[0004] For example, an attempt at performing imaging by using a peptide ligand having an Arg-Gly-Asp (RGD) sequence is reported in Non-Patent Documents 4 and 5 and the like, and an attempt using a non-peptide low-molecular weight compound is reported in Cardiovascular Research, Vol. 78, pp. 395~403, 2008, and the like. In addition, the compound into which ^{18}F of a positron nuclide is introduced (Non-Patent Documents 6 and 7) is used to portray a human tumor (Non-Patent Documents 8 and 9)

Prior Art Documents

Patent Documents

[0005]

Patent Document 1: US6001961A

Patent Document 2: US6130231A

Patent Document 3: US2002/169200A

Patent Document 4: US2001/53853A

Patent Document 5: JP2002-532440A

Patent Document 6: WO2013/048996

Patent Document 7: WO2011/149250A

Non-Patent Documents

[0006]

Non-Patent Document 1: Nature Reviews cancer, Vol. 10, pp. 9-23, 2010

Non-Patent Document 2: Clin. Cancer Res. Vol. 12, pp. 3942-3949, 2006

Non-Patent Document 3: Circulation, Vol. 107, pp. 1046-1052, 2003

Non-Patent Document 4: Cancer Res. Vol. 61, pp. 1781-1785, 2001

Non-Patent Document 5: Cardiovascular Research, Vol. 78, pp. 395-403, 2008

Non-Patent Document 6: Clin. Cancer Res., Vol. 13, pp. 6610-6616, 2007

Non-Patent Document 7: J. Nucl. Med., Vol. 49, pp. 879-886, 2008

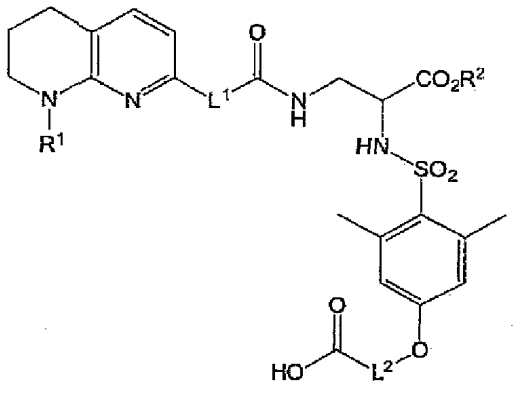
Non-Patent Document 8: Cancer Res., Vol. 62, pp. 6146-6151, 2002

Non-Patent Document 9: Int. J. Cancer., Vol. 123, pp.709-715, 2008

SUMMARY

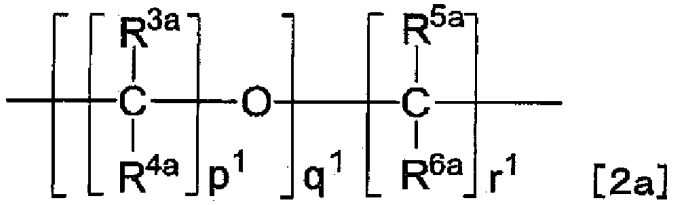
[0006a] In one aspect of the present disclosure, there is provided a method for manufacturing a compound represented by Formula [11] or a salt thereof, comprising:

(1) a step of reacting a compound represented by Formula [1] or a salt thereof



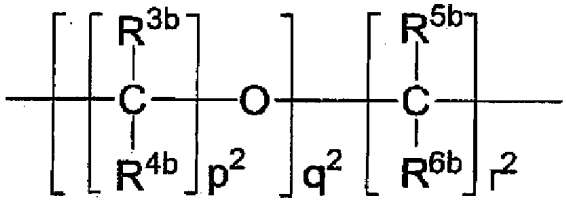
[1]

(in the formula, R^1 represents a hydrogen atom or an amino-protecting group; R^2 represents a carboxyl-protecting group; L^1 represents a group represented by Formula [2a]



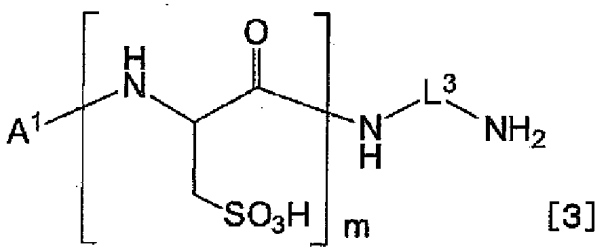
[2a]

(in the formula, R^{3a}, R^{4a}, R^{5a}, and R^{6a} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^1 represents an integer of 1 to 3; q^1 represents an integer of 0 to 3; and r^1 represents an integer of 1 to 6); and L^2 represents a group represented by Formula [2b]



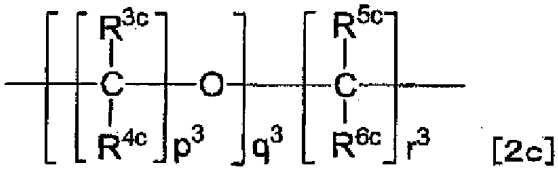
[2b]

