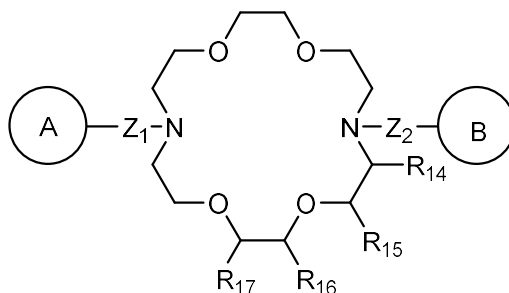


CLAIMS

We claim:

1. A chelator of formula (I):



(I)

wherein:

each of ring A and ring B is independently a 6-10 membered aryl or a 5-10 membered heteroaryl, wherein each of ring A and ring B is optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, OR₁₃, SR₁₃, (CH₂)_pCOOR₁₃, OC(O)R₁₃, N(R₁₃)₂, CON(R₁₃)₂, NO₂, CN, OC(O)N(R₁₃)₂, and X;

each of Z₁ and Z₂ is independently (C(R₁₂)₂)_m or (CH₂)_n-C(R₁₂)(X)-(CH₂)_n;

each X is independently L₁-R₁₁;

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L₁ is absent or a linker;

R₁₁ is a nucleophilic moiety or an electrophilic moiety, or R₁₁ comprises a targeting ligand;

each R₁₂ is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

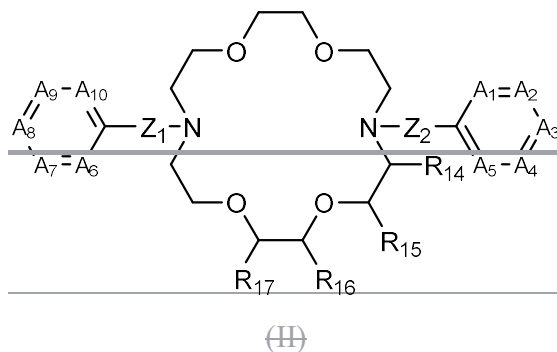
each R₁₃ is independently hydrogen or alkyl;

each of R₁₄, R₁₅, R₁₆, and R₁₇ is independently hydrogen, alkyl, or X,

or alternatively R₁₄ and R₁₅ and/or R₁₆ and R₁₇ are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X;

provided that the chelator comprises at least one X, and when X is present on ring A or ring B, L₁ is a linker or at least one of R₁₂ and R₁₄-R₁₇ is not hydrogen.

2. The chelator of claim 1, being a chelator of formula (II):



wherein:

— A₁ is N or CR₁ or is absent;

— A₂ is N or CR₂;

— A₃ is N or CR₃;

— A₄ is N or CR₄;

— A₅ is N or CR₅;

— A₆ is N or CR₆ or is absent;

— A₇ is N or CR₇;

— A₈ is N or CR₈;

— A₉ is N or CR₉;

— A₁₀ is N or CR₁₀;

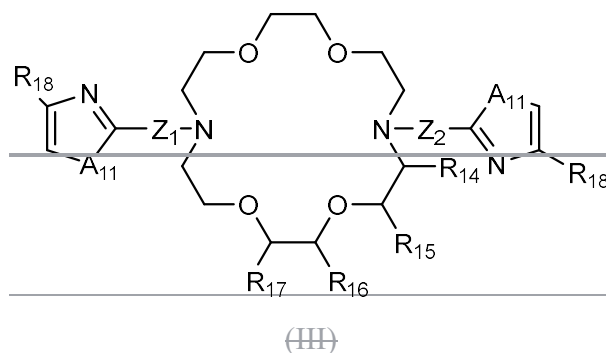
provided that no more than three of A₁, A₂, A₃, A₄, and A₅ are N, and no more than three of A₆, A₇, A₈, A₉, and A₁₀ are N;

each of R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, and R₁₀ is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, —OR₁₃, —SR₁₃, —(CH₂)_pCOOR₁₃, —OC(O)R₁₃, —N(R₁₃)₂, —CON(R₁₃)₂, —NO₂, —CN, —OC(O)N(R₁₃)₂, and —X,

or, alternatively, any two directly adjacent R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, and R₁₀ are taken together with the atoms to which they are attached to form a five or six-membered substituted or unsubstituted carbocyclic or nitrogen-containing ring;

each of Z_1 and Z_2 is independently $-(C(R_{12})_2)_m-$ or $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;
 — each X is independently $-L_1-R_{11}$;
 — each n is independently 0, 1, 2, 3, 4, or 5;
 — each m is independently 1, 2, 3, 4, or 5;
 — each p is independently 0 or 1;
 — L_1 is absent or a linker;
 — R_{11} is a nucleophilic moiety or an electrophilic moiety, or R_{11} comprises a targeting ligand;
 — each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;
 — each R_{13} is independently hydrogen or alkyl;
 each of R_{14} , R_{15} , R_{16} , and R_{17} is independently hydrogen, alkyl, or X ,
 or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X ;
 provided that the chelator comprises at least one X , and when any one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} is X , then L_1 is a linker or at least one of R_{12} and R_{14} - R_{17} is not hydrogen.

