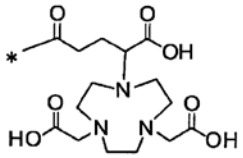
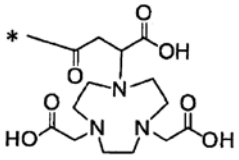
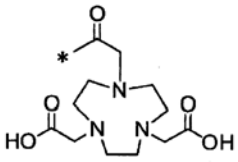
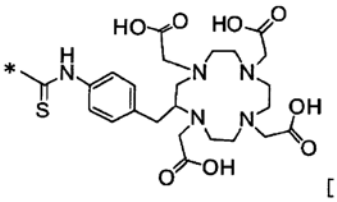
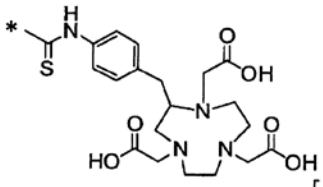

[12]


[13]


[14]


[15]


[16]

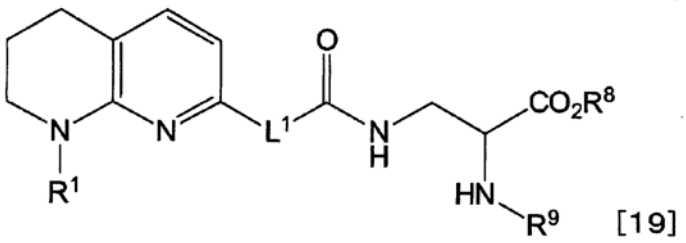

[17]

(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.

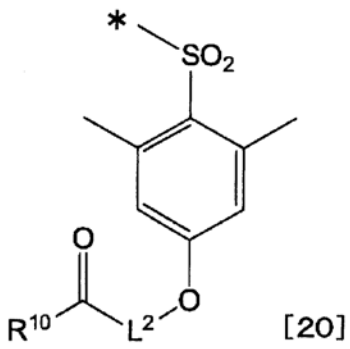
[0006c] In yet another aspect of the present disclosure, there is provided a compound represented by Formula [19] or a salt thereof


[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;

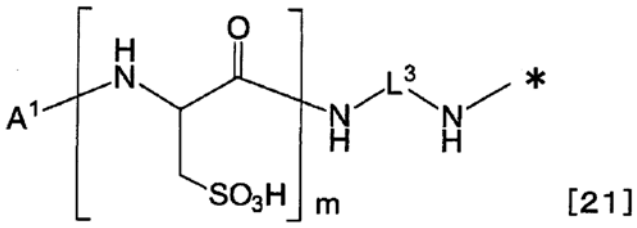
R^9 represents:

- a group represented by Formula [20]



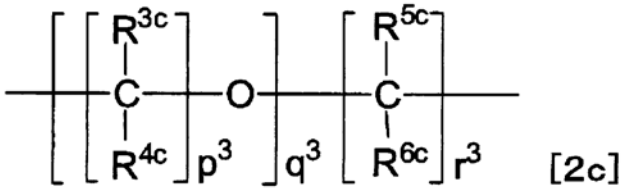
[20]

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



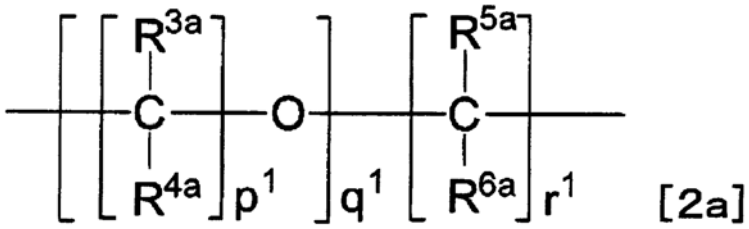
[21]

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



[2c]

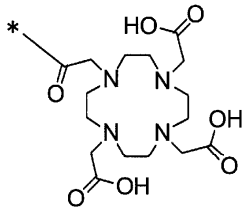
(in the formula, R^{3c}, R^{4c}, R^{5c}, and R^{6c} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^3 represents an integer of 1 to 3; q^3 represents an integer of 0 to 3; and r^3 represents an integer of 1 to 6); A^1 represents any one of the groups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



[2a]

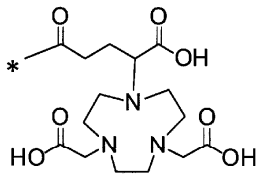
(in the formula, R^{3a}, R^{4a}, R^{5a}, and R^{6a} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^1 represents an integer of 1 to 3; q^1 represents an integer of 0 to 3; and r^1 represents an integer of 1 to 6)).