(in the formula, R^{3b}, R^{4b}, R^{5b}, and R^{6b} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^2 represents an integer of 1 to 3, q^2 represents an integer of 0 to 3; and r^2 represents an integer of 1 to 6)) with a compound represented by Formula [3] or a salt thereof



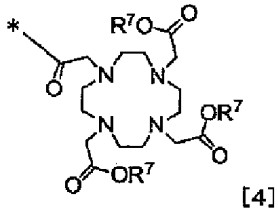
[3]

(in the formula, L^3 represents a group represented by Formula [2c]

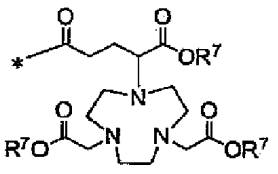


[2c]

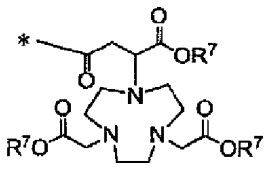
(in the formula, R^{3c}, R^{4c}, R^{5c}, and R^{6c} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^3 represents an integer of 1 to 3; q^3 represents an integer of 0 to 3; and r^3 represents an integer of 1 to 6); A^1 represents any one of the groups represented by Formulae [4] to [9]



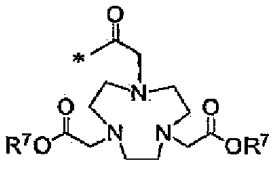
[4]



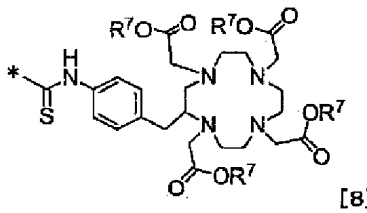
[5]



[6]



[7]



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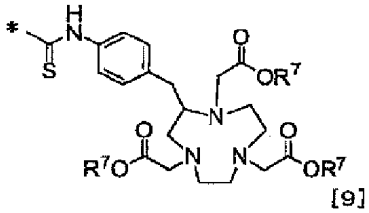
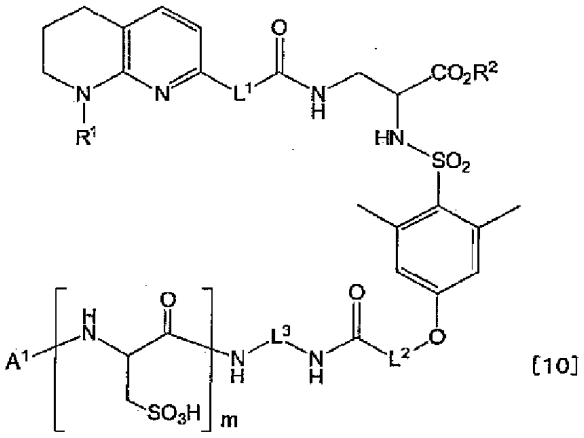


[9]

(in the formulae, * represents a binding position; and R^7's are the same as or different

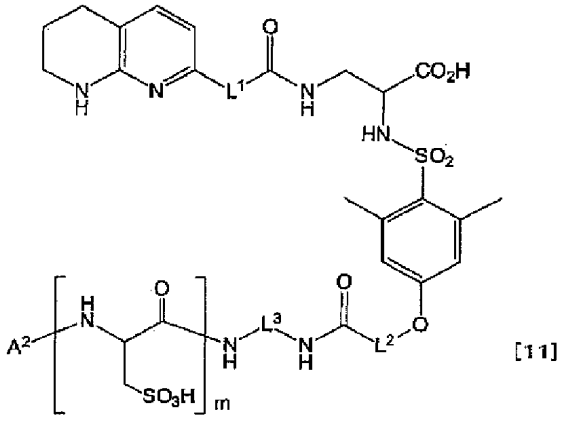
from each other and represent a carboxyl-protecting group); and m represents an integer of 1 to 3)) so as to obtain a compound represented by Formula [10] or a salt thereof;



[10]

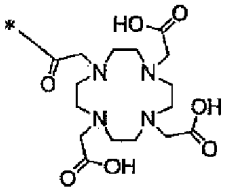
(in the formula, R^1, R^2, L^1, L^2, L^3, A^1, and m have the same definition as R^1, R^2, L^1, L^2, L^3, A^1, and m described above); and

(2) a step of deprotecting the compound represented by Formula [10] or a salt thereof,

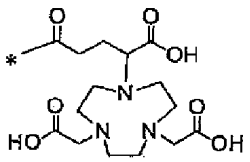


[11]

(in the formula, A^2 represents any one of the groups represented by Formulae [12] to [17]



[12]



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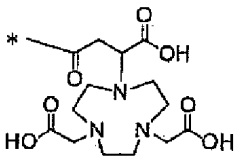