3. The chelator of claim 1, being a chelator of formula (III):

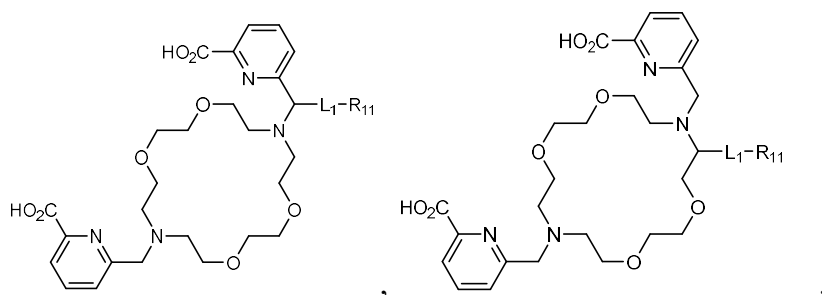


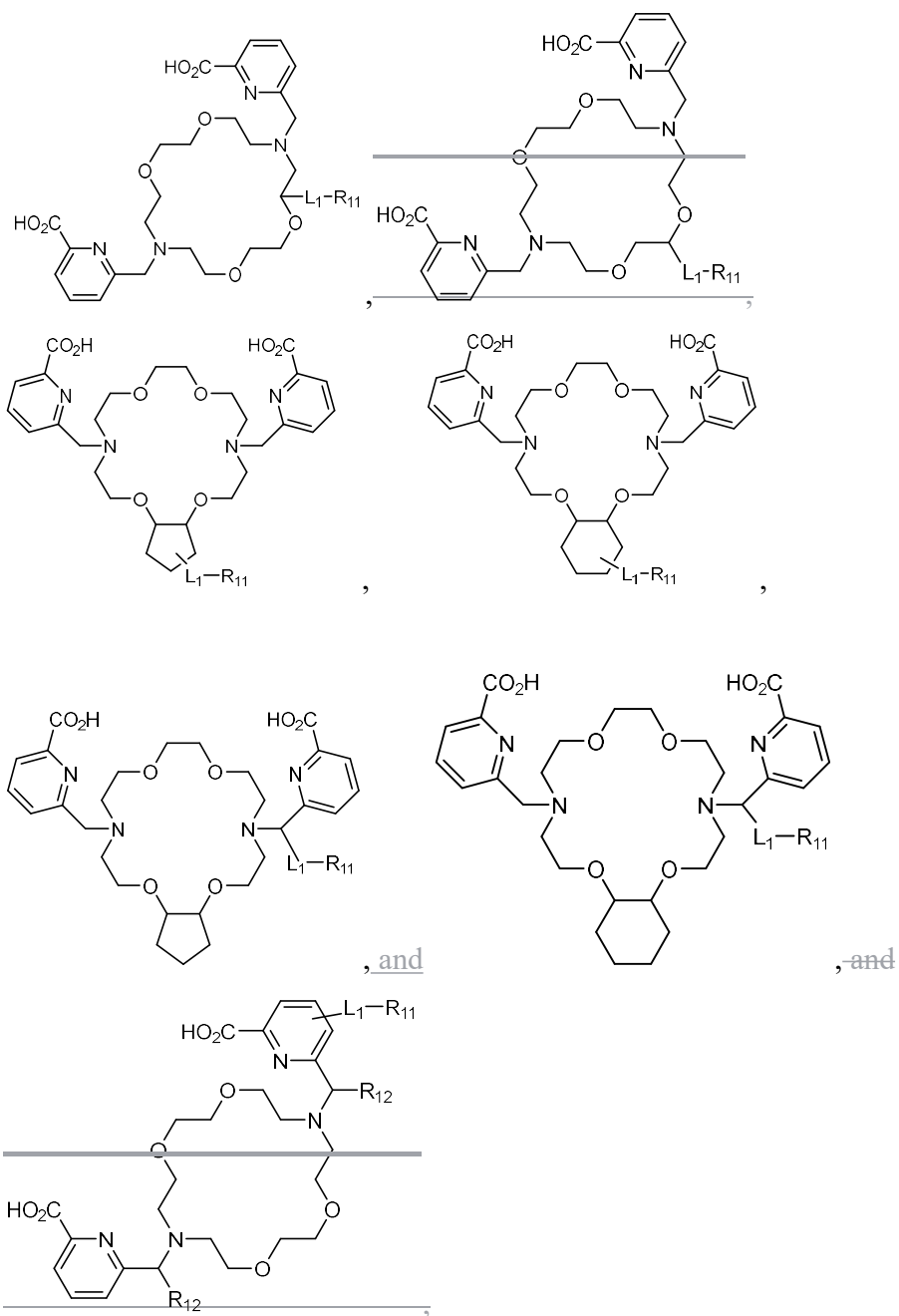
wherein:

— each A_{11} is independently O, S, NMe, or NH;
 each of Z_1 and Z_2 is independently $-(C(R_{12})_2)_m-$ or $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;
 — each X is independently $-L_1-R_{11}$;

- each n is independently 0, 1, 2, 3, 4, or 5;
- each m is independently 1, 2, 3, 4, or 5;
- each p is independently 0 or 1;
- L_1 is absent or a linker;
- R_{11} is a nucleophilic moiety or an electrophilic moiety, or R_{11} comprises a targeting ligand;
- each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;
- each R_{13} is independently hydrogen or alkyl;
- each of R_{14} , R_{15} , R_{16} , and R_{17} is independently hydrogen, alkyl, or X ,
or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X ;
- each R_{18} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, $-CN$, $-OC(O)N(R_{13})_2$, and $-X$,
provided that the chelator comprises at least one X , and when R_{18} is X , then L_1 is a linker or at least one of R_{12} and R_{14} - R_{17} is not hydrogen.

4.1. The Δ chelator of claim 1, wherein the chelator is selected from the group consisting of:





wherein:

L₁ is absent or a linker;

R₁₁ is a nucleophilic moiety or an electrophilic moiety, or R₁₁ comprises a targeting ligand;

10 each R₁₂ is independently hydrogen, -CH₃, or -CH₂CH₃, provided at least one R₁₂ is -CH₃ or -CH₂CH₃.