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



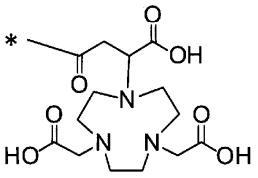
[12]

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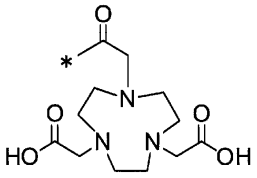
[13]

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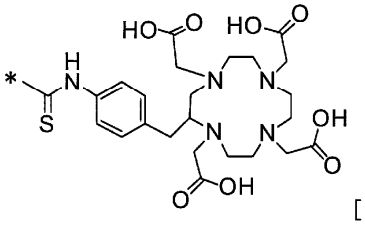
[14]

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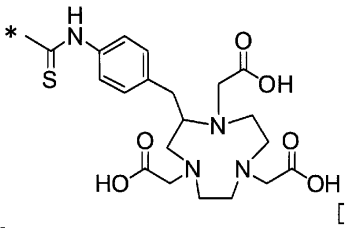
[15]

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[16]

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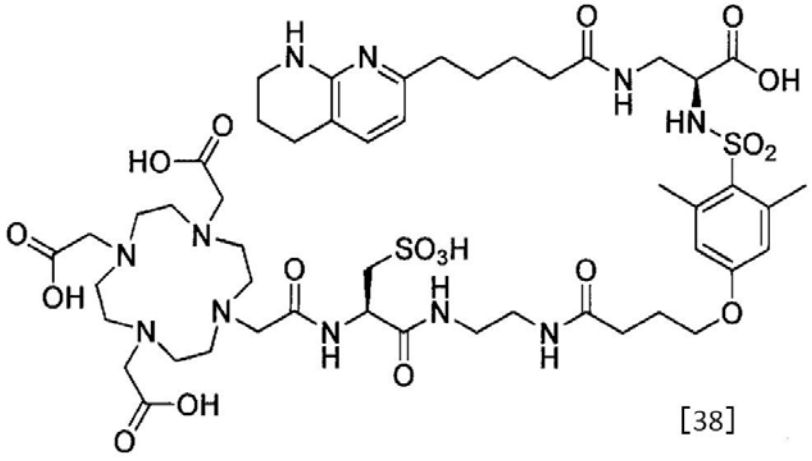


[17]

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

m represents an integer of 1 to 3)).

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



[38]

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

[0006g] 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.

[0006h] 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.

[0006i] 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.

[0006j] 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, wherein the disease involving an integrin is tumor.

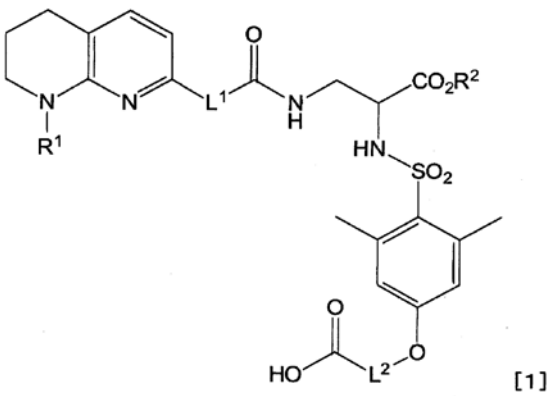
[0006k] In another aspect of the present disclosure, there is provided a use of the complex as described herein in the manufacture of a medicament for the diagnosis of a disease involving an integrin, wherein the disease involving an integrin is tumor.