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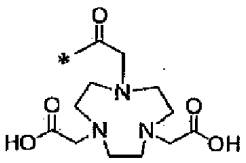

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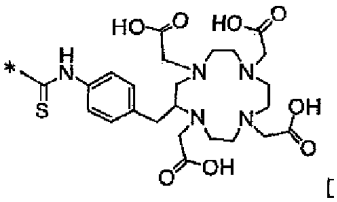

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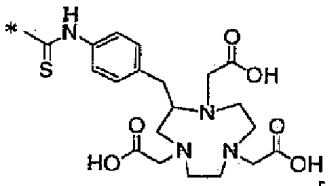


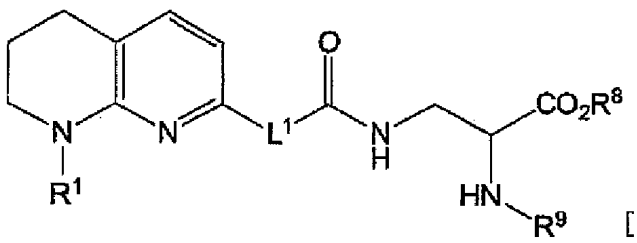
[17]

(in the formulae, * represents a binding position); and L^1, L^2, L^3, and m have the same definition as L^1, L^2, L^3, and m described above).

[0006b] In another aspect of the present disclosure, there is provided a method for manufacturing a metal complex, comprising:

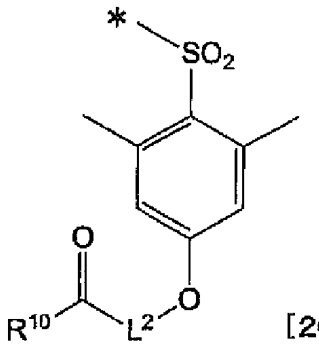
a step of reacting the compound represented by Formula [11] or a salt thereof obtained by the manufacturing method as described herein with a metal ion.

[0006c] In yet another aspect of the present disclosure, there is provided a compound represented by Formula [19] or a salt thereof



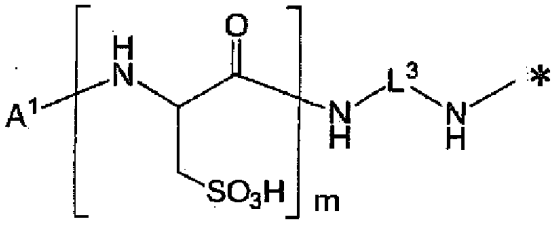
[19]

(in the formula, R^1 represents a hydrogen atom or an amino-protecting group; R^8 represents a C_{2-6} alkyl group which may be substituted or a benzyl group which may be substituted; R^9 represents a hydrogen atom, an amino-protecting group, or a group represented by Formula [20]



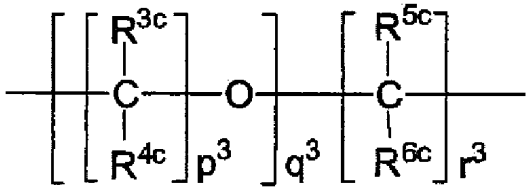
[20]

(in the formula, * represents a binding position; R^{10} represents a hydroxyl group or a group represented by Formula [21]



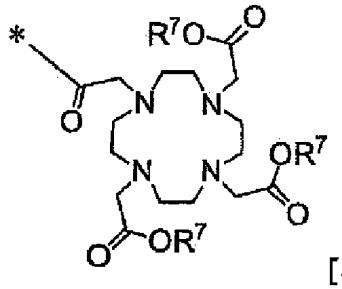
[21]

(in the formula, * represents a binding position, L^3 represents a group represented by Formula [2c]



[2c]

(in the formula, R^{3c}, R^{4c}, R^{5c}, and R^{6c} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^3 represents an integer of 1 to 3; q^3 represents an integer of 0 to 3; and r^3 represents an integer of 1 to 6); A^1 represents any one of the groups represented by Formulae [4] to [9]



[4]

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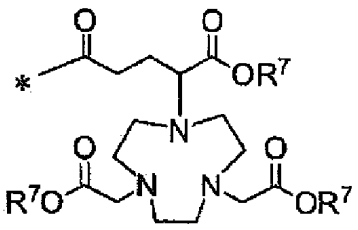

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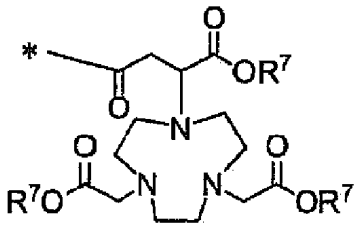

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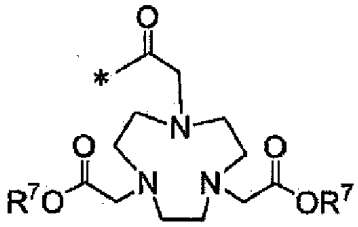

