

CLAIMS

1. A method for producing a radioactive metal-labeled antibody, comprising a step of conducting a click reaction of a radioactive metal complex and a peptide-modified antibody which is site-specifically modified with a peptide to produce the radioactive metal-labeled antibody, wherein the click reaction is performed between a first atomic group of the radioactive metal complex and a second atomic group directly or indirectly linked to the peptide, and the second atomic group is an atomic group containing an azide group, or an atomic group containing trans-cyclooctene, wherein the peptide comprises an amino acid sequence represented by the following formula (i) and consisting of 13 to 17 amino acid residues, and has the second atomic group at the N-terminal or C-terminal of the peptide:

(Xa)-Xaa1-(Xb)-Xaa2-(Xc)-Xaa3-(Xd)... (i)

wherein Xa, Xb, Xc, and Xd are continuous X in the number of a, continuous X in the number of b, continuous X in the number of c, and continuous X in the number of d, respectively,

X is an amino acid residue having neither a thiol group nor a haloacetyl group in the side chain,

a, b, c and d are each independently an integer of not less than one and not more than 5, and satisfy $a+b+c+d \leq 14$,

Xaa1 and Xaa3 are each independently an amino acid residue derived from an amino acid having a thiol group in the side chain, and they are bonded via a disulfide bond or their sulfide groups are bonded via a linker, or

one is an amino acid residue derived from an amino acid having a thiol group in the side chain and the other is an amino acid residue derived from an amino acid having a haloacetyl group in the side chain, and they are bonded via a thioether bond, and

Xaa2 is a lysine residue, an arginine residue, a cysteine residue, an aspartic acid residue, a glutamic acid residue, a 2-aminosuberic acid, or a diamino propionic acid.

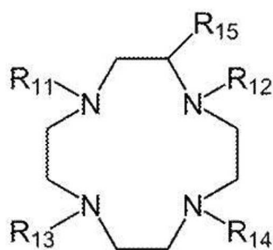
2. The method for producing a radioactive metal-labeled antibody according to claim 1, further comprising a step of reacting the ligand with the radioactive metal to form the radioactive metal complex.

3. The method for producing a radioactive metal-labeled antibody according to claim 2, wherein the ligand and the radioactive metal are reacted by heating.

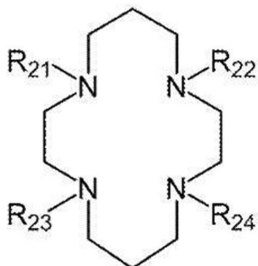
4. The method for producing a radioactive metal-labeled antibody according to claim 2 or 3, wherein the ligand comprises a chelate site coordinated to the radioactive metal, and a modified site to which the first atomic group is bonded.

5. The production method according to claim 4, wherein the chelate site is represented by any one of the following formulas (A) to (K):

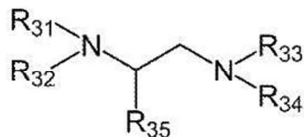
(A)



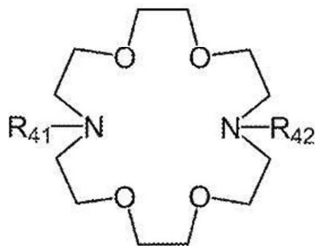
(B)



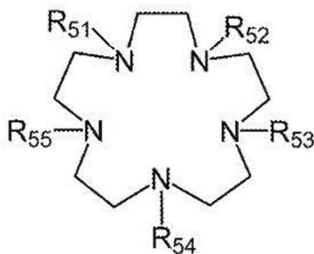
(C)



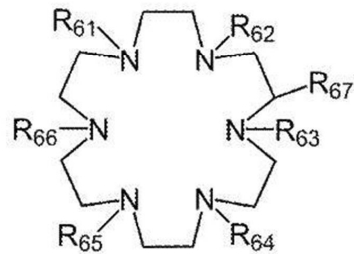
(D)