[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

WHAT IS CLAIMED IS:

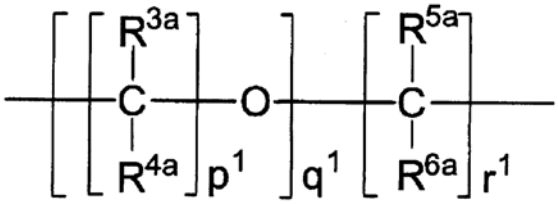
1. A method for manufacturing a compound represented by Formula [11] or a salt thereof, comprising:

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



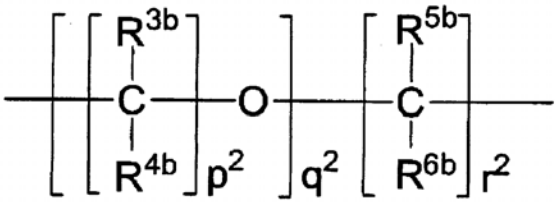
[1]

(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]

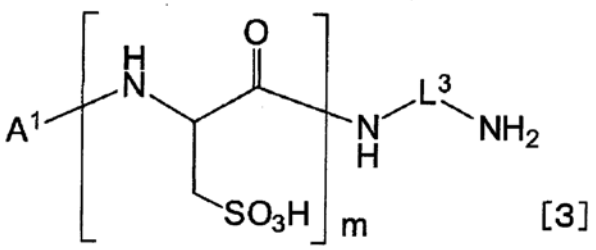
(in the formula, R^{3a}, R^{4a}, R^{5a}, and R^{6a} are the same as or different from each other and represent a hydrogen atom or a $C_{1\text{-}6}$ alkyl group; p^1 represents an integer of 1 to 3; q^1 represents an integer of 0 to 3; and r^1 represents an integer of 1 to 6); and L^2 represents a group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



[2b]

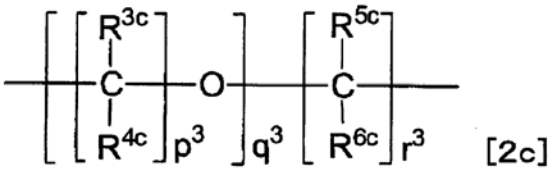
(in the formula, R^{3b}, R^{4b}, R^{5b}, and R^{6b} are the same as or different from each other and represent a hydrogen atom or a $C_{1\text{-}6}$ alkyl group; p^2 represents an integer of 1 to 3, q^2

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



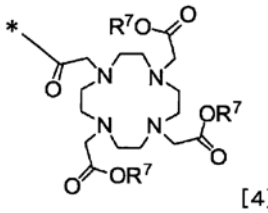
[3]

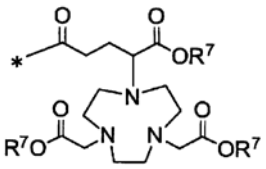
(in the formula, L^3 represents a group represented by Formula [2c]

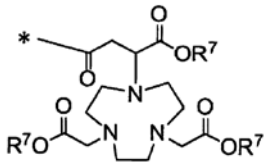


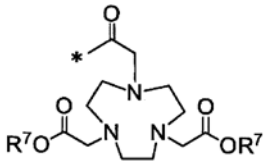
[2c]

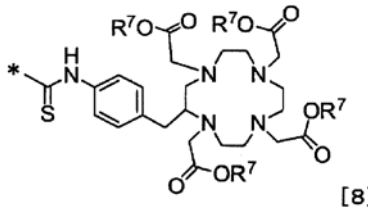
(in the formula, R^{3c}, R^{4c}, R^{5c}, and R^{6c} are the same as or different from each other and represent a hydrogen atom or a $C_{1\text{-}6}$ alkyl group; p^3 represents an integer of 1 to 3; q^3 represents an integer of 0 to 3; and r^3 represents an integer of 1 to 6); A^1 represents any one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

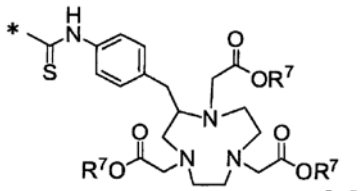

[4]


[5]