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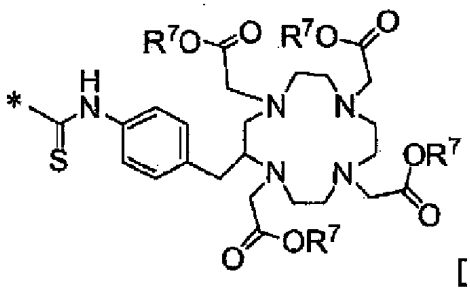

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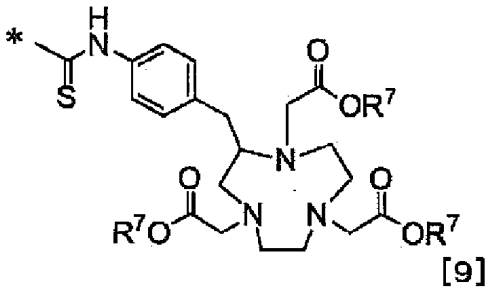
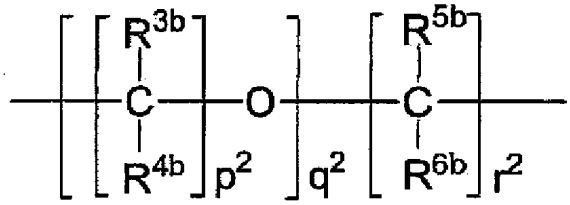


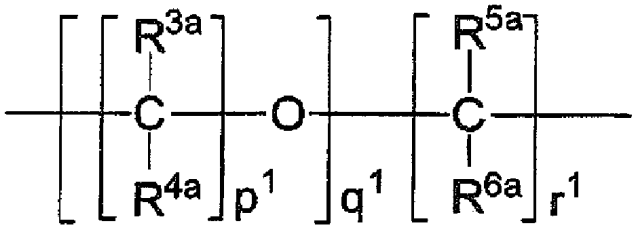
[9]

(in the formulae, * represents a binding position; and R^7 represents a carboxyl-protecting group); and m represents an integer of 1 to 3); L^2 represents a group represented by Formula [2b]



[2b]

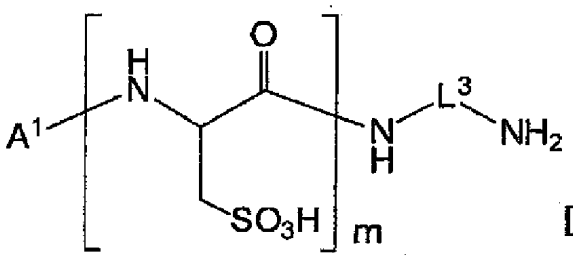
(in the formula, R^{3b}, R^{4b}, R^{5b}, and R^{6b} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^2 represents an integer of 1 to 3; q^2 represents an integer of 0 to 3; and r^2 represents an integer of 1 to 6); and L^1 represents a group represented by Formula [2a]



[2a]

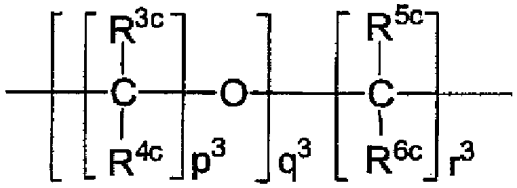
(in the formula, R^{3a}, R^{4a}, R^{5a}, and R^{6a} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^1 represents an integer of 1 to 3; q^1 represents an integer of 0 to 3; and r^1 represents an integer of 1 to 6)).

[0006d] In a further aspect of the present disclosure, there is provided a compound represented by Formula [3] or a salt thereof



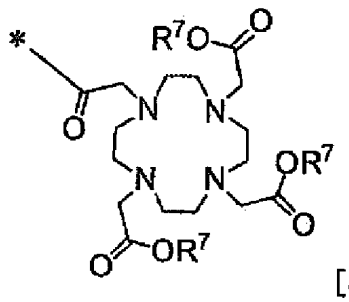
[3]

(in the formula, L^3 represents a group represented by Formula [2c]



[2c]

(in the formula, R^{3c}, R^{4c}, R^{5c}, and R^{6c} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^3 represents an integer of 1 to 3; q^3 represents an integer of 0 to 3; and r^3 represents an integer of 1 to 6); A^1 represents any one of the groups represented by Formulae [4] to [9]



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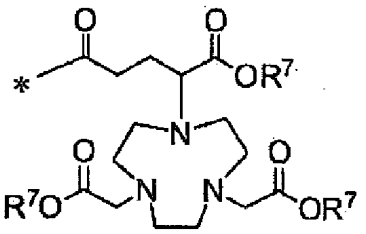

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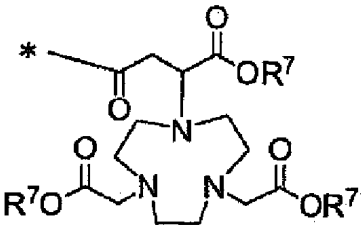

