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(54) Title: EXTRACELLULAR HSP90 (EHSP90)-TARGETED RADIOPHARMACEUTICALS AND USE THEREOF

(57) Abstract: Radiopharmaceutical compounds comprising a targeting moiety that specifically binds to HSP90, in particular, extra-cellular HSP90, a unique linker and a chelator. Also disclosed are pharmaceutical compositions and methods of treating cancer with the same.



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EXTRACELLULAR HSP90 (eHSP90)-TARGETED RADIOPHARMACEUTICALS AND USE THEREOF

BACKGROUND

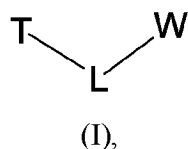
- 5 [1] Heat shock protein 90 (HSP90) is a molecular chaperone that regulates protein folding to ensure correct conformation and translocation and to avoid protein aggregation. Many oncogenic proteins are HSP90 client proteins, such as epidermal growth factor receptor (EGFR) mutant, cyclin dependent kinase 4 (CDK4), hypoxia-inducible factor (HIF)-1 α , and matrix metalloproteinase 2 (MMP2).
- 10 [2] There is a fraction of HSP90 identified at the surface of a number of cell types, i.e., extracellular HSP90 (eHSP90), which can be a useful tumor antigen for eliciting a host immune response. Studies show that eHSP90 plays a crucial role in maintaining oncogenic protein homeostasis and participates in the invasion and metastatic processes of various cancers including breast cancer, which make eHSP90 an attractive target for developing cancer therapy.
- 15 [3] HSP90 inhibition has been shown to have a significant direct impact on cell cycle and DNA repair mechanisms, thus offering great promise in the treatment of a wide variety of solid and hematological malignancies. However, early clinical trials have demonstrated that certain HSP90 inhibitors exhibited limited efficacy and various side effects.
- [4] Therefore, there is a need for improved treatment of cancers with good efficacy and
20 acceptable safety profiles by targeting certain proteins, e.g., eHSP90.

SUMMARY

- [5] The present disclosure encompasses the insight that certain radiopharmaceuticals comprising a targeting moiety that specifically binds to HSP90, in particular, eHSP90, can be effective as
25 HSP90 radioligand therapy (RLT) for treating cancers. Radioactive decay can cause direct physical damage (such as single or double-stranded DNA breaks) or indirect damage (such as by-stander or crossfire effects) to the biomolecules that constitute a cell. Drugs that deliver radionuclides to cancer cells, i.e., radiopharmaceuticals, provide a mechanism to generate DNA damage with anti-cancer therapeutic effect. The present disclosure provides certain
30 radiopharmaceuticals, specifically, small molecule-based radiopharmaceuticals targeting HSP90-overexpressing tumors and using actinium-225 (²²⁵Ac), lutetium-177 (¹⁷⁷Lu) or other suitable

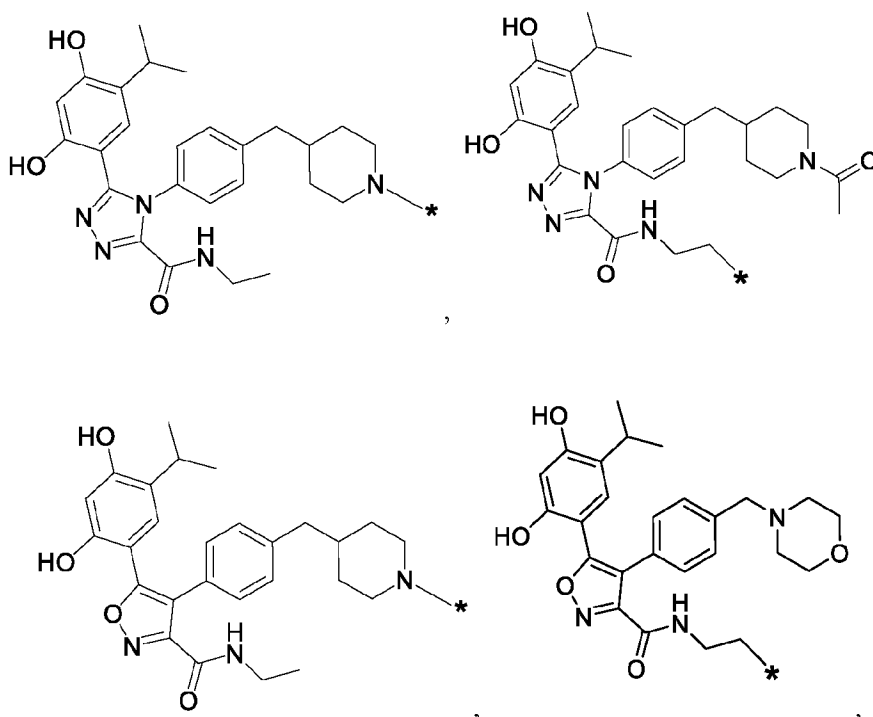
therapeutic radionuclides to target cancer cells to treat or ameliorate cancers such as lung cancer, sarcoma, pancreatic cancer, breast cancer, or colon cancer.

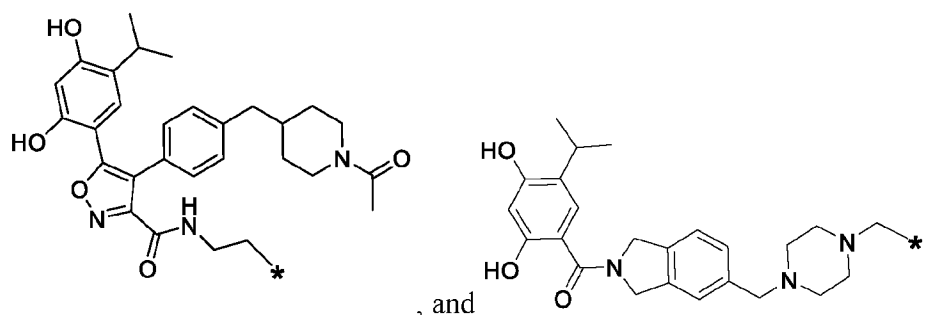
[6] In one aspect, the present disclosure provides compounds of Formula I, or a pharmaceutically acceptable salt thereof:



wherein T is a targeting moiety that binds to HSP90, L is a hydrophilic space linker comprising one or more cyclic or acyclic polyhydroxy groups, and W is a chelator, wherein the compound optionally further comprises a radionuclide chelated by the chelator thereof.

[7] In some embodiments, the targeting moiety is selected from the group consisting of:

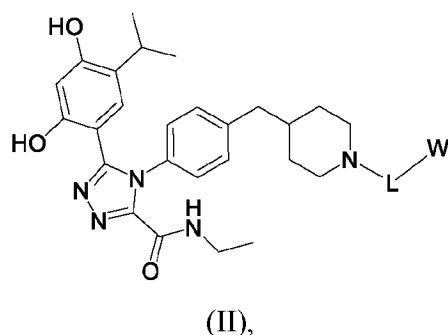




wherein “*” indicates the attachment point to L.

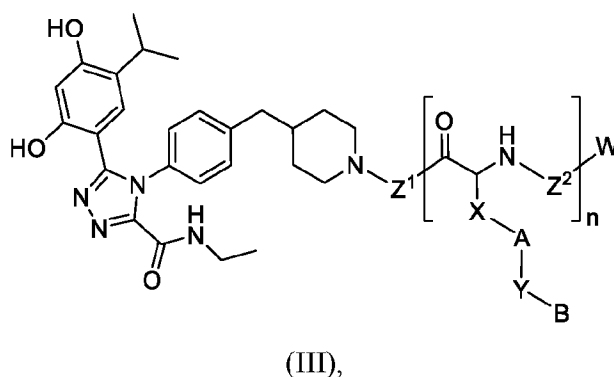
[8] In some embodiments, the compounds of this disclosure specifically bound to extracellular HSP90 (eHSP90).

5 [9] In some embodiments, the compounds of this disclosure have the structure of Formula II:

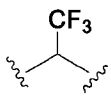
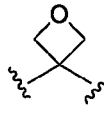
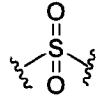


wherein L is a hydrophilic space linker comprising one or more cyclic or acyclic polyhydroxy groups, and W is a chelator selected from the group consisting of DOTA, DOTAGA, NOTA, NODAGA, NODASA, DTPA, TETA, EDTA, TRITA, CDTA, and DFO, wherein the compound binds to HSP90, wherein the compound optionally further comprises a radionuclide chelated by the chelator thereof.

[10] In some embodiments, the compounds of this disclosure have the structure of Formula III:



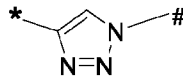
wherein Z^1 and Z^2 each are, independently, absent or a moiety selected from the group consisting

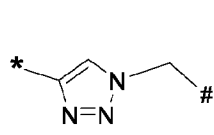
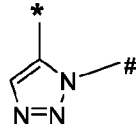
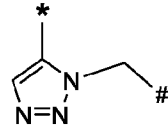
of $C=O$, , , , $(C=O)NR^1$, $NR^1(C=O)NR^2$, $(CH_2CH_2)NR^2$, an amino acid unit, and a combination thereof, in which each of R^1 and R^2 independently is H or C_{1-5} alkyl; n is an integer of 1-5 (inclusive); W is a chelator selected from the group consisting of DOTA, DOTAGA, NOTA, and NODAGA; X is absent or C_{1-5} alkyl; A is absent, $C=O$, $CONR^3$, heterocycle, or heterocycle- C_{1-3} alkyl, R^3 being H or C_{1-5} alkyl; Y is absent, C_{1-5} alkyl, or C_{1-10} heteroalkyl; and B is a cyclic or acyclic polyhydroxy group.

[11] In some embodiments, referring to Formula III, Z^1 , and Z^2 are absent, and n is 1-3.

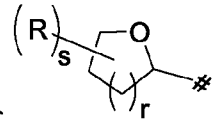
[12] In some embodiments, referring to Formula III, Z^1 is $(C=O)NH(CH_2CH_2)NH$, Z^2 is absent, and n is 1-3.

[13] In some embodiments, referring to Formula III, at least one of Z^1 and Z^2 is an amino acid unit. The amino acid unit can be formed from aspartic acid (Asp), glutamic acid (Glu), 2,4-diaminobutyric acid (Dab), 2,3-diaminopropionic acid (Dap), lysine (Lys), or arginine (Arg).

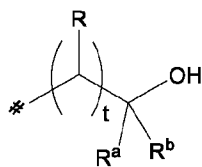
[14] In some embodiments, referring to Formula III, X is C_{1-3} alkyl, A is ,

, , or , and Y is absent, C_{1-5} alkoxy, or C_{2-8} polyethylene glycol, wherein “*” indicates the attachment point to X, and “#” indicates the attachment point to Y.

[15] In some embodiments, referring to Formula III, B is a cyclic polyhydroxy group having the

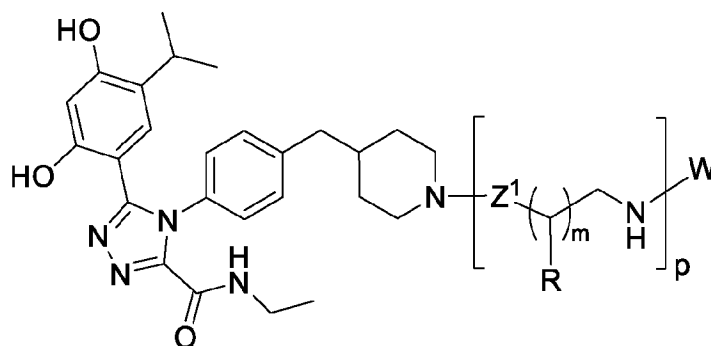
structure of , wherein “#” indicates the attachment point to Y, r is 1-2, s is 3-4, and each R, independently, is OH, $-CH_2OH$, $-CO_2H$, $-CONH_2$, NH_2 , or $NHCOCH_3$, wherein B comprises at least three OH groups.

[16] In some embodiments, referring to Formula III, B is an acyclic polyhydroxy group having

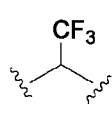
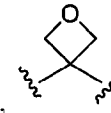


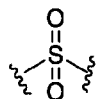
the structure of R^a R^b , wherein “#” indicates the attachment point to Y; t is 2-5; each R, independently, is OH, $-\text{CH}_2\text{OH}$, $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, NH_2 , or NHCOCH_3 ; and R^a and R^b each are H or R^a and R^b together form $\text{C}=\text{O}$, wherein B comprises at least three OH groups.

5 [17] In some embodiments, the compounds of this disclosure have the structure of Formula IV:



(IV),

wherein Z^1 is a moiety selected from the group consisting of $\text{C}=\text{O}$, , ,



, $(\text{C}=\text{O})\text{NR}^1$, $\text{NR}^1(\text{C}=\text{O})\text{NR}^2$, $(\text{CH}_2\text{CH}_2)\text{NR}^2$, an amino acid unit, and a combination

10 thereof, in which each of R^1 and R^2 independently is H or C_{1-5} alkyl; m is an integer of 1-5 (inclusive), p is an integer of 1-4 (inclusive); W is a chelator selected from the group consisting of DOTA, DOTAGA, NOTA, and NODAGA; and R in each occurrence, independently, is OH, $-\text{CH}_2\text{OH}$, $-\text{CO}_2\text{H}$, CONH_2 , NH_2 , or NHCOCH_3 , wherein the compound comprises a hydrophilic space linker containing at least three OH groups.

15 [18] In some embodiments, referring to Formula IV, Z^1 is $\text{C}=\text{O}$, m is 3-4, p is 1-2, and R is OH or $-\text{CH}_2\text{OH}$.

[19] In some embodiments, the compounds of Formulas I-IV feature that each compound comprises a radionuclide selected from the group consisting of ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{66}Ga , ^{67}Ga , ^{68}Ga , ^{82}Rb , ^{86}Y , ^{87}Y , ^{89}Zr , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , $^{117\text{m}}\text{Sn}$,

^{149}Pm , ^{149}Tb , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{198}Au , ^{199}Au , ^{201}Tl , ^{203}Pb , ^{211}At , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th , and ^{229}Th .

[20] In certain embodiments, the radionuclide is selected from the group consisting of ^{68}Ga , ^{89}Zr , ^{90}Y , ^{111}In , ^{177}Lu , and ^{225}Ac .

5 [21] In certain embodiments, the radionuclide is ^{177}Lu or ^{225}Ac .

[22] In another aspect, the present disclosure also covers a pharmaceutical composition comprising one of the compounds set forth above and a pharmaceutically acceptable excipient.

[23] Still within the scope of this disclosure is a method of treating cancer or radiation treatment planning, the method comprising administering to a subject in need thereof one of the
10 compounds set forth above or the above-described pharmaceutical composition.

[24] In some embodiments, the method of treating cancer comprises administering to the subject in need thereof a first dose of one of the compounds or the composition described above in an amount effective for radiation treatment planning, followed by administering subsequent doses of one of the compounds or the composition described above in a therapeutically effective
15 amount.

[25] In some embodiments, the cancer is small-cell lung cancer, non-small-cell lung cancer, sarcoma, pancreatic cancer, breast cancer, or colon cancer.

[26] This disclosure also relates to any one of the compounds provided herein for use in a method of treating cancer.

20 [27] Further covered within this disclosure is use of any of the compounds provided herein in the manufacture of a medicament for the treatment of cancer.

DETAILED DESCRIPTION

[28] The present disclosure relates to radiopharmaceutical compounds comprising a targeting
25 moiety that specifically binds to HSP90, in particular, extracellular HSP90 (eHSP90).

[29] Radio-labelled targeting molecules (also known as radiopharmaceuticals) are designed to target a protein or receptor (e.g., eHSP90) that is upregulated in a disease state and/or specific to diseased cells (e.g., tumor cells) to deliver a radioactive payload to damage and kill cells of interest. Radiopharmaceuticals targeting eHSP90 provided in this disclosure can be used for
30 treating various cancers including, but not limited to, small-cell lung cancer, non-small-cell lung cancer, sarcoma, pancreatic cancer, breast cancer, and colon cancer.

Definitions

Chemical Terms

- [30] The term “alkyl,” as used herein, is inclusive of both straight chain and branched chain saturated groups from 1 to 20 carbons represented as C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl having 1 to 6 carbons, C₁₋₈ alkyl having 1 to 8 carbons, C₁₋₁₀ alkyl having 1 to 10 carbons, or C₁₋₁₂ alkyl having 1 to 12 carbons), unless otherwise specified. Alkyl groups are exemplified by methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl, neopentyl, and the like, and may be optionally substituted with one, two, three, or, in the case of alkyl groups of two carbons or more, four substituents independently selected from the group consisting of: (1) C₁₋₆ alkoxy; (2) C₁₋₆ alkylsulfanyl; (3) amino, as defined herein (e.g., unsubstituted amino (i.e., -NH₂) or a substituted amino (i.e., -N(R^{N1})₂, where R^{N1} is as defined for amino); (4) C₆₋₁₀ aryl-C₁₋₆ alkoxy; (5) azido; (6) halo; (7) (C₂₋₉ heterocyclyl)oxy; (8) hydroxy, optionally substituted with an *O*-protecting group; (9) nitro; (10) oxo (e.g., carboxyaldehyde or acyl); (11) C₁₋₇ spirocyclyl; (12) thioalkoxy; (13) thiol; (14) -CO₂R^{A'}, optionally substituted with an *O*-protecting group and where R^{A'} is selected from the group consisting of (a) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl), (b) C₂₋₂₀ alkenyl (e.g., C₂₋₆ alkenyl), (c) C₆₋₁₀ aryl, (d) hydrogen, (e) C₁₋₆ alk-C₆₋₁₀ aryl, (f) amino-C₁₋₂₀ alkyl, (g) polyethylene glycol of -(CH₂)_{s2}(OCH₂CH₂)_{s1}(CH₂)_{s3}OR', wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C₁₋₂₀ alkyl, and (h) amino-polyethylene glycol of -NR^{N1}(CH₂)_{s2}(CH₂CH₂O)_{s1}(CH₂)_{s3}NR^{N1}, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C₁₋₆ alkyl;
- (15) -C(O)NR^{B'}R^{C'}, where each of R^{B'} and R^{C'} is, independently, selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (16) -SO₂R^{D'}, where R^{D'} is selected from the group consisting of (a) C₁₋₆ alkyl, (b) C₆₋₁₀ aryl, (c) C₁₋₆ alk-C₆₋₁₀ aryl, and (d) hydroxy; (17) -SO₂NR^{E'}R^{F'}, where each of R^{E'} and R^{F'} is, independently, selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl and (d) C₁₋₆ alk-C₆₋₁₀ aryl;
- (18) -C(O)R^{G'}, where R^{G'} is selected from the group consisting of (a) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl), (b) C₂₋₂₀ alkenyl (e.g., C₂₋₆ alkenyl), (c) C₆₋₁₀ aryl, (d) hydrogen, (e) C₁₋₆ alk-C₆₋₁₀ aryl, (f) amino-

C₁₋₂₀ alkyl, (g) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C₁₋₂₀ alkyl, and (h) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$,

wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C₁₋₆ alkyl;

(19) $-NR^{H'}C(O)R^{I'}$, wherein R^{H'} is selected from the group consisting of (a1) hydrogen and (b1) C₁₋₆ alkyl, and R^{I'} is selected from the group consisting of (a2) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl), (b2)

C₂₋₂₀ alkenyl (e.g., C₂₋₆ alkenyl), (c2) C₆₋₁₀ aryl, (d2) hydrogen, (e2) C₁₋₆ alk-C₆₋₁₀ aryl, (f2) amino-C₁₋₂₀ alkyl, (g2) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C₁₋₂₀ alkyl, and (h2) amino-polyethylene glycol of -

$NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C₁₋₆ alkyl; (20) $-NR^{J'}C(O)OR^{K'}$, wherein R^{J'} is selected from the group consisting of (a1) hydrogen and (b1) C₁₋₆ alkyl, and R^{K'} is selected from the group consisting of

(a2) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl), (b2) C₂₋₂₀ alkenyl (e.g., C₂₋₆ alkenyl), (c2) C₆₋₁₀ aryl, (d2) hydrogen, (e2) C₁₋₆ alk-C₆₋₁₀ aryl, (f2) amino-C₁₋₂₀ alkyl, (g2) polyethylene glycol of - $(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C₁₋₂₀ alkyl, and (h2) amino-polyethylene

glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is,

independently, hydrogen or optionally substituted C₁₋₆ alkyl; and (21) amidine. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C₁-alkaryl can be further substituted with an oxo group to afford the respective aryloyl substituent.

[31] The terms “alkylene”, “alkylidene”, and the prefix “alk-,” as used herein, represent a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is exemplified by methylene, ethylene, isopropylene, and the like. The terms “C_{x-y} alkyl,” “C_{x-y} alkylene,” “C_{x-y} alkylidene,” and the prefix “C_{x-y} alk-” represent alkyl or alkylene groups having between x and y carbons. Exemplary values for x are 1, 2, 3, 4, 5, and 6, and exemplary values for y are 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, or 20 (e.g., C₁₋₆, C₁₋₁₀, C₂₋₅, C₂₋₈, C₂₋₁₀, or C₂₋₂₀ alkyl or alkylene). In some embodiments, the alkylene can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for an alkyl group.

[32] The term “alkenyl,” as used herein, represents monovalent straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) containing one or more carbon-carbon double bonds and is exemplified by ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. Alkenyls include both cis and trans isomers. Alkenyl groups may be optionally substituted with 1, 2, 3, or 4 substituent groups that are selected, independently, from amino, aryl, cycloalkyl, or heterocyclyl (e.g., heteroaryl), as defined herein, or any of the exemplary alkyl substituent groups described herein.

[33] The term “alkynyl,” as used herein, represents monovalent straight or branched chain groups from 2 to 20 carbon atoms (e.g., from 2 to 4, from 2 to 6, or from 2 to 10 carbons) containing a carbon-carbon triple bond and is exemplified by ethynyl, 1-propynyl, and the like. Alkynyl groups may be optionally substituted with 1, 2, 3, or 4 substituent groups that are selected, independently, from aryl, cycloalkyl, or heterocyclyl (e.g., heteroaryl), as defined herein, or any of the exemplary alkyl substituent groups described herein.

[34] The term “amino,” as used herein, represents $-N(R^{N1})_2$, wherein each R^{N1} is, independently, H, OH, NO₂, N(R^{N2})₂, SO₂OR^{N2}, SO₂R^{N2}, SOR^{N2}, an *N*-protecting group, alkyl, alkenyl, alkynyl, alkoxy, aryl, alkaryl, cycloalkyl, alkycycloalkyl, carboxyalkyl (e.g., optionally substituted with an *O*-protecting group, such as optionally substituted arylalkoxycarbonyl groups or any described herein), sulfoalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), alkoxycarbonylalkyl (e.g., optionally substituted with an *O*-protecting group, such as optionally substituted arylalkoxycarbonyl groups or any described herein), heterocyclyl (e.g., heteroaryl), alkheterocyclyl (e.g., alkheteroaryl), wherein each of these recited R^{N1} groups can be optionally substituted, as defined herein for each group; or two R^{N1} combine to form a heterocyclyl or an *N*-

protecting group, and wherein each R^{N2} is, independently, H, alkyl, or aryl. Amino groups can be unsubstituted amino (i.e., $-NH_2$) or substituted amino (i.e., $-N(R^{N1})_2$) groups. In a preferred embodiment, amino is $-NH_2$ or $-NHR^{N1}$, wherein R^{N1} is, independently, OH, NO_2 , NH_2 , NR^{N2}_2 , SO_2OR^{N2} , SO_2R^{N2} , SOR^{N2} , alkyl, carboxyalkyl, sulfoalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), alkoxycarbonylalkyl (e.g., t-butoxycarbonylalkyl) or aryl, and each R^{N2} can be H, C_{1-20} alkyl (e.g., C_{1-6} alkyl), or C_{6-10} aryl.

[35] The term “amino acid,” as described herein, refers to a molecule having a side chain, an amino group, and an acid group (e.g., a carboxy group of $-CO_2H$ or a sulfo group of $-SO_3H$), wherein the amino acid is attached to the parent molecular group by the side chain, amino group, or acid group (e.g., the side chain). The term “amino acid” used herein includes both natural amino acids and unnatural amino acids. In some embodiments, the amino acid is attached to the parent molecular group by a carbonyl group, where the side chain or amino group is attached to the carbonyl group. Exemplary side chains include an optionally substituted alkyl, aryl, heterocyclyl, alkaryl, alkheterocyclyl, aminoalkyl, carbamoylalkyl, and carboxyalkyl.

Exemplary amino acids include alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxynorvaline, isoleucine, leucine, lysine, methionine, norvaline, ornithine, phenylalanine, proline, pyrrolysine, selenocysteine, serine, taurine, threonine, tryptophan, tyrosine, and valine. Amino acid groups may be optionally substituted with one, two, three, or, in the case of amino acid groups of two carbons or more, four substituents independently selected from the group consisting of: (1) C_{1-6} alkoxy; (2) C_{1-6} alkylsulfinyl; (3) amino, as defined herein (e.g., unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$, where R^{N1} is as defined for amino); (4) C_{6-10} aryl- C_{1-6} alkoxy; (5) azido; (6) halo; (7) (C_{2-9} heterocyclyl)oxy; (8) hydroxy; (9) nitro; (10) oxo (e.g., carboxyaldehyde or acyl); (11) C_{1-7} spirocyclyl; (12) thioalkoxy; (13) thiol; (14) $-CO_2R^{A'}$, where $R^{A'}$ is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk- C_{6-10} aryl, (f) amino- C_{1-20} alkyl, (g) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g.,

- from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (15) $-C(O)NR^{B'}R^{C'}$, where each of $R^{B'}$ and $R^{C'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk- C_{6-10} aryl; (16) $-SO_2R^{D'}$, where $R^{D'}$ is selected from the group
- 5 consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) C_{1-6} alk- C_{6-10} aryl, and (d) hydroxy; (17) $-SO_2NR^{E'}R^{F'}$, where each of $R^{E'}$ and $R^{F'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl and (d) C_{1-6} alk- C_{6-10} aryl; (18) $-C(O)R^{G'}$, where $R^{G'}$ is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk- C_{6-10} aryl, (f) amino- C_{1-20} alkyl, (g)
- 10 polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is
- 15 an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (19) $-NR^{H'}C(O)R^{I'}$, wherein $R^{H'}$ is selected from the group consisting of (a1) hydrogen and (b1) C_{1-6} alkyl, and $R^{I'}$ is selected from the group consisting of (a2) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b2) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c2) C_{6-10} aryl, (d2) hydrogen, (e2) C_{1-6} alk- C_{6-10} aryl, (f2) amino- C_{1-20} alkyl, (g2)
- 20 polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h2) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently,
- 25 is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (20) $-NR^{J'}C(O)OR^{K'}$, wherein $R^{J'}$ is selected from the group consisting of (a1) hydrogen and (b1) C_{1-6} alkyl, and $R^{K'}$ is selected from the group consisting of (a2) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b2) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c2) C_{6-10} aryl, (d2) hydrogen, (e2) C_{1-6} alk- C_{6-10} aryl, (f2) amino- C_{1-20} alkyl, (g2) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein $s1$ is an integer
- 30 from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer

from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C₁₋₂₀ alkyl, and (h2) amino-polyethylene glycol of -NR^{N1}(CH₂)_{s2}(CH₂CH₂O)_{s1}(CH₂)_{s3}NR^{N1}, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C₁₋₆ alkyl; and (21) amidine. In some embodiments, each of these groups can be further substituted as described herein.