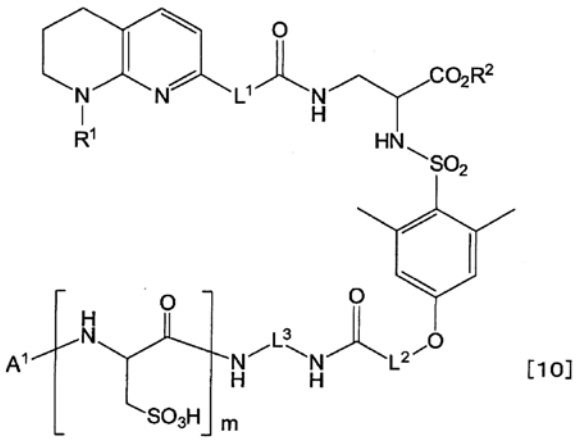

[6]


[7]


[8]

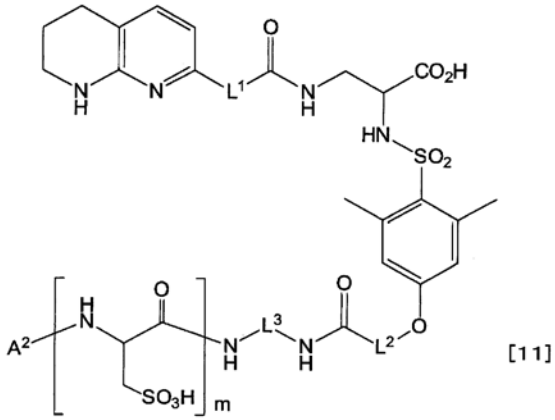

[9]

(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]

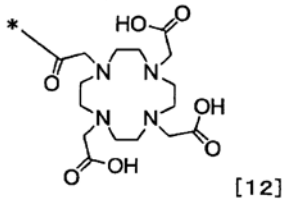
(in the formula, R^1, R^2, L^1, L^2, L^3, A^1, and m have the same definition as R^1, R^2, L^1, L^2, L^3, A^1, and m described above); and

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



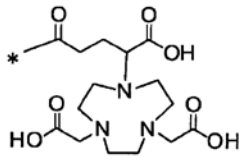
[11]

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



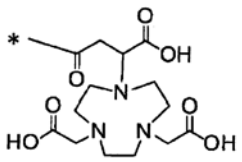
[12]

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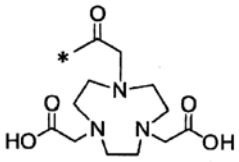
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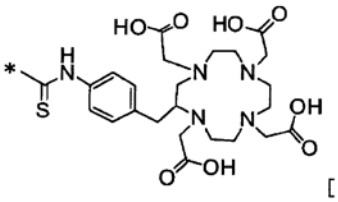
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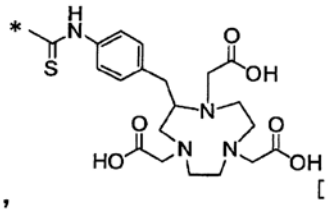
[15]

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[16]

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[17]

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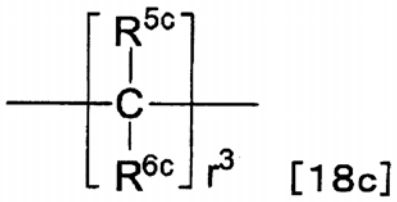
(in the formulae, ∗ represents a binding position); and L^1, L^2, L^3, and m have the same definition as L^1, L^2, L^3, and m described above).

2. The manufacturing method according to claim 1,

wherein R^2 is a $C_{1\text{-}6}$ alkyl group which may be substituted or a benzyl group which may be substituted.

3. The manufacturing method according to claim 1 or 2,

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

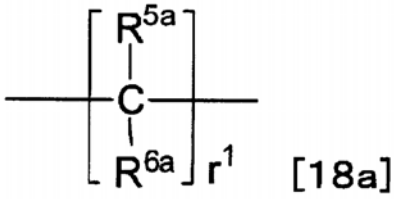


[18c]

(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).