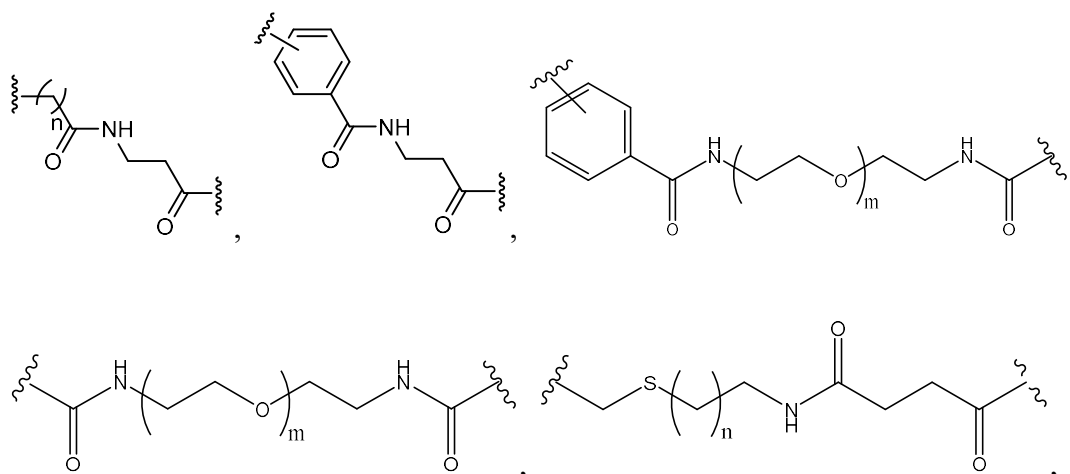
5.2. The chelator of ~~any one of claims 1 to claim 41~~, wherein R_{11} is $-NH_2$, $-NCS$, $-NCO$, $-N_3$, alkynyl, cycloalkynyl, $-C(O)R_{13}$, $-COOR_{13}$, $-CON(R_{13})_2$, maleimido, acyl halide, tetrazine, or trans-cyclooctene.

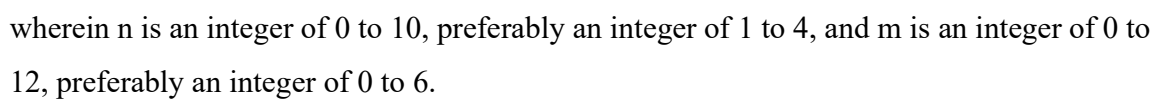
6.3. The chelator of claim 52, wherein R_{11} is ~~cyclooctynyl or a cyclooctynyl derivative~~ selected from the group consisting of bicyclononynyl (BCN), difluorinated cyclooctynyl (DIFO), dibenzocyclooctynyl (DIBO), keto-DIBO, biarylazacyclooctynonyl (BARAC), dibenzozacyclooctynyl (DIBAC, DBCO, ADIBO), dimethoxyazacyclooctynyl (DIMAC), difluorobenzocyclooctynyl (DIFBO), monobenzocyclooctynyl (MOBO), and tetramethoxy dibenzocyclooctynyl (TMDIBO).

7.4. The chelator of claim 63, wherein R_{11} is DBCO or BCN.

8.5. The chelator of ~~any one of claims 1 to claim 41~~, wherein R_{11} comprises ~~a targeting ligand, wherein the targeting ligand comprises~~ an antibody or antigen binding fragment thereof, scaffold protein, small molecule, or aptamer.

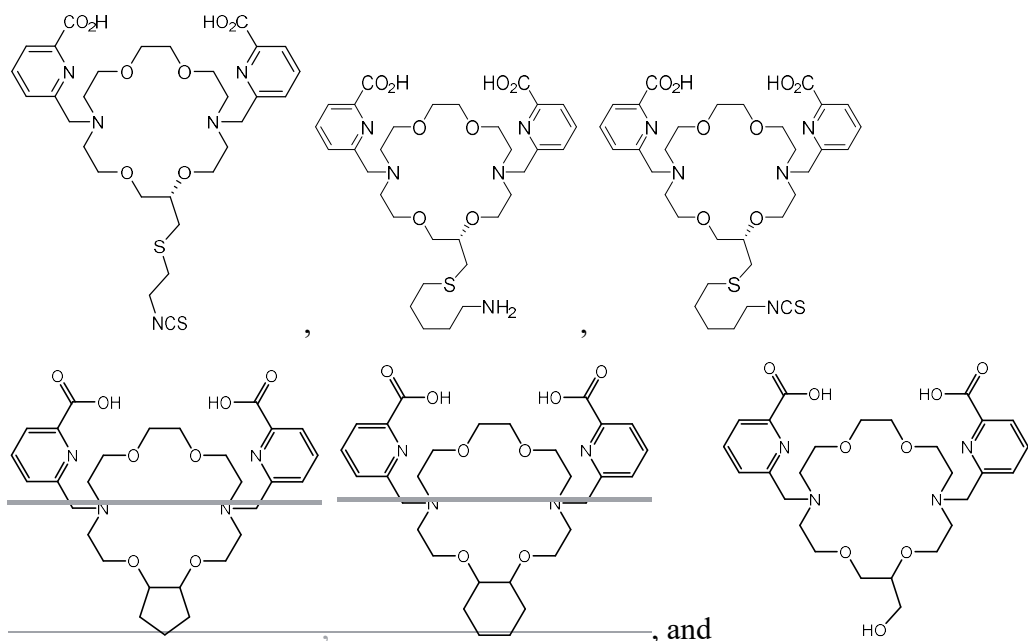
9.6. The chelator of any one of claims ~~14-81-5~~, wherein ~~L1-L1~~ is selected from the group consisting of:





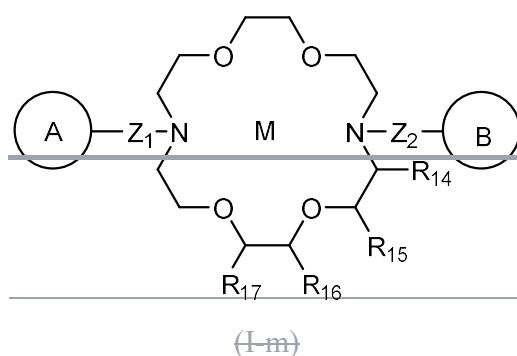
~~10.7.~~ A chelator selected from the group consisting of:





11.8. The chelator of any one of claims 141 to 147, wherein the chelator further comprises a radiometal ion bound to the chelator via coordinate bonding thereby forming a radiometal complex.