[36] The term "aryl," as used herein, represents a mono-, bicyclic, or multicyclic carbocyclic ring system having one or two aromatic rings and is exemplified by phenyl, naphthyl, 1,2-

dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, anthranyl, phenanthrenyl, fluorenyl, indanyl, indenyl, and the like, and may be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of: (1) C₁₋₇ acyl (e.g., carboxyaldehyde); (2) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl, C₁₋₆ alkoxy-C₁₋₆ alkyl, C₁₋₆ alkylsulfinyl-C₁₋₆ alkyl, amino-C₁₋₆ alkyl, azido-C₁₋₆ alkyl, (carboxyaldehyde)-C₁₋₆ alkyl, halo-C₁₋₆ alkyl (e.g., perfluoroalkyl), hydroxy-C₁₋₆ alkyl, nitro-C₁₋₆ alkyl, or C₁₋₆ thioalkoxy-C₁₋₆ alkyl); (3) C₁₋₂₀ alkoxy (e.g., C₁₋₆ alkoxy, such as perfluoroalkoxy); (4) C₁₋₆ alkylsulfinyl; (5) C₆₋₁₀ aryl; (6) amino; (7) C₁₋₆ alk-C₆₋₁₀ aryl; (8) azido; (9) C₃₋₈ cycloalkyl; (10) C₁₋₆ alk-C₃₋₈ cycloalkyl; (11) halo; (12) C₁₋₁₂ heterocyclyl (e.g., C₁₋₁₂ heteroaryl); (13) (C₁₋₁₂ heterocyclyl)oxy; (14) hydroxy; (15) nitro; (16) C₁₋₂₀ thioalkoxy (e.g., C₁₋₆ thioalkoxy); (17) -(CH₂)_qCO₂R^{A'}, where q is an integer from zero to four, and R^{A'} is selected from the group consisting of (a) C₁₋₆ alkyl, (b) C₆₋₁₀ aryl, (c) hydrogen, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (18) -(CH₂)_qCONR^{B'}R^{C'}, where q is an integer from zero to four and where R^{B'} and R^{C'} are independently selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (19) -(CH₂)_qSO₂R^{D'}, where q is an integer from zero to four and where R^{D'} is selected from the group consisting of (a) alkyl, (b) C₆₋₁₀ aryl, and (c) alk-C₆₋₁₀ aryl; (20) -(CH₂)_qSO₂NR^{E'}R^{F'}, where q is an integer from zero to four and where each of R^{E'} and R^{F'} is, independently, selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (21) thiol; (22) C₆₋₁₀ aryloxy; (23) C₃₋₈ cycloalkoxy; (24) C₆₋₁₀ aryl-C₁₋₆ alkoxy; (25) C₁₋₆ alk-C₁₋₁₂ heterocyclyl (e.g., C₁₋₆ alk-C₁₋₁₂ heteroaryl); (26) C₂₋₂₀ alkenyl; and (27) C₂₋₂₀ alkynyl. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C₁-alkaryl or a C₁-

alkheterocyclyl can be further substituted with an oxo group to afford the respective aryloyl and (heterocyclyl)oyl substituent group.

[37] The term “acyl,” as used herein, represents an a radical of general formula $-C(O)R$, where R is an alkyl or aryl group. Examples of an “acyl” group include, but are not limited to, –

5 $C(O)CH_3$, $-C(O)C_2H_5$, and $-C(O)Ph$.

[38] The term “carbonyl,” as used herein, represents a $C(O)$ group, which can also be represented as $C=O$.

[39] The term “carboxy,” as used herein, means $-CO_2H$.

[40] The term “cycloalkyl,” as used herein represents a monovalent saturated or unsaturated non-
 10 aromatic cyclic hydrocarbon group from three to eight carbons represented as C_{3-8} cycloalkyl (e.g., C_{3-5} cycloalkyl having 3 to 5 carbons, C_{3-6} cycloalkyl having 3 to 6 carbons), unless otherwise specified. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicycle heptyl, and the like. When the cycloalkyl group includes one carbon-carbon double bond or one carbon-carbon triple bond, the
 15 cycloalkyl group can be referred to as a “cycloalkenyl” or “cycloalkynyl” group respectively. Exemplary cycloalkenyl and cycloalkynyl groups include cyclopentenyl, cyclohexenyl, cyclohexynyl, and the like. Cycloalkyl groups can be optionally substituted with: (1) C_{1-7} acyl (e.g., carboxyaldehyde); (2) C_{1-20} alkyl (e.g., C_{1-6} alkyl, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylsulfinyl- C_{1-6} alkyl, amino- C_{1-6} alkyl, azido- C_{1-6} alkyl, (carboxyaldehyde)- C_{1-6} alkyl, halo- C_{1-6} alkyl (e.g.,
 20 perfluoroalkyl), hydroxy- C_{1-6} alkyl, nitro- C_{1-6} alkyl, or C_{1-6} thioalkoxy- C_{1-6} alkyl); (3) C_{1-20} alkoxy (e.g., C_{1-6} alkoxy, such as perfluoroalkoxy); (4) C_{1-6} alkylsulfinyl; (5) C_{6-10} aryl; (6) amino; (7) C_{1-6} alk- C_{6-10} aryl; (8) azido; (9) C_{3-8} cycloalkyl; (10) C_{1-6} alk- C_{3-8} cycloalkyl; (11) halo; (12) C_{1-12} heterocyclyl (e.g., C_{1-12} heteroaryl); (13) (C_{1-12} heterocyclyl)oxy; (14) hydroxy; (15) nitro; (16) C_{1-20} thioalkoxy (e.g., C_{1-6} thioalkoxy); (17) $-(CH_2)_qCO_2R^{A'}$, where q is an
 25 integer from zero to four, and $R^{A'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) hydrogen, and (d) C_{1-6} alk- C_{6-10} aryl; (18) $-(CH_2)_qCONR^{B'}R^{C'}$, where q is an integer from zero to four and where $R^{B'}$ and $R^{C'}$ are independently selected from the group consisting of (a) hydrogen, (b) C_{6-10} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk- C_{6-10} aryl; (19) $-(CH_2)_qSO_2R^{D'}$, where q is an integer from zero to four and where $R^{D'}$ is selected from the group consisting of (a) C_{6-10}
 30 alkyl, (b) C_{6-10} aryl, and (c) C_{1-6} alk- C_{6-10} aryl; (20) $-(CH_2)_qSO_2NR^{E'}R^{F'}$, where q is an integer from zero to four and where each of $R^{E'}$ and $R^{F'}$ is, independently, selected from the group

consisting of (a) hydrogen, (b) C₆₋₁₀ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (21) thiol; (22) C₆₋₁₀ aryloxy; (23) C₃₋₈ cycloalkoxy; (24) C₆₋₁₀ aryl-C₁₋₆ alkoxy; (25) C₁₋₆ alk-C₁₋₁₂ heterocyclyl (e.g., C₁₋₆ alk-C₁₋₁₂ heteroaryl); (26) oxo; (27) C₂₋₂₀ alkenyl; and (28) C₂₋₂₀ alkynyl. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C₁-alkaryl or a C₁-alkheterocyclyl can be further substituted with an oxo group to afford the respective aryloyl and (heterocyclyl)oyl substituent group.

[41] The term “halo” or “halogen,” as used herein, represents a halogen selected from bromine, chlorine, iodine, or fluorine.

[42] The terms “heteroalkyl,” as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have each been replaced by nitrogen, oxygen, or sulfur. For example, C₁₋₂₀ heteroalkyl represents an alkyl group comprising one or more of nitrogen, oxygen, or sulfur in addition to 1 to 20 carbons (e.g., C₁₋₆ heteroalkyl having 1 to 6 carbons and one or more of nitrogen, oxygen, or sulfur, C₁₋₈ heteroalkyl having 1 to 8 carbons and one or more of nitrogen, oxygen, or sulfur, C₁₋₁₀ heteroalkyl having 1 to 10 carbons and one or more of nitrogen, oxygen, or sulfur, or C₁₋₁₂ heteroalkyl having 1 to 12 carbons and one or more of nitrogen, oxygen, or sulfur). A typical example of heteroalkyl is polyethylene glycol (PEG), wherein two more of the carbons have each been replaced by oxygen, e.g., C₂₋₂₀ polyethylene glycol (e.g., C₂₋₁₀ polyethylene glycol or C₆₋₈ polyethylene glycol). In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. The terms “heteroalkenyl” and heteroalkynyl,” as used herein refer to alkenyl and alkynyl groups, as defined herein, respectively, in which one or two of the constituent carbon atoms have each been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl and heteroalkynyl groups can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups.

[43] The terms “heterocycloalkyl,” as used herein, refers to a cycloalkyl group, as defined herein, in which one or more of the constituent carbon atoms have each been replaced by nitrogen, oxygen, or sulfur. For example, C₁₋₂₀ heterocycloalkyl represents a cycloalkyl group comprising one or more of nitrogen, oxygen, or sulfur in addition to 1 to 20 carbons (e.g., C₁₋₆ heterocycloalkyl, C₁₋₈ heterocycloalkyl, C₂₋₈ heterocycloalkyl, C₁₋₁₀ heterocycloalkyl, or C₁₋₁₂ heterocycloalkyl).

[44] The term “heteroaryl,” as used herein, represents that subset of heterocyclyls, as defined herein, which are aromatic: i.e., they contain $4n+2$ pi electrons within the mono- or multicyclic ring system. Exemplary unsubstituted heteroaryl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. Examples of heteroaryl include, but are not limited to, furan, oxazole, thiophene, 1,2,3-triazole, 1,2,4-triazine, 1,2,4-triazole, 1,2,5-thiadiazole 1,1-dioxide, 1,2,5-thiadiazole 1-oxide, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,5-triazine, imidazole, isothiazole, isoxazole, pyrazole, pyridazine, pyridine, pyridine-N-oxide, pyrazine, pyrimidine, pyrrole, tetrazole, and thiazole. In some embodiment, the heteroaryl is substituted with 1, 2, 3, or 4 substituents groups as defined for a heterocyclyl group.

[45] The term “oxo” as used herein, represents =O.

[46] The term “polyethylene glycol,” as used herein, represents an alkoxy chain comprised of one or more monomer units, each monomer unit consisting of $-\text{OCH}_2\text{CH}_2-$. Polyethylene glycol (PEG) is also sometimes referred to as polyethylene oxide (PEO) or polyoxyethylene (POE), and these terms may be considered interchangeable for the purpose of this disclosure. For example, a polyethylene glycol may have the structure, $-(\text{CH}_2)_{s2}(\text{OCH}_2\text{CH}_2)_{s1}(\text{CH}_2)_{s3}\text{O}-$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), and each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10).

Polyethylene glycol may also be considered to include an amino-polyethylene glycol of -

$\text{NR}^{\text{N1}}(\text{CH}_2)_{s2}(\text{CH}_2\text{CH}_2\text{O})_{s1}(\text{CH}_2)_{s3}\text{NR}^{\text{N1}}$ -, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl.

[47] The term “isomer,” as used herein, means any tautomer, stereoisomer, enantiomer, or diastereomer of any compound. It is recognized that the compounds can have one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric E/Z isomers) or diastereomers, enantiomers (i.e., (+) or (-)) or cis/trans isomers). Unless otherwise noted, chemical structures depicted herein encompass all of the corresponding stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, e.g., racemates. Enantiomeric and stereoisomeric mixtures of compounds can typically

be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or
5 enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[48] The term “stereoisomer,” as used herein, refers to all possible different isomeric as well as conformational forms which a compound may possess (e.g., a compound of any formula described herein), in particular all possible stereochemically and conformationally isomeric
10 forms, all diastereomers, enantiomers and/or conformers of the basic molecular structure. Some compounds may exist in different tautomeric forms, all of the latter being included within the scope of the present disclosure.

[49] The term “diastereomer,” as used herein means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

15 [50] The term “enantiomer,” as used herein, means each individual optically active form of a compound, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e., at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

20 *Other terms*

[51] As used herein, the term “about” or “approximately” refers to a $\pm 10\%$ variation from the recited quantitative value (and includes the recited quantitative value itself) unless otherwise indicated or inferred from the context. For example, unless otherwise stated or inferred from the context, a dose of about 100 kBq/kg indicates a dose range of $100 \pm 10\%$ kBq/kg, i.e., from 90
25 kBq/kg to 110 kBq/kg, inclusive.

[52] As used herein, the term “administered in combination,” “combined administration,” or “co-administered” means that two or more agents are administered to a subject at the same time or within an interval such that there may be an overlap of an effect of each agent on the patient. Thus, two or more agents that are administered in combination need not be administered
30 together. In some embodiments, they are administered within 90 days (e.g., within 80, 70, 60, 50, 40, 30, 20, 10, 5, 4, 3, 2, or 1 day(s)), within 28 days (e.g., with 14, 7, 6, 5, 4, 3, 2, or 1

day(s), within 24 hours (e.g., 12, 6, 5, 4, 3, 2, or 1 hour(s), or within about 60, 30, 15, 10, 5, or 1 minute of one another. In some embodiments, the administrations of the agents are spaced sufficiently closely together such that a combinatorial effect is achieved.

[53] As used herein, “administering” an agent to a subject includes contacting cells of said
5 subject with the agent.

[54] The term “cancer” refers to any cancer caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas. A “solid tumor cancer” is a cancer comprising an abnormal mass of tissue, e.g., sarcomas, carcinomas, and lymphomas. A “hematological cancer” or “liquid cancer,” as used interchangeably herein, is
10 a cancer present in a body fluid, e.g., lymphomas and leukemias.

[55] The term “chelate” as used herein, refers to an organic compound or portion thereof that can be bonded to a central metal or radiometal atom at two or more points.

[56] The term “conjugate,” as used herein, refers to a molecule that contains a chelating group or metal complex thereof, a linker group, and which optionally contains a therapeutic moiety or a
15 targeting moiety.

[57] The term “therapeutic moiety” as used herein refers to any molecule or any part of a molecule that confers a therapeutic benefit. In some embodiments, the therapeutic moiety is a protein or polypeptide, e.g., an antibody, an antigen-binding fragment thereof. In some embodiments, the therapeutic moiety is a small molecule.

[58] The term “targeting moiety” as used herein refers to any molecule or any part of a molecule that binds to a given target. In some embodiments, the targeting moiety is a protein or polypeptide such as an antibody or antigen binding fragment thereof, a nanobody, an affibody, or a consensus sequence from a Fibronectin type III domain. In some embodiments, the targeting moiety is a peptide or a small molecule.

[59] As used herein, the term “compound,” is meant to include all stereoisomers, geometric isomers, and tautomers of the structures depicted.

[60] The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically
30 substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art,

such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

[61] Compounds of the present disclosure also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Examples prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

[62] At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual sub-combination of the members of such groups and ranges. For example, the term “C₁₋₆ alkyl” is specifically intended to individually disclose methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl. Herein a phrase of the form “optionally substituted X” (e.g., optionally substituted alkyl) is intended to be equivalent to “X, wherein X is optionally substituted” (e.g., “alkyl, wherein said alkyl is optionally substituted”). It is not intended to mean that the feature “X” (e.g., alkyl) per se is optional.

[63] As used herein, the terms “decrease,” “decreased,” “increase,” “increased,” or “reduction,” “reduced,” (e.g., in reference to therapeutic outcomes or effects) have meanings relative to a reference level. In some embodiments, the reference level is a level as determined by the use of said method with a control in an experimental animal model or clinical trial. In some embodiments, the reference level is a level in the same subject before or at the beginning of treatment. In some embodiments, the reference level is the average level in a population not being treated by said method of treatment.

[64] The term an “effective amount” of an agent (e.g., any of the foregoing compounds or conjugates), as used herein, is that amount sufficient to effect beneficial or desired results, such

as clinical results, and, as such, an “effective amount” depends upon the context in which it is being applied.

[65] The term “pharmaceutical composition,” as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient. In some
5 embodiments, the pharmaceutical composition is manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile
10 solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other formulation described herein.

[66] A “pharmaceutically acceptable excipient,” as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being nontoxic and non-inflammatory in a
15 patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluent), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, radioprotectants, sorbents, suspending or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: ascorbic acid, histidine,
20 phosphate buffer, butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone,
25 povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[67] The term “pharmaceutically acceptable salt,” as use herein, represents those salts of the
30 compounds described here that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, or allergic

response. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared *in situ* during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

[68] Compounds may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of compounds, be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines for forming basic salts. Methods for preparation of the appropriate salts are well-established in the art.

[69] Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, among others. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

[70] The term “radiopharmaceutical” or “radioconjugate,” as used herein, refers to any compound or conjugate that includes a radioisotope or radionuclide, such as any of the radioisotopes or radionuclides described herein.

[71] As used herein, the term “radionuclide,” refers to an atom capable of undergoing radioactive

5 decay (e.g., ^3H , ^{14}C , ^{15}N , ^{18}F , ^{35}S , ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{75}Br , ^{76}Br , ^{77}Br , ^{89}Zr , ^{86}Y , ^{87}Y , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{134}Ce , ^{134}La , ^{149}Pm , ^{149}Tb , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{198}Au , ^{199}Au , ^{203}Pb , ^{211}At , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th , ^{229}Th , ^{66}Ga , ^{67}Ga , ^{68}Ga , ^{82}Rb , $^{117\text{m}}\text{Sn}$, or ^{201}Tl). The terms radioactive nuclide, radioisotope, or radioactive isotope may also be used to describe a radionuclide. Radionuclides may be used

10 as detection agents. Exemplary radionuclides used in this disclosure include, but are not limited to, ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{66}Ga , ^{67}Ga , ^{68}Ga , ^{82}Rb , ^{86}Y , ^{87}Y , ^{89}Zr , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , $^{117\text{m}}\text{Sn}$, ^{149}Pm , ^{149}Tb , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{198}Au , ^{199}Au , ^{201}Tl , ^{203}Pb , ^{211}At , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th , and ^{229}Th .

[72] As used herein, and as well understood in the art, “to treat” a condition or “treatment” of the

15 condition (e.g., the conditions described herein such as cancer) is an approach for obtaining beneficial or desired results, such as clinical results. Beneficial or desired results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions; diminishment of extent of disease, disorder, or condition; stabilized (i.e., not worsening) state of disease, disorder, or condition; preventing spread of disease, disorder, or condition; delay or

20 slowing the progress of the disease, disorder, or condition; amelioration or palliation of the disease, disorder, or condition; and remission (whether partial or total), whether detectable or undetectable. In the context of cancer treatment, “ameliorating” may include, for example, reducing incidence of metastases, reducing tumor volume, reducing tumor vascularization and/or reducing the rate of tumor growth. “Palliating” a disease, disorder, or condition means that the

25 extent and/or undesirable clinical manifestations of the disease, disorder, or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to the extent or time course in the absence of treatment.

Chelators

[73] The compounds of Formula I comprise chelating moieties or chelators.

[74] As disclosed herein, the chelator can be selected from the group consisting of DOTA

(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)- α , α' , α'' , α''' -tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DOTPA (1,4,7,10-

5 tetraazacyclododecane-1,4,7,10-tetra propionic acid), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTA-GA anhydride (2,2',2''-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid, DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTMP (1,4,6,10-tetraazacyclodecane-1,4,7,10-tetramethylene phosphonic acid, DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid), CB-TE2A (1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4,11-diacetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), NODA-GA (1,4,7-triazacyclononane-4,7-diacetic acid-1-[2-glutaric acid]), NOTP (1,4,7-triazacyclononane-1,4,7-tri(methylene phosphonic acid), TETPA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrapropionic acid), TETA (1,4,8,11-

15 tetraazacyclotetradecane-1,4,8,11-tetra acetic acid), HEHA (1,4,7,10,13,16-hexaazacyclohexadecane-1,4,7,10,13,16-hexaacetic acid), PEPA (1,4,7,10,13-pentaazacyclopentadecane-N,N',N'',N''',N''''-pentaacetic acid), H₄octapa (N,N'-bis(6-carboxy-2-pyridylmethyl)-ethylenediamine-N,N'-diacetic acid), H₂dedpa (1,2-[[6-(carboxy)-pyridin-2-yl]-methylamino]ethane), H₆phospa (N,N'-(methylenephosphonate)-N,N'-[6-(methoxycarbonyl)pyridin-2-yl]-methyl-1,2-diaminoethane), TTHA (triethylenetetramine-N,N,N',N'',N''',N''''-hexaacetic acid), DO2P (tetraazacyclododecane dimethanephosphonic acid), HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid), EDTA (ethylenediaminetetraacetic acid), Deferoxamine, DTPA (diethylenetriaminepentaacetic acid), DTPA-BMA (diethylenetriaminepentaacetic acid-bismethylamide), and porphyrin.

25 [75] In certain embodiments, the chelator is selected from DOTA, DOTA-GA, NOTA, NODA-GA, NODA-SA, DTPA, TETA, EDTA, TRITA, CDTA, and DFO, which are defined as below:

DOTA stands for 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid,

DOTA-GA, or DOTAGA as used herein, stands for 1,4,7,10-tetraazacyclododecane-1-(glutaric acid)-4,7,10-triacetic acid,

30 NOTA stands for 1,4,7-triazacyclononanetriacetic acid,

NODA-GA, or NODAGA as used herein, stands for 1,4,7-triazacyclononane-N-glutaric acid-N',N''-diacetic acid,

NODA-SA, or NODASA as used herein, stands for 1,4,7- triazacyclononane -1-succinic acid-4,7-diacetic acid,

5 DTPA stands for diethylenetriaminepentaacetic acid,

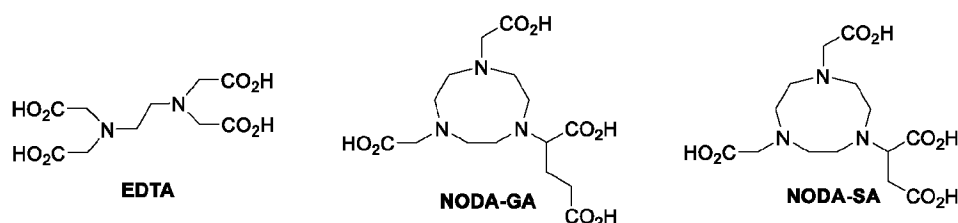
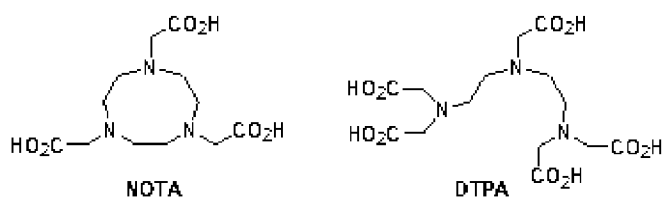
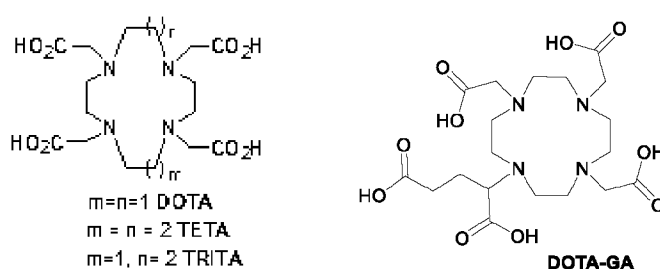
TETA stands for 1,4,8,11-tetraazacyclododecane-1,4,8,11-tetraacetic acid,

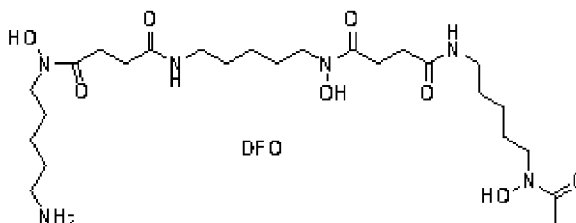
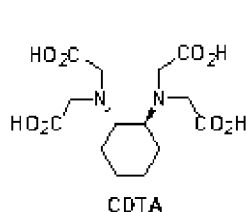
EDTA stands for ethylenediamine-N,N'-tetraacetic acid,

TRITA stands for 1,4,7,10 tetraazacyclotridecane-1,4,7,10-tetraacetic acid,

CDTA stands for *trans*-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid,

10 DFO stands for the Desferal or Desferrioxamine type group of chelators, the chemical name of the non-limiting example is N-[5-({3-[5-(Acetyl-hydroxy-amino)-pentylcarbamoyl]-propionyl}-hydroxy-amino)-pentyl]-N'-(5-amino-pentyl)-N'-hydroxy-succinamide, and with the chemical structures thereof being as follows:





[76] In certain embodiments, the chelator is selected from DOTA, DOTAGA, NOTA, and NODAGA.

5

Radionuclides

[77] The present disclosure includes radiopharmaceuticals each comprising a radionuclide.

Examples of suitable radionuclides include, but are not limited to, ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{66}Ga , ^{67}Ga , ^{67}Cu , ^{68}Ga , ^{69}Er , ^{77}As , ^{82}Rb , ^{89}Zr , ^{86}Y , ^{87}Y , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , ^{111}Ag , ^{121}Sn , ^{127}Te , ^{134}Ce , ^{134}La , ^{142}Pr , ^{143}Pr , ^{149}Pm , ^{149}Tb , ^{151}Pm , ^{159}Gd , ^{153}Sm , ^{161}Tb , ^{166}Dy , ^{166}Ho , ^{169}Yb , ^{172}Tm , ^{175}Yb , ^{177}Lu , $^{117\text{m}}\text{Sn}$, $^{177\text{m}}\text{Sn}$, ^{186}Re , ^{188}Re , ^{188}Rd , ^{198}Au , ^{199}Au , ^{201}Tl , ^{203}Pb , ^{211}At , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th , and ^{229}Th .

10

[78] In some embodiments, the radionuclide is selected from the group consisting of ^{64}Cu , ^{67}Cu , ^{68}Ga , ^{90}Y , ^{111}In , ^{149}Tb , ^{153}Sm , ^{177}Lu , ^{211}At , ^{212}Bi , ^{212}Pb , ^{213}Bi , ^{223}Ra , ^{225}Ac , and ^{227}Th .

15

[79] In some embodiments, the radionuclide is ^{68}Ga , ^{89}Zr , ^{90}Y , ^{111}In , ^{177}Lu , or ^{225}Ac . In certain embodiments, the radionuclide is ^{177}Lu or ^{225}Ac .

[80] In some embodiments, the radionuclide used herein is a beta-emitting radionuclide such as ^{177}Lu . In some embodiments, the radionuclide used herein is an alpha-emitting radionuclide such as ^{225}Ac .

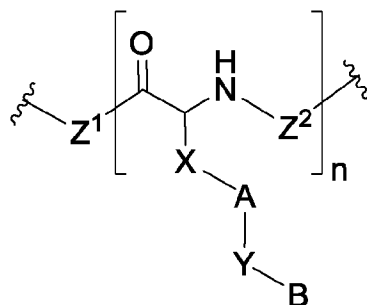
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Linkers

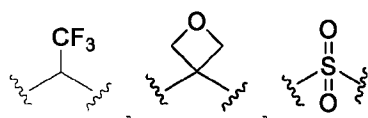
[81] The compounds of the present disclosure comprise a linker as shown within the structure of Formula I, wherein the linker L is a hydrophilic space linker comprising one or more cyclic or acyclic polyhydroxy groups.

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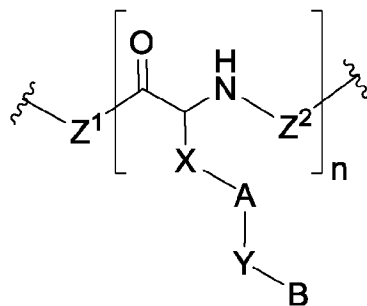
[82] In some embodiments, the linker is a hydrophilic space linker comprising one or more cyclic or acyclic polyhydroxy groups, which include without limitation sugars, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, inositols, and the like.



- 5 [83] In some embodiments, the linker can be featured as Z^1 and Z^2 each are, independently, absent or a moiety selected from the group consisting of C=O,

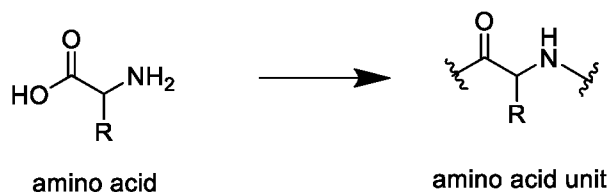


- 10 , (C=O)NR¹, NR¹(C=O)NR², (CH₂CH₂)NR², an amino acid unit, and a combination thereof, in which each of R¹ and R² independently is H or C₁₋₅ alkyl; n is an integer of 1-5 (inclusive); X is absent or C₁₋₅ alkyl; A is absent, C=O, CONR³, heterocycle, or heterocycle-C₁₋₃ alkyl, R³ being H or C₁₋₅ alkyl; Y is absent, C₁₋₅ alkyl, or C₁₋₁₀ heteroalkyl; and B is a cyclic or acyclic polyhydroxy group.