4. The manufacturing method according to any one claims 1 to 3,

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

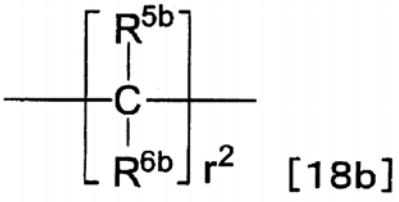


[18a]

(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).

5. The manufacturing method according to any one of claims 1 to 4,

wherein L^2 is 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).

6. The manufacturing method according to any one of claims 1 to 5,

wherein R^1 is a hydrogen atom, a C_{1-6} alkoxycarbonyl group which may be substituted, an arylsulfonyl group which may be substituted, or a heterocyclic sulfonyl group

which may be substituted.

7. The manufacturing method according to any one of claims 1 to 6,

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

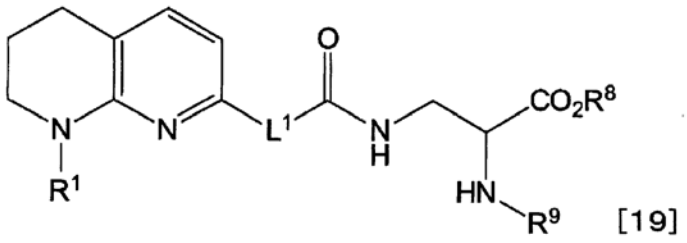
8. The manufacturing method according to any one of claims 1 to 7,

wherein the step of deprotecting is a step of deprotecting by using an acid.

9. 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 according to any one of claims 1 to 7 with a metal ion.

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

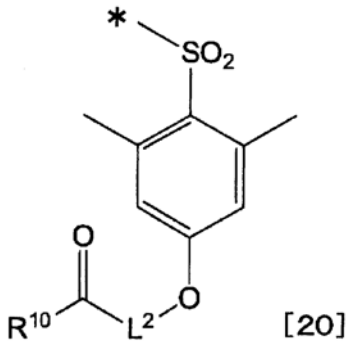


[19]

(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:

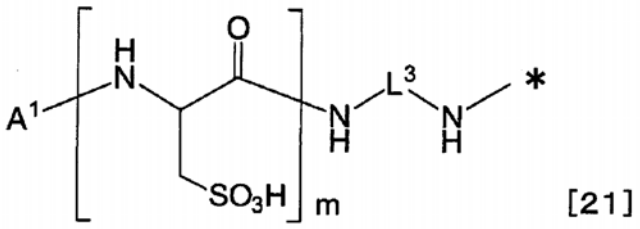
- a group represented by Formula [20]



[20]

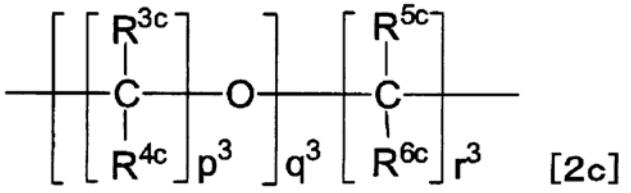
(in the formula, * represents a binding position; R^{10} represents a hydroxyl group or a

group represented by Formula [21]



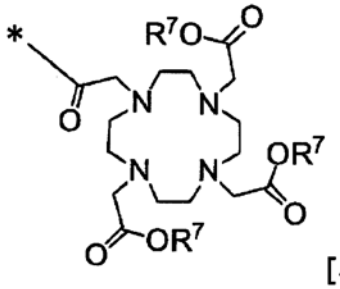
[21]

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



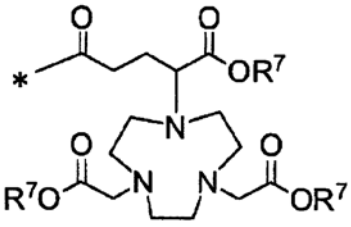
[2c]

(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]



