.34-1.50 (m, 4H), 1.56-1.66 (m, 3H), 1.69-1.80 (m, 3H), 1.83-1.87 (m, 1H), 1.97-2.08 (m, 1H), 2.11 (t, *J* = 6.8
25 Hz, 2H), 2.18 (s, 3H), 2.37 (t, *J* = 7.2 Hz, 2H), 2.42-

2.48 (m, 2H), 3.02 (t, $J = 6.4$ Hz, 2H), 3.15-3.30 (m, 9H), 3.34-3.55 (m, 11H), 3.64-3.70 (m, 3H), 3.76-3.79 (m, 4H), 3.88-3.93 (m, 4H), 4.05-4.10 (m, 3H), 4.22 (s, 2H), 7.04 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 8.0$ Hz, 2H);

MS (ESI) m/z 1121 $[M+H]^+$, 1119 $[M-H]^-$

Preparation of compound Ga-1k

The compound **2k** (2.0 mg, 1.6 μ mol) synthesized in step 5 of Example 7 was dissolved in distilled water (0.5 mL), to which gallium trichloride (2.0 mg, 11 μ mol) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1k** (0.6 mg, 29%) as a white solid.

MS (ESI) m/z 1332 $[M+H]^+$, 1330 $[M-H]^-$

Preparation of compound Ga-1l

The compound **2l** (7.0 mg, 8.5 μ mol) was dissolved in distilled water (0.5 mL), to which gallium trichloride (4.5 mg, 25.6 μ mol) was added, followed by stirring at 70°C for 2 hours. The reaction solution

was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**11** (5.5 mg, 73%) as a white solid.

5

^1H NMR (400 MHz, CDCl_3) δ 1.24-1.40 (m, 2H), 1.42-1.51 (m, 1H), 1.54-1.62 (m, 2H), 1.63-1.94 (m, 1H), 2.06-2.14 (m, 1H), 2.44 (t, $J = 7.2$ Hz, 2H), 3.20-3.40 (m, 9H), 3.49 (d, $J = 8.8$ Hz, 4H), 3.72-3.86 (m, 6H),
10 3.87 (d, $J = 10.4$ Hz, 2H), 3.92-4.00 (m, 3H), 4.04 (s, 2H), 4.10-4.20 (m, 4H);

MS (ESI) m/z 887 $[\text{M}+\text{H}]^+$

Preparation of compound Ga-**1m**

15 The compound **2m** (14 mg, 12.6 μmol) was dissolved in H_2O (0.8 mL), to which gallium trichloride (6.7 mg, 37.9 μmol) was added, followed by stirring at 70°C for 2 hours. The reaction solution was filtered. The filtrate was separated by high performance liquid
20 chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1m** (7.1 mg, 48%) as a white solid.

^1H NMR (400 MHz, D_2O) δ 1.30-1.44 (m, 4H), 1.48-
25 1.54 (m, 2H), 1.58 (bs, 2H), 1.68-1.76 (m, 2H), 1.79-

1.89 (m, 4H), 1.93-1.98 (m, 1H), 2.14-2.17 (m, 1H),
2.21 (d, $J = 1.2$ Hz, 4H), 2.29 (s, 3H), 2.45 (t, $J =$
7.2 Hz, 2H), 2.54-2.57 (m, 2H), 3.15 (t, $J = 6.4$ Hz,
2H), 2.78-3.42 (m, 9H), 3.54 (t, $J = 10$ Hz, 4 H), 3.78
5 (s, 3H), 3.83-3.97 (m, 6H), 4.00-4.11 (m, 4H), 4.16-
4.34 (m, 4 H), 7.16 (dd, $J = 17.6, 7.6$ Hz, 4 H)

MS (ESI) m/z 1174 $[M-H]^-$

Preparation of compound Ga-1n

10 The compound **2n** (9 mg, 10 μ mol) was dissolved in
water (1 mL), to which gallium trichloride (18 mg, 100
 μ mol) dissolved in water (1 mL) was added, followed by
stirring at 70°C for 1 hour. The reaction solution was
filtered. The filtrate was separated by high
15 performance liquid chromatography (HPLC) and dried
using a lyophilizer to give the compound Ga-**1n** (4 mg,
41%) as a solid.

^1H NMR (400 MHz, D_2O) δ 1.94-2.03 (m, 2H), 2.15-
20 2.45 (m, 2H), 2.47-2.54 (m, 3H), 2.63-2.71 (m, 2H),
3.32-3.48 (m, 9H), 3.53-3.72 (m, 15H), 3.78 (s, 2H),
3.90 (s, 4H), 3.95 (d, $J = 10.4$ Hz, 2H), 4.04 (d, $J =$
11.2 Hz, 2H), 4.22 (s, 2H), 4.23-4.33 (m, 3H);

MS (ESI) m/z 961 $[M+H]^+$

25

Preparation of compound Ga-1o

The compound **2o** (7 mg, 8 μ mol) was dissolved in water (0.8 mL), to which gallium trichloride (14 mg, 80 μ mol) dissolved in water (0.8 mL) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried using a lyophilizer to give the compound Ga-**1o** (6 mg, 80%) as a solid.

10

^1H NMR (400 MHz, D_2O) δ 1.95–2.04 (m, 2H), 2.14–2.24 (m, 2H), 2.51–2.68 (m, 5H), 2.73–2.76 (m, 1H), 3.37–3.48 (m, 10H), 3.54–3.79 (m, 20H), 3.91 (s, 4H), 3.96 (d, J = 10.4 Hz, 2H), 4.04 (d, J = 11.2 Hz, 2H), 4.23–4.30 (m, 2H);

15

MS (ESI) m/z 977 $[\text{M}+\text{H}]^+$

Preparation of compound Ga-1p

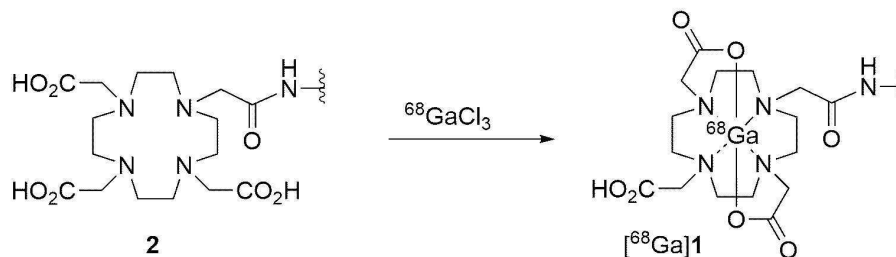
The compound **2p** (9 mg, 10 μ mol) was dissolved in water (1 mL), to which gallium trichloride (18 mg, 10 μ mol) dissolved in water (1 mL) was added, followed by stirring at 70°C for 1 hour. The reaction solution was filtered. The filtrate was separated by high performance liquid chromatography (HPLC) and dried

20

using a lyophilizer to give the compound Ga-**1p** (5 mg, 51%) as a solid.

^1H NMR (400 MHz, D_2O) δ 1.86–2.02 (m, 2H), 2.08–
 5 2.21 (m, 2H), 2.44–2.49 (m, 3H), 2.67–2.73 (m, 1H),
 3.25–3.42 (m, 9H), 3.45–3.59 (m, 8H), 3.66 (s, 2H),
 3.80–3.95 (m, 7H), 4.00–4.10 (m, 4H), 4.15–4.19 (m,
 2H), 4.56–4.59 (m, 2H), 4.64–4.73 (m, 2H), 4.77 (s,
 2H), 7.93 (s, 0.4H), 8.03 (s, 0.6H);
 10 MS (ESI) m/z 998 $[\text{M}+\text{H}]^+$

<Example 14> Preparation of compound [^{68}Ga]1



Preparation of compound [^{68}Ga]1a

15 0.1 N hydrochloric acid (5 mL) was poured into
 $^{68}\text{Ge}/^{68}\text{Ga}$ generator and placed in test tubes (1
 mL/tube). After measuring the radioactivity of each
 test tube, two ^{68}Ga solutions (4.6 mCi, 2 mL) of the
 two test tubes showing high radioactivity were
 20 transferred to the reaction vessel. The compound **2a**
 (200 μg) was dissolved in 1.0 M sodium acetate (0.4

mL)-aqueous hydrochloric acid solution (pH 4.55), which was loaded in a reaction vessel, followed by reaction at 80°C for 10 minutes. The reaction solvent was filtered, and the filtrate was separated by high performance liquid chromatography. The separated solution was diluted with water (10 mL), passed through C-18 SepPak to capture, and washed with water (5 mL). After blowing nitrogen gas to remove moisture, it was eluted with ethanol (1 mL) to give the compound
10 [⁶⁸Ga]**1a** (1.4 mCi).

Conditions of high performance liquid chromatography:

Column: RESTEK AQ (5 μm, 250 mm x 10 mm);
Moving phase: 25% methanol/water (0.1% TFA);
15 Flow rate: 3 mL/min;
UV detector: 230 nm;
Residence time: 12 min.

Preparation of compound [⁶⁸Ga]1b****

20 The compound [⁶⁸Ga]**1b** (2.8 mCi) was obtained by the same manner as described in the preparation of the compound **1a** except that ⁶⁸Ga solution (5.94 mCi, 2 mL) and the compound **2b** (200 μg) were used.