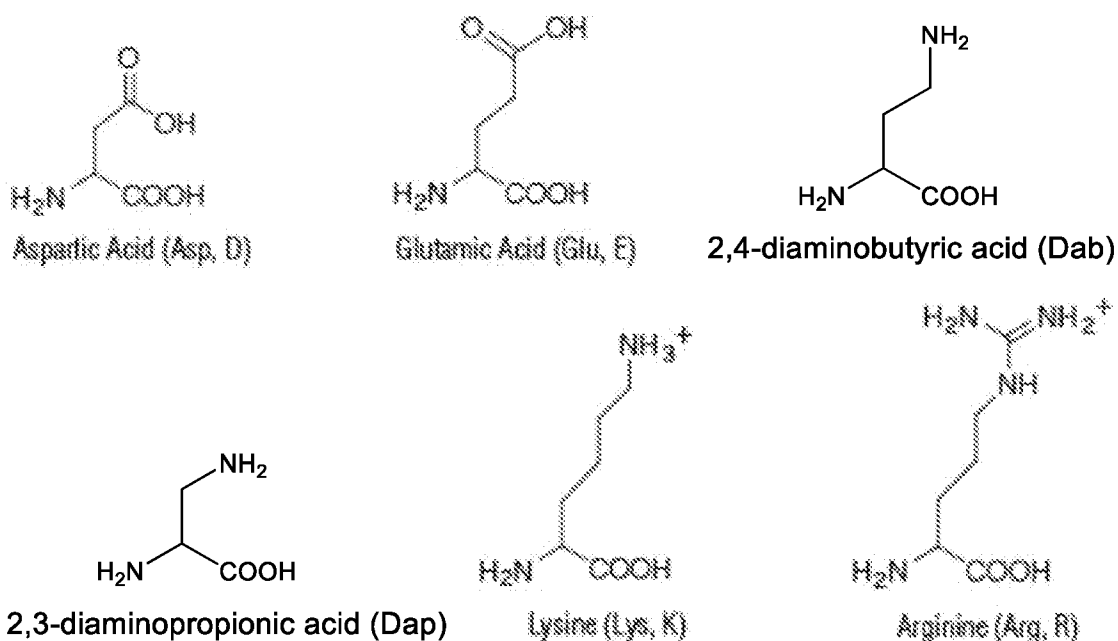
- 15 [84] In some embodiments, the linker can be featured as Z^1 and Z^2 are both absent, and n is 1-3; alternatively, wherein Z^1 is (CH₂CH₂)NH or (C=O)NH(CH₂CH₂)NH, Z^2 is absent, and n is 1-3; alternatively, wherein at least one of Z^1 and Z^2 is an amino acid unit, in which the amino acid unit can be formed from aspartic acid (Asp), glutamic acid (Glu), 2,4-diaminobutyric acid (Dab), 2,3-diaminopropionic acid (Dap), lysine (Lys), or arginine (Arg). In some embodiments, at least one of Z^1 and Z^2 is an amino acid unit formed from Asp.

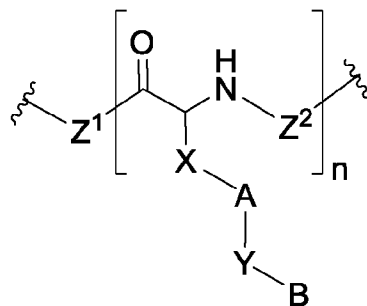
[85] The term “amino acid unit” described herein refers to an organic moiety formed from an amino acid (e.g., a natural amino acid or an unnatural amino acid). Typically, an amino acid unit is formed as shown below:



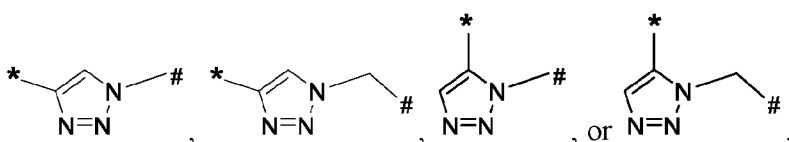
- 5 where R represents an alkyl, cycloalkyl, aryl, or heteroaryl, each of which can be optionally substituted with a suitable substituent described herein; alternatively, R together with the -NH₂ group within the amino acid form a heterocycle. The amino acid or amino acid unit can be in either D- or L-form (i.e., D-enantiomer or L-enantiomer).

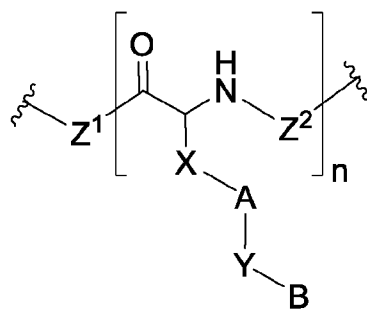
10 [86] In some embodiments, an amino acid unit is formed from aspartic acid (Asp), glutamic acid (Glu), 2,4-diaminobutyric acid (Dab), 2,3-diaminopropionic acid (Dap), lysine (Lys), or arginine (Arg), with their structures shown below:



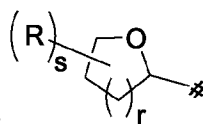


[87] In some embodiments, the linker can be featured as , wherein

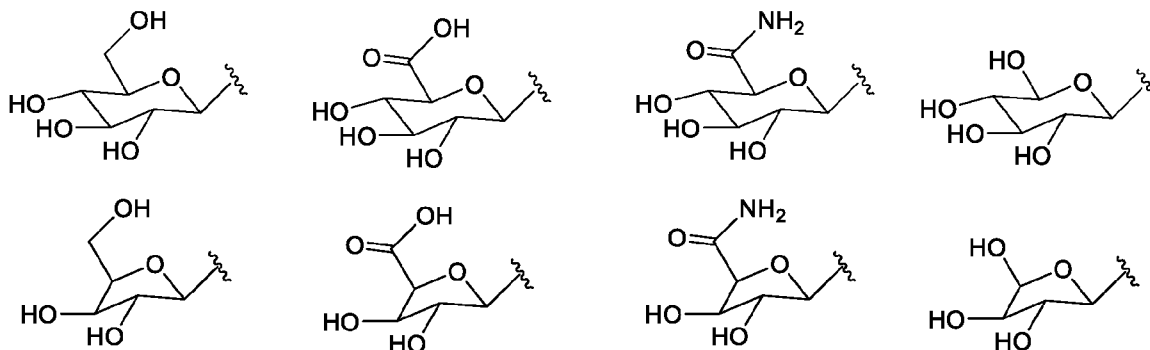
X is C₁₋₃ alkyl, A is , and Y is absent, C₁₋₅ alkoxy, or C₂₋₈ polyethylene glycol, wherein “*” indicates the attachment point to X, and “#” indicates the attachment point to Y.

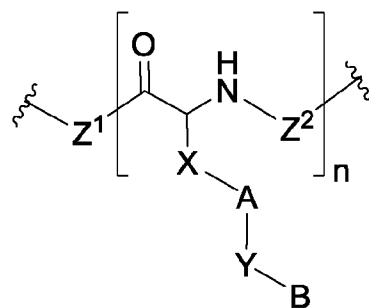


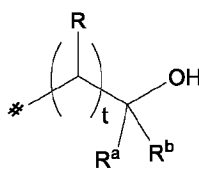
5 [88] In some embodiments, the linker can be featured as , wherein

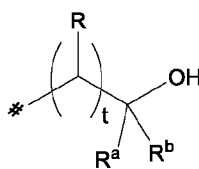


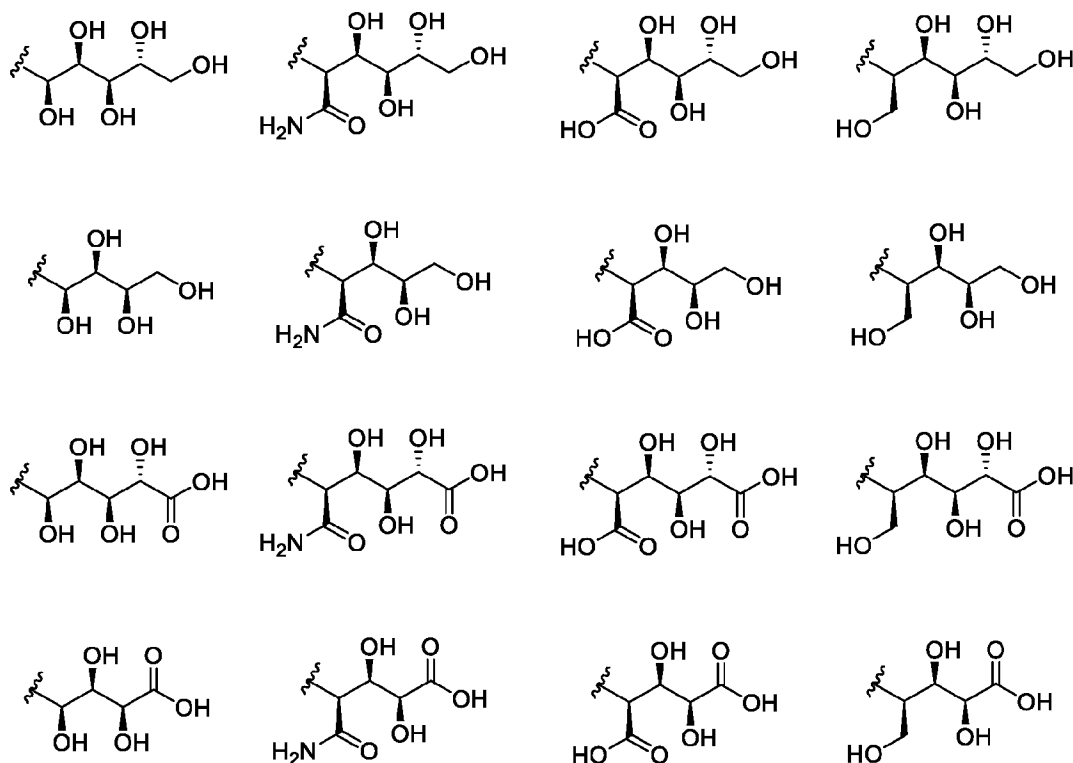
B is a cyclic polyhydroxy group having the structure of , wherein “#” indicates the attachment point to Y, r is 1-2, s is 3-4, and each R, independently, is OH, -CH₂OH, -CO₂H, -CONH₂, NH₂, or NHCOCH₃, wherein B comprises at least three OH groups. In certain embodiments, B is one of the following, or a stereoisomer thereof:

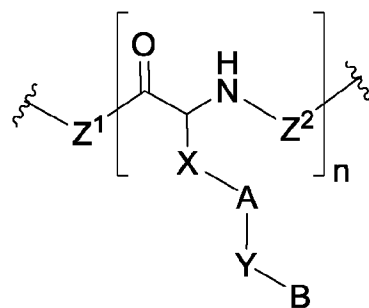




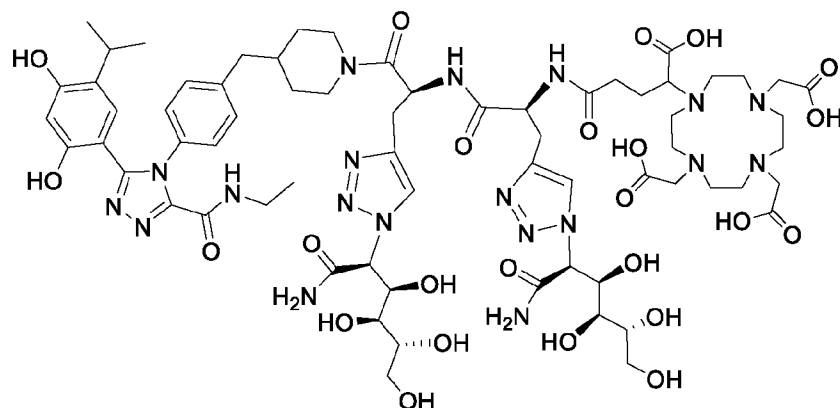
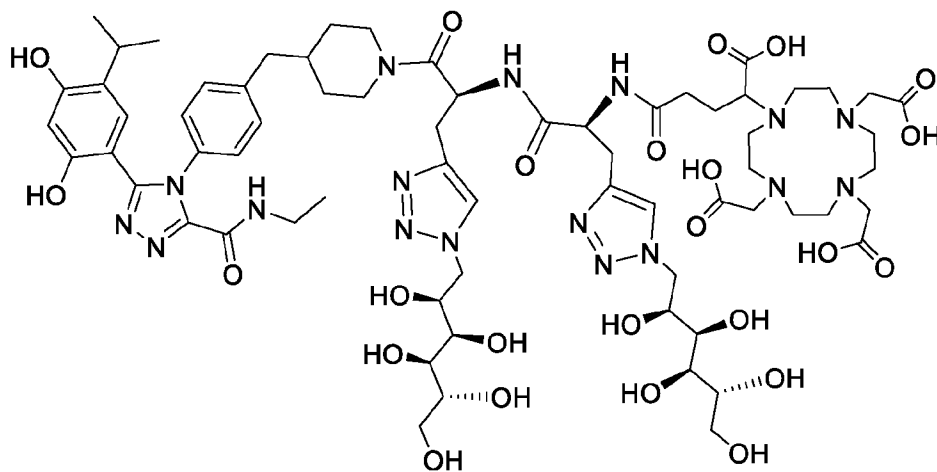
[89] In some embodiments, the linker can be featured as , wherein

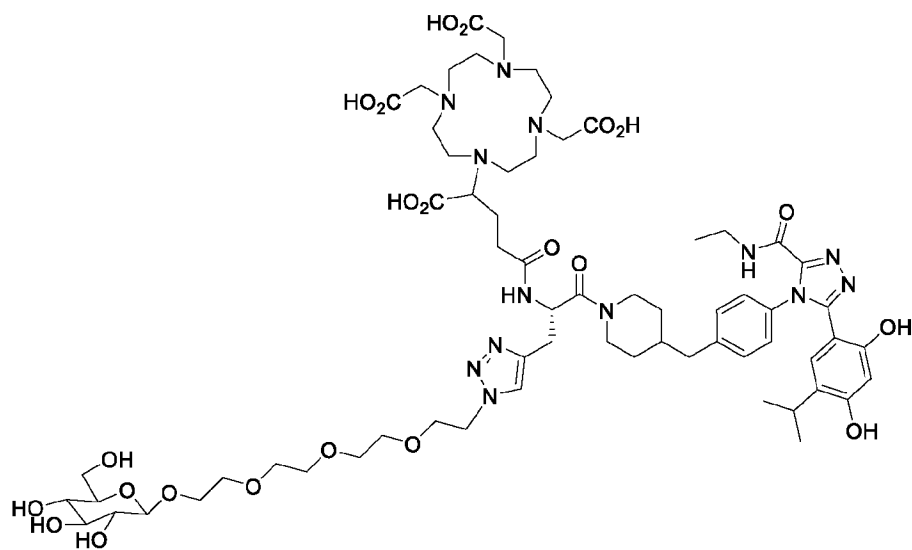
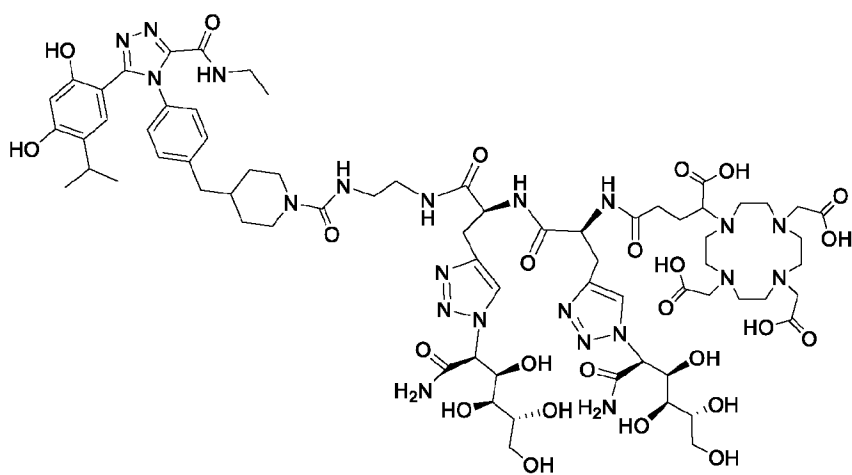
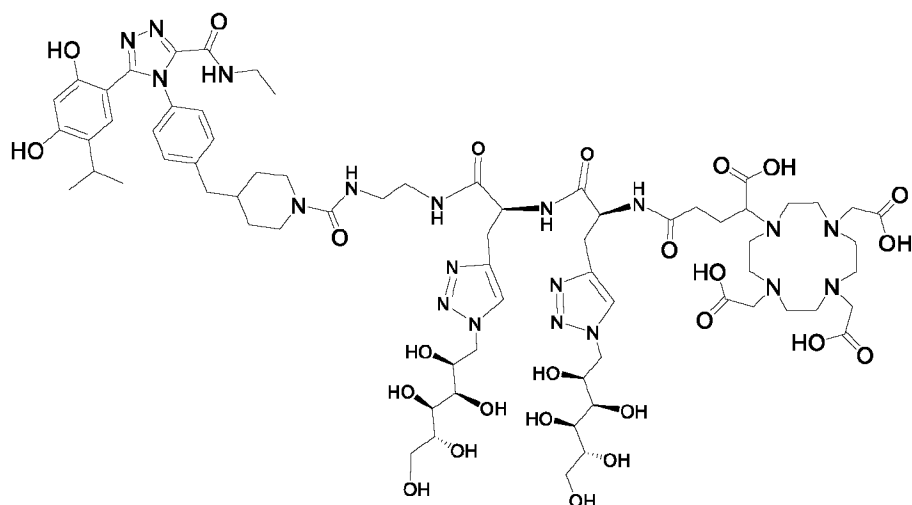
B is an acyclic polyhydroxy group having the structure of , wherein “#” indicates the attachment point to Y; t is 2-5; each R, independently, is OH, -CH₂OH, -CO₂H, -CONH₂, NH₂, or NHCOCH₃; and R^a and R^b each are H or R^a and R^b together form C=O, wherein B comprises at least three OH groups. In certain embodiments, B is one of the following, or a stereoisomer thereof:

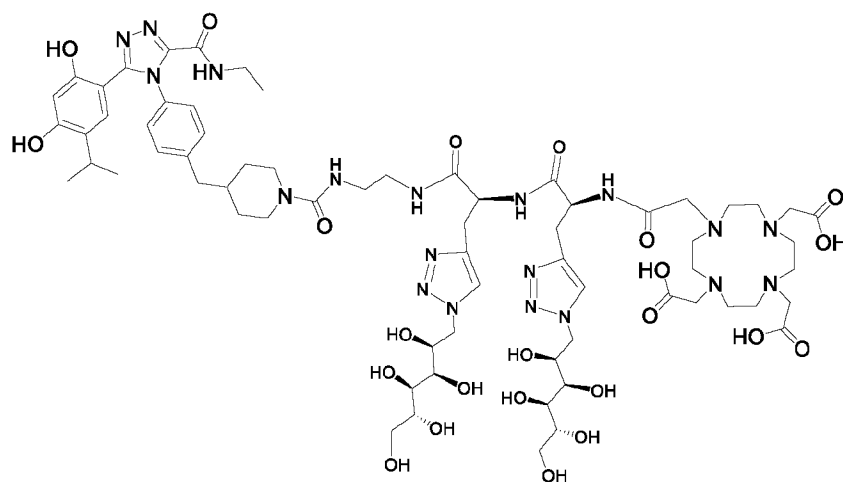
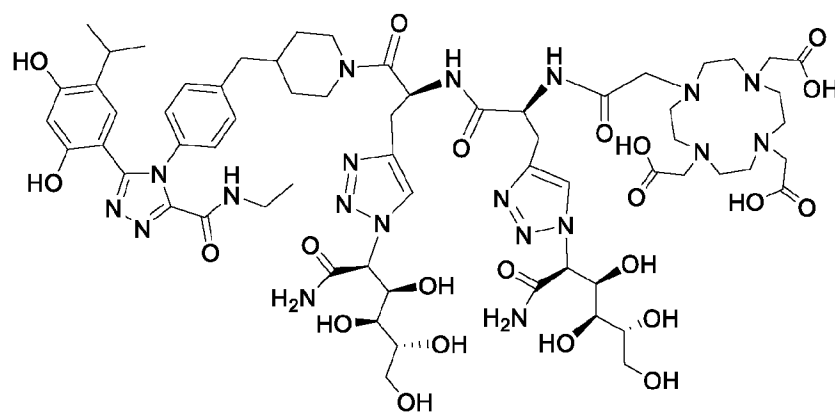
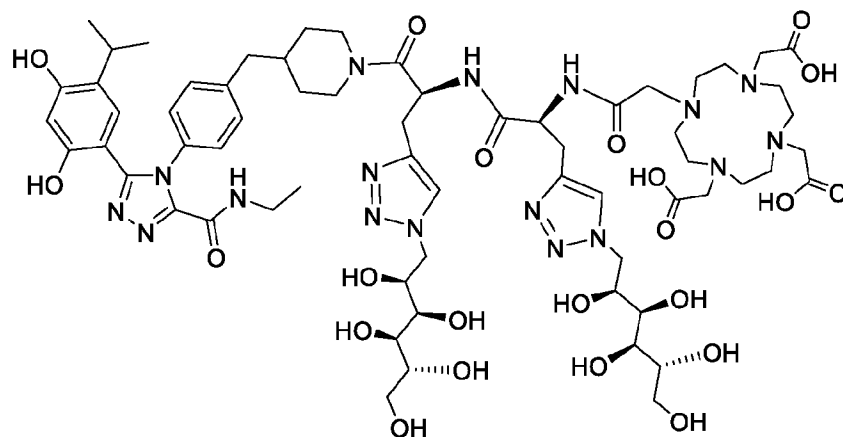


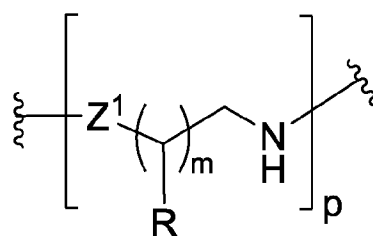
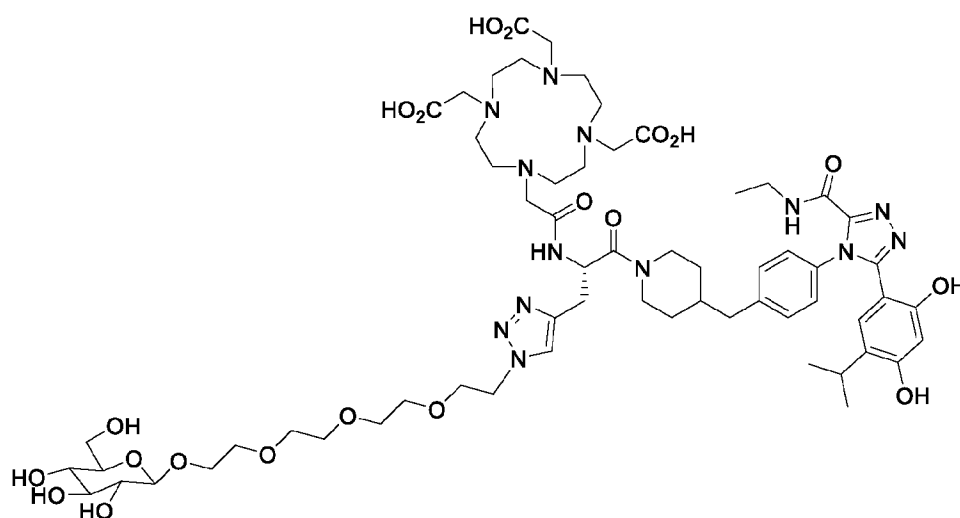
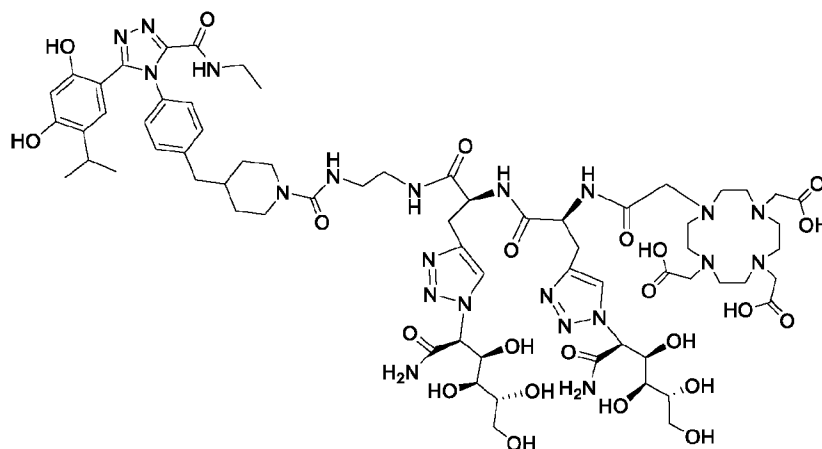


[90] In some embodiments, the linker can be featured as
a representative exemplary compound is one of the following:

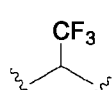
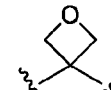


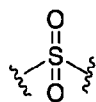




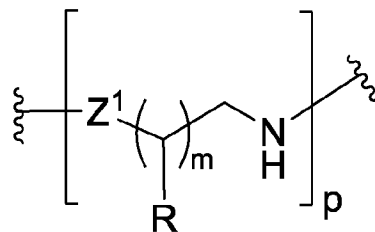


5 [91] In some embodiments, the linker can be featured as

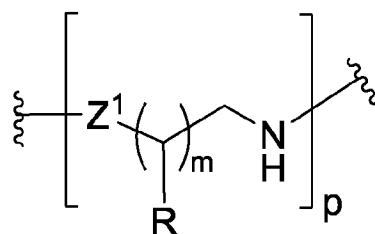
wherein Z^1 is a moiety selected from the group consisting of $C=O$, , ,

, $(C=O)NR^1$, $NR^1(C=O)NR^2$, $(CH_2CH_2)NR^2$, an amino acid unit, and a combination

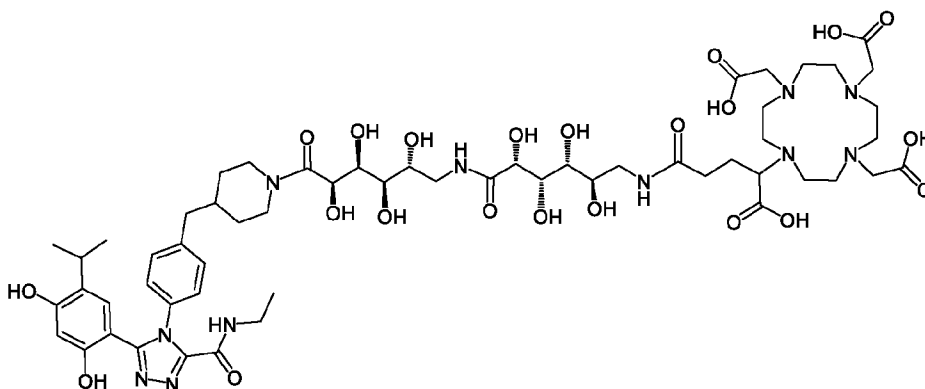
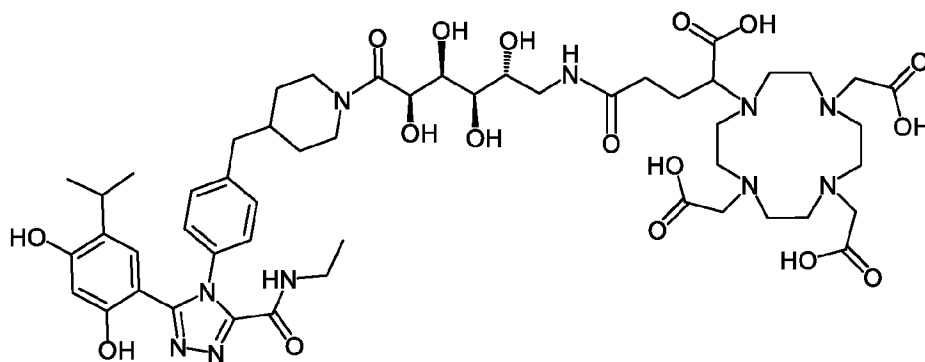
thereof, in which each of R^1 and R^2 independently is H or C_{1-5} alkyl; m is an integer of 1-5 (inclusive), p is an integer of 1-4 (inclusive); and R in each occurrence, independently, is OH, $-CH_2OH$, $-CO_2H$, $CONH_2$, NH_2 , or $NHCOCH_3$, wherein the linker is a hydrophilic space linker comprising at least three OH groups.