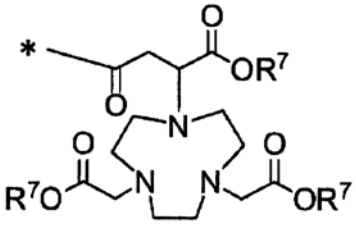
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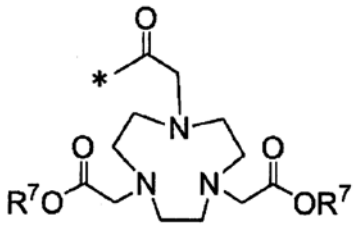
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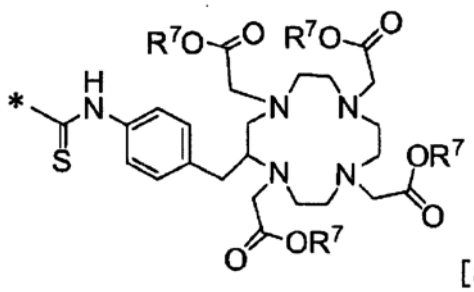
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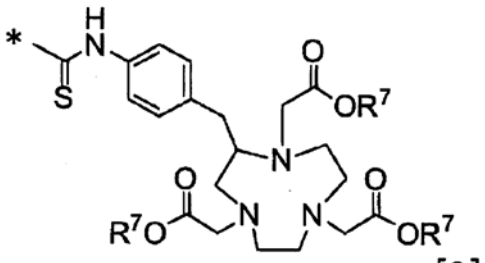
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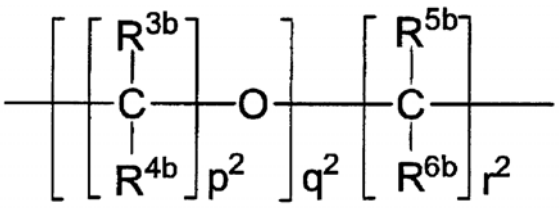
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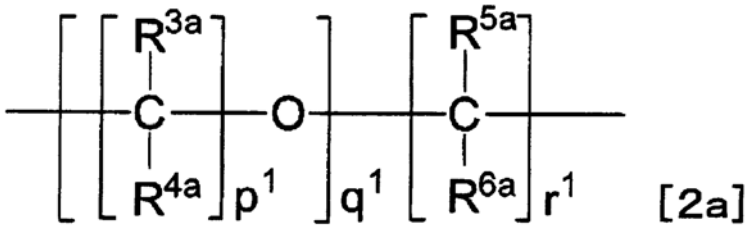
[9]

(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]

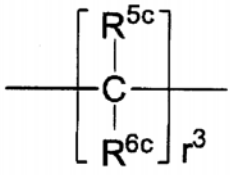


[2a]

(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 $C_{1\text{-}6}$ alkyl group; p^1 represents an integer of 1 to 3; q^1 represents an integer of 0 to 3; and r1 represents an integer of 1 to 6)).

11. The compound according to claim 10 or a salt thereof,
wherein R^8 is a $C_{2\text{-}6}$ alkyl group which may be substituted.

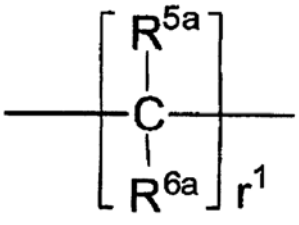
12. The compound according to claim 10 or 11 or a salt thereof,
wherein L^3 is a group represented by Formula [18c]



[18c]

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

13. The compound according to any one of claims 10 to 12 or a salt thereof,
wherein L^1 is a group represented by Formula [18a]



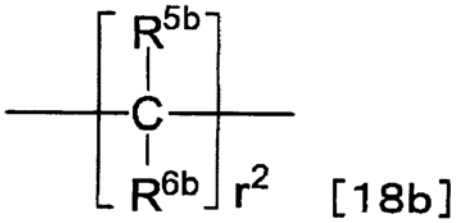
[18a]

(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).