Conditions of high performance liquid
25 chromatography:

Column: YMC-Pack ODS-A (S-5 μm , 12 nm, 250 mm x
10 mm);

Moving phase: 5% ethanol/water (0.1% TFA);

Flow rate: 5 mL/min;

5 UV detector: 254 nm;

Residence time: 32 min.

Preparation of compound [^{68}Ga]1c

The compound [^{68}Ga]1c (2.5 mCi) was obtained by
10 the same manner as described in the preparation of the
compound 1a except that ^{68}Ga solution (5.7 mCi, 2 mL)
and the compound 2c (200 μg) were used.

Conditions of high performance liquid
chromatography:

15 Column: YMC-Pack ODS-A (S-5 μm , 12 nm, 250 mm x
10 mm);

Moving phase: 0-15% 30 min. acetonitrile/water
(0.1% TFA);

Flow rate: 3 mL/min;

20 UV detector: 230 nm;

Residence time: 31 min.

Preparation of compound [^{68}Ga]1e

The compound [^{68}Ga]1e (2.4 mCi) was obtained by
25 the same manner as described in the preparation of the

compound **1a** except that ^{68}Ga solution (5.5 mCi, 2 mL) and the compound **2e** (200 μg) were used.

Conditions of high performance liquid chromatography:

5 Column: YMC-Pack ODS-A (S-5 μm , 12 nm, 250 mm x 10 mm);

Moving phase: 8% ethanol/water (0.1% TFA);

Flow rate: 4 mL/min;

UV detector: 220 nm;

10 Residence time: 14 min.

Preparation of compound [^{68}Ga]1f

The compound [^{68}Ga]**1f** (1.3 mCi) was obtained by the same manner as described in the preparation of the
15 compound **1a** except that ^{68}Ga solution (4.6 mCi, 2 mL) and the compound **2f** (200 μg) were used.

Conditions of high performance liquid chromatography:

Column: Xterra MS C18 (10 μm , 250 mm x 10 mm);

20 Moving phase: 20% ethanol/water (0.1% TFA);

Flow rate: 4 mL/min;

UV detector: 220 nm;

Residence time: 15 min.

Preparation of compound [^{68}Ga]1g

25

The compound [^{68}Ga]**1g** (2.3 mCi) was obtained by the same manner as described in the preparation of the compound **1a** except that ^{68}Ga solution (5.5 mCi, 2 mL) and the compound **2g** (200 μg) were used.

5 Conditions of high performance liquid chromatography:

Column: YMC-Pack ODS-A (S-5 μm , 12 nm, 250 mm x 10 mm);

Moving phase: 25% ethanol/water (0.1% TFA);

10 Flow rate: 4 mL/min;

UV detector: 220 nm;

Residence time: 17 min.

Preparation of compound [^{68}Ga]1h****

15 The compound [^{68}Ga]**1h** (1.3 mCi) was obtained by the same manner as described in the preparation of the compound **1a** except that ^{68}Ga solution (4.6 mCi, 2 mL) and the compound **2h** (200 μg) were used.

20 Conditions of high performance liquid chromatography:

Column: YMC-Pack ODS-A (S-5 μm , 12 nm, 250 mm x 10 mm);

Moving phase: 30% ethanol/water (0.1% TFA);

Flow rate: 4 mL/min;

25 UV detector: 220 nm;

Residence time: 14 min.

Preparation of compound [⁶⁸Ga]1k

The compound [⁶⁸Ga]**1k** (1.1 mCi) was obtained by
5 the same manner as described in the preparation of the
compound **1a** except that ⁶⁸Ga solution (3.9 mCi, 2 mL)
and the compound **2k** (200 µg) were used.

Conditions of high performance liquid
chromatography:

10 Column: Xterra MS C18 (10 µm, 250 mm x 10 mm);
Moving phase: 25% ethanol/water (0.1% TFA);
Flow rate: 4 mL/min;
UV detector: 220 nm;
Residence time: 18 min.

15

Preparation of compound [⁶⁸Ga]1n

The compound [⁶⁸Ga]**1n** (3.8 mCi) was obtained by
the same manner as described in the preparation of the
compound **1a** except that ⁶⁸Ga solution (6.9 mCi, 2 mL)
20 and the compound **2n** (200 µg) were used.

Conditions of high performance liquid
chromatography:

Column: YMC-Pack ODS-A (S-5 µm, 12 nm, 250 mm x
10 mm);
25 Moving phase: 7% acetonitrile/water (0.1% TFA);

Flow rate: 3 mL/min;
UV detector: 220 nm;
Residence time: 13 min.

5 **Preparation of compound [⁶⁸Ga]1o**

The compound [⁶⁸Ga]1o (2.1 mCi) was obtained by the same manner as described in the preparation of the compound 1a except that ⁶⁸Ga solution (5.4 mCi, 2 mL) and the compound 2o (200 µg) were used.

10 Conditions of high performance liquid chromatography:

Column: YMC-Pack ODS-A (S-5 µm, 12 nm, 250 mm x 10 mm);

Moving phase: 7% ethanol/water (0.1% TFA);

15 Flow rate: 4 mL/min;

UV detector: 220 nm;

Residence time: 20 min.

Preparation of compound [⁶⁸Ga]1p

20 The compound [⁶⁸Ga]1p (2.1 mCi) was obtained by the same manner as described in the preparation of the compound 1a except that ⁶⁸Ga solution (5.8 mCi, 2 mL) and the compound 2p (200 µg) were used.

25 Conditions of high performance liquid chromatography:

Column: RESTEK AQ (250 mm x 10 mm);
Moving phase: 15% methanol/water (0.1% TFA);
Flow rate: 3 mL/min;
UV detector: 220 nm;
5 Residence time: 15 min.

<Example 15> Preparation of compound [⁶⁴Cu]1b

The aqueous hydrochloric acid solution in which
[⁶⁴Cu]CuCl₂ (7.3 mCi) was dissolved was heated at 90°C
10 and dried while blowing nitrogen gas. After drying,
0.1 mL of 0.1 M sodium citrate (pH 5.5) in which the
compound 2b (100 µg) was dissolved was added thereto,
followed by reaction at 60°C for 10 minutes. Upon
completion of the reaction, water (0.3 mL) was added
15 to the reaction mixture, filtered, and washed twice
with water (0.3 mL). The filtrate was separated by
high performance liquid chromatography, passed through
C-18 SepPak to capture, washed with 5 mL of water, and
poured 1 mL of ethanol to give the compound [⁶⁴Cu]1b
20 (5.22 mCi).

Conditions of high performance liquid
chromatography:

Column: Xterra MS C18 (10 µm, 250 mm x 10 mm);
Moving phase: 50% acetonitrile/water (0.1% TFA);
25 Flow rate: 4 mL/min;

UV detector: 230 nm;

Residence time: 17.5 min.

<Example 16> Preparation of compound [¹⁷⁷Lu]1g

5 The compound **2g** (200 µg) dissolved in 1.0 M
sodium acetate (0.4 mL)-aqueous hydrochloric acid
solution (pH 4.88) was loaded in a reaction vessel
containing Lu-177 (2.2 mCi), followed by reaction at
80°C for 10 minutes. The reaction was filtered, and
10 the filtrate was separated by high performance liquid
chromatography. The separated solution was diluted
with water (10 mL), passed through C-18 SepPak to
capture, and washed with water (5 mL). After blowing
nitrogen gas to remove moisture, it was eluted with
15 ethanol (1 mL) to give the compound [¹⁷⁷Lu]**1g** (1.36
mCi).

Column: YMC-Pack ODS-A (S-5 µm, 12 nm, 250 mm x
10 mm);

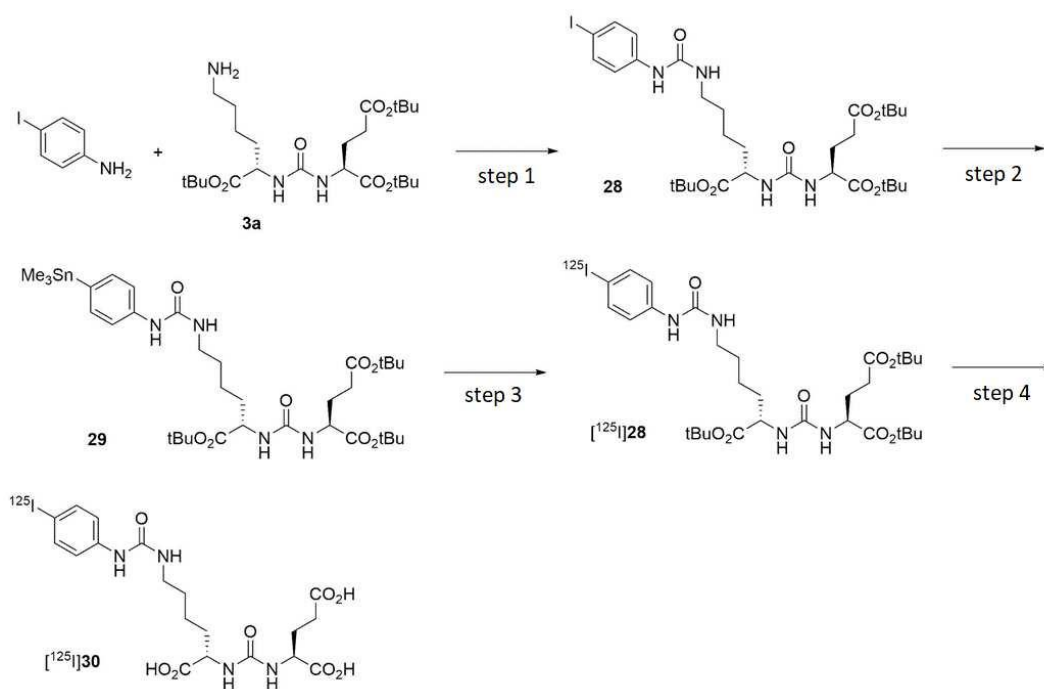
Moving phase: 25% ethanol/water (0.1% TFA);

20 Flow rate: 4 mL/min;

UV detector: 220 nm;

Residence time: 19 min.