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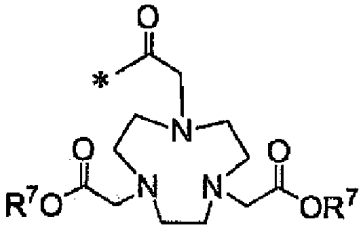

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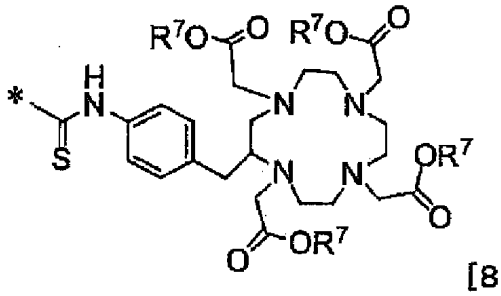

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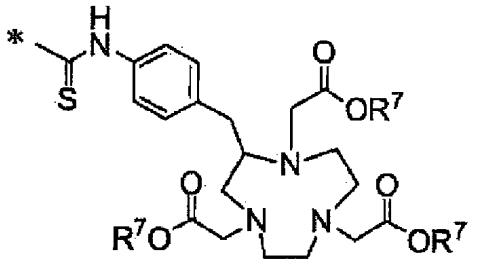
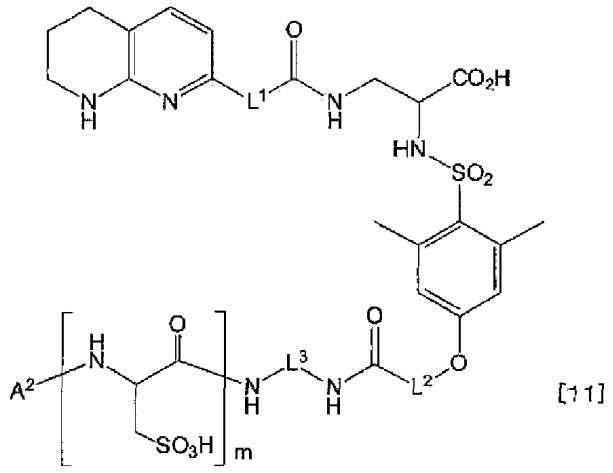


[9]

(in the formulae, * represents a binding position; and R^7 represents a carboxyl-protecting group); and m represents an integer of 1 to 3).

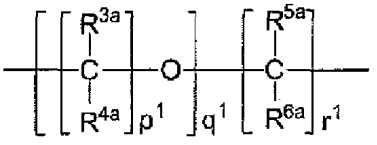
[0006e] In another aspect of the present disclosure, there is provided a compound represented by Formula [11] or a salt thereof



[11]

(in the formula,

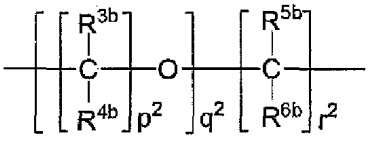
L^1 represents a group represented by Formula [2a]



[2a]

(in the formula, R^{3a}, R^{4a}, R^{5a}, and R^{6a} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^1 represents an integer of 1 to 3; q^1 represents an integer of 0 to 3; and r^1 represents an integer of 1 to 6); and

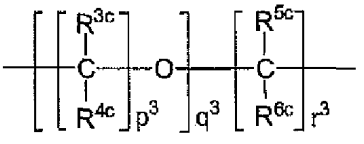
L^2 represents a group represented by Formula [2b]



[2b]

(in the formula, R^{3b}, R^{4b}, R^{5b}, and R^{6b} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^2 represents an integer of 1 to 3; q^2 represents an integer of 0 to 3; and r^2 represents an integer of 1 to 6); and

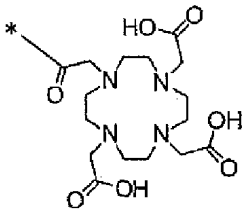
L^3 represents a group represented by Formula [2c]



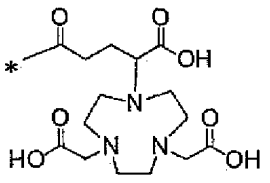
[2c]

(in the formula, R^{3c}, R^{4c}, R^{5c}, and R^{6c} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^3 represents an integer of 1 to 3; q^3 represents an integer of 0 to 3; and r^3 represents an integer of 1 to 6); and

A^2 represents any one of the groups represented by Formulae [12] to [17]



[12]



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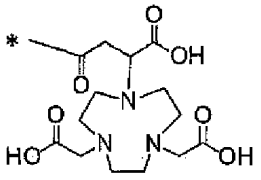