14. The compound according to any one of claims 10 to 13 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).

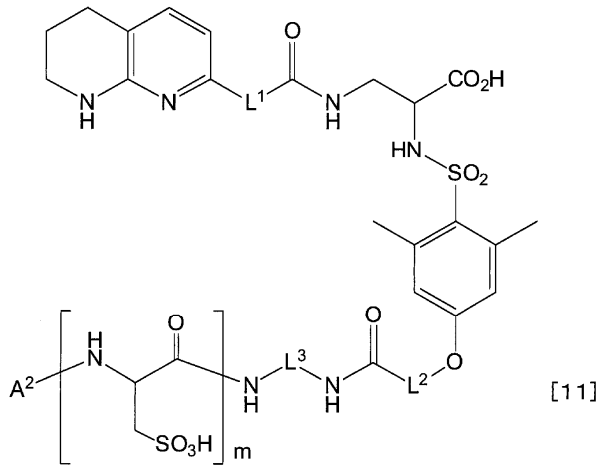
15. The compound according to any one of claims 10 to 14 or a salt thereof,

wherein R^1 is a hydrogen atom, a C_{1-6} alkoxycarbonyl group which may be substituted, an arylsulfonyl group which may be substituted, or a heterocyclic sulfonyl group which may be substituted.

16. The compound according to any one of claims 10 to 15 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.

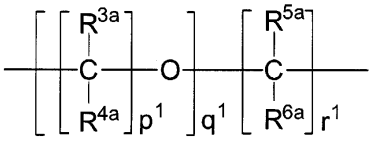
17. A compound represented by Formula [11] or a salt thereof



[11]

(in the formula,

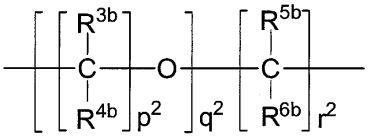
L^1 represents a group represented by Formula [2a]



[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 $C_{1\text{-}6}$ 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

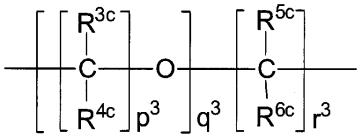
L^2 represents a group represented by Formula [2b]



[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 $C_{1\text{-}6}$ 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

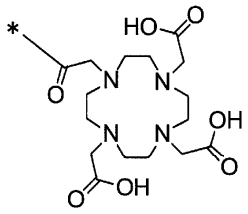
L^3 represents a group represented by Formula [2c]



[2c]

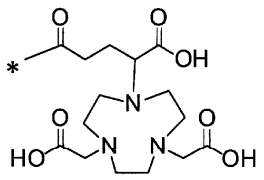
(in the formula, R^{3c}, R^{4c}, R^{5c}, and R^{6c} are the same as or different from each other and represent a hydrogen atom or a C_{1-6} alkyl group; p^3 represents an integer of 1 to 3; q^3 represents an integer of 0 to 3; and r^3 represents an integer of 1 to 6); and

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



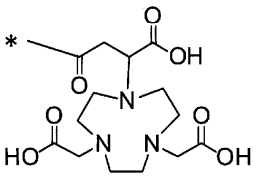
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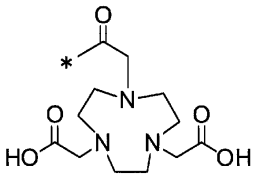
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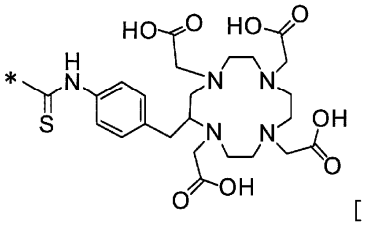
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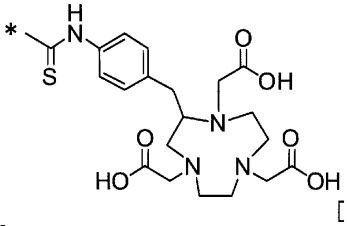
[15]

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[16]

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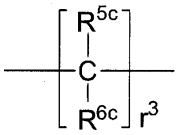
[17]

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

m represents an integer of 1 to 3)).

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

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

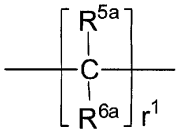


[18c]

(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).

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

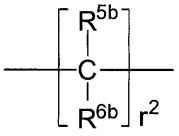
wherein L^1 is a group represented by Formula [18a]



[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).