<Comparative Example 1> Synthesis of compound
25 [¹²⁵I]**30**



Step 1: Preparation of compound 28

Triphosgene (21 mg, 71 vvoμ) was dissolved in dichloromethane (5 vM), to which 4-iodoaniline (45 vη,
 5 0.205 vvoμ) dissolved in dichloromethane (5 vM) was slowly added at 0°C. Triethylamine (0.57 vM, 0.410 vvoμ) was added thereto, followed by stirring at 0°C for 30 minutes. The compound **3a** (100 vη, 0.205 vvoμ) dissolved in dichloromethane (10 vM) was slowly added
 10 thereto at 0°C, and triethylamine (0.57 vM, 0.410 vvoμ) was also added. The mixture was stirred for 5 hours while slowly raising the temperature to room temperature. The reaction mixture was concentrated under reduced pressure, and the concentrate was

separated by column chromatography (2% methanol/dichloromethane) to give the compound **28** (66 mg, 44%) as a white liquid.

5 ^1H NMR (400 MHz, CDCl_3) δ 1.20–1.27 (m, 2H), 1.37 (s, 9H), 1.40 (s, 9H), 1.44 (s, 9H), 1.47–1.57 (m, 2H), 1.71–1.81 (m, 2H), 1.83–1.91 (m, 1H), 2.03–2.11 (m, 1H), 2.37 (sext, J = 8.2 Hz, 2H), 3.01–3.07 (m, 1H), 3.51–3.56 (m, 1H), 3.97–4.01 (m, 1H), 4.26–4.32
10 (m, 1H), 5.75 (d, J = 7.2 Hz, 1H), 6.31 (q, J = 3.4 Hz, 1H), 6.40 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.90 (s, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 24.5, 27.1, 27.8, 27.9, 28.0, 29.6, 31.7, 32.0, 39.1, 53.8, 54.9, 81.0, 81.8,
15 83.6, 83.7, 120.2, 137.5, 140.2, 155.6, 158.5, 171.8, 172.0, 175.3;

MS (ESI) m/z 733 $[\text{M}+\text{H}]^+$

Step 2: Preparation of compound 29

20 The compound **28** (50 mg, 0.068 mmol) synthesized in step 1 above was dissolved in dioxane (1.0 mL), to which hexamethyl ditin ($(\text{Me}_3\text{Sn})_2$, 0.43 mL, 0.206 mmol) and bis(triphenylphosphine)palladium(II) dichloride ($(\text{P}(\text{C}_6\text{H}_5)_3)_2\text{PdCl}_2$, 4.8 mL, 5 mmol) were added in that
25 order, followed by stirring at 110°C for 1.5 hours.

The mixture was cooled to room temperature, to which an aqueous potassium fluoride solution (50 vM) was added, followed by stirring for 1 hour. The reactant was filtered, and the organic compound was extracted using ethylacetate. The collected organic solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was separated by column chromatography (triethylamine:ethylacetate:n-hexane, 1:40:59) to give the compound **29** (28 mg, 53%) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 0.25 (s, 9H), 1.22-1.29 (m, 2H), 1.38 (s, 9H), 1.41 (s, 9H), 1.43 (s, 9H), 1.48-1.59 (m, 2H), 1.72-1.78 (m, 1H), 1.81-1.91 (m, 1H), 2.05-2.13 (m, 2H), 2.34-2.43 (m, 2H), 3.04-3.09 (m, 1H), 3.51-3.55 (m, 1H), 4.04 (pent, J = 4.9 Hz, 1H), 4.33 (sext, J = 4.5 Hz, 1H), 5.73 (d, J = 6.8 Hz, 1H), 6.23 (br s, 1H), 6.32 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.73 (s, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ -9.5, 24.2, 27.4, 27.8, 27.9, 28.0, 29.7, 31.8, 32.1, 39.1, 53.7, 54.7, 80.9, 81.7, 83.5, 118.4, 133.6, 136.2, 140.4, 155.9, 158.3, 171.9, 172.2, 175.1;

MS (ESI) m/z 771 $[\text{M}+2\text{H}]^+$

Step 3: Preparation of compound [¹²⁵I]28

The compound **29** (100 μ g) obtained in step 2 above was dissolved in ethanol (0.250 μ M), to which sodium
5 [¹²⁵I] iodide solution (3.2 mCi, 50 μ M) was added, followed by stirring at room temperature. 1 M aqueous hydrochloric acid solution (0.10 mL) and 3% H₂O₂ were added thereto, followed by stirring at room temperature for 10 minutes. 0.1 M sodium thiosulfate
10 solution (0.20 mL) was added to the reaction mixture, to which distilled water (18 mL) was added. This solution was passed through C-18 SepPak and washed with distilled water (20 mL). After pouring acetonitrile (2.0 mL) on the C-18 Sep-Pak, nitrogen
15 was blown into the solution to remove acetonitrile.

Step 4: Preparation of compound [¹²⁵I]30

Dichloromethane (0.2 mL) and trifluoroacetic acid (0.8 mL) were sequentially added to the reaction
20 vessel containing the reaction mixture obtained in step 3 above, followed by stirring at room temperature for 20 minutes. The reaction solvent was eliminated by blowing nitrogen, and then distilled water (2.0 mL) was added thereto. This solution was separated by high

performance liquid chromatography (HPLC) to give the compound [^{125}I]20 (1.1 mCi, 24%).

HPLC conditions:

Column, XTerra MS C18 (250 mm x 10 mm); Moving
5 phase, 30% acetonitrile/water (0.1% TFA); Flow rate, 5
mL/min; UV, 254 nm; Residence time, 10.4 min.

**<Reference Example 1> Preparation of prostate
cancer cell lines and nude mice**

10 A human prostate cancer cell line (22RV1) used
herein was purchased from American Type Culture
Collection (ATCC). PC3 PIP (PSMA⁺) and PC3 flu (PSMA⁻
) , the human prostate cancer cell lines, were provided
by Dr. Martin G. Pomper (Johns Hopkins Medical School,
15 Baltimore, MD). The human prostate cancer cell lines
were maintained in RPMI1640 medium supplemented with
10% fetal bovine serum (FBS) and 1%
antibiotic/antifungal agent. In the culture of PC3 PIP
(PSMA⁺) and PC3 flu (PSMA⁻) cell lines, puromycin was
20 additionally added at the concentration of 2 $\mu\text{g/mL}$.

As test animals, 6 weeks old male nude mice
(Narabio, Seoul, Korea) were used.

**<Experimental Example 1> Measurement of
25 lipophilicity (logP)**

Each of the [^{68}Ga]**1** compounds (1~2 mCi) synthesized in Example 14 was transferred into a vial, and the solvent was removed, to which 1 mL of n-octanol and 1 mL of PBS were added, and the lid was well closed, followed by mixing with a vortex for 1 minute. After the layers were separated, 0.1 mL was taken from each layer and the radiation dose was measured. The radiation dose was measured by repeating 3 times, and the mean value was obtained.

10

【Table 1】

LogP values of [^{68}Ga]**1** compounds

[^{68}Ga] 1	logP
[^{68}Ga] 1b	-2.56
[^{68}Ga] 1c	-2.65
[^{68}Ga] 1e	-2.88
[^{68}Ga] 1g	-2.42
[^{68}Ga] 1h	-1.89
[^{68}Ga] 1n	-3.06

<Experimental Example 2> Measurement of binding capacity

15

To confirm the binding capacity of the compounds of the present invention to PSMA, the following experiment was performed.

RPMI1640 supplemented with 1% BSA (bovine serum albumin) was used as a buffer solution.