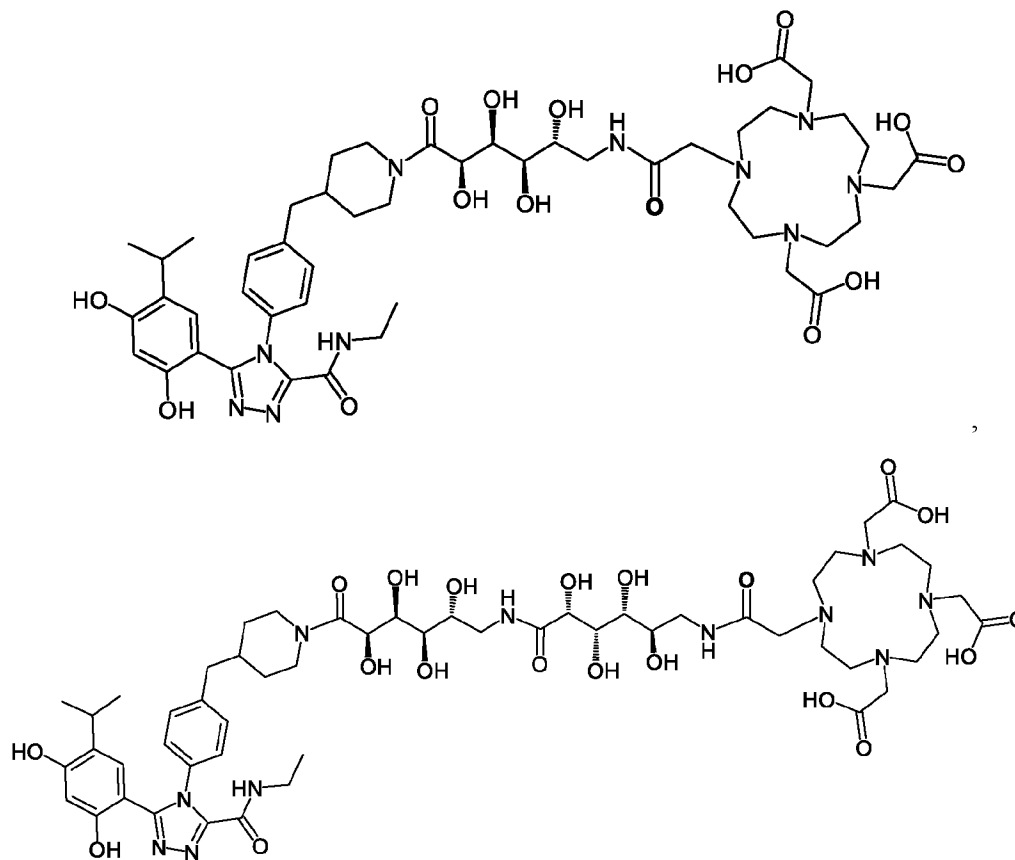


- 5 [92] In some embodiments, the linker can be featured as Z^1 is $C=O$, m is 3-4, p is 1-2, and R is OH or $-CH_2OH$.

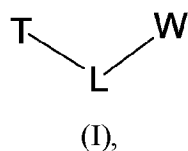


[93] In some embodiments, the linker can be featured as a representative exemplary compound is one of the following:

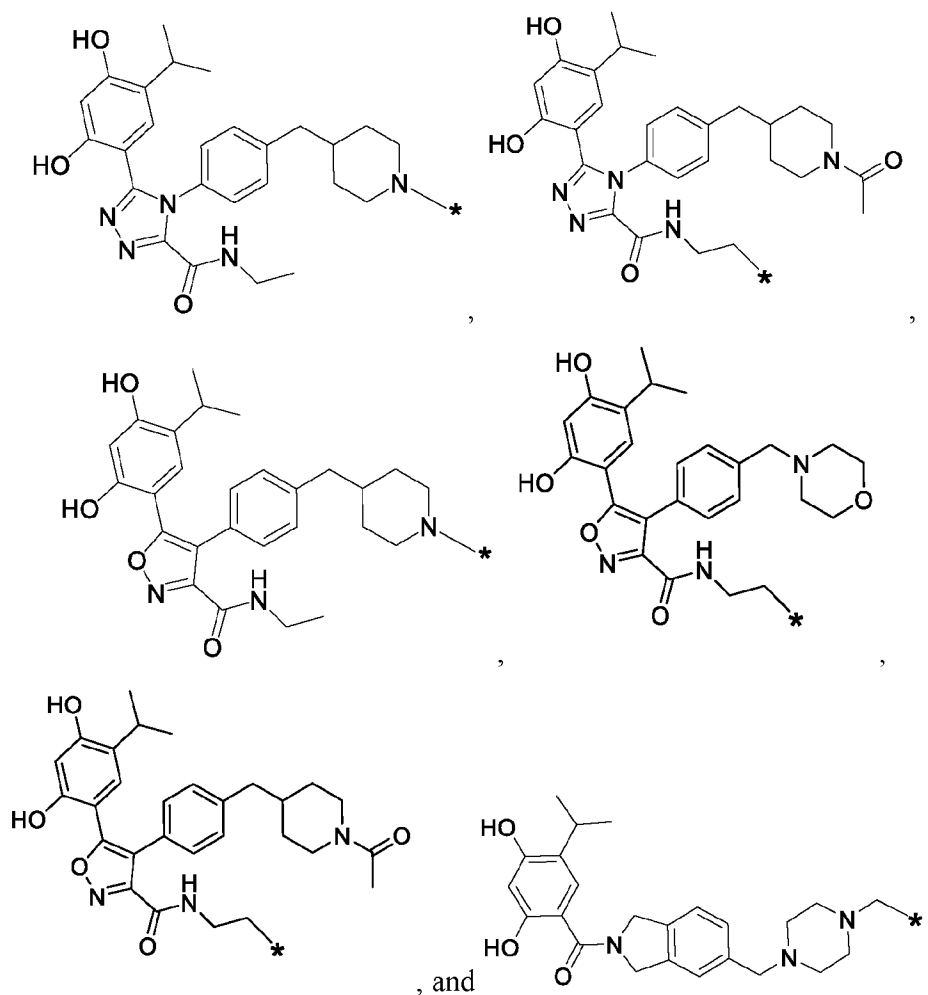




[94] In some embodiments, the compounds of this disclosure have a structure of Formula I:

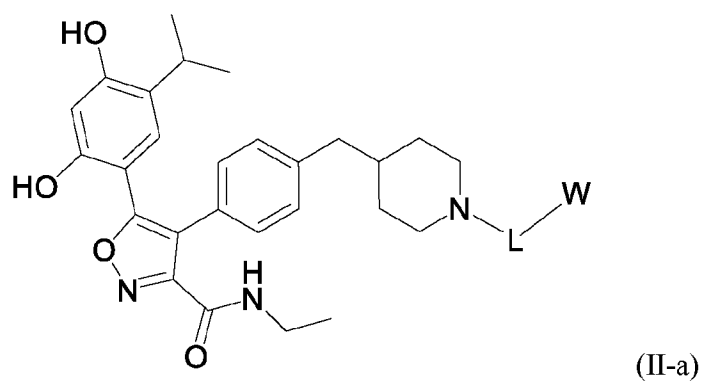


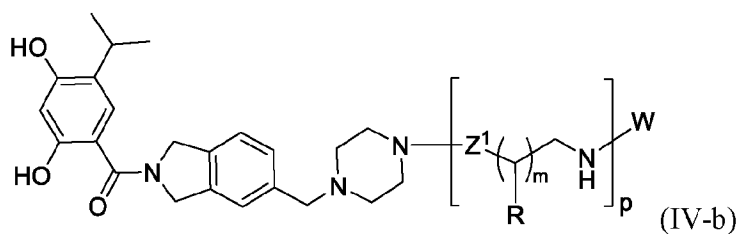
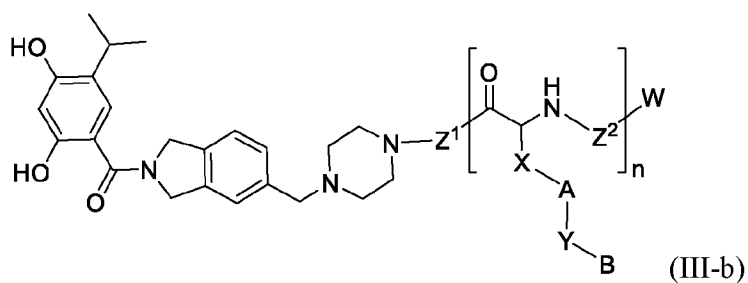
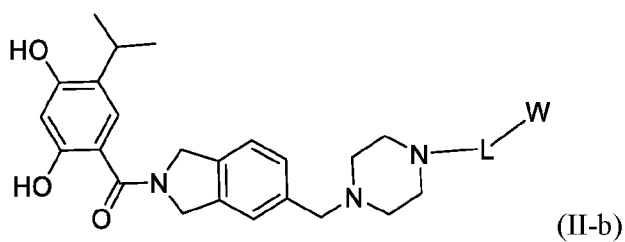
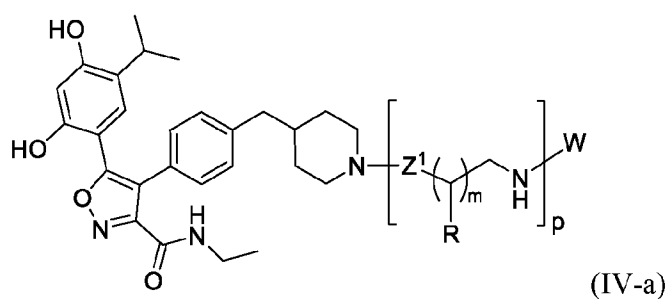
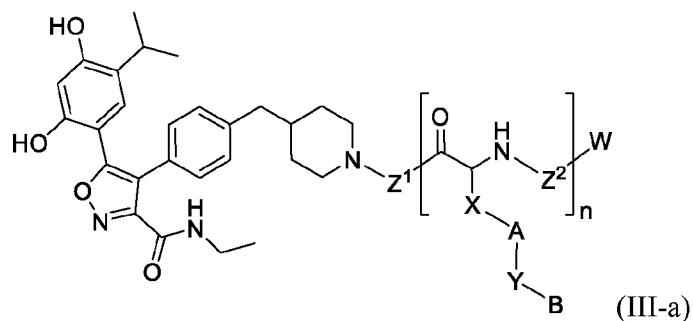
wherein T is a targeting moiety that binds to HSP90, L is a hydrophilic space linker comprising one or more cyclic or acyclic polyhydroxy groups, and W is a chelator, wherein the compound optionally further comprises a radionuclide chelated by the chelator thereof, wherein the targeting moiety is selected from the group consisting of:



wherein "*" indicates the attachment point to L.

- 5 [95] In some embodiments, the compounds of this disclosure have a structure selected from one of the following Formulas (II-a), (III-a), (IV-a), (II-b), (III-b), and (IV-b):





wherein each of the variables in Formulas (II-a), (III-a), (IV-a), (II-b), (III-b), and (IV-b) can respectively be any of the moieties described herein for Formulas II, III, and IV, and wherein the compound optionally further comprises a radionuclide chelated by the chelator thereof.

Subjects

[96] In some disclosed methods, a therapy (e.g., comprising a therapeutic agent) is administered to a subject. In some embodiments, the subject is a mammal, e.g., a human.

[97] In some embodiments, the subject has cancer or is at risk of developing cancer. For

5 example, the subject may have been diagnosed with cancer. The cancer may be a primary cancer or a metastatic cancer. Subjects may have any stage of cancer, e.g., stage I, stage II, stage III, or stage IV with or without lymph node involvement and with or without metastases. Provided compositions may prevent or reduce further growth of the cancer and/or otherwise ameliorate the cancer (e.g., prevent or reduce metastases). In some embodiments, the subject does not have
10 cancer but has been determined to be at risk of developing cancer, e.g., because of the presence of one or more risk factors such as environmental exposure, presence of one or more genetic mutations or variants, family history, etc. In some embodiments, the subject has not been diagnosed with cancer.

[98] In some embodiments, the cancer is small-cell lung cancer, non-small-cell lung cancer,
15 sarcoma, pancreatic cancer, breast cancer, or colon cancer.

Administration and dosage*Effective doses*

[99] The present disclosure provides methods of using a compound of Formula I for treating
20 clinical indications expressing HSP90, with the compound administered to a subject (e.g., a human) in an amount therapeutically effective for such treatment.

[100] This disclosure also covers combination therapies in which the amounts of each therapeutic may or may not be, on their own, therapeutically effective. In some embodiments, therapeutic combinations as disclosed herein are administered to a subject in a manner (e.g.,
25 dosing amount and timing) sufficient to cure or at least partially arrest the symptoms of the disorder and its complications. In the context of a single therapy (a “monotherapy”), an amount adequate to accomplish this purpose is defined as a “therapeutically effective amount,” an amount of a compound sufficient to substantially improve at least one symptom associated with the disease or a medical condition. The “therapeutically effective amount” typically varies
30 depending on the therapeutic. For known therapeutic agents, the relevant therapeutically effective amounts may be known to or readily determined by those of skill in the art.

[101] For example, in the treatment of cancer, an agent or compound that decreases, prevents, delays, suppresses, or arrests any symptom of the disease or condition would be therapeutically effective. A therapeutically effective amount of an agent or compound is not required to cure a disease or condition but will provide a treatment for a disease or condition such that the onset of the disease or condition is delayed, hindered, or prevented, or the disease or condition symptoms are ameliorated, or the term of the disease or condition is changed or, for example, is less severe or recovery is accelerated in an individual. For example, a treatment may be therapeutically effective if it causes a cancer to regress or to slow the cancer's growth.

[102] The dosage regimen (e.g., amounts of each therapeutic, relative timing of therapies, etc.) that is effective for these uses may depend on the severity of the disease or condition and the weight and general state of the subject. For example, the therapeutically effective amount of a particular composition comprising a therapeutic agent applied to mammals (e.g., humans) can be determined by the person of ordinary skill in the art with consideration of individual differences in age, weight, and the condition of the mammal. Because certain conjugates of the present disclosure exhibit an enhanced ability to target cancer cells and residualize, the dosage of these compounds can be lower than (e.g., less than or equal to about 90%, 75%, 50%, 40%, 30%, 20%, 15%, 12%, 10%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.1% of) the equivalent dose of required for a therapeutic effect of the unconjugated agent. Therapeutically effective and/or optimal amounts can also be determined empirically by those of skill in the art. Thus, lower effective doses can also be determined by those of skill in the art.

[103] Single or multiple administrations of a radiopharmaceutical or a composition (e.g., a pharmaceutical composition comprising a therapeutic agent or a radiopharmaceutical) can be carried out with dose levels and pattern being selected by the treating physician. The dose and administration schedule can be determined and adjusted based on the severity of the disease or condition in the subject, which may be monitored throughout the course of treatment according to the methods commonly practiced by clinicians or those described herein.

[104] As provided above, a radiopharmaceutical compound of this disclosure may be administered in combination with another therapeutic agent. In the disclosed combination therapy methods, the first and second therapies may be administered sequentially or concurrently to a subject. For example, a first composition comprising a first therapeutic agent and a second composition comprising a second therapeutic agent may be administered sequentially or

concurrently to a subject. Alternatively, a composition comprising a combination of a first therapeutic agent and a second therapeutic agent may be administered to the subject.

[105] In some embodiments, the radiopharmaceutical is administered in a single dose. In some embodiments, the radiopharmaceutical is administered more than once, i.e., multiple doses.

5 When the radiopharmaceutical is administered more than once, the dose of each administration may be the same or different.

[106] In some embodiments, compositions (such as compositions comprising radiopharmaceuticals) are administered for radiation treatment planning or diagnostic purposes. When administered for radiation treatment planning or diagnostic purposes, compositions may
10 be administered to a subject in a diagnostically effective dose and/or an amount effective to determine the therapeutically effective dose. In some embodiments, a first dose of disclosed conjugate or a composition (e.g., pharmaceutical composition) thereof is administered in an amount effective for radiation treatment planning, followed administration of a combination therapy including a conjugate as disclosed herein and another therapeutic.

15 [107] Pharmaceutical compositions comprising one or more agents (e.g., radiopharmaceuticals) can be formulated for use in accordance with disclosed methods and systems in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation. Examples of suitable formulations are found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th
20 ed., 1985. For a brief review of methods for drug delivery, see, e.g., Langer (*Science* 249:1527-1533, 1990).

Formulations

[108] Pharmaceutical compositions may be formulated for parenteral, intranasal, topical, oral,
25 or local administration, such as by a transdermal means, for prophylactic and/or therapeutic treatment. Pharmaceutical compositions can be administered parenterally (e.g., by intravenous, intramuscular, or subcutaneous injection), or by oral ingestion, or by topical application or intraarticular injection at areas affected by the vascular or cancer condition. Examples of additional routes of administration include intravascular, intra-arterial, intratumor,
30 intraperitoneal, intraventricular, intraepidural, as well as nasal, ophthalmic, intrascleral, intraorbital, rectal, topical, or aerosol inhalation administration. Also specifically contemplated

are sustained release administration, by such means as depot injections or erodible implants or components. Suitable compositions include compositions comprising include agents (e.g., compounds as disclosed herein) dissolved or suspended in an acceptable carrier, preferably an aqueous carrier, e.g., water, buffered water, saline, or PBS, among others, e.g., for parenteral administration. Compositions may contain pharmaceutically acceptable auxiliary substances to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents, or detergents, among others. In some embodiments, compositions are formulated for oral delivery; for example, compositions may contain inert ingredients such as binders or fillers for the formulation of a unit dosage form, such as a tablet or a capsule. In some embodiments, compositions are formulated for local administration; for example, compositions may contain inert ingredients such as solvents or emulsifiers for the formulation of a cream, an ointment, a gel, a paste, or an eye drop.

[109] Compositions may be sterilized, e.g., by conventional sterilization techniques, or sterile filtered. Aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 6 and 7, such as 6 to 6.5. In some embodiments, compositions in solid form are packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents, such as in a sealed package of tablets or capsules. In some embodiments, compositions in solid form are packaged in a container for a flexible quantity, such as in a squeezable tube designed for a topically applicable cream or ointment.

Analytical Assays

[110] Provided below are analytical assays for characterizing the compounds of Formula I.

[111] Analytical HPLC-MS is performed using a Waters Acquity HPLC-MS system comprised of a Waters Acquity Binary Solvent Manager, a Waters Acquity Sample Manager, a Water Acquity Column Manager (column temperature 30 °C), a Waters Acquity Photodiode Array Detector (monitoring at 254 nm and 214 nm), a Waters Acquity TQD with electrospray ionization and a Waters Acquity BEH C18, 2.1 x 50 mm (1.7 µm) column or using a Waters UPLC-MS-Xevo TQS -Cronos system. Preparative HPLC is performed using a Waters HPLC

system comprised of a Waters 1525 Binary HPLC pump, a Waters 2489 UV/Visible Detector (monitoring at 254 nm and 214 nm) and a Waters XBridge Prep C18 19 x 100 mm (5 µm) column or Waters XBridge Prep Phenyl 19 x 100 mm (5 µm).

[112] . Preparative HPLC is performed using a Waters HPLC system comprised of a Waters 1525 Binary HPLC pump, a Waters 2489 UV/Visible Detector (monitoring at 254 nm and 214 nm) and a Waters XBridge Prep C18 19 x 100 mm (5 µm) column or Waters XBridge Prep Phenyl 19 x 100 mm (5 µm).

[113] HPLC elution method 1: Waters Acquity BEH C18 2.1 x 50 mm (1.7 µm) column; mobile phase A: H₂O (0.1% v/v TFA); mobile phase B: acetonitrile (0.1% v/v TFA); flow rate = 0.3 mL/min; wavelength = 214, 254 nm; initial = 90% A, 3 min = 0% A, 3.5 min = 0% A, 4 min = 90% A, 5 min = 90% A.

[114] HPLC elution method 2: Waters Acquity BEH C18 2.1 x 50 mm (1.7 µm) column; mobile phase A: H₂O (0.1% v/v TFA); mobile phase B: acetonitrile (0.1% v/v TFA); flow rate = 0.3 mL/min; wavelength = 214, 254 nm; initial = 90% A, 8 min = 0% A, 10 min = 0% A, 11 min = 90% A, 12 min = 90% A.

[115] HPLC elution method 3: Waters Acquity BEH C18 2.1 x 50 mm (1.7 µm) column; mobile phase A: H₂O (0.1% v/v Formic Acid); mobile phase B: acetonitrile (0.1% v/v Formic Acid); flow rate = 0.3 mL/min; wavelength = 214, 254 nm; initial = 90% A, 3 min = 0% A, 3.5 min = 0% A, 4 min = 90% A, 5 min = 90% A.

[116] HPLC elution method 4: Waters Acquity BEH C18 2.1 x 50 mm (1.7 µm) column; mobile phase A: H₂O (0.1% v/v Formic Acid); mobile phase B: acetonitrile (0.1% v/v Formic Acid); flow rate = 0.3 mL/min; wavelength = 214, 254 nm; initial = 90% A, 8 min = 0% A, 10 min = 0% A, 11 min = 90% A, 12 min = 90% A.

[117] Actinium-225 (²²⁵Ac) was supplied by the U.S. Department of Energy Isotope Program in the Office of Science for Nuclear Physics or the Canadian Nuclear Laboratories. Lutetium-177 (¹⁷⁷Lu) was received from ITM Pharma Solutions GmbH or Monrol. Indium-111 (¹¹¹In) was received from BWXT Medical.

[118] RadioTLC was performed with Bioscan AR-2000 Imaging Scanner, carried out on iTLC-SG glass microfiber chromatography paper (Agilent Technologies, SGI0001) or iTLC-SA glass microfiber chromatography paper (Agilent Technologies, A120B12).

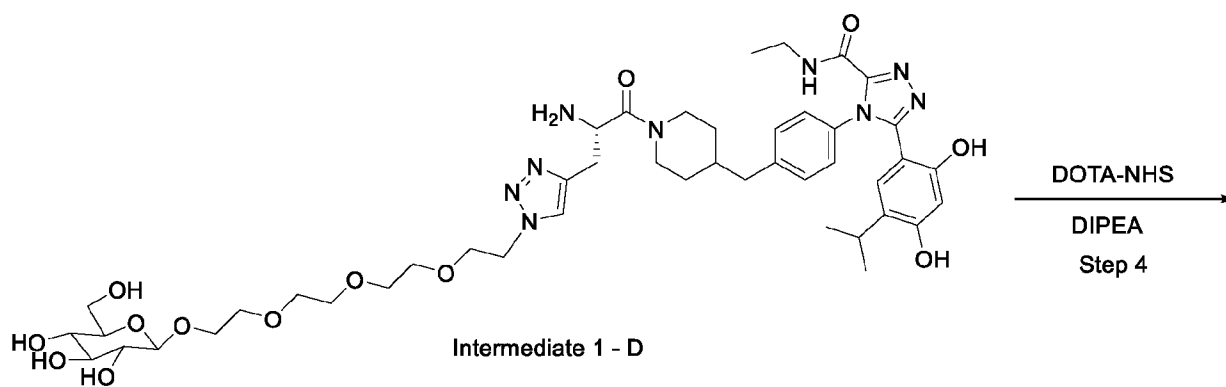
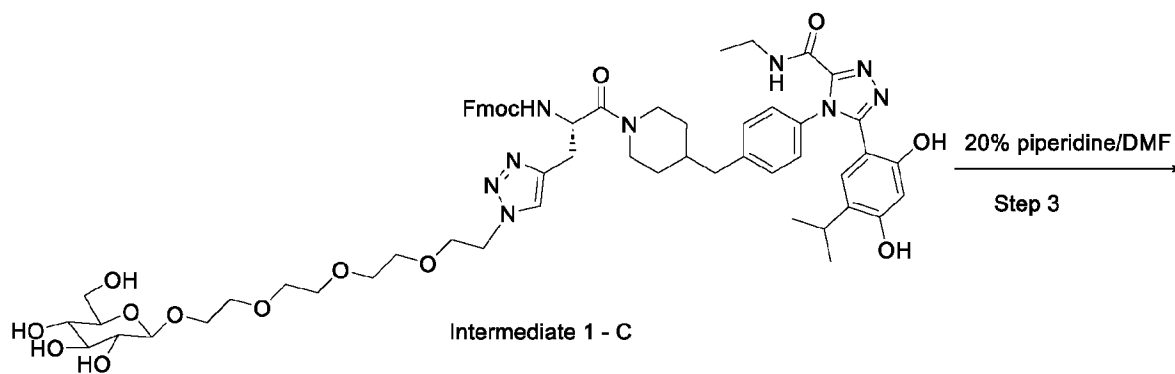
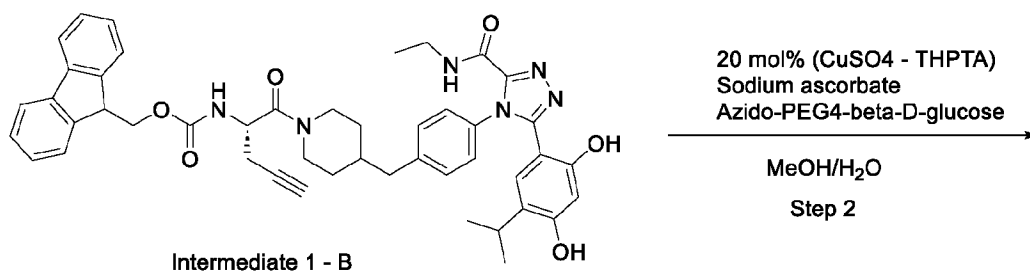
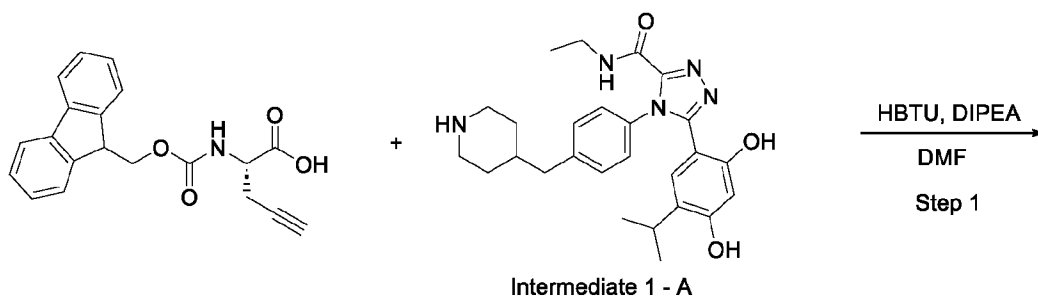
[119] Radioactive HPLC was performed using a Waters system comprised of a Waters 1525 Binary HPLC pump, a Waters 2489 UV/Visible Detector (monitoring at 254 and 214 nm), a Bioscan Flow Count radiodetector (FC-3300) and a reverse phase (C18) column, or an Agilent 1260 Infinity II LC system comprised of a G7111B Quat Pump, a G7129A Vial sampler, a G1364F analytical scale fraction collector, a G7114A variable wavelength detector (monitoring at 254 nm), a G7116A 1260 MCT column unit, a Bioscan Flow Count radiodetector (FC-3300), and a reverse phase (C18) column.