12. A radiometal complex comprising a chelator bound to an alpha-emitting radiometal ion via coordinate bonding, wherein the radiometal complex has the structure of formula (I-m):

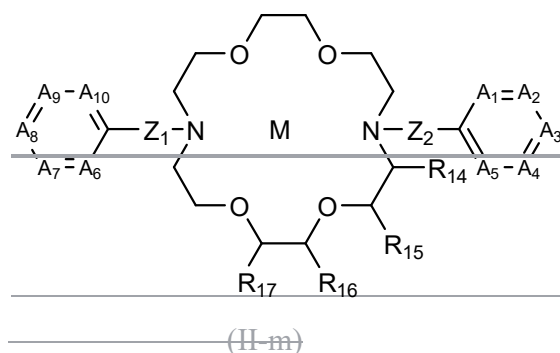


wherein:

M is a radiometal ion, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

~~each of ring A and ring B is independently a 6-10 membered aryl or a 5-10 membered heteroaryl, wherein each of ring A and ring B is optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, —OR₁₃, —SR₁₃, —(CH₂)_pCOOR₁₃, —OC(O)R₁₃, —N(R₁₃)₂, —CON(R₁₃)₂, —NO₂, —CN, —OC(O)N(R₁₃)₂, and X; each of Z₁ and Z₂ is independently —(C(R₁₂)₂)_m or —(CH₂)_n—C(R₁₂)(X)—(CH₂)_n;~~
~~each X is independently —L₁—R₁₁;~~
~~each n is independently 0, 1, 2, 3, 4, or 5;~~
~~each m is independently 1, 2, 3, 4, or 5;~~
~~each p is independently 0 or 1;~~
~~L₁ is absent or a linker;~~
~~R₁₁ is a nucleophilic moiety or an electrophilic moiety, or R₁₁ comprises a targeting ligand;~~
~~each R₁₂ is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;~~
~~each R₁₃ is independently hydrogen or alkyl;~~
~~each of R₁₄, R₁₅, R₁₆, and R₁₇ is independently hydrogen, alkyl, or X, or alternatively R₁₄ and R₁₅ and/or R₁₆ and R₁₇ are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X;~~
~~provided that the radiometal complex comprises at least one X, and when X is present on ring A or ring B, L₁ is a linker or at least one of R₁₂ and R₁₄—R₁₇ is not hydrogen.~~

13. The radiometal complex of claim 12, being a radiometal complex of formula (H-m):



wherein:

— M is a radiometal ion, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

— A₁ is N or CR₁ or is absent;

— A₂ is N or CR₂;

— A₃ is N or CR₃;

— A₄ is N or CR₄;

— A₅ is N or CR₅;

— A₆ is N or CR₆ or is absent;

— A₇ is N or CR₇;

— A₈ is N or CR₈;

— A₉ is N or CR₉;

— A₁₀ is N or CR₁₀;

provided that no more than three of A₁, A₂, A₃, A₄, and A₅ are N, and no more than three of A₆, A₇, A₈, A₉, and A₁₀ are N;

each of R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, and R₁₀ is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, OR₁₃, SR₁₃, (CH₂)_pCOOR₁₃, OC(O)R₁₃, N(R₁₃)₂, CON(R₁₃)₂, NO₂, CN, OC(O)N(R₁₃)₂, and X;

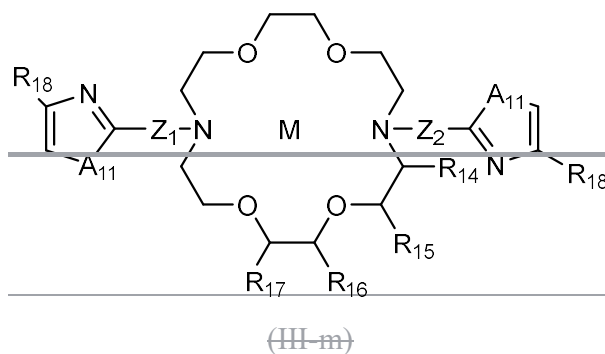
or, alternatively, any two directly adjacent R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, and R₁₀ are taken together with the atoms to which they are attached to form a five or six-membered substituted or unsubstituted carbocyclic or nitrogen-containing ring;

each of Z₁ and Z₂ is independently —(C(R₁₂)₂)_m— or —(CH₂)_n—C(R₁₂)(X)—(CH₂)_n—;

— each X is independently —L₁—R₁₄;

- each n is independently 0, 1, 2, 3, 4, or 5;
- each m is independently 1, 2, 3, 4, or 5;
- each p is independently 0 or 1;
- L_4 is absent or a linker;
- R_{11} is a nucleophilic moiety or an electrophilic moiety, or R_{11} comprises a targeting ligand;
- each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;
- each R_{13} is independently hydrogen or alkyl;
- each of R_{14} , R_{15} , R_{16} , and R_{17} is independently hydrogen, alkyl, or X ,
or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X ;
- provided that the radiometal complex comprises at least one X , and when any one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} is X , then L_4 is a linker or at least one of R_{12} and R_{14} - R_{17} is not hydrogen.