20

[¹²⁵I]**30** (0.1 nM) obtained in Comparative Example 1 was added to a vessel containing 22RV1 cells (5X10⁴), to which the compound represented by formula 1 was loaded at 9 concentrations (1.00 x 10⁻⁴ ~ 1.00 x 10⁻¹² M), followed by stirring at 37°C for 2 hours. Upon completion of the stirring, the vessel was washed with PBS solution (2 mL) three times, and then the radioactivity was measured using a gamma counter (2480 WIZARD2 Gamma Counter PerkinElmer Co., MA). The 50% inhibition concentration (IC₅₀) for each compound was calculated using a GraphPad Prism program (GraphPad Software, Inc., CA)

Table 2 below is a table showing the binding affinity (IC₅₀) of each compound, and the K_d value of the compound [¹²⁵I]**30** was measured to be 0.13 nM. (Maresca, K. P. et al., 2009, J. Med. Chem. 52, 347-357)

【Table 2】

Compound	IC ₅₀ (nM)	K _i value (nM)
Ga- 1a	570.70±135.97	69.88±29.78
Ga- 1b	237.49±47.13	18.73±1.87
Ga- 1c	21.20±2.06	3.76±0.37
Ga- 1d	75.28±18.61	18.62±4.60
Ga- 1e	47.41±1.78	12.94±0.49
Ga- 1f	25.66±5.06	8.12±1.60
Ga- 1g	18.40±0.35	5.82±0.11
Ga- 1h	11.00±0.35	3.00±0.10

Ga- 1i	68.99±3.27	14.36±0.68
Ga- 1j	60.41±3.61	12.57±0.75
Ga- 1k	63.85±6.09	12.70±1.07
Ga- 1n	174.13±3.87	32.09±0.71
Ga- 1o	1140.29±82.36	282.09±20.37
Ga- 1p	702.95±144.61	129.54±26.65

As shown in Table 2, the compounds Ga-**1a** and Ga-**1b** of Example 13 of the present invention are compounds that do not have a carboxylic acid in the nitrogen of the lysine residue. In particular, Ga-**1a** showed a relatively low binding force to PSMA. On the other hand, Ga-**1c** having a structure similar to Ga-**1a** is a compound having a carboxylic acid in the nitrogen of the lysine residue, and it can be seen that the binding force to PSMA was about 18.6 times higher than that of Ga-**1a**. This is because one (R463) of three arginine residues, called an arginine patch, in the binding region of PSMA and the carboxylic acid bound to the nitrogen of the lysine residue of the compound represented by formula 1 of the present invention form a strong salt bridge interaction.

In addition, the carboxylic acid of the lysine residue in the compound represented by formula 1 of the present invention not only greatly improved the binding capacity to PSMA, but also increased the hydrophilicity of the compound to lower the non-

specific binding *in vivo* and removed it more quickly in normal organs.

The compounds Ga-**1f**, Ga-**1g** and Ga-**1h** have a phenyl group or a substituted phenyl group, and it was confirmed that they have a higher binding capacity than the compound Ga-**1e** having a similar structure without a phenyl group. Among them, the 4-iodophenyl-bonded compound Ga-**1h** had the highest binding capacity.

10

<Experimental Example 3> Experiment of MicroPET/CT imaging of mice transplanted with prostate cancer cell lines

A tumor model was prepared by subcutaneously injecting PSMA⁺ PC-3 PIP cells (a human prostate cancer cell line) to the right side of the nude mouse hind leg. Each of the ⁶⁸Ga-labeled compounds [⁶⁸Ga]**1e**, [⁶⁸Ga]**1g**, [⁶⁸Ga]**1h** and [⁶⁸Ga]**1k** was intravenously injected with 5.5 to 6.5 MBq (148-175 μ Ci/200 μ L), and PET/CT images were obtained using small animal INVEON PET/CT (Siemens medical solutions, Knoxville,. USA) for 60 minutes. After 150 minutes, 270 minutes, and 390 minutes, PET/CT images were also obtained for 30 minutes. The obtained PET/CT image results were

quantitatively analyzed using Inveon™ Research Workplace (IRW).

Figures 1, 2, 3, and 4 are graphs showing the quantitative analysis results of MicorPET/CT images for [⁶⁸Ga]**1e**, [⁶⁸Ga]**1g**, [⁶⁸Ga]**1h**, and [⁶⁸Ga]**1k** in % injected dose (ID)/g, and summarized in Tables 3, 4, 5, and 6, respectively.

[⁶⁸Ga]**1e** was found to be rapidly excreted through the kidney and bladder at the initial stage after injection, and it was confirmed that it selectively bound to PSMA⁺ PC-3 PIP tumors at a level of 4.05±0.64% ID/g at 270 minutes after injection (Figure 1, Table 3).

In the case of [⁶⁸Ga]**1g**, it was confirmed that the residence time in the blood was increased due to the albumin binding capacity of the phenyl group, and the tumor intake was increased over time. Compared to the compound [⁶⁸Ga]**1e**, the tumor intake of 13.00±4.95% ID/g, which was increased by about 3 times at 270 minutes, was confirmed (Figure 2, Table 4).

In the case of [⁶⁸Ga]**1h** and [⁶⁸Ga]**1k**, due to the albumin binding capacity of the substituted phenyl group, the residence time in the blood was increased and the tumor intake was confirmed to increase over

time, and the tumor intake continued to increase after 390 minutes.

The compound [^{68}Ga]**1h** showed the tumor intake of $16.75 \pm 0.92\%$ ID/g at 390 minutes (Figure 3, Table 5),
 5 and the compound [^{68}Ga]**1k** showed the tumor intake of $18.25 \pm 4.17\%$ ID/g at 390 minutes (Figure 4, Table 6).

In addition, it was confirmed that all of the compounds [^{68}Ga]**1e**, [^{68}Ga]**1g**, [^{68}Ga]**1h** and [^{68}Ga]**1k** were rapidly excreted out of the body as the intake in
 10 the kidney was decreased after 150 minutes.

【Table 3】

[^{68}Ga]**1e** intake of each mouse organ over time (%ID/g)

Time	Tumor (PIP)	Kidney	Bladder	Liver	Muscle
10	2.33 ± 0.36	21.37 ± 9.18	19.37 ± 0.32	4.76 ± 0.42	1.46 ± 0.14
20	3.64 ± 0.49	10.96 ± 4.32	47.31 ± 7.34	1.96 ± 0.22	1.38 ± 0.11
30	4.08 ± 0.60	10.88 ± 7.09	55.82 ± 12.46	1.29 ± 0.05	0.95 ± 0.13
40	4.44 ± 0.48	14.92 ± 13.57	60.63 ± 15.48	1.00 ± 0.03	0.61 ± 0.05
50	4.56 ± 1.03	15.84 ± 15.60	64.24 ± 12.76	0.80 ± 0.02	0.53 ± 0.05
60	4.73 ± 0.98	15.72 ± 16.29	67.80 ± 8.56	0.65 ± 0.04	0.35 ± 0.05
150	4.20 ± 0.42	0.70 ± 0.02	31.85 ± 35.57	0.06 ± 0.01	0.02 ± 0.01
270	4.05 ± 0.64	0.41 ± 0.16	1.45 ± 1.62	0.03 ± 0.01	0.01 ± 0.01

15

【Table 4】

[⁶⁸Ga]**1g** intake of each mouse organ over time
(%ID/g)

Time	Tumor (PIP)	Kidney	Bladder	Liver	Muscle
10	2.18±0.63	16.40±0.1 0	2.28±0.11	9.55±2.22	1.49±1.64
20	4.42±1.50	19.80±0.7 3	6.98±2.51	7.26±1.06	1.88±2.00
30	5.43±1.94	21.18±2.1 7	13.51±5.8 3	6.10±0.50	1.69±1.78
40	6.43±2.32	22.74±3.4 8	18.89±8.8 4	5.38±0.22	1.61±1.69
50	7.33±2.76	24.20±4.6 0	22.76±10. 86	4.75±0.07	1.54±1.62
60	8.29±2.99	25.78±4.7 2	24.74±11. 23	4.41±0.03	1.32±1.33
150	11.4±5.23	15.75±11. 53	42.3±41.5 8	0.45±0.11	0.21±0.03
270	13.00±4.9 5	12.45±9.6 9	12.05±2.7 6	0.22±0.01	0.06±0.02

5 【Table 5】

[⁶⁸Ga]**1h** intake of each mouse organ over time
(%ID/g)

Time	Tumor (PIP)	Kidney	Bladder	Liver	Muscle	Heart
10	1.94±0. 35	13.26±2 .36	2.12±0. 39	14.96±0 .03	2.24±0. 15	24.69±0 .20
20	3.74±0. 97	12.56±0 .86	2.91±0. 69	12.71±0 .03	2.97±0. 35	21.30±0 .11
30	5.00±1. 41	12.61±0 .71	3.14±0. 51	10.37±0 .12	2.98±0. 34	17.38±0 .04
40	6.22±1. 75	13.51±0 .46	4.52±0. 97	8.86±0. 35	3.28±0. 23	15.25±0 .15
50	7.12±2. 07	13.44±0 .71	8.26±4. 41	7.83±0. 45	3.25±0. 36	13.52±0 .55

60	7.90±2. 46	13.60±1 .72	12.62±5 .31	7.19±0. 49	3.14±0. 20	12.14±0 .91
150	9.90±4. 53	6.40±1. 41	19.45±1 2.23	2.80±0. 99	1.70±0. 57	5.55±2. 19
270	14.20±0 .00	7.45±1. 63	15.90±4 .53	3.00±0. 28	1.70±0. 14	5.75±0. 21
390	16.75±0 .92	5.85±0. 92	22.80±9 .90	2.35±0. 07	1.30±0. 14	3.90±0. 42

【Table 6】

[⁶⁸Ga]**1k** intake of each mouse organ over time
(%ID/g)

Time	Tumor (PIP)	Kidney	Bladder	Liver	Muscle	Heart
10	1.85±0. 25	11.16±1 .35	4.12±0. 45	11.99±4 .72	2.26±0. 75	21.67±0 .44
20	3.22±0. 38	11.21±1 .62	4.68±0. 22	11.09±3 .46	2.91±1. 21	20.10±0 .29
30	3.94±0. 38	10.89±1 .36	4.68±0. 45	10.04±2 .73	3.09±0. 91	18.33±0 .13
40	4.40±0. 36	11.06±1 .02	4.75±0. 21	9.31±2. 32	3.32±1. 20	17.22±0 .35
50	5.03±0. 33	10.80±1 .20	4.83±0. 18	8.73±2. 11	3.24±1. 07	16.06±0 .38
60	5.45±0. 16	10.96±1 .18	4.81±0. 24	8.22±1. 79	3.49±1. 28	15.03±0 .27
150	11.00±2 .12	11.40±1 .13	18.10±6 .51	5.00±1. 41	2.75±1. 20	7.85±1. 63
270	15.70±4 .24	9.25±0. 78	20.10±4 .53	3.60±0. 71	2.15±0. 78	5.10±0. 85
390	18.25±4 .17	7.70±0. 71	14.25±0 .64	2.25±0. 64	1.20±0. 56	3.80±1. 41

5

**<Experimental Example 4> Biodistribution test
with mice transplanted with prostate cancer cell lines**

After 270 minutes of [⁶⁸Ga]**1e** and [⁶⁸Ga]**1g** injection, microPET/CT images were obtained for 30 minutes, and then each organ (blood, muscle, fat, heart, lung, liver, spleen, stomach, intestine, kidney, bone and tumor) was extracted and the radioactivity thereof was measured using a gamma counter.