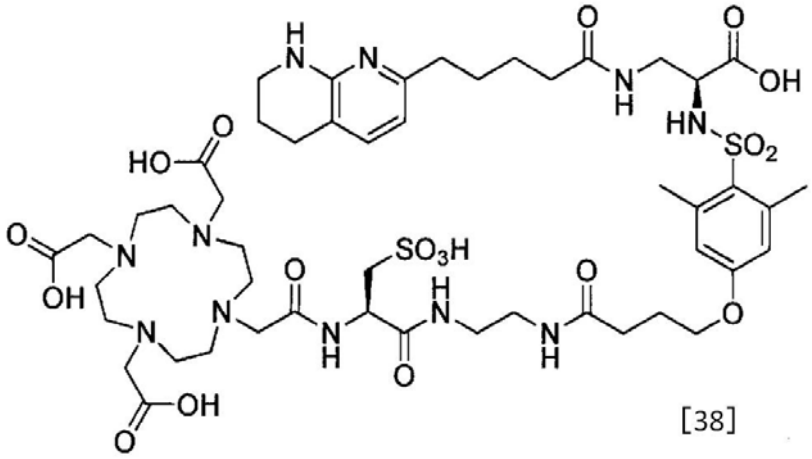
20. The compound according to any one of claims 17 to 19 or a salt thereof,
wherein L^2 represents a group represented by Formula [18b]



[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).

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



[38]

22. The compound according to any one of claims 17 to 21 which is obtained by the method of any one of claims 1 to 8.

23. A complex of the compound according to claim 17 to 22 or the salt with a metal.

24. The complex according to claim 23, wherein the metal is a cytotoxic radioactive metal.

25. The complex according to claim 23 or 24, for use in the treatment of a disease involving an integrin.

26. The complex according to claim 23, wherein the metal is a noncytotoxic radioactive metal.

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

28. The complex for use according to claim 25 or 27, wherein the disease involving an integrin is tumor.

29. Use of the complex according to claim 23 or 24 in the manufacture of a medicament for the treatment of a disease involving an integrin, wherein the disease involving an integrin is tumor.

30. Use of the complex according to claim 26 in the manufacture of a medicament for the diagnosis of a disease involving an integrin, wherein the disease involving an integrin is tumor.

31. The complex according to claim 24 or 25, wherein the cytotoxic radioactive metal is α-ray-emitting nuclide or β-ray-emitting nuclide.

32. The complex according to any one claims 24, 25 and 31, wherein the cytotoxic radioactive metal is a metal selected from the group consisting of 90Y, 114mIn, 117mSn, 186Re, 188Re, 64Cu, 67Cu, 59Fe, 89Sr, 198Au, 203Hg, 212Pb, 165Dy, 103Ru, 149Tb, 161Tb, 212Bi, 166Ho, 165Er, 153Sm, 177Lu, 213Bi, 223Ra, 225Ac, and 227Th.

33. The complex according to any one of claims 24, 25, 31 and 32, wherein the cytotoxic radioactive metal is a metal selected from the group consisting of 64Cu, 67Cu, 90Y, 166Ho, 153Sm, 177Lu, 212Pb, and 225Ac.

34. The complex according to any one of claims 24, 25 and 31 to 33, wherein the cytotoxic radioactive metal is 177Lu.

35. The complex according to claim 26 or 27, wherein the noncytotoxic radioactive metal is a gamma ray-emitting nuclide or a positron-emitting nuclide.

36. The complex according to any one of claims 26, 27 and 35, wherein the noncytotoxic radioactive metal is a metal selected from the group consisting of an 18F aluminum complex, 18F gallium complex, 18F indium complex, 18F lutetium complex, 18F thallium complex, 99mTc, 111In, 113mIn, 114mIn, 67Ga, 68Ga, 82Rb, 86Y, 87Y, 152Tb, 155Tb, 201Tl, 51Cr, 52Fe, 57Co, 58Co, 60Co, 82Sr, 85Sr, 197Hg, 44Sc, 62Cu, 64Cu, and 89Zr.

37. The complex according to any one of claims 26, 27, 35 and 36, wherein the noncytotoxic radioactive metal is a metal selected from the group consisting of an 18F aluminum complex, 111In, 64Cu, 67Ga, 68Ga, and 89Zr.

38. The complex according to any one of claims 26, 27, 25 to 37, wherein the noncytotoxic radioactive metal is 68Ga.