14. The radiometal complex of claim 12, being a radiometal complex of formula (III-m):

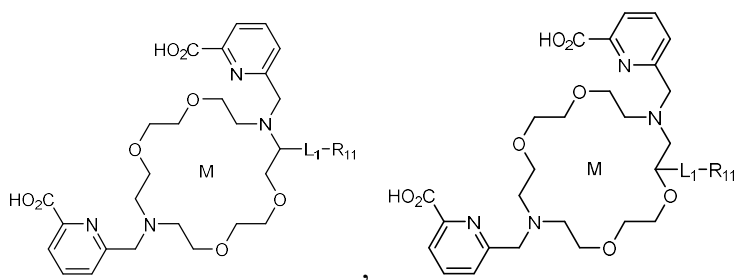


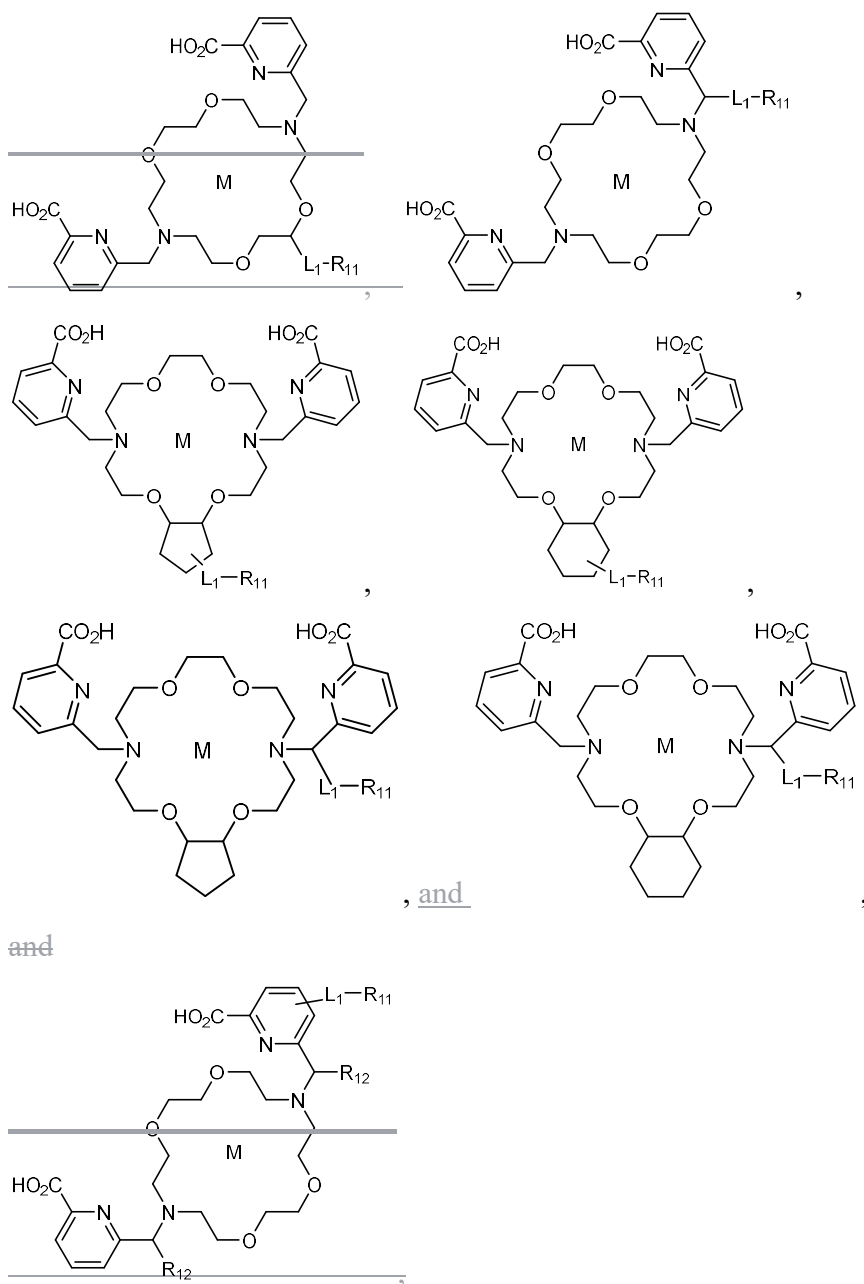
wherein:

- M is a radiometal ion, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);
- each A_{11} is independently O, S, NMe, or NH;
- each of Z_1 and Z_2 is independently $-(C(R_{12})_2)_m$ or $-(CH_2)_n-C(R_{12})(X)-(CH_2)_n$;

- each X is independently L_1-R_{11} ;
- each n is independently 0, 1, 2, 3, 4, or 5;
- each m is independently 1, 2, 3, 4, or 5;
- each p is independently 0 or 1;
- L_1 is absent or a linker;
- R_{11} is a nucleophilic moiety or an electrophilic moiety, or R_{11} comprises a targeting ligand;
- each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;
- each R_{13} is independently hydrogen or alkyl;
- each of R_{14} , R_{15} , R_{16} , and R_{17} is independently hydrogen, alkyl, or X, or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X; and
- each R_{18} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, $-CN$, $-OC(O)N(R_{13})_2$, and X, provided that the radiometal complex comprises at least one X, and when R_{18} is X, then L_1 is a linker or at least one of R_{12} and R_{14} - R_{17} is not hydrogen.