Table 7 shows the intake of each organ 5 hours after the injection of [⁶⁸Ga]**1e** or [⁶⁸Ga]**1g**.

Biodistribution was confirmed 5 hours after the compound injection. As a result, [⁶⁸Ga]**1g** containing a phenyl group showed a higher tumor intake rate (%ID/g) of more than 10%, which was about 1.4 times higher than that of [⁶⁸Ga]**1e**.

【Table 7】

Radioactivity of [⁶⁸Ga]**1e** and [⁶⁸Ga]**1g** in mouse organ

	[⁶⁸ Ga] 1e	[⁶⁸ Ga] 1g
Blood	0.01±0.00	0.02±0.03
Muscle	0.01±0.00	0.01±0.00
Fat	0.01±0.00	0.11±0.15
Heart	0.01±0.00	0.02±0.01
Lung	0.02±0.01	0.07±0.07
Liver	0.02±0.01	0.03±0.01
Spleen	0.01±0.00	0.20±0.27
Stomach	0.02±0.02	0.02±0.02
Intestine	0.09±0.08	0.09±0.08
Kidney	0.82±0.51	9.15±11.26

Bone	0.00±0.00	0.01±0.01
PSMA+ PIP	7.34±5.49	10.48±1.05

Meanwhile, the compound represented by formula 1 according to the present invention can be formulated in various forms depending on the purpose of use. The following illustrates some formulation methods in which the compound represented by formula 1 according to the present invention is contained as an active ingredient, but the present invention is not limited thereto.

10

<Manufacturing Example 1> Preparation of pharmaceutical formulations

1-1. Preparation of powders

Compound of formula 1	500 mg
Lactose	100 mg
Talc	10 mg

15

Powders were prepared by mixing all the above components, which were filled in airtight packs.

1-2. preparation of tablets

20

Compound of formula 1	500 mg
Corn starch	100 mg
Lactose	100 mg

Magnesium stearate 2 mg

Tablets were prepared by mixing all the above components by the conventional method for preparing tablets.

5

1-3. Preparation of capsules

Compound of formula 1 500 mg

Corn starch 100 mg

Lactose 100 mg

10 Magnesium stearate 2 mg

Capsules were prepared by mixing all the above components, which were filled in gelatin capsules according to the conventional method for preparing capsules.

15

1-4. Preparation of injectable solution

Compound of formula 1 500 mg

Sterilized distilled water proper amount

PH regulator proper amount

20 Injectable solutions were prepared by mixing all the above components, putting the mixture into 2 Ml ampoules and sterilizing thereof by the conventional method for preparing injectable solutions.

1-5. Preparation of liquid formulations

25

Compound of formula 1	100 mg
Isomerized sugar	10 g
Mannitol	5 g
Purified water	proper amount

5 All the above components were dissolved in purified water. After adding lemon flavor, total volume was adjusted to be 100 mL by adding purified water. Liquid formulations were prepared by putting the mixture into brown bottles and sterilizing thereof
10 by the conventional method for preparing liquid formulations.

As mentioned above, the present invention has been described in detail through the preferred
15 preparative examples, examples and experimental examples, but the scope of the present invention is not limited to the specific examples, and should be interpreted by the appended claims. In addition, those of ordinary skill in the art should understand that
20 many modifications and variations are possible without departing from the scope of the present invention.

INDUSTRIAL APPLICABILITY

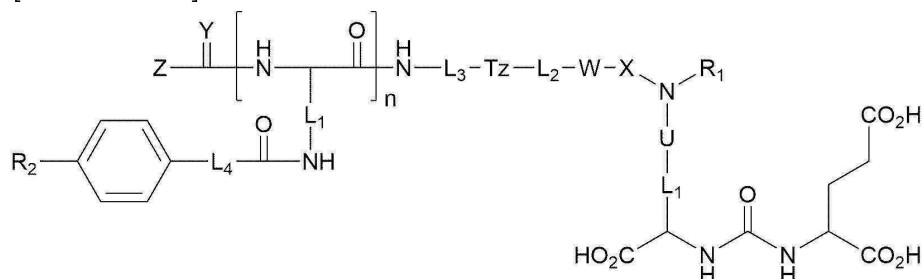
25 The present invention relates to a pharmaceutical

composition for diagnosing and treating prostate cancer, capable of targeting PSMA, and a compound provided by one aspect of the present invention has a glutamine-urea-lysine compound to which a radioactive
5 metal-coupled chelator is structurally coupled and to which an aryl group that can additionally bind to PSMA protein is coupled. Coupling between the glutamine-urea-lysine compound and the chelator includes a polar spacer so as to serve the role of reducing in vivo
10 nonspecific coupling and exhibit an effect of being rapidly removed from vital organs, but not from prostate cancer. These characteristics lower the radiation exposure, which is caused by a therapeutic radioisotope-coupled compound, to normal tissue and
15 organs, and thus reduce side effects. In addition, a compound that contains a phenyl group having a coupling force with albumin has an increased residence time in the blood, thereby becoming more accumulated in prostate cancer.

WHAT IS CLAIMED IS:

1. A compound represented by formula 1, a stereoisomer thereof, a hydrate thereof, or a pharmaceutically acceptable salt thereof:

[Formula 1]



In formula 1,

L₁ is -(CH₂)_a-, wherein a is an integer of 1 ~ 8;

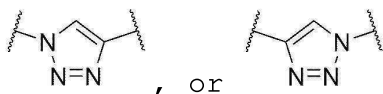
U is a bond, or $-C(O)-$;

R₁ is -L₅-CO₂H, wherein L₅ is -(CH₂)_b-, wherein b is an integer of 1 ~ 6;

X is a bond, or $-C(0)-$;

W is a bond, or -NA₁-, A₁ is hydrogen, or -(CH₂)_c-pyridyl, wherein c is an integer of 0 ~ 3;

L₂ is a bond, or -(CH₂)_d-, wherein d is an integer of 1 ~ 8;



Tz is a bond, $\text{N}=\text{N}$, or $\text{N}=\text{N}$;

L₃ is C₁₋₁₂ straight or branched alkylene, wherein one or more carbon atoms in alkylene can be replaced by oxygen atoms;

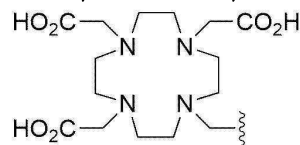
L₄ is -(CH₂)_e-, wherein e is an integer of 1 ~ 6;

n is an integer of 0 ~ 1;

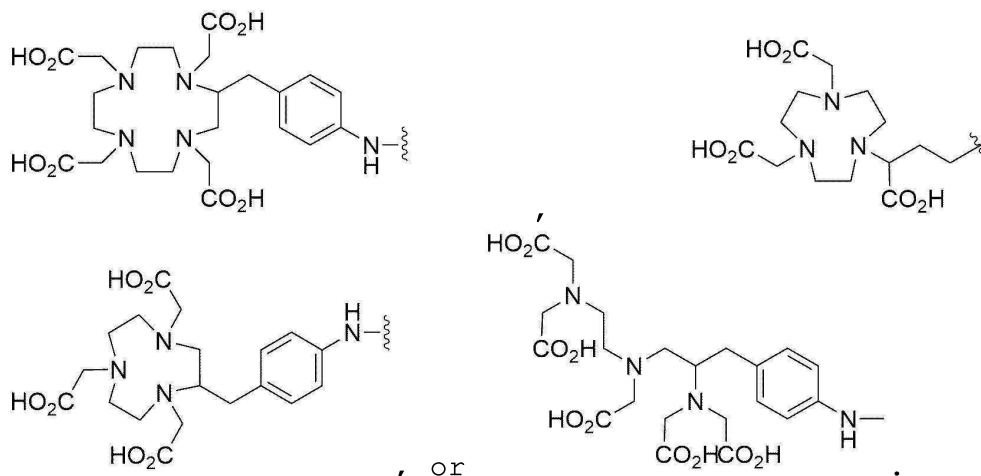
R₂ is hydrogen, C₁₋₅ straight or branched alkyl, or halogen;

Y is oxygen;

Z is a chelator including a radioactive metal, wherein the radioactive metal is Ga-68, Cu-64, Cu-67, Y-90, Sc-47, In-111, Sn-117m, Lu-177, Bi-212, Bi-213, Pb-212, Ra-223, or Ac-



225, and the chelator is



2. The compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof according to claim 1, wherein:

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 6;