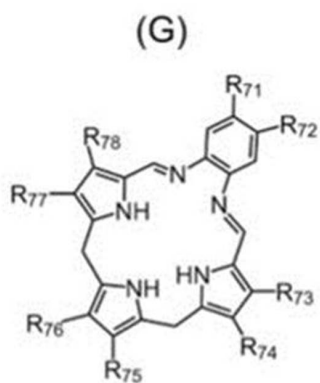
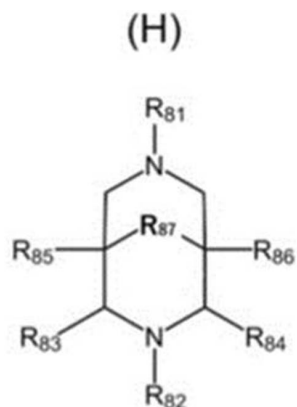
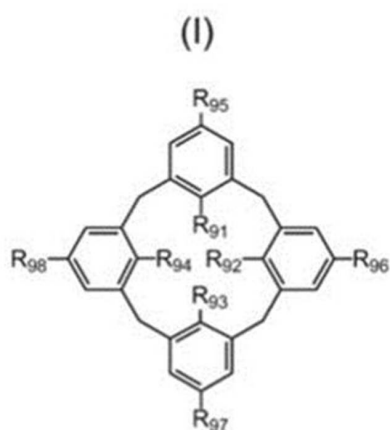
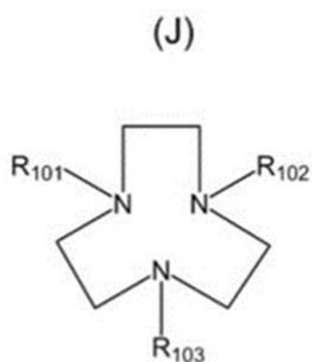
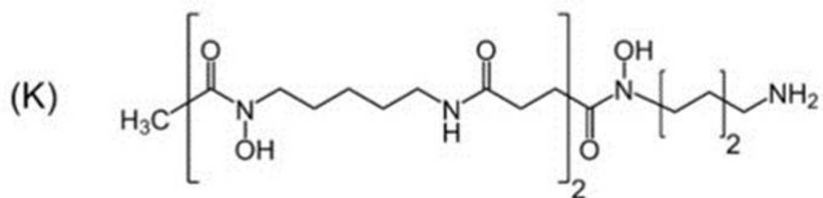


(E)



(F)





in the formula (A), R_{11} , R_{13} and R_{14} are each independently a group consisting of $-(CH_2)_pCOOH$, $-(CH_2)_pC_5H_5N$, $-(CH_2)_pPO_3H_2$, $-(CH_2)_pCONH_2$ or $-(CHCOOH)(CH_2)_pCOOH$, one of R_{12} and R_{15} is a hydrogen atom, a carboxyl group, or a carboxyalkyl group having 2 or 3 carbon atoms, the other is a group bonded to the modified site, and p is an integer of not less than 0 and not more than 3,

in the formula (B), R_{21} , R_{22} , R_{23} and R_{24} are each independently a carboxyl group or a carboxyalkyl group having a carbon number of 2 or 3, and any one group of R_{21} ,

R₂₂, R₂₃ or R₂₄ is bonded to the modified site,

in the formula (C), R₃₁, R₃₂, R₃₃ and R₃₄ are each independently a group composed of an atomic group having a hydrogen atom and not less than 2 and not more than 10 carbon atoms, and optionally containing a nitrogen atom or an oxygen atom, and R₃₅ is a group bonded to the modified site,

in the formula (D), one of R₄₁ and R₄₂ is a group composed of an atomic group having a hydrogen atom and not less than 5 and not more than 20 carbon atoms and containing one or more kinds selected from nitrogen atom, oxygen atom and sulfur atom, and the other is a group bonded to the modified site,

in the formula (E), R₅₁, R₅₂, R₅₃, R₅₄ and R₅₅ are each independently a carboxyl group, or a carboxyalkyl group having a carbon atom number of 2 or 3, and any one group of R₅₁, R₅₂, R₅₃, R₅₄ or R₅₅ is bonded to the modified site,

in the formula (F), R₆₁, R₆₂, R₆₃, R₆₄, R₆₅ and R₆₆ are each independently a carboxyl group, or carboxyalkyl group having a carbon atom number of 2 or 3, and R₆₇ is a group bonded to the modified site,

in the formula (G), R₇₁ and R₇₂ are -O(CH₂CH₂O)_nCH₃ (n is an integer of not less than 1 and not more than 5), R₇₃, R₇₅, R₇₆ and R₇₈ are each independently an alkyl group having a carbon atom number of not less than 1 and not more than 5, one of R₇₄ and R₇₇ is a hydroxyalkyl group having a carbon number of not less than 1 and not more than 5, and the other is a group bonded to the modified site,

in the formula (H), R₈₁ and R₈₂ are each independently an alkyl group having a carbon number of not less than 1 and not more than 5, a terminal of the alkyl group may be substituted by a pyridyl group substituted by one or more carboxyl groups, R₈₇ is -CHOH or -C=O, any one group of R₈₁, R₈₂ or R₈₇ is a group bonded to the modified site, R₈₃ and R₈₄ are optionally substituted pyridinyl groups, R₈₅ and R₈₆ are each independently -COOR_a, and R_a is an alkyl group having a carbon number of not less than 1 and not more than 5,

in the formula (I), R₉₁, R₉₂, R₉₃ and R₉₄ are each

independently -OCH₂COOH, any one group of R₉₁, R₉₂, R₉₃ or R₉₄ is a group bonded to the modified site, and R₉₅, R₉₆, R₉₇ and R₉₈ are each independently an alkyl group having a carbon number of not less than 1 and not more than 6, and

in the formula (J), R₁₀₁, R₁₀₂ and R₁₀₃ are each independently a carboxyl group or a carboxyalkyl group having a carbon atom number of 2 or 3, or at least one of R₁₀₁, R₁₀₂ and R₁₀₃ in the formula (J) is a group bonded to the modified site and the other group is a carboxyl group, or a carboxyalkyl group having a carbon atom number of 2 or 3.