15.9. The A radiometal complex of any one of claims 12-14, wherein the radiometal complex is selected from the group consisting of:





wherein:

M is actinium-225 (^{225}Ac), L_1 is absent or a linker; and

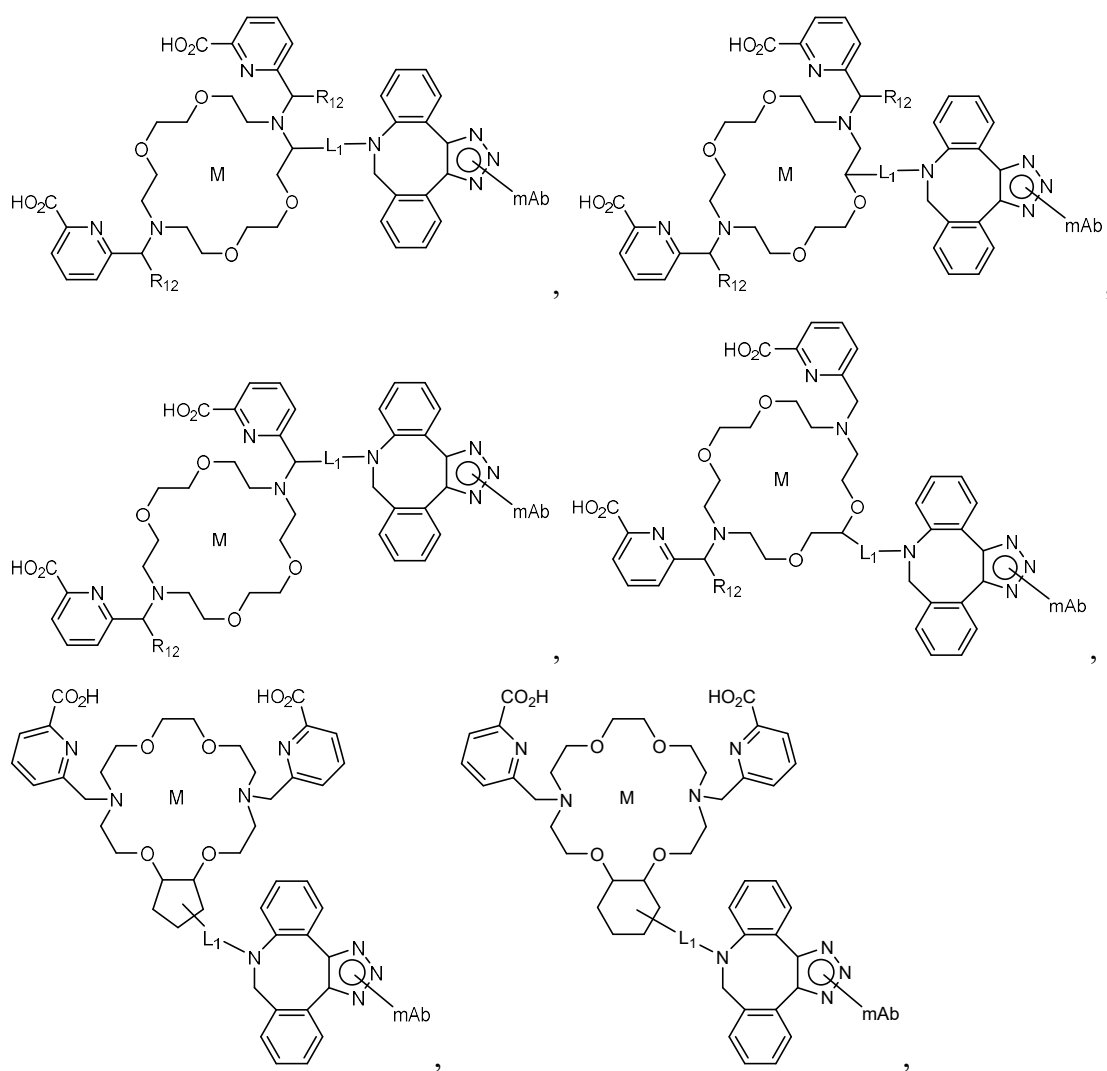
R_{11} is a nucleophilic moiety or an electrophilic moiety, or R_{11} comprises a targeting ligand; and

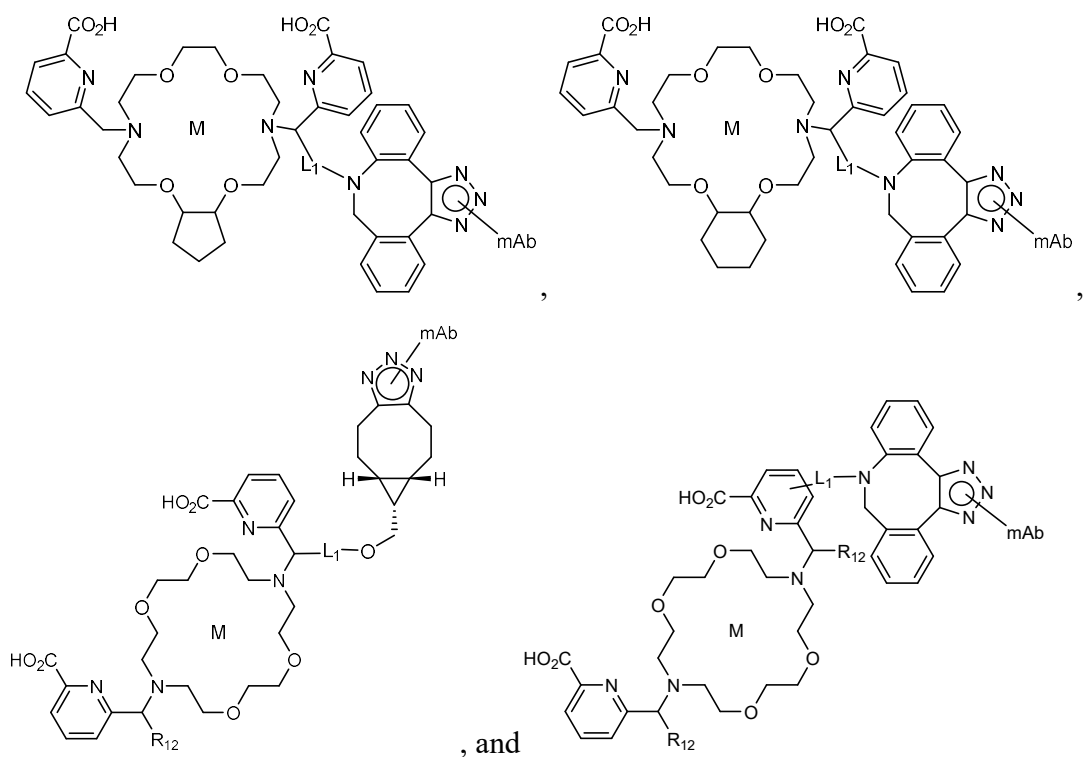
each R_{12} is independently hydrogen, $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$, provided at least one R_{12} is $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$.