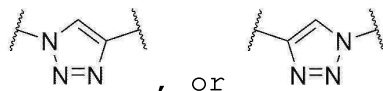
U is a bond, or $-C(O)-$;

R_1 is $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$, wherein b is an integer of 1 ~ 4;

X is a bond, or $-C(O)-$;

W is a bond, or $-NA_1-$, A_1 is hydrogen, or $-(CH_2)_c$ -pyridyl, wherein c is an integer of 0 ~ 1;

L_2 is a bond, or $-(CH_2)_d-$, wherein d is an integer of 1 ~ 6;



Tz is a bond, or $-N=N-$;

L_3 is C_{1-10} straight or branched alkylene, wherein one or more carbon atoms in alkylene can be replaced by oxygen atoms;

L_4 is $-(CH_2)_e-$, wherein e is an integer of 2 ~ 4;

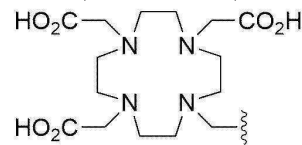
n is an integer of 0 ~ 1;

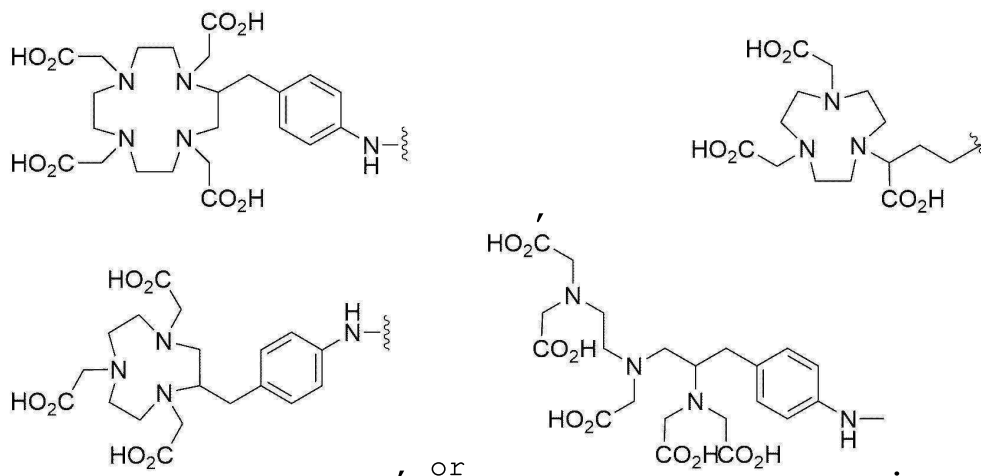
R_2 is hydrogen, C_{1-3} straight or branched alkyl, or halogen;

Y is oxygen;

Z is a chelator including a radioactive metal, wherein the radioactive metal is Ga-68, Cu-64, Cu-67, Y-90, Sc-47, In-111, Sn-117m, Lu-177, Bi-212, Bi-213, Pb-212, Ra-223, or Ac-225,

and the chelator is





3. The compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof according to claim 1, wherein:

L_1 is $-(CH_2)_a-$, wherein a is an integer of 2 ~ 4;

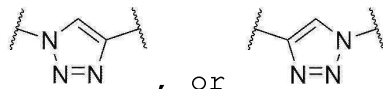
U is a bond, or $-C(O)-$;

R_1 is $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$, wherein b is an integer of 1 ~ 2;

X is a bond, or $-C(O)-$;

W is a bond, or $-NA_1-$, wherein A_1 is hydrogen or pyridyl;

L_2 is a bond, or $-(CH_2)_d-$, wherein d is an integer of 1 ~ 2;



Tz is a bond, or $-N=N-$;

L_3 is C_{1-8} straight alkylene, wherein one or more carbon atoms in alkylene can be replaced by oxygen atoms;

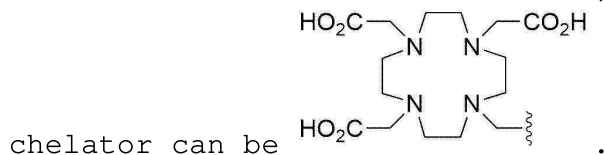
L_4 is $-(CH_2)_3-$;

n is an integer of 0 ~ 1;

R_2 is hydrogen, methyl or halogen;

Y is oxygen;

Z is a chelator including a radioactive metal, wherein the radioactive metal is Ga-68, Cu-64, or Lu-177, and the



4. The compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound represented by formula 1 is selected from the group consisting of the following compounds:

;

i



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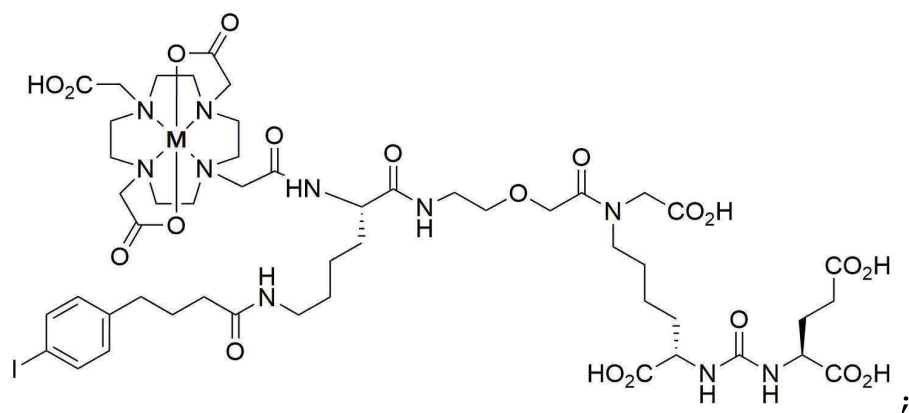


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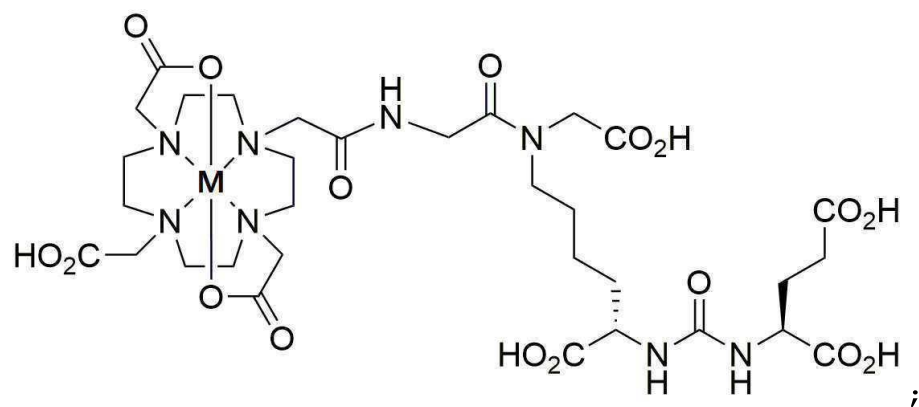


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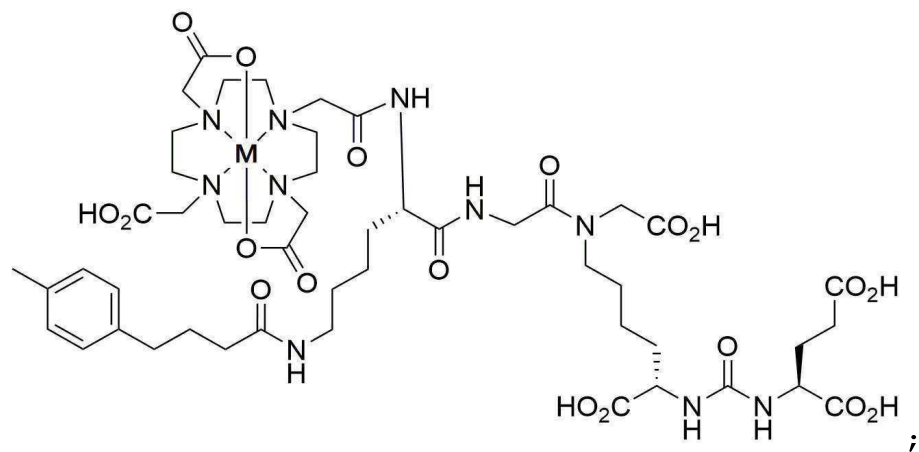




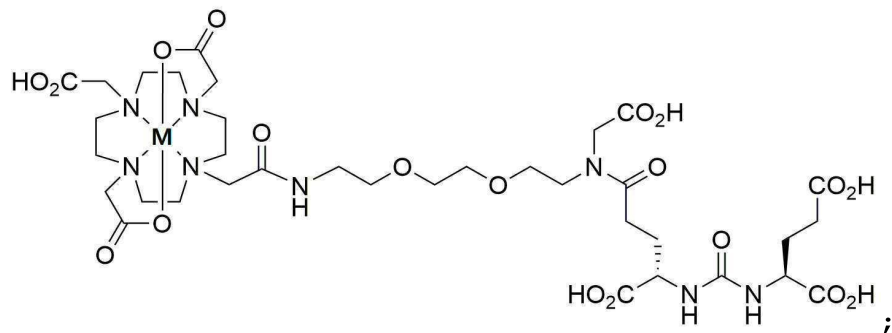
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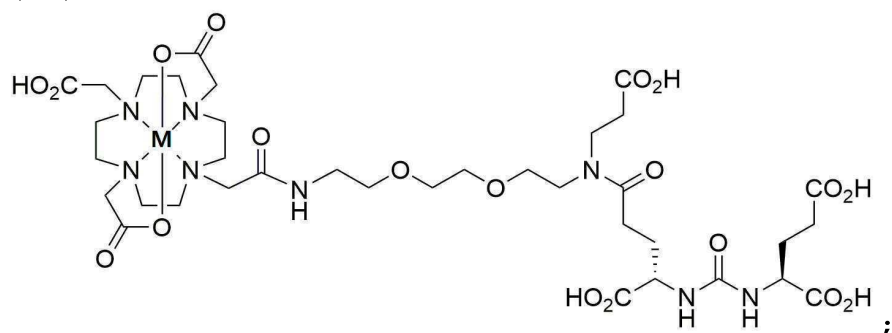
(13)