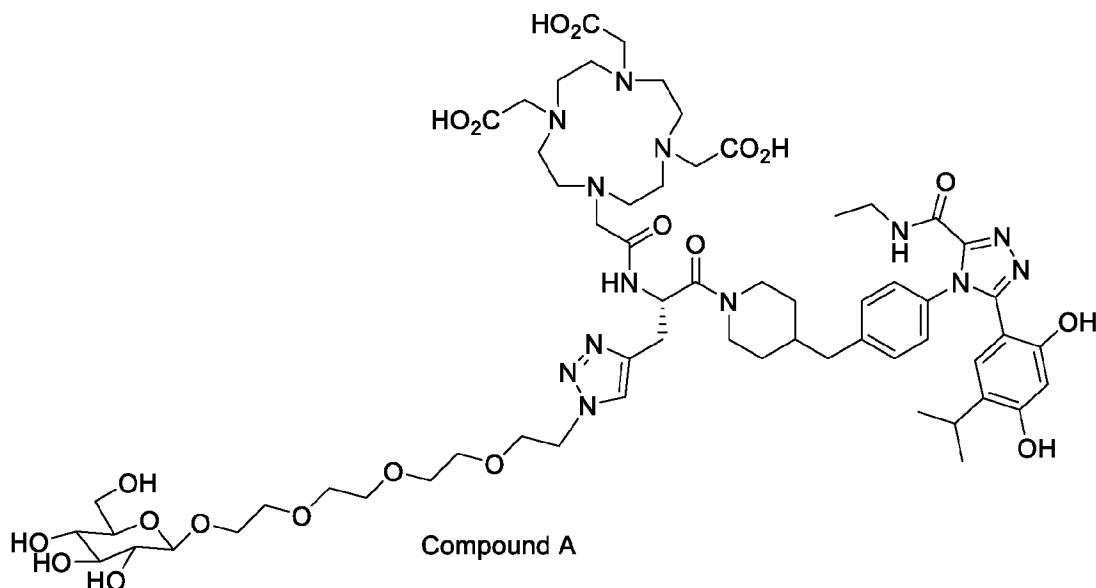
EXAMPLES

Example 1. Synthesis of Radiopharmaceuticals Comprising Compounds of Formula I

[120] Compounds of Formula I comprise conjugates targeting HSP90, which can be radiolabeled with a radionuclide such as Indium-111 (^{111}In), Lutetium-177 (^{177}Lu), or Actinium-225 (^{225}Ac) to form radionuclide-chelated radiopharmaceuticals. The synthesis of compounds of Formula I, or their radionuclide-chelated radiopharmaceuticals, can be referred to WO 2020/205948. Below are the synthetic schemes or protocols that can be followed to synthesize the corresponding compounds. A person of ordinary skill in the art would have been able, based on the disclosures provided herein and the knowledge in the field, to prepare the depicted compounds and their structurally similar analogs (e.g., compounds with different chelators such as DOTA, NOTA, and NODA-GA).

Scheme 1: Synthesis of 2,2',2''-(10-(2-(((*S*)-1-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4*H*-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-1-oxo-3-(1-(2-(2-(2-(((2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**Compound A**):





Step 1: Synthesis of (9H-Fluoren-9-yl)methyl (S)-(1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-1-oxopent-4-yn-2-yl)carbamate

5 **(Intermediate 1 – B):**

[121] To a 20 mL scintillation vial with a stir bar was loaded 5-(2,4-Dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(piperidin-4-ylmethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide **(Intermediate 1 – A)** as the HCl salt (20 mg, 39.6 μmol , 1 equiv.), Fmoc-L-propargylglycine (13.7 mg, 39.6 μmol , 1 equiv.), HBTU (15.5 mg, 39.6 μmol , 1 equiv.) followed by DMF (2 mL).

10 Lastly, DIPEA (13.8 μL , 79.2 μmol , 2 equiv.) was added and the reaction was stirred at room temperature (24 $^{\circ}\text{C}$) and monitored by HPLC-MS. After 2 h additional DIPEA (6.9 μL , 39.6 μmol , 1 equiv.) was added and the reaction was stirred for 1 h further then stopped by concentration under vacuum. The crude product was purified by reverse phase -C18 column chromatography to give **Intermediate 1 – B** (24.2 mg, 56%, purity: 93%) as a clear residue as the TFA salt. An aliquot was analyzed by HPLC-MS elution using elution method 1; retention

15 time: 2.90 min; MS (positive ESI): found m/z 781.0 $[\text{M}+\text{H}]^{+}$; $\text{C}_{46}\text{H}_{49}\text{N}_6\text{O}_6$ (calc. 781.4).

Step 2: Synthesis of (9H-Fluoren-9-yl)methyl ((S)-1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-1-oxo-3-(1-(2-(2-(2-(2-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-

20

yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)propan-2-yl)carbamate (**Intermediate 1 – C**):

[122] To a solution of **Intermediate 1 – B** (3.2 mg, 3.0 μmol , 1 equiv.) and Azido-PEG4-beta-D-glucose (1.3 mg, 3.3 μmol , 1.1 equiv.) in methanol (100 μL) and a stir bar was added

5 $\text{CuSO}_4 \cdot \text{THPTA}$ (2.42 μL , 0.60 μmol , 0.2 equiv.) freshly prepared from 0.5 M aqueous solutions of CuSO_4 and THPTA in analogy to *J. Am. Chem. Soc.* 2017, 139, 3528. Lastly, sodium ascorbate (12.0 μL of a 0.5 M aqueous solution, 6.0 μmol , 2 equiv.) was added to the reaction and stirred at room temperature (22 $^\circ\text{C}$) and monitored by HPLC-MS. After 50 min the reaction was stopped by concentration under vacuum and the crude product was purified by preparative

10 C18 HPLC to afford **Intermediate 1 – C** (2.0 mg, 47%, purity: 99%) as a white solid as the TFA salt. An aliquot was analyzed by HPLC-MS elution using elution method 2; retention time: 4.21 min; MS (positive ESI): found m/z 1162.2 $[\text{M}+\text{H}]^+$; $\text{C}_{60}\text{H}_{76}\text{N}_9\text{O}_{15}$ (calc. 1162.5).

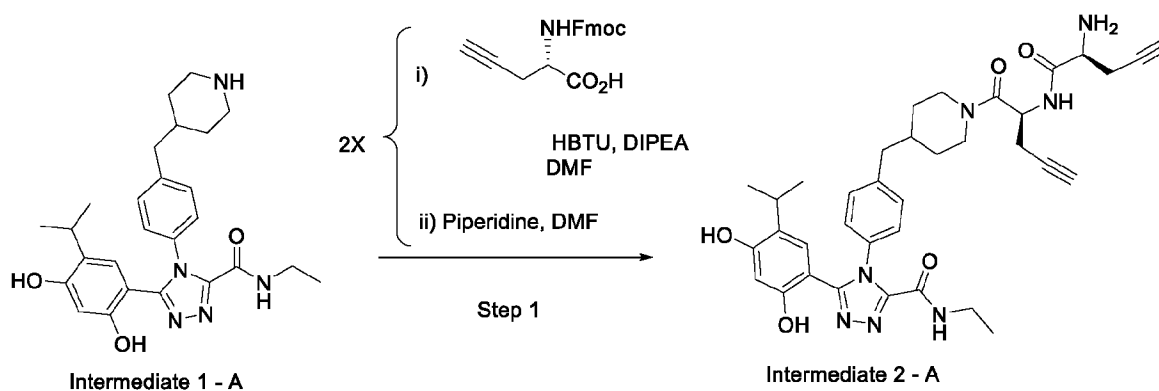
Step 3: Synthesis of 4-(4-(((1-((S)-2-Amino-3-(1-(2-(2-(2-(2-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)propanoyl)piperidin-4-yl)methyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide (**Intermediate 1 – D**):

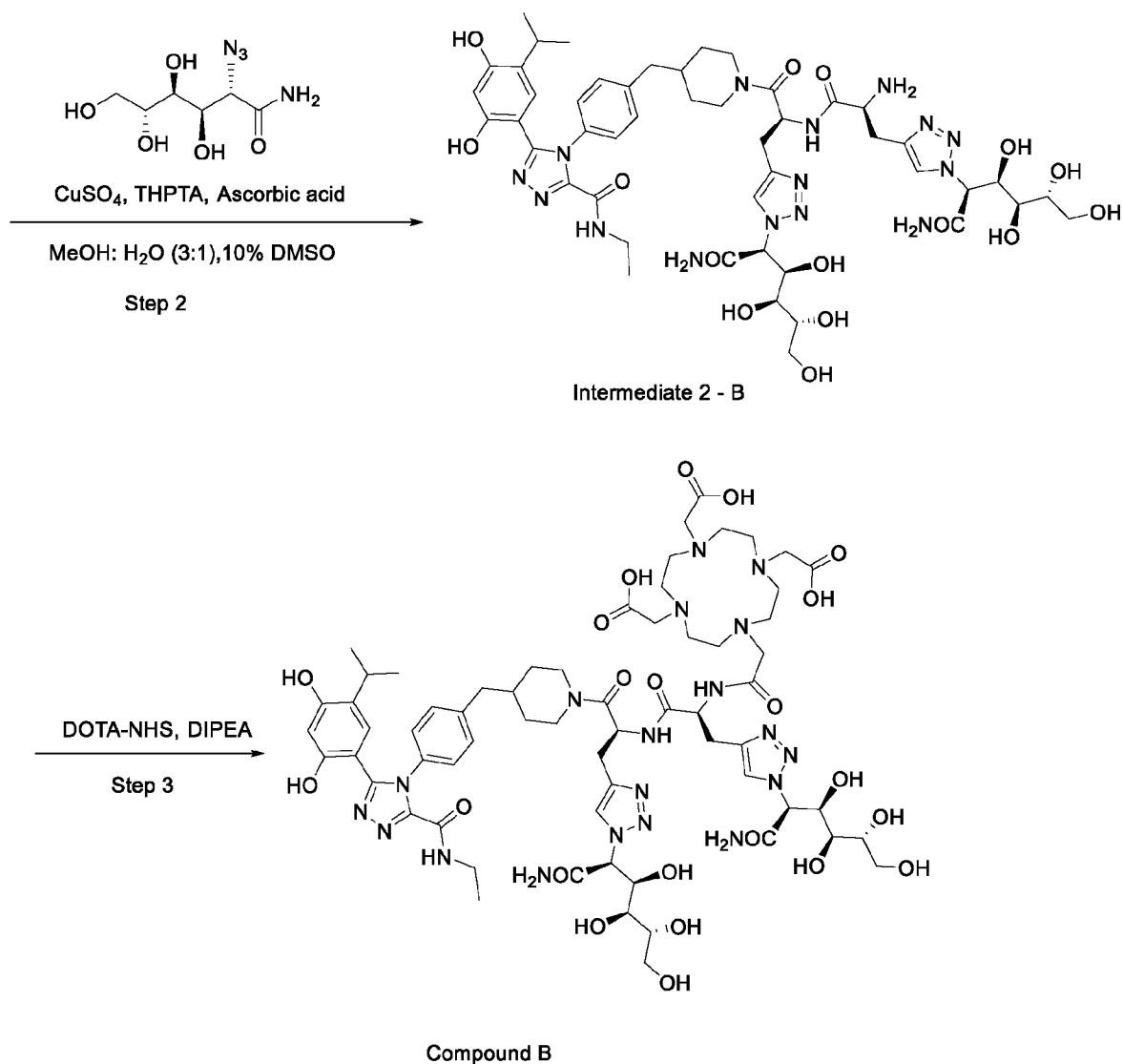
[123] To a vial containing **Intermediate 1 – C** (1.0 mg, 0.72 μmol , 1 equiv.) was added a freshly prepared solution of 20% v/v piperidine in anhydrous DMF (1 mL) and a stir bar. The reaction was then stirred at room temperature (22 $^\circ\text{C}$) and monitored by HPLC-MS. After 10 min the reaction was stopped by concentration under vacuum and the crude product was purified by preparative C18 HPLC to afford **Intermediate 1 – D** (0.8 mg, 91%, purity: 96%) as a white solid as the TFA salt. An aliquot was analyzed by HPLC-MS elution using elution method 1; retention time: 1.56 min; MS (positive ESI): found m/z 940.6 $[\text{M}+\text{H}]^+$; $\text{C}_{45}\text{H}_{66}\text{N}_9\text{O}_{13}$ (calc. 940.5).

Step 4: Synthesis of 2,2',2''-(10-(2-(((S)-1-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-1-oxo-3-(1-(2-(2-(2-(2-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)propan-2-yl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**Compound A**):

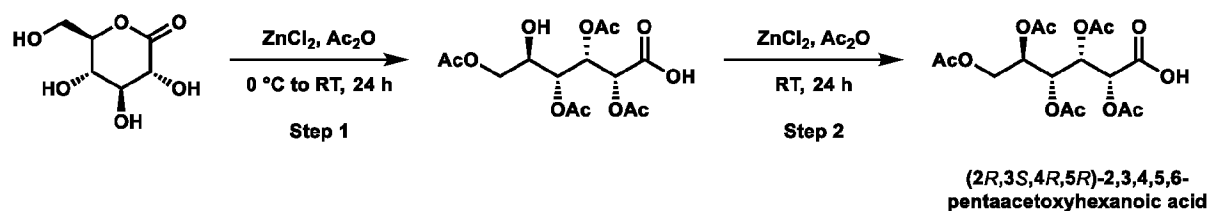
[124] To a vial containing **Intermediate 1 – D** (0.8 mg, 0.7 μ mol, 1 equiv.) was added a stir bar, anhydrous DMF (0.5 mL) and DOTA-NHS ester HPF₆-TFA salt (0.7 mg, 0.8 μ mol, 1.2 equiv). Lastly, DIPEA (0.5 μ L, 2.7 μ mol, 4 equiv.) was added and the reaction was stirred at room temperature (22 °C) and monitored by HPLC-MS. The reaction was redosed with DIPEA after 1 h and 2.5 h (1 μ L, 5.4 μ mol, 8 equiv. and 2 μ L, 10.8 μ mol, 16 equiv. additions respectively) as well as redosed at 3h 15 min with DOTA-NHS ester HPF₆-TFA salt (0.8 mg, 0.9 μ mol, 1.4 equiv.) and DIPEA (1 μ L, 5.4 μ mol, 8 equiv.). The reaction was then stopped after 1.5 h by concentration under vacuum and the crude product was purified by preparative C18 HPLC to afford **Compound A** (0.4 mg, 44%, purity: 99%) as a white solid as the TFA salt. An aliquot was analyzed by HPLC-MS elution using elution method 2; retention time: 2.47 min; MS (positive ESI): found m/z 1326.3 $[M+H]^+$; C₆₁H₉₂N₁₃O₂₀ (calc. 1326.6).

Scheme 2: Synthesis of 2,2',2''-(10-(2-(((S)-3-(1-((2S,3R,4S,5R)-1-Amino-3,4,5,6-tetrahydroxy-1-oxohexan-2-yl)-1H-1,2,3-triazol-4-yl)-1-(((S)-3-(1-((2S,3R,4S,5R)-1-amino-3,4,5,6-tetrahydroxy-1-oxohexan-2-yl)-1H-1,2,3-triazol-4-yl)-1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**Compound B**)





Scheme 3: Synthesis of (2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-Pentaacetoxyhexanoic acid



5

Step 1: Synthesis of 2,3,4,6-Tetra-O-acetyl-D-gluconic acid

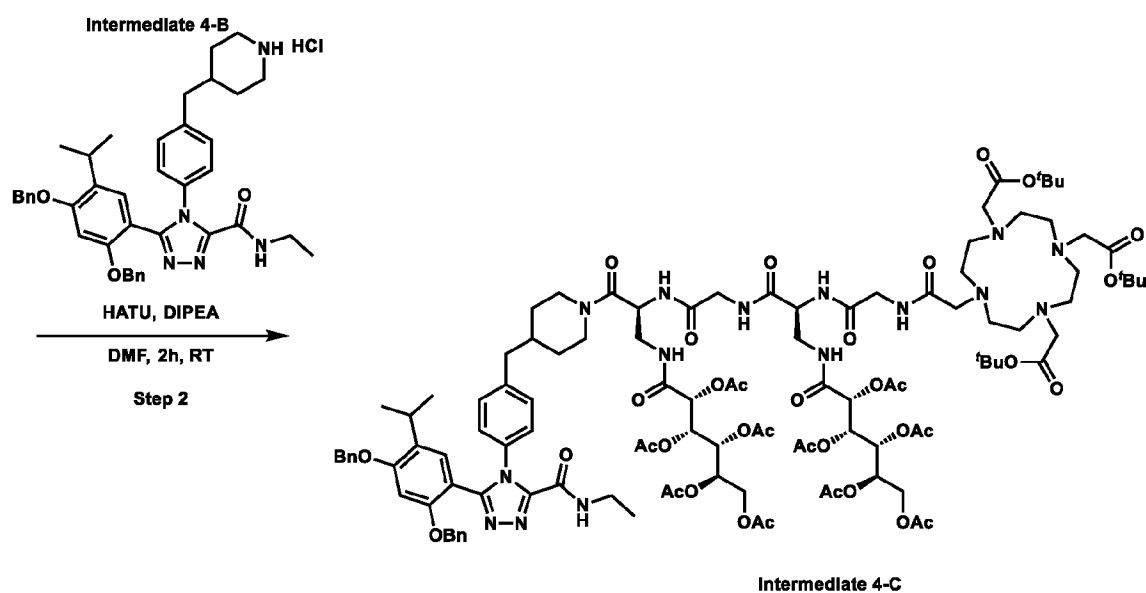
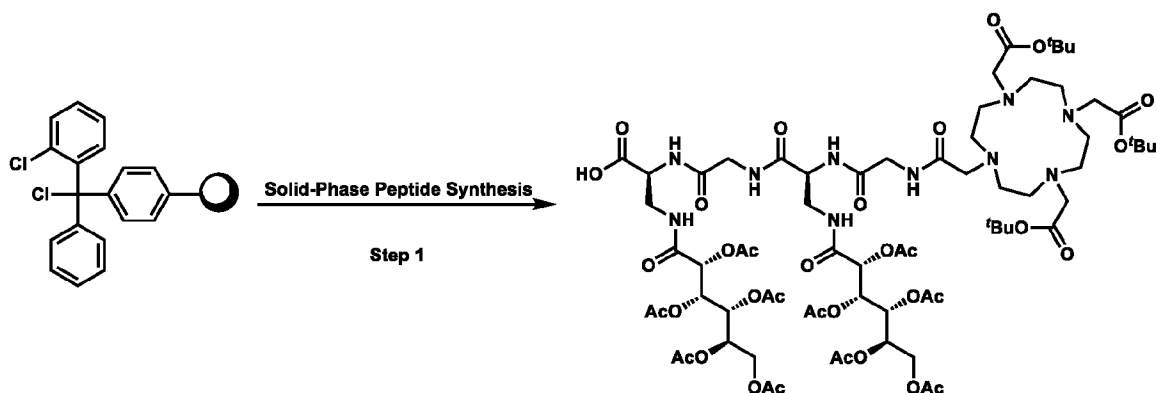
This compound was prepared according to the literature (*Org. Synth.* **1961**, *41*, 79). Briefly, zinc (II) chloride (0.23 g, 1.68 mmol) was added to 3 mL of acetic anhydride and cooled on an ice/water bath. D-glucono- δ -lactone (0.50 g, 2.81 mmol) was added, and the mixture stirred for 1 hour, at which point the mixture was allowed to warm to room temperature and stirred for 24 hours. 12 mL of water was added and stirring continued until the solution was homogeneous. The solution was placed in the refrigerator overnight, at which point crystals had formed. These were collected by vacuum filtration, washed with several portions of ice-cold water, and dried under vacuum to give the product as a colourless, crystalline solid (562 mg, 55%). MS (ESI+) m/z calculated for $C_{14}H_{20}NaO_{11}$ $[M+Na]^+$ 387.1; found 387.2.

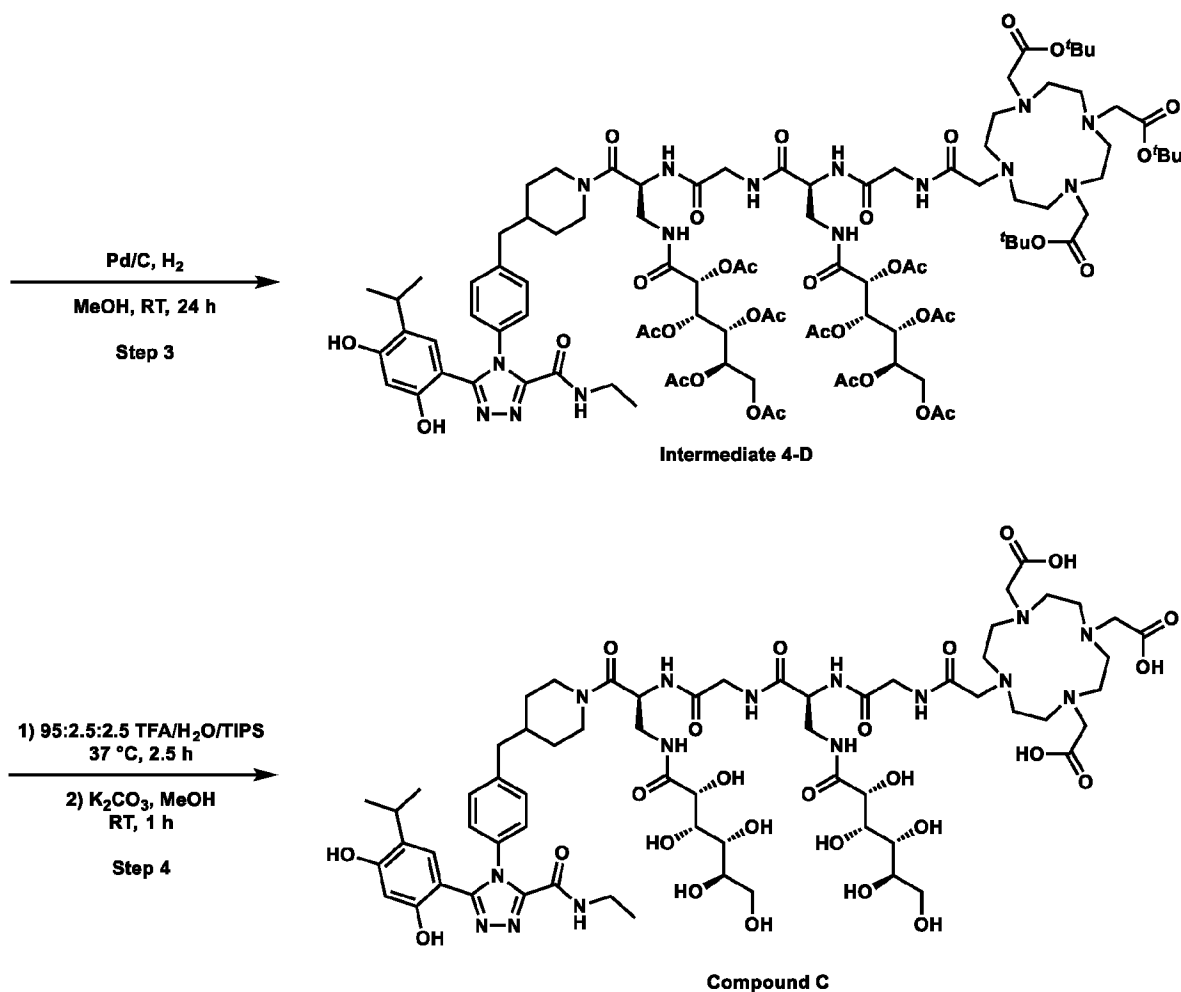
Step 2: Synthesis of 2,3,4,5,6-Penta-O-acetyl-D-gluconic acid

This compound was prepared according to the literature (*Org. Synth.* **1961**, *41*, 79) with some modification. Briefly, zinc (II) chloride (0.20 g, 1.47 mmol) was added to 2 mL of acetic anhydride and the solution stirred for 10 minutes. 2,3,4,6-Tetra-O-acetyl-D-gluconic acid (0.55 g, 1.51 mmol) was added and the mixture stirred at room temperature overnight. 10 mL of water was added, and the mixture stirred until the solution was homogeneous. The mixture was transferred to a separatory funnel and extracted with chloroform (3 x 5 mL). The combined organics were washed with brine (10 mL) and dried over anhydrous sodium sulfate. The solution was filtered and evaporated under reduced pressure. 5 mL of toluene was added, and the solvent evaporated. This was repeated several times to remove all traces of acetic acid. The final product was obtained as a colourless syrup which solidified upon storage in the freezer (517 mg, 84%). MS (ESI+) m/z calculated for $C_{16}H_{22}NaO_{12}$ $[M+Na]^+$ 429.1; found 429.2.

Scheme 4: Synthesis of (2*R*,3*R*,4*S*,5*R*,9*S*,15*S*,19*R*,20*S*,21*R*,22*R*)-9-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4*H*-1,2,4-triazol-4-yl)benzyl)piperidine-1-carbonyl)-6,11,14,18-tetraoxo-15-(2-(2-(4,7,10-tris(2-(*tert*-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetamido)acetamido)-7,10,13,17-tetraazatricosane-1,2,3,4,5,19,20,21,22,23-decayl decaacetate 2,2',2''-(10-((7*S*,13*S*,17*R*,18*S*,19*R*,20*R*)-13-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4*H*-1,2,4-triazol-4-yl)benzyl)piperidine-1-carbonyl)-17,18,19,20,21-pentahydroxy-2,5,8,11,16-pentaoxo-7-(((2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-

pentahydroxyhexanamido)methyl)-3,6,9,12,15-pentaazahenicosyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (**Compound C**)





Step 1: Synthesis of (2*S*,8*S*,12*R*,13*S*,14*R*,15*R*)-12,13,14,15-Tetraacetoxy-4,7,11,18-tetraoxo-2-(((2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentaacetoxyhexanamido)methyl)-8-(2-(2-(4,7,10-tris(2-(*tert*-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetamido)acetamido)-17-oxa-3,6,10-triazanonadecanoic acid (**Intermediate 4-A**):

The protected peptide was synthesized by solid-phase peptide synthesis (SPPS) on 2-chlorotritylchloride resin (Chem-Impex, 0.72 mmol/g, 139 mg, 0.1 mmol). Fmoc-Dap(alloc)-OH (205 mg, 0.50 mmol) was dissolved in DMF (4 mL) with potassium iodide (16 mg, 0.1 mmol) and DIPEA (174 μ L, 1.0 mmol). The resulting solution was combined with the resin and stirred at room temperature overnight. Fmoc deprotection was performed for 5 and 15 minutes with 20% piperidine in DMF. Subsequent couplings were performed using 0.3 mmol of protected amino acids (Fmoc-Gly-OH, Fmoc-Dap(alloc)-OH, Fmoc-Gly-OH), 0.3 mmol of HBTU and 0.6 mmol

of DIPEA in DMF for 1 hour. Coupling of DOTA(OtBu)₃ (172 mg, 0.3 mmol) was performed with 0.3 mmol HATU and 0.6 mmol of DIPEA in DMF for 1 hour. Deprotection of alloc protecting groups was performed with Pd(PPh₃)₃ (35 mg, 0.03 mmol) and PhSiH₃ (216 mg, 2 mmol) in DCM for 45 minutes. 2,3,4,5,6-Penta-O-acetyl-D-gluconic acid (243 mg, 0.6 mmol) was then coupled with 0.6 mmol HATU and 1.2 mmol DIPEA in DMF for 1.5 hours. Couplings were monitored by Kaiser test. After the final coupling, the resin was washed thoroughly with DCM. Cleavage from resin was performed with 20% HFIP in DCM (5 mL) for 30 minutes. The resin was drained and washed with DCM (2 mL), and the combined washings were concentrated under a stream of air. The resulting crude protected peptide was dissolved in 1:1 MeOH/H₂O and purified by reversed-phase flash chromatography (Biotage 12 g Sfar C18, 30-80% MeOH/H₂O + 0.1% TFA). Purified protected peptide **Intermediate 4-A** was obtained as a colourless film (49 mg, 30%, purity: 96%). An aliquot was analyzed by HPLC-MS using elution method 4; retention time: 3.41 min; MS (ESI+) *m/z* calculated for C₇₀H₁₁₁N₁₀O₃₄ [M+H]⁺ 1635.7; found 1636.5. ¹H NMR* (700 MHz, DMSO-*d*₆) δ 12.85 (s, 1H), 8.63 (s, 1H), 8.29 (t, *J* = 6.2 Hz, 1H), 8.16 (t, *J* = 6.2 Hz, 1H), 8.09 (t, *J* = 5.8 Hz, 2H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 2H), 5.51 (q, *J* = 4.5 Hz, 2H), 5.33 (ddd, *J* = 7.4, 6.2, 4.8 Hz, 2H), 5.15 (dd, *J* = 10.2, 4.0 Hz, 2H), 4.98 (qd, *J* = 6.4, 3.4 Hz, 2H), 4.41 – 4.37 (m, 1H), 4.28 – 4.23 (m, 3H), 4.16 (s, 1H), 4.12 (ddd, *J* = 12.2, 6.4, 1.8 Hz, 2H), 4.04 (s, 2H), 3.89 – 3.78 (m, 2H), 3.78 – 3.70 (m, 1H), 3.57 (s, 2H), 3.52 – 3.43 (m, 1H), 3.42 – 3.37 (m, 1H), 3.35 – 3.28 (m, 1H), 3.28 – 3.22 (m, 1H), 3.17 (s, 1H), 3.13 (s, 1H), 3.10 – 3.02 (m, 1H), 3.03 – 2.90 (m, 5H), 2.87 – 2.79 (m, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 6H), 2.00 (s, 3H), 1.99 (s, 6H), 1.49 (s, 9H), 1.40 (s, 18H). (*Protons obscured by H₂O not reported).