~~16.10.~~ A radioimmunoconjugate comprising the radiometal complex of ~~any one of~~
~~claims 12 to claim 15-9~~ conjugated to an antibody or antigen binding fragment thereof.

~~17.11.~~ The radioimmunoconjugate of claim ~~16~~10, wherein the antibody or antigen
 binding fragment thereof is linked to R₁₁ of the radiocomplex via a triazole moiety.

~~18.12.~~ A radioimmunoconjugate having a structure selected from the group consisting
 of:





wherein:

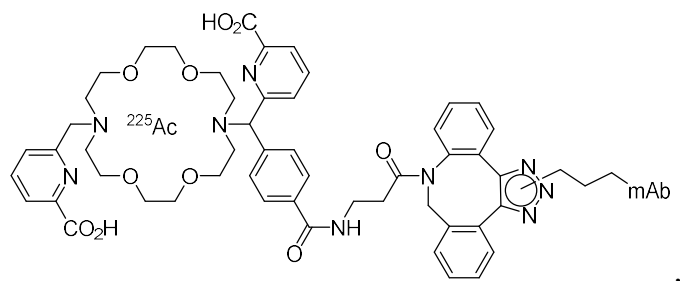
M is a radiometal ion, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

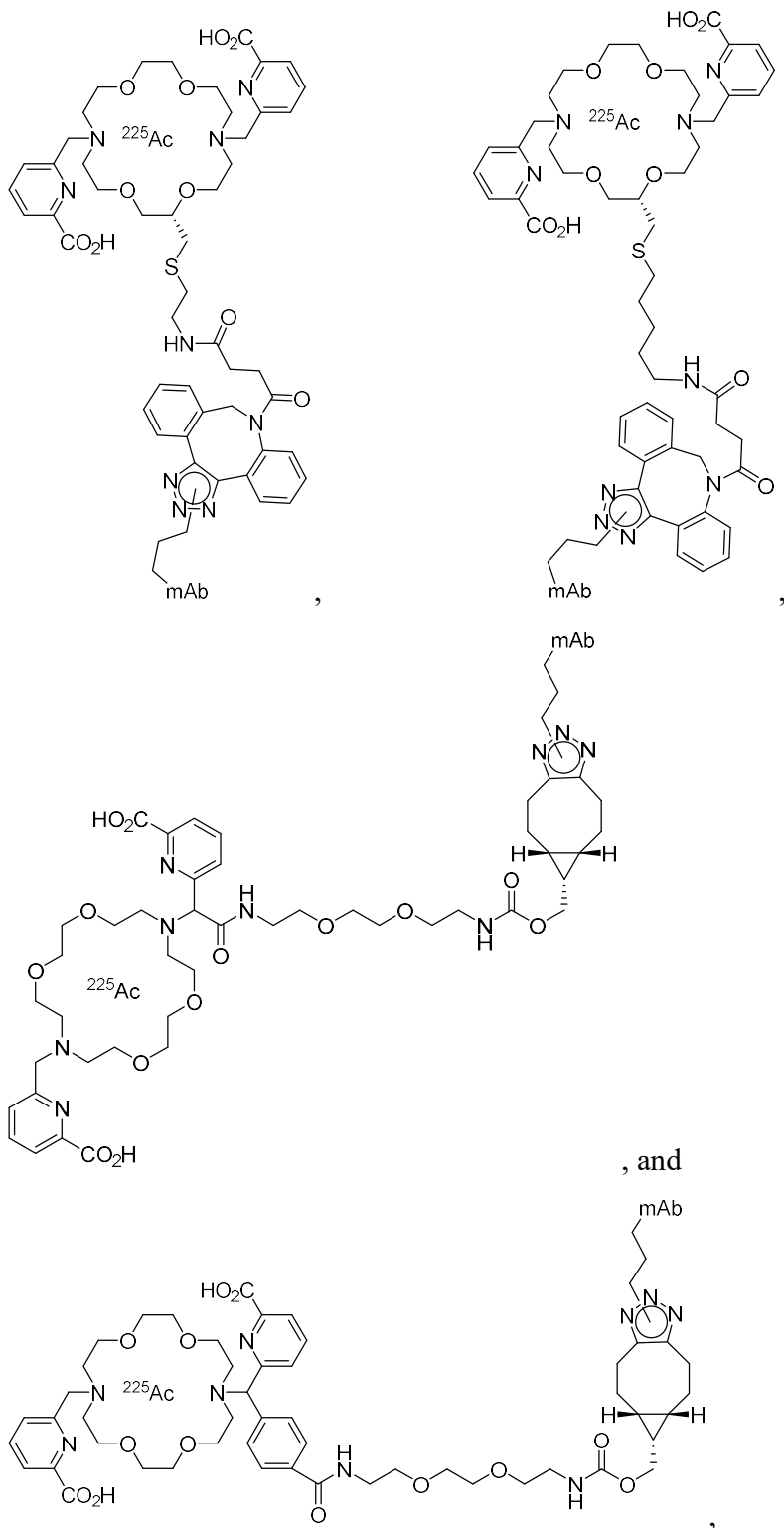
L_1 is a linker;

mAb is an antibody or antigen binding fragment thereof;

each R_{12} is independently hydrogen, $-\text{CH}_3$, or $-\text{CH}_2\text{CH}_3$, provided at least one R_{12} is $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$.