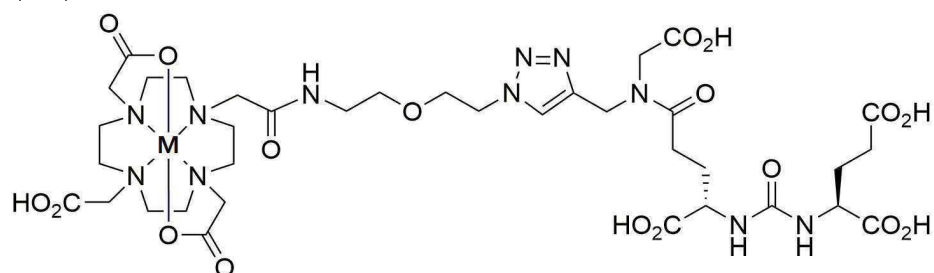
(14)



(15)



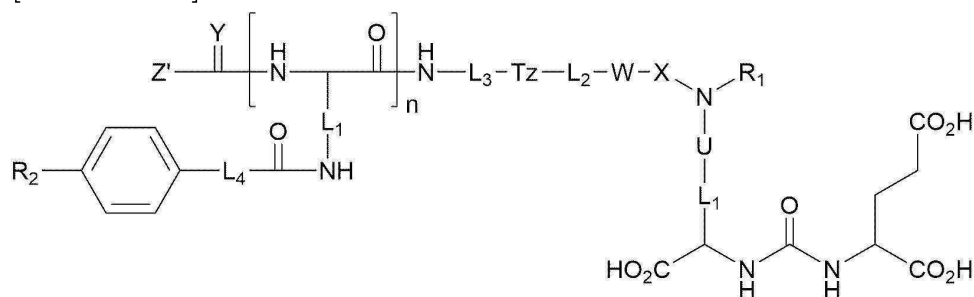
(16)



(In the above formulas, M is a radioactive metal, and the radioactive metal is as defined in claim 1).

5. A compound represented by formula 2, a stereoisomer thereof, a hydrate thereof, or a pharmaceutically acceptable salt thereof:

[Formula 2]



In formula 2,

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 8;

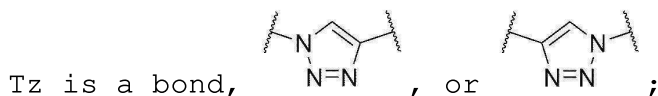
U is a bond, or $-C(O)-$;

R_1 is $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$, wherein b is an integer of 1 ~ 6;

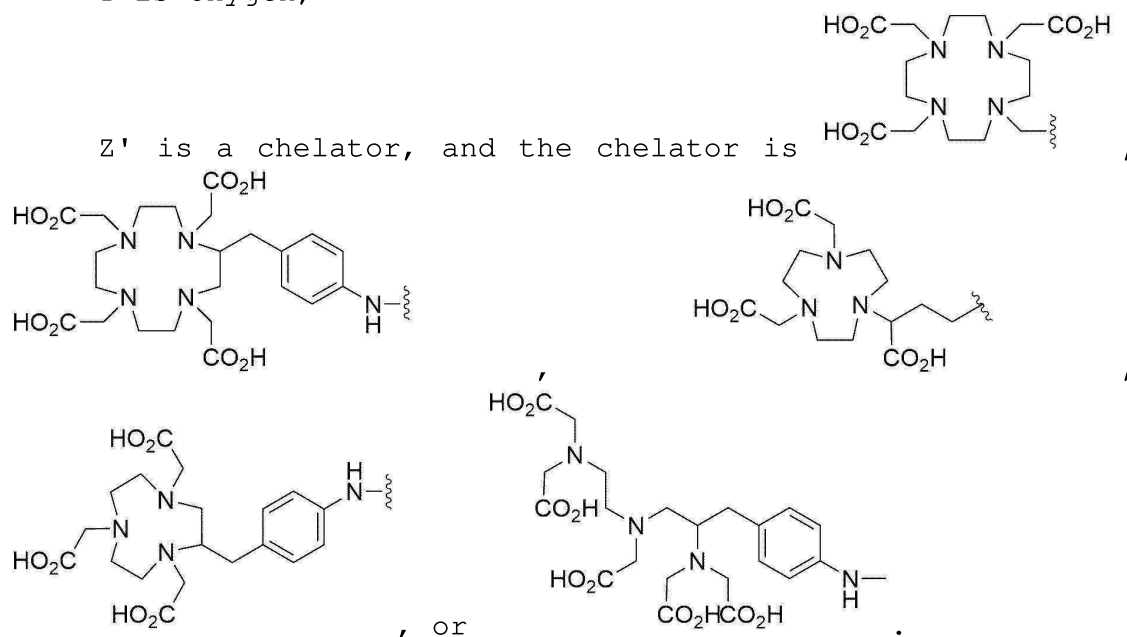
X is a bond, or $-C(O)-$;

W is a bond or $-NA_1-$, and A_1 is hydrogen or $-(CH_2)_c-$ pyridyl, wherein c is an integer of 0 ~ 3;

L_2 is a bond or $-(CH_2)_d-$, wherein d is an integer of 1 ~ 8;

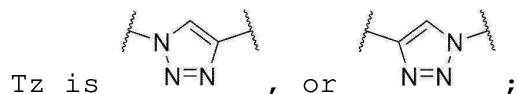


L_3 is C_{1-12} straight or branched alkylene, wherein one or more carbon atoms in alkylene can be replaced by oxygen atoms;
 L_4 is $-(CH_2)_e-$, wherein e is an integer of 1 ~ 6;
 n is an integer of 0 ~ 1;
 R_2 is hydrogen, C_{1-5} straight or branched alkyl, or halogen;
 Y is oxygen;

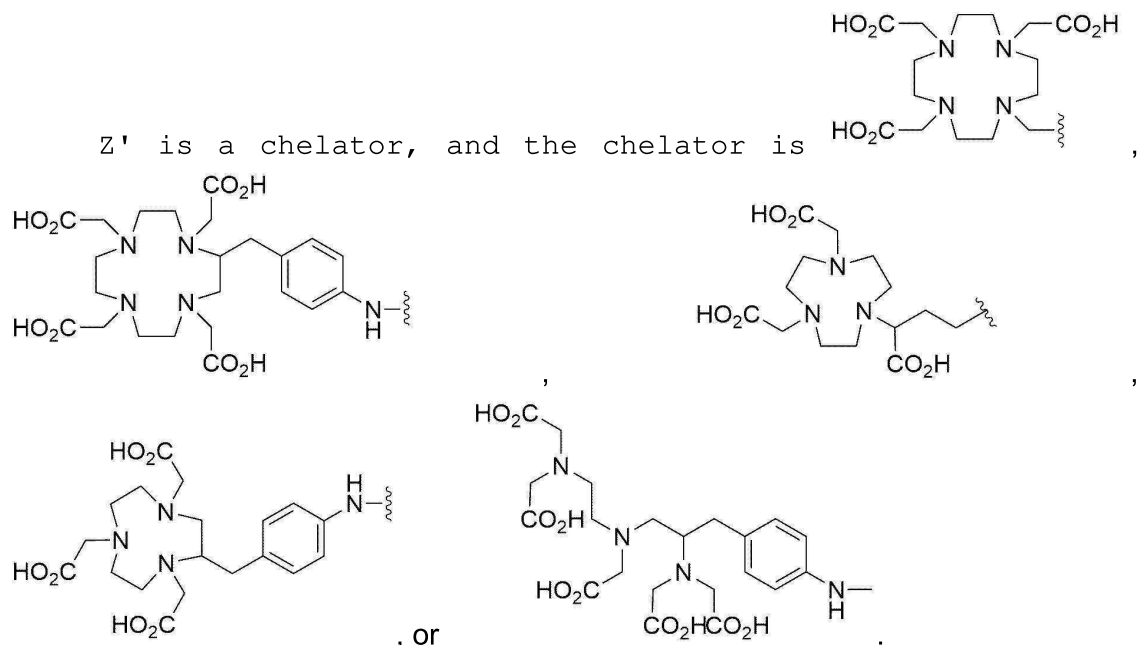


6. The compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof according to claim 5, wherein:

L_1 is $-(CH_2)_a-$, wherein a is an integer of 1 ~ 6;
 U is a bond, or $-C(O)-$;
 R_1 is $-L_5-CO_2H$, wherein L_5 is $-(CH_2)_b-$, wherein b is an integer of 1 ~ 4;
 X is a bond, or $-C(O)-$;
 W is a bond or $-NA_1-$, and A_1 is hydrogen or $-(CH_2)_c$ -pyridyl;
 L_2 is a bond or $-(CH_2)_d-$, wherein d is an integer of 1 ~ 6;