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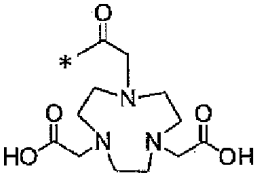
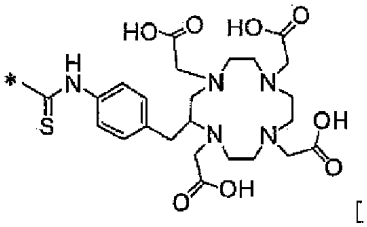
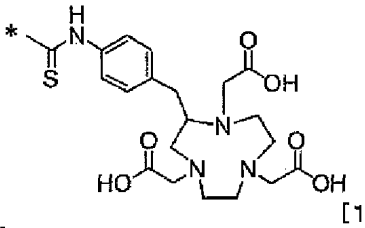


[15]



[16]

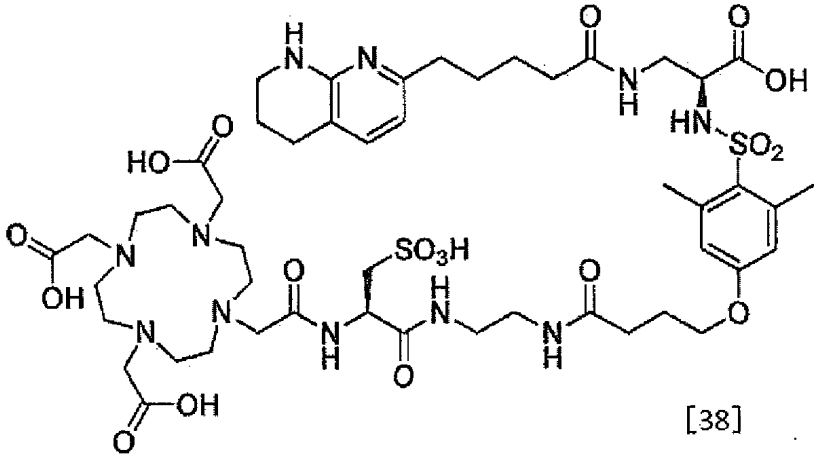


[17]

(in the formulae, * represents a binding position);

m represents an integer of 1 to 3)).

[0006f] In yet another aspect of the present disclosure, there is provided a compound represented by Formula [38] or a salt thereof.



[38]

[0006g] In another aspect of the present disclosure, there is provided the compound as described herein which is obtained by the method as described herein.

[0006h] In a further aspect of the present disclosure, there is provided a complex of the compound as described herein or the salt with a metal.

[0006i] In another aspect of the present disclosure, there is provided the complex as described herein, for use in the treatment of a disease involving an integrin.

[0006j] In yet another aspect of the present disclosure, there is provided the complex as described herein, for use in the diagnosis of a disease involving an integrin.

[0006k] In a further aspect of the present disclosure, there is provided a use of the complex as described herein in the manufacture of a medicament for the treatment of a disease involving an integrin.

[0006l] In another aspect of the present disclosure, there is provided a use of the complex as described herein in the manufacture of a medicament for the diagnosis of a disease involving an integrin.

[0007] According to the knowledge of the inventors of the present disclosure, a nitrogen-containing compound represented by the following Formula [11] is an excellent integrin-binding compound which exhibits high integrating properties and persistency with

2,2'-(7-((R)-1-carboxy-4-(((R)-1-((2-(4-(4-(N-((S)-1-carboxy-2-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamide)ethyl)sulfamoyl)-3,5-dimethylphenoxy)pentanamide)ethyl)amino)-1-oxo-3-sulfopropan-2-yl)amino)-4-oxobutyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (hereinafter, referred to as a compound B as well), and the like.

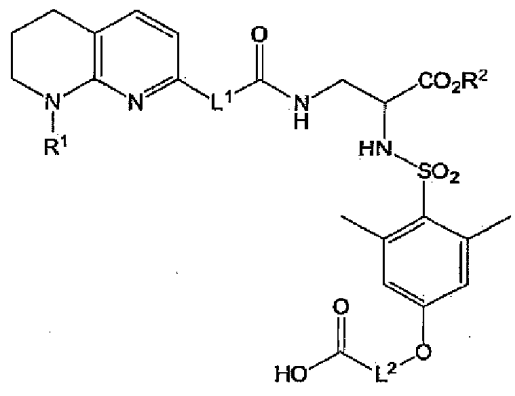
[0018] Objects of the present disclosure are to provide an efficient method for manufacturing a nitrogen-containing compound used for manufacturing a treatment agent for treating integrin-related diseases or a salt thereof and to provide a manufacturing intermediate of the compound or the salt.

[0019] In order to achieve the aforementioned objects, the inventors of the present disclosure repeated thorough research. As a result, they found that, by the following manufacturing method, a nitrogen-containing compound used for manufacturing a treatment agent for treating integrin-related diseases or a salt thereof can be efficiently manufactured. Furthermore, they found that the following manufacturing intermediate is an intermediate advantageous for efficiently manufacturing the nitrogen-containing compound used for manufacturing a treatment agent for treating integrin-relaetd diseases or a salt thereof. Based on what they found, the inventors accomplished the present disclosure.