6. The method for producing a radioactive metal-labeled antibody according to any one of claims 1 to 5, wherein the radioactive metal is ⁴⁴Sc, ⁵¹Cr, ⁵⁷Co, ⁵⁸Co, ⁶⁰Co, ⁵⁹Fe, ⁶⁷Ga, ⁶⁸Ga, ⁶⁴Cu, ⁶⁷Cu, ⁸⁹Sr, ⁸⁹Zr, ⁹⁰Y, ^{99m}Tc, ¹⁰³Ru, ¹¹¹In, ¹⁵³Sm, ¹⁶⁵Dy, ¹⁶⁶Ho, ¹⁷⁷Lu, ¹⁸⁶Re, ¹⁸⁸Re, ¹⁹⁸Au, ²⁰¹Tl, ¹⁹⁷Hg, ²⁰³Hg, ²¹²Bi, ²¹³Bi, ²¹²Pb, ²²⁷Th or ²²⁵Ac.

7. The method for producing a radioactive metal-labeled antibody according to claim 6, wherein the radioactive metal is an α ray-emitting nuclide.

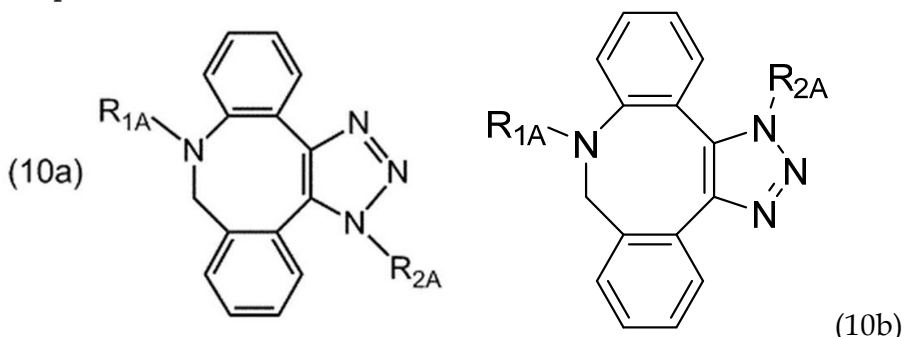
8. The method for producing a radioactive metal-labeled antibody according to any one of claims 1 to 7, wherein the click reaction is performed at 50°C or below.

9. The method for producing a radioactive metal-labeled antibody according to any one of claims 1 to 8, wherein the peptide-modified antibody is site-specifically modified with 1 molecule or 2 molecules of peptide per 1 molecule of the antibody.

10. A radioactive metal-labeled antibody site-specifically modified with a peptide, wherein

the radioactive metal complex is directly or indirectly linked to the peptide, and a triazole skeleton-containing structure represented by the following formula (10a) or (10b) is present between the peptide and the radioactive

metal complex, or a pyridazine skeleton-containing structure is present between the peptide and the radioactive metal complex:



wherein (10a) and (10b) are isomers that may be present at any ratio,

wherein R_{1A} is a binding site with a modified site or a chelate site, and R_{2A} is a binding site with a peptide, and wherein the peptide comprises an amino acid sequence represented by the following formula (i) and consisting of 13 to 17 amino acid residues, and has the second atomic group at the N-terminal or C-terminal of the peptide:

(Xa)-Xaa1-(Xb)-Xaa2-(Xc)-Xaa3-(Xd)... (i)

wherein Xa, Xb, Xc, and Xd are continuous X in the number of a, continuous X in the number of b, continuous X in the number of c, and continuous X in the number of d, respectively,

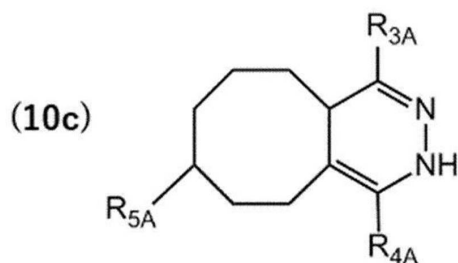
X is an amino acid residue having neither a thiol group nor a haloacetyl group in the side chain,

a, b, c and d are each independently an integer of not less than one and not more than 5, and satisfy $a+b+c+d \leq 14$,