Step 2: Synthesis of (2R,3R,4S,5R,9S,15S,19R,20S,21R,22R)-9-(4-(4-(3-(2,4-Bis(benzyloxy)-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-1-carbonyl)-6,11,14,18-tetraoxo-15-(2-(2-(4,7,10-tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetamido)acetamido)-7,10,13,17-tetraazatricosane-1,2,3,4,5,19,20,21,22,23-decyl decaacetate (Intermediate 4-C):

Intermediate 4-A (45 mg, 0.03 mmol), HATU (10.5 mg, 0.03 mmol) and DIPEA (24 μL, 0.14 mmol) were dissolved in DMF (2 mL) and stirred at room temperature for 5 minutes. **Intermediate 4-B** (21 mg, 0.03 mmol) was added and stirring continued for 2 hours. The solvent

was evaporated under reduced pressure. The crude was redissolved in 60% MeOH/H₂O and purified by reversed-phase flash chromatography (Biotage 12 g Sfär C18, 60-100% MeOH/H₂O + 0.1% TFA). Pure **Intermediate 4-C** was obtained as a colourless film (30.4 mg, 49%, purity: 97%). An aliquot was analyzed by HPLC-MS using elution method 4; retention time: 4.74 min; MS (ESI+) m/z calculated for C₁₁₀H₁₅₅N₁₅O₃₆ [M+2H]²⁺ 1131.5; found 1132.2. ¹H NMR* (700 MHz, DMSO-*d*₆) δ 8.98 (t, J = 5.9 Hz, 1H), 8.60 (s, 1H), 8.34 – 7.95 (m, 4H), 7.42 – 7.39 (m, 4H), 7.39 – 7.30 (m, 4H), 7.25 (t, J = 7.7 Hz, 2H), 7.12 – 7.08 (m, 2H), 7.06 – 7.02 (m, 1H), 7.02 – 6.98 (m, 2H), 6.77 (d, J = 5.3 Hz, 1H), 5.53 – 5.45 (m, 2H), 5.37 – 5.31 (m, 2H), 5.18 – 5.10 (m, 2H), 5.09 (s, 2H), 5.01 – 4.97 (m, 1H), 4.99 – 4.95 (m, 3H), 4.89 – 4.80 (m, 1H), 4.39 (q, J = 7.2, 6.8 Hz, 1H), 4.28 – 4.22 (m, 2H), 4.16 (s, 1H), 4.11 (dd, J = 12.2, 6.3 Hz, 2H), 4.05 (s, 2H), 3.99 – 3.66 (m, 2H), 3.63 – 3.25 (m, 7H), 3.20 – 3.16 (m, 2H), 3.15 – 3.06 (m, 1H), 3.01 – 2.91 (m, 1H), 2.90 (s, 1H), 2.74 (s, 1H), 2.56 – 2.52 (m, 1H), 2.49 – 2.45 (m, 1H), 2.12 – 2.03 (m, 10H), 2.02 – 1.94 (m, 17H), 1.74 (s, 1H), 1.61 – 1.56 (m, 2H), 1.48 (s, 9H), 1.40 (s, 18H), 1.05 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 6.3 Hz, 6H). (*Protons obscured by H₂O not reported).

Step 3: Synthesis of (2R,3R,4S,5R,9S,15S,19R,20S,21R,22R)-9-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-1-carbonyl)-6,11,14,18-tetraoxo-15-(2-(2-(4,7,10-tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetamido)acetamido)-7,10,13,17-tetraazatricosane-1,2,3,4,5,19,20,21,22,23-decayl decaacetate (Intermediate 4-D):

To a 5 mL microwave vial containing a stirbar was added 10% Pd/C (8 mg, 30% w/w). The vial was sealed with a septum and purged with nitrogen. **Intermediate 4-C** (25 mg, 0.01 mmol) dissolved in 2 mL of MeOH was added to the vial. The vial was then purged with hydrogen gas (balloon) and stirred at room temperature for 24 hours. The vial was purged with nitrogen and the resulting solution filtered through a 0.2 μ m syringe filter. The solvent was evaporated under reduced pressure and the resulting product **Intermediate 4-D** used without further purification. Colorless film (23 mg, quant., purity: 95%). An aliquot was analyzed by HPLC-MS using elution method 3; retention time: 2.05 min. MS (ESI+) m/z calculated for C₉₆H₁₄₃N₁₅O₃₆ [M+2H]²⁺ 1041.5; found 1042.1.

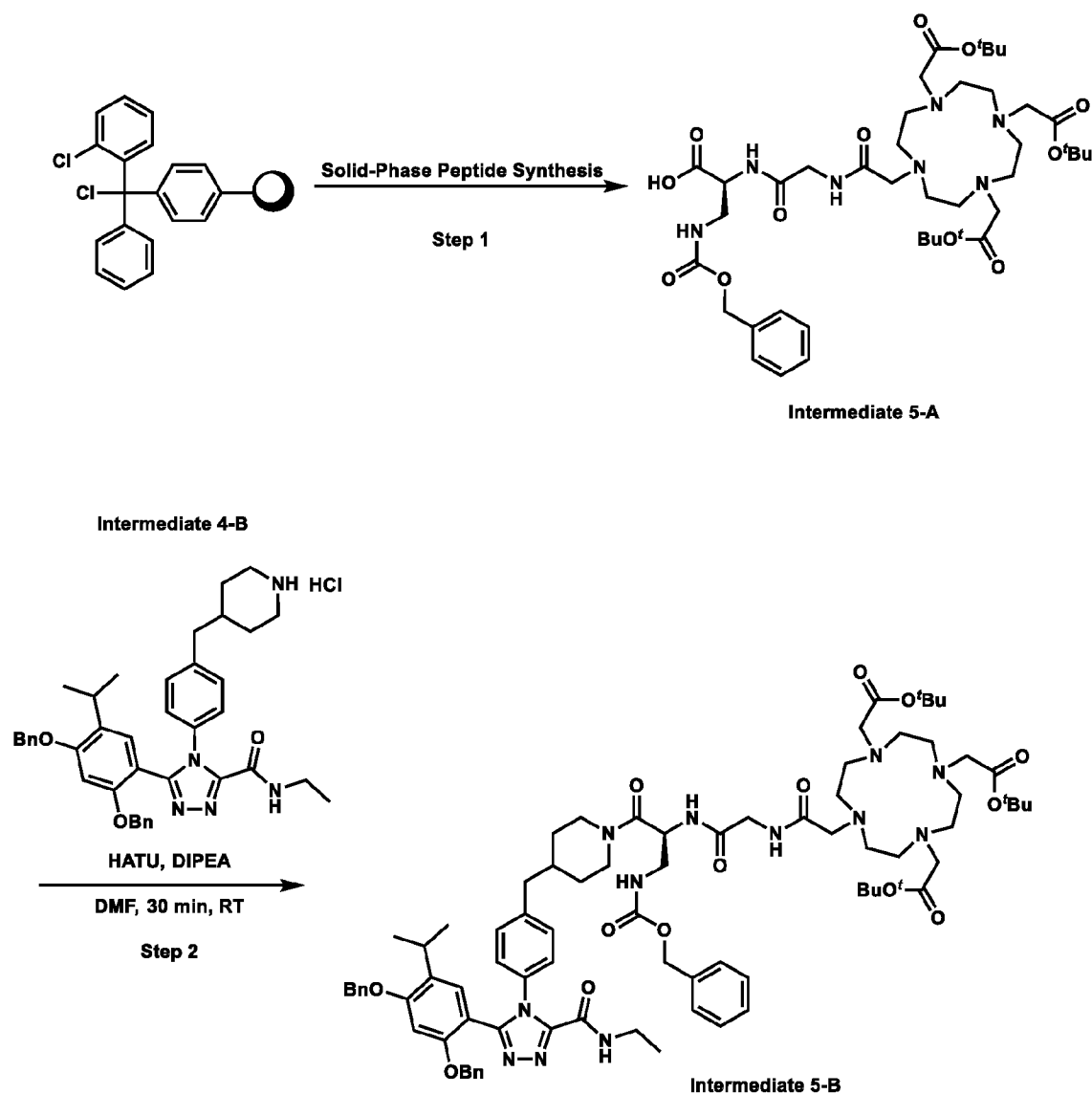
Step 4: Synthesis of 2,2',2''-(10-((7S,13S,17R,18S,19R,20R)-13-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-1-carbonyl)-17,18,19,20,21-pentahydroxy-2,5,8,11,16-pentaoxo-7-(((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamido)methyl)-3,6,9,12,15-pentaazahenicosyl)-1,4,7,10-

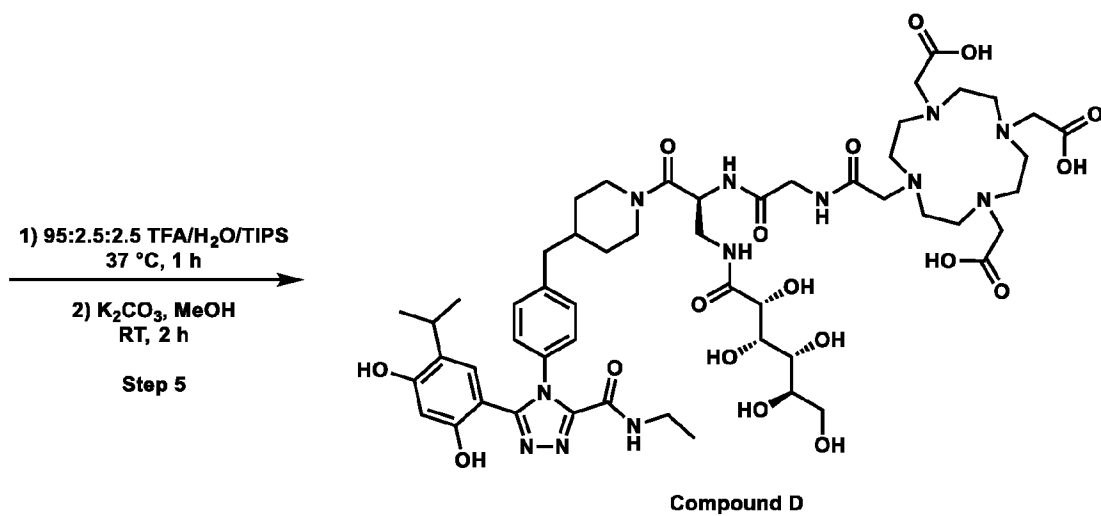
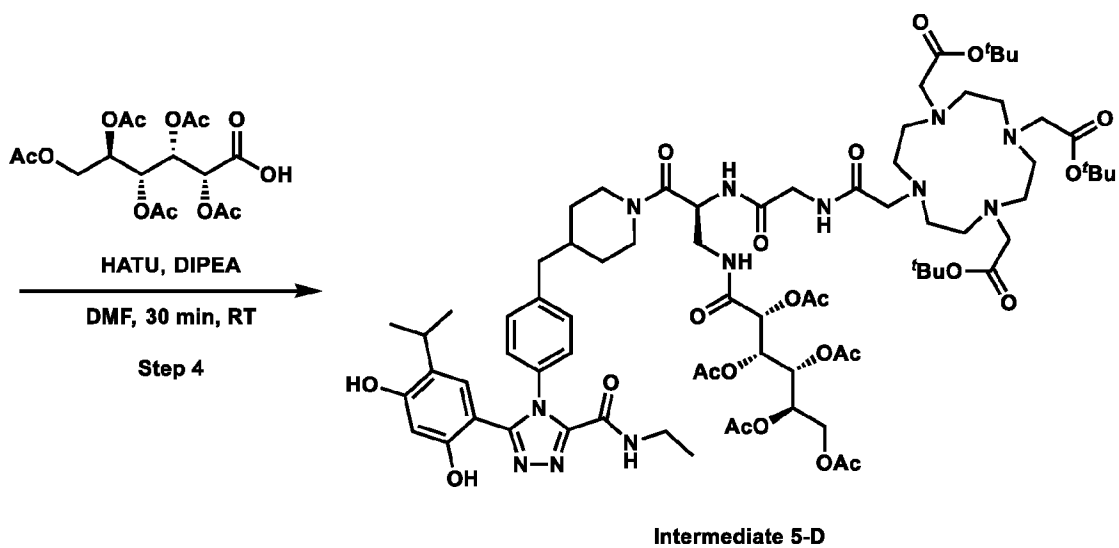
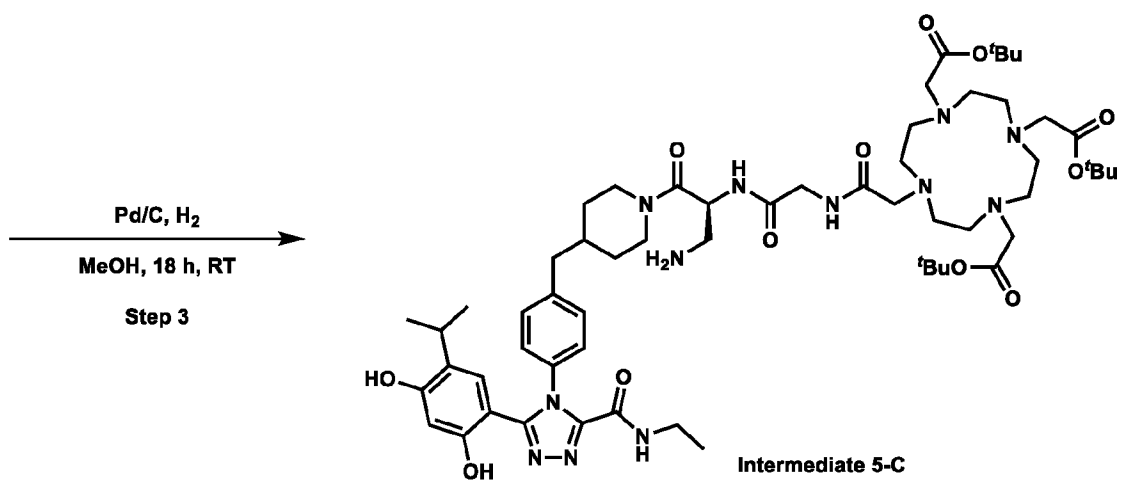
5 *tetraazacyclododecane-1,4,7-triyl)triacetic acid (Compound C):*

Intermediate 4-D (23 mg, 0.01 mmol) was dissolved in 2 mL of 95:2.5:2.5 TFA/TIPS/H₂O and heated to 37 °C for 2 hours. The solution was then concentrated under a stream of air, dissolved in 2 mL of MeOH and the solvent evaporated under reduced pressure. The resulting residue was then dissolved in 2 mL of MeOH followed by the addition of potassium carbonate (8 mg, 0.06 mmol) and stirred at room temperature for 1 hour. The reaction mixture was filtered through a 0.2 µm syringe filter to remove excess salts, and then TFA was added until the pH was ~2. The solvent was evaporated, and the resulting residue redissolved in 0.8 mL of 10% DMSO/H₂O and purified by preparative HPLC (Mobile phase: Solvent A = H₂O; (EMD, HPLC Grade) (0.1% TFA (v/v)), Solvent B = MeCN; (EMD, LCMS Grade) (0.1% TFA (v/v)). Elution Profile: 20 min method: =
10 initial = 10% B, 2 min = 10% B, 15 min = 40% B, 18 min = 100% B, 20 min = 10% B (linear gradient). Waters Xbridge C18 19 x 100 mm with guard column). The product fractions were combined and evaporated under reduced pressure. The product was then redissolved in deionized water and lyophilized to give pure **Compound C** TFA salt as a white, fluffy solid (8.9 mg, 50%, purity: 97%). An aliquot was analyzed by HPLC-MS using elution method 4; retention time: 2.36
15 min. MS (ESI+) *m/z* calculated for C₆₄H₉₈N₁₅O₂₆ [M+H]⁺ 1492.7; found 1493.3. ¹H NMR* (700 MHz, DMSO-*d*₆) δ 9.83 (s, 1H), 8.95 (t, *J* = 6.1 Hz, 1H), 8.63 (s, 1H), 8.34 – 8.13 (m, 2H), 7.99 (dd, *J* = 23.6, 8.2 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.78 – 7.67 (m, 1H), 7.30 – 7.23 (m, 4H), 6.60 – 6.56 (m, 1H), 6.36 (s, 1H), 4.96 – 4.84 (m, 2H), 4.62 – 4.55 (m, 2H), 4.37 – 4.29 (m, 5H), 4.14 – 4.01 (m, 7H), 4.01 – 3.95 (m, 3H), 3.94 – 3.85 (m, 4H), 3.84 – 3.77 (m, 2H), 3.78 – 3.69 (m, 3H),
20 3.61 – 3.55 (m, 3H), 3.54 – 3.46 (m, 6H), 3.46 – 3.28 (m, 12H), 3.16 (p, *J* = 7.2 Hz, 4H), 3.14 – 3.05 (m, 6H), 3.04 – 2.94 (m, 2H), 2.91 (p, *J* = 7.0 Hz, 1H), 2.63 – 2.56 (m, 1H), 2.57 – 2.52 (m, 1H), 1.83 – 1.74 (m, 1H), 1.72 – 1.63 (m, 1H), 1.63 – 1.55 (m, 1H), 1.31 – 1.12 (m, 1H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.81 (dd, *J* = 6.7, 2.9 Hz, 6H). (*Protons obscured by H₂O not reported).

30 **Scheme 5:** Synthesis of (2R,3R,4S,5R)-6-(((S)-3-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-3-oxo-2-(2-(2-(4,7,10-tris(2-(tert-

butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetamido)acetamido)propyl)amino)-6-oxohexane-1,2,3,4,5-pentayl pentaacetate (2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentaacetoxyhexanoate 2,2',2''-(10-(2-(((*S*)-1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4*H*-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-1-oxo-3-((2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanamido)propan-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (**Compound D**):





Step 1: Synthesis of (S)-3-(((Benzyloxy)carbonyl)amino)-2-(2-(2-(4,7,10-tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetamido)acetamido)propanoic acid
(Intermediate 5-A)

The protected peptide was synthesized by solid-phase peptide synthesis (SPPS) on 2-chlorotritylchloride resin (Chem-Impex, 0.72 mmol/g, 139 mg, 0.1 mmol). Fmoc-Dap(Cbz)-OH (230 mg, 0.5 mmol) was dissolved in DMF (4 mL) with potassium iodide (16 mg, 0.1 mmol) and DIPEA (174 μ L, 1.0 mmol). Fmoc deprotection was performed for 5 and 15 minutes with 20% piperidine in DMF. Subsequent couplings were performed using 0.3 mmol of protected amino acids (Fmoc-Gly-OH, DOTA(OtBu)₃), 0.3 mmol of HBTU and 0.6 mmol of DIPEA in DMF for 1 hour. Couplings were monitored by Kaiser test. After the final coupling, the resin was washed thoroughly with DCM. Cleavage from resin was performed with 20% HFIP in DCM (5 mL) for 30 minutes. The resin was drained and washed with DCM (2 mL), and the combined washings were concentrated under a stream of air. The resulting crude protected peptide was dissolved in 1:1 MeOH/H₂O and purified by reversed-phase flash chromatography (Biotage 12 g Sfar C18, 50-80% MeOH/H₂O + 0.1% TFA). Pure protected peptide **Intermediate 5-A** was obtained as a colourless solid (74 mg, 87%, purity: 97%). An aliquot was analyzed by HPLC-MS using elution method 4; retention time: 3.19 min; MS (ESI+) *m/z* calculated for C₄₁H₆₈N₇O₁₂ [M+H]⁺ 850.5; found 850.6. ¹H NMR (700 MHz, DMSO-*d*₆) δ 8.78 (s, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 7.51 – 7.38 (m, 2H), 7.38 – 7.26 (m, 5H), 5.02 (q, *J* = 12.5 Hz, 2H), 4.36 (q, *J* = 6.0 Hz, 1H), 4.25 – 4.10 (m, 2H), 4.10 – 3.97 (m, 2H), 3.89 – 3.74 (m, 2H), 3.68 – 3.23 (m, 14H), 3.21 – 2.78 (m, 10H), 1.47 (s, 9H), 1.39 (s, 18H).

Step 2: Synthesis of tri-tert-Butyl 2,2',2''-(10-(6-(4-(4-(3-(2,4-bis(benzyloxy)-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-1-carbonyl)-3,8,11-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)(S)-triacetate
(Intermediate 5-B):

Intermediate 5-A (61 mg, 0.07 mmol), HATU (27 mg, 0.07 mmol) and DIPEA (63 μ L, 0.36 mmol) were dissolved in DMF (2 mL) and stirred for 5 minutes prior to the addition of **Intermediate 4-B** (54 mg, 0.08 mmol). After stirring at room temperature for 30 minutes, the solvent was evaporated under reduced pressure. The crude was redissolved in 1:1 MeOH/H₂O and purified by reversed-phase flash chromatography (Biotage 12 g Sfar C18, 50-100% MeOH/H₂O +

0.1% TFA). Pure **Intermediate 5-B** was obtained as a colourless solid (67 mg, 63%, purity: 98%). An aliquot was analyzed by HPLC-MS using elution method 3; retention time: 4.94 min. MS (ESI+) m/z calculated for $C_{81}H_{111}N_{12}O_{14}$ $[M+H]^+$ 1475.8; found 1476.9. ^1H NMR (700 MHz, DMSO- d_6) δ 8.98 (t, J = 5.9 Hz, 1H), 8.72 (br s, 1H), 8.30 – 8.15 (m, 1H), 7.41-7.23 (m, 14H),
5 7.11-6.96 (m, 5H), 6.77 (s, 1H), 5.08-4.93 (m, 7H), 4.38-2.37 (multiplets overlapping with resid H₂O and DMSO, 40H), 1.75-1.65 (m, 1H), 1.47 (br s, 9H), 1.39 (br s overlapping with 1.38 br s, 9H), 1.38 (br s overlapping with 1.39 br s, 9H), 1.05 (t, J = 7.2 Hz, 3H), 1.02-1.00 (m, 6H).

10 *Step 3: Synthesis of Tri-tert-butyl 2,2',2''-(10-(2-((2-((3-amino-1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-1-oxopropan-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)(S)-triacetate (Intermediate 5-C):*

To a 5 mL microwave vial containing a stirbar was added 10% Pd/C (9 mg, 30% w/w). The vial
15 was sealed with septum and purged with nitrogen. **Intermediate 5-B** (30 mg, 0.02 mmol) was added in 2 mL of MeOH. The vial was then purged with hydrogen gas (balloon) and stirred at room temperature for 18 hours. The vial was purged with nitrogen and the resulting solution filtered through a 0.2 μ m syringe filter. The solvent was evaporated under reduced pressure and the resulting product used without further purification. **Intermediate 5-C** was obtained as a
20 colourless solid (23 mg, 98%, purity: 97%). An aliquot was analyzed by HPLC-MS using elution method 4; retention time: 1.65 min; MS (ESI+) m/z calculated for $C_{59}H_{93}N_{12}O_{12}$ $[M+H]^+$ 1161.7; found 1161.9.

Step 4: Synthesis of (2R,3R,4S,5R)-6-(((S)-3-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-3-oxo-2-(2-(2-(4,7,10-tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetamido)acetamido)propyl)amino)-6-oxohexane-1,2,3,4,5-pentayl pentaacetate (Intermediate 5-D):

2,3,4,5,6-Penta-*O*-acetyl-D-gluconic acid (10 mg, 0.02 mmol), HATU (9 mg, 0.02 mmol) and DIPEA (17 μ L, 0.1 mmol) were dissolved in DMF (1 mL) and stirred at room temperature for 5
30 minutes. **Intermediate 5-C** (23 mg, 0.02 mmol) dissolved in 1 mL of DMF was added and the mixture stirred at room temperature for 30 minutes. The solvent was evaporated, and the crude

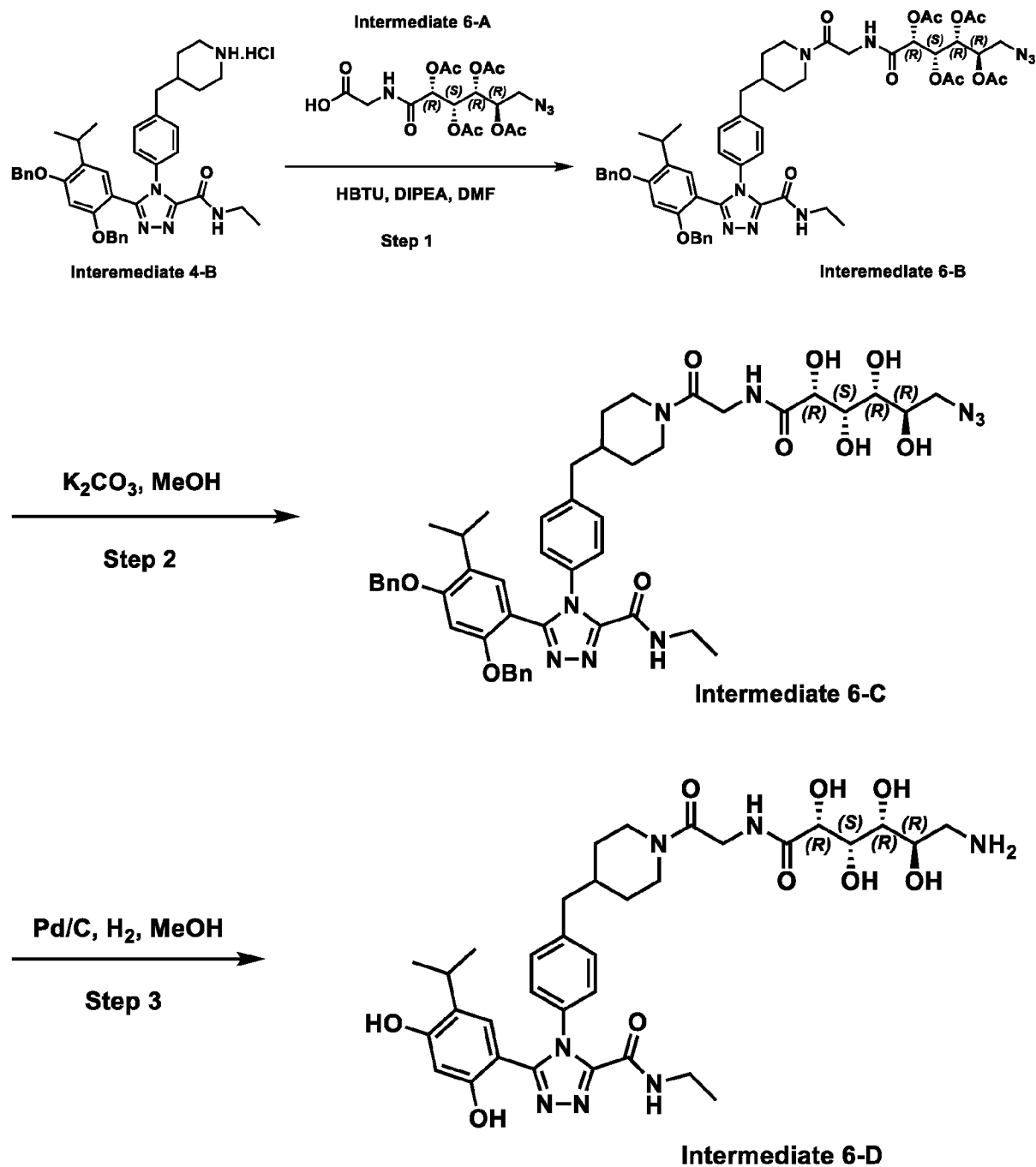
redissolved in 1 mL of DMSO. Crude product was purified by preparative HPLC (Mobile phase: Solvent A = H₂O; (EMD, HPLC Grade) (0.1% TFA (v/v)), Solvent B = MeCN; (EMD, LCMS Grade) (0.1% TFA (v/v)). Elution Profile: 20 min method: = initial = 10% B, 2 min = 10% B, 15 min = 100% B, 18 min = 100% B, 20 min = 30% B (linear gradient). Waters XBridge C18 19 x 100 mm column with guard). **Intermediate 5-D** was obtained as a colourless solid (16.7 mg, 54%, purity: 90%). An aliquot was analyzed by HPLC-MS using elution method 4; retention time: 2.05 min; MS (ESI+) *m/z* calculated for C₇₅H₁₁₃N₁₂O₂₃ [M+H]⁺ 1549.8; found 1549.9.