[0020] That is, the present disclosure provides the following.

<1> A method for manufacturing a compound represented by Formula [11] or a salt thereof, comprising (1) a step of reacting a compound represented by Formula [1] or a salt thereof

[0021]



[1]

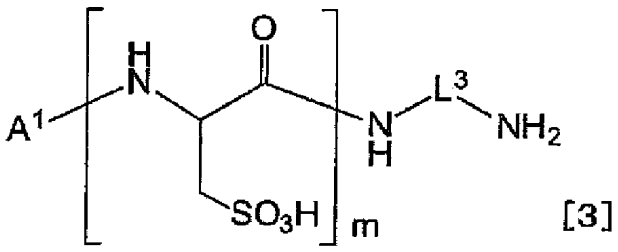
[0022] (in the formula, R^1 represents a hydrogen atom or an amino-protecting group; R^2 represents a carboxyl-protecting group; L^1 represents a group represented by Formula [2a]

[0023]

<16> The compound described in any one of <10> to <15> or a salt thereof, in which R^7 is a C_{1-6} alkyl group which may be substituted or a benzyl group which may be substituted.

<17> A compound represented by Formula [3] or a salt thereof

[0057]



[3]

[0058] (in the formula, L^3, A^1, and m have the same definition as L^3, A^1, and m described above).

<18> The compound described in <17> or a salt thereof, in which R^7 is a C_{1-6} alkyl group which may be substituted or a benzyl group which may be substituted.

[0059] According to the manufacturing method of the present disclosure, it is possible to industrially obtain a novel nitrogen-containing compound having high optical purity or a salt thereof in a simple manner through short steps.

Furthermore, the manufacturing intermediate of the present disclosure is useful as an intermediate of a novel nitrogen-containing compound or a salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0060] Fig. 1 shows results obtained by imaging an integrin expression tumor by PET using [^{64}Cu]-(compound A).

Fig. 2 shows results obtained by imaging an integrin expression tumor by PET using [^{64}Cu]-(compound B).

Fig. 3 shows results obtained by imaging an integrin expression tumor by using a gamma camera.

Fig. 4 shows results obtained by imaging an integrin expression tumor in an intracranial tumor model.

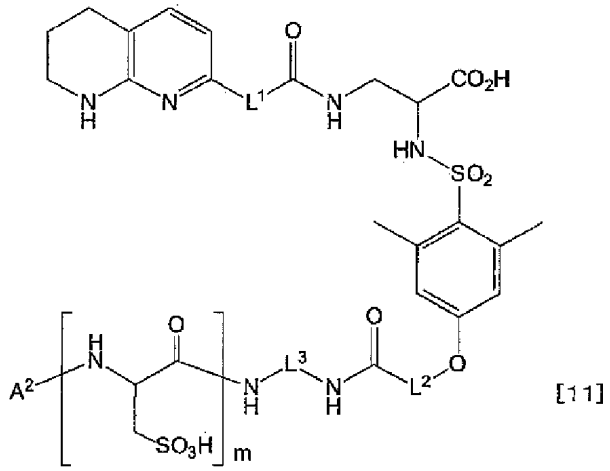
Fig. 5 shows a trend of radioactivity concentration in blood of a monkey for which [^{111}In]-(compound A) is used.

Fig. 6 shows results obtained by temporally performing planar imaging on a monkey

18. The compound according to claim 17 or a salt thereof,

wherein R^7 is a C_{1-6} alkyl group which may be substituted or a benzyl group which may be substituted.

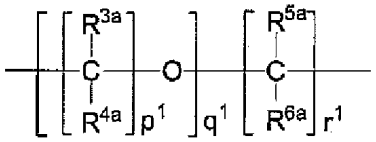
19. A compound represented by Formula [11] or a salt thereof



[11]

(in the formula,

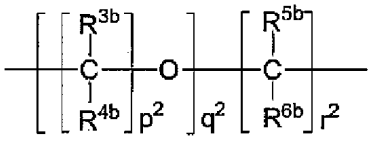
L^1 represents a group represented by Formula [2a]



[2a]

(in the formula, R^{3a}, R^{4a}, R^{5a}, and R^{6a} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^1 represents an integer of 1 to 3; q^1 represents an integer of 0 to 3; and r^1 represents an integer of 1 to 6); and

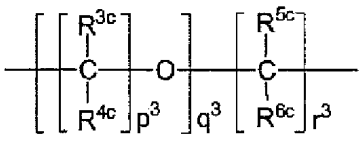
L^2 represents a group represented by Formula [2b]



[2b]

(in the formula, R^{3b}, R^{4b}, R^{5b}, and R^{6b} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^2 represents an integer of 1 to 3; q^2 represents an integer of 0 to 3; and r^2 represents an integer of 1 to 6); and

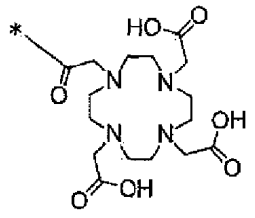
L^3 represents a group represented by Formula [2c]