Xaa1 and Xaa3 are each independently an amino acid residue derived from an amino acid having a thiol group in the side chain, and they are bonded via a disulfide bond, or one is an amino acid residue derived from an amino acid having a thiol group in the side chain and the other is an amino acid residue derived from an amino acid having a haloacetyl group in the side chain, and they are bonded via a thioether bond, and

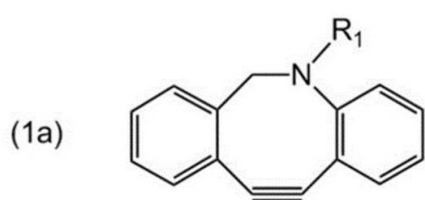
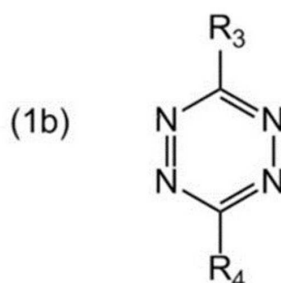
Xaa2 is a lysine residue, an arginine residue, a cysteine residue, an aspartic acid residue, a glutamic acid residue, a 2-aminosuberic acid, or a diamino propionic acid.

11. The radioactive metal-labeled antibody according to claim 10, comprising a pyridazine skeleton-containing structure represented by the following formula (10c) between the peptide and the radioactive metal complex:



wherein one of R_{3A} and R_{4A} is a hydrogen atom, a methyl group, a phenyl group or a pyridyl group, and the other is a binding site with a modified site or a chelate site, and R_{5A} is a linking site with a peptide.

12. Use of a chelate linker in the method according to any one of claims 1 to 9, wherein the chelate linker comprises a chelate site coordinated to a radioactive metal, and a modified site to which a first atomic group capable of click reaction is bonded, wherein the first atomic group is an atomic group represented by the following formula (1a) or (1b):

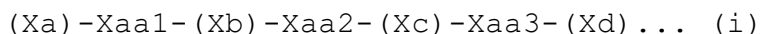


in the formula (1a), R_1 is a binding site with a modified site or a chelate site, and in the formula (1b), one of R_3 and R_4 is a binding site with a modified site or a chelate site, and the other is a hydrogen atom, a methyl group, a phenyl group or a pyridyl group.

13. Use of a peptide-modified antibody in the method

according to any one of claims 1 to 9, wherein the peptide-modified antibody is represented by the following formula (i) and site-specifically modified by a peptide comprising an amino acid sequence consisting of 13 to 17 amino acid residues, which antibody comprising

a second atomic group capable of click reaction is linked to the N-terminal or C-terminal of the peptide, wherein the second atomic group is an atomic group represented by the following formula (2a) or (2b):



wherein Xa, Xb, Xc, and Xd are continuous X in the number of a, continuous X in the number of b, continuous X in the number of c, and continuous X in the number of d, respectively,

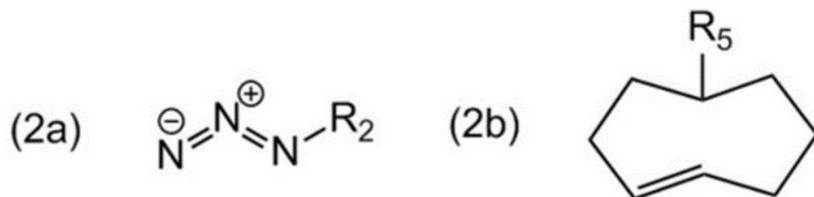
X is an amino acid residue having neither a thiol group nor a haloacetyl group in the side chain,

a, b, c and d are each independently an integer of not less than one and not more than 5, and satisfy $a+b+c+d \leq 14$,

Xaa1 and Xaa3 are each independently an amino acid residue derived from an amino acid having a thiol group in the side chain, and they are bonded via a disulfide bond or their sulfide groups are bonded via a linker, or

one is an amino acid residue derived from an amino acid having a thiol group in the side chain and the other is an amino acid residue derived from an amino acid having a haloacetyl group in the side chain, and they are bonded via a thioether bond, and

Xaa2 is a lysine residue, an arginine residue, a cysteine residue, an aspartic acid residue, a glutamic acid residue, a 2-aminosuberic acid, or a diamino propionic acid,



in the formula (2a), R_2 is a linking site with the N-terminal or C-terminal of the peptide, and in the formula (2b), R_5 is

a linking site with the N-terminal or C-terminal of the peptide.

14. The antibody according to claim 13, wherein the peptide-modified antibody is site-specifically modified with 1 molecule or 2 molecules of the peptide per 1 molecule of the antibody.