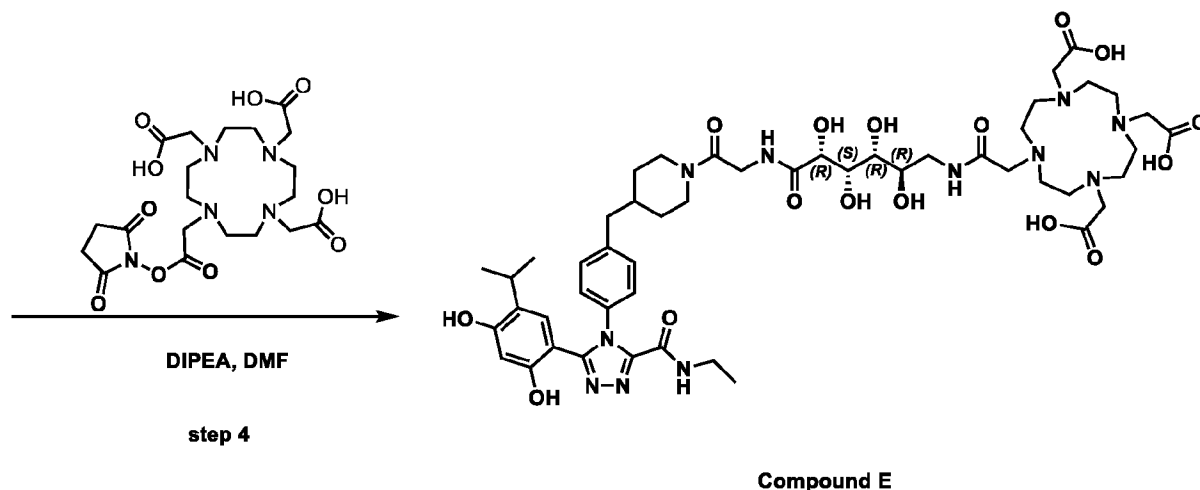
Step 5: Synthesis of 2,2',2''-(10-(2-(((S)-1-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-1-oxo-3-((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamido)propan-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (Compound D):

Intermediate 5-D (5.7 mg, 3.7 μmol) was dissolved in 2 mL of TFA/TIPS/H₂O (95:2.5:2.5) and heated to 37 °C for 2 hours. The solution was then concentrated under a stream of air, dissolved in 2 mL of MeOH and the solvent evaporated under reduced pressure. The resulting residue was then dissolved in 2 mL of MeOH followed by the addition of potassium carbonate (2.5 mg, 18.4 μmol) and the mixture stirred at room temperature for 2 hours. The reaction mixture was filtered through a 0.2 μm syringe filter to remove excess salts, and then TFA was added until the pH was ~2. The solvent was evaporated, and the resulting residue redissolved in 2:1 H₂O/ACN + 0.1% TFA (0.9 mL) and purified by preparative HPLC (Mobile phase: Solvent A = H₂O; (EMD, HPLC Grade) (0.1% TFA (v/v)), Solvent B = MeCN; (EMD, LCMS Grade) (0.1% TFA (v/v)). Elution Profile: 20 min method: = initial = 5% B, 2 min = 5% B, 15 min = 60% B, 18 min = 100% B, 20 min = 5% B (linear gradient). Waters XBridge C18 19 x 100 mm with guard column). Product fractions were evaporated under reduced pressure, redissolved in deionized water and lyophilized to obtain **Compound D** TFA salt as a colourless, fluffy solid (2.0 mg, 36%, purity: 94%). An aliquot was analyzed by HPLC-MS using elution method 3; retention time: 2.42 min. MS (ESI+) *m/z* calculated for C₅₃H₇₉N₁₂O₁₈ [M+H]⁺ 1171.6; found 1171.8.

Scheme 6: Synthesis of 2,2',2''-(10-(2-(((2R,3R,4S,5R)-6-((2-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-2-

oxoethyl)amino)-2,3,4,5-tetrahydroxy-6-oxohexyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**Compound E**):





Step 1: Synthesis of 4-(4-((1-Acetylpiperidin-4-yl)methyl)phenyl)-N-(2-aminoethoxy)-5-(2,4-bis(benzyloxy)-5-isopropylphenyl)-4H-1,2,4-triazole-3-carboxamide (Intermediate 6-B): To a 20 mL scintillation vial with a stir bar was added ((2*R*,3*S*,4*R*,5*R*)-2,3,4,5-tetraacetoxy-6-azidohexanoyl)glycine (**Intermediate 6-A**, synthesized using in-house protocol), (20.0 mg, 0.04 mmol, 1 equiv.) and 3 mL DMF. The reaction mixture was cooled to 0 °C and DIPEA, (39.42 µL, 29.25 mg, 0.22 mmol, 4 equiv.), followed by HBTU, (19.3 mg, 0.05 mmol, 1.1 equiv.) was added and stirred for 20 min at 0 °C. The solution was brought to room temperature and stirred for 10 min and then 5-(2,4-bis(benzyloxy)-5-isopropylphenyl)-*N*-ethyl-4-(4-(piperidin-4-ylmethyl)phenyl)-4*H*-1,2,4-triazole-3-carboxamide hydrochloride (**Intermediate 4-B**, 30.8 mg, 0.04 mmol, 1 equiv.) was added as solid. The reaction was stirred at room temperature and reaction monitored by LC-MS. After 1h, an additional 0.5 equiv. of HBTU, DIPEA, and **Intermediate 4-B** added, continued stirring for 1h. Reaction stopped after 1h and solvent evaporated under vacuum to give the crude product, which was purified by RP chromatography to afford **Intermediate 6-B** (11.5 mg, 23%, purity: 95%) as a brown film. HPLC-MS elution using elution method 1; retention time: 6.22 min; MS (positive ESI): found m/z 1073.5 $[M+H]^+$; C₅₆H₆₆N₉O₁₃ (calc. 1072.5).

*Step 2: Synthesis of 4-(4-((1-(((2*R*,3*S*,4*R*,5*R*)-6-Azido-2,3,4,5-tetrahydroxyhexanoyl)glycyl)piperidin-4-yl)methyl)phenyl)-5-(2,4-bis(benzyloxy)-5-isopropylphenyl)-*N*-ethyl-4*H*-1,2,4-triazole-3-carboxamide (Intermediate 6-C):* To a 20 mL scintillation vial containing **Intermediate 6-B** (11.5 mg, 10.73 µmol, 1 equiv.) was added 2 mL of methanol followed by potassium carbonate (6.0 mg, 0.04 mmol, 4 equiv.). Stirred at room

temperature and reaction monitored by LC-MS. After 1h at room temperature complete deprotection of the acetyl protecting groups observed by LCMS. The reaction mixture was filtered through a 0.2 μ m syringe filter and evaporated to give the crude **Intermediate 6-C** (10 mg, 98%, purity: 95%) as colorless film. HPLC-MS elution using elution method 1; retention time: 5.07 min; MS (positive ESI): found m/z 904.9 $[M+H]^+$; $C_{48}H_{58}N_9O_9$ (calc. 904.4).

Step 3: Synthesis of 4-(4-((1-(((2R,3S,4R,5R)-6-Amino-2,3,4,5-tetrahydroxyhexanoyl)glycyl)piperidin-4-yl)methyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide (Intermediate 6-D): To a flask containing **Intermediate 6-C** (9.7 mg, 7.34 μ mol, 1 equiv.), methanol (3.5 mL) was added followed by 10% Pd/C (3.9 mg, 3.67 μ mol, 0.5 equiv.) at room temperature. The reaction mixture was degassed under vacuum and subjected to hydrogen gas *via* a balloon. The reaction stirred overnight and was monitored by HPLC-MS. After stirring overnight, the reaction was incomplete, so additional Pd/C (6 mg) was added, and the reaction mixture subjected again to hydrogen gas as above. The reaction was stopped after 25 hours, filtered through Acrodisc One (0.2 μ m PTFE) syringe filter and the solvent evaporated under vacuum to give the crude **Intermediate 6-D** (12 mg, quantitative, purity: 52%) as colorless film. HPLC-MS elution using elution method 4; retention time: 3.05 min; MS (positive ESI): found m/z 698.6 $[M+H]^+$; $C_{34}H_{48}N_7O_9$ (calc. 698.4).

Step 4: 2,2',2''-(10-(2-((4-((2-(4-(4-((1-Acetylpiperidin-4-yl)methyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-4H-1,2,4-triazole-3-carboxamido)ethyl)carbamoyl)benzyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (Compound E): To a vial containing **Intermediate 6-D** (5.1 mg, 5.9 μ mol, 1 equiv.) was added 1.5 ml DMF, followed by 2,2',2''-(10-(2-((2,5-Dioxopyrrolidin-1-yl)oxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (NHS-DOTA) (7.0 mg, 8.8 μ mol, 1.5 equiv.), and DIPEA (1.0 μ L, 0.76 mg, 5.9 μ mol, 1 equiv.) at room temperature. The reaction mixture was stirred at room temperature and was monitored by LC-MS. After 1h additional NHS-DOTA (1 mg) was added. Reaction stopped after 2h 45mins and solvent evaporated under vacuum to give the crude product, which was purified by HPLC to afford **Compound E** (0.8 mg, 9.8%, purity: 91%) as a white solid, as TFA salt. HPLC-MS elution using elution method 4; retention time: 2.70 min; MS (positive ESI): found m/z 1107.0 $[M+Na]^+$; $C_{50}H_{73}N_{11}NaO_{16}$ (calc. 1106.5).

Example 2. Method for Radiolabeling Disclosed Compounds

[125] Prior to radiolabeling, a stock solution of each **Compound** was made by dissolving the appropriate quantity of **Compound** in sodium acetate buffer.

[126] A 1.5 mL Eppendorf tube was charged with the desired **Compound** followed by sodium acetate buffer to raise the total volume as desired (0.05-0.5 mL). Next, a solution of [¹⁷⁷Lu]LuCl₃ or [¹¹¹In]InCl₃ or [²²⁵Ac] in hydrochloric acid solution was added and the mixture heated. After heating the reaction for a desired amount of time, iTLC analysis of the reaction mixture (solid phase: Silica gel (SG) or silicid acid (SA) plate; mobile phase: 0.02 M citrate buffer with 5 % MeOH) indicated a radiochemical conversion (RCC) of >95 %. To the reaction mixture, sodium acetate buffer solutions of sodium *L*-ascorbate and diethylenetriamine-pentaacetic acid calcium trisodium salt hydrate (DTPA) were added. iTLC and reverse phase HPLC at end-of-synthesis (EOS) indicated the formation of the desired radiolabeled products (≥95 % radiochemical purity).

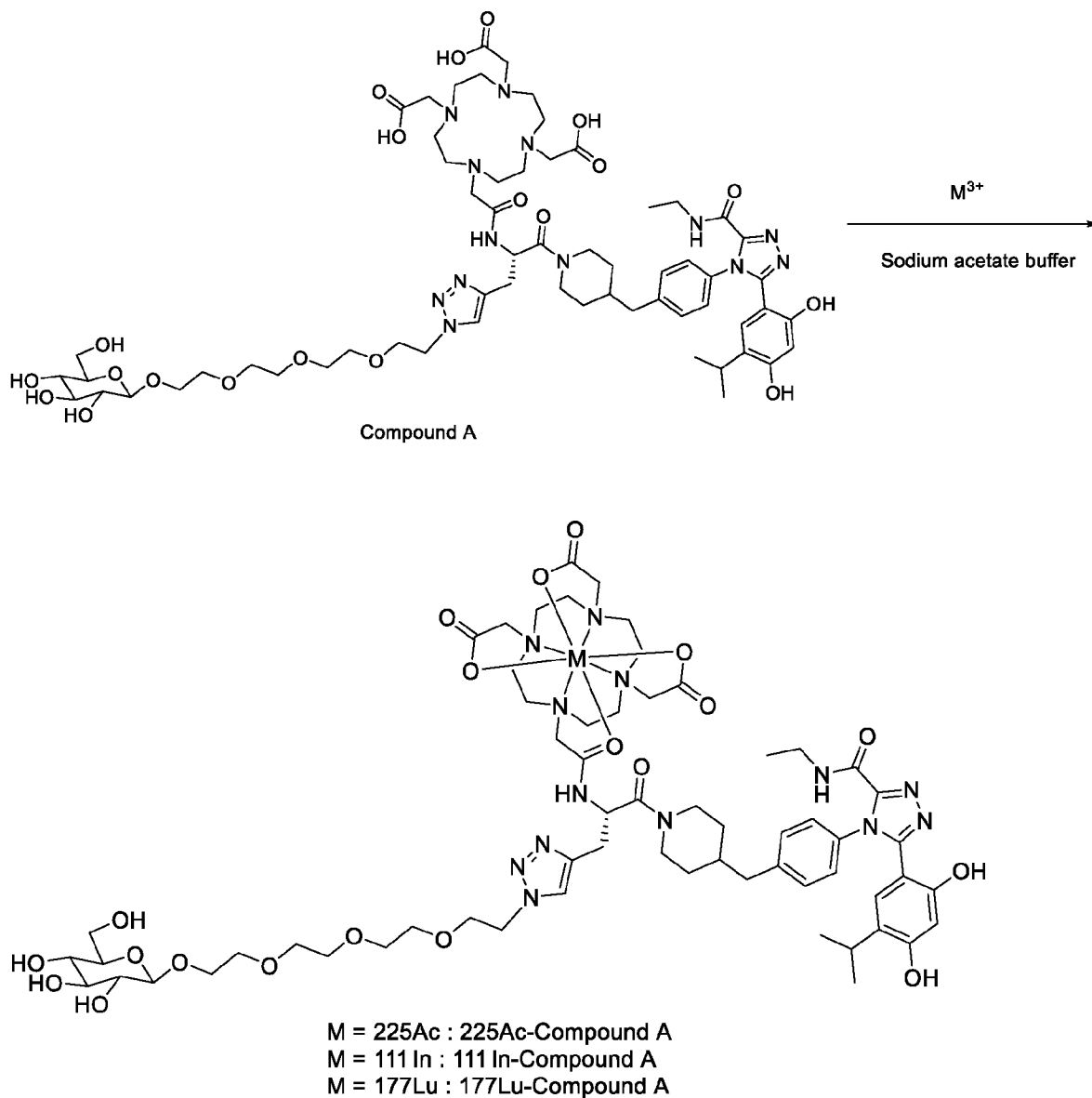
[127] **Table 1: Radiolabeling of Compounds with [¹⁷⁷Lu]LuCl₃**

Compound	RCP of ¹⁷⁷ Lu-Compound at EOS
Compound A	97%
Compound C	98%
Compound D	98%

[128] **Table 2: Radiolabeling of Compounds with [¹¹¹In]InCl₃**

Compound	RCP of In111-Compound at EOS
Compound A	95%
Compound C	97%
Compound D	98%

Scheme 7: Sample radiolabeling of a Compound featuring a DOTA chelator with [¹⁷⁷Lu]LuCl₃, [¹¹¹In]InCl₃, or [²²⁵Ac]



5 **Example 3. *In Vitro* HSP90 Binding Studies of Radiopharmaceuticals Comprising Compounds of Formula I**

[129] HSP90 binding is determined using a cell-free binding affinity assay, where human recombinant HSP90 protein is coated onto a Reacti-Bind® microtiter plate. Plates are incubated at 4 °C overnight and then washed 3 times with cold PBS containing 0.05% Tween-20 (PBS-T).

- 10 Plates are equilibrated to room temperature, blocked for 1 hour on ice with PBS-T containing 0.2% gelatin, followed by 3 washes with PBS-T. Increasing concentrations of Radiolabeled (Lu-

177) conjugates are incubated in duplicate in the absence (total binding) or presence (non-specific binding) of unlabeled conjugate, and incubated at 37 °C for 1 hour with gentle shaking. Wells are then rinsed three times with PBS-T, and stripped with a solution of 20 mM sodium acetate, pH 3.0 for up to 20 minutes at room temperature, followed by neutralization with an equal amount of 0.1N NaOH solution. Samples are transferred into gamma counting tubes and analyzed for Lu-177 content by gamma counter. Results are plotted relative to molar concentration of labeled conjugate, where specific binding affinity (K_d) is calculated using Graph Pad Prism. Binding affinity (K_d) results are summarized in Table 3, where 0 nM < A ≤ 3 nM, and B > 3 nM.

[130] Table 3. Binding affinities (K_d) of selected compounds to recombinant Hsp90α or β isoforms

Compound	K _d (nM)	
	Hsp90α	Hsp90β
Compound A	B	B
Compound C	A	A
Compound D	A	A

Example 4. Biodistribution Studies of Radiopharmaceuticals Comprising Compounds of Formula I

[131] In an animal model, Lutetium-177 (Lu-177) accumulation is measured in tumor, blood and healthy tissues of NCI-H460 tumor-bearing mice. Tumor bearing mice are dosed with 20 μCi of Lu-177 conjugates. At the time points indicated (ranging from 1h to 72h), mice are sacrificed and tumor, liver, kidneys and blood are isolated. All tissues are analyzed for Lu-177 content by gamma counter, and Lu-177 uptake can be determined as percentage injected dose per gram of tissue (%ID/g). Average radioligand uptake (%ID/g, n = 3) is summarized in Table 4.

[132] Table 4. Biodistribution of selected compounds in tumor-bearing mice.

Compound Lu-177	BioD (%ID/g)											
	1h				4h				24h			
	tumor	blood	liver	kidney	tumor	blood	liver	kidney	tumor	blood	liver	kidney
Compound A	8.98	2.36	5.13	4.71	5.71	0.71	5.04	4.38	1.60	0.02	2.46	1.64
Compound C	9.61	5.91	2.62	8.18	8.27	1.36	3.36	5.19	5.27	0.02	2.95	4.49
Compound D	12.16	7.20	4.03	8.65	10.93	1.57	7.07	9.29	7.48	0.04	3.08	4.66

Example 5. *In Vivo* Studies of Radiopharmaceuticals Comprising Compounds of Formula I

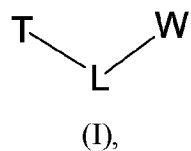
[133] Using an *in vivo* model, overall survival and tumor growth regression in HSP90 expressing NCI-H460 tumor-bearing mice will be evaluated to determine the *in vivo* efficacy of the compounds of Formula I. Mice implanted with HSP90 expressing NCI-H460 xenograft tumors will be treated with various concentrations and doses of Ac-225 labelled HSP90 targeting conjugates (ranging from 0.1 to 3 μ Ci of activity) of Formula I administered intravenously via tail vein injection to evaluate *in vivo* efficacy. Tumor measurements will be taken 2-3 times per week for at least 28 days with vernier calipers in two dimensions to evaluate tumor growth, and body weight, along with overall body condition and general behaviour will be assessed daily. Tumor volumes (V; in mm^3) will be calculated as $V = 0.5 \times L \text{ (length)} \times W^2 \text{ (width)}$, and expressed as relative tumor volumes (tumour volume on day X divided by tumor volume on day of dosing). If necessary, the effectiveness of single and multiple doses of the compounds of Formula I will be evaluated. Pre-administration or co-administration of non-radioconjugated HSP90 targeting conjugates with the compounds of Formula I and the effect on tumor regression and overall survival of HSP90 expressing xenograft tumour bearing mice can also be assessed.

OTHER EMBODIMENTS

[134] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



wherein

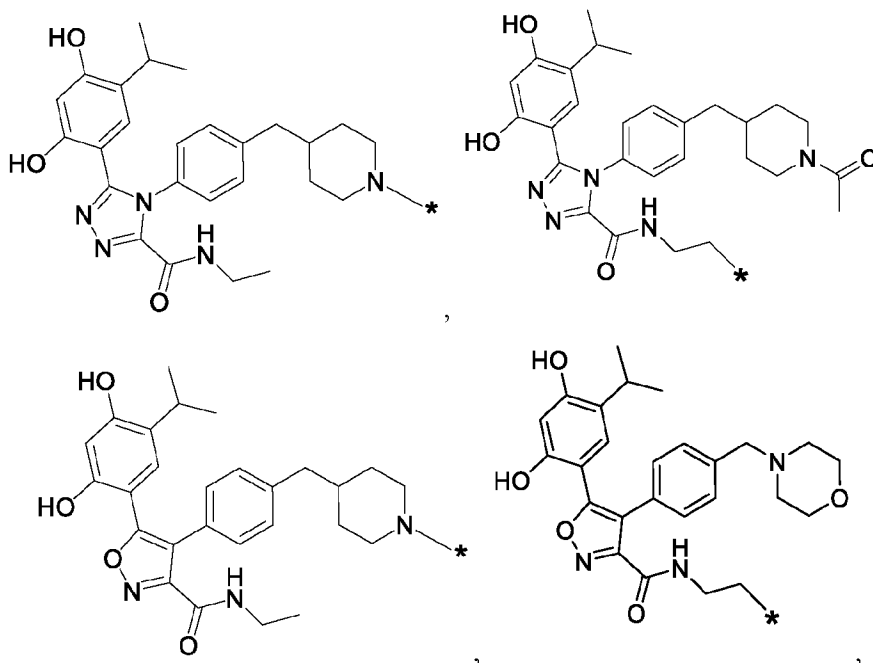
T is a targeting moiety that binds to HSP90,

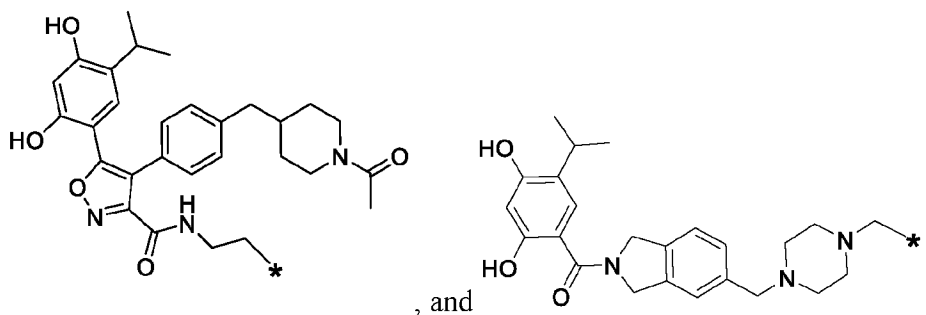
L is a hydrophilic space linker comprising one or more cyclic or acyclic polyhydroxy groups, and

W is a chelator,

wherein the compound optionally further comprises a radionuclide chelated by the chelator thereof.

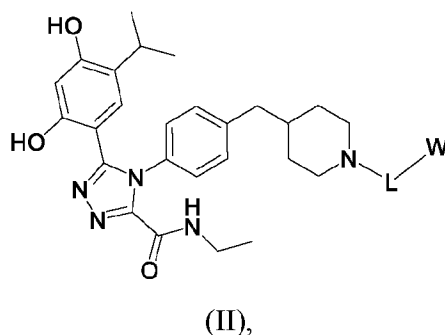
2. The compound of claim 1, wherein the targeting moiety is selected from the group consisting of:





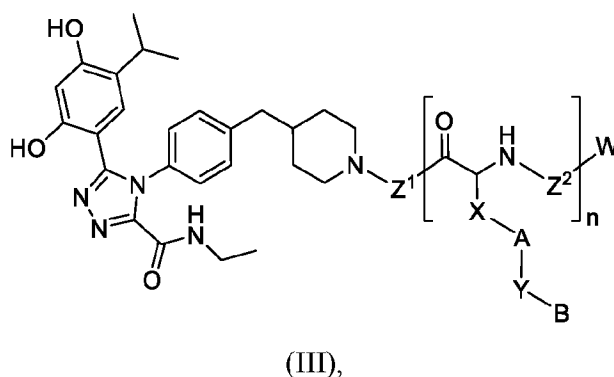
wherein “*” indicates the attachment point to L.

3. The compound of claim 1, having the structure of Formula II:

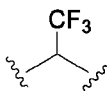
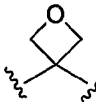


wherein L is a hydrophilic space linker comprising one or more cyclic or acyclic polyhydroxy groups, and W is a chelator selected from the group consisting of DOTA, DOTAGA, NOTA, NODAGA, NODASA, DTPA, TETA, EDTA, TRITA, CDTA, and DFO, wherein the compound binds to HSP90, wherein the compound optionally further comprises a radionuclide chelated by the chelator thereof.

4. The compound of claim 3, having the structure of Formula III:



wherein Z^1 and Z^2 each are, independently, absent or a moiety selected from the group

consisting of $C=O$, , , , $(C=O)NR^1$, $NR^1(C=O)NR^2$, $(CH_2CH_2)NR^2$, an amino acid unit, and a combination thereof, in which each of R^1 and R^2 independently is H or C_{1-5} alkyl;

n is an integer of 1-5 (inclusive);

W is a chelator selected from the group consisting of DOTA, DOTAGA, NOTA, and NODAGA;

X is absent or C_{1-5} alkyl;

A is absent, $C=O$, $CONR^3$, heterocycle, or heterocycle- C_{1-3} alkyl, R^3 being H or C_{1-5} alkyl;

Y is absent, C_{1-5} alkyl, or C_{1-10} heteroalkyl; and

B is a cyclic or acyclic polyhydroxy group.

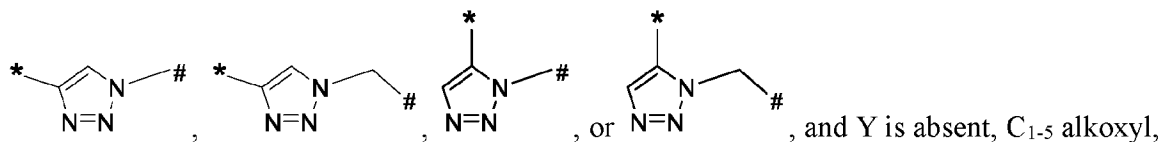
5. The compound of claim 4, wherein Z^1 and Z^2 are absent, and n is 1-3.

6. The compound of claim 4, wherein Z^1 is $(C=O)NH(CH_2CH_2)NH$, Z^2 is absent, and n is 1-3.

7. The compound of claim 4, wherein at least one of Z^1 and Z^2 is an amino acid unit.

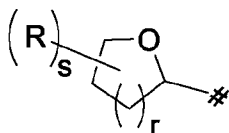
8. The compound of claim 7, wherein the amino acid unit is formed from aspartic acid (Asp), glutamic acid (Glu), 2,4-diaminobutyric acid (Dab), 2,3-diaminopropionic acid (Dap), lysine (Lys), or arginine (Arg).

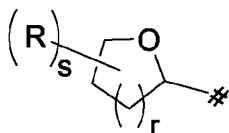
9. The compound of any one of claims 4-8, wherein X is C_{1-3} alkyl, A is



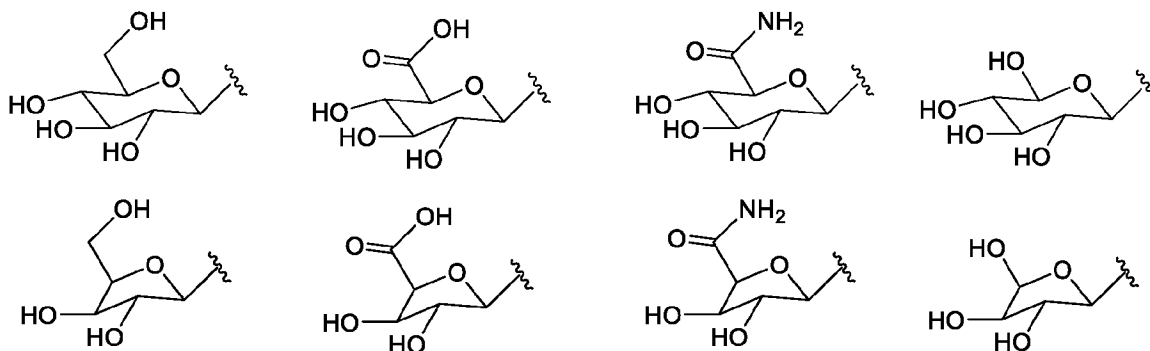
or C₂₋₈ polyethylene glycol, wherein “*” indicates the attachment point to X, and “#” indicates the attachment point to Y.