L_3 is C_{1-10} straight or branched alkylene, wherein one or more carbon atoms in alkylene can be replaced by oxygen atoms;
 L_4 is $-(CH_2)_3-$;
 n is an integer of 0 ~ 1;
 R_2 is hydrogen, C_{1-3} straight or branched alkyl, or halogen;
 Y is oxygen;



7. The compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof according to claim 5, wherein:

L₁ is $-(CH_2)_a-$, wherein a is an integer of 2 ~ 4;

U is a bond, or $-C(O)-$;

R₁ is $-L_5-CO_2H$, wherein L₅ is $-(CH_2)_b-$, wherein b is an integer of 1 ~ 2;

X is a bond, or $-C(O)-$;

W is a bond or $-NA_1-$, and A₁ is hydrogen or pyridyl;

L₂ is a bond or $-(CH_2)_d-$, wherein d is an integer of 1 ~ 2;

Tz is a bond,

, or

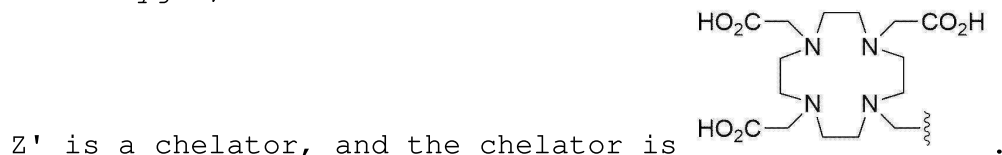
L₃ is C₁₋₈ straight alkylene, wherein one or more carbon atoms in alkylene can be replaced by oxygen atoms;

L₄ is $-(CH_2)_3-$;

n is an integer of 0 ~ 1;

R₂ is hydrogen, methyl, or halogen;

Y is oxygen;



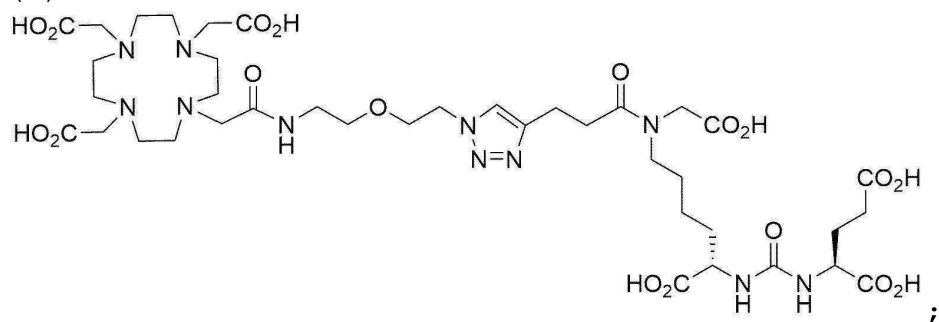
8. The compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof according to claim 5, wherein the compound represented by

formula 2 is selected from the group consisting of the following compounds:

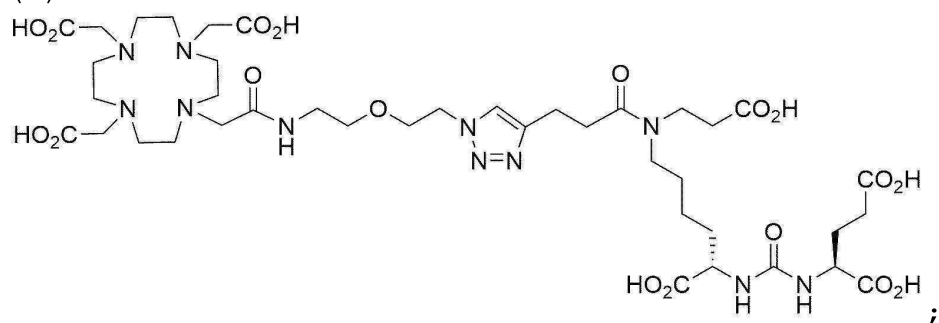
;

;

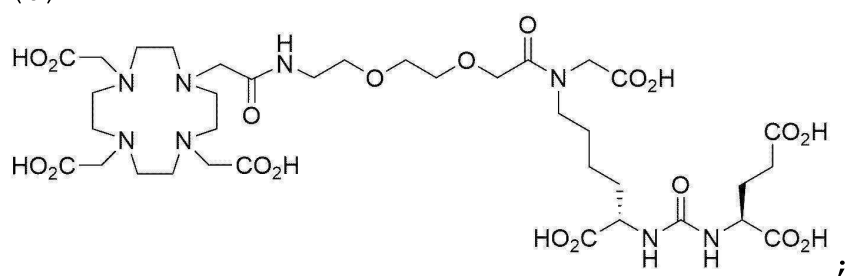
(3)



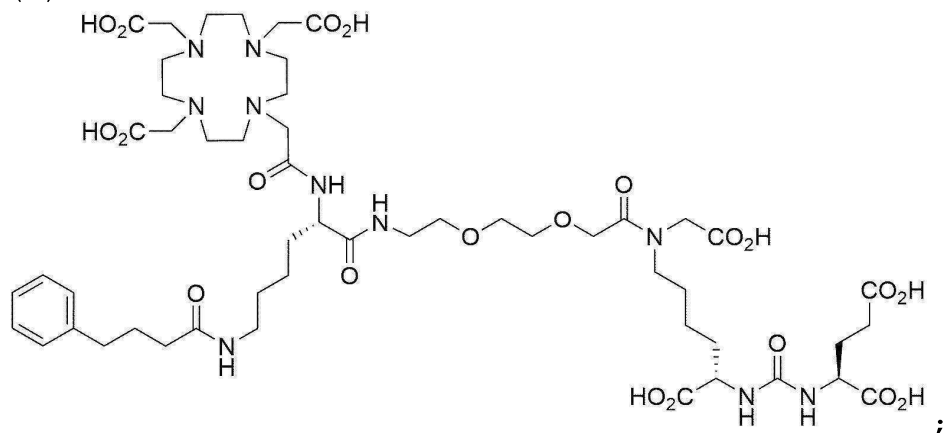
(4)



(5)

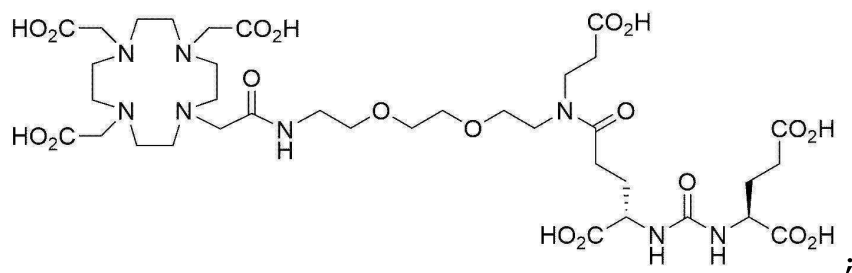


(6)

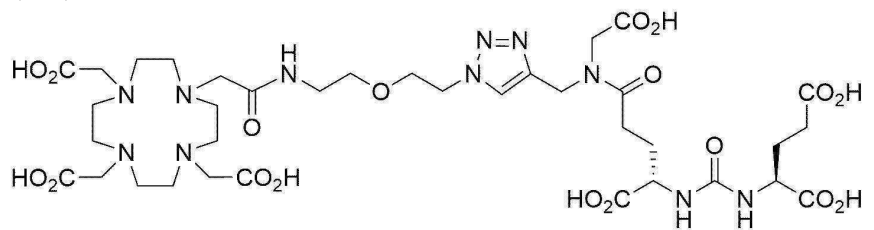


CC1=CC=C(C=C1)CCC(=O)NCC[C@H](C(=O)NCCOCOCOC(=O)NCC(=O)O)C(=O)NCC[C@H](C(=O)NCC[C@H](C(=O)O)C(=O)NCC[C@H](C(=O)O)C(=O)O)C(=O)OOC(=O)C[C@H](NC(=O)C[C@H](N)C(=O)NCCOCCOC(=O)NCC[C@H](N)C(=O)CCc1ccc(I)cc1)C(=O)NCC[C@H](N)C(=O)COC(=O)OOC(=O)C1CN(CCN(CCN(CCN1C(=O)NCCOC(=O)NCC(=O)O)CCCN(C(=O)O)C)CC(C(=O)O)C)CC(C(=O)O)CCc1ccc(cc1)CCCC(=O)NCC[C@H](NC(=O)[C@@H](NC(=O)NCCOC(=O)NCCC[C@H](NC(=O)N[C@@H](C(=O)O)C(=O)O)C(=O)O)C(=O)O)CN2CCN(CC(CCN2C(=O)O)C(=O)O)C(=O)O





(16)



9. A composition for diagnosing prostate cancer comprising the compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof of claim 1 as an active ingredient.

10. The composition for diagnosing prostate cancer according to claim 9, wherein the composition diagnoses prostate cancer by selectively binding the compound to PSMA (Prostate-Specific Membrane Antigen) over-expressed in prostate cancer cells.

11. A pharmaceutical composition for preventing or treating prostate cancer comprising the compound, the stereoisomer thereof, the hydrate thereof, or the pharmaceutically acceptable salt thereof of claim 1 as an active ingredient.