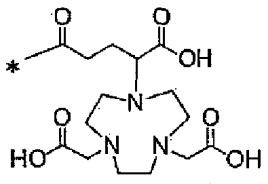
[2c]

(in the formula, R^{3c}, R^{4c}, R^{5c}, and R^{6c} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^3 represents an integer of 1 to 3; q^3 represents an integer of 0 to 3; and r^3 represents an integer of 1 to 6); and

A^2 represents any one of the groups represented by Formulae [12] to [17]



[12]



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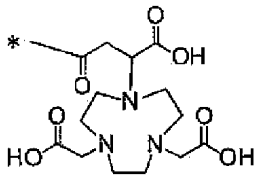

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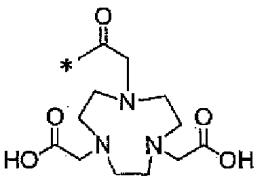

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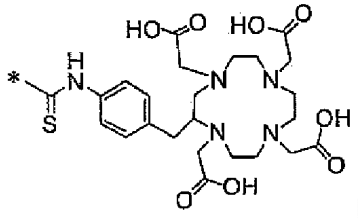
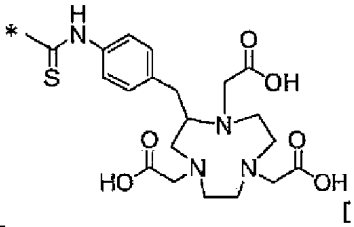


[16]



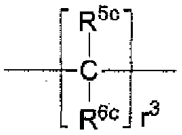
[17]

(in the formulae, * represents a binding position);

m represents an integer of 1 to 3)).

20. The compound according to claim 19 or a salt thereof,

wherein L^3 is a group represented by Formula [18c]

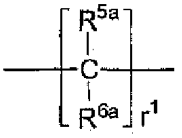


[18c]

(in the formula, R^{5c} and R^{6c} may be the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; and r^3 represents an integer of 1 to 6).

21. The compound according to claim 19 or 20 or a salt thereof,

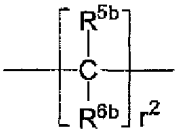
wherein L^1 is a group represented by Formula [18a]



[18a]

(in the formula, R^{5a} and R^{6a} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; and r^1 represents an integer of 1 to 6).

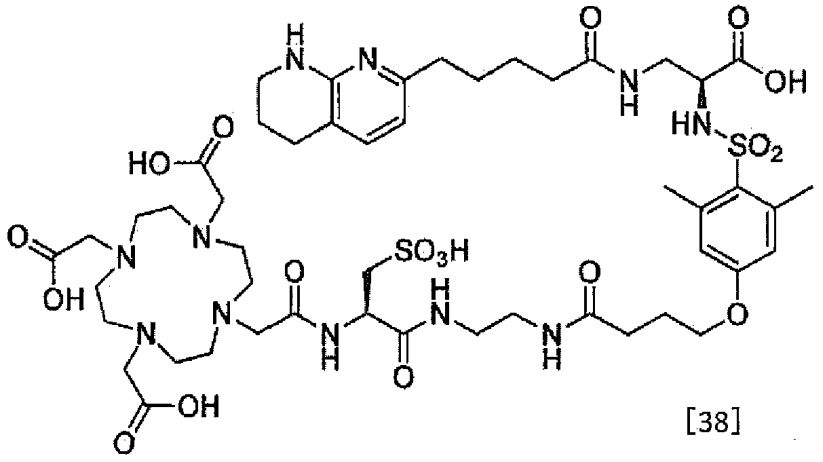
22. The compound according to any one of claims 19 to 21 or a salt thereof, wherein L^2 represents a group represented by Formula [18b]



[18b]

(in the formula, R^{5b} and R^{6b} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; and r^2 represents an integer of 1 to 6).

23. A compound represented by Formula [38] or a salt thereof.



[38]

24. The compound according to any one of claims 19 to 23 which is obtained by the method of any one of claims 1 to 8.

25. A complex of the compound according to claim 19 to 24 or the salt with a metal.

26. The complex according to claim 25, wherein the metal is a cytotoxic radioactive metal.

27. The complex according to claim 25 or 26, for use in the treatment of a disease involving an integrin.

28. The complex according to claim 25, wherein the metal is a noncytotoxic radioactive metal.

29. The complex according to claim 28, for use in the diagnosis of a disease involving an integrin.

30. The complex for use according to claim 27 or 29, wherein the disease involving an integrin is tumor.

31. Use of the complex according to claim 25 or 26 in the manufacture of a medicament for the treatment of a disease involving an integrin.

32. Use of the complex according to claim 28 in the manufacture of a medicament for the diagnosis of a disease involving an integrin.

33. The use according to claim 31 or 32, wherein the disease involving an integrin is tumor.