10. The compound of any one of claims 4-9, wherein B is a cyclic polyhydroxy group

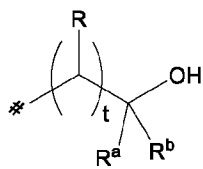


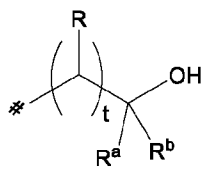
having the structure of , wherein “#” indicates the attachment point to Y, r is 1-2, s is 3-4, and each R, independently, is OH, -CH₂OH, -CO₂H, -CONH₂, NH₂, or NHCOCH₃, wherein B comprises at least three OH groups.

11. The compound of any one of claims 4-10, wherein B is one of the following, or a stereoisomer thereof:

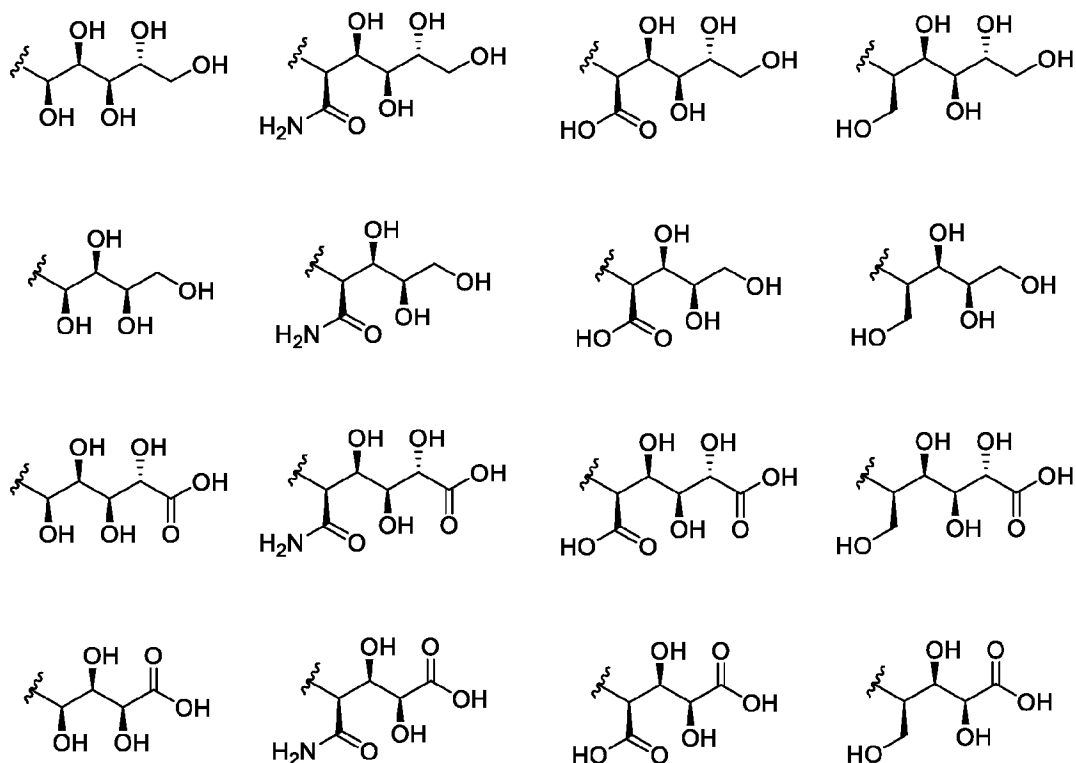


12. The compound of any one of claims 4-9, wherein B is an acyclic polyhydroxy



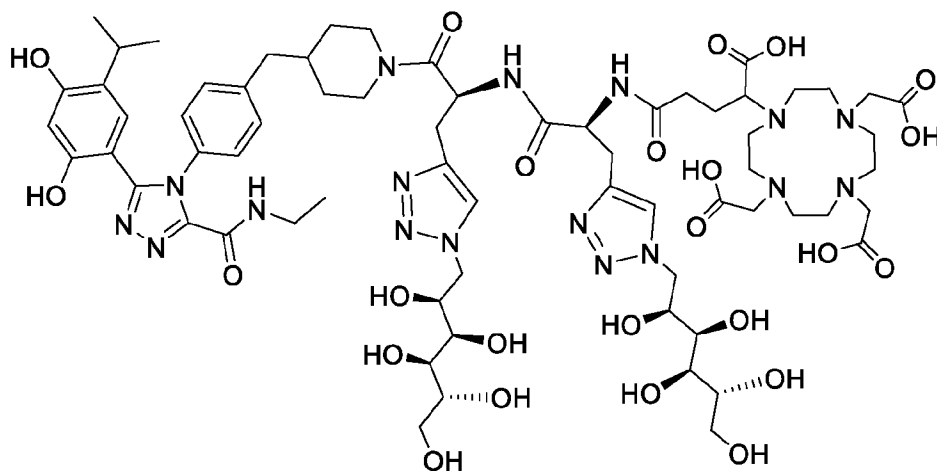
group having the structure of , wherein “#” indicates the attachment point to Y; t is 2-5; each R, independently, is OH, -CH₂OH, -CO₂H, -CONH₂, NH₂, or NHCOCH₃; and R^a and R^b each are H or R^a and R^b together form C=O, wherein B comprises at least three OH groups.

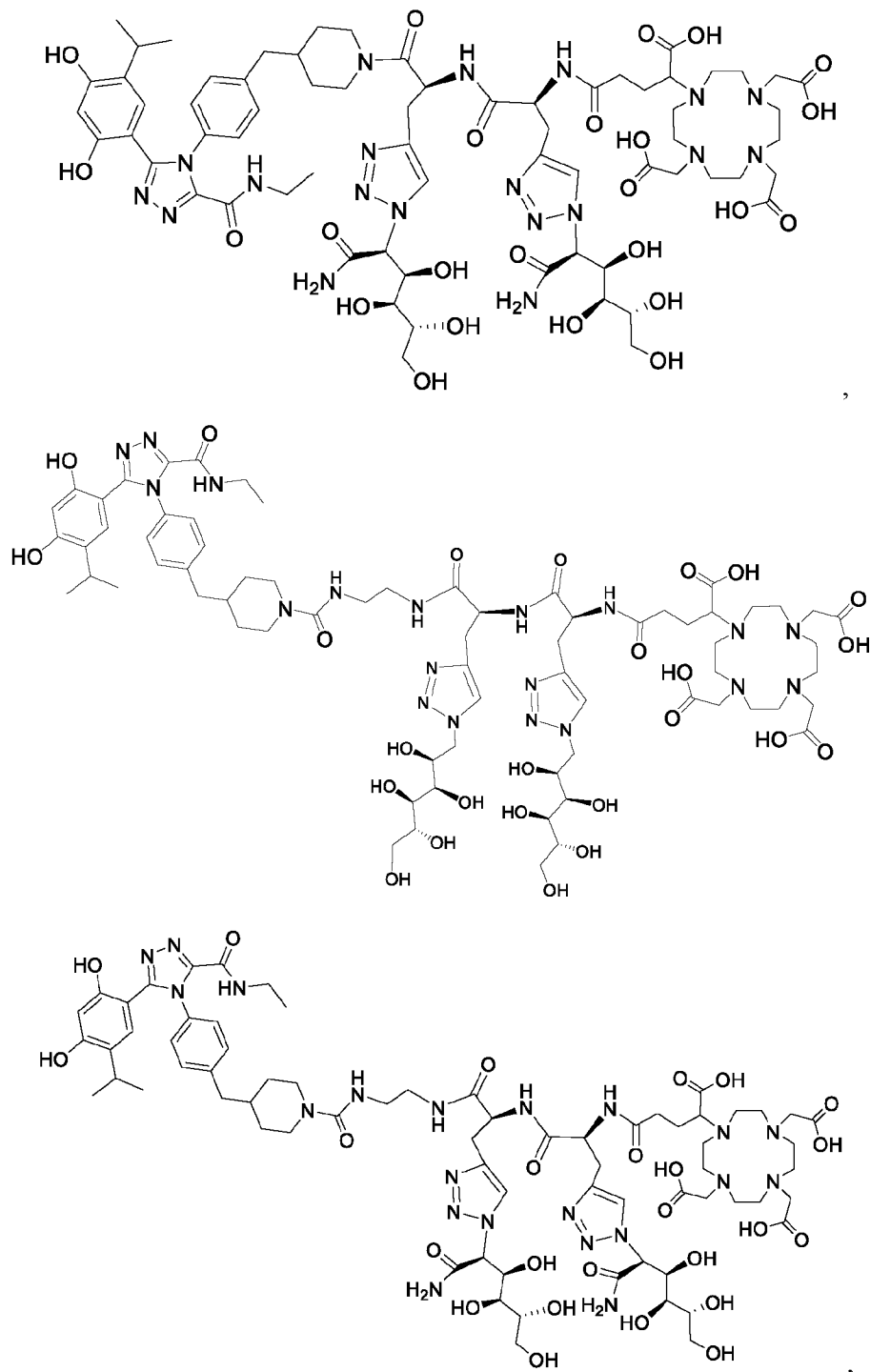
13. The compound of any one of claims 4-9 and 12, wherein B is one of the following, or a stereoisomer thereof:

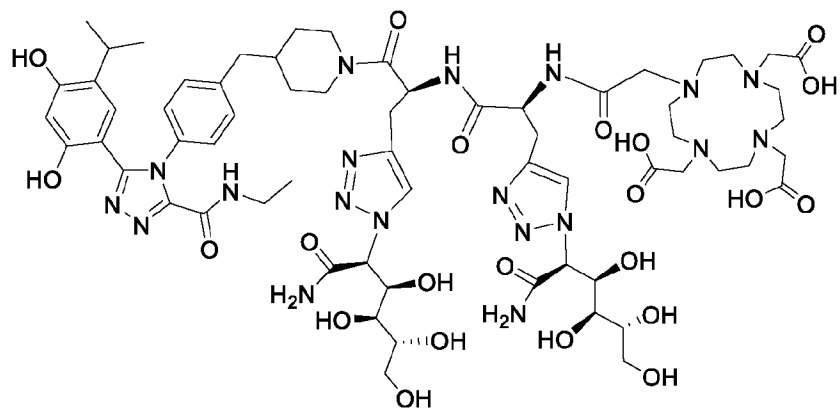
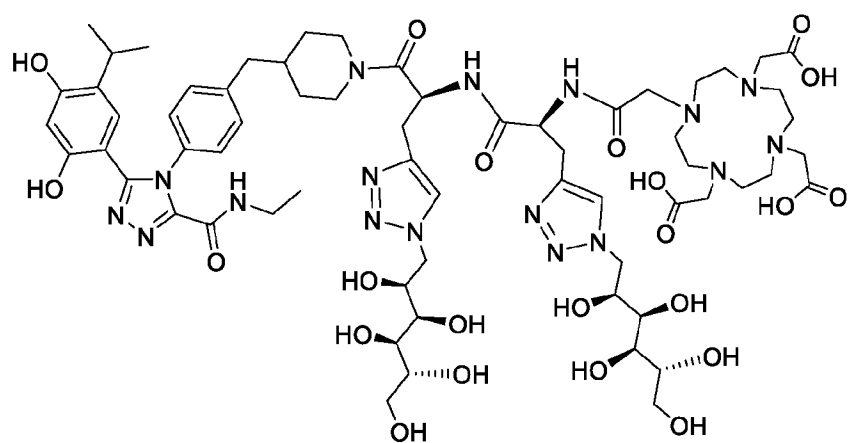
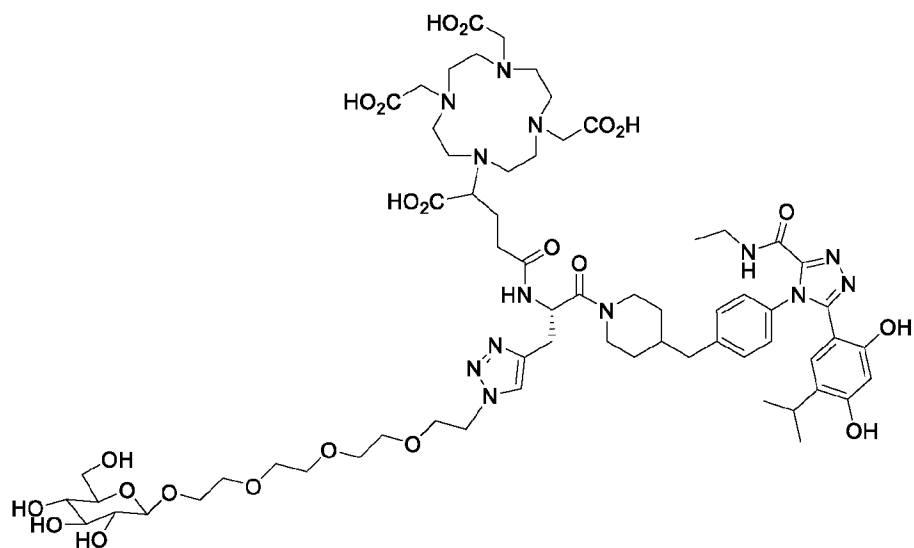


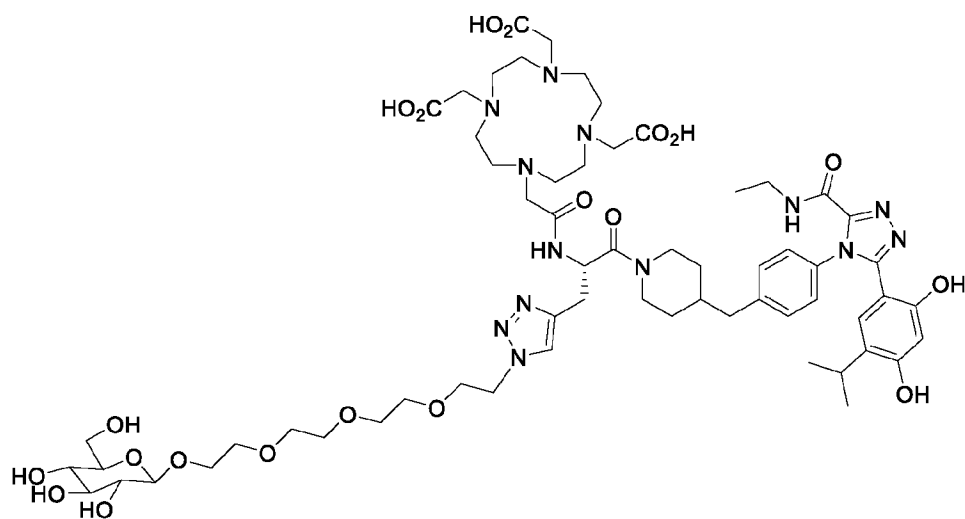
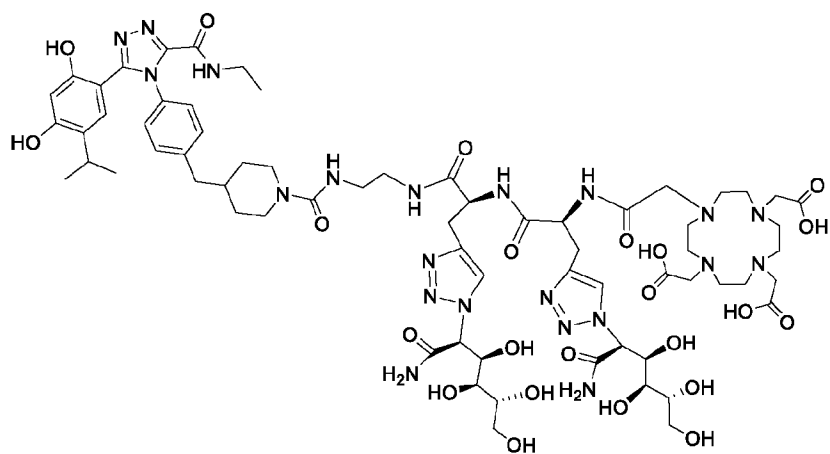
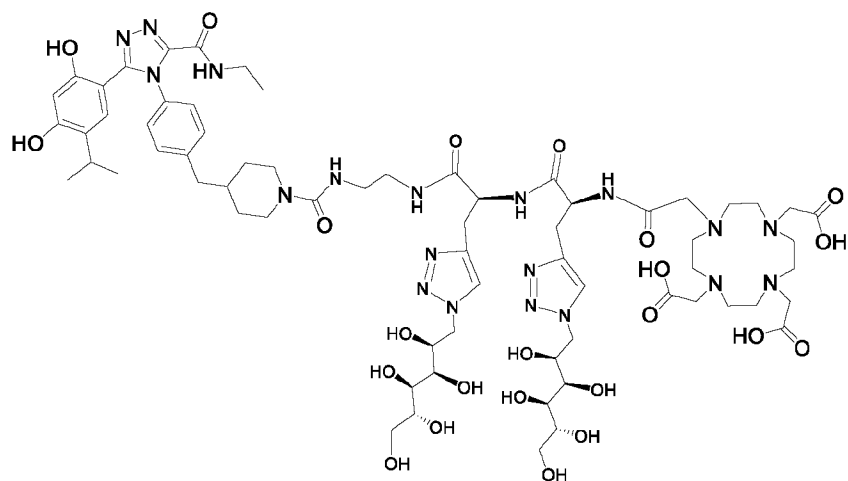
14. The compound of any one of claims 1-13, wherein W is DOTA or DOTAGA.

15. The compound of any one of claims 1-4, wherein the compound is one of the following, or a stereoisomer thereof:

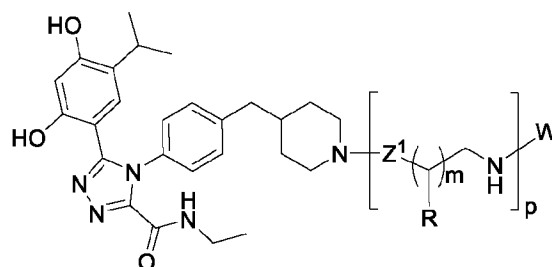




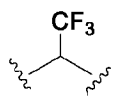
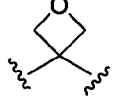
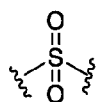




16. The compound of claim 3, having the structure of Formula IV:



(IV),

wherein Z^1 is a moiety selected from the group consisting of $C=O$, , , , $(C=O)NR^1$, $NR^1(C=O)NR^2$, $(CH_2CH_2)NR^2$, an amino acid unit, and a combination thereof, in which each of R^1 and R^2 independently is H or C_{1-5} alkyl;

m is an integer of 1-5 (inclusive), p is an integer of 1-4 (inclusive);

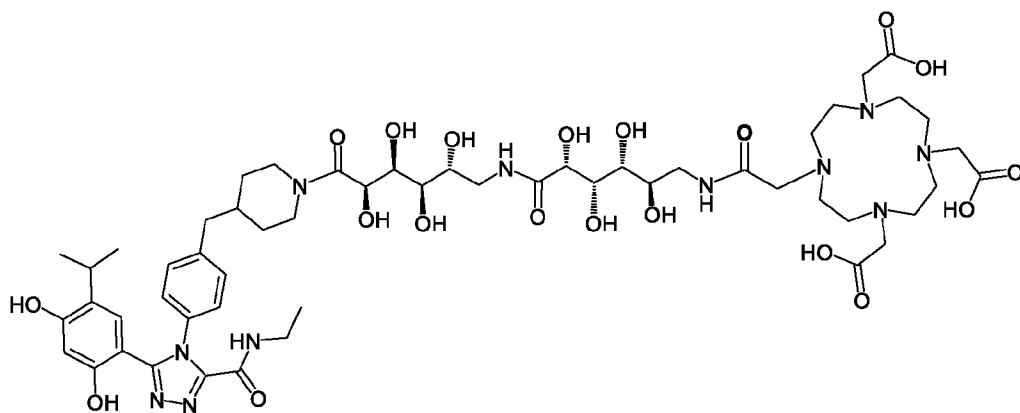
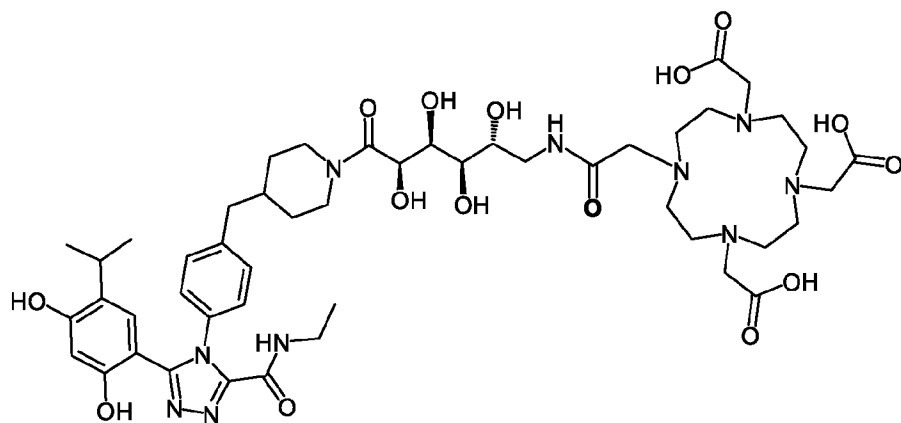
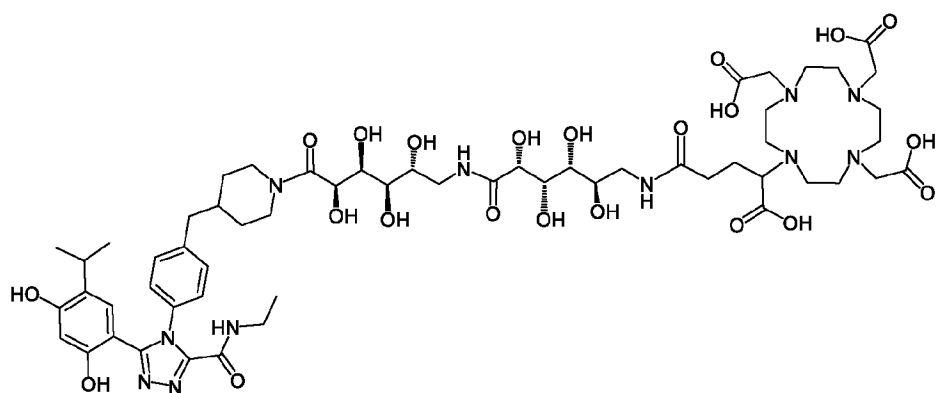
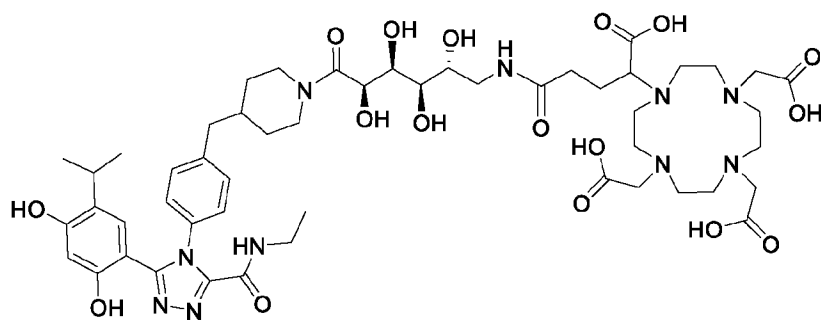
W is a chelator selected from the group consisting of DOTA, DOTAGA, NOTA, and NODAGA; and

R in each occurrence, independently, is OH, $-CH_2OH$, $-CO_2H$, $-CONH_2$, NH_2 , or $NHCOCH_3$, wherein the compound comprises a hydrophilic space linker containing at least three OH groups.

17. The compound of claim 16, wherein Z^1 is $C=O$, m is 3-4, p is 1-2, and R is OH or $-CH_2OH$.

18. The compound of claim 16 or 17, wherein W is DOTA or DOTAGA.

19. The compound of any one of claims 16-18, wherein the compound is one of the following, or a stereoisomer thereof:



20. The compound of any one of claims 1-19, wherein the compound comprises a radionuclide selected from the group consisting of ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{66}Ga , ^{67}Ga , ^{68}Ga , ^{82}Rb , ^{86}Y , ^{87}Y , ^{89}Zr , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , $^{117\text{m}}\text{Sn}$, ^{149}Pm , ^{149}Tb , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{198}Au , ^{199}Au , ^{201}Tl , ^{203}Pb , ^{211}At , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th , and ^{229}Th .

21. The compound of claim 20, wherein the radionuclide is selected from the group consisting of ^{68}Ga , ^{89}Zr , ^{90}Y , ^{111}In , ^{177}Lu , and ^{225}Ac .

22. The compound of claim 21, wherein the radionuclide is ^{225}Ac .

23. A pharmaceutical composition comprising a compound of any one of claims 1–22 and a pharmaceutically acceptable excipient.

24. A method of treating cancer, wherein the method comprises administering to a subject in need thereof a compound of any one of claims 1–22 or the composition of claim 23 in a therapeutically effective amount.

25. The method of claim 24, wherein the cancer is small-cell lung cancer, non-small-cell lung cancer, sarcoma, pancreatic cancer, breast cancer, or colon cancer.

26. A compound of any one of claims 1-22, or the pharmaceutical composition of claim 23, for use in a method of treating cancer.

27. Use of a compound of any one of claims 1-22, or the pharmaceutical composition of claim 23, in the manufacture of a medicament for the treatment of cancer.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2024/050467

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C07K 5/097** (2006.01), **A61K 51/04** (2006.01), **A61K 51/08** (2006.01), **A61P 35/00** (2006.01),
C07D 401/14 (2006.01), **C07H 15/26** (2006.01) (more IPCs on the last page)

CPC: , A61K 51/088 (2020.05), A61K 51/0491 (2020.01), A61K 51/0497 (2020.01),
A61P 35/00 (2020.01), C07D 401/14 (2020.01) (more CPCs on the last page)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07K 5/097, A61K 51/04, A61K 51/08, A61P 35/00, C07D 401/14, C07H 15/26, C07K 5/037.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

STN Registry and CAPLUS, Questel Orbit, Espacenet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CA 3135174 (WHITE ET AL.) 08 October 2020 (08-10-2020) Compounds 33-47, 54-60, 68-90, and T1	1-27
A	CA 3094719 (BILODEAU ET AL.) 10 October 2019 (10-10-2019) Conjugates 1-10	1-27
P,A	WO2024044755 (LEAMON ET AL.) 29 February 2024 (29-02-2024)	1-27

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* "A" "D" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance document cited by the applicant in the international application earlier application or patent but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
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Date of the actual completion of the international search
27 May 2024 (27-05-2024)

Date of mailing of the international search report
03 June 2024 (03-06-2024)

Name and mailing address of the ISA/CA
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2024/050467

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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		CN113710246A	26 November 2021 (26-11-2021)
		EP3946320A1	09 February 2022 (09-02-2022)
		EP3946320A4	28 December 2022 (28-12-2022)
		IL286847A	31 October 2021 (31-10-2021)
		JP2022527821A	06 June 2022 (06-06-2022)
		KR20210148157A	07 December 2021 (07-12-2021)
		SG11202109761TA	28 October 2021 (28-10-2021)
		TW202102268A	16 January 2021 (16-01-2021)
		US2022184217A1	16 June 2022 (16-06-2022)
		WO2020205948A1	08 October 2020 (08-10-2020)
CA3094719A1	10 October 2019 (10-10-2019)	AU2019249160A1	22 October 2020 (22-10-2020)
		CN112074288A	11 December 2020 (11-12-2020)
		EP3773670A1	17 February 2021 (17-02-2021)
		EP3773670A4	09 March 2022 (09-03-2022)
		IL277791A	30 November 2020 (30-11-2020)
		JP2021521106A	26 August 2021 (26-08-2021)
		JP7487110B2	20 May 2024 (20-05-2024)
		KR20200140271A	15 December 2020 (15-12-2020)
		TW202005667A	01 February 2020 (01-02-2020)
		US2021145971A1	20 May 2021 (20-05-2021)
		WO2019195384A1	10 October 2019 (10-10-2019)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2024/050467

IPC:

C07K 5/037 (2006.01)

CPC:

C07H 15/26 (2020.01), C07K 5/02 (2020.01), C07K 5/0215 (2020.01), C07K 5/0821 (2020.01),
A61K 2121/00 (2020.01)