19.13. The radioimmunoconjugate of claim 18, wherein the radioimmunoconjugate is selected from the group consisting of:





wherein mAb is an antibody or antigen binding fragment thereof, preferably, the antibody or antigen binding fragment thereof that binds specifically to a tumor antigen, more

preferably, the mAb is selected from PSMB127, Pertuzumab, Cetuximab, Panitumumab, Herceptin, and H11B6.

20.14. A method of preparing a radioimmunoconjugate, the method comprising:

contacting the chelator of claim 8 with a radiometal ion, thereby forming a radiometal complex bound to the targeting ligand.

21.15. The method of claim 20.14, wherein the targeting ligand is an antibody or antigen binding fragment thereof.

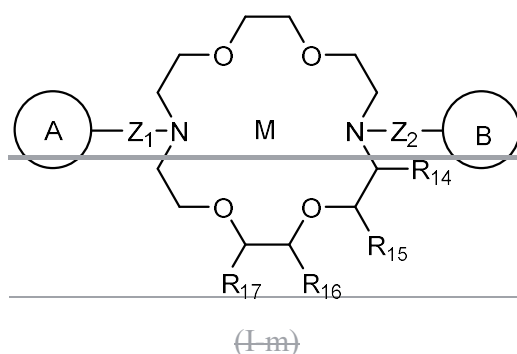
22. A method of preparing a radioimmunoconjugate, the method comprising:

(i) providing a modified polypeptide comprising the antibody or antigen binding fragment thereof covalently linked to an azido group;

(ii) providing a chelator complex comprising a chelator covalently linked to an alkynyl group or cycloalkynyl group;

(iii) contacting the modified polypeptide with the chelator complex under a condition to allow the azido group to react with the alkynyl group or cycloalkynyl group to thereby form an immunoconjugate; and

(iv) contacting the immunoconjugate with an alpha-emitting radiometal ion to thereby form the radioimmunoconjugate, the radioimmunoconjugate comprising a radiocomplex comprising the alpha-emitting radiometal ion bound to the chelator, wherein the radiocomplex has the structure of formula (I-m):



wherein:

~~— M is a radiometal ion, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);
 — each of ring A and ring B is independently a 6-10 membered aryl or a 5-10 membered heteroaryl, wherein each of ring A and ring B is optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocycyl, heteroaryl, OR_{13} , SR_{13} , $(\text{CH}_2)_p\text{COOR}_{13}$, OC(O)R_{13} , $\text{N(R}_{13})_2$, $\text{CON(R}_{13})_2$, NO_2 , CN , $\text{OC(O)N(R}_{13})_2$, and X;
 each of Z_1 and Z_2 is independently $(\text{C(R}_{12})_2)_m$ or $(\text{CH}_2)_n\text{C(R}_{12})\text{(X)}(\text{CH}_2)_n$;
 — each X is independently L_1R_{11} ;
 — each n is independently 0, 1, 2, 3, 4, or 5;
 — each m is independently 1, 2, 3, 4, or 5;
 — each p is independently 0 or 1;
 — L_1 is absent or a linker;
 — R_{11} is an alkynyl or cycloalkynyl group;
 — each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocycyl, or heteroaryl;
 — each R_{13} is independently hydrogen or alkyl;
 each of R_{14} , R_{15} , R_{16} , and R_{17} is independently hydrogen, alkyl, or X,
 or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X;
 provided that the radiometal complex comprises at least one X, and when X is present on ring A or ring B, L_1 is a linker or at least one of R_{12} and $\text{R}_{14}\text{--R}_{17}$ is not hydrogen.~~

23. A method of preparing a radioimmunoconjugate, the method comprising:
 (i) providing a modified antibody or antigen binding fragment thereof comprising the antibody or antigen binding fragment thereof covalently linked to an azido group;
 (ii) providing a radiocomplex comprising an alpha-emitting radiometal ion bound to a chelator via coordinate bonding, wherein the chelator is covalently linked to an alkynyl group or cycloalkynyl group; and

or alternatively R₁₄ and R₁₅ and/or R₁₆ and R₁₇ are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X;

provided that the radiometal complex comprises at least one X, and when X is present on ring A or ring B, L₁ is a linker or at least one of R₁₂ and R₁₄-R₁₇ is not hydrogen.

24. The method of either of claims 22 or 23, wherein R₁₁ is cyclooctynyl or a cyclooctynyl derivative selected from the group consisting of bicyclononyl (BCN), difluorinated cyclooctynyl (DIFO), dibenzocyclooctynyl (DIBO), keto-DIBO, biarylazacyclooctynonyl (BARAC), dibenzoazacyclooctynyl (DIBAC, DBCO, ADIBO), dimethoxyazacyclooctynyl (DIMAC), difluorobenzocyclooctynyl (DIFBO), monobenzocyclooctynyl (MOBO), and tetramethoxy dibenzocyclooctynyl (TMDIBO).

25.16. A pharmaceutical composition comprising the radioimmunoconjugate of any one of claims 16-19, 10-13, and a pharmaceutically acceptable carrier.

26.17. Use of a therapeutically effective amount of the pharmaceutical composition of claim 25-16 in the manufacture of a medicament for selectively targeting neoplastic cells for radiotherapy in a subject in need thereof.

27.18. Use of a therapeutically effective amount of the pharmaceutical composition of claim 25-16 in the manufacture of a medicament for treating a neoplastic disease or disorder in a subject in need thereof.

28.19. Use of a therapeutically effective amount of the pharmaceutical composition of claim 25-16 in the manufacture of a medicament for treating cancer in a subject in need thereof.

29.20. The pharmaceutical composition of claim 25-16 for use as a medicament.